CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Electron-Catalyzed Fluoroalkylation of Vinyl Azides

Authors: Emily Mackay; Armido Studer

To be cited as: Chem. Eur. J. 10.1002/chem.201602855

Link to VoR: http://dx.doi.org/10.1002/chem.201602855

Supported by
ACES

WILEY-VCH

COMMUNICATION WILEY-VCH

Electron-Catalyzed Fluoroalkylation of Vinyl Azides

Emily G. Mackay[a] and Armido Studer*[a]

[a] Dr. Emily Mackay, Prof. Dr. A. Studer, Westfälische Wilhelms Universität, Organisch-Chemisches Institut, Corrensstrasse 40, 48149 Münster (Germany), Fax: (+49) 251-833-6523 E-mail: studer@uni-muenster.de

Abstract: The transition-metal free fluoroalkylation of vinyl azides is herein reported. This operationally simple reaction employs the Togni reagent as a CF_3 source, Bu_4NI as an initiator, and occurs under electron-catalysis. A range of readily prepared starting materials are functionalized using this approach to produce both phenanthridines and quinoxalin-2-ones.

The introduction of trifluoromethyl groups is an important area of organic chemistry, due to the unique ability of fluoroalkyl groups to modify the chemical and physical properties of biologically active compounds,[1] often leading to drastic changes in bioavailability and bioactivity. As a result of this, much research has been conducted in the area of trifluoromethylation. Phenanthridines[2] and quinoxalinones[3] are important molecules on the pharmaceutical landscape (Figure 1).

Figure 1 (about here)

Typically, the synthesis of perfluoroalkylated heterocycles proceeds via the direct functionalization of the pre-formed heterocycle.[4] An alternative approach, however, is to introduce the perfuoroalkyl group concurrently with formation of a heteroarene ring. For the synthesis of quinoxalinones there exists only one such method.[5] In the case of phenanthridine synthesis a handful of examples have been reported.[6] While the majority of these examples require the use of a transition metal catalyst, a select few do not.[6a-d] In one such example, reported by our group in 2013,[6a] the trifluoromethyl group is introduced in an electron-catalyzed process using the Togni reagent **3**[7] (see Table 1) as a CF_3 source, and Bu_4NI as an initiator. This process employs ortho-isocyanobiaryls as substrates, forming the C-C bond depicted in red. Further research in this area appeared later in the year.[6b-d] In a strategically different approach, heteroarenes can be formed using the addition of a trifluoromethyl radical onto a vinyl azide,[8] this time forming the C-N bond depicted in red. Interestingly this approach generates the trifluoromethylated phenanthridines with an extra methylene spacer, allowing complementarity to the earlier approach. This strategic disconnection has been recently used by the groups of Chiba[6d] and Yu[5] for the synthesis of both phenanthridines and quinoxalinones, and it was our belief that this reaction should be feasible without the use of any transition metal, employing electron-catalysis.[9] It was with this in mind that we set about the synthesis of vinyl azide substrates **1** and **4** according to literature procedures (see the Supporting Information).[5,6e]

Scheme 1 (about here)

We were delighted to find that upon exposure of vinyl azide **1a** to the conditions previously developed for the trifluoromethylation of ortho-isocyanobiaryls [Bu_4NI (5 mol%), Togni-reagent (2 equiv.), Cs_2CO_3 (2 equiv.), 1,4-dioxane, 2 h, 80 °C],[6a] the target phenanthridine **2aa** was obtained in 74% isolated yield (Table 1, entry 1). The pentafluoroethyl analogue **2ab** could also be accessed using this method (Table 1, entry 2). We found that both electron-withdrawing and -donating groups were tolerated at the *para*-position of the phenyl ring (see **2b** and **2c**, Table 1, entries 3 and 4), and a substituent at the *ortho*-position did not reduce the yield of the reaction (**2d**, Table 1, entry 5). When a fluorine atom was introduced at the *meta*-position of the phenyl ring, a 1:1 mixture of regioisomers **2ea** and **2eb** was formed (Table 1, entry 6). Finally, it was observed that the addition of a substituent onto the aryl ring tether, the reaction proceeded smoothly, giving the target phenanthridine **2f** in 76% yield (Table 1, entry 7).

Table 1 (about here)

Having achieved success in the preparation of phenanthridines with our electron-catalyzed reaction, our attention turned to the synthesis of the quinoxalinones. The preparation of the starting α-azidyl acrylamides **4** is described in the SI. When we exposed *N*-phenyl acrylamide **4a** to our standard conditions, the targeted quinoxalinone **5a** was isolated in a somewhat lower yield of 51% (Table 2, entry 1). This reduced yield compared to the phenanthridine series held true for all of the quinoxalinone compounds screened. This is not unexpected since the electrophilic trifluoromethyl radical is known to react less efficiently with electron poorer alkenes.[10] Interestingly, in the case of the quinoxalinone series, we were unable to isolate any target material when the pentafluoroethyl Togni reagent was used in the reaction (Table 2, entry 2). No target material was observed when either the 2,5-dimethyl **4b**, or the 2-methyl substrate **4c** were screened (Table 2, entries 3 and 4), indicating that a substituent at the *ortho*-position hindered the reaction in this series. *Meta*-isopropyl substituted analogue **4d** gave the target material in 34% yield, as a 1:1 mixture of regioisomers **5da** and **5db** (Table 2, entry 5). Turning now to substituents at the *para* position, we found that when including electron-withdrawing (Table 2, entries 6 and 7) and electron-donating substituents (Table 2, entry 8), as well as alkyl chains (Table 2, entry 9), the reaction proceeded smoothly, giving the target quinoxalinones **5e**-**h** in somewhat modest yields.

Table 2 (about here)

A proposed mechanism for the heteroarene synthesis is illustrated in Scheme 2. In this mechanism, the initiator Bu_4NI formally liberates an electron, which is then able to reductively cleave the Togni reagent **3** to form the ortho-iodobenzoate anion and the

trifluoromethyl radical.[11] Addition of the trifluoromethyl radical to the vinyl azide, followed by loss of nitrogen, provides iminyl radical **7**. An intramolecular addition of this radical to the pendant aryl ring leads to the cyclohexadienyl radical **8**, a highly acidic species. Following deprotonation by the *ortho*-iodobenzoate anion (or the stoichiometric Cs_2CO_3 base), the heteroarene radical anion **9** is generated that can formally liberate an electron, propagating the catalytic cycle, and forming the product heteroarene **10**.

Scheme 2 (about here)

In summary, we have presented an approach for the synthesis of fluoroalkylated phenanthridines and quinoxalinones starting with readily prepared vinyl azides. This electron-catalyzed process uses the commercially available Togni reagent **3**, along with Bu_4NI as an initiator, to form the fluoroalkyl radical. This reaction proceeds without the need for a transition metal catalyst, and forms not only the C-CF_3 bond, but also the new heteroarene ring.

Experimental Section

Typical Procedure for the Trifluoromethylation of Vinyl Azides 1 and 4: Under an argon atmosphere, vinyl azide **1a** (100 mg, 0.45 mmol, 1.0 mol equiv.), NBu_4I (7.5 mg, 0.023 mmol, 5 mol%), Cs_2CO_3 (295 mg, 0.905 mmol, 2.0 mol equiv.), and Togni reagent (334 mg, 0.905 mmol, 2.0 mol equiv.) were dissolved in dry dioxane (2.25 mL). The reaction vial was then sealed, and stirred at 80 °C for 2 h. The reaction mixture was then cooled to room temperature, and dry loaded onto a silica column. Flash chromatography (silica gel, pentane to 10% EtOAc/pentane) afforded the target phenanthridine **2a** as an off-white solid (87 mg, 74 %).

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG) for funding this work.

Keywords: Electron catalysis • vinyl azides • phenanthridines • quinoxalinones

[1] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330; c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422-518.

[2] a) N. Hatae, E. Fujita, S. Shigenobu, S. Shimoyama, Y. Ishihara, Y. Kurata, T. Choshi, T. Nishiyama, C. Okada, S. Hibino, *Bioorg. Med. Chem. Lett.* **2015**, *25,* 2749–2752; b) L.-M. Tumir, M. R. Stojković, I.Piantanida, *Beilstein J. Org. Chem.* **2014,** *10,* 2930–2954; c) T. Ishikawa, *Med. Res. Rev.* **2001**, *21*, 61-72.

[3] a) Y. Ramli, A. Moussaif, K. Karrouchi, E. M. Essassi, *J. Che.* **2014**, 1-21; L. Xun, Y. Kang-hui, L. Wei-lu, X. Wen-fang, *Drugs Future* **2006**, *31*, 1-11; c) A. Carta, S. Piras, G. Loriga, G. Paglietti, *Mini Rev. Med. Chem.* **2006**, *11*, 1179-1200.

[4] X.-F. Wu, H. Neumann, M. Bell, *Chem. Asian J.* **2012**, *7*, 1744-1754.

[5] T. Yang, H. Zhu, W. Yu, *Org. Biomol. Chem.* **2016**, *14*, 3376-3384.

[6] a) B. Zhang, C. Mück-Lichtenfeld, C. G. Daniliuc, A. Studer, *Angew. Chem., Int. Ed.* **2013**, *52*, 10792-10795; b) Q. Wang, X. Dong, T. Xiao, L. Zhou, *Org. Lett.* **2013**, *15*, 4846-4849; c) Y. Cheng, H. Jiang, Y. Zhang, S. Yu, *Org. Lett.* **2013**, *15*, 5520-5523; d) Y.-F. Wang, G. H. Lonca, M. Le Runigo, S. Chiba, *Org. Lett.* **2014**, *16*, 4272-4275; e) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang, S. Yu, *Angew. Chem., Int. Ed.* **2013**, *52*, 13289-13292; f) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu, J. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2743-2747; g) W. Fu, M. Zhu, C. Xu, G. Zou, Z. Wang, B. Ji, *J. Fluor. Chem.* **2014**, *168*, 50-54. For a review, see h) B. Zhang, A. Studer, *Chem. Soc. Rev.* **2015**, *44*, 3505-3521.

[7] J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650-682.

[8] Other examples using vinyl azides as radical acceptors, see: a) A. Suzuki, M. Tabata, M. Ueda, *Tetrahedron Lett.* **1975**, 2195-2198; b) S. Chiba, *Chimia* **2012**, *66*, 377-381; c) Y.-F. Wang, G. H. Lonca, S. Chiba, *Angew. Chem., Int. Ed.* **2014**, *53*, 1067-1071.

[9] a) A. Studer, D. P. Curran, *Nat. Chem.* **2014**, *6*, 765-773; b) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58-102.

[10] M. Hartmann, Y. Li, A. Studer, *Org. Biomol. Chem.* **2016**, *14*, 206-210.

[11] The exact initiation process is not known. We currently assume that the iodide anion reacts with the Togni reagent via substitution of the carboxylate substituent at the I(III)-atom to give an iodine(III)reagent bearing a very weak I-I-bond. Homolysis of the weak I-I-bond leads to an iodine atom, the CF_3-radical and the ortho-iodobenzoate anion.

Legends to Schemes and Tables

Figure 1. Pharmaceutically important and biologically active phenanthridines and quinoxalinones.

Scheme 1. Two distinct methods for the synthesis of trifluoromethylated phenanthridines, forming the C-CF_3 bond and the heterocycle concomitantly.

Scheme 2. Proposed mechanism for the trifluoromethylation of vinyl azides.

Table 1. Synthesis of phenanthridines from vinyl azides[a]

Table 2. Synthesis of quinolinones from vinyl azides **4**[a]

Entry for the Table of Contents

Electrons do the job! A transition-metal free radical fluoroalkylation of vinyl azides employing the Togni reagent as a CF_3 source and Bu_4NI as an initiator to give phenanthridines and quinoxalin-2-ones in moderate to good yields is reported. Cascades occur by electron-catalysis, starting materials are readily prepared and experiments are easy to conduct.

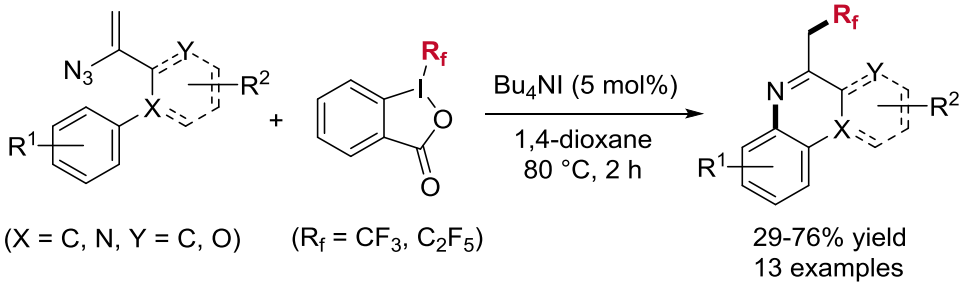
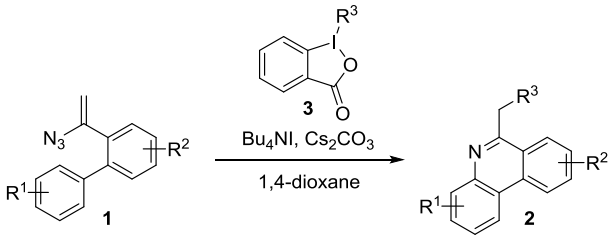
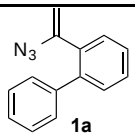
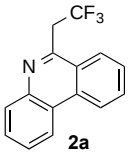
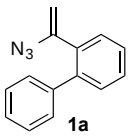
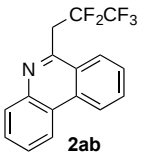
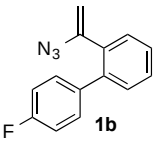
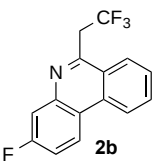
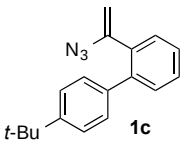
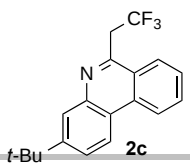
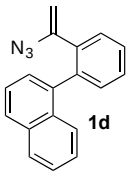
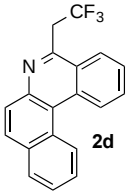
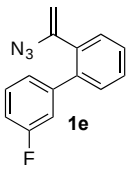
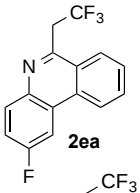
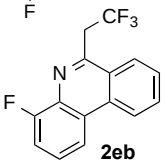
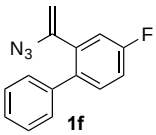
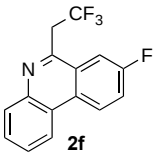


Table 1. Synthesis of phenanthridines from vinyl azides[a]



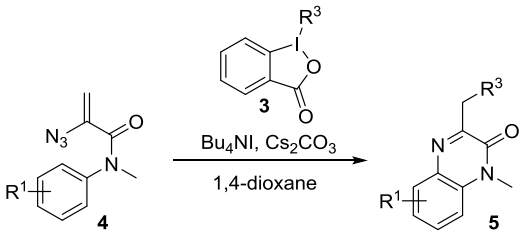
	Substrate	Time	Product(s)	Yield[b]
1	 1a	2 h	 2a	74%
2[c]	 1a	3 h	 2ab	57%
3	 1b	2 h	 2b	64%
4	 1c	2 h	 2c	66%

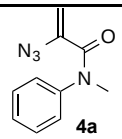
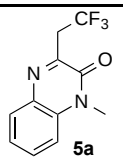
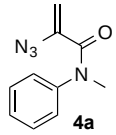
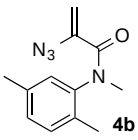
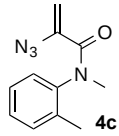
10.1002/chem.201602855

5	 **1d**	2 h	 **2d**	66%
6	 **1e**	2 h	 **2ea**  **2eb**	69% **2ea**:**2eb** = 1:1
7	 **1f**	2 h	 **2f**	76%

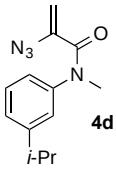
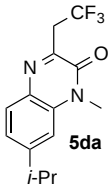
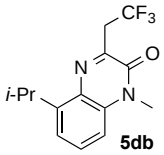
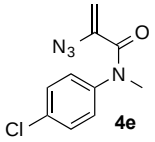
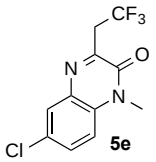
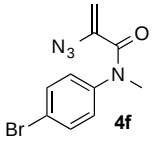
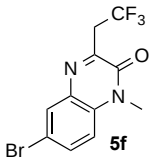
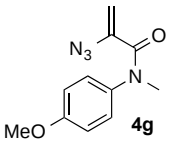
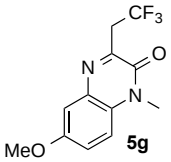
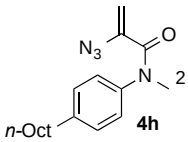
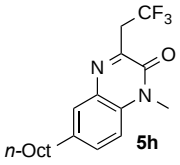
[a] Conditions: 2.0 equiv. Togni reagent **3**, 2.0. equiv. Cs_2CO_3, 0.05 equiv. Bu_4NI, 1,4-dioxane, 80 °C. [b] Isolated yield. [c] Pentafluoroethyl Togni reagent (2.0 equiv.) used in place of Togni reagent.

Table 2. Synthesis of quinolinones from vinyl azides **4**[a]



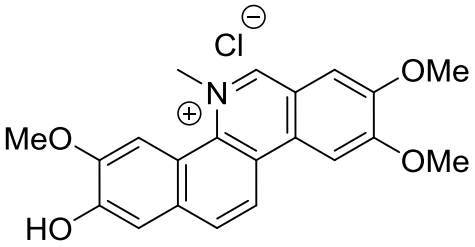
	Substrate	Time	Product(s)	Yield[a]
1	 **4a**	1 h	 **5a**	51%
2[b]	 **4a**	18 h	-	-
3	 **4b**	18 h	-	-
4	 **4c**	18 h	-	-

10.1002/chem.201602855

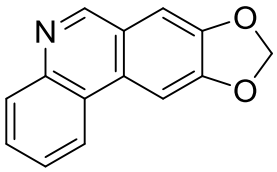
5	 **4d**	2 h	 **5da**	34%
			 **5db**	**5ea**:**5eb** = 1:1
6	 **4e**	2 h	 **5e**	31%
7	 **4f**	2 h	 **5f**	29%
8	 **4g**	2 h	 **5g**	39%
9	 **4h**	2 h	 **5h**	41%

[a] Conditions: 2.0 equiv. Togni reagent **3**, 2.0. equiv. Cs_2CO_3, 0.05 equiv. Bu_4NI, 1,4-dioxane, 80 °C. [b] Isolated yield. [c] Pentafluoroethyl Togni reagent (2.0 equiv.) used in place of Togni reagent.

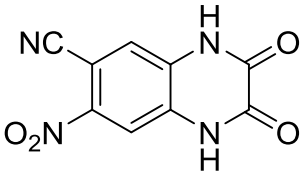
Figure 1:



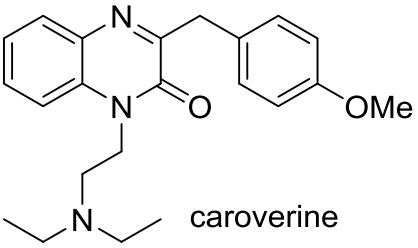
fagaronine



trisphaeridine



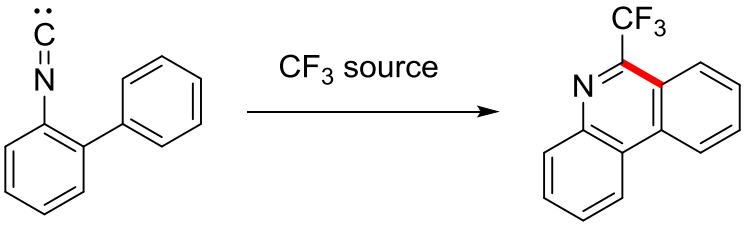
CNQX



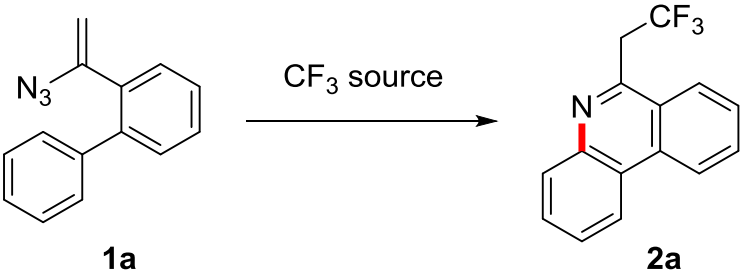
caroverine

Scheme 1:

Trifluoromethylation of arylisonitriles:



Trifluoromethylation of vinyl azides:



1a **2a**

Scheme 2: