

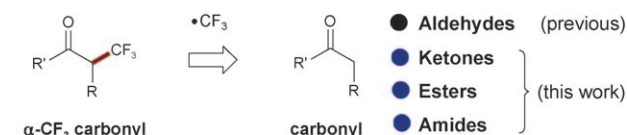
Photoredox Catalysis: A Mild, Operationally Simple Approach to the Synthesis of α -Trifluoromethyl Carbonyl Compounds

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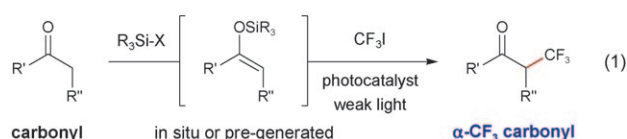
The unique physical and chemical advantages conferred by the C–F bond have led to the broad exploitation of this motif throughout the pharmaceutical,^[1] materials,^[2] and agrochemical^[3] sectors. In drug design, for instance, incorporation of polyfluorinated alkyl groups, such as CF₃ moieties, can profoundly impact the activity, metabolic stability, lipophilicity, and bioavailability of lead compounds.^[1,4] Not surprisingly, the development of methods for the production of carbonyl-based synthons bearing α -CF₃ substitution has emerged as a central objective in the field of chemical synthesis. Although important recent advances have been made toward this goal, there are currently few operationally simple methods for the conversion of enolates (or enolate equivalents) to α -trifluoromethylated carbonyl motifs. Standard alkylation methods are generally not productive, due to the negative polarization of the trifluoromethyl moiety, thus specially tailored reagents have been developed to furnish an electrophilic CF₃ equivalent.^[5] Alternatively, in recent years, a set of radical (Et₃B/O₂) and organometallic (Rh-catalyzed) approaches have been pursued to introduce the trifluoromethyl species through enolate derivatives.^[6,7] While these methods offer significant progress toward solving the “ α -CF₃ carbonyl problem”, issues of substrate scope, cryogenic temperatures, and regioselectivity of CF₃ incorporation remain prominent concerns. Herein, we describe a mild, operationally simple, room temperature method for the α -trifluoromethylation of enolsilanes, achieved through application of our recently described photoredox catalysis strategy.^[8,9] Furthermore, a one-pot protocol has been developed to enable the rapid fluoroalkylation of ketones, esters, and amides, without the isolation of pre-generated enolsilane intermediates.

Design plan: Recently, our laboratory established a new activation mode for the direct enantioselective alkylation of aldehydes. Termed photoredox organocatalysis, this novel strategy exploits a synergistic relationship between chiral amine and organometallic photoredox catalysts as a means to access electrophilic alkyl radicals that rapidly combine with enamines under ambient conditions.^[8] We postulated that the mechanistic logic underlying photoredox catalysis could be extended to devise a simple yet general approach to the α -

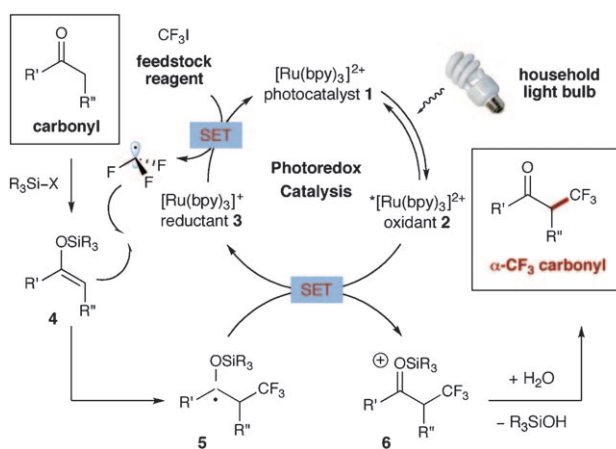
Access to novel CF₃ synthons: photoredox trifluoromethylation



Photoredox organocatalysis: weak-light •CF₃ generation



trifluoromethylation of a range of enolates or enolate equivalents [Eq. (1)]. In this context, we elected to employ enolsilanes and silylketene acetals as suitable enolic substrates, given their synthetic accessibility and well-established capacity to combine with electrophilic coupling partners.^[10] As outlined in Scheme 1, we proposed that photoexcitation of [Ru(bpy)₃]²⁺ (**1**) using a household light bulb, followed by single-electron reduction of **2** should rapidly generate [Ru(bpy)₃]⁺ (**3**).^[11] As we have previously described, this potent one-electron reductant can readily participate in single-electron transfer (SET) with CF₃I to generate the electrophilic trifluoromethyl radical, which we hoped would rapidly combine with enolsilane **4** to furnish α -silyloxy radical **5**. The oxidation potential of **5** is anticipated to be sufficiently low to allow for facile oxidation by *[Ru(bpy)₃]²⁺ (**2**) (*E*_{1/2red} = 0.79 V vs. SCE in MeCN)^[12] to generate silyloxocarbenium **6**, an



Scheme 1. Proposed mechanism for carbonyl α -trifluoromethylation.

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unstable species that should rapidly undergo hydrolysis to yield the desired α -trifluoromethylated carbonyl product.^[13]

As shown in Table 1, our initial studies confirmed the feasibility of the proposed trifluoromethylation when the *tert*-butyldimethylsilyl (TBS) substituted enolsilane **7** was

Table 1: Trifluoromethylation of enolsilanes: initial studies.

Entry	SiR ₃ ^[a]	Variation from above conditions	Yield [%]
1	TBS	none	35
2	TBS	no light	0
3	TBS	no photocatalyst	< 1
4	TBS	no base	< 1
5	TBS	+ H ₂ O ^[b]	45
6	TBS	+ H ₂ O ^[b] in THF ^[c]	53
7	TIPS	+ H ₂ O ^[b] in THF ^[c]	84
8	TIPS	+ H ₂ O ^[b] in THF ^[c] + iPr ₂ NEt ^[b,d]	94

[a] TBS: *tert*-butyldimethylsilyl; TIPS: triisopropylsilyl. [b] 1.5 equivalents. [c] THF used instead of DMF. [d] Instead of Et₃N.

exposed to CF₃I, 0.5 mol% [Ru(bpy)₃Cl₂] (**1**), and a 26 W household fluorescent lamp in the presence of 1.5 equivalents of Et₃N in DMF (entry 1, 35% yield). Importantly, no alkylation was observed when either amine base, [Ru(bpy)₃Cl₂] catalyst, or light was excluded from this protocol (entries 2–4). Early investigations further revealed the importance of employing a tertiary amine base to serve both as a sacrificial reductant and to scavenge the deleterious HI byproduct.^[11,14,15] With this in mind, the reaction efficiency was further enhanced by 1) the use of a more reducing and more basic amine base, *i*Pr₂NEt, 2) incorporation of a less acid-labile silyl group (TIPS) on the enolsilane substrate, and 3) the addition of water to aid in the capture of the putative silyl cation intermediate (entries 5–8, 45–94% yield). Indeed, the observed levels of reaction efficiency using 0.5 mol% [Ru(bpy)₃Cl₂] (**1**) with triisopropylsilyl-substituted enolsilane **7** in the presence of THF-H₂O and *i*Pr₂NEt, established these conditions as optimal for further exploration.

As revealed in Table 2, a broad range of ketone-derived enolsilanes that exhibit diverse electronic and steric properties readily participate in this new photoredox trifluoromethylation protocol. Specifically, this fluoroalkylation strategy is tolerant to enolsilane coupling partners that incorporate arenes, nitriles, and halogens (entries 1–7, 66–92%), as well as sulfides, ethers, and carbamates (entries 10–13, 59–73%). Moreover, sterically demanding substrates (entry 15, adamantyl, 84%), as well as large ring sizes (entry 14, 68%), are accommodated with minimal impact on yield. Intriguingly, we observe an important structural bifurcation in that TIPS-derived enolsilanes of aromatic ketones (entries 1–7, 66–92% yield) typically achieve higher yields, whereas for aliphatic ketones, TES-substituted enolsilanes provide generically higher yields in this trifluoromethylation protocol (entries 8–15, 59–84% yield). Interestingly, this trend is also

Table 2: Trifluoromethylation of enolsilanes: ketone scope.

Entry	Product	Yield ^[a]	
	R = 1: H	92%	4: I 83%
	2: OMe	78%	5: Br 85%
	3: CN	66%	6: Cl 85%
			7: F 80%
	8: 72% ^[b]		10: X = O ^[e] 64%
	9: 74% ^[c,d]		11: X = S ^[e] 72%
			12: R = Boc ^[e] 73%
			13: R = Cbz ^[e] 59%
	14: 68% ^[e]		15: 84% ^[b]
			16: 76%

[a] Yield of isolated product; SiR₃ = TIPS unless otherwise noted. [b] TES ether employed. [c] TBS ether employed. [d] 2.2:1 d.r. [e] With NaHCO₃ in MeCN and TES ether.

maintained in the formation of quaternary carbon centers (entry 16, 76% yield).

We next sought to examine the applicability of this trifluoromethylation strategy to other carbonyl classes, specifically silylketene acetal and N,O-acetal substrates derived from ester and amide synthons (Table 3). To our initial surprise, we observed that silylketene acetals of δ -valerolac-

Table 3: Trifluoromethylation of enolsilanes: esters and amides.

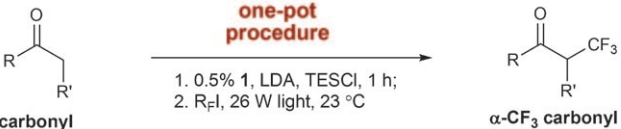
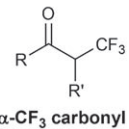
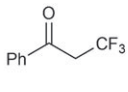
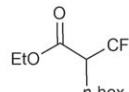
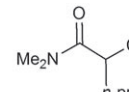
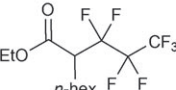
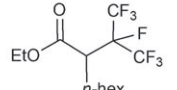
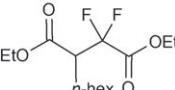
Entry	Product	Yield ^[a]	
	1: 85%		2: 86%
			3: 74% ^[b,c]
	4: 76%		5: 84% ^[b]

[a] Yield of isolated products. [b] 0.5 mol% 1-H₂O, Et₃N, isoamyl alcohol employed. [c] In MeCN.

tone underwent rapid alkylation in the presence of the 26 W fluorescent light, without the requirement of the photoredox catalyst $[\text{Ru}(\text{bpy})_3\text{Cl}_2]$ (entry 1, 85% yield). In this case we assume that a photon-induced charge-transfer complex mechanism is likely operative.^[16] Notably, these photoredox catalyst-free trifluoromethylation conditions can be successfully utilized with a range of silylketene acetals and N,O-acetals, provided monosubstituted enols are employed (entries 2 and 4, 76–86% yield). Indeed, the more sterically demanding disubstituted silylketene acetals were found to be significantly less activated toward α -trifluoromethylation using this alternative light-induced charge-transfer mechanism, providing only moderate alkylation yields after extended reaction times (24 h). Fortunately, high levels of trifluoromethylation efficiency could be re-established for these structurally encumbered substrates using our standard $[\text{Ru}(\text{bpy})_3\text{Cl}_2]$ -catalyzed photoredox conditions (entries 3 and 5, 74–84% yield).

As a demonstration of the synthetic utility of our catalytic photoredox protocol, we have developed a facile, two-step, one-flask procedure for the direct α -trifluoromethylation of a broad range of carbonyl-containing substrates (Table 4). As

Table 4: Direct, one-pot α -perfluoroalkylation of carbonyl compounds.

 carbonyl one-pot procedure 1. 0.5% 1, LDA, TESCl, 1 h; 2. $\text{R}_\text{F}\text{I}$, 26 W light, 23 °C  α-CF_3 carbonyl		
 1: α-CF_3 ketone 76% yield^[a]	 2: α-CF_3 ester 78% yield	 3: α-CF_3 amide 67% yield
 4: α-perfluoropropyl ester 83% yield	 5: α-perfluoro isopropyl ester 75% yield	 6: α-difluoro diester 92% yield

[a] TBSOTf, $i\text{Pr}_2\text{EtN}$ used instead of TESCl, LDA.

shown, the enolsilane is first formed in situ in the presence of photocatalyst **1**, silylating agent, and an appropriate base. The resultant enolsilane (without isolation or purification) is then exposed to α -trifluoromethylation conditions to generate the target α -alkylation adduct in a single reaction vessel. This procedure was found to be applicable to ketone, ester, and amide substrates, delivering the desired products with good overall efficiency (entries 1–3, 67–78% yield).

Importantly, this one-pot protocol is also amenable to a range of α -fluoroalkylations. When subjected to the outlined procedure, ethyl caprylate underwent perfluoroalkylation (n -propyl and isopropyl) and difluoroalkylation with excellent levels of reaction efficiency (entries 4–6, 75–92% yield).

In summary, we have introduced a new photoredox-based method that allows for facile α -trifluoromethylation of

enolsilanes, silylketene acetals and N,O-acetals derived from a broad range of ketone, ester, and amide substrates. Moreover, we have devised a one-pot protocol that enables the rapid and trivial installation of the trifluoromethyl moiety, as well as other fluoroalkyl groups, directly to a wide array of carbonyl systems. We expect this novel protocol to be of broad utility in the synthesis of biologically active organo-fluorine containing medicinal agents.

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