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# Synthesis of Polyfluoroalkyl Aza-Polycyclic Aromatic Hydrocarbons Enabled by Addition of Perfluoroalkyl Radicals onto Vinyl Azides

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Supporting Information

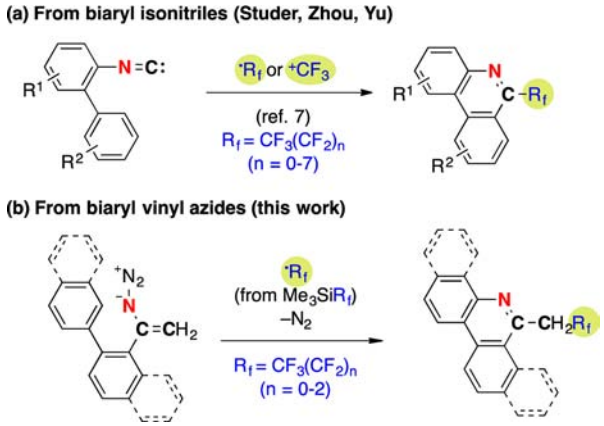
**ABSTRACT:** Radical perfluoroalkylation of α-(biaryl-2-yl)vinyl azides is capable of supplying polyfluoroalkyl aza-polycyclic aromatic hydrocarbons (aza-PAHs). Commercially available $Me_3SiR_f$ ($R_f$ = $CF_3$, $C_2F_5$, and $C_3F_7$) are employed as the sources of perfluoroalkyl radicals upon oxidation with $PhI(OAc)_2$. The addition of perfluoroalkyl radicals to biarylvinyl azides generates the corresponding iminyl radicals, which subsequently cyclize with the intramolecular arene moiety, furnishing aza-PAH skeletons having polyfluoroalkyl ($R_fCH_2$) function.


The incorporation of perfluoroalkyl groups ($R_f$) onto organic molecules is capable of altering their chemical, physical, and biological properties[1] which leads to broad applications of fluorine-containing molecules in the fields of medicinal chemistry and material sciences. In this context, a variety of perfluoroalkylation reactions have been developed to prepare diverse fluorine-containing molecules.[2] Especially, the synthesis of azaheterocycles having a per- or polyfluoroalkyl group at a specific position has drawn considerable attention,[3] owing to the potent and broad applications of azaheterocycles in various fields.[4]

Phenanthridine derivatives have shown a broad spectrum of biological activity[5] and optoelectronic properties.[6] Installation of the polyfluoroalkyl function might render these compounds more valuable in the subject of drug discovery and material-based applications. However, a few methods have been exploited to date for the construction of phenanthridines and their derivatives with installation of the polyfluoroalkyl group.[7,8] Very recently, Studer,[7a] Zhou,[7b] and Yu[7c,d] have independently developed synthetic methods of 6-perfluoroalkyl phenanthridines through radical or ionic perfluoroalkylation of biaryl isonitriles (Scheme 1a). We describe herein a new protocol to access phenanthridines and their derivatives (*aza-polycyclic aromatic hydrocarbons: aza-PAHs*) having trifluoroethyl or other perfluoroalkylmethylene moieties,[9] which is enabled by oxidative radical perfluoroalkylation of readily accessible α-(biaryl-2-yl)vinyl azides (Scheme 1b). Readily available and handled perfluoroalkyltrimethylsilanes ($Me_3SiR_f$) could be utilized as the sources of perfluoroalkyl radicals under $PhI(OAc)_2$-mediated oxidative reaction conditions.[10]

Vinyl azides have been utilized as a versatile synthon for the synthesis of various nitrogen-containing molecules.[11] By taking advantage of vinyl azides as a potential radical acceptor,[12] we have recently disclosed an oxidative radical trifluoromethylation reaction of vinyl azides that led to the formation of α-trifluoromethyl ($CF_3$) azines (Scheme 2a).[13] In this process,

**Scheme 1. Synthesis of Polyfluoroalkyl Phenanthridine Derivatives**




the $CF_3$ radical generated from $Me_3SiCF_3$ upon oxidation with $PhI(OAc)_2$ adds to the C=C bond of vinyl azides to form α-$CF_3$ iminyl radicals that readily dimerize to afford α-$CF_3$ azines. On this basis, we envisioned that the putative iminyl radicals could be trapped with an intramolecular aryl function installed at the *ortho*-position of α-arylvinyl azides such as **1a**, enabling C–N bond forming cyclization to construct trifluoroethyl phenanthridines such as **2a** (Scheme 2b).

A brief outline for the preparation of α-(biaryl-2-yl)vinyl azides **1** is shown in Scheme 3. The biaryl structure was constructed by the Pd-catalyzed Suzuki–Miyaura coupling of arylboronic acids and *ortho*-bromoaryl aldehydes, which was followed by the Wittig olefination. The vinyl azide function was then readily installed by following the modified Hassner

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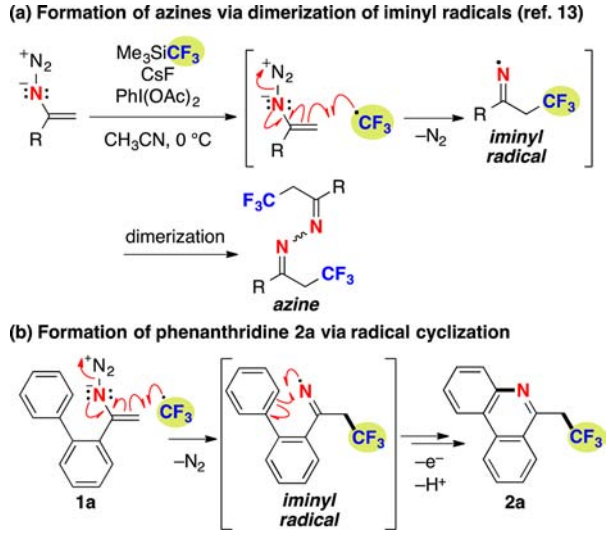
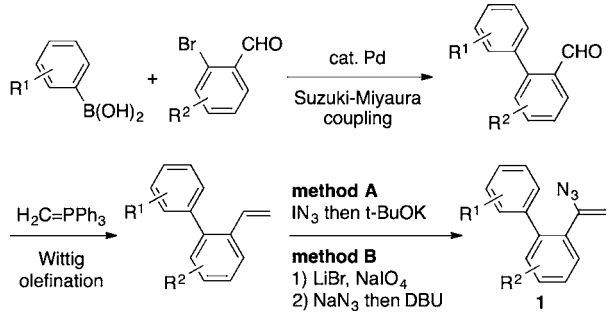
**Scheme 2. Trifluoromethylation of Vinyl Azides for the Formation of Azines and Phenanthridines**




**Scheme 3. Preparation of α-(Biaryl-2-yl)vinyl Azides 1**

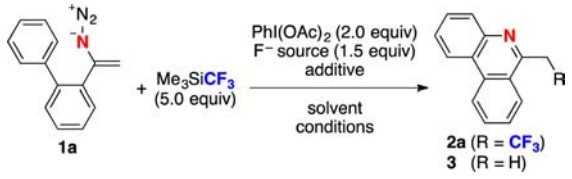



method[14] via addition of $IN_3$ followed by elimination of HI with *t*-BuOK (method A) or via a sequence of dibromonation, diazidation, and elimination of $HN_3$ with DBU (method B) (see the Supporting Information for more details).

To test this hypothesis as shown in Scheme 2b, we examined the reaction of α-(biaryl-2-yl)vinyl azide **1a** with $Me_3SiCF_3$.[15] The reaction of **1a** with $Me_3SiCF_3$ (5 equiv) in the presence of $PhI(OAc)_2$ (2.0 equiv) and CsF (1.5 equiv) in $CH_3CN$ proceeded as expected at 0 °C to afford 6-trifluoroethylphenanthridine **2a** in 60% yield, along with formation of 6-methylphenanthridine (**3**) as a side product in 6% yield (Table 1, entry 1).[16] It is noted that the corresponding azine derived from dimerization of the putative iminyl radical intermediate was not observed at all. In order to improve the reaction efficiency for the synthesis of phenanthridine **2a**, optimization of the reaction conditions was then undertaken (see the Supporting Information for mode details). Use of KF instead of CsF under otherwise identical reaction conditions also provided phenanthridine **2a**, while the yield was moderate (entry 2). Interestingly, the addition of benzoquinone (BQ, 0.2 equiv) dramatically enhanced the reaction[17] to give **2a** in 86% yield with perfect inhibition of formation of **3** (entry 3). No reaction with 95% recovery of vinyl azide **1a** was observed only with 2 equiv of BQ in the absence of $PhI(OAc)_2$ (entry 4). Switching the solvent to DMF could accelerate the reaction, but the yield of **2a** was only 69% (entry 5).

It is worthy to note that the reactions of vinyl azide **1a** with $Me_3SiC_2F_5$ and $Me_3SiC_3F_7$ proceedeed well under the

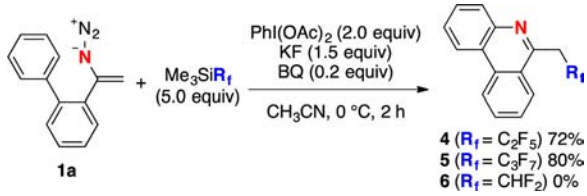
**Table 1. Optimization of the Reaction Conditions**[a]




| entry | solvent | $F^-$ source | additive [equiv] | conditions | **2a** [%][b] |
|---|---|---|---|---|---|
| 1 | MeCN | CsF | – | 0 °C, 1 h | 60[c] |
| 2 | MeCN | KF | – | 0 °C, 2 h | 50 |
| 3 | MeCN | KF | BQ (0.2) | 0 °C, 2 h | 91 (86)[d] |
| 4[e] | MeCN | KF | BQ (2.0) | 0 °C–rt, 21 h | 0[f] |
| 5 | DMF | KF | BQ (0.2) | 0 °C, 5 min | 69 |

[a]Unless otherwise noted, the reactions were carried out on the scale of 0.3–0.5 mmol of vinyl azide **1a** with 5 equiv of $Me_3SiCF_3$ under a nitrogen atmosphere. [b]$^1$H NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [c]6-Methylphenanthridine (**3**) was formed in 6% yield. [d]Isolated yield of **2a**. [e]The reaction was conducted in the absence of $PhI(OAc)_2$. [f]**1a** was recovered in 95% yield. BQ = benzoquinone.

**Scheme 4. Perfluoroalkylation of Vinyl Azide 1a**




optimized reaction conditions (Scheme 4), leading to the corresponding 6-polyfluoroalkylphenanthridines **4** and **5**, respectively, in good yields, while the use of $Me_3SiCHF_2$ did not result in the desired phenanthridine construction at all.

The generality of this transformation was next explored using a variety of biarylvinyl azides **1** for the synthesis of trifluoroethyl-substituted phenanthridines and other aza-polycyclic aromatic hydrocarbons (aza-PAHs)[18,19] (Scheme 5). Biarylvinyl azides bearing electron-donating and -withdrawing functional groups could be converted to the corresponding phenanthridines in good yields (for **2b–2i**). In order to test the regioselectivity of the C–N bond forming cyclization step, a couple of substrates possessing a *meta*-substituted benzene ring were subjected to the present reaction conditions (for **2j–2l**). In all cases, the cyclization occurred preferentially at the sterically more hindered position (marked in purple) with an acceptable level of regioselectivity. The reaction of 2-(1-azidovinyl)-1-phenylnaphthalene (**1m**) provided trifluoroethyl tetracyclic benzo[*k*]phenanthridine **2m** in 67% yield. For the reaction of vinyl azide **1n** having a 2-naphthyl moiety, the C–N bond formation occurred exclusively at the α-carbon (marked in purple), enabling selective synthesis of trifluoroethyl aza-chrysene (benzo[*c*]phenanthridine) **2n**. This interesting regioselectivity in the cyclization onto the 2-naphthyl moiety was capable of constructing pentanuclear aza-PAHs, dibenzo-[*c*,*k*]phenanthridine **2o** and dibenzo[*c*,*d*]phenanthridine **2p**, from the corresponding vinyl azides. The tetra- and pentanuclear aza-PAHs **2m–2p** exhibited quite good solubility in commonly used organic solvents such as ethyl acetate, THF, chloroform, and toluene, thereby demonstrating the unique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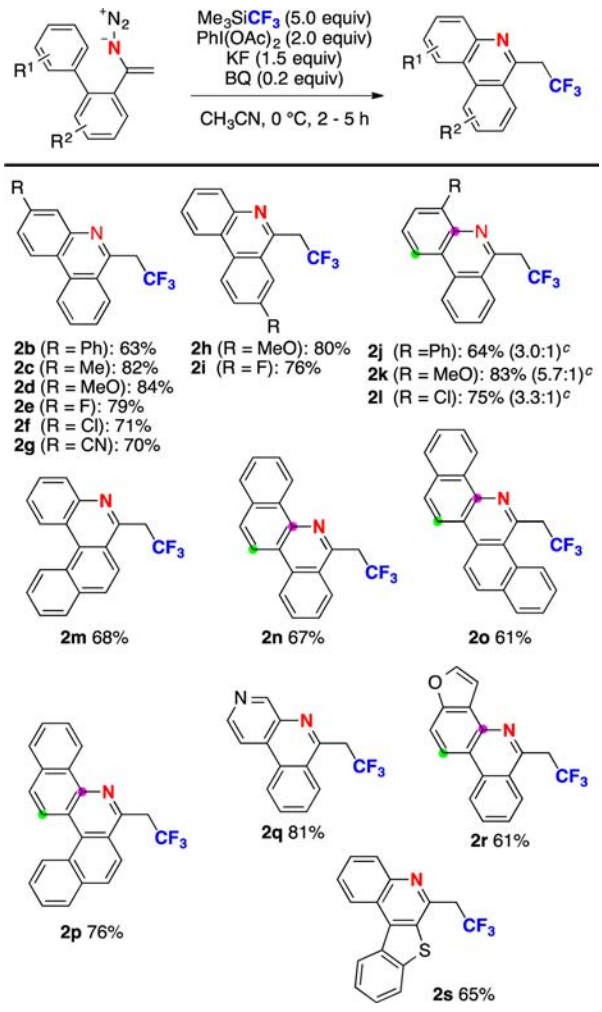
**Scheme 5. Substrates Scope on Synthesis of Triflluoroethyl Aza-PAHs 2**[a,b]




[a]The reactions were carried out by treatment of the vinyl azides **1** (0.3−0.5 mmol) and $Me_3SiCF_3$ (5 equiv) with $PhI(OAc)_2$ (2 equiv), KF (1.5 equiv), and benzoquinone (0.2 equiv) in $CH_3CN$ (0.1 M) at 0 °C under a nitrogen atmosphere. [b] Isolated yields were recorded above. [c] The ratio of regioisomers was determined by $^1H$ NMR analysis. Major isomers were shown above.

effect arising from the trifluoroethyl group (see the Supporting Information for more details).

Introduction of additional heteroatoms onto polycyclic aza-aromatic frameworks was also attempted. The reactions of vinyl azides having pyridyl and benzofuranyl motifs were viable to afford the desired cyclized products **2q** and **2r** in 82% and 61% yields, respectively. In the case of cyclization onto the benzofuran motif, the resulting aza-PAH **2r** was obtained as a single product via selective C−N bond formation at the carbon marked in puple. A benzothiophene moiety was also compatible with the present oxidative conditions, affording aza-PAH **2s** in 65% yield.

In summary, we have developed a concise approach to assemble polyfluoroalkyl aza-polycyclic aromatic hydrocarbons (aza-PAHs) by an oxidative radical perfluoroalkylation of biarylvinyl azides. Readily available and easily handled $Me_3SiR_f$ are utilized as the perfluoroalkyl radical sources under the oxidative operation in the presence of $PhI(OAc)_2$ with the assistance of KF and a catalytic amount of benzoquinone. We anticipate that the present method might be readily adopted to supply various aza-PAHs for potential use in medicinal and material-based applications.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization of new 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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