# <u>LETTERS</u>

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

Yi-Feng Wang, Geoffroy Hervé Lonca, Maïwenn Le Runigo, and Shunsuke Chiba\*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

**Supporting Information** 

**ABSTRACT:** Radical perfluoroalkylation of  $\alpha$ -(biaryl-2-yl)vinyl azides is capable of supplying polyfluoroalkyl aza-polycyclic aromatic hydrocarbons (aza-PAHs). Commercially available Me<sub>3</sub>SiR<sub>f</sub> (R<sub>f</sub> = CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, and C<sub>3</sub>F<sub>7</sub>) are employed as the sources of perfluoroalkyl radicals upon oxidation with PhI(OAc)<sub>2</sub>. 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<sub>f</sub>CH<sub>2</sub>) function.



T he incorporation of perfluoroalkyl groups  $(R_f)$  onto organic molecules is capable of altering their chemical, physical, and biological properties<sup>1</sup> 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.<sup>2</sup> Especially, the synthesis of azaheterocycles having a per- or polyfluoroalkyl group at a specific position has drawn considerable attention,<sup>3</sup> owing to the potent and broad applications of azaheterocycles in various fields.<sup>4</sup>

Phenanthridine derivatives have shown a broad spectrum of biological activity<sup>5</sup> and optoelectronic properties.<sup>6</sup> Installation of the polyfluoroalkyl function might render these compounds more valuable in the subject of drug discovery and materialbased applications. However, a few methods have been exploited to date for the construction of phenanthridines and their derivatives with installation of the polyfluoroalkyl group.<sup>7,8</sup> Very recently, Studer,<sup>7a</sup> Zhou,<sup>7b</sup> and Yu<sup>7c,d</sup> 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  $\alpha$ -(biaryl-2-yl)vinyl azides (Scheme 1b). Readily available and handled perfluoroalkyltrimethylsilanes (Me<sub>3</sub>SiR<sub>f</sub>) could be utilized as the sources of perfluoroalkyl radicals under PhI(OAc)<sub>2</sub>-mediated oxidative reaction conditions.<sup>10</sup>

Vinyl azides have been utilized as a versatile synthon for the synthesis of various nitrogen-containing molecules.<sup>11</sup> By taking advantage of vinyl azides as a potential radical acceptor,<sup>12</sup> we have recently disclosed an oxidative radical trifluoromethylation reaction of vinyl azides that led to the formation of  $\alpha$ -trifluoromethyl (CF<sub>3</sub>) azines (Scheme 2a).<sup>13</sup> In this process,

Scheme 1. Synthesis of Polyfluoroalkyl Phenanthridine Derivatives

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



the CF<sub>3</sub> radical generated from Me<sub>3</sub>SiCF<sub>3</sub> upon oxidation with PhI(OAc)<sub>2</sub> adds to the C=C bond of vinyl azides to form  $\alpha$ -CF<sub>3</sub> iminyl radicals that readily dimerize to afford  $\alpha$ -CF<sub>3</sub> 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  $\alpha$ -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  $\alpha$ -(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

 Received:
 July 9, 2014

 Published:
 July 28, 2014

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

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



Scheme 3. Preparation of  $\alpha$ -(Biaryl-2-yl)vinyl Azides 1

radical



method<sup>14</sup> 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<sub>3</sub> 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  $\alpha$ -(biaryl-2-yl)vinyl azide 1a with Me<sub>3</sub>SiCF<sub>3</sub>.<sup>15</sup> The reaction of 1a with Me<sub>3</sub>SiCF<sub>3</sub> (5 equiv) in the presence of PhI(OAc)<sub>2</sub> (2.0 equiv) and CsF (1.5 equiv) in CH<sub>3</sub>CN proceeded as expected at 0 °C to afford 6-trifluoroethylphenanthridine 2a in 60% yield, along with formation of 6methylphenanthridine (3) as a side product in 6% yield (Table 1, entry 1).<sup>16</sup> 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<sup>17</sup> 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<sub>3</sub>SiC<sub>2</sub>F<sub>5</sub> and Me<sub>3</sub>SiC<sub>3</sub>F<sub>7</sub> proceedeed well under the

Table 1. Optimization of the Reaction Conditions<sup>a</sup>



<sup>*a*</sup>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<sub>3</sub>SiCF<sub>3</sub> under a nitrogen atmosphere. <sup>*b*1</sup>H NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. <sup>*c*</sup>6-Methylphenanthridine (3) was formed in 6% yield. <sup>*d*</sup>Isolated yield of 2a. <sup>*e*</sup>The reaction was conducted in the absence of PhI(OAc)<sub>2</sub>. <sup>*f*</sup>1a was recovered in 95% yield. BQ = benzoquinone.



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)<sup>18,19</sup> (Scheme 5). Biarvlvinyl 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-(1azidovinyl)-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  $\alpha$ -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,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

Scheme 5. Substrates Scope on Synthesis of Trifluoroethyl Aza-PAHs  $2^{a,b}$ 



<sup>a</sup>The reactions were carried out by treatment of the vinyl azides 1 (0.3-0.5 mmol) and Me<sub>3</sub>SiCF<sub>3</sub> (5 equiv) with PhI(OAc)<sub>2</sub> (2 equiv), KF (1.5 equiv), and benzoquinone (0.2 equiv) in CH<sub>3</sub>CN (0.1 M) at 0 °C under a nitrogen atmosphere. <sup>b</sup> Isolated yields were recorded above. <sup>c</sup> The ratio of regioisomers was determined by <sup>1</sup>H 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 azaaromatic 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.

## AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: shunsuke@ntu.edu.sg.

# Notes

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education. Y.-F.W. is thankful for a 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 Strasbroug, respectively.

## REFERENCES

(1) (a) Kirsch, P. Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications; Wiley-VCH: Weinheim, 2013. (b) Fluorine in Medicinal Chemistry and Chemical Biology; Ojima, I., Eds.; Wiley-Blackwell: Chichester, 2009. (c) Bégué, J.-P.; Bonnet-Delpon, D. Bioorganic and Medicinal Chemistry of Fluorine; Wiley-VCH: Hoboken, NJ, 2008. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Chem. Soc. Rev. 2008, 37, 320–330.

(2) For selected recent reviews on perfluoroalkylations including trifluoromethylation: (a) Merino, E.; Nevado, C. Chem. Soc. Rev. 2014, in press, DOI: 10.1039/C4CS00025K. (b) Liang, T.; Neumann, C. N.; Ritter, T. Angew. Chem., Int. Ed. 2013, 52, 8214–8264. (c) Barata-Vallejo, S.; Postigo, A. Coord. Chem. Rev. 2013, 257, 3051–3069. (d) Jin, Z.; Hammond, G. B.; Xu, B. Aldrichimica Acta 2012, 45, 67–83. (e) Wu, X.-F.; Neumann, H.; Beller, M. Chem.—Asian J. 2012, 7, 1744–1754. (f) Macé, Y.; Magnier, E. Eur. J. Org. Chem. 2012, 2479–2494. (g) Studer, A. Angew. Chem., Int. Ed. 2012, 51, 8950–8958. (h) Ye, Y.; Sanford, M. S. Synlett 2012, 23, 2005–2013. (i) Tomashenko, O. A.; Grushin, V. V. Chem. Rev. 2011, 111, 4475–4521.

(3) A recent review: Gakh, A. A.; Shermolovich, Y. Curr. Top. Med. Chem. 2014, 14, 952–965. Selected recent examples: (a) Zhang, B.; Studer, A. Org. Lett. 2014, 16, 1216–1219. (b) Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. Org. Lett. 2013, 16, 504– 507. (c) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. Angew. Chem., Int. Ed. 2013, 52, 4000–4003. (d) Kong, W.; Casimiro, M.; Merino, E. B.; Nevado, C. J. Am. Chem. Soc. 2013, 135, 14480–14483. (e) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. Nature 2012, 492, 95–99. (f) Nagib, D. A.; MacMillan, D. W. C. Nature 2011, 480, 224–228. (g) Chu, L.; Qing, F.-L. J. Am. Chem. Soc. 2011, 134, 1298–1304. (h) Ji, Y. N.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Proc. Natl. Acad. Sci. U.S.A. 2011, 108, 14411–14415.

(4) For recent reviews on applications of azaheterocycles, see: (a) Thomas, G. L.; Johannes, C. W. Curr. Opin. Chem. Biol. 2011, 15, 516–522. (b) Tohme, R.; Darwiche, N.; Gali-Muhtasib, H. Molecules 2011, 16, 9665–9696. (c) Dandapani, S.; Marcaurelle, L. A. Curr. Opin. Chem. Biol. 2010, 14, 362–370. (d) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Curr. Opin. Chem. Biol. 2010, 14, 347–361. (e) Carey,

#### **Organic Letters**

(5) (a) Dubost, E.; Dumas, N.; Fossey, C.; Magnelli, R.; Butt-Gueulle, S.; Ballandonne, C.; Caignard, D. H.; Dulin, F.; Sopkova de-Oliveira Santos, J.; Millet, P.; Charnay, Y.; Rault, S.; Cailly, T.; Fabis, F. J. Med. Chem. 2012, 55, 9693–9707. (b) Fuchino, H.; Kawano, M.; Mori-Yasumoto, K.; Sekita, S.; Satake, M.; Ishikawa, T.; Kiuchi, F.; Kawahara, N. Chem. Pharm. Bull. 2010, 58, 1047–1050. (c) Bernardo, P. H.; Wan, K.-F.; Sivaraman, T.; Xu, J.; Moore, F. K.; Hung, A. W.; Mok, H. Y. K.; Yu, V. C.; Chai, C. L. L. J. Med. Chem. 2008, 51, 6699–6710.

(6) (a) Stevens, N.; O'Connor, N.; Vishwasrao, H.; Samaroo, D.; Kandel, E. R.; Akins, D. L.; Drain, C. M.; Turro, N. J. J. Am. Chem. Soc. 2008, 130, 7182–7183. (b) Bondarev, S. L.; Knyukshto, V. N.; Tikhomirov, S. A.; Pyrko, A. N. Opt. Spectrosc. 2006, 100, 386–393.
(c) Zhang, J.; Lakowicz, J. R. J. Phys. Chem. B 2005, 109, 8701–8706.
(7) (a) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. Angew. Chem., Int. Ed. 2013, 52, 10792–10795. (b) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. Org. Lett. 2013, 15, 4846–4849. (c) Cheng, Y.; Jiang, H.; Zhang, Y.; Yu, S. Org. Lett. 2013, 15, 5520–5523. (d) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. Angew. Chem., Int. Ed. 2013, 52, 13289–13292.

(8) For other recent reports on the synthesis of fluoroalkyl phenanthridines catalyzed by transition metals, see: (a) Sun, X.; Yu, S. Org. Lett. **2014**, *16*, 2938–2941. (b) Li, Y.; Zhu, J.; Zhang, L.; Wu, Y.; Gong, Y. Chem.—Eur. J. **2013**, *19*, 8294–8299. (c) Wang, W.-Y; Feng, X.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. J. Org. Chem. **2013**, *78*, 6025–6030.

(9) Recent examples of the synthesis of trifluoroethyl-containing molecules and their potential utilities: (a) Xu, S.; Chen, H.-H.; Dai, J.-J.; Xu, H.-J. Org. Lett. **2014**, *16*, 2306–2309. (b) Hwang, J.; Park, K.; Choe, J.; Min, H.; Song, K. H.; Lee, S. J. Org. Chem. **2014**, *79*, 3267–3271. (c) Feng, Y.-S.; Xie, C.-Q.; Qiao, W.-L.; Xu, H.-J. Org. Lett. **2013**, *15*, 936–939. (d) Zhao, T. S. N.; Szabó, K. J. Org. Lett. **2013**, *15*, 936–939. (d) Zhao, T. S. N.; Szabó, K. J. Org. Lett. **2013**, *15*, 936–939. (e) Liu, C.-B.; Meng, W.; Li, F.; Wang, S.; Nie, J.; Ma, J.-A. Angew. Chem., Int. Ed. **2012**, *51*, 6227–6230. (f) Liang, A.; Li, X.; Liu, D.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. Chem. Commun. **2012**, *48*, 8273–8275. (g) Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. Org. Lett. **2011**, *13*, 3596–3599 and ref 3e.

(10) For reviews on perfluoroalkyl radicals: (a) Barata-Vallejo, S.; Postigo, A. *Eur. J. Org. Chem.* **2012**, 1889–1899. (b) Dolbier, W. R. *Chem. Rev.* **1996**, *96*, 1557–1584.

(11) For a review, see: Jung, N.; Bräse, S. Angew. Chem., Int. Ed. 2012, 51, 12169–12170.
(b) Chiba, S. Chimia 2012, 66, 377–381.
(c) Chiba, S. Synlett 2011, 23, 21–44.
(d) Stokes, B. J.; Driver, T. G. Eur. J. Org. Chem. 2011, 4071–4088.
(e) Driver, T. G. Org. Biomol. Chem. 2010, 8, 3831–3846.
(f) Banert, K. The Chemistry of Vinyl, Allenyl, and Ethynyl Azides. In Organic Azides: Syntheses and Applications; Bräse, S., Banert, K., Eds.; Wiley: Chichester, 2010; pp 115–166.

(12) (a) Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. J. Am. Chem. Soc. 2011, 133, 6411–6421. (b) Ng, E. P. J.; Wang, Y.-F.; Chiba, S. Synlett 2011, 783–786. (c) Wang, Y.-F.; Chiba, S. J. Am. Chem. Soc. 2009, 131, 12570–12572. (d) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. Org. Lett. 2008, 10, 5019–5022.

(13) Wang, Y.-F.; Lonca, G. H.; Chiba, S. Angew. Chem., Int. Ed. 2014, 53, 1067–1071.

(14) (a) Hassner, A.; Fowler, F. W. Tetrahedron Lett. **1967**, *8*, 1545–1548. (b) Fowler, F. W.; Hassner, A.; Levy, L. A. J. Am. Chem. Soc. **1967**, *89*, 2077–2082.

(15) For reviews on utilization of Me<sub>3</sub>SiCF<sub>3</sub>, see: (a) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* 2014, in press, DOI: 10.1021/ cr400473a. (b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757–786.

(16) Preliminary mechanistic studies for the formation of 3 are discussed in the Supporting Information.

(17) There are reports that a catalytic amount of BQ could enhance the efficiency of  $PhI(OAc)_2$ -mediated trifluoromethylation reactions;

see: Wu, X. Y.; Chu, L. L.; Qing, F. L. Tetrahedron Lett. 2013, 54, 249–251 and ref 7b.

(18) Selected recent reports on material-based application of aza-PAHs: (a) Martens, S. C.; Zschieschang, U.; Wadepohl, H.; Klauk, H.; Gade, L. H. Chem.—Eur. J. **2012**, 18, 3498–3509. (b) Hao, L.; Jiang, W.; Wang, Z. Tetrahedron **2012**, 68, 9234–9239. (c) Wei, J.; Han, B.; Guo, Q.; Shi, X.; Wang, W.; Wei, N. Angew. Chem., Int. Ed. **2010**, 49, 8209–8213. (d) Takase, M.; Enkelmann, V.; Sebastiani, D.; Baumgarten, M.; Müllen, K. Angew. Chem., Int. Ed. **2007**, 46, 5524– 5527.

(19) Selected recent reports on biological studies of aza-PAHs:
(a) Peddinghaus, S.; Brinkmann, M.; Bluhm, K.; Sagner, A.; Hinger, G.; Braunbeck, T.; Eisenträger, A.; Tiehm, A.; Hollert, H.; Keiter, S. H. *Reprod. Toxicol.* 2012, 33, 224–232. (b) Hawliczek, A.; Nota, B.; Cenijn, P.; Kamstra, J.; Pieterse, B.; Winter, R.; Winkens, K.; Hollert, H.; Segner, H.; Legler, J. *Reprod. Toxicol.* 2012, 33, 213–223. (c) Beníšek, M.; Kubincová, P.; Bláha, L.; Hilscherová, K. *Toxicol. Lett.* 2011, 200, 169–175.