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Synthesis of 9,10-Phenanthrenes via Palladium-Catalyzed Aryne Annulation by *o*-Halostyrenes and Formal Synthesis of (±)-Tylophorine

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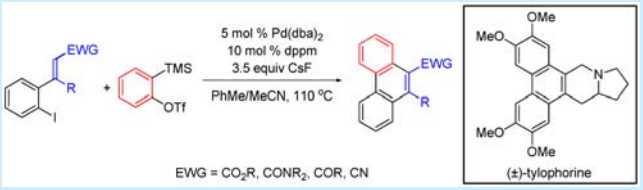
Supporting Information

ABSTRACT: A novel palladium-catalyzed annulation reaction of in situ generated arynes and *o*-halostyrenes has been developed. This methodology affords moderate to excellent yields of substituted phenanthrenes and is tolerant of a variety of functional groups such as nitrile, ester, amide, and ketone. This annulation chemistry has been successfully applied to the formal total synthesis of a biologically active alkaloid (±)-tylophorine.



Phenanthrenes are valuable skeletons found in numerous biologically active natural products and medicinal compounds.[1] For example, phenanthroindolizine-based tylophora alkaloids, which were isolated primarily from the Asclepiadaceae family,[2] possess interesting biological activities against cancer,[3] asthma,[4] anaphylaxis,[5] inflammation, and bacterial infection[5,6] (Figure 1). Phenanthrenes are also a common structural motif in

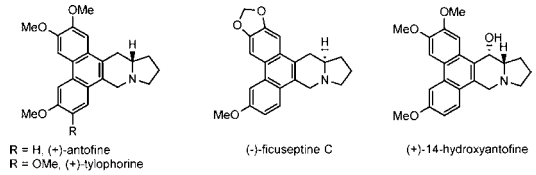
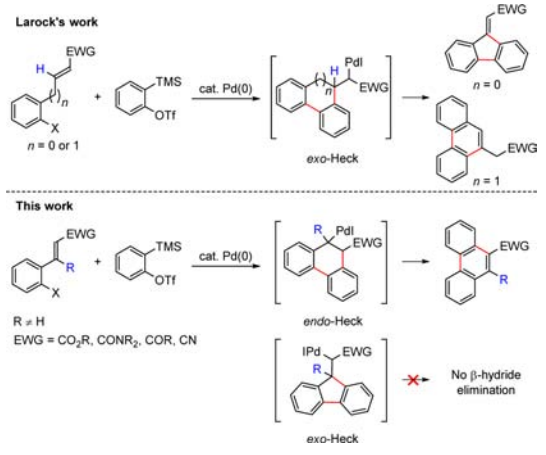


Figure 1. Biologically active phenanthroindolizidine alkaloids.

material science because of their unique photochemical and electroluminescent properties.[7] Traditional synthetic approaches to phenanthrenes include the intramolecular cyclization of a stilbene[8] or a biaryl compound,[9] the carbocyclization of alkynylated biaryl derivatives,[10] or co-cyclization of arynes.[11] Although useful, these methods often suffer from multistep syntheses,[8] poor regioselectivity,[11] or functional group incompatibility.[10] Therefore, efficient methods with greater diversity of substituents for the synthesis of functionalized phenanthrene derivatives are still highly desirable.

Recently, arynes and heterocyclic arynes generated from *o*-silylaryl triflate[12] have been applied in various novel synthetic methodologies, including transition-metal-catalyzed transformations.[13] Larock reported a convenient and general palladium-catalyzed aryne annulation by *o*-halostyrenes to synthesize 9-fluorenylidenes and 9-phenanthrenes via arylpalladium(II) aryne insertion and intramolecular *exo*-Heck reaction (Scheme 1).[14]

Scheme 1. Palladium-Catalyzed Aryne Annulation by *o*-Halostyrenes



Inspired by Larock's work, we envisioned that 9,10-phenanthrenes would be produced via arylpalladium(II) aryne insertion and intramolecular *endo*-Heck reaction when the R group is not a proton (Scheme 1). Herein, we report our results on the synthesis of 9,10-phenanthrenes via palladium-catalyzed annulation of in situ generated arynes and readily available *o*-halostyrenes and its application in the formal total synthesis of the anticancer natural alkaloid (±)-tylophorine.

We commenced our studies by examining the effects of reaction parameters on the yield for the palladium-catalyzed aryne annulation using ethyl (*E*)-3-(2-iodophenyl)but-2-enoate (**1a**) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate

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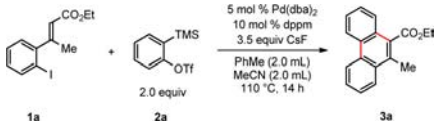
(**2a**) (Table 1). Under the best conditions described in Table 1, the reaction afforded 61% isolated yield of ethyl 10-methylphenanthrene-9-carboxylate (**3a**) by employing 0.20 mmol of **1a**, 2.0 equiv of **2a**, 3.5 equiv of CsF, 5 mol % of $Pd(dba)_2$, and 10 mol % of dppm in toluene/acetonitrile (v/v = 1:1, 4 mL) at 110 °C for 14 h. Decreasing the reaction temperature to 100 °C led to a lower yield (entry 2), as did changing the ratio of toluene to acetonitrile (entries 3 and 4). Increasing the amount of the benzyne precursor **2a** to 2.5 equiv did not improve the yield of phenanthrene **3a** (entry 5). However, reducing **2a** to 1.5 equiv resulted in a lower yield of 53% (entry 6). Addition of 1.0 equiv of $NaHCO_3$ did not have an impact on the isolated yield (entry 7). Replacing the ligand from dppm to more hindered ligands such as P(*o*-Tol)$_3$, BINAP, or dppf unfortunately afforded lower yields (entries 8−10). A lower loading of the catalyst (2.5 mol %) and ligand (5 mol %) led to a lower yield of the desired product **3a** in 33% (entry 11).

Table 1. Effect of Reaction Parameters on Palladium-Catalyzed Benzyne Annulation of *o*-Halostyrenes[a]



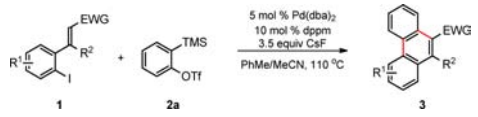
1a 2a 3a

entry	change from standard conditions	yield[b] (%)
1	none	61
2	100 °C instead of 110 °C	54
3	PhMe (3.0 mL) and MeCN (1.0 mL)	40
4	PhMe (1.0 mL) and MeCN (3.0 mL)	52
5	2.5 equiv of **2a**	59
6	1.5 equiv of **2a**	53
7	2.5 equiv of CsF and 1.0 equiv of $NaHCO_3$	61
8	10 mol % of P(*o*-Tol)$_3$	56
9	10 mol % of BINAP	39
10	10 mol % of dppf	51
11	2.5 mol % of $Pd(dba)_2$ and 5 mol % of dppm	33

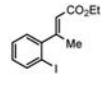
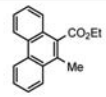
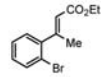
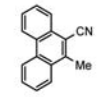
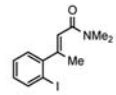
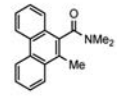
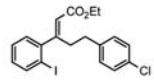
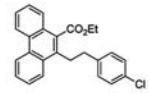
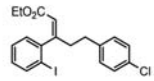
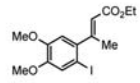
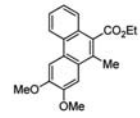
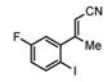
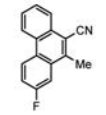
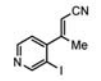
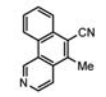
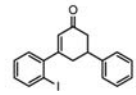
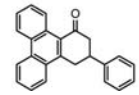
[a]Representative procedure: **1a** (0.20 mmol), **2a**, $Pd(dba)_2$, ligand, CsF, and solvent (4 mL) were placed in a 4-dram vial, and the reaction was stirred at the desired temperature for 14 h. [b]Isolated yield.

The scope and limitations of this palladium-catalyzed aryne annulation process were next examined (Table 2). Under our standard conditions, the model system ethyl (*E*)-3-(2-iodophenyl)but-2-enoate (**1a**) with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) as the benzyne precursor gave a 61% isolated yield of the desired product **3a** (entry 1). The less reactive aryl bromide **1b** also underwent the annulation reaction to produce **3a**, albeit in a lower yield of 38% (entry 2). Other styrene derivatives bearing an electron-withdrawing group (EWG) such as nitrile (**1c**) or amide (**1d**) also participated in this annulation process, generating the desired phenanthrenes **3b** and **3c** in 87% and 82% yield, respectively (entries 3 and 4). Both (*E*)- and (*Z*)-styrenes **1e** and **1f** can be employed, and the *E*-isomer ethyl (*E*)-5-(4-chlorophenyl)-3-(2-iodophenyl)pent-2-enoate (**1e**) gave a slightly higher yield of 58% than the corresponding *Z*-isomer **1f** (entries 5 and 6). *o*-Halostyrenes substituted with an electron-donating methoxy group (**1g**) or an electron-withdrawing fluorine atom (**1h**) underwent the annulation smoothly to generate the desired phenanthrene products **3e** and **3f** in good yields (entries 7 and 8). Unfortunately, pyridine was not tolerated in this process as *o*-halostyrenes **1i** decomposed during the reaction (entry 9).

Table 2. Synthesis of 9,10-Phenanthrenes by the Palladium-Catalyzed Benzyne Annulation of *o*-Halostyrenes[a]



1 2a 3

entry	*o*-halostyrene		product		yield[b]
1		**1a**		**3a**	61
2		**1b**		**3a**	38
3		**1c**		**3b**	87
4		**1d**		**3c**	82
5		**1e**		**3d**	58
6		**1f**		**3d**	53
7		**1g**		**3e**	59
8		**1h**		**3f**	69
9		**1i**		**3g**	0
10		**1j**		**3h**	31

[a]Representative procedure: **1** (0.20 mmol), **2a** (0.40 mmol), $Pd(dba)_2$ (5 mol %), dppm (10 mol %), CsF (3.5 equiv), and 1:1 PhMe/MeCN (4 mL) were placed in a 4-dram vial, and the reaction was stirred at 110 °C for 14 h. [b]Isolated yield.

Interestingly, cyclohex-2-en-1-one **1j** also participated in this process to afford the desired dihydrotriphenylen-1-(2*H*)-one (**3h**) in a 31% yield (entry 10).

The scope of this protocol was further established by examining the annulation reaction of (*E*)-3-(2-iodophenyl)but-2-enenitrile (**1c**) and various *o*-silylaryl triflates (Table 3). Both electron-rich silyl triflates **2b** and **2c** and electron-poor silyl triflate **2d** furnished the desired phenanthrenes in good yields (entries 1−3). Additionally, naphthalyne derived from **2e** afforded the expected product **3l** in a satisfactory 83% yield (entry 4). In the case of silylaryl triflate **2f** with a methoxy substituent at the 3-position, excellent regioselectivity was observed as only **3m** was obtained, albeit in a moderate 48% yield (entry 5). The low yield of **3m** was presumably caused by steric hindrance during the intramolecular Heck reaction (see

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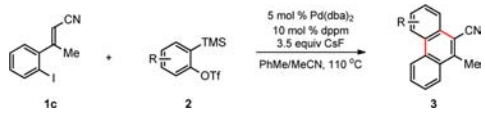
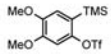
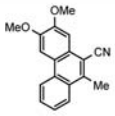
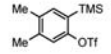
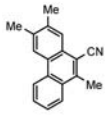
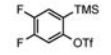
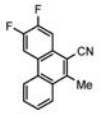
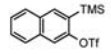
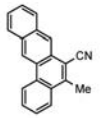
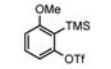
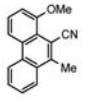
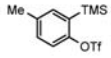
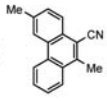
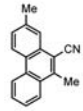
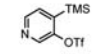
Table 3. Scope of Silylaryl Triflates[a]



entry	silylaryl triflate		product(s)		yield[b]
1		**2b**		**3i**	68
2		**2c**		**3j**	98
3		**2d**		**3k**	51
4		**2e**		**3l**	83
5		**2f**		**3m**	48
6		**2g**	 	**3n** **3o**	93 (1 : 1)
7		**2h**	 	**3p**	**3q** 0

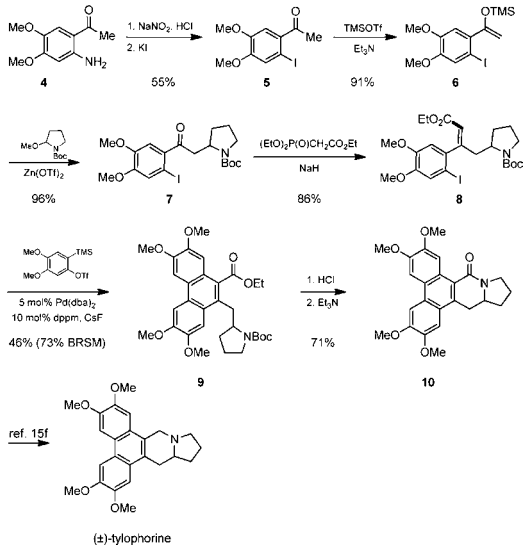
[a]Representative procedure: **1c** (0.20 mmol), **2** (0.40 mmol), $Pd(dba)_2$ (5 mol %), dppm (10 mol %), CsF (3.5 equiv), and 1:1 PhMe/MeCN (4 mL) were placed in a 4-dram vial, and the reaction was stirred at 110 °C for 14 h. [b]Isolated yield.

intermediate **III** in Scheme 3). The reaction of an unsymmetrical 4-methylbenzyne (from **2g**) also took place smoothly, giving a 1:1 mixture of inseparable regioisomers **3n** and **3o** in a 93% overall yield (entry 6). The 3,4-pyridyne from Garg's 3,4-pyridine precursor[12c] **2h** unfortunately did not afford any of the desired products (entry 7). We reasoned that 3,4-pyridyne could be unstable at 110 °C. In fact, compound **2h** completely decomposed within 1.5 h in PhMe/MeCN (1:1) when heated with CsF at 110 °C.

To further demonstrate the synthetic utility of this aryne annulation chemistry, we applied this methodology to the synthesis of a biologically interesting alkaloid (±)-tylophorine[15] which exhibits potent cytotoxic activity against a broad range of human cancer cells (Scheme 2).[3]

We initiated our synthesis by converting amine **4** to 2-iodoacetophenone **5** via a Sandmeyer reaction in a 52% yield.[16] The pyrrolidine unit was incorporated into ketone **5** through silyl enol ether−acyliminium ion coupling over two steps in an almost quantitative yield.[17] Horner−Wadsworth−Emmons olefination of ketone **7** provided the requisite α,β-unsaturated ester **8** as a 7:1 mixture of Z/E isomers in an 86% overall yield.[18] Palladium-catalyzed aryne annulation of **8** with 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2b**) afforded

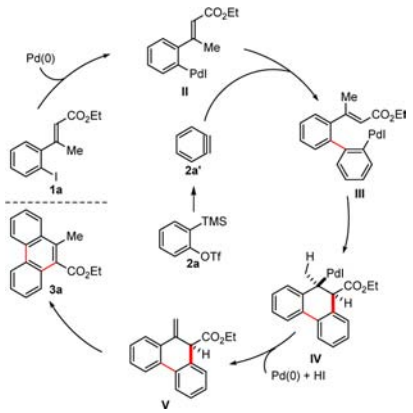
Scheme 2. Total Synthesis of (±)-Tylophorine



a 46% yield of phenanthrene **9** (73% based on recovery of starting material **8**). Deprotection of the Boc group followed by intramolecular cyclization generated lactam **10**, which can be reduced to (±)-tylophorine in one step via a literature procedure.[15f]

We propose a mechanism for this process as illustrated in Scheme 3 by employing aryl halide **1a** and aryne precursor **2a** as

Scheme 3. Proposed Mechanism



an example. It is believed that Pd(0) adds oxidatively to the aryl halide **1a** to generate the arylpalladium(II) intermediate **II**, which in turn reacts with the aryne intermediate **2a′** generated in situ from aryne precursor **2a**, to afford arylpalladium intermediate **III**. The *syn* addition of palladium−carbon bond in this intermediate across the neighboring carbon-cabon double bond forms intermediate **IV**, which converts to the phenanthrene product **3a** by *syn* β-hydride elimination and further isomerization of the resulting *exo* olefin intermediate **V**.

In summary, we have developed a novel palladium-catalyzed aryne annulation by *o*-halostyrenes, which affords good yields of substituted 9,10-phenanthrenes. This methodology is tolerant of a variety of functional groups including cyano, ester, amide, ketone, and methoxy group and provides a convenient and general approach to this important class of aromatic hydrocarbons. This annulation chemistry has been successfully applied

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to the formal synthesis of the biologically interesting alkaloid (±)-tylophorine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00558.

Detailed experimental procedures, characterization data, and copies of the ^{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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