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Organofluorine Compounds

Radical Trifluoroacetylation of Alkenes Triggered by a Visible-Light-Promoted C–O Bond Fragmentation of Trifluoroacetic Anhydride

*Kun Zhang[+], David Rombach[+], Nicolas Yannick Nötel, Gunnar Jeschke, and Dmitry Katayev**

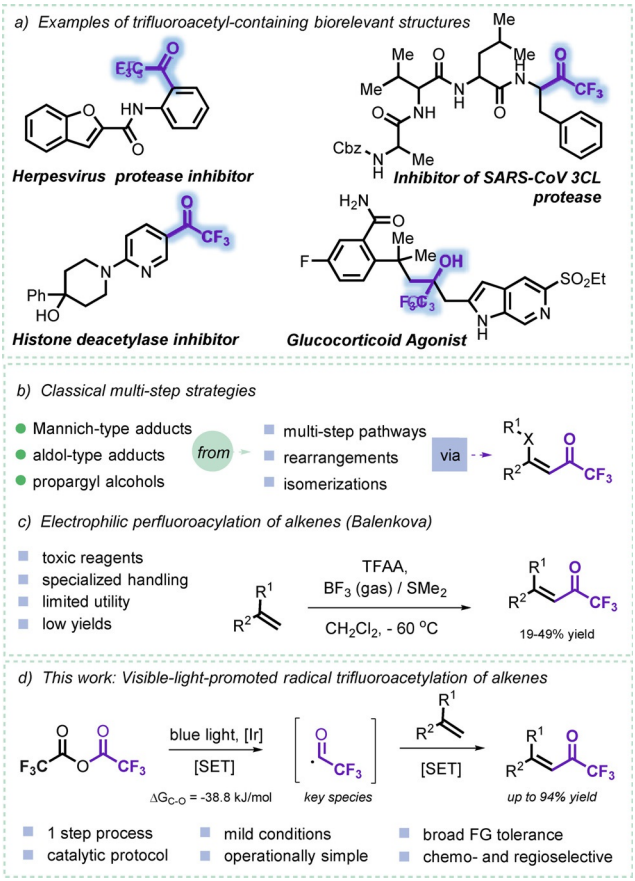
Dedicated to Professor Peter Kündig on the occasion of his 75th birthday

Abstract: *We report a mild and operationally simple trifluoroacylation strategy of olefines, that utilizes trifluoroacetic anhydride as a low-cost and readily available reagent. This light-mediated process is fundamentally different from conventional methodologies and occurs through a trifluoroacyl radical mechanism promoted by a photocatalyst, which triggers a C–O bond fragmentation. Mechanistic studies (kinetic isotope effects, spectroelectrochemistry, optical spectroscopy, theoretical investigations) highlight the evidence of a fleeting CF_3CO radical under photoredox conditions. The trifluoroacyl radical can be stabilized under CO atmosphere, delivering the trifluoroacetylation product with higher chemical efficiency. Furthermore, the method can be turned into a trifluoromethylation protocol by simply changing the reaction parameters. Beyond simple alkenes, this method allows for chemo- and regioselective functionalization of small-molecule drugs and common pharmacophores.*

Introduction

Direct incorporation of the trifluoromethyl (CF_3) group into the core of the molecules has been extensively studied and is an important synthetic strategy in the design of new pharmaceutical agents.[1–11] Advances in this field have been made possible by the availability of various radical,[12–15] nucleophilic[16–18] and electrophilic trifluoromethylation reagents that can efficiently be activated under mild and catalytic conditions.[19–21]

Trifluoromethyl ketones[22,23] are a special subset of fluorinated compounds that have relevant applications in biological and medicinal chemistry.[24–27] Owing to the high electronegativity of the CF_3 group, the electrophilic carbonyl center of trifluoromethyl ketones can undergo various transformations as well as promote the molecule binding affinity with the biological target.[28] Recent studies have shown that these functionalized derivatives act as potential enzyme inhibitors towards Herpesvirus protease,[29] Histone deacetylase,[30] SARS-CoV 3CL protease[31,32] and serve as well as a precursor for clinically used glucocorticoid receptor agonists[33] (Scheme 1 a). In the context of synthetic chemistry, α,β-unsaturated trifluoromethyl ketones are indispensable building blocks with an inherent ability to react with bifunctional nucleophiles in synthetic sequences involving trifluor-



Scheme 1. Motivation and design of trifluoroacylation reaction. [a] examples of CF_3CO-containing biorelevant molecules; [b] multi-step strategies; [c] electrophilic process; [d] this work.

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omethyl- and trifluoroacyl-containing heterocycles, medicinal compounds, and fluorinated analogues of natural products.[34]

Despite the development of methods for the construction of CF_3-containing compounds, that has been an area of great interest, the preparation of α,β-unsaturated trifluoromethyl ketones remains a fundamental challenge for synthetic chemists. Traditional methods for the synthesis of CF_3-enone adducts employed classical approaches based on Mannich type reactions,[35] aldol-type condensations,[36–38] and additionally several methods rely on rearrangements[39–41] (Scheme 1 b). It has also been shown previously that methyl cinnamates can undergo reactions with $TMSCF_3$ to form the corresponding CF_3-enones.[42] However, these strategies are limited to electron rich alkenes and make use of prefunctionalized building blocks containing a CF_3 group, that are often difficult to access. Direct functionalization of the sp^2 C–H bond of alkenes with a trifluoroacyl group would be advantageous for the step-economic synthesis of α,β-unsaturated trifluoromethyl ketones. Trifluoroacetic anhydride (TFAA) is a precious acylation reagent in synthesis, however due to its electronic properties, this reagent is inactive for trifluoroacetylation of non-activated alkenes. In the early 1990s, Balenkova and co-workers reported the method for the activation of TFAA by freshly in situ generated BF_3(gas)/Me_2S complex at −60 °C, allowing for the direct olefinic trifluoroacetylation ostensibly via an electrophilic pathway (Scheme 1 c).[43] Although these methods provide routes for the synthesis of CF_3-enone derivatives, the requirement of complex and harsh reaction conditions, multi-step chemical pathways and lack of chemo- and regioselectivity, restrict synthetic chemists to access this privileged class of unsaturated ketones.[34] Hence, a mild, direct and practical approach towards the trifluoroacetylation of alkenes that does not require prefunctionalized starting materials remains in high demand at both, an academic and industrial level. During the preparation of this manuscript a patent by Su et al. has been published that reports direct acylation of electron rich styrene derivatives by anhydrides.[44] Herein, we report a robust, efficient, and operationally simple strategy for the trifluoroacylation of alkenes with trifluoroacetic anhydride, that is enabled by photoredox catalysis.

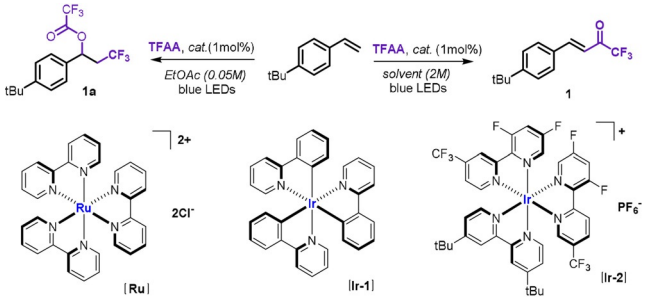
Results and Discussion

The photocatalytic decarboxylative strategy reported by Stephenson and co-workers for the perfluoroalkylation of hetero(aromatic) compounds demonstrated a conceptual platform to generate fluoroalkyl radical species from cheap and readily available reagents, for example, perfluoroalkyl anhydrides.[45] Since this pioneering study, the method has successfully been implemented towards the synthesis of various classes of organic structures, including complex molecules and materials.[46–50] Based on voltammetric measurements and augmented with calculations, we assumed that trifluoroacetic anhydride with an observable reduction onset at around −1.2 V (vs. SCE) should undergo an irreversible, exergonic, and reductive single electron transfer (SET) process to afford the corresponding radical ion species in the presence of a photocatalyst operating under oxidative quenching conditions. The ensuing (O)C–O bond fragmentation could preferentially afford the CF_3CO radical species ($\Delta G = -20.1$ kJ mol^{-1} in favor of the trifluoroacyl radical) and trifluoroacetate anion. The latter reactive radical intermediate would be trapped in situ with an alkene substrate and eventually lead to the formation of trifluoroacylated adduct (Figure 1 d). However, since the liberated $CF_3(CO)$ radical has only a limited lifetime and undergoes fragmentation to $CF_3^{\bullet}$ and CO,[51] the overall process has to be operated under well-controlled reaction conditions. The use of a photoredox catalyst such as tris-(2-phenylpyridine) iridium (III) [$Ir(ppy)_3$] was seen prevailing due to its sufficiently low reduction potential of the excited state of $E_0(Ir^{IV}/Ir^{III*}) = -1.73$ V (vs. SCE). To check the feasibility of this transformation, a systematic screening of different reaction parameters including photocatalysts, solvents, and concentrations has been carefully evaluated, and key results are presented in Table 1. Indeed, operating under [$Ru(bpy)_3(PF_6)_2$] catalysis, only trace amounts of trifluoroacetylation product of 4-tert-butylstyrene could be detected.

While carrying out the process in the presence of catalytic amounts of $Ir(ppy)_3$ (1 mol %) in ethyl acetate (EtOAc) under blue-light irradiation in a high-intensity visible-light photoreactor for 12 hours led to the formation of **1** in 79 % yield (entries 1–3, Table 1) in both a chemoselective and regioselective fashion. Further screening of solvents and concentrations revealed no beneficial effects of optimization these both parameters (entries 4–9). Using optimal reaction conditions, no significant reactivity was observed in the dark or without a catalyst (entries 10–11). We were also pleased to find that reducing the concentration to 0.05 M led to the formation of only difunctionalized adduct **1a** in 85 % (entry 12). Notably, no redox mediator such as pyridine N-oxide is required to forge an alkene fluoroalkylation pathway.

The newly developed trifluoroacetylation protocol is characterized by a fairly simple reaction setup involving the irradiation of 2.0 equivalents of TFAA and 1 mol % of commercially available photocatalyst $Ir(ppy)_3$ in EtOAc for 12 h. With these optimized reaction conditions in hand, the applicability of the protocol was examined with respect to a wide array of readily available olefins and resulted in up to 94 % isolated yield of the corresponding α,β-unsaturated trifluoromethyl ketones as the (*E*)-isomer (unless otherwise indicated in Table 2). Aryl substituted olefines containing both electron donating and electron withdrawing common functional groups at *ortho*-, *meta*- and *para*-positions were successfully trifluoroacylated in 40–85 % isolated yields. It is noteworthy that halogen substituents (**3**, **5**, **6**, **9**, **12**) and ester (**7**) groups remained untouched under the reaction conditions, allowing further structural elaboration besides the trifluoroacetyl group. Alkene building blocks including di- and trisubstituted aryl substrates (**9**–**13**) furnished the corresponding unsaturated ketones in 76–94 % chemical yields. Substrates adorned with a substituent flanking the α-position of styrene (**14**–**26**) as well as alkenes bearing polycyclic aromatic hydrocarbons (**27**, **28**) and heterocyclic systems **29**–**31** (**31** including SC-XRD), all gave the desired trifluoroacylated adducts. Similarly, the key precursors (**32**, **33** and **34**) of most

Table 1: Effects of reaction parameters on trifluoroacetylation of **1**.



Entry[a]	Cat. (mol%)	Solvent	Yield [%]
1	[Ru] (1%)	EtOAc	trace
2	[Ir]-1 (1%)	EtOAc	79 (**1**)
3	[Ir]-2 (1%)	EtOAc	36 (**1**)
4	[Ir]-1 (1%)	CH_3CN	56 (**1**)
5	[Ir]-1 (1%)	CH_2Cl_2	42 (**1**)
6	[Ir]-1 (1%)	DMSO	trace
7	[Ir]-1 (1%)	acetone	trace
8	[Ir]-1 (1%)	THF	19 (**1**)
9	[Ir]-1 (1%)	DMF	trace
10[b]	[Ir]-1 (1%)	EtOAc	trace
11	–	EtOAc	trace
12[c]	[Ir]-1 (1%)	EtOAc	85 (**1a**)

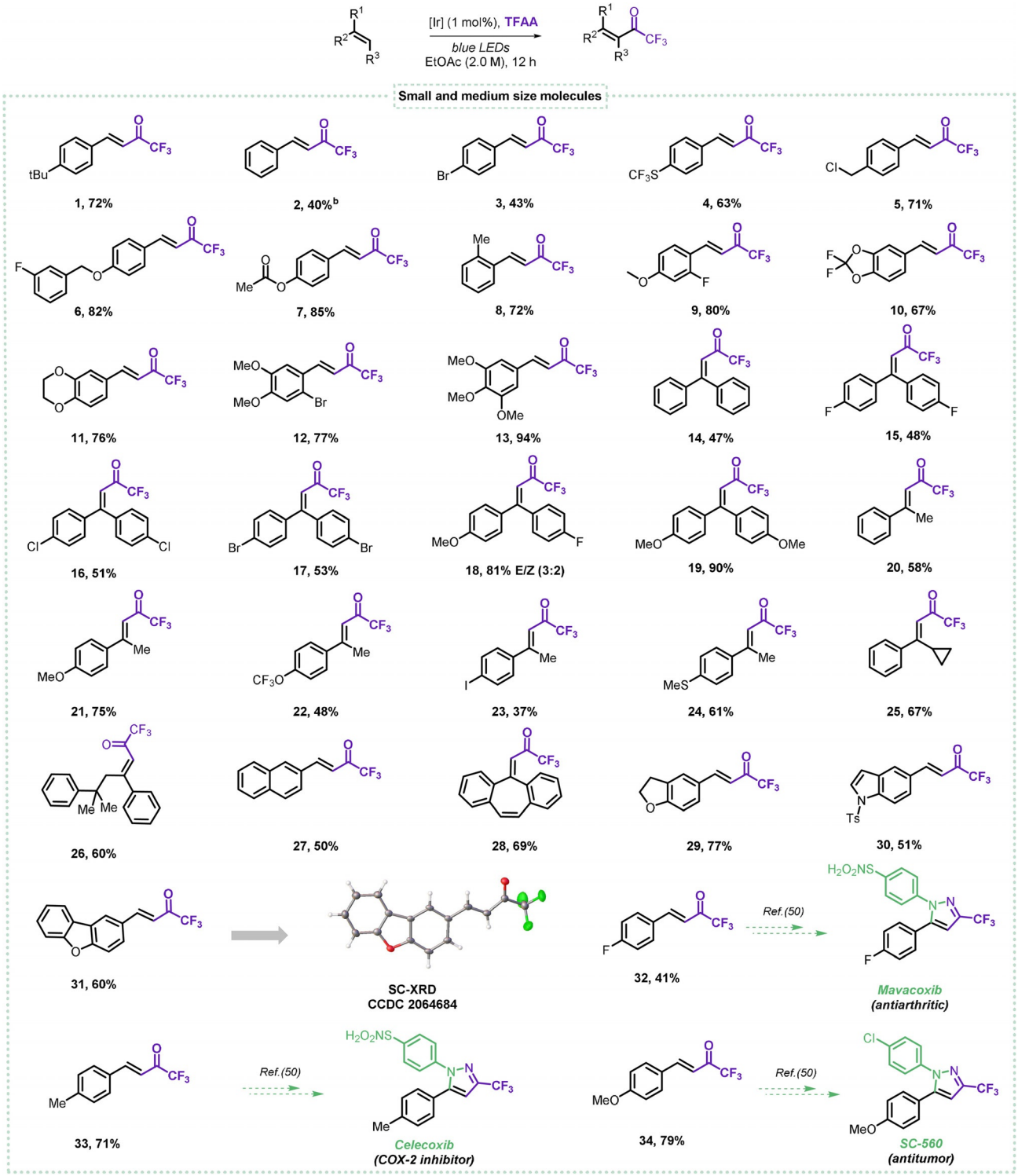
[a] General conditions: 4-*tert*-butylstyrene (1.0 equiv), [catalyst] (1 mol%), and TFAA (2.0 equiv) were irradiated in solvent (2.0 M) with 350 W blue light at ambient temperature for 12 h. Yields of **1** and **1a** were determined by GC-MS against an internal standard of n-decane. [b] In the dark. [c] 0.05 M in EtOAc.

recognized anti-inflammatory drugs bearing trifluoromethylated pyrazole moieties such as Mavacoxib, Celecoxib, and SC-560[52–55] were all synthesized using this photoredox protocol in satisfactory yields. In most cases, we were unable to observe trifluoromethylated or difunctionalized alkene adducts. Having enabled for the trifluoroacetylation of alkenes with a simple reagent, we subsequently investigated the application of our protocol in late-stage functionalization. In recent decades, trifluoroacetyl-containing compounds have proven to be an important class of molecules for the preparation of biorelevant substances, and as such we foresaw that our approach could be of particular value in the context of medicinal chemistry. (Table 3). Each of these architecturally complex molecules underwent alkene trifluoroacetylation to deliver the corresponding CF_3-enone adducts in moderate to good yields. For example, derivatives of L-camphanic acid (**35**), naproxen (**36**), and (−)-10-camphorsulfonylamide (**37**) selectively underwent trifluoromethylacetylation reaction demonstrating the protocol's tolerance to amides and sulfonamides. Our protocol was also successfully applied in the trifluoroacetylation of a series of known drugs and naturally occurring derivatives including clofibrate (**38**), AHTN (**39**), vitamin E (**40**), menthol (**41**), estrone (**42**), vanillin (**43**) and fenofibrate (**46**) with good chemical efficiency. The reaction conditions were also suitable for more structurally complex bioactive precursors. Derivatives from cholesterol (**44**) and nitogenin (**45**) bearing several unsaturated fragments with long alkyl side chains underwent trifluoroacetylation exclusively at the less-hindered olefin. However, the substrate scope was limited to aryl substituted alkenes and could not be expanded to aliphatic compounds. To demonstrate the utility of this protocol, at first, a photocatalytic functionalization of 4-tert-butylstyrene with a CF_3CO group has been performed on 15.6 mmol scale without significant decrease in isolated yield (67%) (Figure 1). For further applications, we successfully prepared trifluoromethylated heterocyclic systems with different heteroatoms (S-, O-, and N-) and of different ring-size. The synthesis of these products via a direct trifluoromethylcarbonation pathway using conventional methodologies remains a great challenge (Figure 1).

Next, we turned to investigation of the mechanism of the reaction using a combined experimental, spectroscopic and computational approach on the level of DFT and DLPNO-CCSD(T) (see the Supporting Information, computational chemistry for details). Owing to the very high reduction potential of the excited state of the catalyst ($E_0(Ir^{IV}/Ir^{III*}) = -1.73$ V vs. SCE)[56] we considered the initiation of the catalytic cycle by single electron photoreduction of TFAA (**A**) by the excited state of the catalyst (**B***) which previously has not been described. Yet, the initiation pathway of forming acyl radicals has recently been reviewed.[57] The viability of this mechanistic pathway has been confirmed by computational experiments, showing an exergonic extrusion of trifluoroacetate (-20.1 kJ mol^{-1} at 298 K) from **C** which is only turned exergonic by its strongly positive TdS term of 60 kJ mol^{-1} in solution. Experimentally, this hypothesis is fully consistent with cyclic voltammetry data, indicating an onset potential of -1.2 V (vs. SCE) of the irreversible reduction of TFAA (see Supporting Information, Figure S3 & S5), as well as with Stern–Volmer quenching studies that indicated a highly efficient quenching of the excited T_1-state of **B** by **A** ($k = 2 \times 10^9$ mol^{-1} s^{-1}) (Figure 2C).

In contrast, only weak quenching of **B*** was observed in the presence of styrene or TFA (see Supporting Information, Figure S22 & S23). This is aligned with very low reduction potentials of -2.6 V[58] and T_1 energies of ca. 60–65 kcal mol^{-1}, that are typical for α-unsubstituted styrenes[59] and excludes both, electron and energy transfer by $Ir(ppy)_3$* ($T_1 = 55.2$ kcal mol^{-1}).[60] Significant singlet state contributions to the reaction mechanism by ^{1}**B*** were excluded due to ultrafast sub-ps depopulation of the S_1 state ^{1}**B*** by intersystem crossing ($k_{ISC,calc} = 6.9 \times 10^{12}$ s^{-1}).[61] However, the weak quenching effect of trifluoroacetic acid could potentially be attributed to some formation of CF_3CO radicals by single electron reduction of the $CF_3COOH_2^+$ formed by autoprotolysis in minor amounts, followed by dehydration. Further, under irradiation of a solution of the catalyst in the presence of TFAA a new characteristic weak broad absorption feature between 500 to 700 nm was observed, which also has been found by electrochemical oxidation of $Ir(ppy)_3$ in MeCN (see Figure 2B). This feature was assigned to the Ir^{IV} cation.[62] Simultaneously a novel emission between 470 nm to 520 nm was detected. The initial build-up of $Ir(ppy)_3^+$ is in agreement with the proposed irreversible and fast fragmentation of the radical anion **C** under formation of the metastable CF_3CO radical and trifluoroacetate. To shine even more light into the reaction mechanism, we combined the photochemical deple-

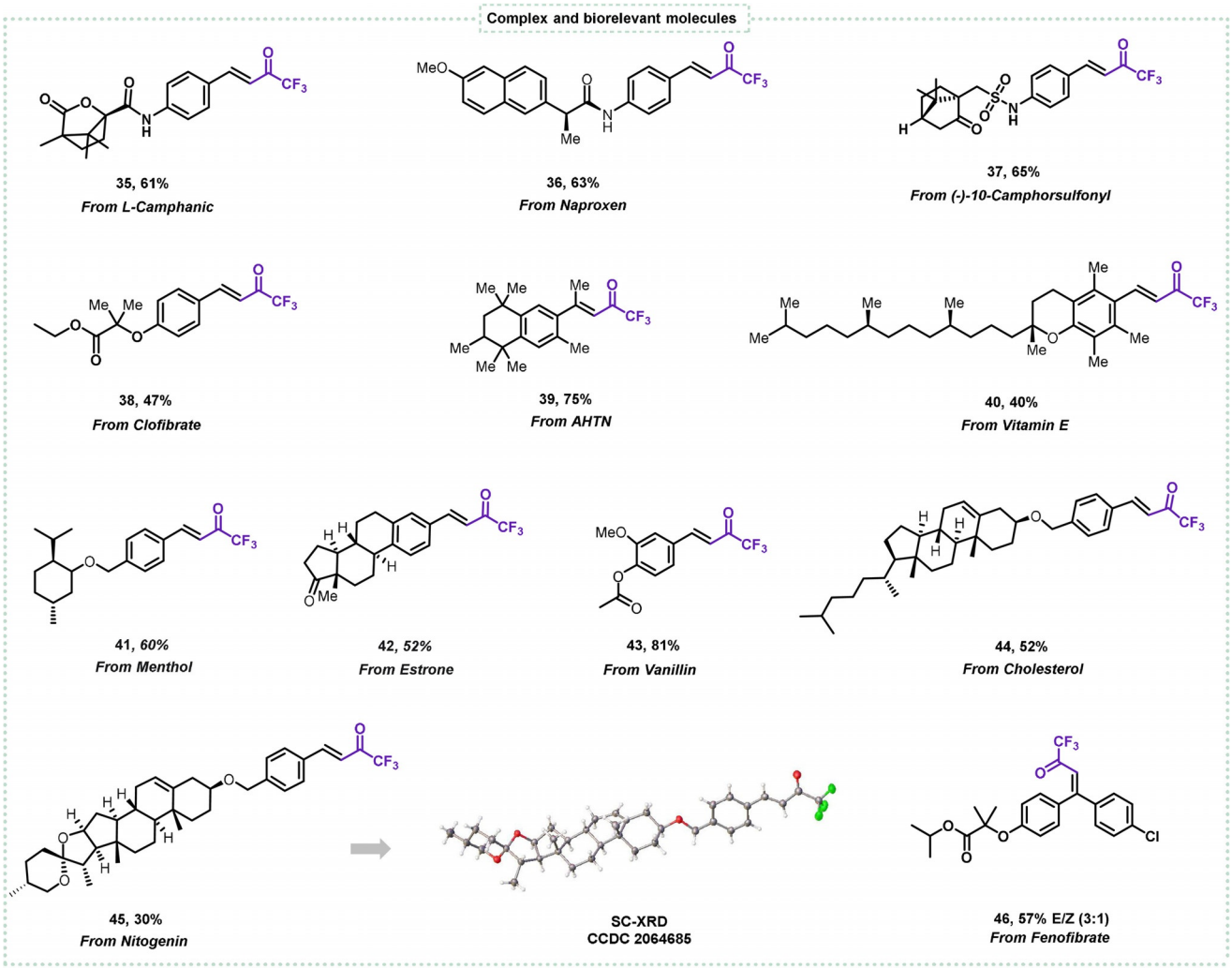
Table 2: Representative scope of the alkene C(sp^2)-H trifluoroacetylation.[a]



[a] Alkene (1.0 equiv), [Ir] = $Ir(ppy)_3$ (1 mol%), and TFAA (2.0 equiv) were irradiated in EtOAc (2.0 M) in a 350 W blue LED reactor at ambient temperature for 12 h. Isolated yields are reported. Isolated products composing of both (*E*) and (*Z*) are reported in parenthesis (ratio). [b] Volatile compound. Yield of 58% determined by ^{19}F NMR analysis with an internal standard. Crystal structure of **31** as ORTEP with ellipsoids set at 50% probability.[76]

tion of the excited state **B** by TFAA with cyclovoltammetric analysis. Irradiation of the mixture **B** and TFAA in MeCN over 6 min at 448 nm caused full depletion of the Ir^{III}/Ir^{IV} feature of **B** in cyclic voltammetry and a new species oxidized at 0.6 V vs. Fc^+/Fc appeared, indicating an irreversible oxidation of $Ir(ppy)_3$. This was also observed in UV/Vis

Table 3: Direct trifluoroacetylation of complex molecules and biorelevant compounds.[a]



[a] Standard reaction conditions. Isolated yields are reported. Crystal structure of **45** as ORTEP with ellipsoids set at 50% probability.[76]

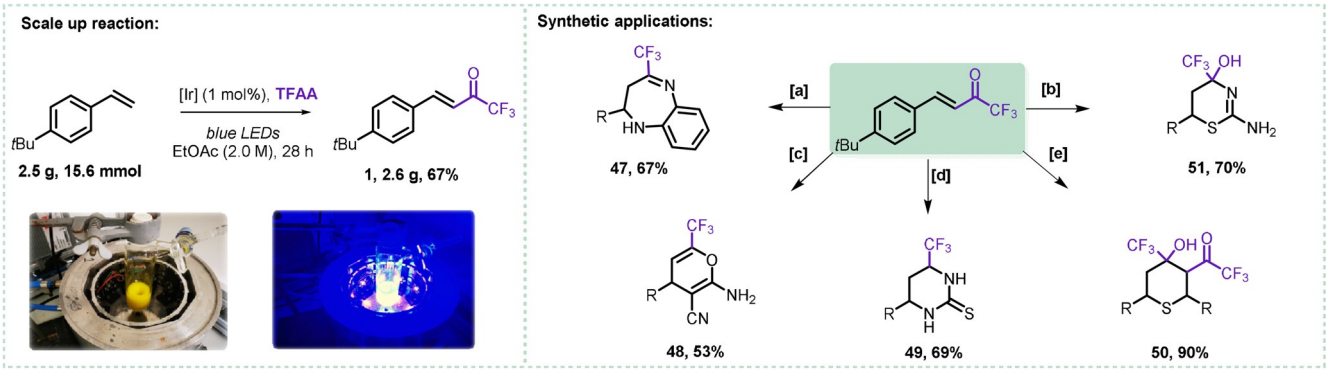


Figure 1. Scale-up and applications in the synthesis of various trifluoromethylated heterocycles. [a] 1,2-phenylenediamine (2.0 equiv), EtOH, 80 °C, 20 h; [b] $SC(NH_2)_2$ (1.5 equiv), EtOH, 80 °C, 23 h, HCl; [c] pyrrolidine (0.12 equiv), $CH_2(CN)_2$ (1.0 equiv), benzene, 80 °C, 20 h; [d] $SC(NH_2)_2$ (1.5 equiv), Na (4.0 equiv), EtOH, 80 °C, 48 h; [e] $S(NH_4)_2$ (0.74 equiv), EtOH, rt, 1 h.

spectroscopic analysis (see Figure 2B and C). The same experiment in the presence of ^{t}Bu-styrene resulted in a preservative effect on the Ir^{III}/Ir^{IV} couple **B/B**$^+$, corroborating the mechanistic hypothesis of a back electron transfer by radical **H** (see Figure 2E and S4–S11).

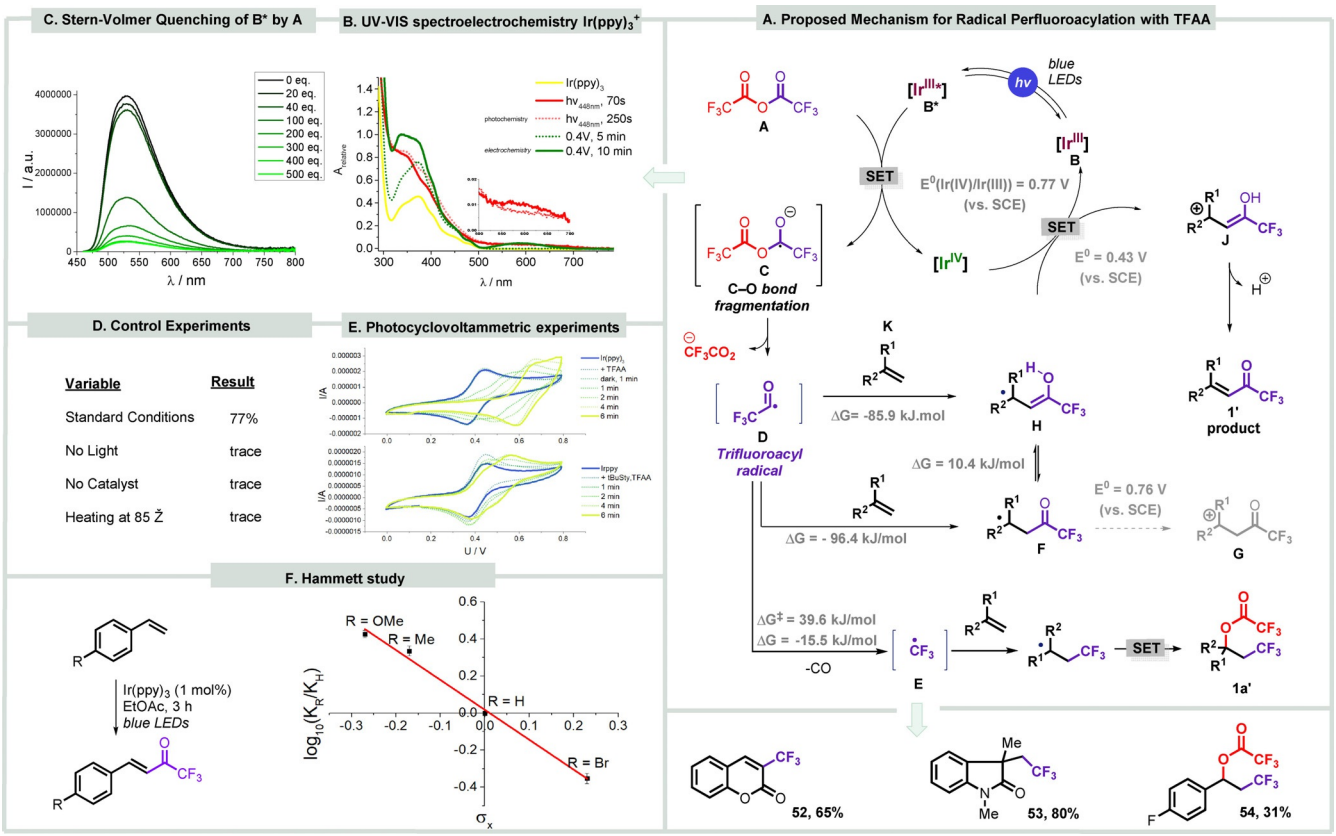


Figure 2. Mechanistic studies. A) Proposed catalytic cycles. B) Comparison of the UV/Vis spectra of irradiation of $(Ir(ppy)_3$ in the presence of TFAA with the electrochemical formation of Ir^{IV} by spectroelectro chemistry. Spectra were scaled for a better comparability. C) Stern–Volmer quenching of $Ir(ppy)_3$* by TFAA. D) Control experiments. E) Photocyclovoltammetric experiments. F) Hammett equation.

The results of the substrate scope were at this stage extensively analyzed. It turned out that the use of 4-fluorostyrene led to the formation of the two reaction products (**1′** and **1a′**) that could be isolated in 48 % (**32**) and 31 % (**54**) yield, respectively. Furthermore, exclusive formation of CF_3 adducts **52** and **53** using other electron-deficient olefins followed this trend and fully outcompeted any addition of radical **D** to the substrate. These results hinted on comparable rates of a bimolecular reaction of **D** with the substrate (see Supporting Information, Figure S43) and the unimolecular decarbonylation of the $COCF_3$ radical (**D** & **TS-1**), offering a potential handle for switchability. While the fragmentation forming CO and the $^{\bullet}CF_3$ radical (**E**) was found to be exergonic ($K \approx 1.7 \times 10^3$ M) we continued to investigate the kinetics of this process. In good agreement with the previous experimental data in the gas phase ($\Delta G^{\ddagger} = 41.9$–$51.9$ kJ mol^{-1})[63–69] our theoretical investigations confirmed a low decarbonylation barrier in solution ($\Delta G^{\ddagger} = 39.6$ kJ mol^{-1}) resulting in a half-lifetime of radical **D** of $t_{1/2} \approx 0.98$ µs in solution applying Eyring's theory ($\kappa = 1$). Due to the competitive formation of the CF_3 radical, we expected a high sensitivity of the product outcome dependent on the collision probability with the substrate. Indeed, we found that low substrate concentrations (0.01 M) resulted in almost exclusive formation of the CF_3 product **1a′**, while increasing substrate concentration up to 2.0 M shifted the product distribution towards the trifluorocarbonylated compound **1′**. This finding corroborates the mechanistic proposal of the initial addition of **D** to the substrate **K**.

The formation of an electron deficient intermediate (**F**) during the first irreversible step was also indicated by a Hammett study (see Figure 2F) showing a significant negative reaction parameter ($\rho = -1.61$). It is in good correlation with our experimental findings that styrene derivatives bearing electron-withdrawing substituents undergo trifluoroacetylation slower than electron-rich derivatives (see Figure 2A, bottom line).

Although this generally imposes some limitations on the method, we considered the equilibrium between radicals **D** and **E**, as another adjusting screw potentially capable of overcoming these limitations. The equilibrium is expected to be shifted towards radical **D** if the partial pressure of CO is increased. We were thrilled by the observed continuous shift of the product distribution under variation of the partial pressure of CO from 1 to 10 bar, finally almost completely suppressing of the formation of the trifluoromethylation product **1a′** (Figure 3B). The calculation of the reduction potential of benzylic radical **F** ($E_0 = 0.76$ V (vs. SCE) indicated an almost vanishing driving force for back electron transfer to Ir^{IV} ($E_0(Ir^{IV}/Ir^{III}) = 0.77$ V vs. SCE)[54] in order to form the benzylic cation species **60.** This value is in good agreement with reported data for benzylic radicals and comparable to the parent benzyl radical ($E_0 = 0.73$ V) rather

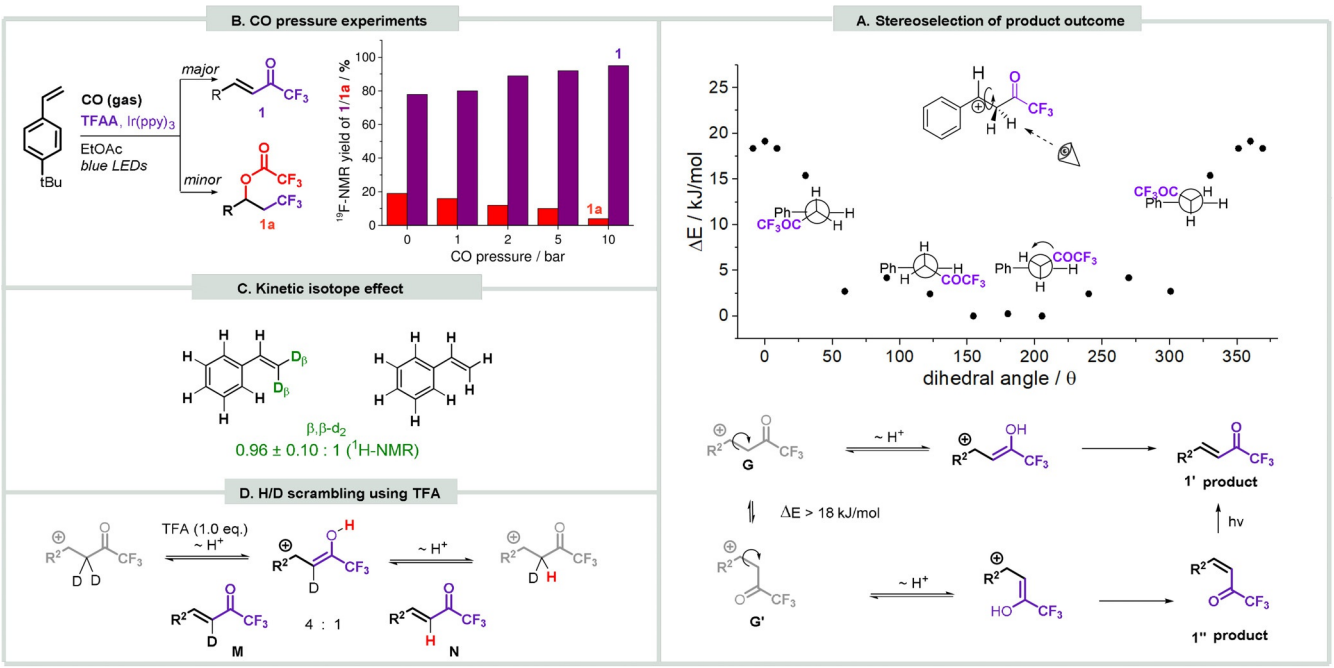


Figure 3. Mechanistic studies. A) Potential energy surface scan of the α-β-bond of the carbonyl shows favored antiperiplanar configuration of the trifluorocarbonyl moiety. Irradiation (blue LEDs, 450 nm) of 1'' (Z-2) has been performed in the presence of $Ir(ppy)_3$ (1 mol%) in EtOAc. B) CO pressure experiments. C) KIE experiment. D) H/D scrambling experiment.

than the phenylethyl radical ($E_0 = 0.37$ V), showing levelling out of hyperconjugative and inductive effects.[70]

The electronic structure of **F** suggested a potential enolizability forming the conjugate enole **H-cis** or **H-trans**. The localized radical **F** was found to be thermodynamically slightly more stable by about 10.4 kJ mol^{-1} indicating a keto-enol equilibrium. However, the reduction potential of the enol tautomers **H-cis/J-cis** (**H-trans/J-trans**) showed a lowering of the reduction potential to 0.43 (0.47 V) (vs. SCE) renting the back electron transfer to Ir^{IV} exergonic by 32.8 kJ mol^{-1}. To further support this hypothesis, the trifluoroacetylation reaction of tert-butylstyrene in the presence of 1.0 equivalent of TFA was carried out. We were pleased to find a 1:4 mixture of α-H (**N**) and α-D (**M**) labeled reaction products, confirming the existence of a significantly long lived keto-enole equilibrium (see Figure 3 D). Furthermore, the absence of any H/D scrambling during incubation of the reaction product **1** with TFA excludes potential reprotonation of the product causing this effect and rules out a simple deprotonation of **G** to **1′** (Figure 2 A).

Next, kinetic isotope effect measurements using β-d_2 labelled styrene as substrate, allowed to determine the β-contributions to the overall kinetic isotope effects which were expected to be characteristic for radical attack on styrenes. Addition of the CF_3CO radical to the styrene molecule was found to be strongly exergonic ($\Delta_R G^0 = 96.4$ kJ mol^{-1}) and irreversible and is the only step expected to be reflected in an observable kinetic isotope effect under competition conditions. Our mechanistic proposal is aligned with an observed α-secondary kinetic isotope effect of about 0.96 ± 0.02 per α-H/$D_{\alpha\text{-CO}}$ using β-d_2 styrene as substrate (see Supporting Information for details). For similar radical attack reactions on styrene derivatives α-KIEs of 0.88–0.95 was previously observed due to rehydridisation of the α-C from sp^2 to sp^3.[72]

Furthermore, a series of experiments using d_8-styrene was carried out to gain more insight into the complementary contributions to the overall kinetic isotope effect. Due to a potentially underlying unknown side products in both, optimized GCMS and GC-FID data, the determined kinetic isotope effects was flawed by a significantly large errors and could not be interpreted to support or discard our mechanistic proposal. However, a significant involvement of the highly reducing enolate anion **L** ($E_0(1/\mathbf{L}) = -1.59$ V vs. SCE) (see Supporting Information, Figure S59) to the dominant reaction pathway is unlikely due to the formation of TFA as a side product but cannot be ruled out. Alternatively, this step might also directly employ a proton coupled electron transfer as previously described for the corresponding anions.[73–75]

Last but not least, the reasons for the complete stereoselectivity of the process was investigated in due course. In this mechanistic model, the conformation of **G** is controlling the configuration of the preferentially formed enol. A potential energy surface scan around the C_{benzyl}-$C_{\alpha\text{-}CH_2}$ bond, which is expected to be the stereodetermining conformer, revealed the origin of this finding. The minimum energy conformation ($\Theta_{Cbz\text{-}C\alpha\text{-}CH_2} = 154.6°$) of **G** turned out to be lower by more than 19 kJ mol^{-1} comparing with the alternative Z-conformation **G′** ($\Theta_{Cbz\text{-}C\alpha\text{-}CH_2} = 0°$), indicating the preference for the formation of E-product (see Figure 3 A and Supporting Information). However, to elucidate the possibility of a Z→E isomerization of primarily formed Z-α,β-unsaturated trifluoromethyl ketones under our reaction conditions, we investigated the photoisomerization of (*Z*)-**2** under blue LED irradiation. Indeed, after irradiation of the

reaction solution for 12 hours, a 2:1 mixture of isomers with the excess of thermodynamically favorable E-configuration was detected (see Supporting Information, p. 83).

Our attempts to get further insight into the process of formation and the fate of the key radicals by light-dependent EPR-spectroscopy were not successful (for details, see Supporting Information) due to the high reactivity of TFAA and the presumably short lifetime of the two radicals under the reaction conditions. Neither a quantum yield determination turned out to be successful owing to the heterogenicity of the reaction mixture.

Conclusion

We have developed an efficient and practical protocol where the simple reagent TFAA undergoes chemo- and regioselective trifluoroacylation reaction with a broad range of alkenes including complex natural products to access α,β-unsaturated trifluoromethyl ketone derivatives. Detailed mechanistic studies have provided evidence that C-CF_3 and C-$COCF_3$ bond formation can be controlled by the chosen reaction conditions. With this remarkable disclosure, we anticipate that this trifluoroacetylation approach will be a valuable tool for the synthetic chemist in drug discovery and development in the future.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: late-stage functionalization · organofluorine compounds · photoredox · radical mechanisms · radical trifluoroacetylation

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