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

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Abstract: Trifluoromethyl ketones are not only found in drug like substances, but are also considered as key synthons for the preparation of various fluorinated heterocyclic molecules. Access to such trifluoromethyl ketone derivatives typically requires the incorporation of the trifluoromethyl group, or a surrogate moiety, at the beginning of a multi-step synthetic sequence. However, direct trifluoroacylation of alkenes could potentially provide a highly efficient and straightforward method for the synthesis of α,β-unsaturated trifluoromethyl ketones. Here 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 an trifluoroacyl radical mechanism promoted by a photocatalyst. Beyond simple alkenes, this method allows for chemo- and regioselective functionalization of small-molecule drugs and common pharmacophores.

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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 special subset of the fluorinated compounds that have relevant applications in biological and medicinal chemistry.[24-27] Owing to the high electronegativity of the CF_3 group, an 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] (Fig. 1a). 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 trifluoromethyl- 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,[36,37] and additionally several methods rely on rearrangements[38-40] (Fig. 1b). 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

90's, Balenkova and co-workers reported the method for the activation of TFAA by in situ generated BF_3(gas)/Me_2S complex at -60 °C, allowing direct olefinic trifluoroacetylation ostensibly via an electrophilic pathway (Fig. 1c).[41,42] 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. Herein, we report a robust, efficient, and operationally simple strategy for the trifluoroacylation of alkenes with trifluoroacetic anhydride, that is enabled by photoredox catalysis.

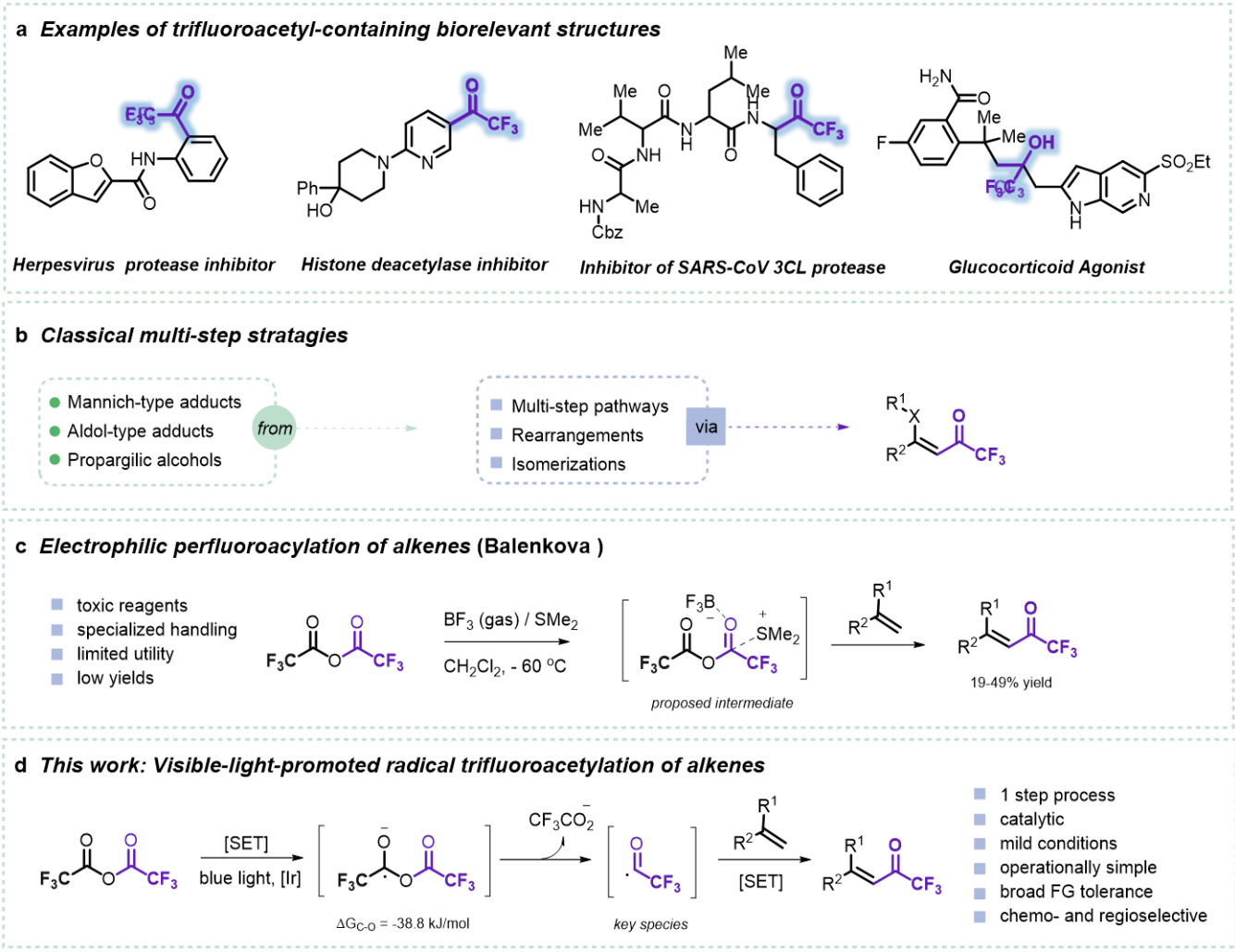
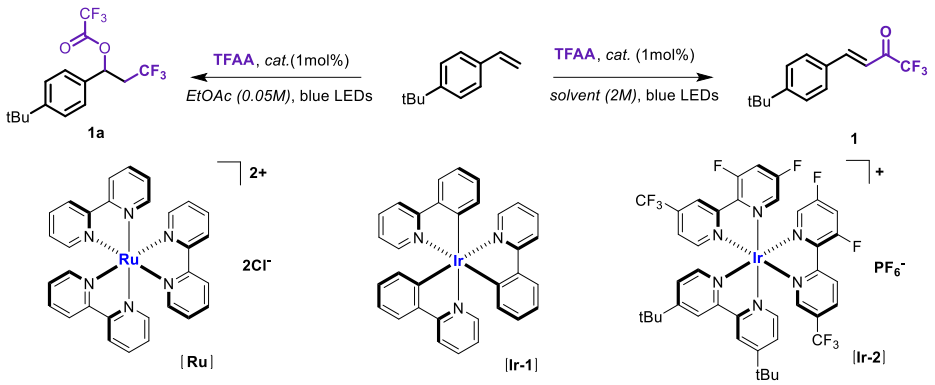


Fig.1 Motivation and design of trifluoroacylation reaction. a, Examples of CF_3(CO)-containing biorelevant molecules. **b**, multi-step strategies. **c**, electrophilic process. **d**, this work.

Results and discussion

Reaction development. 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, e. g. perfluoroalkyl anhydrides.[43] Since this pioneering study, the method has successfully been implemented towards the functionalization of various classes of organic structures, including complex molecules and materials.[44-48] Based on voltammetric measurements and augmented with in silico work, we assumed that trifluoroacetic anhydride with an observable reduction onset at around −1.1 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 $CF_3(CO)$ radical species (ΔG = - 20.1 kJ/mol in favor of the trifluoroacyl radical) and trifluoroacetate anion. The latter reactive radical intermediate would be trapped in situ with an alkene substrate and lead to the formation of trifluoroacylated adduct (Fig. 1d). However, since the liberated $CF_3(CO)$ radical has only a limited lifetime and undergoes fragmentation to $CF_3^{\bullet}$ and CO,[49] 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 $E_0(Ir(IV)/Ir(III)^*) = -1.73V$ (vs. SCE). In order 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.

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



entry	cat (mol%)	solvent	yield (%) [a]
1	[Ru] (1%)	EtOAc	Trace
2	[Ir]-1 (1%)	EtOAc	79 (**1**)
3	[Ir]-2 (1%)	EtOAc	36 (**1**)
4	[Ir]-1 (1%)	MeCN	56 (**1**)
5	[Ir]-1 (1%)	DCM	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	–	EtOAc	Trace
11	–	EtOAc	Trace
12[b]	[Ir]-1 (1%)	EtOAc	63 (**1a**)

[a]General conditions: 4-*tert*-Butylstyrene (1 equiv), [catalyst] (1 mol%), and TFAA (2 equiv) were irradiated in solvent (2 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](0.05 M) concentration in EtOAc was used.

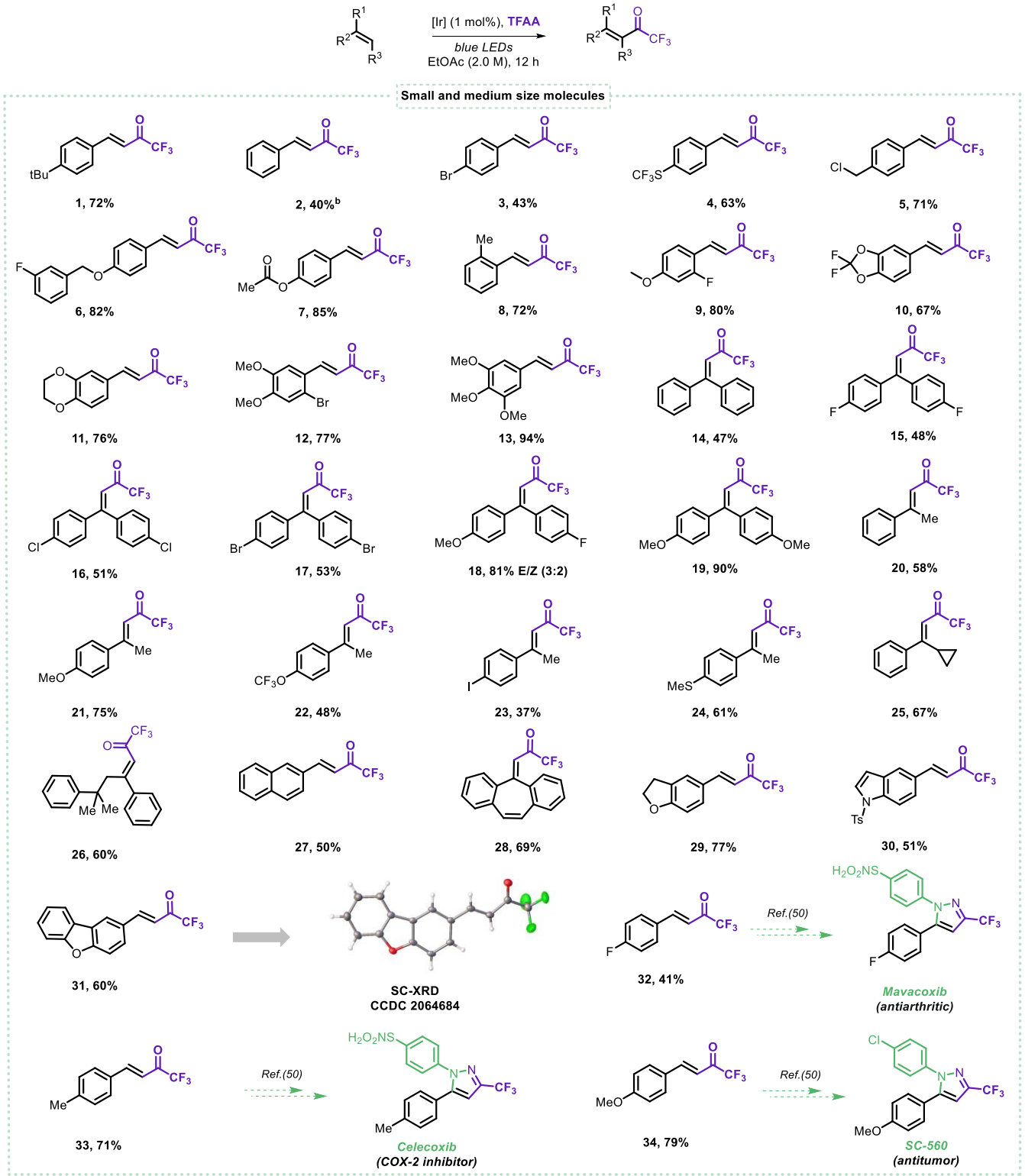
While carrying out the process in the presence of catalytic amounts of $Ir(ppy)_3$ (1 mol%) in ethyl acetate (EtOAc) under blue-light irradiation in high-intensity visible-light photoreactors for 12 hours led to the formation of **1** in 79% yield (entries 1-3, Table 1) in both a chemoselective and regioselective fashion. Further screening of the solvents and concentrations revealed the beneficial effects of optimizing these both parameters (entries 4-9). In addition, the reaction does not proceed 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 63% (entry 12). Notably, no redox mediator such as pyridine N-oxide is required to forge an alkene fluoroalkylation pathway.

Reaction scope and synthetic application.

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**) group remain untouched under the reaction conditions, allowing further structural elaboration besides the trifluoroacetyl group. Alkene building blocks including di- and tri-substituted 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 recognized anti-inflammatory drugs bearing trifluoromethylated pyrazole moieties such as Mavacoxib, Celecoxib and SC-560[50-52] were all synthesized using this photoredox protocol in satisfactory yields. In most cases, we were unable to observe trifluoromethylated or difunctionalized alkene adducts.

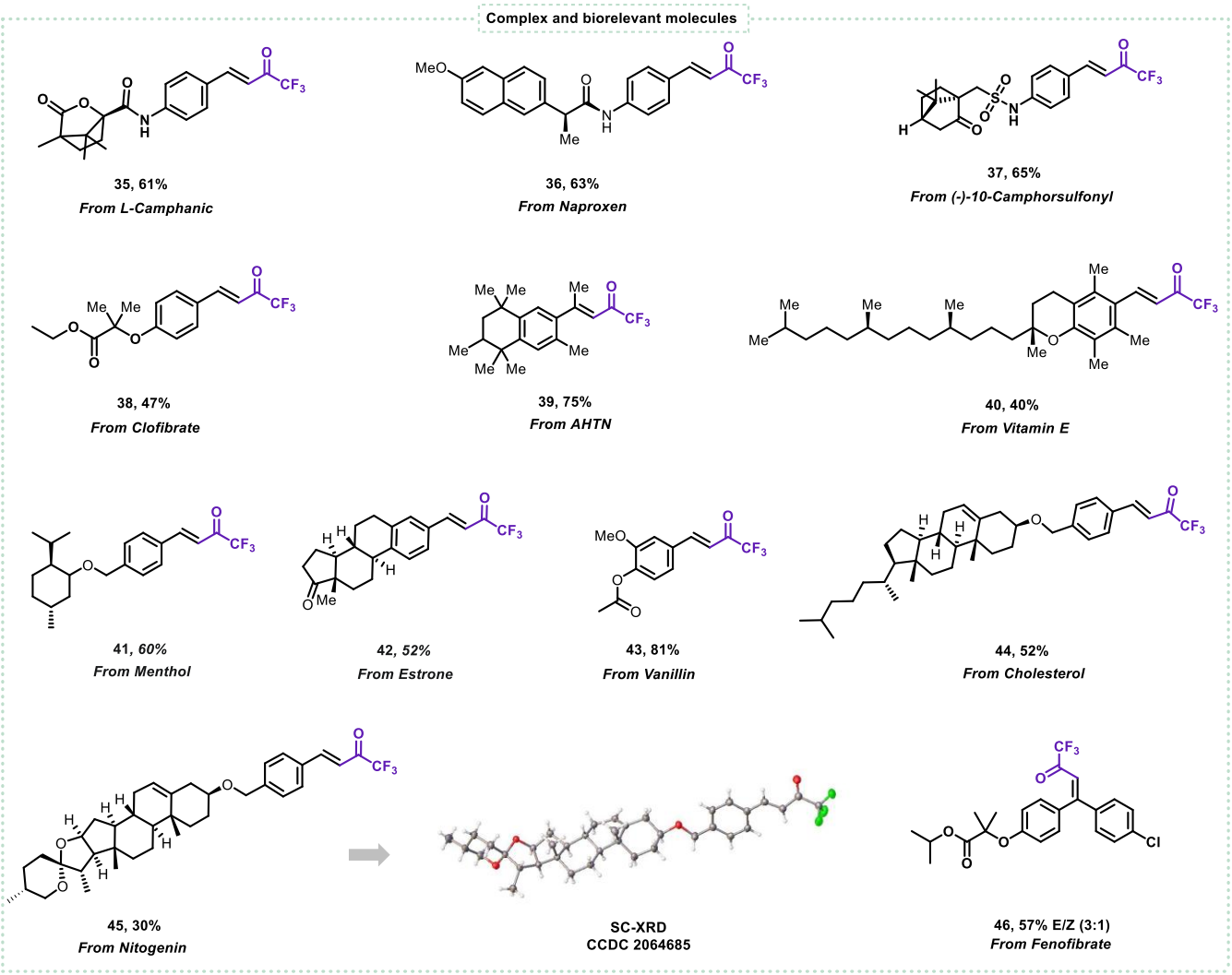
Having developed trifluoroacetylation of alkenes with a simple reagent, we subsequently investigated the application of our protocol in late-stage functionalization. Trifluoroacetyl-containing compounds have in recent decades proven to be an important class of molecules for the preparation of biorelevant 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

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 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.

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



[a] Standard reaction conditions. Isolated yields are reported.

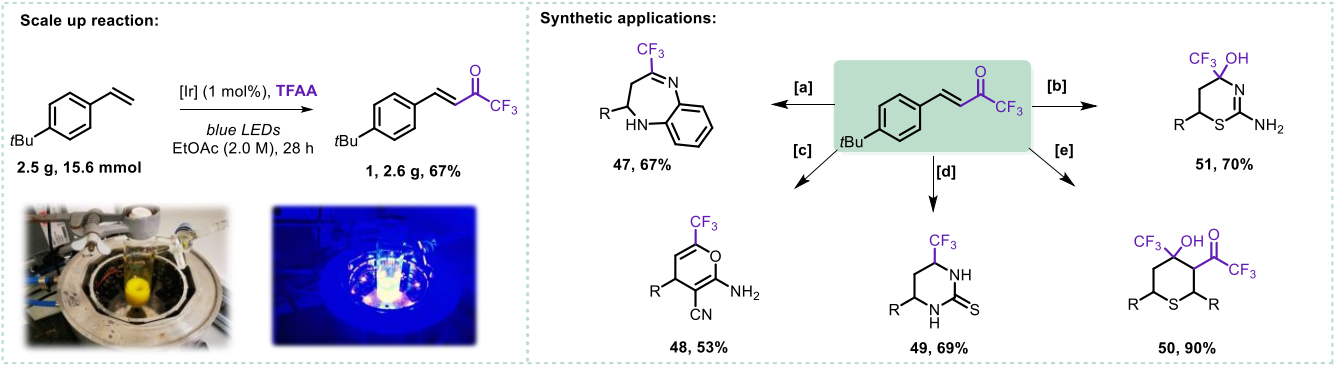


Fig. 2. Scale-up and applications in the synthesis of various trifluoromethylated heterocycles. [a] $SC(NH_2)_2$ (1.5 equiv), EtOH, 80 ºC, 23 h, HCl; [b]; 1,2-phenylenediamine (2.0 equiv), EtOH, 80 ºC, 20 h; [c]; pyrrolidine (0.12 equiv), $CH_2(CN)_2$ (1.0 equiv), benzene, 80 ºC, 20 h; [d]; $SC(NH_2)_2$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

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.

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%) (**Fig. 2**). For further applications, we successfully prepared trifluoromethylated heterocyclic systems with different heteroatoms (S-, O-, and N-) and of different ring-size. The synthesis these products via a direct pathway using conventional methodologies remains a great challenge (**Fig. 2**).

Mechanistic considerations.

Next, we turned to investigation of the mechanism of the reaction by a combined experimental, spectroscopic and computational approach on the level of DFT and DLPNO-CCSD(T) (see ESI for details). Due to the very high reduction potential of the excited state of the catalyst of E_0(Ir(*IV*)/Ir(*III*)*) = -1.73V (vs. SCE)[54] we considered the initiation of the catalytic cycle by single electron photoreduction of TFAA (**54**) by the excited state of the catalyst (**55***) which previously has not been described. However, this is consistent with cyclic voltammetry data indicating an onset potential of −1.1 V (vs. SCE) of an irreversible reduction of TFAA. Stern-Volmer quenching studies indicated highly efficient quenching of the excited T_1-state of **55** by **54** ($K_{SV} = 2 \cdot 10^9$ $mol^{-1}s^{-1}$). Under irradiation of a solution of the catalyst in the presence of TFAA a new emission feature between 470 nm to 520 nm was observed which could be

attributed to formation of the presumably generated Ir(IV) cation species which has been shown by correspondence of the UV-VIS absorption signatures after irradiation of a sample by a blue-LED and the electrochemically generated species observed by UV-Vis spectroscopy (see **Fig. 3**). The build-up of Ir(IV) is in agreement with an irreversible and fast fragmentation of the radical anion **56** under formation of the metastable $^{\bullet}COCF_3$ radical and trifluoroacetate. This has been corroborated by in-silico experiments, showing an exergonic extrusion of trifluoroacetate (−15.5 kJ/mol at 293K). The initial observation of a strong concentration dependence of the product distribution between $COCF_3$- and CF_3- containing products indicated a competition between unimolecular decarbonylation of the primarily formed $COCF_3$ radical (**57**) via transition state **TS-1** and bimolecular product formation (see ESI Fig. S43). The decarbonylation barrier in solution was calculated to be ($\Delta G^{\ddagger} = 39.6$ kJ/mol) and is in good agreement with the previously reported values in the gas phase[55-61] translating into a half-lifetime of radical **57** of about $t_{1/2} \sim 0.87$ µs in solution ($\kappa = 1$). The decarbonylation under formation of CO and the $^{\bullet}CF_3$ radical (**58**) further was found to be exergonic indicating an equilibrium constant of $K \sim 1.7 \cdot 10^3$ M between both species. We therefor expected a high sensitivity of the product outcome dependent on the collision probability with the substrate due to the competition of unimolecular and bimolecular channels. Indeed, we found that low substrate concentrations (0.01 M) resulted in almost exclusive formation of the CF_3 product, while increasing substrate concentrations up to 2 M shifted the product distribution towards the trifluorocarbonylated compound **1′** corroborating the mechanistic proposal of initial addition of **57** to the substrate **63**. Furthermore, due to the slow reactivity of electron-deficient alkenes, the formation of exclusively CF_3 adducts **52** and **53** has been observed, confirming a fast decarbonylation process of **57**. The mechanistic scenario was further challenged by a series of experiments under variation of the partial pressure of CO from 1 to 5 bar. The product distribution indicated a constant tendency towards an increasing amount of $COCF_3$ product due to an increase in the concentration of the $^{\bullet}COCF_3$ radical in the reaction mixture. Unfortunately, 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 ESI)

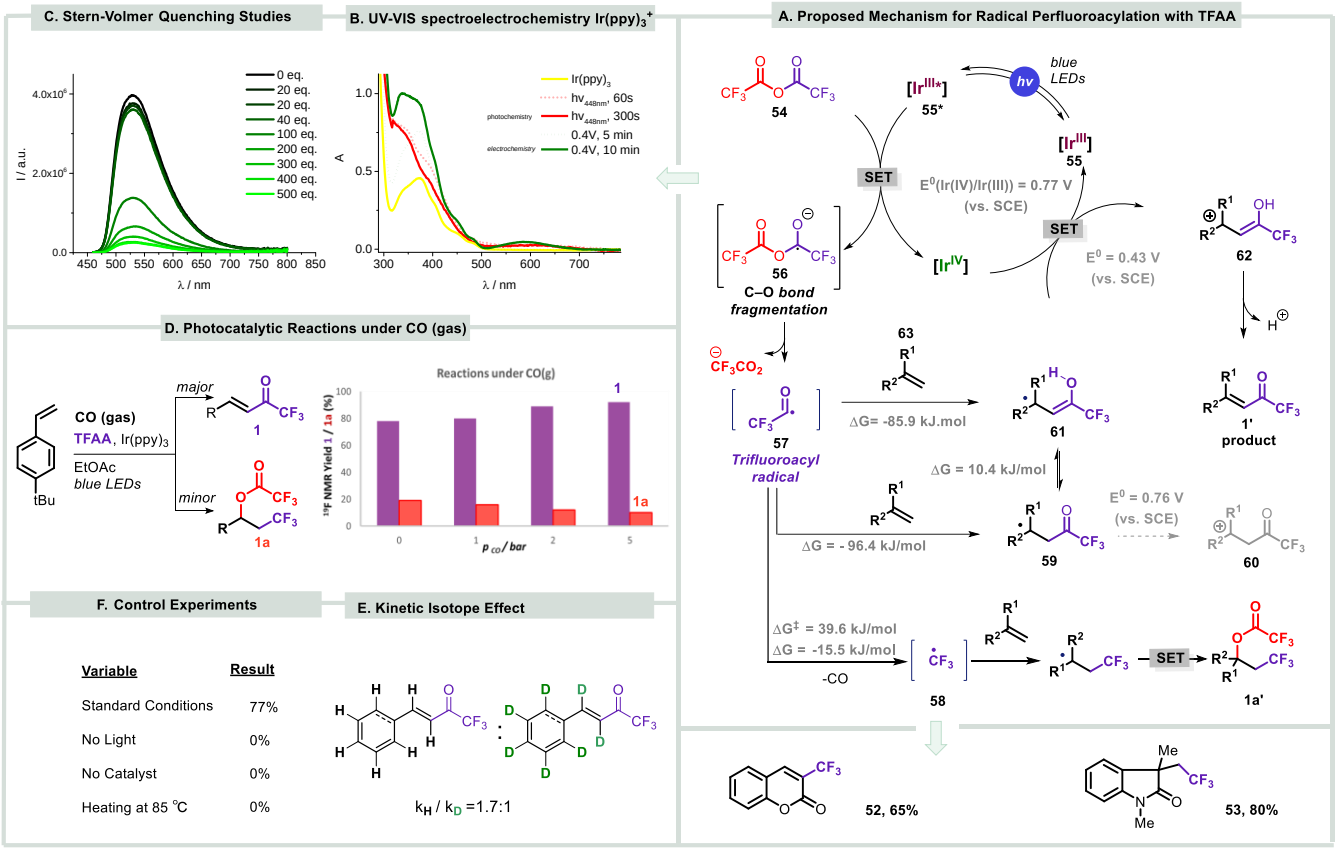


Fig. 3. Mechanistic studies. A, Stern-Volmer quenching studies. **B**, UV-VIS spectroelectrochemistry of $Ir(IV)^{+}$ species. **C**, Experiments under CO pressure. **D**, Plausible catalytic cycle. **E**, KIE studies. **F**, Control experiments.

due to the high reactivity of TFAA and the presumably short lifetime of the two radicals under the reaction conditions. Next, we turned our attention to the feasibility of the back electron transfer from benzylic radical **59** which has been calculated to have a reduction potential of 0.76 V (vs. SCE). This indicates an almost vanishing driving force for back electron transfer to Ir(IV) (E_0(Ir(*IV*)/Ir(*III*)) = 0.77V vs. SCE)[54] in order to form benzylic cation species **60.** The electronic structure of **59** suggested a prior enolization of the benzylic radical **59** forming the two conjugated enolate intermediates **61-cis** and **61-trans**. Surprisingly, the resonance stabilization was overcompensated by the lower stability of the CF_3-enol, and the localized radical **59** was found to be thermodynamically more stable by about 10.4 kJ/mol. However, calculating the reduction potential of the enol tautomers **61-cis** and **61-trans** to its conjugated cations **62-cis** and **62-trans** indicated a reduction potential of only 0.43 V (vs. SCE), therefore renting the back electron transfer to Ir(IV) exergonic by 32.8 kJ/mol. In addition, an overall deuterium kinetic isotope

effect of k_H/k_D= 1.3 per deuterium further hints on the existence of conjugation effects (for extensive discussions, see ESI). However, this step might also directly employ a proton coupled electron transfer as previously described for the corresponding anions.[62-64] On basis of these electrochemical characteristics, we propose a slow depopulation of the equilibrium **59/61** through the reductive quenching by the Ir(IV) ground state. The subsequent irreversible deprotonation of the strongly acidic cation **62** with trifluoroacetate or the TFAA-radical anion occurs with the concurrent formation of the reaction product.

Conclusion

In summary, 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 under different 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.

Methods

General procedure for photocatalytic trifluoroacetylation of alkenes. A 10-mL glass microwave vial was charged with photocatalyst (1 mol%). The contents of the vial were then subject to 3x argon/vacuum cycles. Anhydrous EtOAc was added and the reaction mixture was sparged with argon for 3 min. Finally, the substrate (1.0 equiv) and TFAA (2.0 equiv) were introduced to the reaction mixture via microsyringe. The obtained red solution was stirred at room temperature under blue LED irradiation. After 12 hours, water was added to the reaction mixture and the product was extracted with CH_2Cl_2 (3x10 ml). The solvent was removed under reduced pressure, and the crude product(s) were subsequently purified by flash column chromatography over silica gel as indicated.

Data availability

The data supporting the findings of this study are available in the article and its Supplementary Information. Metrical parameters for the structures of **26** and **42** (See Supplementary Information) are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference no. CCDC-2064684, and CCDC-2064685, respectively.

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Author contributions

K.Z. and D.R. contributed equally to this work. K.Z. conceived the project and performed the experiments. D.R. predominantly designed and performed the mechanistic studies. N.Y.N. participated in preliminary experiments. G.J. and D.R. performed EPR measurements. D.K., K.Z., and D.R. wrote the manuscript. All authors contributed to discussions, commented and edited manuscript.

Competing interests

The authors declare no competing interests.

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