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Marina Briand, Linh Thai, Flavien Bourdreux, Nicolas Vanthuyne, Xavier Moreau, et al.. Remote Radical Trifluoromethylation: A Unified Approach to the Selective Synthesis of γ -Trifluoromethyl α,β -Unsaturated Carbonyl Compounds. *Organic Letters*, 2022, 24 (51), pp.9375-9380. 10.1021/acs.orglett.2c03676 . hal-03936896

HAL Id: hal-03936896

<https://hal.science/hal-03936896>

Submitted on 14 Mar 2023

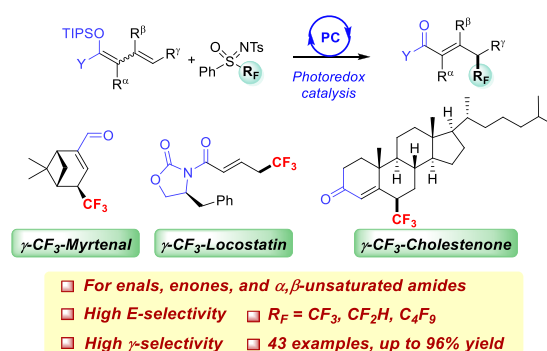
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Remote Radical Trifluoromethylation: A Unified Approach to the Selective Synthesis of γ -Trifluoromethyl α,β -Unsaturated Carbonyl Compounds

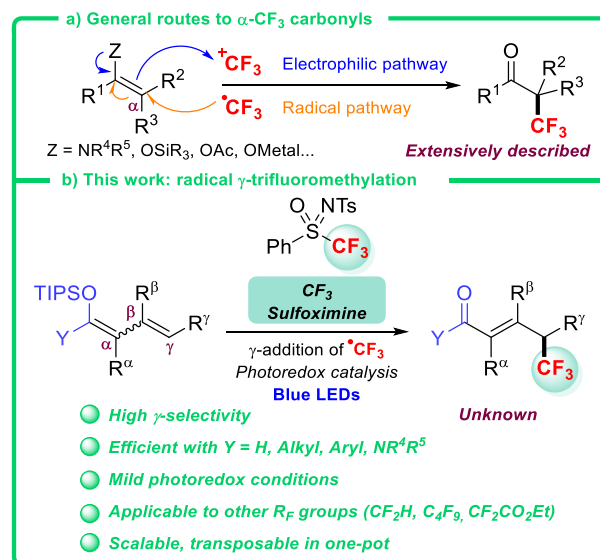
Marina Briand, Linh D. Thai, Flavien Bourdreux, Nicolas Vanthuyne, Xavier Moreau, Emmanuel Magnier, Elsa Anselmi, and Guillaume Dagousset*

ABSTRACT: Site-selective trifluoromethylation of silyl dienol ethers derived from α,β -unsaturated aldehydes, ketones, and amides was achieved for the first time in the remote γ position. This photoredox catalyzed process is quite general to compounds bearing many functionalities and is applicable to the late-stage functionalization of biorelevant molecules. The use of *S*-perfluoroalkyl sulfoximines as $\cdot R_F$ radical sources enables the generalization of the reaction to other perfluoroalkyl groups ($R_F = CF_2H, C_4F_9$). Importantly, an unprecedented enantioselective $C(sp^3)-H$ perfluoroalkylation process is disclosed.



The incorporation of a CF_3 group into organic molecules imparts profound changes in their physicochemical and biological properties. As a result, the number of bioactive molecules with a trifluoromethyl or perfluoroalkyl group has increased exponentially in the past 20 years.¹ Undoubtedly, this fact accounts for the increasing number of methods which have recently been reported for the trifluoromethylation of various organic scaffolds.² Among them, the synthesis of α - CF_3 carbonyl compounds from the corresponding enolate equivalents (silyl enol ether, enol acetate, metal enolate, enamine) has been thoroughly investigated, under either electrophilic³ or radical-based⁴ conditions (Scheme 1a). Surprisingly, despite these extensive studies, the corresponding vinylogous trifluoromethylation of α,β -unsaturated carbonyl compounds in the γ position remains almost unprecedented. Such γ -functionalization of vinylogous dienolate-type substrates is indeed highly challenging, in terms of both site selectivity (both α and γ sites are reactive) and enantioselectivity (the γ site is located in a more distal position). To the best of our knowledge, a single example was described on a very peculiar skeleton: Umemoto and co-workers reported the electrophilic trifluoromethylation of a bicyclic silyl dienol ether, leading to a γ - CF_3 enone with a sulfonium as reagent.⁵ We initially tried to extend the scope of this methodology on more classical substrates. With standard linear silyl dienol ethers as well with steroid derivatives, many unidentified fluorinated byproducts were produced and the transformation occurred with a very low yield (see Supporting Information (SI) for details). This may be due to the poor

Scheme 1. State-of-the-Art



nucleophilic character of silyl dienol ethers⁶ combined with the difficulty to access a strong CF₃⁺ electrophile.⁷

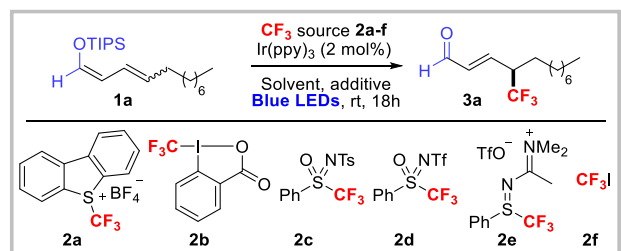
Consequently, the γ -trifluoromethylation of α,β -unsaturated carbonyl compounds still faces many major unsolved challenges: (i) No versatile trifluoromethylation protocol for the synthesis of γ -CF₃ enals or γ -CF₃ α,β -unsaturated amides has been reported so far; (ii) the trifluoromethylation process should occur with high regioselectivity for the γ position, as well as high *E*-diastereoselectivity; (iii) A highly ambitious enantioselective version is still unknown to date. Instead of using a classical electrophilic pathway, we reasoned that a completely unexplored radical approach could fundamentally bring solutions to all these issues.

Considering the mild reaction conditions provided by photoredox catalysis⁸ and the ability of silyl dienol ethers to efficiently trap radicals in the γ position,⁹ a photocatalyzed trifluoromethylation method is expected to selectively afford the desired γ -CF₃ adduct for all kinds of α,β -unsaturated carbonyl compounds (Scheme 1b). Herein, we report an unprecedented methodology for the general and unified synthesis of γ -CF₃ α,β -unsaturated aldehydes, ketones, and amides under mild photoredox-catalyzed conditions. Importantly, preliminary results on an unknown enantioselective organocatalytic/photoredox dual catalytic protocol are also disclosed for the first time.

We initially chose triisopropylsilyl (TIPS) dienol ether **1a** derived from (*E*)-2-dodecenal as the model substrate. Radical trifluoromethylation of **1a** under photoredox-catalyzed conditions with Umemoto's reagent **2a** afforded the expected product **3a** in 69% NMR yield with complete site selectivity (entry 1). Other CF₃ sources **2b–2f** were then tried (entries 2–6). While Togni's reagent **2b** and CF₃I **2f** were inefficient, sulfoximine-based reagents **2c–2e**, readily produced in multi-gram scale,¹⁰ were quite promising.¹¹ Notably, *N*-tosyl *S*-CF₃ sulfoximine **2c** compared to reagent **2a** showed an equally high level of efficiency. Moreover, sulfoximines bearing other perfluoroalkyl groups are readily available which offers an advantage over other reagents. Reagent **2c** was therefore selected for the further optimization of the process. Screening other parameters (additives, solvent, stoichiometry, concentration) led to the optimal conditions providing **3a** in 68% isolated yield after 18 h of irradiation (entry 7, see SI for more details). In addition, a one-pot two-step synthesis of γ -CF₃-dodecenal **3a** from (*E*)-2-dodecenal could also be performed, with almost no erosion of the overall yield (entry 10). It is also worth noting that **3a** was obtained in all cases as one single *E* isomer, even though substrate **1a** was engaged as a mixture of diastereomers. Other silylated groups were also tested with no impact on site selectivity, and the TIPS group was selected for stability reasons.

Once our optimal conditions were determined, we turned our attention to the application scope of this new methodology (Scheme 2). Various α -unbranched γ -CF₃ enals **3a–3h** bearing a large array of functional groups (alkene, ester, nitrile, epoxy, Br, phthalimido) were efficiently prepared. α -Aryl and α -alkyl substrates were also successfully engaged in this photoredox-mediated protocol, leading to the corresponding trifluoromethylated enals **3i–3m** in up to 72% yield. In some cases, the isolated yields were lower than the corresponding ¹⁹F NMR yields; this decrease in yield could be attributed to either the high volatility of the fluorinated enals or the difficulty in separating them from triisopropylsilanol (TIPSOH), produced as a byproduct during the process. Nonetheless, it is worth

Table 1. Optimization Studies for the γ -Trifluoromethylation of Silyl Dienol Ether **1a^a**



Entry	CF ₃ source	Solvent	Additive	Yield (%) ^b
1	2a	CH ₂ Cl ₂	K ₂ HPO ₄	69
2	2b	CH ₂ Cl ₂	K ₂ HPO ₄	3
3	2c	CH ₂ Cl ₂	K ₂ HPO ₄	65
4	2d	CH ₂ Cl ₂	K ₂ HPO ₄	51
5	2e	CH ₂ Cl ₂	K ₂ HPO ₄	23
6	2f	CH ₂ Cl ₂	K ₂ HPO ₄	6
7 ^{c,d}	2c	CH ₂ Cl ₂ /MeCN	–	77 (68) ^e
8 ^{d,f}	2c	CH ₂ Cl ₂ /MeCN	–	–
9 ^{c,d,g}	2c	CH ₂ Cl ₂ /MeCN	–	–
10 ^h	2c	CH ₂ Cl ₂ /MeCN	–	60

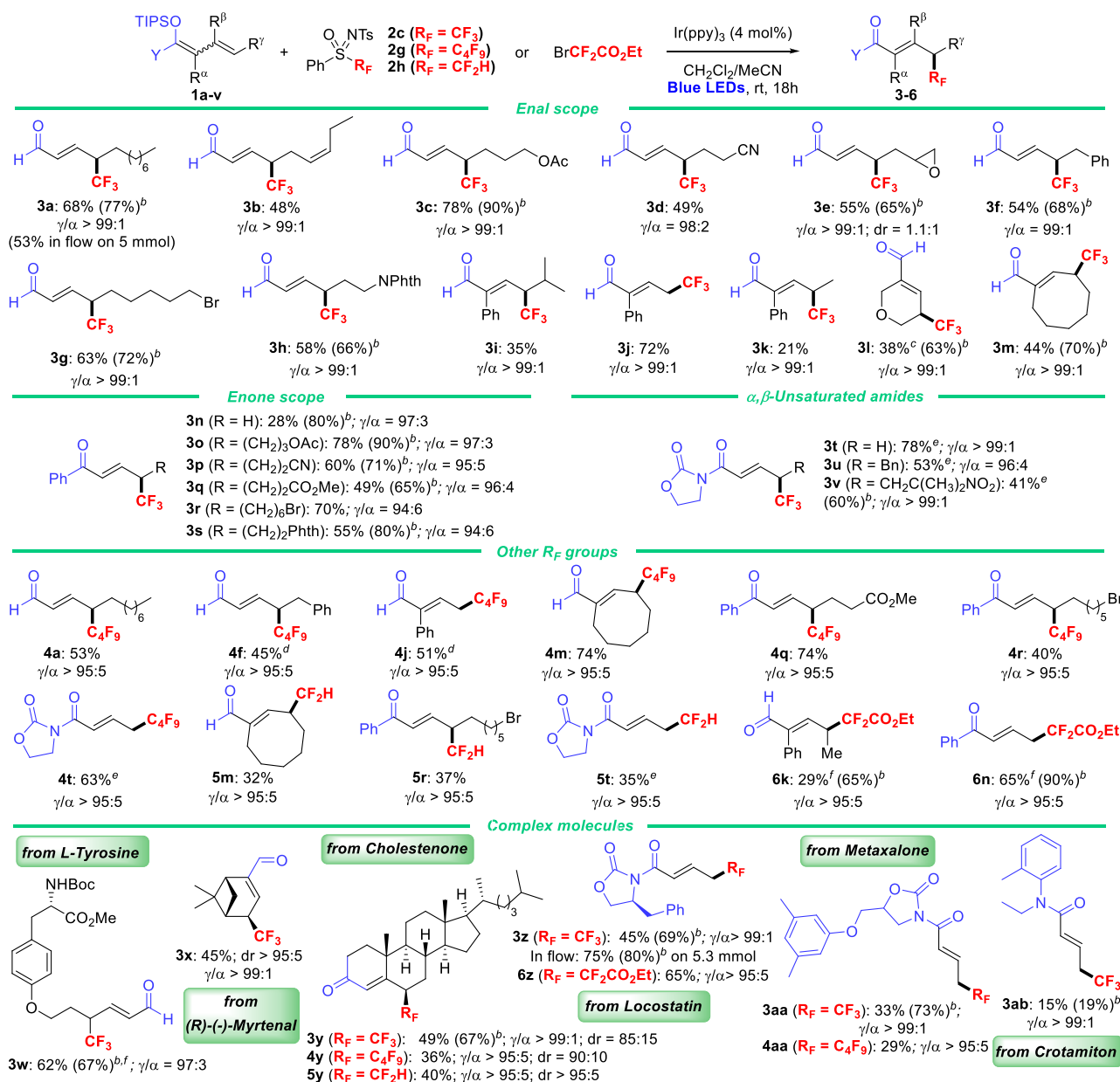
^aGeneral conditions: **1a** (0.15 mmol), **2** (0.225 mmol), Ir(ppy)₃ (0.003 mmol), additive (0.3 mmol) in 1.5 mL of solvent irradiated with 5 W blue LEDs at rt for 18 h. ^bYields determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard. ^cWith 4 mol % of Ir(ppy)₃. ^dIn 3 mL of solvent. ^eYield into brackets refers to chromatographically pure product. ^fWithout Ir(ppy)₃. ^gWithout irradiation. ^hTwo-step one-pot procedure from (*E*)-2-dodecenal. See SI for more details.

noting that both α -substituted and α -unsubstituted enals were formed with almost perfect site selectivity ($\gamma/\alpha > 98:2$ in all cases).

To demonstrate the synthetic utility of this novel photocatalyzed process, an experiment on 5 mmol of substrate **1a** was performed using continuous-flow techniques. With a flow rate of 0.5 mL·min⁻¹ (residence time of 20 min), 575 mg of γ -CF₃ enal **3a** could be isolated, showing the simplicity to scale up the process. With these first results for enals in hand, we next attempted to apply our method for the synthesis of other γ -CF₃ carbonyl compounds. Pleasingly, various γ -CF₃ enones **3n–3s** and γ -CF₃ α,β -unsaturated imides **3t–3v** were successfully produced in good yields.^{12,13} Once again this mild photocatalyzed process was perfectly compatible with many functionalities (ester, nitrile, nitro).

Having established the general and versatile character of our new methodology to access γ -CF₃ α,β -unsaturated compounds, we then turned our attention to the introduction of other relevant fluoroalkyl moieties (R_F).¹⁴ We were pleased to see that *S*-perfluorobutyl sulfoximine **2g** and *S*-difluoromethyl sulfoximine **2h** (Hu's reagent)¹⁵ readily reacted under our optimized photoredox conditions: the corresponding compounds **4–5** were isolated in up to 74% yield with equally high γ -selectivity. Furthermore, ethyl bromodifluoroacetate smoothly reacted with silyl dienol ethers **1k,n**, furnishing the desired γ -difluoroacetylated enal **6k** and enone **6n**, respectively. A key feature of photocatalyzed methodologies consists of the late-stage functionalization of complex molecules, a very useful tool in modern drug discovery.¹⁶ Pleasingly, compounds **1w–1ab** derived from *L*-tyrosine, (*R*)-(-)-myrtenal, 4-cholesten-3-one, Locostatin, Metaxalone, and Crotamiton

Scheme 2. Reaction Scope for the γ -Trifluoromethylation/ γ -Perfluoroalkylation of α,β -Unsaturated Carbonyls^a



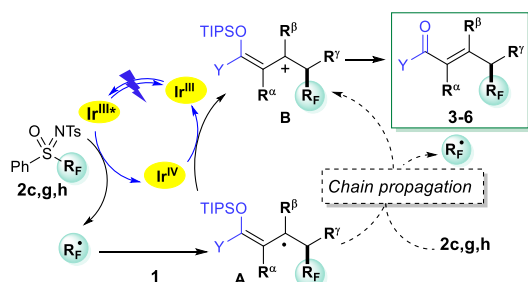
^aGeneral conditions: **1** (0.15 mmol), **2** (0.225 mmol), Ir(ppy)₃ (0.006 mmol), in 3 mL of CH₂Cl₂/MeCN irradiated with SW blue LEDs at rt for 18 h. The γ/α ratio was determined by analysis of ¹⁹F NMR spectra of the crude reaction mixtures. Unless otherwise noted, given yields refer to chromatography pure products. ^bYields into brackets refer to ¹⁹F NMR yield of product **3–6** using PhOCF₃ as internal standard. ^cLow isolated yield due to the volatility of the product. ^dYield of the corresponding alcohol isolated after reduction with NaBH₄. See ESI for more details. ^eReaction performed with 18W blue LEDs irradiation. ^fReaction performed with 2 equiv of K₂CO₃ as additive.

were successfully transformed into the corresponding γ -R_F α,β -unsaturated compounds.

As both light and photocatalyst were needed for the reaction (see Table 1, entries 8–9), a mechanism involving a radical pathway was assumed. To verify this hypothesis, the redox potential of **2c** was measured using cyclic voltammetry. The found value (−1.73 V vs SCE) indicated that **2c** may be reduced by the excited state of Ir(ppy)₃ ($E_{1/2}^{\text{red}} = -1.73$ V vs SCE), following an oxidative quenching photoredox cycle. This was confirmed by Stern–Volmer luminescence quenching experiments which showed that Ir*(ppy)₃ was efficiently quenched by sulfoximine **2c** (see SI for more details). Based on

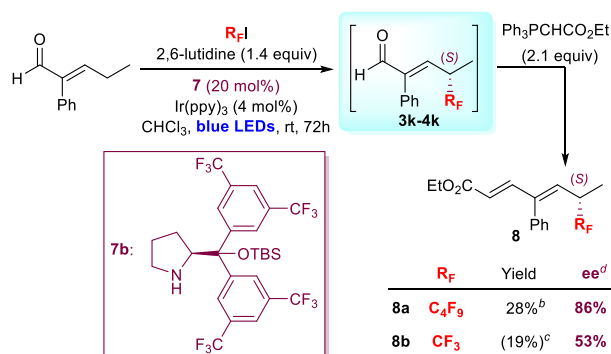
these observations, we propose a mechanism in which the perfluoroalkyl radical $\cdot\text{R}_F$, generated by one-electron reduction from the corresponding sulfoximine, adds onto substrate **1** in a γ -selective manner, leading to the stabilized allylic radical intermediate **A** (Scheme 3). The latter is then oxidized by Ir^{IV}, regenerating the ground-state photocatalyst Ir(ppy)₃ together with the formation of the corresponding carbocation **B**, which rapidly evolves into the desired product **3–6**. The measured quantum yield $\Phi = 0.25$ suggested that an alternative radical chain mechanism (generation of $\cdot\text{R}_F$ from reduction of **2** by intermediate **A**) was not the major pathway operating in this process.

Scheme 3. Proposed Mechanism



It is worth noting that, for most of these new γ - R_F α,β -unsaturated compounds 3–6, the perfluoroalkyl group is attached to a stereogenic carbon atom. Given the importance of chiral fluorinated molecules,¹⁷ we next sought to examine the possibility of controlling the enantioselectivity of our new perfluoroalkylation process under a dual photoredox/organocatalytic system. However, if photoredox/enamine dual catalysis has been widely used for enantioselective α -functionalization of aldehydes,¹⁸ including α -perfluoroalkylation,^{4d,e} the analogous photoredox/dienamine dual catalysis remains largely unexplored and much more challenging.¹⁹ Initial attempts with 2-phenyl-2-pentalen as the model substrate and sulfoximine **2g** as the $\cdot C_4F_9$ source failed to give any product. However, by switching to C_4F_9I as the radical source and by adapting the reaction conditions (see SI for complete optimization table), we were delighted to see that the corresponding γ - C_4F_9 enal **4k**, subsequently transformed into ester **8a** in order to avoid any partial racemization, was produced with a high level of enantioselectivity (86% ee, Scheme 4). The absolute(S) configuration of the major

Scheme 4. Enantioselective Remote Perfluoroalkylation of Enals^a



^aSee SI for optimization details. ^bYield over two steps. ^c¹⁹F NMR yield of the first step using PhOCF₃ as internal standard. ^dEnantiomeric excess was determined by chiral HPLC analysis.

enantiomer was assigned by comparison of the experimental ECD (electronic circular dichroism) spectra with DFT calculations (see SI for more details). A similar reaction with CF₃I led to product **8b** with an erosion of enantioselectivity (53% ee), most probably due to the smaller size of the CF₃ radical. However, this represents the first example of a catalytic enantioselective C–H remote perfluoroalkylation reaction.

In conclusion, we have developed a unified approach for the synthesis of γ - R_F α,β -unsaturated compounds. The key characteristics of this mild photoredox methodology are as

follows: (i) it occurs with perfect *E*-diastereoselectivity and very high γ regioselectivity; (ii) it is applicable to a wide range of functionalized enals, enones, and α,β -unsaturated amides, including many complex biorelevant molecules; (iii) it is compatible with a series of perfluoroalkyl groups ($R_F = CF_3, CF_2H, C_4F_9, CF_2CO_2Et$). Importantly, an enantioselective version was achieved for the first time by using a dual photoredox/dienamine catalytic system. Further developments in the field of remote organocatalytic functionalizations are currently underway and will be reported in due course.

ABBREVIATIONS

dr, diastereomeric ratio; ECD, electronic circular dichroism; EDA, electron donor–acceptor; ee, enantiomeric excess; NHC, *N*-heterocyclic carbene; SCE, saturated calomel electrode

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