Radical Reactions

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Silver-Catalyzed Hydrotrifluoromethylation of Unactivated Alkenes with CF_3SiMe_3**

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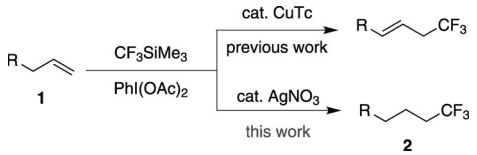
As a result of the strong electron-withdrawing nature and large hydrophobic domain of the trifluoromethyl group (CF_3), the incorporation of a trifluoromethyl group into organic molecules can dramatically modify a variety of properties, including lipophilicity, metabolic stability, and bioavailability.[1] Notably, many billion-dollar pharmaceuticals as well as agrochemicals contain a trifluoromethyl group. Therefore, intensive attention has been recently paid to the development of new methods for the introduction of the trifluoromethyl group into organic compounds.[2,3] Recently, significant advances have been achieved in transition-metal-mediated/catalyzed trifluoromethylation.[3–7] For example, in the presence of a palladium[4,5] or copper[6,7] catalyst the replacement of a halide, boron, or even C–H bond with a trifluoromethyl group can be accomplished under mild reaction conditions. In addition, two rare but interesting examples of silver-mediated direct trifluoromethylation of aryl C–H bonds also have been reported.[8] Silver is readily available and silver-mediated/catalyzed reactions have emerged as versatile synthetic methods for a wide range of organic transformations,[9] including fluorination reactions,[10] trifluoromethylthiolation reactions,[11] and trifluoromethoxylation reactions.[12] The exploration of metal catalysts such as silver, as opposed to palladium and copper, could lead to new opportunities for trifluoromethylation. Despite the pioneering work of Sanford and Bräse,[8] current silver-mediated trifluoromethylation reactions are limited to the construction of C_{aryl}–CF_3 bonds. Furthermore, these transformations require stoichiometric silver salts to generate the reactive intermediate $AgCF_3$. To address these limitations, we herein describe a silver-catalyzed hydrotrifluoromethylation of unactivated alkenes.

In contrast to the significant achievements that have been made in the trifluoromethylation of aromatic compounds, the trifluoromethylation of alkenes, especially unactivated alkenes, is still underdeveloped.[2d] Recently, copper-catalyzed trifluoromethylation of terminal alkenes or allylsilanes with electrophilic trifluoromethylating reagents has been developed, thus providing a series of trifluoromethylated allylic compounds.[13] Very recently, several groups successfully developed the oxytrifluoromethylation of alkenes using electrophilic trifluoromethylating reagents in the presence or absence of metal catalysts.[14] At the same time, our group also developed a copper-catalyzed oxidative trifluoromethylation of terminal alkenes using the Ruppert–Prakash reagent (CF_3SiMe_3), thus offering a complementary method to electrophilic allylic trifluoromethylation (Scheme 1).[15] During the course of our investigations, we found that the hydrotrifluoromethylated product **2** was formed as the major



Scheme 1. Deprotonative trifluoromethylation versus hydrotrifluoromethylation. CuTc = copper(I) thiophene-2-carboxylate.

product in the absence of the copper catalyst. This reaction is interesting in terms of the fact that selective formation of the hydrotrifluoromethylated product by radical trifluoromethylation of alkenes remains challenging because of the competitive radical atom-transfer processes and deprotonative trifluoromethylation,[2d,13,14] and only a few examples of electrochemical hydrotrifluoromethylation of alkenes have been reported.[16,17] Herein, we report the first example of a silver-catalyzed hydrotrifluoromethylation of unactivated alkenes with CF_3SiMe_3 as the trifluoromethyl source and $PhI(OAc)_2$ as the oxidant. The success of this reaction rests on the use of a silver(I) salt and a H donor to inhibit the competitive deprotonative trifluoromethylation reaction. This method provides a wide range of the trifluoromethylated alkanes, which usually are produced by either a two-step reaction involving a radical trifluoromethylation/dehalogenation sequence[18] or hydrogenation of trifluoromethylated alkenes.[16a,19]

We initially examined the hydrotrifluoromethylation of 4-phenyl-1-butene (**1a**) with CF_3SiMe_3 by using the reaction conditions for the oxidative trifluoromethylation of terminal alkenes. After screening bases, oxidants, and reaction temperatures (see Table S1 in the Supporting Information), we found that the hydrotrifluoromethylation of **1a** proceeded at room temperature in the presence of $PhI(OAc)_2$ as an oxidant and NaOAc as a base, thus giving the desired product **2a** in 47% yield together with the deprotonative trifluoromethylated side products **3a** and **4a** (Table 1, entry 1). We surmised that

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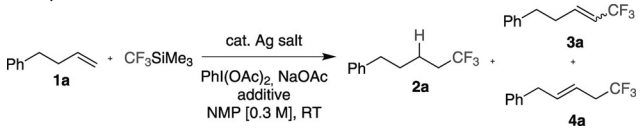
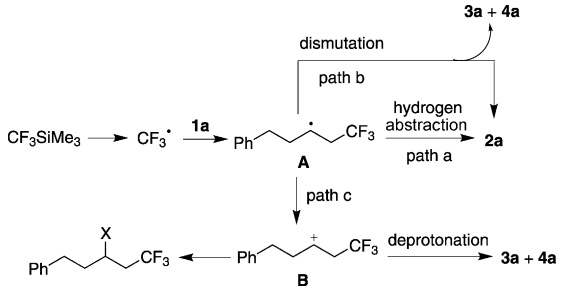
Table 1: Optimization of reaction conditions for the hydrotrifluoromethylation of **1**.[a]



Entry	Catalyst (10 mol%)	Additive (equiv)	**2a** Yield [%][b,c]	**2a**/**3a**/**4a**[d]
1	–	–	47	8:2:1
2	AgOTf	–	64	14:2:1
3	AgF	–	51	8:2:1
4	AgOAc	–	63	9:2:1
5	$AgNO_3$	–	70	10:2:1
6	$AgNO_3$	Bu_3SnH (1.0)	36	18:8:1
7	$AgNO_3$	Et_3SiH (2.0)	34	13:4:1
8	$AgNO_3$	1,3-dioxolane (10.0)	59	13:6:1
9	$AgNO_3$	1,4-CHD (2.0)	45	only **2a**
10	$AgNO_3$	1,4-CHD (1.0)	75	114:3:1
11[e]	$AgNO_3$	1,4-CHD (1.0)	92	35:2:1

[a] Reaction conditions: **1** (0.3 mmol), CF_3SiMe_3 (1.2 mmol, 4.0 equiv), $PhI(OAc)_2$ (0.6 mmol, 2.0 equiv), NaOAc (0.6 mmol, 2.0 equiv), Ag salt, addictive, NMP (1 mL, [0.3 M]), RT, 6 h, nitrogen atmosphere. [b] Yields determined by ^{19}F NMR spectroscopy using hexafluorobenzene as an internal standard. [c] Remaining mass balance was the recovered starting material (entries 1–10). [d] Ratios were determined by GC. [e] A second portion of CF_3SiMe_3 (1.2 mmol, 4.0 equiv), $PhI(OAc)_2$ (0.6 mmol, 2.0 equiv), NaOAc (0.6 mmol, 2.0 equiv), 1,4-CHD (0.3 mmol, 1.0 equiv) was added after 4 h. NMP = *N*-methylpyrrolidone.

the hydrotrifluoromethylated products result from H abstraction of the radical **A**, which is generated from the addition of the CF_3 radical to the alkene (Scheme 2, path a). In concert with this possible pathway, we hypothesized that an efficient formation of the radical species **A** would rely on the smooth

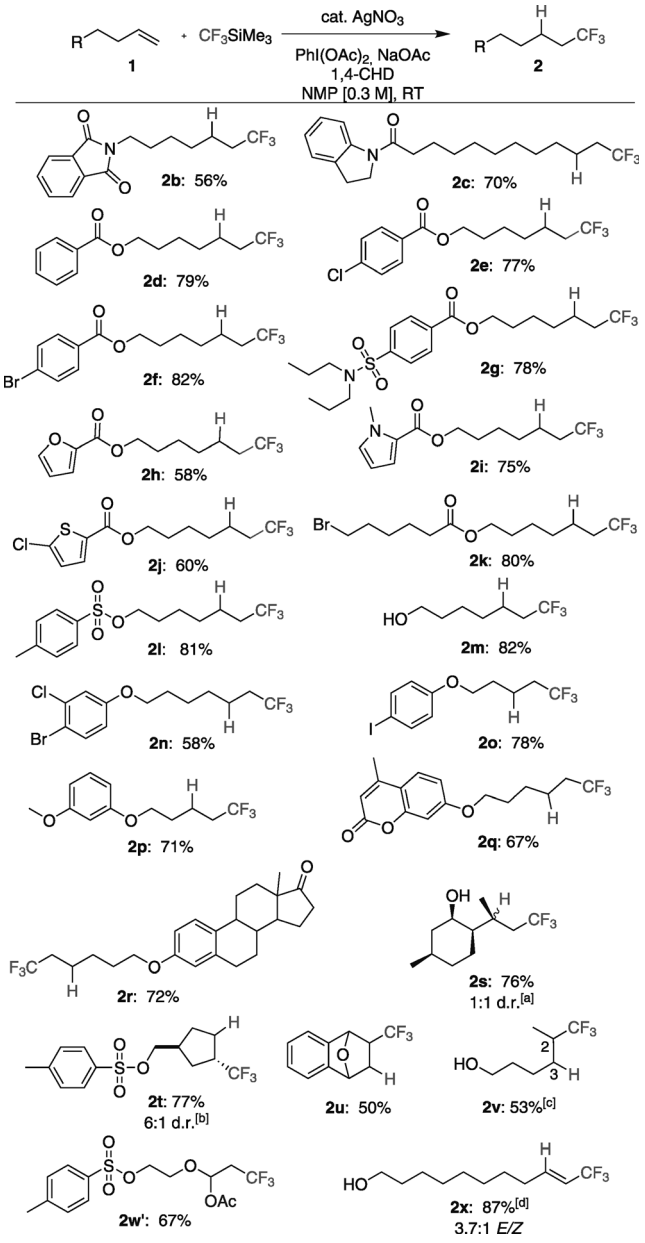


Scheme 2. Proposed mechanism.

generation of the CF_3 radical from CF_3SiMe_3 under oxidative conditions. Given that **A** might have the tendency to either undergo dismutation to give the corresponding alkane (**2a**) and alkenes (**3a** and **4a**) (Scheme 2, path b),[16f] or to be oxidized to the cationic species **B** followed by deprotonation[13] or nucleophilic attack (Scheme 2, path c),[14c,e] a sufficient H donor should inhibit these undesired processes. With these considerations in mind, we began to examine additives that would promote the generation of the CF_3 radical and various H donors that would facilitate the H-abstraction process.

Inspired by the elegant work on the silver-mediated trifluoromethylation of arenes with CF_3SiMe_3, in which CF_3 radical intermediates have been suggested,[8] we evaluated a series of various silver(I) salts and found they could facilitate the hydrotrifluoromethylation of **1a**, and reactions conducted with a catalytic amount of $AgNO_3$ provided higher yields than those conducted with AgOTf, AgF, and AgOAc (Table 1, entries 2–5). Under these reaction conditions, the formation of the desired product **2a** with variable quantities of the trifluoromethylated alkenes **3a** and **4a** was obtained, and not only decreased the reaction efficiency but also complicated purification (entries 1–5). To suppress the formation of these side products, various H donors were screened (entries 6–9). Upon addition of H donors such as Bu_3SnH (1.0 equiv), Et_3SiH (2.0 equiv), and 1,3-dioxolane (10.0 equiv), the yields of the desired product dramatically decreased, although the ratios of the desired product to the trifluoromethylated alkenes (**2a**/**3a**/**4a**) were slightly higher (entries 6–8). Interestingly, the addition of 2.0 equivalents of 1,4-cyclohexadiene (1,4-CHD) completely inhibited the formation of the trifluoromethylated alkenes and selectively yielded product **2a** as a single compound, albeit with a lower yield (entry 9). Decreasing the amount of 1,4-CHD from 2.0 equivalents to 1.0 equivalents resulted in a significant improvement of the conversion of substrate **1a** and afforded product **2a** in 75% yield with an excellent selectivity (entry 10). To further drive the reaction to completion, another portion of CF_3SiMe_3, $PhI(OAc)_2$, NaOAc, and 1,4-CHD was added after 4 hours, thus providing the desired product in 92% yield (entry 11).

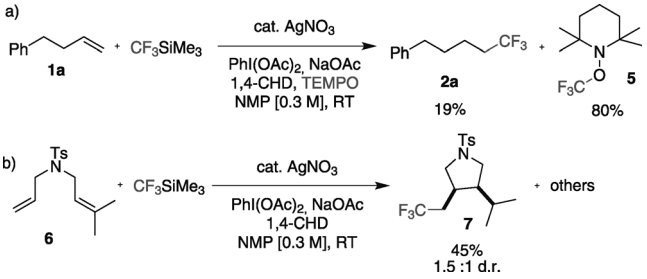
With the optimized reaction conditions in hand, we next investigated the substrate scope of the silver-catalyzed hydrotrifluoromethylation of unactivated alkenes and found that a variety of terminal alkenes can be transformed into the corresponding products in moderate to good yields (Scheme 3). The mild reaction conditions employed allowed for high functional group compatibility and a wide array of functional groups, including amides, esters, sulfonamides, heterocycles, alkyl bromides, sulfonic esters, alcohols, ketones, and epoxy groups were well tolerated (**2b**–**2m**, **2q**–**2x**). Notably, substrates bearing chloro, bromo, and even iodo substitutents on the arene rings are compatible with this catalytic system, and all reactions afforded the desired products in yields within the 58–82% range, thus providing opportunities for additional transformations (**2e**, **2f**, **2j**, **2n**, **2o**). Terminal olefins derived from probenecid, 4-methylumbelliferone, and estrone proceeded smoothly under the reaction conditions, and the corresponding trifluoromethylated alkanes were obtained in moderate yields (**2g**, **2q**, **2r**). In addition, 1,1-disubstituted terminal alkenes are also viable for our method. The reaction of (−)-isopulegol gave the product **2s** in 76% yield without any diastereoselectivity (1:1 d.r.). It is remarkable that 1,2-disubstituted cyclic and acyclic internal alkenes were found to undergo the desired transformation efficiently, thus furnishing the trifluoromethylated products in moderate to good yields (**2t**–**2v**). The reaction of asymmetric internal alkene *cis*-4-hexen-1-ol showed a moderate regioselectivity (C2/C3 = 5.3:1) and the regioisomer **2v** was obtained as the major product. Further investigations



Scheme 3. Substrate scope of silver-catalyzed hydrotrifluoromethylation of unactivated alkenes with CF_3SiMe_3. Yields are those of the isolated products. Reaction conditions: **1** (1.0 mmol), CF_3SiMe_3 (4.0 mmol), $PhI(OAc)_2$ (2.0 mmol), NaOAc (2.0 mmol), $AgNO_3$ (0.1 mmol), 1,4-CHD (1.0 mmol), NMP (3 mL), RT, nitrogen atmosphere, and a second portion of CF_3SiMe_3 (4.0 mmol), $PhI(OAc)_2$ (2.0 mmol), NaOAc (2.0 mmol), 1,4-CHD (1.0 mmol) was added after 4 h. [a] Diastereomeric ratio determined by ^{19}F NMR analysis of the crude reaction mixture. [b] Obtained as a mixture of diastereoisomers, the diastereomeric ratio determined by ^{19}F NMR spectroscopy. [c] Obtained as a mixture of regioisomers, C2/C3 = 5.3:1, as determined by ^{19}F NMR spectroscopy. [d] Without 1,4-CHD.

revealed that the electronic properties of alkenes had profound effects on this transformation. Electron-poor alkene benzyl acrylate did not react under the standard reaction conditions. In contrast, the reaction of an electron-rich vinyl ether proceeded smoothly to give the acetoxytrifluoromethylated product **2w′** instead of the expected hydrotrifluoromethylated product. We surmised that as a result of the electronic effect of the adjacent alkoxy group, the radical intermediate **A** would be highly prone to oxidation and subsequent nucleophilic attack on the resulting cationic intermediate to give the unexpected acetoxytrifluoromethylated product (Scheme 2). Finally, terminal alkynes were also examined, and the corresponding trifluoromethylated alkene **2x** was obtained in 87% yield and moderate *E*/*Z* ratio.

As mentioned above, we initially hypothesized that this reaction proceeded by a pathway involving an in situ generated CF_3 radical species with subsequent radical addition and H abstraction to eventually afford the desired hydrotrifluoromethylation product (Scheme 2). To figure out whether the CF_3 radical intermediate was involved in the reaction, the inhibition experiment of olefin **1a** was conducted with the addition of TEMPO (1.0 equiv), a trap for the CF_3 radical utilized in previous reports,[8a,13b,e,14b] and the desired product **2a** was obtained in only 19% yield together with the TEMPO adduct **5** in 80% yield (Scheme 4a). Furthermore, the reaction of **6**, a radical clock, with



Scheme 4. Mechanistic experiments involving a) TEMPO and b) a radical clock. TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl, Ts = 4-toluenesulfonyl.

CF_3SiMe_3 under the standard reaction conditions gave the trifluoromethylated pyrrolidine **7** in 45% yield (1.5:1 d.r.; Scheme 4b). These experiments suggest that the involvement of a CF_3 radical species is possible under the current reaction conditions. Considering the fact that a small amount of trifluoromethylated olefins was formed in almost all cases, we cannot rule out the possibility that a second alkyl radical **A** would undergo dismutation or oxidation/deprotonation to give trifluoromethylated alkenes (Scheme 2, paths b and c). However, the high selectivity in the formation of trifluoromethylated alkanes over trifluoromethylated olefins indicates that the major route to the hydrotrifluoromethylated product was a H abstraction from a H donor, and not dismutation of **A**. Further investigation will be required to elucidate the nature of this hydrotrifluoromethylation process.

In summary, we have developed a silver-catalyzed hydrotrifluoromethylation of simple alkenes using nucleophilic CF_3SiMe_3 in the presence of $PhI(OAc)_2$. The mild reaction conditions allow efficient access to a series of trifluoromethylated alkanes bearing a wide range of functional groups. A preliminary mechanistic investigation suggests that a CF_3 radical species is likely involved in the current transformation.

Experimental Section

General procedure for the silver-catalyzed hydrotrifluoromethylation of unactivated alkenes: An oven-dried reaction tube was charged with $PhI(OAc)_2$ (2.0 mmol), NaOAc (2.0 mmol), $AgNO_3$ (0.1 mmol), and **1b** (1.0 mmol). The tube was sealed with a septum, evacuated, and backfilled with argon (repeated three times). Then, NMP (3 mL), 1,4-CHD (1.0 mmol), and CF_3SiMe_3 (4.0 mmol) were added. After stirring at room temperature for 4 h, a second portion of CF_3SiMe_3 (4.0 mmol), $PhI(OAc)_2$ (2.0 mmol), NaOAc (2.0 mmol), and 1,4-CHD (1.0 mmol) was added. The reaction mixture was stirred for another 6 h at room temperature before work-up. The reaction solution was filtered by Celite, eluted with diethyl ether, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified with silica gel column chromatography (eluent: hexanes/ethyl acetate 30:1) to provide pure product **2b**.

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