

PhI(OAc)₂-Mediated Radical Trifluoromethylation of Vinyl Azides with Me₃SiCF₃**

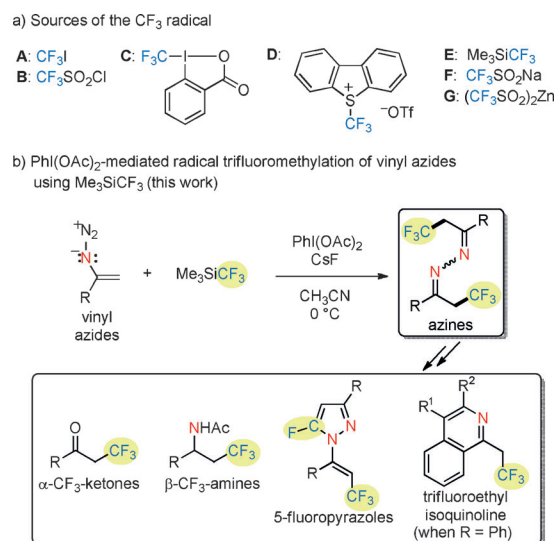
Yi-Feng Wang, Geoffroy Hervé Lonca, and Shunsuke Chiba*

Abstract: The fluorine-containing organic motif is becoming privileged in pharmaceuticals, agrochemicals, and functional materials, owing to its unique properties such as electron-withdrawing character, metabolic stability, and lipophilicity. Described herein is the PhI(OAc)₂-mediated radical trifluoromethylation of vinyl azides with Me₃SiCF₃ to efficiently generate α -trifluoromethyl azines. The resulting α -trifluoromethyl azines were successfully transformed to valuable fluorine-containing molecules such as α -trifluoromethyl ketones, β -trifluoromethyl amines, 5-fluoropyrazoles, and trifluoroethyl isoquinolines.

A variety of methods for installation of the CF₃ unit (trifluoromethylation) have been developed to access CF₃-containing molecules because of their importance in pharmaceutical and material sciences.^[1,2] Specifically, use of the CF₃ radical^[2e,f] has recently received considerable attention for trifluoromethylation in which various CF₃ radical precursors have been utilized under redox reaction conditions (Scheme 1 a), including CF₃X (**A**: X = I or **B**: X = SO₂Cl),^[3] the Togni reagent **C**,^[4] Umemoto reagent **D**,^[5] Ruppert–Prakash reagent (Me₃SiCF₃) **E**,^[6] and Langlois/Baran reagent (CF₃SO₂M; **F**: M = Na or **G**: M = Zn).^[7]

Among those radical trifluoromethylation reagents, Me₃SiCF₃ has many advantages such as low cost, and easy handling and storage.^[8] Single-electron oxidation of Me₃SiCF₃ generates the CF₃ radical. Most of the methods mainly rely on the stoichiometric use of transition-metal complexes such as silver^[6a,c,f] and copper^[6b] salts as the promoters, while a few silver-catalyzed versions with PhI(OAc)₂ as the stoichiometric oxidant have recently been demonstrated by the groups of Qing^[6c] and Greaney.^[6d] However, radical trifluoromethylation protocols with Me₃SiCF₃ in the absence of transition-metals have rarely been achieved.^[9]

Vinyl azides have served as versatile materials for the synthesis of various nitrogen-containing molecules, especially, azaheterocycles.^[10] Vinyl azides work as a radical acceptor. Using this chemical reactivity, we have recently developed



Scheme 1. Trifluoromethylation with the CF₃ radical.

methods for the synthesis of aza-heterocycles based on Mn^{III}-mediated/catalyzed radical reactions of vinyl azides with cyclopropanols or 1,3-dicarbonyl compounds.^[11] The continued interest in radical reactions of vinyl azides motivated us to investigate the reactions of the CF₃ radical with vinyl azides, and the CF₃ radical generated oxidatively from Me₃SiCF₃ adds to the C=C bond of vinyl azides to form α -trifluoromethyl iminyl radicals. Subsequent conversions of the transient iminyl radicals were envisioned. Herein, we disclose a PhI(OAc)₂-mediated oxidative trifluoromethylation of vinyl azides with Me₃SiCF₃ to afford α -trifluoromethyl azines, which could be readily transformed into valuable fluorine-containing synthons such as α -trifluoromethyl ketones, β -trifluoromethyl amines, 5-fluoropyrazoles, and trifluoroethyl isoquinoline (Scheme 1 b). The present trifluoromethylation with vinyl azides could be run in the absence of transition metals, and the preliminary mechanistic investigation revealed that the CF₃ radical is likely involved in the trifluoromethylation.

We commenced our study by using the vinyl azide **1a** with Me₃SiCF₃ (3 equiv) and CsF (2 equiv) in the presence of AgOTf (5 mol %) and PhI(OAc)₂ (1.5 equiv). The reaction proceeded smoothly at 0 °C in CH₃CN, thus providing the azine **2a** as a mixture of *E/Z* isomers in 80 % yield,^[12] and is likely formed by dimerization of the transient α -trifluoromethyl iminyl radical (Table 1, entry 1).^[13] Notably, **2a** was also formed in 84 % yield even in the absence of the Ag catalyst (entry 2). Switching the fluoride source from CsF to KF resulted in a sluggish reaction (entry 3). Further screening

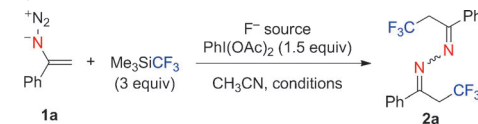
[*] Dr. Y.-F. Wang, G. H. Lonca, Prof. S. Chiba

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University Singapore 637371 (Singapore)
E-mail: shunsuke@ntu.edu.sg

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Table 1: Optimization of the reaction conditions.^[a]

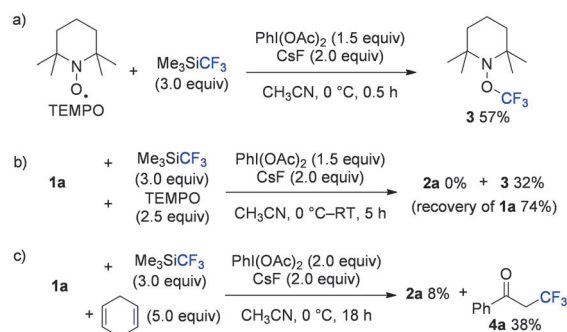


Entry	F [−] source [equiv]	Conditions	Yield [%] ^[b]
1 ^[c]	CsF (2)	0 °C, 2 h	80
2	CsF (2)	0 °C, 2 h	84
3	KF (2)	0 °C–RT, 24 h	70
4	CsF (1.5)	0 °C, 20 min	96
5	CsF (1)	0 °C, 1 h	74
6	CsF (0.5)	0 °C, 3 h	72
7 ^[d]	–	0 °C–RT, 24 h	0 ^[e]

[a] Unless otherwise noted, the reactions were carried out on a 0.3–0.5 mmol scale of **1a** with 3 equiv of Me₃SiCF₃ in CH₃CN (0.1 M) under a nitrogen atmosphere. [b] Combined yields of *E,E*, *E,Z*, and *Z,Z* isomers (1.8:1.2:1) of **2a** determined by ¹⁹F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard. The major isomer is *E,E*, while the stereochemistry of the minor two isomers was not assigned. [c] The reaction was carried out in the presence of 5 mol % of AgOTf. [d] Instead of CsF, 2 equiv of NaOAc was utilized. [e] **1a** was recovered in 70 % yield.

of the reaction parameters revealed that the amount of CsF and the reaction time are crucial to obtaining higher yields of **2a**. The yield of **2a** was dramatically improved to 96 % by using 1.5 equivalents of CsF and quenching the reaction immediately upon the consumption of **1a** within 20 minutes (entry 4).^[14] Reducing the amount of CsF to 1 equivalent led to the longer reaction time and lowered the yield of **2a** (entry 5). Even by using 0.5 equivalents of CsF, **1a** could be consumed within 3 hours (entry 6), thus affording the product **2a** in 72 % yield. However, no reaction took place in the absence of CsF, only with 2 equivalents of NaOAc (entry 7).^[15]

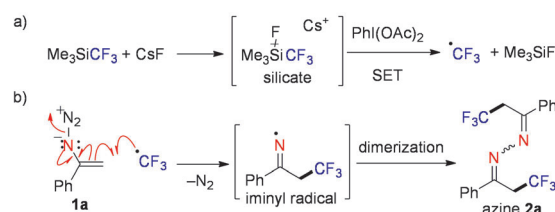
To gain insight into the reaction mechanism of the trifluoromethylation of **1a** for the formation of **2a**, control experiments with TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) were examined (Scheme 2a,b). The reaction of Me₃SiCF₃ under the present oxidative reaction conditions in the presence of TEMPO afforded the TEMPO–CF₃ adduct **3** in 57 % yield (determined by ¹⁹F NMR spectroscopy; Scheme 2a).^[4b,6c,f] Moreover, the formation of **2a** was completely inhibited when TEMPO (2.5 equiv) was added to the reaction mixture, and the formation of **3** was instead observed along with 74 % recovery of **1a** (Scheme 2b). These observa-



Scheme 2. Investigation of the reaction mechanism.

tions implicated the presence of the CF₃ radical in the present reaction.^[16] When the reaction was conducted in the presence of 1,4-cyclohexadiene (5 equiv), **2a** was obtained in only 8 % yield along with 38 % yield of the α-trifluoromethyl ketone **4a** (Scheme 2c). The α-trifluoromethyl ketone **4a** is formed presumably by hydrolysis of the NH imine intermediate, which is generated by H-radical abstraction of the putative α-trifluoromethyl iminyl radical.

Based on these observations, a proposed reaction pathway for the formation of **2a** is depicted in Scheme 3. The reaction of Me₃SiCF₃ with CsF forms the silicate,^[17] which is oxidized by PhI(OAc)₂ by a single-electron transfer (SET) to generate the trifluoromethyl radical (Scheme 3a). The resulting trifluoromethyl radical adds to **1a** to form the iminyl radical intermediate, which immediately dimerizes to give **2a** (Scheme 3b).



Scheme 3. A proposed reaction mechanism.

Having developed a method for construction of **2a**, we next explored molecular transformations of **2a** into valuable fluorine-containing materials. At first, we aimed to develop a facile procedure for the synthesis of **4a** by hydrolysis of **2a**.^[3c,f–h,5f,7a,18] Indeed, the crude reaction mixture containing **2a** was treated with 3N HCl (3 equiv) in THF, thus affording **4a** in 81 % yield (Table 2, entry 1). Following the established procedure, the generality of this α-trifluoromethyl ketone synthesis was examined using a series of vinyl azides (**1**). α-Aryl-substituted vinyl azides were readily transformed into the corresponding α-trifluoromethyl ketones **4** in good yields (Table 2, entries 2–8). The addition of the CF₃ radical to trisubstituted vinyl azides (**1i**, **1j**, and **1p**) proceeded smoothly to give the corresponding ketones **4** in good yields. Notably, heteroaryl motifs such as benzothiophene (**1k**), benzofuran (**1l**), and oxazole (**1m**) were compatible under the present reaction conditions, thus furnishing the desired ketones **4**. α-Alkyl-substituted vinyl azides (**1n–p**) were also capable of coupling with the CF₃ radical efficiently, thus demonstrating the broad applicability of the present process.

We next turned our attention to the reduction of the azines **2** to prepare β-trifluoromethyl amine derivatives.^[4f,5a] The azine **2a** was subjected to a suspension of Zn dust in AcOH,^[19] which was then treated with Ac₂O, thus delivering the acetamide **5a** in 61 % yield (Scheme 4). The reduction of the azine **2i** derived from the trisubstituted vinyl azide **1i** resulted in the acetamide **5i** in 65 % yield as a mixture of diastereomers (d.r. = 1.3:1). Similarly, the benzofuran vinyl azide **1l** as well as alkyl vinyl azide **1n** could be converted into

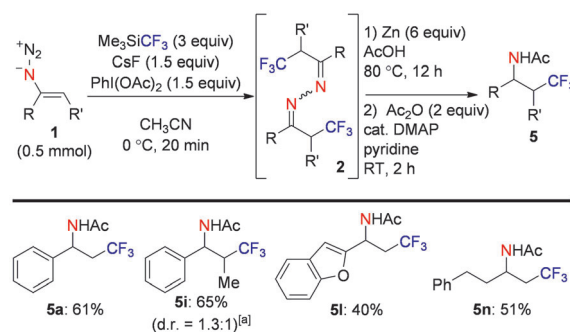
Table 2: Substrate scope on synthesis of α -trifluoromethyl ketones **4**.^[a]

Entry	1	4 Yield [%] ^[b]
1	1a (R = H)	4a : 81 %
2	1b (R = 2-Me)	4b : 70 %
3	1c (R = 4-Me)	4c : 91 %
4	1d (R = 4-MeO)	4d : 80 %
5	1e (R = 3-Br)	4e : 81 %
6	1f (R = 4-Br)	4f : 86 %
7	1g (R = 3-NO ₂)	4g : 72 %
8	1h	4h : 85 %
9	1i	4i : 82 %
10	1j	4j : 66 %
11	1k	4k : 82 %
12	1l	4l : 62 %
13	1m	4m : 62 %
14	1n	4n : 80 %
15	1o	4o : 70 %

Table 2: (Continued)

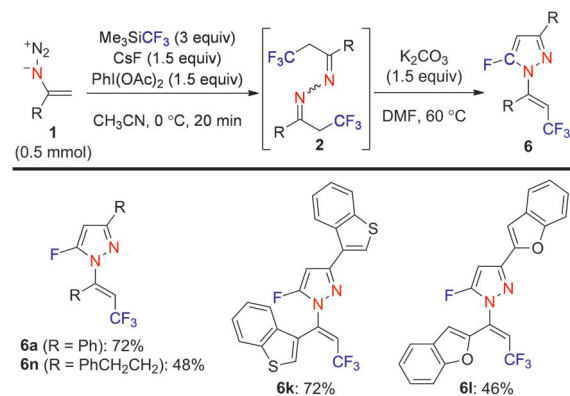
Entry	1	4 Yield [%] ^[b]
16 ^[c]	1p	4p : 70 %

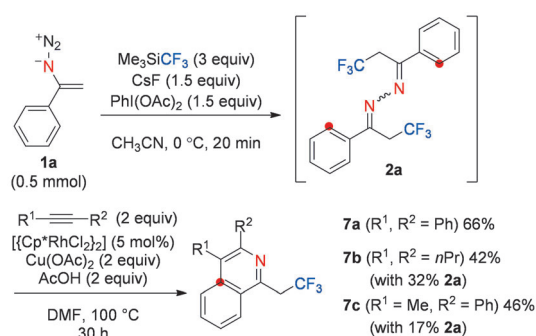
[a] The reactions were carried out by treatment of the vinyl azides **1** (0.5 mmol) and Me₃SiCF₃ (3 equiv) with PhI(OAc)₂ (1.5 equiv) and CsF (1.5 equiv) in CH₃CN (5 mL) at 0 °C under a nitrogen atmosphere. After aqueous work-up, the resulting crude reaction mixture was treated with 3 N HCl (3 equiv) in THF at 80 °C for 12–30 h. [b] Yields of the products **4** upon isolation. [c] The corresponding azine **2p** was treated with 6 N HCl (6.0 equiv) in THF at 80 °C for 30 h.


Scheme 4. Synthesis of β -trifluoromethyl amines **5**. [a] The diastereomer ratio was determined by ¹H NMR spectroscopy.

the corresponding acetamides **5l** and **5n** in 40 % and 51 % yields, respectively.

We further explored robust conversions of the α -trifluoromethyl azines **2** for synthesis of fluorine-containing azahe-trocycles, which are of great importance from the stand points of biological and medicinal applications.^[1] In that respect, treatment of the crude reaction mixture of **2a** with K₂CO₃ in DMF delivered *N*-trifluoromethylalkenyl-5-fluoropyrazole (**6a**) in 72 % yield based on **1a** (Scheme 5).^[20] The alkyl vinyl azides **1n** as well as heteroaryl-substituted vinyl azides **1k** and **1l** could be converted into the corresponding 5-fluoropyrazoles **6** in moderate to good yields.^[21]


Scheme 5. Synthesis of the 5-fluoropyrazoles **6**.



Scheme 6. Synthesis of trifluoroethylisoquinolines.

As another example, we found that the Rh^{III}-catalyzed aromatic C–H alkenylation of **2a** with internal alkynes allowed the synthesis of the trifluoroethyl isoquinolines **7a–c** in moderate to good yields (Scheme 6).^[22] In this process, the nitrogen atom of **2a** functioned as the intramolecular directing group to facilitate *ortho*-aryl C–H bond rhodation. These approaches associated with the present radical trifluoromethylation enable facile accesses to fluorine-containing aza-heterocycles from readily available vinyl azides **1** and Me₃SiCF₃.

In summary, we have developed PhI(OAc)₂-mediated radical trifluoromethylation of vinyl azides using Me₃SiCF₃, and it allows construction of α -trifluoromethyl azines. Moreover, facile protocols were devised to convert α -trifluoromethyl azines into valuable fluorine-containing compounds such as α -trifluoromethyl ketones, β -trifluoromethyl amines, 5-fluoropyrazoles, and trifluoroethyl isoquinoline. We expect that the present radical trifluoromethylation of vinyl azides is capable of supplying a new approach for synthesis of biologically and medicinally important fluorine-containing molecules.

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