## COMMUNICATION

# Photoorganocatalysed and visible light photoredox catalysed trifluoromethylation of olefins and (hetero)aromatics in batch and continuous flow†

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Trifluoromethylation of olefins and (hetero)aromatics with sodium triflinate as CF₃ source and readily accessible benzophenone derivatives as photosensitisers has been developed in batch and flow. The use of an iridium-based photocatalyst enables the trifluoromethylation to proceed under visible light irradiation.

Olefins are important building blocks for the synthesis of complex molecules, as they can readily be functionalised by reductive or oxidative methods to give rise to other functional groups such as epoxides, alcohols, amines and halides.[1] In recent years, direct trifluoromethylation of olefins has received increased attention,[2] as molecules with fluorinated groups show different properties compared to their hydrogenated counter-parts. A change in $pK_a$, lipophilicity and conformation can be achieved which is of interest in agrochemical and medical research.[3] Enormous work had been carried out in the field of trifluoromethylation of organic molecules[4] and many reports describe the oxidative trifluoromethylation of olefins and aromatic compounds using gaseous $CF_3I$,[5] corrosive and volatile trifluoromethanesulfonyl chloride ($CF_3SO_2Cl$)[6] or more complex electrophilic reagents such as Umemoto's reagent or Togni's reagent.[7] The reductive trifluoromethylation has been less explored,[8a,b] especially using sodium triflinate (Langlois' reagent, $CF_3SO_2Na$), one of the cheapest and most convenient reagents for trifluoromethylation.[8c]

In the late 80's and beginning of 90's, electrochemical oxidation of trifluoroacetic acid and addition of $CF_3$ onto activated olefins was demonstrated.[9] In 2002, Langlois performed the trifluoromethylation of unactivated olefins with potassium triflinate under electrochemical conditions.[10] More recently, $CF_3I$ as a source of $CF_3$ radical was used for a ytterbium/organoboron-promoted addition to unsaturated acyl-oxazolidinones under oxidative conditions, with exclusive β-selectivity.[11] The β-trifluoromethylation of chalcones using S-(trifluoromethyl)diphenylsulfonium triflate was also achieved.[12] Furthermore, the photocatalytic addition of sodium triflinate onto unactivated olefins or heteroaromatics was developed.[13,14] Several other groups performed the transition-metal-catalysed or photoredox-catalysed trifluoromethylation of unactivated or electron-rich olefins using $TMSCF_3$, Umemoto's reagent, or Togni's reagent as $CF_3$ radical source.[2]

Electron-deficient olefins were much less explored, as the $CF_3$ radical is widely considered as electrophilic, destabilised σ-type radical. As such electron-deficient olefins should not readily react with the $CF_3$-radical.
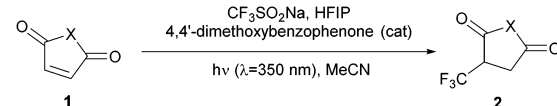
As part of our interest in synthesis of fluorinated organic molecules[15] as well as in photoorgano- photoredox-catalysis,[16–18] we decided to explore the trifluoromethylation of electron-deficient olefins and (hetero)aromatics. In 2000, we demonstrated the radical addition of tertiary amines onto furanone derivatives under near-UV irradiation ($\lambda$ = 350 nm) using 4,4′-dimethoxybenzo-phenone as a stable sensitiser.[17a] Based on these results and encouraged by a renewal of interest in near-UV-light photocatalysed transformations,[19] we wondered whether sodium triflinate could form $CF_3$ radicals under similar conditions. The successful accomplishment of such a trifluoromethlyation would provide a simple, economical and straightforward introduction of a $CF_3$-group under mild reaction conditions.

After extensive reaction optimisation, we discovered that simply mixing equimolar amounts of N-phenylmaleimide and sodium triflinate in acetonitrile, in the presence of 10 mol% of 4,4′-dimethoxybenzophenone and hexafluoroisopropanol (HFIP) as additive gave the desired hydrotrifluoromethylated product in good yields after only 6 hours.[20]

Regarding the scope of the reaction, we were pleased to observe that various functional groups including halides, esters and methoxy groups were tolerated on the aryl part of the maleimide derivative (Table 1). The position of the group was found to be of importance, as neither N-(p-nitrophenyl)- nor N-(p-methoxyphenyl)maleimide partook the reaction, but in contrast, both electron-withdrawing and electron-donating groups

[a] Institute of Organic Chemistry, RWTH Aachen, Landoltweg 1, 52074, Aachen, Germany. E-mail: Magnus.Rueping@rwth-aachen.de, quentin.lefebvre@ens-lyon.org

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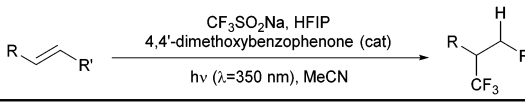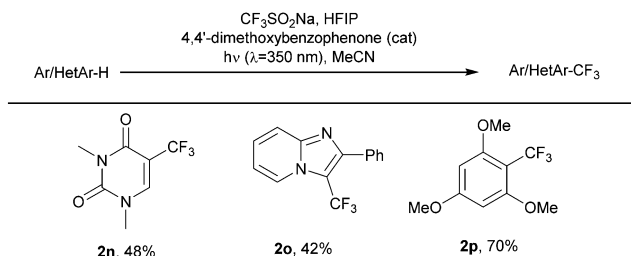**Table 1**  Scope of the trifluoromethylation of electron-deficient olefins[a]



| Product | X | Yield[b] (%) |
|---|---|---|
| **2a** | PhN | 61 |
| **2b** | 4-Cl-PhN | 39 |
| **2c** | 3-Br-PhN | 47 |
| **2d** | 2-Me-PhN | 61 |
| **2e** | 2-CF$_3$-PhN | 49 |
| **2f** | 2-CO$_2$Me-PhN | 48 |
| **2g** | 2-OMe-PhN | 27 |
| **2h** | MeN | (52) |
| **2i** | $^n$BuN | (42) |
| **2j** | BnN | 41 (55) |
| **2k** | CyN | (41) |
| **2l** | O | (48) |
| **2m** | Dimethyl maleate | (51) |

[a] Reaction conditions: 0.1 mmol **1**, 1.0 equiv. sodium triflinate, 0.1 equiv. 4,4′-dimethoxybenzophenone, 5 equiv. hexafluoroisopropanol in 5 mL of dry, degassed acetonitrile, irradiated for 6 h at 350 nm in a Rayonet reactor. [b] Yield of isolated products after column chromatography. Yields in brackets are determined by NMR spectroscopy using ethyl trifluoroacetate as internal standard.

were tolerated when placed at the *ortho* position. Aliphatic maleimides reacted equally well, giving the trifluoromethylated products in good yields. Maleic anhydride and dimethyl maleate were also competent substrates.

To our delight, prototypical heteroaromatic substrates also underwent the reaction (Scheme 1).

Reactions in continuous flow can have numerous advantages over standard batch reactions, in particular in the field of photochemistry.[21] Therefore, we decided to compare the kinetics of trifluoromethylation of *N*-phenylmaleimide in batch and flow. A spectacular improvement was observed using a photo-flow setup. Complete conversion was observed after only 30 min, while six hours are needed for batch reaction (see ESI†). This rate-enhancement in photo-flow was observed for different substrates. In all cases, conversion was complete after 30 minutes and the products were isolated in comparable or even better yields compared to the reaction in batch (Table 2). Additionally, **2a** could easily be reduced in 70% yield to give *N*-phenyl-3-trifluoromethylpyrrolidine **3a**, an ubiquitous motif in drugs and radiotracers and described in more than ten patents (Scheme 2).[22,23]



**Scheme 1**  Scope of the trifluoromethylation of aromatic molecules. Yield of isolated products after column chromatography. Reaction conditions: see text and ESI.†

**Table 2**  Comparison of batch and flow conditions[a]



| Product | Method | Reaction time | Yield[b] (%) |
|---|---|---|---|
| **2a** | Batch | 6 h | 61 |
| **2a** | Flow | 30 min | 54 |
| **2b** | Batch | 6 h | 39 |
| **2b** | Flow | 30 min | 47 |
| **2g** | Batch | 6 h | 27 |
| **2g** | Flow | 30 min | 49 |

[a] Reaction conditions: see ESI. [b] Isolated yield after column chromatography.
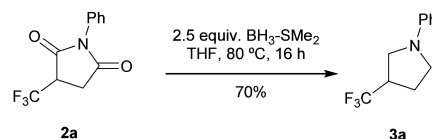


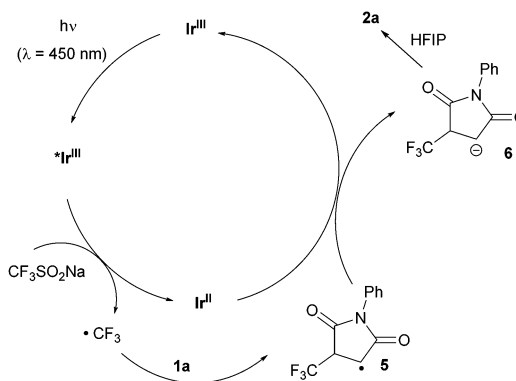**Scheme 2**  Derivatization of the trifluoromethylated product.

Subsequently, we performed several experiments to get an insight into the reaction mechanism and more specifically to understand the role of HFIP.[24] When stoichiometric amounts of 4,4′-dimethoxybenzophenone and sodium triflinate were irradiated in acetonitrile, the product of addition of CF$_3$ onto the carbon–oxygen bond was obtained in 11–13% yield both in presence and absence of HFIP, and no reaction was observed in the dark. This observation rules out a proton-coupled electron transfer mechanism for the oxidation of sodium triflinate. No product of addition onto the maleimide derivative was observed in the absence of sensitizer, without HFIP or without light.[25] The addition of one equivalent of TEMPO completely inhibited the reaction, but no TEMPO-CF$_3$ was observed. This can be rationalised considering the potential *vs.* SCE of the species in solution: $E_{ox}$(sodium triflinate) = 1.05 V, $E_{ox}$(TEMPO) = 0.76 V, $E_{1/2}^{red*}$ (4,4′-dimethoxybenzophenone) = 1.25 V.[26] Therefore, TEMPO might compete with sodium triflinate for oxidation by the photosensitiser.[27] This confirms that the reaction proceeds *via* a redox process between sodium triflinate and the sensitiser. We previously reported the addition of isopropanol onto furanone derivatives under photoorganocatalysis, but when we repeated this reaction using HFIP instead of isopropanol, no product was obtained. Therefore, a mechanism including a hydrogen abstraction from the tertiary carbon of HFIP is precluded. As reports on the hexafluoroisopropoxy radical are almost non-existent,[28] we believe that HFIP acts as a proton donor and not as a hydrogen atom donor (Scheme 3). 4,4′-Dimethoxybenzophenone is excited by the 350 nm light and intersystem crossing rapidly occurs to give the excited triplet state. Redox reaction with sodium triflinate gives the CF$_3$ radical with release of SO$_2$. This radical adds onto the maleimide derivative while the ketyl radical is protonated by HFIP. Subsequent hydrogen transfer regenerates the sensitiser and gives the hydrotri-fluoromethylated product. The reaction between the two reactive intermediates at low concentration is favored by the fact that the ketyl radical is particular stable as it was previously discussed.[16f,17c]
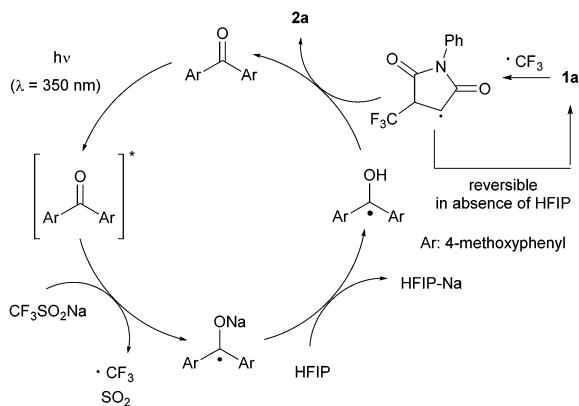
**Scheme 3** Proposed mechanism for the photoorganocatalysed trifluoromethylation of electron-deficient olefins.



**Scheme 4** Proposed mechanism for the photoorganocatalysed trifluoromethylation of electron-deficient olefins.

In order to make this transformation more broadly applicable, we wondered whether it could also be performed under visible light irradiation, using an appropriate organo- or metal-based photocatalyst. Using Mes-AcrBF$_4$ (Fukuzumi's catalyst) under irradiation at 450 nm led to incomplete conversion after 24 h and the product was formed in only 11% yield according to $^{19}$F NMR (Table 3).

Pleasingly, the highly oxidising iridium photocatalyst Ir[dF(CF$_3$)-ppy]$_2$(dtbbpy)PF$_6$ **4** ($E_{1/2}^{red*}$ (*Ir$^{III}$/Ir$^{II}$) = 1.21 V *vs.* SCE)$^{29}$ was as efficient as 4,4'-dimethoxybenzophenone, delivering the expected products in comparable or higher yields with longer reaction times but lower catalyst loadings. Remarkably, this protocol was highly suitable for heteroaromatic substrates, giving the trifluoromethylated uracil derivative **2n** in 72% yield, compared to 48% under the previously optimised reaction conditions. To investigate the mechanism of this reaction, we attempted the hydrotrifluoromethylation of **1a** without HFIP. Although the conversion was not complete, **2a** was still obtained after work-up in 26% yield. Therefore, we believe that this reaction proceeds as depicted in Scheme 4: upon irradiation at 450 nm, the iridium photocatalyst **4** reaches its excited state, which oxidizes sodium

triflinate to give a CF$_3$ radical and the corresponding Ir$^{II}$ species. After addition of the CF$_3$ radical onto the maleimide derivative, the resulting radical **5** is reduced by the Ir$^{II}$ to generate **4** and a maleimide anion **6**, which can be protonated by HFIP to give the final product **2a**. In the absence of HFIP, the anion does not react as fast as its radical counterpart and can be protonated during work-up.

In summary, we have developed the first photoorganocatalytic trifluoromethylation of electron-deficient olefins using a very simple and inexpensive benzophenone derivative as organic photocatalyst. These conditions could be directly used without further optimisation for the trifluoromethylation of (hetero)aromatics, thus giving an unified method for the direct trifluoromethylation of organic molecules using sodium triflinate as a cheap and safe alternative to other CF$_3$ radical sources such as CF$_3$I or CF$_3$SO$_2$Cl. The use of a photo-flow setup led to dramatically decreased reactions times, which shows the potential of our method for rapid scale-up and in-line synthesis. We also demonstrated that this transformation proceeds with similar or even higher yields using visible light and an iridium-based photocatalyst. Thus, the new methodology will find applications in drug discovery and in the synthesis of complex fluorinated molecules.

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**Table 3** Reactions using visible light and other photoredox catalysts$^a$



| Product | Photocatalyst (mol%) | Reaction time (h) | Yield$^b$ (%) |
|---|---|---|---|
| **2a** | Mes-AcrBF$_4$ (10) | 24 | (11)$^c$ |
| **2a** | Ir[dF(CF$_3$)ppy]$_2$ (dtbbpy)PF$_6$ **4** (1) | 16 | 62 |
| **2b** | **4** (1) | 16 | 54 |
| **2d** | **4** (1) | 18 | 66 |
| **2j** | **4** (1) | 18 | 62 |
| **2k** | **4** (1) | 17 | 60 |
| **2n** | **4** (1) | 18 | 72$^d$ |

$^a$ Reaction conditions: 0.1 mmol **1**, 1.0 equiv. sodium triflinate, 0.1 or 0.01 equiv. photocatalyst, 5 equiv. hexafluoroisopropanol in 5 mL of dry, degassed acetonitrile, irradiated for the indicated time at 450 nm (blue LEDs). $^b$ Isolated yield after column chromatography. Yields in brackets are determined by NMR spectroscopy using ethyl trifluoroacetate as internal standard. $^c$ Incomplete conversion. $^d$ 3 equiv. sodium triflinate.

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