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Efficient Synthesis of 9-Aryldihydrophenanthrenes by a Cascade Reaction Involving Arynes and Styrenes

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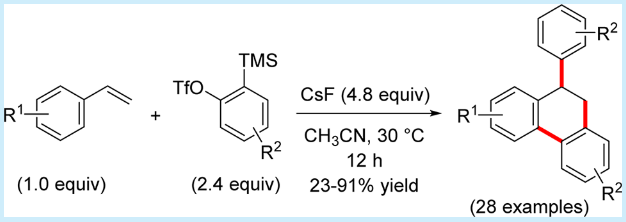
Supporting Information

ABSTRACT: A mild, general, and transition-metal-free protocol for the synthesis of 9,10-dihydrophenanthrenes is reported. The aryne generated by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates undergoes an efficient cascade reaction initiated by the Diels–Alder reaction with the differently substituted styrenes leading to the formation of 9-aryl-9,10-dihydrophenanthrene derivatives in moderate to good yields.



9,10-Dihydrophenanthrene derivatives are common structural units in various biologically active natural products.[1] For example, the natural product juncusol,[2] isolated from the plant *Juncus roemerianus*, has been reported to possess anticancer and antimicrobial activity, lusianthridin[3] isolated from the orchid *Lusia indiuisa* has been found to show α,α-diphenyl-2-piorylhydrasyl (DPPH) free-radical scavenging activity, and orchinol[4] isolated from *Orchis militaris* shows antifungal activity (Figure 1). Due to their diverse biological activity, 9,10-dihydrophenanthrenes are interesting synthetic targets. Consequently, the search for efficient and flexible synthetic methods toward this structural motif has attracted much attention in synthetic organic chemistry.[5]

The synthesis of 9,10-dihydrophenanthrenes has been known to utilize transition-metal-catalyzed cyclization reactions involving arynes.[6,7] Based on our interest in the transition-metal-free carbon−carbon and carbon-heteroatom bond-forming reactions using arynes,[8] we envisioned that the [4 + 2] cycloaddition reaction between arynes generated by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates[9] with styrenes could result in a straightforward access to 9,10-dihydrophenanthrenes. This will be interesting as the utility of styrenes as the 4π-component in Diels−Alder reactions utilizing a carbon−carbon double bond, which is involved in aromaticity,[10] can also meet with problems involving polymerizations[11] as side reactions. Notably, the reaction of styrene with aryne generated from 2-bromofluorobenzene leading to the formation of 9-phenyl 9,10-dihydrophenanthrene was reported by Dilling as early as 1966.[12] However, this reaction is limited to only one example. Subsequently, the reaction of aryne with α-methyl styrene furnishing three products in low yields was developed by Wolthuis and Cady.[13] Moreover, the reaction of tetrahalogenated arynes with styrenes leading to the Diels−Alder adduct was reported by Heaney and co-workers.[14] Intriguingly, in these reports, the substrate scope appears to be very narrow, and the yields are relatively low and hence a general system remains to be established. Herein, we report a mild, general, and efficient reaction of arynes with styrenes proceeding via a cascade reaction initiated by the Diels−Alder reaction leading to the highly selective synthesis of 9-aryl-9,10-dihydrophenanthrene derivatives in moderate to good yields and with broad scope.

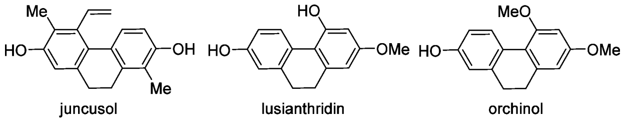
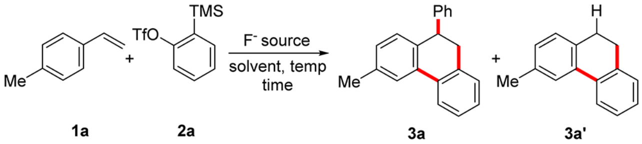


Figure 1. Selected naturally occurring 9,10-dihydrophenanthrenes.

Table 1. Optimization of the Reaction Conditions[a]



entry	F⁻ source	solvent	temp (°C)	time (h)	yield of **3a** (%)[b]	yield of **3a′** (%)[b]
1	*CsF*	*CH_3CN*	*30*	*12*	*77 (73)*	*<5*
2[c]	KF	THF	30	12	59	21
3	TBAF	THF	30	12	<1	<1
4	CsF	CH_3CN	60	12	71	<5
5	CsF	CH_3CN	30	6	69	<5
6[d]	CsF	CH_3CN	30	12	74	<5

[a]Standard conditions: **1a** (0.25 mmol), **2a** (0.60 mmol), fluoride source (4.8 equiv), solvent (1.0 mL), 30 °C, and 12 h. [b]The yields were determined by ^1H NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield on 0.50 mmol scale in parentheses. [c]4.8 equiv of 18-crown-6 was used as an additive. [d]2.0 equiv of **2a** and 4.0 equiv of CsF was used.

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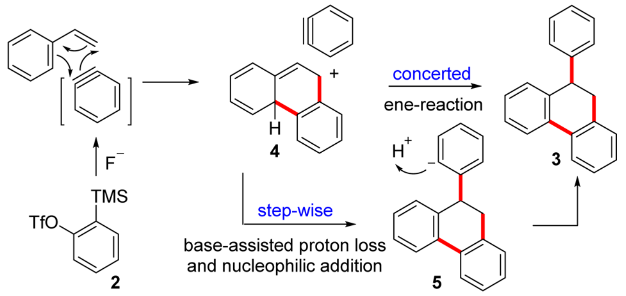
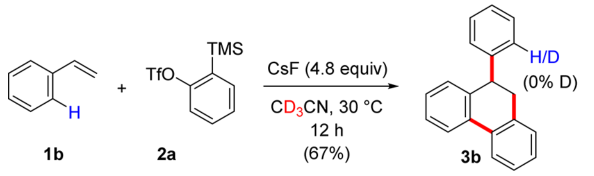
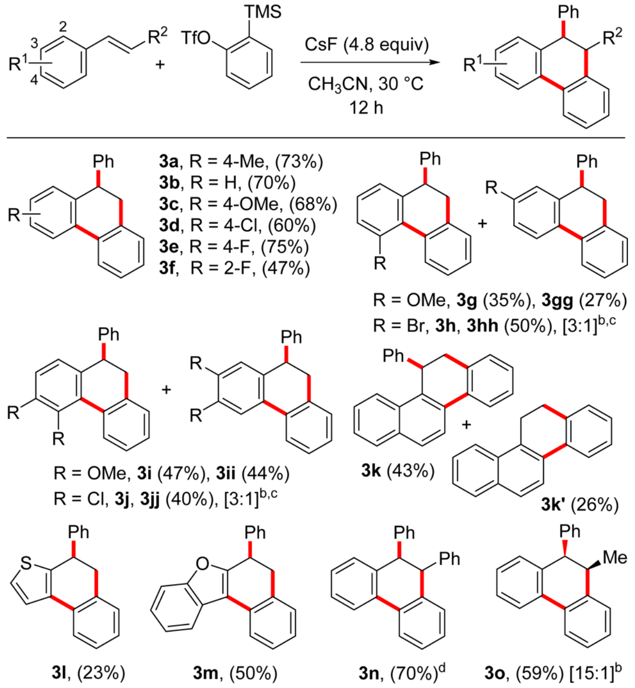
Scheme 1. Proposed Mechanism of the Reaction



Scheme 2. Reaction in CD_3CN



Scheme 3. Substrate Scope of the Cascade Reaction: Variation of Styrenes[a]



[a] General conditions: **1** (0.50 mmol), **2a** (1.20 mmol), CsF (4.8 equiv), CH_3CN (2.0 mL), 30 °C, and 12 h. Yields of the isolated products are given. [b] Determined by ^{1}H NMR. [c] Inseparable mixture of regioisomers. [d] 17% of 1:1 adduct was also isolated.

Scheme 4. Reaction of Arynes with Substituted Styrenes

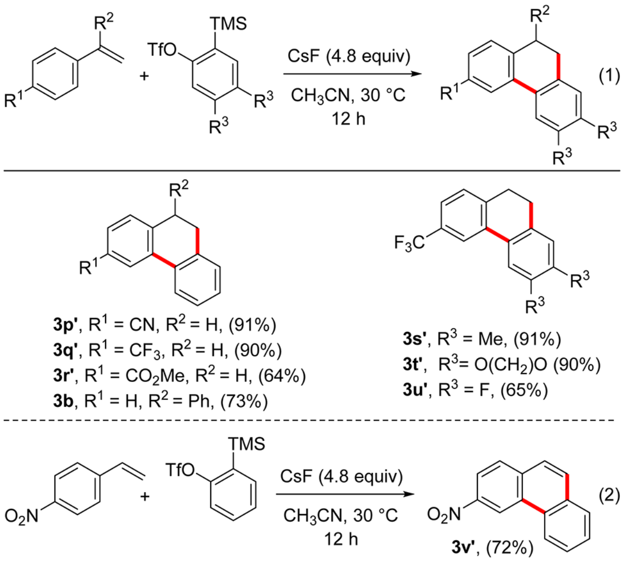
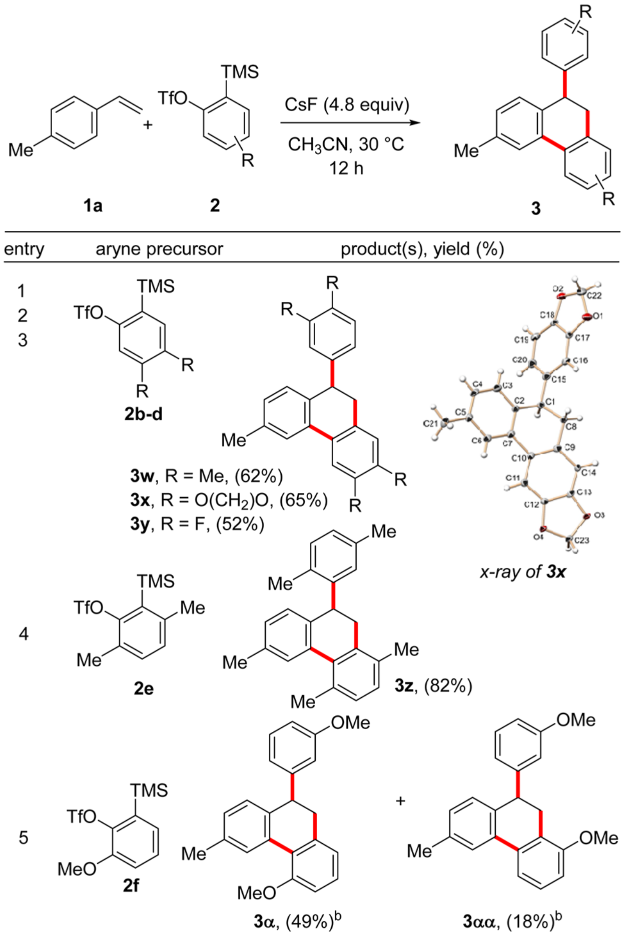


Table 2. Variation of the Aryne Moiety[a]



[a] General conditions: **2a** (1.20 mmol), **1** (0.50 mmol), CsF (4.8 equiv), CH_3CN (2.0 mL), 30 °C and 12 h. Yields of the isolated products are given. [b] Reaction was run on 0.25 mmol scale.

The present study commenced with the treatment of 1-methyl-4-vinylbenzene **1a** and the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **2a**[9] using 4.8 equiv of CsF in CH_3CN as the solvent. Under these conditions, a facile reaction occurred, leading to the formation of 9-phenyl-9,10-dihydrophenanthrene derivative **3a** in 77% yield (73% isolated yield).[15] Interestingly, the product **3a′** derived from the initial Diels–Alder reaction followed by proton transfer was observed only in trace amounts (based on ^{1}H NMR spectroscopy, Table 1, entry 1). When the reaction was carried out using KF (in the presence of 18-crown-6) as the fluoride source, **3a** was formed in a reduced yield of 59%, whereas **3a′** was formed in 21% (entry 2). The use of tetrabutylammonium fluoride (TBAF) as fluoride source was not found to be beneficial (entry 3).

Increasing the reaction temperature and reducing the reaction time lowered the yield of **3a** (entries 4 and 5). Lowering the amount of **2a** below 2.4 equiv lowered the yield of **3a** (entry 6).

The mechanistic rationale for this cascade process is shown in Scheme 1. The reaction of styrene with aryne generated from **2** lead to the generation of the adduct **4**. This adduct **4** can add to another molecule of electrophilic aryne in a concerted ene reaction leading to the formation of the desired product **3**.[16] Alternatively, in a stepwise pathway, **4** can be deprotonated by the basic medium followed by nucleophilic addition to another molecule of aryne generating intermediate **5**, which can be protonated leading to the formation of **3**.

An indication for the Diels–Alder/ene cascade reaction comes from the fact that the reaction of **1b** with **2a** carried out in CD_3CN resulted in the smooth formation of the corresponding protonated product **3b** in 67% (Scheme 2). The incorporation no deuterium in the product sheds light on a concerted process.

Regarding the scope of this cascade reaction (Scheme 3), the unsubstituted styrene worked well and various styrenes with electronically dissimilar groups at the 4-position of the aromatic ring of **1** were well tolerated, furnishing 9-aryl-9,10-dihydrophenanthrene derivatives in good yields and excellent selectivity for the cascade product (**3a**–**e**). Moreover, substitution is tolerated at 2-position of the aromatic ring of **1** resulting in the desired product in moderate yield (**3f**). As anticipated, styrenes with substituent at the 3-position of the aromatic ring resulted in the formation of regioisomers. When the substituent was −OMe, the regioisomers were separable by column chromatography and the products **3g** and **3gg** were isolated in 35% and 27% yield, respectively. However, when the substituent was Br, the regioisomers **3h** and **3hh** were inseparable and were observed in 50% overall yield and 3:1 ratio. Additionally, 3,4-disubstituted styrenes afforded regioisomeric products in moderate to good yields (**3i**, **3ii** and **3j**, **3jj**). The reaction of 1-vinylnaphthalene afforded the cascade product **3k** in 43% along with the 1:1 adduct **3k′** in 26% yield. Interestingly, 2-vinylthiophene and 2-vinylbenzofuran also furnished the desired product albeit in low to moderate yields, further expanding the scope of this cascade reaction (**3l**, **3m**). In addition, *trans*-stilbene afforded the 9,10-diaryl 9,10-dihydrophenanthrene **3n** in 70% along with the 1:1 adduct **3b** in 17% yield. Furthermore, *β*-methyl styrene underwent efficient cascade reaction with arynes leading to the formation of 9-methyl-10-phenyl-9,10-dihydrophenanthrene in 59% yield and a good diastereomeric ratio of 15:1 in favor of the *cis* isomer.

Notably, the reaction of aryne with styrenes having an electron-withdrawing group at the 4-position of the ring afforded the 1:1 adduct derived from the initial Diels–Alder reaction followed by proton transfer in good yield (Scheme 4, eq 1, **3p′**–**r′**). In these cases, the cascade product was observed in only <10% yield.[17,18] Moreover, the reaction of 1,1-diphenylethylene **1s** with aryne furnished the 1:1 adduct **3b** in 73%. Furthermore, this reaction worked well with electronically different aryne precursors, and the desired dihydrophenanthrenes were isolated in good yields (**3s′**–**u′**). Rather unexpectedly, the reaction of aryne with 4-nitrostyrene resulted in the formation of 3-nitrophenanthrene **3v′** in 72% yield (Scheme 4, eq 2).[19]

Next, we examined the effect of varying the substituents on the aryne precursor **2** (Table 2). Electronically diverse 4,5-disubstituted symmetrical aryne precursors **2b**–**d** readily furnished the 9-phenyl-9,10-dihydrophenanthrene derivatives **3w**–**y** in moderate to good yields (entries 1–3). In the case of **3x**, the structure was unequivocally confirmed by single-crystal X-ray analysis.[20] Notably, some of the fluorinated 9,10-dihydrophenanthrenes are known to have potential applications as liquid crystalline materials.[21] Moreover, the 3,6-dimethyl-substituted symmetrical aryne precursor **2e** worked well to afford the product **3z** in 82% yield (entry 4). In addition, 3-methoxyaryne generated from **2f** furnished a separable mixture of regioisomers **3*α*** and **3*αα*** in ∼3:1 ratio and overall yield of 67%, further expanding the scope of this reaction (entry 5). Formation of two products in this case is due to the possibility of two Diels–Alder adducts formed between styrene **1a** and aryne **2f**.

In conclusion, we have developed a mild, general, and efficient procedure for the synthesis of functionalized 9,10-dihydrophenanthrenes by a unique cascade reaction involving arynes and styrenes.[22] The present method utilized styrenes as an unconventional diene component in the Diels–Alder reaction. The protocol presented herein is likely to find application for the transition-metal-free synthesis of 9,10-dihydrophenanthrene derivatives.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, single-crystal X-ray data of **3x**, and characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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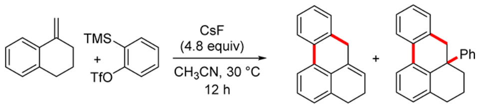
(17) It may be noted that the difference in reactivity of fluoro-substituted styrenes and other electron-withdrawing styrenes with arynes is unclear at this stage.

(18) Interestingly, reaction of 4-(trifluoromethyl)styrene with 4.0 equiv of aryne precursor also furnished the same result with no improvement in yield of cascade product.

(19) Moreover, the reaction of aryne with the olefin **6** furnished the adduct **7** in 65% yield and **8** in 20% yield. The product **7** may be formed by the Diels−Alder reaction between **6** and aryne followed by dehydrogenation and **8** may be formed by the cascade reaction.



6 **2a** **7** (65%) **8** (20%)

(20) CCDC-960058 (**3x**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(22) It may be mentioned that the preliminary studies toward intercepting the Diels−Alder adduct **4** (Scheme 1) with a different eneophile, however, failed.