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Catalytic hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes *via* an organic photoredox system†

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Herein is presented a direct method for the metal-free hydrotrifluoromethylation of alkenes. The method relies on the single electron oxidation of a commercially available sodium trifluoromethanesulfinate salt (CF_3SO_2Na, Langlois reagent) by *N*-Me-9-mesityl acridinium as a photoredox catalyst. Methyl thiosalicylate is used as a substoichiometric H-atom donor for aliphatic alkenes, and thiophenol is used as a stoichiometric H-atom donor for styrenyl substrates. The substrate scope for the transformation is broad, including mono-, di- and trisubstituted aliphatic and styrenyl alkenes, with high regioselectivity in nearly all cases examined.

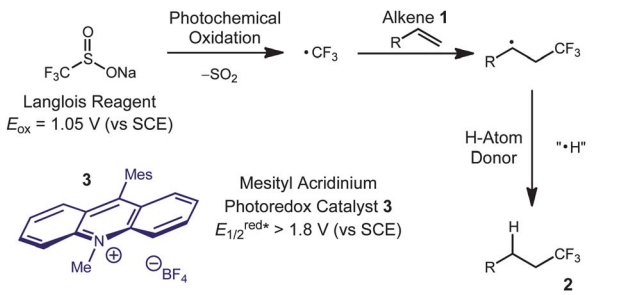
Introduction

The incorporation of fluorine into complex molecular architectures has become almost irreplaceable in pharmaceutical chemistry.[1] The chemical stability and electron withdrawing character of fluoro and trifluoromethyl substituents reliably renders medicinal lead compounds more active by affecting absorption and distribution, diminishing metabolic oxidation, and enhancing binding affinity.[2] Fluorinated compounds also have importance in the agrochemical industry,[3] and in the synthesis of (^{18}F) positron emission tomography (PET) radiolabels.[4] The interest in fluorinated compounds has led to the development of numerous nucleophilic, electrophilic, and radical manifolds for the trifluoromethylation of aldehydes, ketones, anhydrides, amides, imides, imines, sulfonates, enones and activated carbon nucleophiles to generate Csp^3–CF_3 bonds.[5] A number of palladium-, copper-, and iron-catalyzed methods[6] for the trifluoromethylation of aryl halides,[6c] vinyl sulfonates,[6f] aryl boronic acids,[6g] and potassium vinyltrifluoroborates[6h] have replaced less efficient organotransition-metal-mediated procedures for the construction of Csp^2–CF_3 bonds.[7] Additionally, palladium-catalyzed procedures for the direct C–H trifluoromethylation of aryl compounds containing a wide variety of directing groups have been reported.[8] Radical trifluoromethylations provide additional utility as they proceed with high chemoselectivity under mild and convenient conditions.[9] Photoredox catalysis[10] has provided access to reactive trifluoromethyl radicals within several pragmatic contexts.[11]

Herein we report an organic photoredox catalysis system for the hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes using a commercially available sodium trifluoromethanesulfinate salt. While there have been numerous reports for the trifluoromethylation of alkenes,[12–15] there have been only two reports of catalytic hydrotrifluoromethylation reactions for unactivated alkenes to date.[16] This disclosure allows for the regioselective hydrotrifluoromethylation of mono-, di-, and trisubstituted aliphatic alkenes and styrenes using an inexpensive and shelf-stable reagent. To the best of our knowledge this current method constitutes the only selective hydrotrifluoromethylation reaction of styrenes to date.

Results and discussion

Langlois and coworkers originally reported the oxidation of sodium trifluoromethanesulfinate (CF_3SO_2Na, Langlois reagent) to trifluoromethyl radicals in the context of reactions with electron rich aromatics.[17] Interestingly, Langlois also reported the electrochemical hydrotrifluoromethylation of



Scheme 1 Proposed hydrotrifluoromethylation method using photoredox catalysis.

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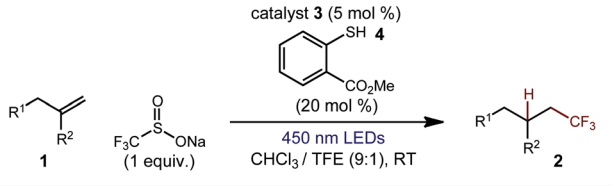
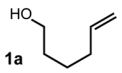
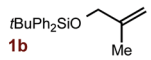
three alkenes using CF_3SO_2K. The yields of the hydrotrifluoromethylation adducts were, however, low (~8 to 20%) due to the formation of significant quantities of oxidative byproducts.[17c]

We hypothesized that the oxidation of Langlois reagent using a photoredox catalyst could serve as a useful entry point towards developing a selective hydrotrifluoromethylation (Scheme 1). Trifluoromethanesulfinate salts have readily accessible oxidation potentials (E_{ox} = 1.05 V *vs.* SCE, CF_3SO_2K),[17c] and a number of organic photoredox catalysts could presumably be used to generate transient quantities of CF_3 radical. The electrophilic CF_3 radical is known to undergo rapid reactions with alkenes,[9a] and we envisaged a method whereby a select hydrogen-atom donor could be used to intercept the adducts before oxidation (deprotonative trifluoromethylation) would occur.

We began our investigation using *N*-Me-9-mesityl acridinium (**3**) as the photoredox catalyst as acridinium species have sufficient excited-state reduction potentials ($E_{1/2}^{red}$* > 1.8 V *vs.* SCE), and are known to mediate a number of photocatalytic oxygenation reactions.[18,19] Optimization studies were simultaneously performed on two different substrates, 5-hexen-1-ol (**1a**) and silyl-protected β-methallyl alcohol (**1b**), in order to provide a method that was generally applicable to a broad class of alkenes. A wide variety of parameters were examined including trifluoromethyl source, reaction solvent, stoichiometry, cosolvent, additives, and H-atom donors.[19] The optimization efforts led to the development of a general set of conditions presented below (Table 1, entries 1–3, and 7). Solvent mixtures of chloroform were optimal, with dichloroethane providing somewhat lower yields. Dichloromethane, nitromethane, acetonitrile, and other polar aprotic solvents failed to furnish appreciable yields of the desired products. Somewhat surprisingly, the hydrotrifluoromethylation products were only observed in small quantities unless 2,2,2-trifluoroethanol (TFE) was used as a cosolvent, even when other putative H-atom donors were included (entries 6 and 8). TFE could not be used as the exclusive reaction solvent, presumably due to solubility issues, and other alcohols (including methanol) provided inferior results under the conditions tested. Gouverneur and coworkers have recently shown that the C_α–H bond of methanol can serve as the hydrogen atom source in a related hydrotrifluoromethylation reaction.[16b,20] While not absolutely necessary for reactivity, substoichiometric quantities of thiols greatly improved the yield and product distributions for most alkenes tested (entry 9). A number of aromatic thiols were similarly effective, but methyl thiosalicylate (**4**) was employed in most cases due to its commercial availability and inoffensive odor. For reproducibility, reactions were typically prepared under an atmosphere of nitrogen with 5 mol% acridinium photocatalyst. However, catalyst loading could be reduced to 1 mol% without deleterious effects, and full exposure to air throughout the course of the reaction had little effect on yield for the substrates tested (entries 4 and 5). The zinc trifluoromethanesulfinate salt ($Zn(CF_3SO_2)_2$) that has proven widely successful for the trifluoromethylation of heterocycles,[9c,d] was less effective under the standard conditions (entry 10). It is unclear whether this observation is due to an inherent difference in reactivity, or is simply the result of solvent incompatibility. The remainder of the mass balance for the hydrotrifluoromethylation reactions was starting material, and longer reaction times afforded higher chemical yields (entry 3).

Table 1 Selected optimization experiments for the hydrotrifluoromethylation of alkenes **1a** and **1b**

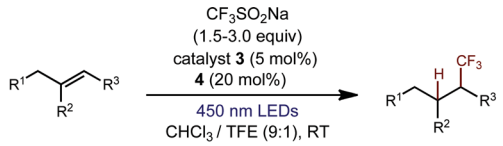


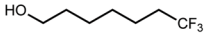
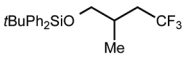
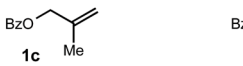
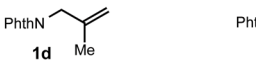
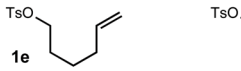
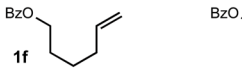
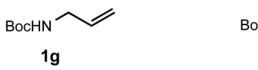
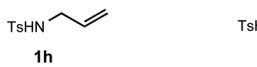
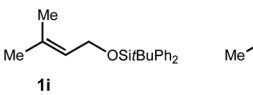
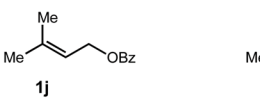
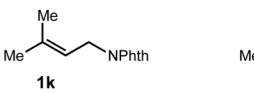
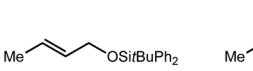
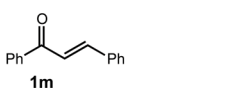
Entry	Substrate	Conditions[a]	Time	Yield[b]
1	 1a	"*Standard*"	8 hr	27%
2	**1a**	**"*Standard*"**	**24 hr**	**44%**
3	1a	"*Standard*"	48 hr	59%
4	1a	*Open to Air*	24 hr	43%
5	1a	*1 mol% **3***	24 hr	45%
6	1a	*No TFE*	48 hr	<5%[c]
7	 **1b**	**"*Standard*"**	**48 hr**	**78%**
8	1b	*No TFE*	48 hr	10%[c]
9	1b	*No **4***	48 hr	47%
10	1b	$Zn(SO_2CF_3)_2$ instead of NaO_2SCF_3	48 hr	15%[d]

[a] Standard reaction conditions: alkene (1 equiv.), Langlois reagent (CF_3SO_2Na, 1 equiv.), **3** (5 mol%), and **4** (20 mol%) were taken under N_2 and dissolved in $CHCl_3$–TFE (9 : 1) [0.2 M]. Irradiation was at 450 nm for the time period indicated. [b] Yields are the average of three separate trials by GC against internal standard. [c] Entries 6 and 8 were prepared in $CHCl_3$ with no TFE, but still contained **4** (20 mol%). [d] Yield for entry 10 is for a single trial.

The optimized hydrotrifluoromethylation conditions proved generally successful for a wide range of unactivated aliphatic mono-, di-, and trisubstituted alkenes. Similar to other radical-based trifluoromethylation procedures,[12,16] terminal alkenes and geminally disubstituted alkenes were well tolerated. Unprotected alcohols were compatible (Table 2, entry 1), as well as silyl (entry 2), ester (entries 3 and 6), and sulfonyl (entry 5) protected analogues. Phthalamide (entry 4), carbamate (entry 7), and sulfonyl (entry 8) moieties were all viable protecting groups for unsaturated amine substrates. Terminal alkenes in close proximity to electron withdrawing groups proved more recalcitrant (entry 7 and 8). To the best of our knowledge, there have been no reports of catalytic hydrotrifluoromethylation of tri-alkyl substituted alkenes. However, under our optimized conditions, trisubstituted alkenes provided yields similar to the mono- and geminally disubstituted alkenes (entries 9–11). Vicinally disubstituted alkenes (entry 12) gave low regioselectivity (1.1–1.3 : 1),

Table 2 Substrate scope for the hydrotrifluoromethylation of aliphatic mono-, di-, and trisubstituted alkenes[a]



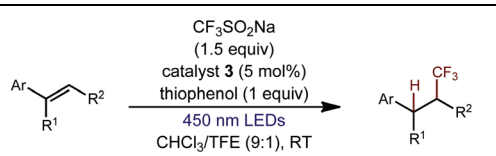
Entry	Substrate	Product	Yield[b]
1	**1a**		50%
2	**1b**		54%
3	**1c**		69%
4	**1d**		66%
5	**1e**		64%
6	**1f**		42%
7	**1g**		25%
8	**1h**		32%
9	**1i**		51%[a] 74%[c]
10	**1j**		54%
11	**1k**		69%
12	**1l**		45%[d]
13	**1m**		31%[e]

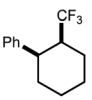
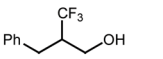
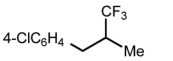
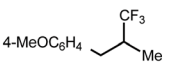
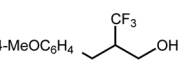
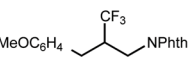
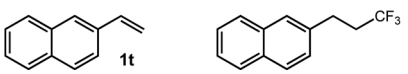
[a] Standard reaction conditions: alkene, Langlois reagent (1.5–3.0 equiv.), **3** (5 mol%), and **4** (20 mol%) were taken under N_2 and dissolved in $CHCl_3$–TFE (9 : 1) [0.2 M]. Irradiation was at 450 nm for 24 h, unless otherwise noted. Entries 2–4: 1.5 equiv. Langlois reagent. Entries 1, and 5–12: 2.0 equiv. Langlois reagent. [b] Average isolated yield for no less than two trials. [c] Performed on a 10 mmol scale with 2.0 equiv. Langlois reagent, and an irradiation time of 48 h. Isolated yield for a single trial. [d] Average isolated yield for both regioisomers (C2/C3 = 1.3 : 1, ^{19}F NMR). [e] Entry 13: 3.0 equiv. Langlois reagent. Average isolated yield for both regioisomers (C2/C3 = 1.1 : 1, ^{19}F NMR).

and were similarly affected by electron withdrawing groups proximal to the alkene (entry 13, *trans*-chalcone). In order to test the practicality of the reported method, we chose to evaluate the hydrotrifluoromethylation on a gram scale. The allylic silyl ether **1i** was subjected to the standard conditions on a 10 mmol scale, with the only alteration to the method being the irradiation time (48 h). The hydrotrifluoromethylated product was isolated in 74% yield (entry 9).

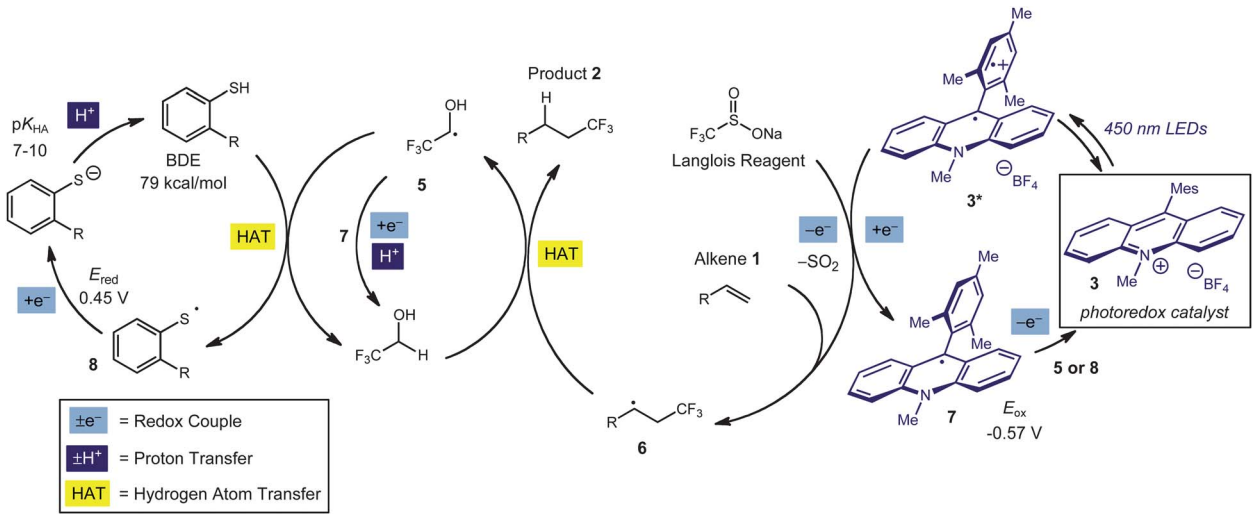
Once we had demonstrated the hydrotrifluoromethylation of several classes of aliphatic alkenes, we next turned our attention to styrenes. Styrenes pose unique challenges with regard to unproductive polymerization and oxidation reactions. Coincidentally, 1-phenyl-1-cyclohexene (**1n**) was one of the three alkenes originally examined within Langlois' electrochemical method. Langlois reported a low yield (~10%) for the reaction and cited the oxidized trifluoromethyl alkene as a major byproduct.[17c] We ultimately found that a variety of styrenyl substrates could be efficiently hydrotrifluoromethylated if one equivalent of thiophenol was used as the source of hydrogen atom.[21] Under these conditions 1-phenyl-1-cyclohexene (**1n**) provided the desired product with diastereoselectivity (12 : 1) favouring the *cis* isomer (Table 3, entry 1). Similar to the alkyl-substituted alkenes, styrenes with unprotected alcohol groups were tolerated (Table 3, entries 2 and 5). β-Substituted styrenes

Table 3 Substrate scope for the hydrotrifluoromethylation of styrenes[a]



Entry	Substrate	Product	Yield[b]
1	**1n**		51%[c]
2	**1o**		51%
3	**1p**		56%
4	**1q**		64%
5	**1r**		67%
6	**1s**		41%
7	**1t**		29%

[a] Standard reaction conditions: alkene, Langlois reagent (1.5 equiv.), **3** (5 mol%), and thiophenol (1 equiv.) were taken under N_2 and dissolved in $CHCl_3$–TFE (9 : 1) [0.2 M]. Irradiation was at 450 nm for 24 h. [b] Average isolated yield for no less than two trials. [c] Product was isolated as an inseparable mixture of diastereomers (*cis*/*trans* = 12 : 1, ^{19}F NMR).



Scheme 2 Proposed mechanism for the hydrotrifluoromethylation of alkenes using photoredox catalysis.

with both electron withdrawing (entry 3), and electron donating (entries 4–6) groups were similarly productive. Terminal styrenes were the most challenging class of alkenes in this reaction protocol due to the propensity for polymerization and the high volatility of products. Despite this, 2-vinylnaphthalene gave the expected hydrotrifluoromethylated product in modest yield (entry 7, 29%). The remaining mass balance for the styrenyl substrates was typically comprised of oligomeric and polymeric species. Analysis of the crude reaction mixtures by GC-MS and ^{19}F NMR indicated that oxidative[12] (deprotonative) trifluoromethylation products were not formed in any of the reactions with aliphatic or styrenyl alkenes.

Conclusions

While many of the factors governing reactivity in this transformation remain unclear, a tentative mechanism can be proposed (Scheme 2). Excitation of *N*-Me-9-mesityl acridinium (**3**) leads to the oxidation of Langlois reagent and generation of the electrophilic trifluoromethyl radical after the expulsion of SO_2 (*vide supra*). Addition of the trifluoromethyl radical to the alkene proceeds with anti-Markovnikov selectivity, producing the corresponding carbon-centered radical (**6**). The existence of **6** is implicated by the observation of byproducts corresponding to dimers of **6** (particularly in the case of substrate **1a**), observed when unoptimized conditions are employed (no thiol).

Alkyl-substituted alkenes reliably provided hydrotrifluoromethylated products without the use of thiols (Table 1, entry 9), and TFE as a cosolvent was essential for reactivity (Table 1, entries 6 and 8). Therefore, the fluorinated alcohol must be considered as a possible H-atom donor. This postulate is in agreement with Gouverneur's report that the C_α–H bond of methanol can serve as the hydrogen atom source in the related transformation.[16b,20] The beneficial effect of methyl thiosalicylate (**4**) and thiophenol could be attributed to multiple factors. Both aromatic thiols are expected to have bond dissociation energies well below TFE (BDE for **4** and thiophenol = 79 kcal mol^{-1}; BDE for TFE = 95 kcal mol^{-1}).[20b,22,23] Acridine radical **7** (E_{ox} for **7** = −0.57 V *vs.* SCE)[18c] may also be more capable of reducing thiyl radicals (E_{red} = 0.45 V *vs.* SCE)[24] compared to the trifluoromethyl ketyl radical (unknown redox couple). While it is difficult to rationalize thiol regeneration by TFE deprotonation (pK_{HA} for TFE = 12.4),[25] the trifluoromethyl ketyl radical is likely several orders of magnitude more acidic that the parent alcohol.[26] A measurable portion of the thiol mass balance is recovered as dimeric disulfides at the end of the reactions, and the catalytic turnover may be limited by inefficiencies in the previously described reduction and protonation steps.

An alternative mechanism whereby the carbon-centered β-trifluoromethyl radical (**6**) reacts directly with a thiol (not shown) is difficult to rule out. Analysis of crude reaction mixtures by ^{19}F NMR indicates several fluorinated compounds in trace quantities, but stoichiometric quantities of TFE oxidative byproducts (trifluoroacetaldehyde or trifluoroacetic acid) are not readily apparent. This could be considered circumstantial evidence for the eventual reduction of the trifluoromethyl ketyl radical (**5**), but further mechanistic studies are required.

In summation, we have demonstrated a mild and efficient method for the hydrotrifluoromethylation of alkenes using an organic photoredox catalyst. Substoichiometric quantities of methyl thiosalicylate are used as hydrogen atom donor for aliphatic alkenes and stoichiometric quantities of thiophenol are used for styrenyl alkenes. This catalyst system is tolerant of a range of functional groups. Excluding the two 1,2-disubstituted alkenes presented in Table 2 (entries 12 and 13), all products are obtained as exclusive anti-Markovnikov regioisomers. The substrate scope for the method is very broad and should provide rapid access to desirable trifluoromethylated products.

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Notes and references

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