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<th>Synthesis of polyfluoroalkyl aza-polycyclic aromatic hydrocarbons enabled by addition of perfluoroalkyl radicals onto vinyl azides (Main article)</th>
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<td>Author(s)</td>
<td>Wang, Yi-Feng; Lonca, Geoffroy Hervé; Le Runigo, Maïwenn; Chiba, Shunsuke</td>
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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 Placeholder

ABSTRACT: Radical perfluoroalkylation of α-(biaryl-2-yl)vinyl azides is capable of supplying polyfluoroalkyl aza-polycyclic aromatic hydrocarbons (aza-PAHs). Commercially available Me$_3$SiR$_f$ (R$_f$ = CF$_3$, C$_2$F$_5$, and C$_3$F$_7$) 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$_f$CH$_2$) function.

The incorporation of perfluoroalkyl groups (R$_f$) onto organic molecules is capable of altering their chemical, physical and biological properties which leads to wide 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. Especially, synthesis of azaheterocycles having a per- or polyfluoroalkyl group at the specific position has drawn considerable attention, owing to the potent and broad applications of azaheterocycles in various fields.

Phenanthridine derivatives have shown a broad spectrum of biological activity and optoelectronic properties. 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 construction of phenanthridines and their derivatives with installation of the polyfluoroalkyl group. Very recently, Studer, Zhou, and Yu have independently developed synthetic methods of 6-perfluoroalkyl phenanthridines through radical or ionic perfluoroalkylation of biaryl isonitriles (Scheme 1-a). We describe herein a new protocol to access phenanthridines and their derivatives (aza-polycyclic aromatic hydrocarbons: aza-PAHs) having trifluoroethyl or other perfluoroalkylmethylene moieties, that is enabled by oxidative radical perfluoroalkylation of readily accessible α-(biaryl-2-yl)vinyl azides (Scheme 1-b). Readily available and handled perfluoroalkyltrimethylsilanes (Me$_3$SiR$_f$) could be utilized as the sources of perfluoroalkyl radicals under PhI(OAc)$_2$-mediated oxidative reaction conditions.

(a) From biaryl isonitriles (Studer, Zhou, Yu)  
(b) From biaryl vinyl azides (this work)

Vinyl azides have been utilized as a versatile synthons for synthesis of various nitrogen-containing molecules. Taking advantage of vinyl azides as a potential radical acceptor, we have recently disclosed oxidative radical trifluoromethylation reaction of vinyl azides, that led to the formation of α-trifluoromethyl (CF$_3$) azines (Scheme 2-a). In this process, the CF$_3$ radical generated from Me$_3$SiCF$_3$ 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 trifluoromethyl phenanthridines such as 2a (Scheme 2-b).

**Scheme 2.** Trifluoromethylation of vinyl azides for the formation of azines and phenanthridines.

(a) Formation of azines via dimerization of iminyl radicals (ref. 13)

(b) Formation of phenanthridine 2a via radical cyclization

A brief outline for the preparation methods of α-(biaryl-2-yl)vinylic 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, that was followed by the Wittig olefination. The vinyl azide function was then readily installed by following the modified Hassner’s method 14 via addition of IN₃ followed by elimination of HI with t-BuOK (method A) or via a sequence of dibromonation, diazidation, and elimination of HN₃ with DBU (method B) (see the Supporting Information for more details).

**Scheme 3.** Preparation of α-(biaryl-2-yl)vinylic azides 1.

To test this hypothesis as shown in Scheme 2-b, we examined the reaction of α-(biaryl-2-yl)vinylic azide 1a with Me₃SiCF₂. 15 The reaction of 1a with Me₃SiCF₂ (5 equiv) in the presence of PhI(OAc)₂ (2.0 equiv) and CsF (1.5 equiv) in CH₃CN proceeded as expected at 0 °C to afford 6-trifluoromethylphenanthridine 2a in 60% yield, along with formation of 6-methylphenanthidine (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 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 phenanthidine 2a, while the yield was moderate (entry 2). Interestingly, addition of benzoquinone (BQ, 0.2 equiv) dramatically enhanced the reaction17 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, while the yield of 2a was only 69% yield (entry 5).

**Table 1.** Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>F⁻ source</th>
<th>additive [equiv]</th>
<th>conditions</th>
<th>2a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>CsF</td>
<td>–</td>
<td>0 °C, 1 h</td>
<td>60°</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>KF</td>
<td>–</td>
<td>0 °C, 2 h</td>
<td>50°</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>KF</td>
<td>BQ (0.2)</td>
<td>0 °C, 2 h</td>
<td>91° (86)°</td>
</tr>
<tr>
<td>4°</td>
<td>MeCN</td>
<td>KF</td>
<td>BQ (2.0)</td>
<td>0 °C–rt, 21 h</td>
<td>0°</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>KF</td>
<td>BQ (0.2)</td>
<td>0 °C, 5 min</td>
<td>69°</td>
</tr>
</tbody>
</table>

° Unless otherwise noted, the reactions were carried out in the scale of 0.3-0.5 mmol of vinyl azide 1a with 5 equiv of Me₃SiCF₂ under a nitrogen atmosphere. ° ° H NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. ° ° ° 6-Methylphenanthidine (3) was formed in 6% yield. ° Isolated yield of 2a. ° ° The reaction was conducted in the absence of PhI(OAc)₂. ° 1a was recovered in 95% yield. BQ = benzoquinone.

It is worthy to note that the reactions of vinyl azide 1a with Me₃SiCF₂ and Me₃SiF₂ were carried out well under the optimized reaction conditions (Scheme 4), leading to the corresponding 6-perfluoroalkylphenanthridines 4 and 5, respectively, in good yields, while the use of Me₃SiCHF₂ did not result in the desired phenanthridine construction at all.

**Scheme 4.** Perfluoroalkylation of vinyl azide 1a.

Generality of this transformation was then explored using a variety of biarylvinyl azides 1 for synthesis of trifluoromethyl-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-2l). 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) in an acceptable level of regioselectivity. The reaction of 2-(1-azidovinyl)-1-phenyl-naphthalene (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 azachrysene (benzo[c]phenanthridine) 2n. This interesting regioselectivity in the cyclization onto the 2-naphthyl moiety was capable of constructing pentanuclear aza-PAHs, dibenzo[c,]phenanthridine 2o and dibenzo[c,]phenanthridine 2p from the corresponding vinyl azides. These tetra- and penta-nuclear 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 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 benzofuranyl motif, the resulting aza-PAHs 2r was obtained as a single product via selective C-N bond formation at the carbon marked in purple. A benzothiophene moiety was also compatible with the present oxidative conditions, affording aza-PAHs 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$_3$SiR$_4$ 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 anticipated that the present method might be readily adopted for supplying various aza-PAHs potentially capable for 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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(i) Tomshenko, O. A.; Grushin, V. V. Chem. Rev. 2011, 111, 4475–4521.


(6) Preliminary mechanistic studies for the formation of 3 are discussed in the Supporting information.

(7) There are reports that a catalytic amount of BQ could enhance the efficiency of Ph(OAc)2-mediated trifluoromethylation reactions, see: Wu, Y.; Chai, L. L.; Qin, F. L. Tetrahedron Lett. 2013, 54, 249–251, and ref. 7b.
