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Trifluoromethylation of Unactivated Alkenes with Me_3SiCF_3 and *N*-Iodosuccinimide

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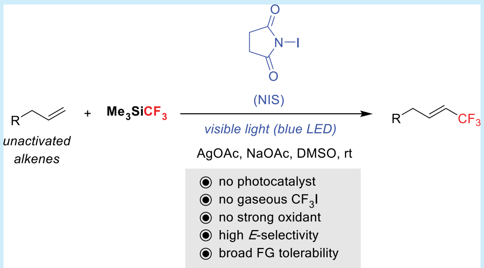
Supporting Information

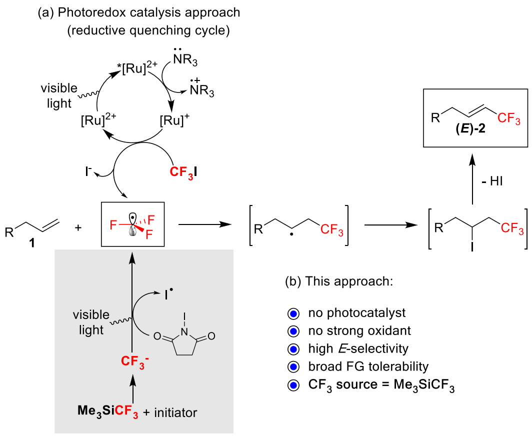
ABSTRACT: A novel approach to the trifluoromethylation of unactivated alkenes is presented. This reaction is promoted by *N*-iodosuccinimide (NIS) under visible light irradiation without the need for photocatalysts. The mild conditions allow the direct synthesis of useful trifluoromethylated (*E*)-alkenes from readily available alkene feedstocks with excellent functional group tolerability. In addition, using easy-to-handle and commercial Me_3SiCF_3 instead of gaseous CF_3I as the CF_3 source is highly attractive for industrial-scale applications.



Unactivated alkenes are among the most abundant chemical feedstocks in organic synthesis.[1] They are readily available in bulk quantities at low costs from petrochemical and renewable resources and possess a characteristic reactivity profile. For this reason, alkene functionalization has become the staple method for constructing new carbon−carbon bonds.[2] Direct trifluoromethylation of unactivated alkenes is a powerful tool for introducing the trifluoromethyl group into organic molecules ($C-CF_3$ bond formation). Despite enormous progress in the field of trifluoromethylation methodology,[3] this area remains underdeveloped. Pioneering work on copper-catalyzed trifluoromethylation of terminal alkenes allowed the efficient construction of allylic $C-CF_3$ bonds.[4] Hydrotrifluoromethylation of unactivated alkenes was also achieved by photoredox catalysis and other conditions to provide a net addition of "$H-CF_3$" across the double bond.[5,6] In view of the importance of organofluorine compounds for pharmaceutical, agrochemical, and material applications,[7] the development of new methods for the synthesis of trifluoromethylated molecules directly from simple alkenes is of high relevance.

Vinylic trifluoromethylation of unactivated alkenes is unique for creating a Csp^2-CF_3 bond in the product, which constitutes a formal vinylic C−H bond functionalization that is distinct from other trifluoromethylation processes.[4−6] The resulting trifluoromethylated alkenes are not only key structural motifs in drug candidates[7] but also synthetically useful substrates for C−F bond activations.[8] Typically these compounds were prepared from prefunctionalized alkenes via cross-coupling-type reactions[9] with the limitations of poor atom economy and moderate *E*/*Z* selectivity. Significant improvement was brought about by visible light photoredox catalysis to directly convert unactivated alkenes to alkenyl-CF_3 products with excellent *E*-selectivity under mild conditions.[10] In the seminal report,[10a] a Ru-based photocatalyst was employed in a reductive quenching cycle to generate an electrophilic CF_3 radical from trifluoromethyl iodide (CF_3I) (Scheme 1a). This radical then adds to an alkene **1** to give the trifluoromethylated secondary carbon radical. An additional base DBU was required to act as both a reductive quencher and a base for hydrogen iodide elimination leading to the final alkenyl-CF_3 product **2**. The choice of CF_3I as the CF_3 radical source was universal in the photocatalytic alkene trifluoromethylation.[10,11] Despite its utility and low cost, using CF_3I (gas, bp = −22.5 °C) in a routine operation and on an industrial scale can be challenging.[12] We herein report an alternative protocol for generating the CF_3 radical from Ruppert-Prakash reagent (Me_3SiCF_3, liquid, bp = 54−55 °C),[13] a formal CF_3 anion equivalent, in the presence of *N*-iodosuccinimide (NIS) and visible light (Scheme 1b). This

Scheme 1. Vinylic Trifluoromethylation of Unactivated Alkenes



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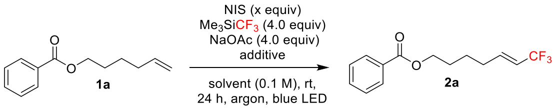
redox-neutral approach does not require photocatalysts and alleviates the use of gaseous CF_3I.

Oxidative allylic trifluoromethylation,[14a] hydrotrifluoromethylation,[14b] and fluorotrifluoromethylation[14c] of unactivated alkenes using Me_3SiCF_3 have been successfully developed by Qing's group. These processes were transition-metal-mediated and required a strong oxidant such as $PhI(OAc)_2$ for the presumable generation of CF_3 radical from CF_3 anion. To the best of our knowledge, *vinylic* trifluoromethylation of unactivated alkenes with Me_3SiCF_3 is unknown. We decided to circumvent this limitation by employing a common inexpensive reagent *N*-iodosuccinimide for its two roles: (1) as a mild oxidant; (2) as an iodine source for the iodotrifluoromethylated intermediate[10a,d] prior to elimination. The hypothesis includes the base of known NIS-promoted oxidative transformations under visible light;[15] however, whether NIS is capable of generating the CF_3 radical from Me_3SiCF_3 remained unclear from the outset.

We chose the unactivated alkene **1a** in the optimization studies for its higher boiling point and ease of preparation. Excess Me_3SiCF_3 (CF_3 source) and NaOAc (initiator) were adopted based on related trifluoromethylation conditions.[14b,13c,d] Various reaction parameters were subsequently screened (Table 1),[16] and the initial results showed that, under irradiation with blue LED at room temperature in DMF with 3.0 equiv of NIS, the corresponding trifluoromethylated alkene product **2a** was formed in 38% yield and good *E*/*Z*-selectivity (94:6) (entry 1). Increasing the equivalents of NIS gave a higher yield (62%), but no further improvement was achieved with increased equivalents (entries 2–3). In these experiments, we also observed small amounts (4–6%) of hydrotrifluoromethylated products that were difficult to separate from **2a**. Substituting NIS with NBS, NCS, or I_2 gave no conversion at all. Next, additive effects were explored. We first added the Ru-based photocatalyst and found that the yield was only increased to 53% (entry 4), which is in contrast with the excellent yields obtained by similar photoredox catalysts with CF_3I.[10a] Silver(I) salts are known activators for NIS,[17a] yet adding a catalytic amount of $AgNO_3$ did not change the yield. However, using 1.2 equiv significantly enhanced the yield (73%); a larger excess was not useful (entries 5–7). Various other silver(I) salts were also tested and were found to be inferior to $AgNO_3$, except AgOAc, which gave same results (entry 8). Considering the wider commercial availability and less hazardous nature of AgOAc, we decided to continue the optimization with AgOAc. Silver was unique in this reaction, and other metal salts such as CuCl, $FeCl_2$, and $FeCl_3$ only gave traces of products along with unreacted starting materials even though $FeCl_3$ has been shown to activate NIS in iodination reactions.[16,17b] We also varied the amounts of Me_3SiCF_3/NaOAc, and 4.0 equiv of each was optimal. Solvent screening revealed that DMSO was more suitable than DMF due to the complete inhibition of hydrotrifluoromethylated side products (entries 9–10). Other less polar solvents including 1,4-dioxane, dichloromethane, toluene, and diethyl ether led to poor solubilities of the reaction mixture. In DMSO, only 2.0 equiv of NIS were needed to achieve the same yield (entries 11–12). Extensive screening of the initiator for Me_3SiCF_3 was carried out[16] showing that carboxylates were superior in this reaction compared to other commonly used initiators such as carbonate[10a] and fluoride.[10c] For instance, sodium benzoate and potassium/lithium acetate all gave similar yields as sodium acetate. However, reactions carried out without NaOAc (even using larger excess of AgOAc) caused sharp decreases in yield (entries 13–14). Irradiation was crucial for the reaction. The reactivity was dramatically reduced without light (8% yield), even after heating at 80 °C (13% yield, entry 15).[16] The reaction parameters did not seem to have significant impact on the *E*/*Z*-selectivities; in all cases, the *E*-alkene predominated.

Table 1. Optimization Studies for NIS-Promoted Trifluoromethylation of Alkene 1a with Me_3SiCF_3

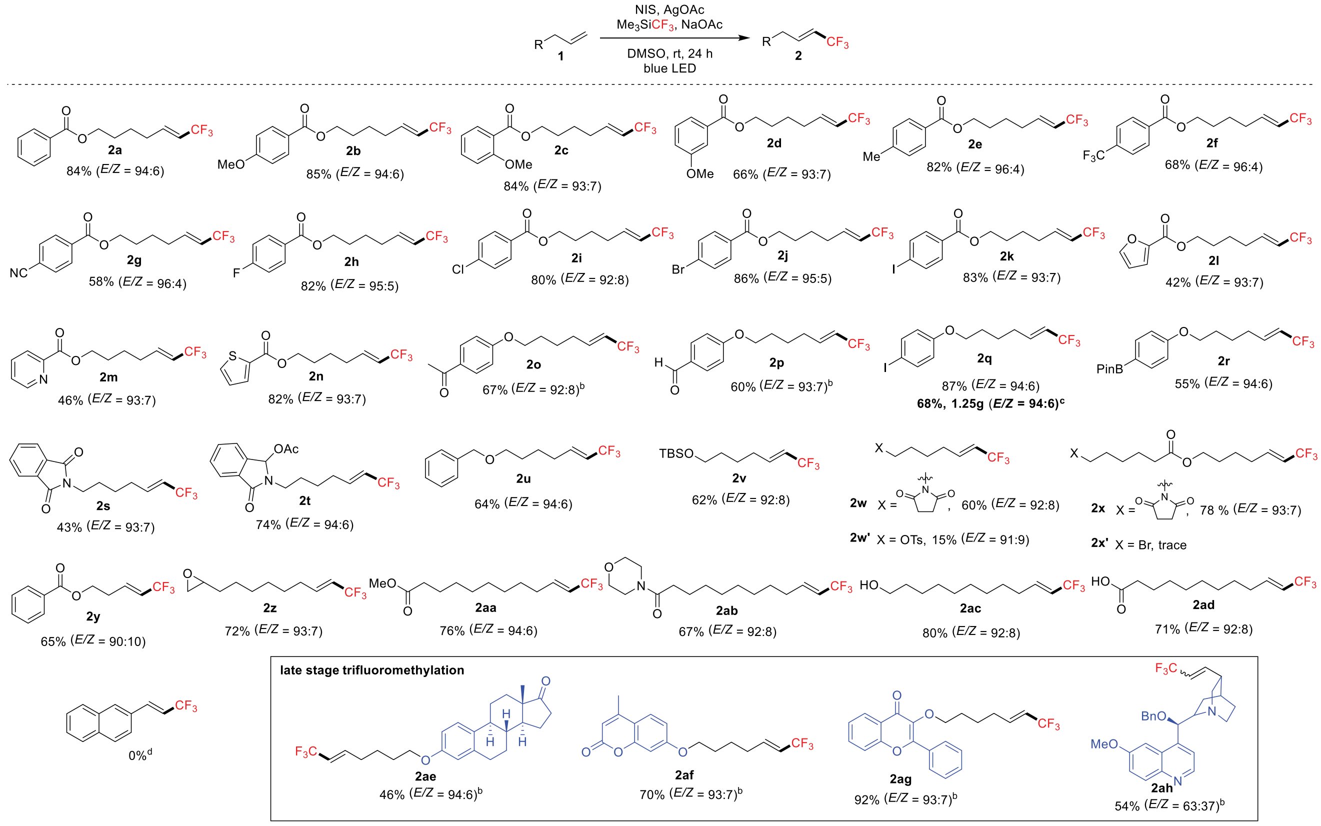


entry	*x*	additive (equiv)	solvent	yield % (*E*/*Z*)[a]
1	3.0	none	DMF	38 (94:6)
2	4.0	none	DMF	62 (92:8)
3	5.0	none	DMF	42 (93:7)
4	3.0	$Ru(bpy)_3Cl_2·6H_2O$ (0.025)	DMF	53 (93:7)
5	3.0	$AgNO_3$ (0.2)	DMF	38 (93:7)
6	3.0	$AgNO_3$ (1.2)	DMF	73 (93:7)
7	3.0	$AgNO_3$ (2.0)	DMF	74 (92:8)
8	3.0	AgOAc (1.2)	DMF	73 (93:7)
9	3.0	AgOAc (1.2)	MeCN	33 (96:4)
10	3.0	AgOAc (1.2)	DMSO	76 (93:7)
11	**2.0**	**AgOAc (1.2)**	**DMSO**	**76** (93:7)
12	1.0	AgOAc (1.2)	DMSO	37 (94:6)
13[b]	2.0	AgOAc (1.2)	DMSO	30 (94:6)
14[b]	2.0	AgOAc (5.2)	DMSO	15 (93:7)
15[c]	2.0	AgOAc (1.2)	DMSO	13 (92:8)

[a] Yield and *E*/*Z* ratio were determined by ^{19}F NMR analysis of the crude mixture versus an internal standard (benzotrifluoride). [b] Without NaOAc. [c] No irradiation, at 80 °C.

By applying the optimized conditions to readily available unactivated alkenes **1**, a library of trifluoromethylated alkenes **2** were rapidly generated in one step with good *E*-selectivities (Scheme 2). The advantages of the mild conditions (room temperature and no strong oxidant) were reflected in the excellent functional group tolerance. Ester derivatives (**2a–n**) bearing electron-donating/electron-withdrawing aromatic substituent groups (**2b–g**), aryl halides (**2h–k**), and heteroaryl groups (**2l–n**) were shown to be compatible. Phenol derivatives (**2o–p**) containing ketone and aldehyde functionalities mainly gave the desired products despite the fact that these carbonyl groups are highly susceptible to nucleophilic additions[13c,d] by Me_3SiCF_3.[18] Aryl iodide (**2q**) and boronate (**2r**), which are useful cross-coupling partners, were also tolerated. Gram-scale synthesis of **2q** was also feasible with recovered unreacted starting material (94% yield brsm). Phthalimide derivatives (**2s–t**),[18] benzyl and silyl ethers (**2u–v**), were suitable substrates. However, in cases where good leaving groups are present in the substrates (**1w** OTs, **1x** Br), the major products obtained were the succinimide derivatives (**2w–x**) via S_N2 displacements. A shorter carbon chain analog (**2y** vs **2a**) was obtained with a somewhat lower yield and *E*/*Z* ratio. An allylbenzene derivative gave a mixture of alkenyl-CF_3 (36%, ^{19}F NMR, *E*/*Z* = 94:6) and allyl-CF_3[10a] (8%, ^{19}F NMR) products. The longer carbon chain epoxide (**2z**), ester (**2aa**), and amide (**2ab**) were all tolerated. Oxidation of aliphatic alcohols such as **1ac** catalyzed by AgOAc in the presence of NIS and light is known,[15a] yet in our reaction this substrate was chemoselectively converted to **2ac**

Scheme 2. Scope of Trifluoromethylated Alkenes **2**[a]

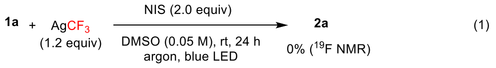


[a]General conditions: **1** (0.3 mmol), NIS (0.6 mmol), AgOAc (0.36 mmol), Me_3SiCF_3 (1.2 mmol), NaOAc (1.2 mmol), DMSO (3.0 mL), under argon. The *E*/*Z* ratio was determined by ^{19}F NMR analysis of the crude mixture. [b]Larger excess of AgOAc (0.45 mmol) was used to inhibit side product formation. [c]Used 1.51 g (5.0 mmol) of **1q**, DMSO (0.2 M). [d]Recovered starting material.

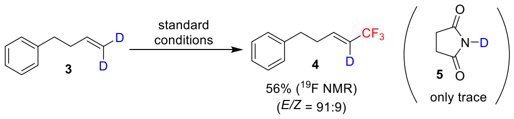
in a good yield as the sole product. Even carboxylic acid **2ad** was compatible, which is rarely employed in the usually basic conditions involving Me_3SiCF_3. These protecting-group-free approaches for directly accessing functionalized trifluoromethylated alkenes are useful for enhancing step economy. It is worth noting that Ag-catalyzed trifluoromethylation of arene C−H bonds with Me_3SiCF_3 in DMSO at room temperature has been reported,[19a] yet our reactions were devoid of any aryl-CF_3 side products which was likely due to the absence of strong oxidants such as $PhI(OAc)_2$. Styrene derivatives were unreactive under these conditions. Such limitation also existed in previously reported photocatalytic methods.[10a,d,20] Finally, late-stage trifluoromethylation of natural product derivatives was achieved to install tethered trifluoromethylated alkene units to the estrone (**2ae**), umbelliferone (**2af**), flavone (**2ag**), and quinine (**2ah**) cores.[21] This strategy allows the selective placement of the CF_3 group in bioactive molecules in the last step which will be highly attractive for medicinal chemistry research.[7]

Mechanistic studies were subsequently carried out to gain more insights into the reaction. Subjecting **1a** to preformed $AgCF_3$[22] in the presence of NIS with irradiation did not afford any product **2a** (eq 1), thus ruling out the presence of $AgCF_3$ in the reaction mixture.

Using a deuterium-labeled substrate **3** in standard conditions (cf. Scheme 2) gave the desired product **4** with one retained deuterium (eq 2). No significant amount of deuterated succinimide **5** was observed thus suggesting that succinimide may not be the base for D-I elimination.



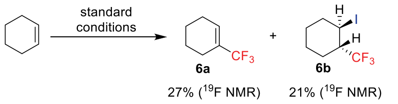
(1)



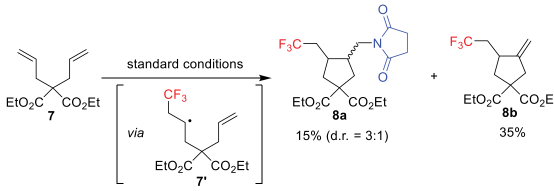
(2)

Cyclohexene also reacted under standard conditions to form the trisubstituted alkenyl-CF_3 product **6a**, while at the same time producing the *anti*-iodotrifluoromethyl product **6b**, which could not undergo HI elimination for alkene formation (eq 3).[10a]

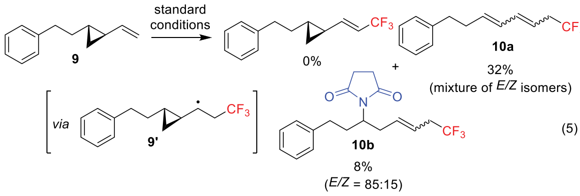
Furthermore, we employed substrate **7**, a radical clock[4a] in the reaction to probe the radical mechanism (eq 4). Cyclopentane derivatives **8a** and **8b** were obtained mainly, which can be explained by the 5-*exo-trig* cyclization of the radical species **7′** after the C−CF_3 bond-forming event. Ultimately an alkyl iodide should be formed at a primary carbon, which either underwent S_N2 displacement with succinimide to give **8a** or HI elimination to give alkene **8b**.[16] Another radical clock cyclopropane **9** was also used providing exclusively the ring-opened products **10a** (HI elimination product) and **10b** (S_N2 displacement product) (eq 5), which should derive from the initial radical intermediate **9′**.[16] These studies strongly support the addition of a CF_3 radical to the alkene resulting in a carbon-based radical species such as **7′** or **9′**.[23]



(3)

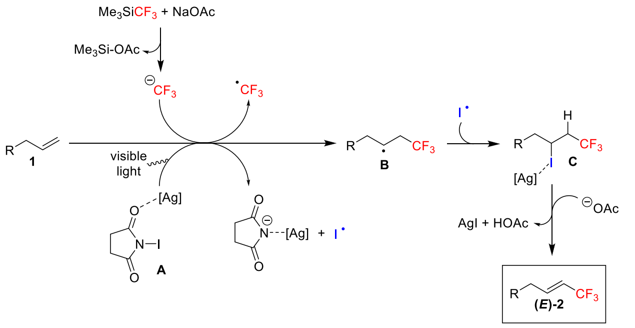


(4)



(5)

Scheme 3. A Plausible Mechanism



Based on these studies and literature examples, we propose the following mechanism to rationalize product formation (Scheme 3). Light promotes the cleavage of the N–I bond of NIS resulting in an iodine radical.[15] This process is further enhanced synergistically by the complexation of NIS (complex **A**) with a silver(I) salt which acts as a Lewis acid.[17a,16] The optimization studies clearly showed the benefits of adding AgOAc and using light (cf. Table 1, entries 1, 8, and 15). Meanwhile, a CF_3 anion is generated from Me_3SiCF_3 and NaOAc, which is effectively oxidized to the CF_3 radical. Such type of oxidation has been described using a strong oxidant $PhI(OAc)_2$;[14b,c] however in our case, the N–I bond cleavage process couples with this oxidation step conveniently resulting in the formation of a succinimide anion.[24] No extra oxidant is required. Addition of the electron-deficient CF_3 radical to alkene **1** affords the trifluoromethylated secondary carbon radical **B**.[10a,d] Radical clock experiments supported the existence of this radical intermediate (cf. eqs 4–5). Rapid recombination of radical **B** with the iodine radical leads to the iodotrifluoromethyl intermediate **C**,[25] as evidenced by the detection of compound **6b** (cf. eq 3). The displacement products **8a** and **10b** also provided support for the presence of alkyl iodides (cf. eqs 4–5). Finally, intermediate **C** undergoes E2 elimination of HI to predominantly generate the *E*-alkene product **2**.[10a] Here we propose acetate acting as the base, instead of succinimide, due to its higher concentration in the reaction system (large excess of NaOAc) and the absence of significant amounts of deuterated succinimide **5** (cf. eq 2). A stronger base DBU has been employed for such elimination;[10a] in our case, the silver(I) salt can facilitate the dehydrohalogenation process forming less soluble AgI and driving the reaction forward, which also explains why stoichiometric amounts of silver are required (cf. Table 1, entries 5–6) and a weaker base acetate is equally effective. The *dual roles* of the reagents in this system are most intriguing: (1) acetate acting as both an initiator for Me_3SiCF_3 and a base for HI elimination; (2) NIS acting as both an oxidant for CF_3 anion and an iodine radical source; (3) silver(I) salt acting as both an activator for NIS and a facilitator for dehydrohalogenation. The impact of such a multifunctional system is a highly streamlined process without the need for an extra oxidant/reductant.

In conclusion, we have developed a new approach toward trifluoromethylation of unactivated alkenes, which allows the rapid generation of a wide array of synthetically useful and pharmaceutically important trifluoromethylated alkenes with high *E*-selectivities. Compared to other methods,[10,14] this protocol has the following advantages: (1) using easy-to-handle Me_3SiCF_3 instead of gaseous CF_3I as the CF_3 source; (2) using NIS as a mild oxidant instead of $PhI(OAc)_2$; (3) direct access of the alkenyl product **2** from **1** without separately adding a base to the iodotrifluoromethyl intermediate **C**; (4) using a visible light source (commonly available and cheap blue LED) without precious metal photocatalysts. Further investigation of the combination of NIS and light for alkene activation is ongoing in our laboratory.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00332.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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