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Palladium-Catalyzed Synthesis of 9-Fluorenylidenes through Aryne Annulation

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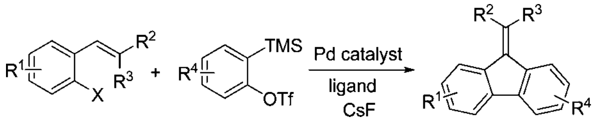
ABSTRACT



The palladium-catalyzed annulation of arynes by substituted *o*-halostyrenes produces substituted 9-fluorenylidenes in good yields. This methodology provides this important carbocyclic ring system in a single step, which involves the generation of two new carbon−carbon bonds, occurs under relatively mild reaction conditions, and tolerates a variety of functional groups, including cyano, ester, aldehyde, and ketone groups.

9-Fluorenylidenes are key structural units found in many compounds possessing biological activity. Derivatives of 9*H*-fluoren-9-ylidenes, commonly known as 9-fluorenylidenes, are pharmaceutically and cosmetically significant. The 9-fluorenylidene derivative paranylene is used in dispersible formulations of anti-inflammatory agents,[1] while the 9-fluorenylidene derivative lumefantrine is used in dermatological and photostable cosmetic compositions.[2] 3-Fluoren-9-ylidene-2′-hydroxy-3-phenylpropiophenone exhibits thermochromic properties.[3] 2,4,7-Trinitro-9-fluorenylmethacrylate (TNFMN) has been used to study the donor−acceptor interactions of poly(FIMA)s with different tacticities.[4]

Due to the pharmaceutical and biological importance of these compounds, the synthesis of 9-fluorenylidenes is important. In the literature, 9-fluorenylidenes are mainly synthesized, either from 9*H*-fluoren-9-one derivatives using a Wittig reaction[5] or from 9*H*-fluorene derivatives.[6]

Transition-metal-catalyzed annulation reactions are very valuable from a synthetic point of view.[7] The Pd-catalyzed annulation of alkynes by substituted aryl and vinylic halides has been employed for the synthesis of a variety of carbocycles and heterocycles,[8] and some of these reactions have also been recently extended to arynes. The major difficulty in employing arynes is the high reactivity of arynes[9] compared to alkynes and the harsh reaction conditions often needed to generate arynes in situ. A common problem associated with the high reactivity of arynes is their Pd-

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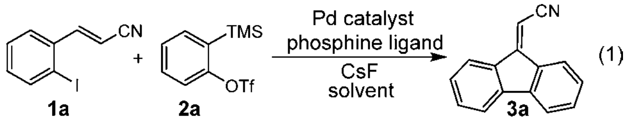
catalyzed cyclotrimerization[10] to form polycyclic aromatic hydrocarbons. Also, the harsh reaction conditions often required to obtain arynes severely limit the functional group compatibility of the chemistry. It has been reported that the silylaryl triflate **2a** in the presence of CsF generates benzyne under very mild reaction conditions.[11] This method of aryne generation has been used in our research laboratories and reported in the literature for a variety of electrophilic and nucleophilic reactions,[12] Pd-catalyzed annulation reactions,[13] cycloaddition reactions,[14] and insertion reactions.[15]

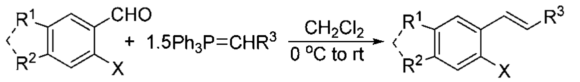
The palladium-catalyzed alkyne annulation of methyl 3-(2-iodophenyl)acrylate has been reported in the literature.[16] To the best of our knowledge, analogous palladium-catalyzed aryne insertions and subsequent cyclization of *o*-halostyrenes have not been reported previously. We report herein an efficient approach to 9-fluorenylidenes, which proceeds in good yields from starting materials that are readily available or easy to synthesize, and involves a palladium-catalyzed annulation of arynes.



(*E*)-3-(2-Iodophenyl)acrylonitrile (**1a**) was used as a model system for optimization of the reaction conditions using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) as the aryne precursor. We optimized the reaction conditions with respect to different ratios of the acetonitrile/toluene solvent system; the phosphine ligands P(*o*-tolyl)$_3$, tris(2,4,6-trimethoxyphenyl)phosphine, tris(2,6-dimethoxyphenyl)phosphine, tri(2-methoxyphenyl)phosphine, tri(2-furyl)phosphine, [(CH$_3$)$_3$P•AgI]$_4$, tri(*tert*-butyl)phosphine, 2-(di-*tert*-butylphosphino)biphenyl, xantphos, dppp, dppf, and dppm; the temperatures (85, 100, 110, and 120 °C) at which the reaction is run; the amount of the aryne precursor; the amount of CsF; and various Pd(dba)$_2$ catalyst loadings (5−20 mol %) with different ratios of Pd(dba)$_2$ catalyst to dppm ligand. Our "optimal" procedure involves heating 0.3 mmol of **1a**, 1.5 equiv of **2a**, 10 mol % of Pd(dba)$_2$, 20 mol % of dppm, and 3.0 equiv of CsF in 5 mL of 1:1 acetonitrile/toluene at 110 °C in a sealed vial for 24 h.

After obtaining our best reaction conditions for the aryne annulation, we examined the scope of this reaction on various substrates. Aryl halides **1a** and **1g** were obtained from commercial sources. Aryl halides **1e**, **1h**, and **1i** were prepared by standard Wittig chemistry (Scheme 1), using commercially available aldehydes **4a** and **4b**, while **4c** was prepared according to a literature procedure.[17] Aryl halides **1b**,[18] **1c**,[18] **1d**,[19] and **1f**[20] were prepared according to literature procedures. The benzyne precursor **2a** is commercially available, while the aryne precursor **2b**[14] has been prepared according to a literature procedure.

Scheme 1. Starting Material Preparation



	X	R^1, R^2	R^3		X	R^1, R^2	R^3	time (h)	%
4a	I	H, H	CHO	**1e**	I	H, H	CHO	48	39
4b	Br	OMe, OMe	CO$_2$Et	**1h**	Br	OMe, OMe	CO$_2$Et	12	36
4c	I	OCH$_2$O	CN	**1i**	I	OCH$_2$O	CN	24	52

The reaction of aryl iodide **1a** under our optimized conditions with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) as the benzyne precursor gave an 91% isolated yield of the desired product **3a** (Table 1, entry 1). Compound **3a** was obtained in a slightly lower 79% yield, when the reaction was carried out using the corresponding aryl bromide, (*E*)-3-(2-bromophenyl)acrylonitrile (**1b**). The improved yield from the aryl iodide is no doubt a direct result of the more facile oxidative addition of aryl iodides over aryl bromides. The *cis* isomer (*Z*)-3-(2-bromophenyl)acrylonitrile (**1c**) gave a slightly lower yield of 72% than the corresponding *trans* isomer, (*E*) 3-(2-bromophenyl)acrylonitrile (**1b**) (compare entries 2 and 3). With an ethyl ester as the electron-withdrawing group (EWG) on the double bond of the *o*-halostyrene **1d**, the yield dropped to 75% under our optimized conditions (compare entries 2 and 4). With an aldehyde as the EWG on the *o*-halostyrene **1e**, a 76% yield of the desired product **3c** was obtained (entry 5). The yield is comparable to that obtained with an ester group present on the double bond of the *o*-halostyrene. With a ketone present in the *o*-halostyrene **1f**, the yield dropped to 61% (entry 6). When a stronger electron-withdrawing nitro group was placed on the *o*-halostyrene, the reaction failed to give the desired product **3e** (entry 7). Instead, we observed the formation of a polymeric residue. We believe 2-(2-nitrovi-

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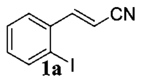
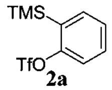
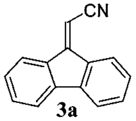
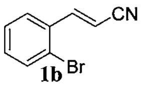
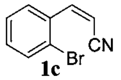
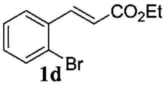
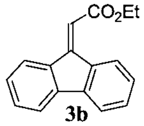
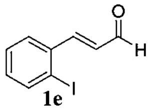
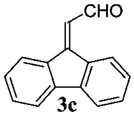
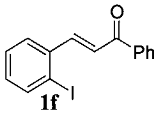
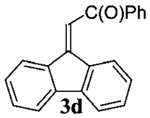
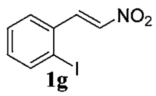
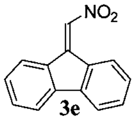
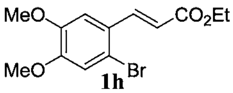
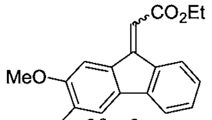
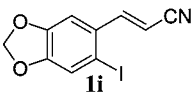
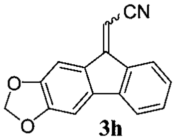
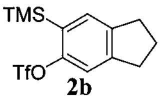
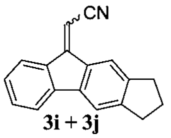
Table 1. Synthesis of 9-Fluorenylidenes by the Palladium-Catalyzed Aryne Annulation of *o*-Halostyrenes[a]

entry	*ortho*-halostyrene	benzyne precursor	product(s)	% isolated yield
1	 **1a**	 **2a**	 **3a**	91
2	 **1b**	**2a**	**3a**	79
3	 **1c**	**2a**	**3a**	72
4	 **1d**	**2a**	 **3b**	75
5	 **1e**	**2a**	 **3c**	76
6	 **1f**	**2a**	 **3d**	61
7	 **1g**	**2a**	 **3e**	0
8	 **1h**	**2a**	 **3f + 3g**	<5[b]
9	 **1i**	**2a**	 **3h**	73[c]
10	**1a**	 **2b**	 **3i + 3j**	82[d] [1:11]

[a] Representative procedure: *o*-halostyrene **1a**−**i** (0.3 mmol), silylaryl triflate **2a**,**b** (1.5 equiv), 10 mol % of Pd(dba)$_2$, 20 mol % of dppm, CsF (3 equiv) and 1:1 $CH_3CN/PhCH_3$ (5 mL) were placed in a 4 dram vial. The vial was sealed with a screw cap. The reaction was then stirred at 110 °C for 24 h. [b] GC yields. [c] Eight percent of a minor isomer is observed by GC analysis. [d] The ratio was determined by ^1H NMR spectroscopy.

nyl)iodobenzene (**1g**) undergoes polymerization under our reaction conditions.

When electron-donating methoxy groups were placed on the aryl bromide **1h**, we obtained an extremely poor yield (<5%), presumably because oxidative addition to palladium is unfavorable in such electron-rich aryl bromides (compare entries 4 and 8). On the other hand, the electron-rich substrate **1i** with a carbon−iodine, instead of a carbon−bromine bond, gave the desired product in a 73% yield (entry 9). The stereochemistry of the major product has not been rigorously established, but is assumed to be the less hindered *E*-isomer. Eight percent of a minor isomer has also been observed.

We have also studied the scope of the reaction using a different aryne precursor. The aryl iodide **1a** upon reaction with the aryne precursor **2b** gave the desired compounds **3i** and **3j** as a 1:11 mixture of inseparable isomers in an 82% overall yield (entry 10). It is unclear as to which stereoisomer is the major product. The *o*-halo allylic benzene, ethyl (*E*)-4-(2-iodophenyl)but-2-enoate, on reaction with **2a** gave a modest 62% yield of the ethyl (phenanthren-9-yl)acetate (Figure 1). The reactions to obtain the phenanthrene nucleus are under further investigation.

We propose the following possible mechanisms for these reactions based on the known reactions of organopalladium

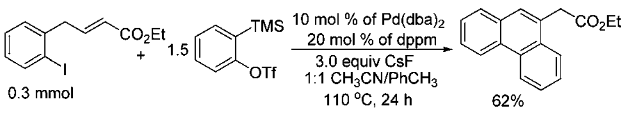
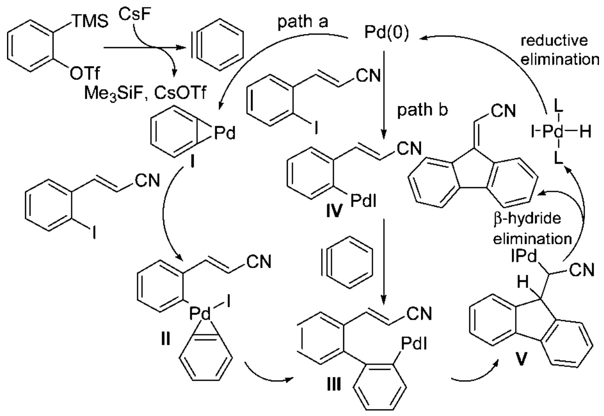


Figure 1. Synthesis of ethyl (phenanthren-9-yl)acetate.

compounds with alkynes (Scheme 2).[8] The reaction can follow two pathways, path a or path b. In path a, the aryne generated from the triflate in the presence of the fluoride source coordinates with Pd(0), affording palladacycle **I**.[21] Oxidative addition of the aryl halide to **I** might generate an arylpalladium(IV) complex **II**. Upon reductive elimination, complex **II** could afford a new arylpalladium intermediate **III**. Alternatively, according to path b, Pd(0) might add oxidatively to the aryl halide to afford the arylpalladium(II) intermediate **IV**, which in turn might add to the aryne[22] to afford arylpalladium intermediate **III**. Regardless of how intermediate **III** is generated, the palladium−carbon bond in this intermediate can then add across the neighboring carbon−carbon double bond to afford intermediate **V**, which directly affords the fluorenylidene product by *β*-hydride elimination.

Scheme 2. Tentative Mechanisms



Our investigation has shown that a range of fluorenylidenes can be obtained from simple starting materials that are readily available or easily synthesized, using a one step palladium-catalyzed aryne insertion of *o*-halostyrenes. The arynes are obtained in situ under mild reaction conditions from the corresponding 2-(trimethylsilyl)aryl trifluoromethanesulfonates and CsF. Our methodology is tolerant of a variety of functional groups, including cyano, ester, aldehyde, ketone, and methoxy groups, which can provide a handle for further organic transformations. This methodology provides a very convenient and general approach to this important class of aromatic hydrocarbons.

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Supporting Information Available: General experimental procedures and spectral data for all previously unreported starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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