Trifluoromethylation

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$PhI(OAc)_2$-Mediated Radical Trifluoromethylation of Vinyl Azides with Me_3SiCF_3**

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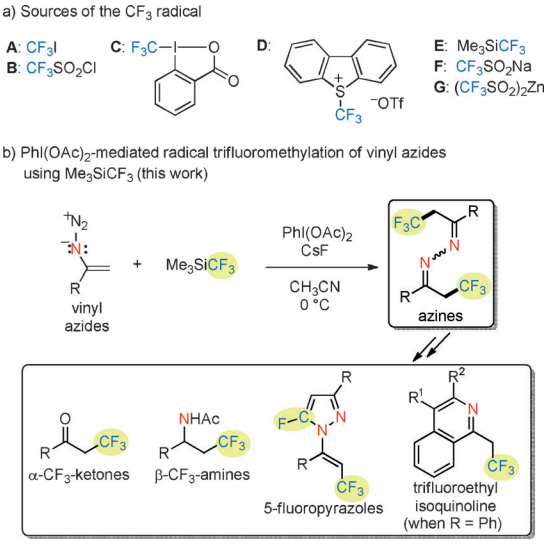
Abstract: *The fluorine-containing organic motif is becoming privileged in pharmaceuticals, agrochemicals, and functional materials, owing to its unique properties such as electron-withdrawing character, metabolic stability, and lipophilicity. Described herein is the $PhI(OAc)_2$-mediated radical trifluoromethylation of vinyl azides with Me_3SiCF_3 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 CF_3 unit (trifluoromethylation) have been developed to access CF_3-containing molecules because of their importance in pharmaceutical and material sciences.[1,2] Specifically, use of the CF_3 radical[2e,f] has recently received considerable attention for trifluoromethylation in which various CF_3 radical precursors have been utilized under redox reaction conditions (Scheme 1a), including CF_3X (**A**: X = I or **B**: X = SO_2Cl),[3] the Togni reagent **C**,[4] Umemoto reagent **D**,[5] Ruppert–Prakash reagent (Me_3SiCF_3) **E**,[6] and Langlois/Baran reagent (CF_3SO_2M; **F**: M = Na or **G**: M = Zn).[7]

Among those radical trifluoromethylation reagents, Me_3SiCF_3 has many advantages such as low cost, and easy handling and storage.[8] Single-electron oxidation of Me_3SiCF_3 generates the CF_3 radical. Most of the methods mainly rely on the stoichiometric use of transition-metal complexes such as silver[6a,e,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 Me_3SiCF_3 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 CF_3 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 CF_3 radical with vinyl azides, and the CF_3 radical generated oxidatively from Me_3SiCF_3 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 Me_3SiCF_3 to afford α-trifluoromethyl azines, which could be readily transformed into valuable fluorine-contatining synthons such as α-trifluoromethyl ketones, β-trifluoromethyl amines, 5-fluoropyrazoles, and trifluoroethyl isoquinoline (Scheme 1b). The present trifluoromethylation with vinyl azides could be run in the absence of transition metals, and the preliminary mechanistic investigation revealed that the CF_3 radical is likely involved in the trifluoromethylation.

We commenced our study by using the vinyl azide **1a** with Me_3SiCF_3 (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 CH_3CN, 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

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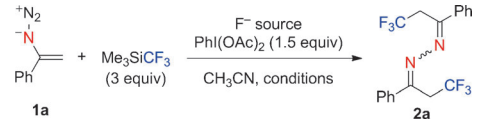
Table 1: Optimization of the reaction conditions.[a]

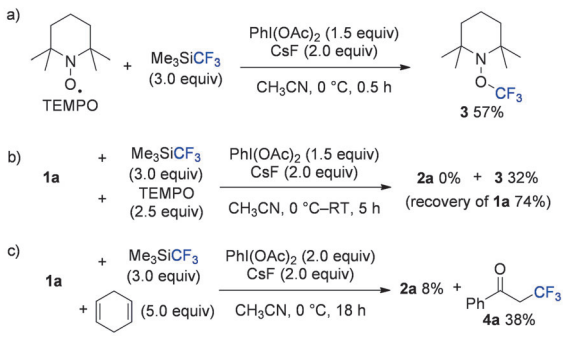


Entry	F^- source [equiv]	Conditions	Yield [%][b]
1[c]	CsF (2)	0 °C, 2 h	80
2	CsF (2)	0 °C, 2 h	84
3	KF (2)	0 °C–RT, 24 h	70
4	CsF (1.5)	0 °C, 20 min	96
5	CsF (1)	0 °C, 1 h	74
6	CsF (0.5)	0 °C, 3 h	72
7[d]	–	0 °C–RT, 24 h	0[e]

[a] Unless otherwise noted, the reactions were carried out on a 0.3–0.5 mmol scale of **1a** with 3 equiv of Me_3SiCF_3 in CH_3CN (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 ^{19}F 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.

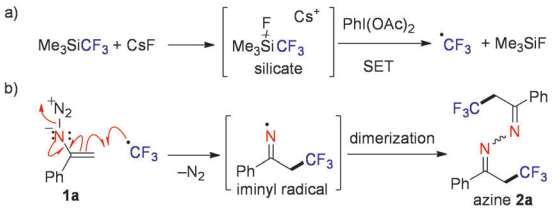
of the reaction parameters revealed that the amount of CsF and the reaction time are crucial to obtaining higher yields of **2a**. The yield of **2a** was dramatically improved to 96% by using 1.5 equivalents of CsF and quenching the reaction immediately upon the consumption of **1a** within 20 minutes (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 Me_3SiCF_3 under the present oxidative reaction conditions in the presence of TEMPO afforded the TEMPO-CF_3 adduct **3** in 57% yield (determined by ^{19}F NMR spectroscopy); Scheme 2a).[4h,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 observations implicated the presence of the CF_3 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.



Scheme 2. Investigation of the reaction mechanism.

Based on these observations, a proposed reaction pathway for the formation of **2a** is depicted in Scheme 3. The reaction of Me_3SiCF_3 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).

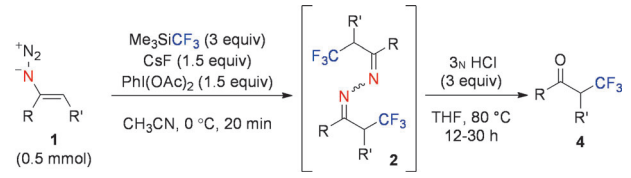


Scheme 3. A proposed reaction mechanism.

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 CF_3 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 CF_3 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 Ac_2O, 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 benzofuranyl 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]



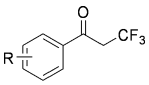
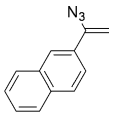
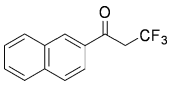
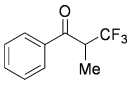
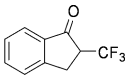
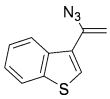
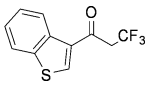
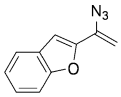
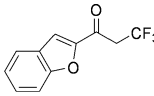
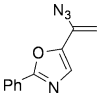
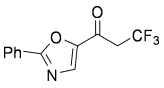
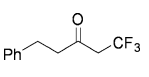
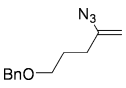
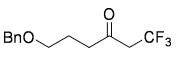
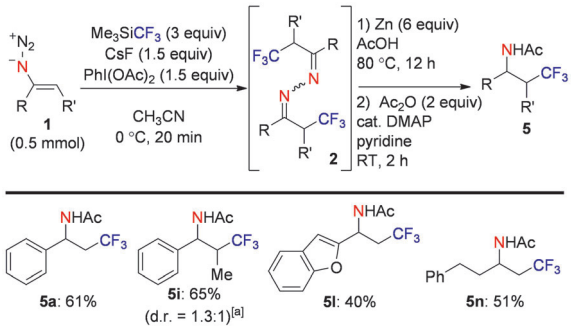
Entry	**1**	**4** Yield [%][b]
		
1	**1a** (R = H)	**4a**: 81%
2	**1b** (R = 2-Me)	**4b**: 70%
3	**1c** (R = 4-Me)	**4c**: 91%
4	**1d** (R = 4-MeO)	**4d**: 80%
5	**1e** (R = 3-Br)	**4e**: 81%
6	**1f** (R = 4-Br)	**4f**: 86%
7	**1g** (R = 3-NO_2)	**4g**: 72%
		
8	**1h**	**4h**: 85%
		
9	**1i**	**4i**: 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%

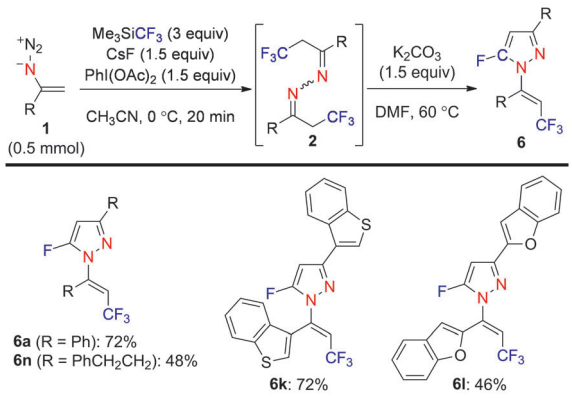
[a] The reactions were carried out by treatment of the vinyl azides **1** (0.5 mmol) and Me_3SiCF_3 (3 equiv) with $PhI(OAc)_2$ (1.5 equiv) and CsF (1.5 equiv) in CH_3CN (5 mL) at 0°C under a nitrogen atmosphere. After aqueous work-up, the resulting crude reaction mixture was treated with 3 N HCl (3 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 6N HCl (6.0 equiv) in THF at 80°C for 30 h.



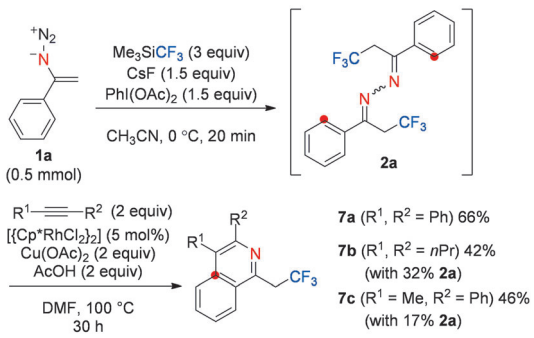
Scheme 4. Synthesis of β-trifluoromethyl amines **5**. [a] The diastereomer ratio was determined by ^{1}H NMR spectroscopy.

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 azaheterocycles, 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 K_2CO_3 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 azaheterocycles from readily available vinyl azides **1** and Me_3SiCF_3.

In summary, we have developed $PhI(OAc)_2$-mediated radical trifluoromethylation of vinyl azides using Me_3SiCF_3, 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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