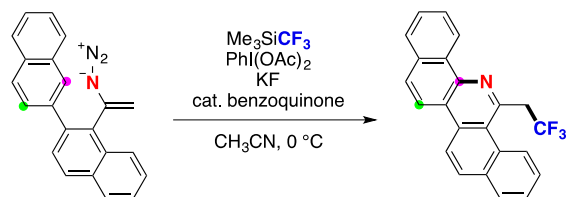


Synthesis of Polyfluoroalkyl Aza-Polycyclic Aromatic Hydrocarbons Enabled by Addition of Perfluoroalkyl Radicals onto Vinyl Azides

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Supporting Information Placeholder



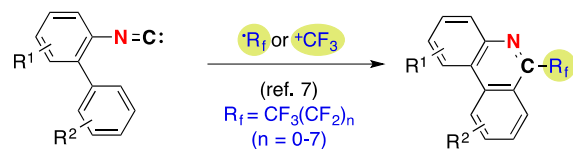
ABSTRACT: Radical perfluoroalkylation of α -(biaryl-2-yl)vinyl azides is capable of supplying polyfluoroalkyl aza-polycyclic aromatic hydrocarbons (aza-PAHs). Commercially available Me_3SiR_f ($\text{R}_f = \text{CF}_3$, C_2F_5 , and C_3F_7) are employed as the sources of perfluoroalkyl radicals upon oxidation with $\text{PhI}(\text{OAc})_2$. 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 properties¹ 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.² Especially, synthesis of azaheterocycles having a per- or polyfluoroalkyl group at the specific position has drawn considerable attention,³ owing to the potent and broad applications of azaheterocycles in various fields.⁴

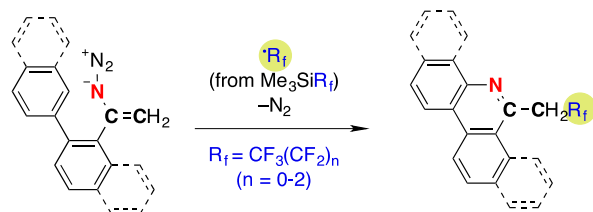
Phenanthridine derivatives have shown a broad spectrum of biological activity⁵ and optoelectronic properties.⁶ Installation of the polyfluoroalkyl function might render these compounds more valuable in the subject of drug discovery and material-based applications. However, a few methods have been exploited to date for 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 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,⁹ 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_3SiR_f) could be utilized as the sources of perfluoroalkyl radicals under $\text{PhI}(\text{OAc})_2$ -mediated oxidative reaction conditions.¹⁰

Scheme 1. Synthesis of polyfluoroalkyl phenanthridine derivatives.

(a) From biaryl isonitriles (Studer, Zhou, Yu)



(b) From biaryl vinyl azides (this work)

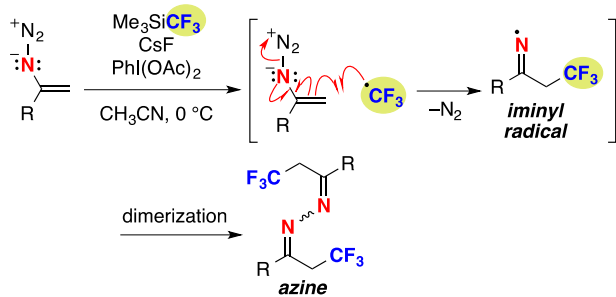


Vinyl azides have been utilized as a versatile synthon for synthesis of various nitrogen-containing molecules.¹¹ By taking advantage of vinyl azides as a potential radical acceptor,¹² we have recently disclosed oxidative radical trifluoromethylation reaction of vinyl azides, that led to the formation of α -trifluoromethyl (CF_3) azines (Scheme 2-a).¹³ In this process, the CF_3 radical generated from Me_3SiCF_3 upon oxidation with $\text{PhI}(\text{OAc})_2$ adds to the $\text{C}=\text{C}$ 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**,

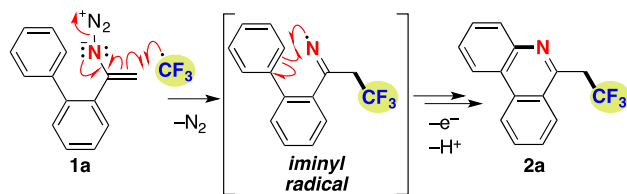
enabling C-N bond forming cyclization to construct trifluoroethyl phenanthridines such as **2a** (Scheme 2-b).

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

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

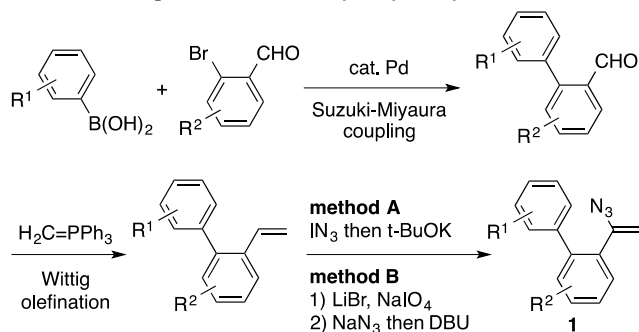


(b) Formation of phenanthridine **2a** via radical cyclization



A brief outline for the preparation methods of α -(biaryl-2-yl)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, that was followed by the Wittig olefination. The vinyl azide function was then readily installed by following the modified Hassner's method¹⁴ via addition of IN_3 followed by elimination of HI with *t*-BuOK (method A) or via a sequence of dibromination, diazidation, and elimination of HN_3 with DBU (method B) (see the Supporting Information for more details).

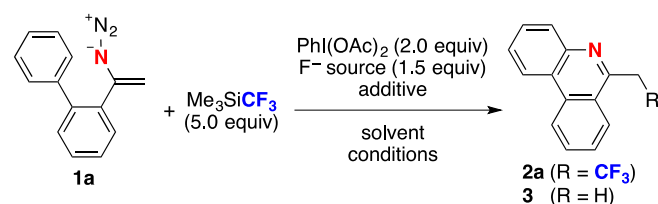
Scheme 3. Preparation of α -(biaryl-2-yl)vinyl azides **1**.



To test this hypothesis as shown in Scheme 2-b, 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 $\text{PhI}(\text{OAc})_2$ (2.0 equiv) and CsF (1.5 equiv) in CH_3CN proceeded as expected at $0\text{ }^\circ\text{C}$ 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 synthesis of phenanthridine **2a**, optimi-

zation of the reaction conditions was then undertaken (see the Supporting Information for more details). Use of KF instead of CsF under otherwise identical reaction conditions also provided phenanthridine **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 $\text{PhI}(\text{OAc})_2$ (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^a

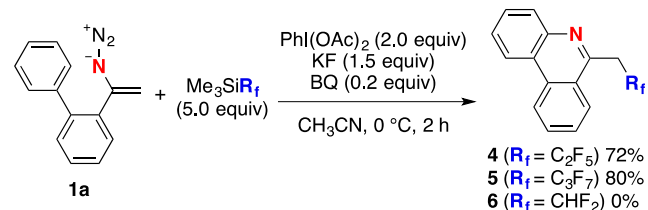


entry	solvent	F ⁻ source	additive [equiv]	conditions	2a [%] ^b
1	MeCN	CsF	–	$0\text{ }^\circ\text{C}$, 1 h	60 ^c
2	MeCN	KF	–	$0\text{ }^\circ\text{C}$, 2 h	50
3	MeCN	KF	BQ (0.2)	$0\text{ }^\circ\text{C}$, 2 h	91 (86) ^d
4 ^e	MeCN	KF	BQ (2.0)	$0\text{ }^\circ\text{C}$ –rt, 21 h	0 ^f
5	DMF	KF	BQ (0.2)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

^a 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 Me_3SiCF_3 under a nitrogen atmosphere. ^b ¹H 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 $\text{PhI}(\text{OAc})_2$. ^f **1a** was recovered in 95% yield. BQ = benzoquinone.

It is worthy to note that the reactions of vinyl azide **1a** with $\text{Me}_3\text{SiC}_2\text{F}_5$ and $\text{Me}_3\text{SiC}_3\text{F}_7$ were carried out well under the optimized reaction conditions (Scheme 4), leading to the corresponding 6-polyfluoroalkylphenanthridines **4** and **5**, respectively, in good yields, while the use of $\text{Me}_3\text{SiCHF}_2$ did not result in the desired phenanthridine construction at all.

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



Generality of this transformation was next explored using a variety of biarylvinyl azides **1** for 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) in 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-chrysenes (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. These 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 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 benzofuran 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-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_3SiR_f are utilized as the perfluoroalkyl radical sources under the oxidative operation in the presence of $\text{PhI}(\text{OAc})_2$ 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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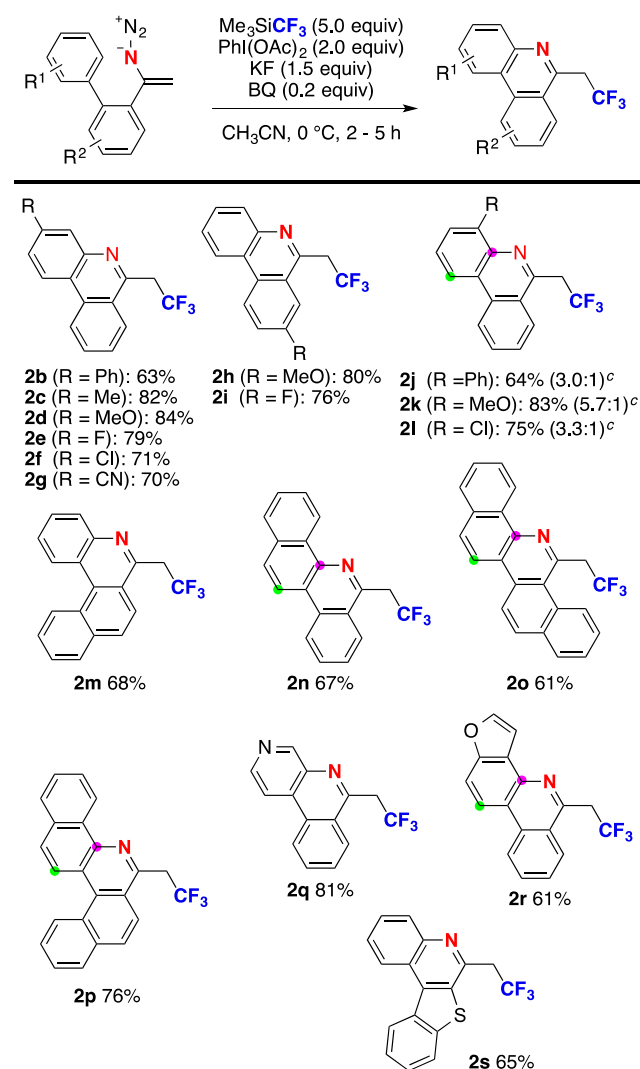
Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education. Y.-F. W. thanks Lee Kuan Yew postdoctoral fellowship (the LKY PDF). G. H. L. and M. L. R. are grateful for the financial support from Ecole Polytechnique and University of Strasbourg, respectively.

Scheme 5. Substrates scope on synthesis of trifluoroethyl 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 $\text{PhI}(\text{OAc})_2$ (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.

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