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Hydroxytrifluoroethylation and Trifluoroacetylation Reactions via SET Processes

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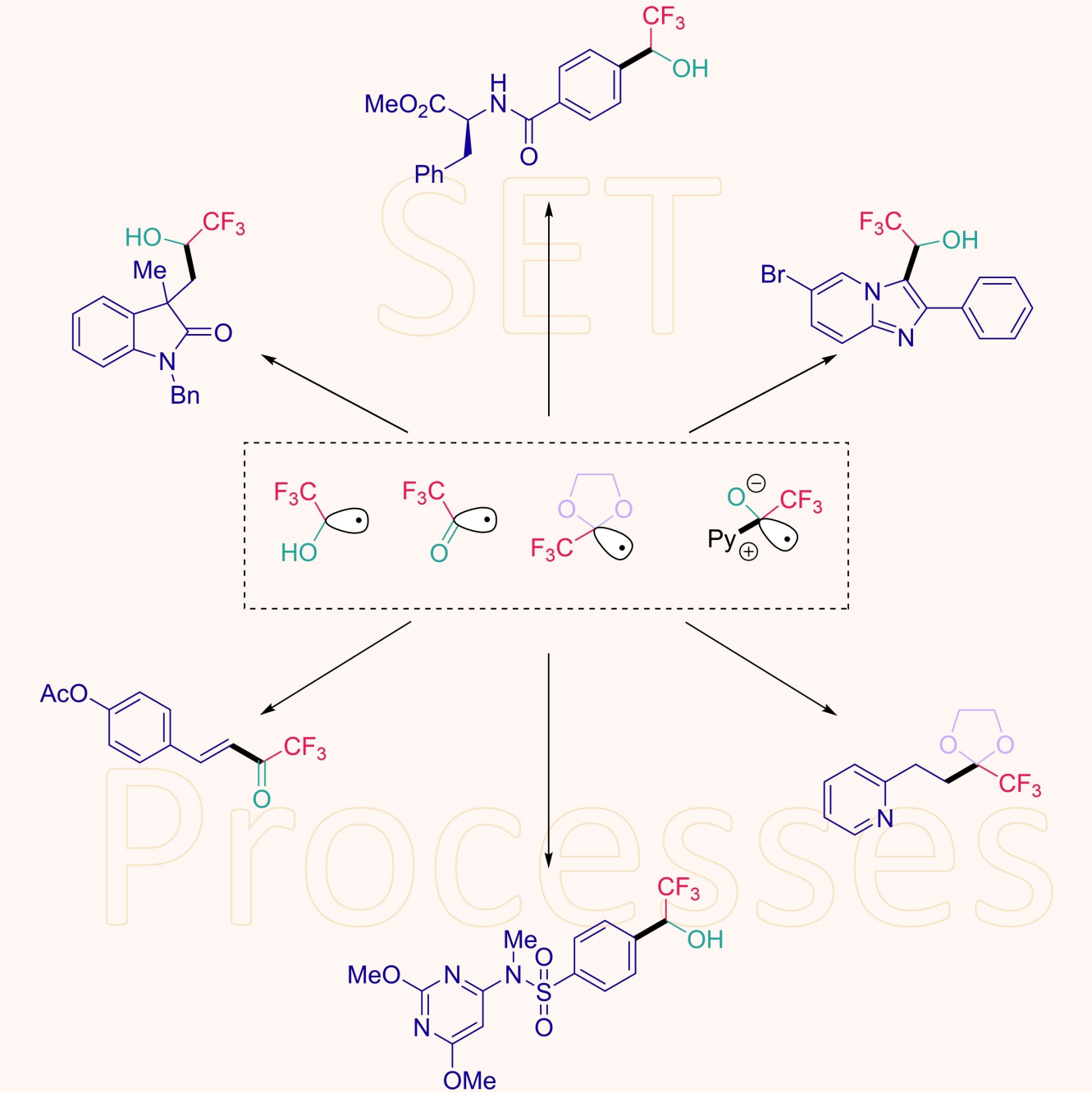

Hydroxytrifluoroethyl and trifluoroacetyl groups are of utmost importance in biologically active compounds, but methods to tether these motifs to organic architectures have been limited. Typically, the preparation of these compounds relied on the use of strong bases or multistep routes. The renaissance of radical chemistry in photocatalytic, transition metal mediated, and hydrogen atom transfer (HAT) processes have allowed the installation of these medicinally relevant fluorinated motifs. This review provides an overview of the methods available for the direct synthesis of hydroxytrifluoroethyl- and trifluoroacetyl-derived compounds governed by single-electron transfer processes.

1. Introduction

Organofluorine chemistry is an exciting and appealing research area, and it is unsurprising that it has called the attention of numerous researchers for decades, including medicinal and material chemists.[1] This discipline has found wide applications ranging from polymers[2] or catalysts[3] to pharmaceuticals,[4] being an essential topic in organic chemistry.

Fluoro-pharmaceuticals are a subset of organofluorinated compounds that are significantly relevant in medicinal chemistry and agrochemicals.[4a] Typically, this subgroup of pharmaceuticals represents around 20–25% of the marketed drugs, and over 40% of the new small molecule drugs in 2018 and 2019.[4c] The benefits of tethering a fluorinated group in a small molecule drug range from metabolic stability, lipophilicity or bioavailability compared to their non-fluorinated analogue.[5] Thus, the high representation of fluoro-pharmaceuticals is directly related to the typically better physicochemical properties provided. Traditionally, the most popular fluorinated groups tethered in pharmaceuticals have been the fluorine atom and the trifluoromethyl group.[6] Another interesting motif is the *gem*-difluoromethylene group, which is recently receiving great attention due to its bioisosteric behavior as carbonyl and alcohol functional groups.[7]

Within the fluoro-pharmaceuticals bearing a trifluoromethyl group in their skeleton, important and representative moieties are the 1-hydroxy-2,2,2-trifluoroethyl and 2,2,2-trifluoroacetyl groups. These two functionalized trifluoromethylated entities are presented in several pharmaceuticals, such as Befloxatone (Figure 1).[8] Given the importance of these functionalities, the development of strategies for the direct installation into organic backbones is receiving great attention.[9] Generally, 1-hydroxy-2,2,2-trifluoroethylated compounds can be addressed by a nucleophilic addition of the trifluoromethyl group to carbonyls. Then, upon oxidation event the trifluoroacetylated compounds are obtained.[10] Recently, the development of synthetic methods driven by single-electron transfer (SET) processes has opened a new avenue for the direct introduction of 1-hydroxy-2,2,2-trifluoroethyl and 2,2,2-trifluoroacetyl groups in organic molecules and will be discussed in this review.

Processes mediated by SET events are inherently related to the formation and subsequent reaction of free radical species, which historically have been considered chaotic and uncontrollable.[11] However, accessing these open-shell species in a safe, controlled, and efficient manner is possible using different available synthetic tools.[12] Photoredox and transition metal catalysis facilitate the generation of these highly reactive species in modern organic radical chemistry. Of note, the ability to activate redox-labile substrates by transition metals[13] and/or photoredox catalysts[14] has enabled reactions under exceptional mild conditions compared to two-electron modes of activation, covering new chemical space. Importantly, metallaphotoredox catalysis has also demonstrated its usefulness to engage this mode of reactivity.[15] Numerous research groups have disclosed creative applications for the installation of different functional groups, including medicinally relevant fluorinated scaffolds.[16] The trifluoromethyl group has been one of the most popular,[17,18] however relevant scaffolds such as the hydroxytrifluoroethyl and trifluoroacetyl groups are receiving great attention and are of interest for this review. From a retrosynthetic point of view, hydroxytrifluoroethylated molecules can be disconnected by radical synthon **A**, whereas radical synthon **B** corresponds to trifluoroacetylated organic compounds. Radical synthon **A** has been accessed from synthetic equivalents **1**–**3**. On the other hand, radical synthon **B** can be obtained as well from readily available reagent **4** (Figure 2). Additionally, radical synthon **C**, which can be considered as a masked trifluoroacetyl radical, can be formed via **5** starting from trifluoropyruvate. Recently, pyridine-derived radical synthon **D** has been accessed from **4**.

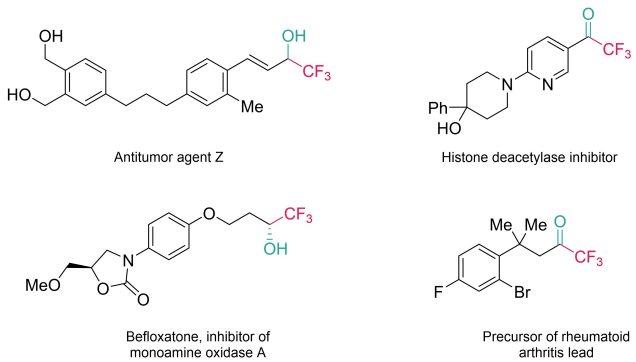

Figure 1. Representative hydroxytrifluoroethylated and trifluoroacetylated organic molecules in medicinal chemistry.

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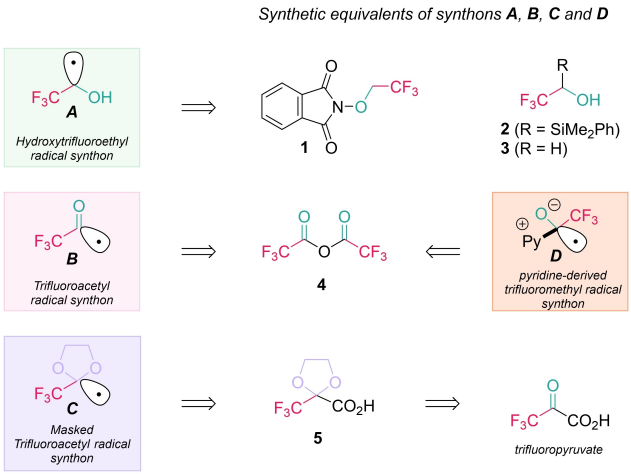

Figure 2. Hydroxytrifluoroethyl radical synthon (**A**), trifluoroacetyl radical synthon (**B**) and masked trifluorocetyl radical synthon (**C**) and their corresponding synthetic equivalents discussed in this review.

This review aims to provide general guidance for the design of synthetic methods for the synthesis of hydroxytrifluoroethylated and trifluoroacetylated molecules via SET processes based on recent advances proceeding through radical synthons **A**, **B**, **C** and **D**. Photoinduced, transition metal catalyzed and metal-free methods for hydroxytrifluoroethylation and trifluoroacetylation are discussed. Of note, in the last two years, the direct introduction of hydroxytrifluoroethyl and trifluoroacetyl groups in oxetanes,[19] cyclopropanes,[20] and others[21] has been reported through other non-SET based visible-light mediated modes of activation and they are not included in this contribution.

2. Radical-Mediated Hydroxytrifluoroethylation

2.1. Via Photoinduced Methods

Early 2020, *N*-alkoxyphthalimides proved to be suitable alkyl radical precursors via unconventional 1,2-hydrogen atom transfer (1,2-HAT) by a serendipitous discovery in a C(sp^3)–H allylation reaction (**1b** to **A** in Scheme 1).[22] Lan and Chen tested a variety of *N*-alkoxyphthalimides containing C(sp^3)–H bonds adjacent to carbonyl, cyano, trifluoromethyl (**1**) and

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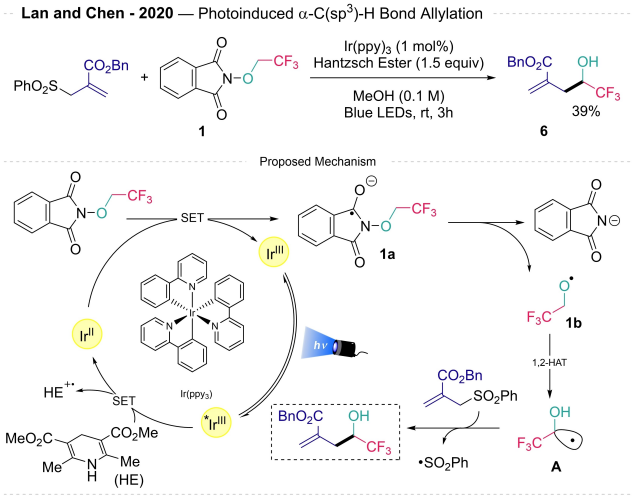
Prof. Roser Pleixats received her PhD from the Universitat Autònoma de Barcelona (UAB) in 1984, under the supervision of Prof. Marcial Moreno Mañas. After a postdoctoral stay at the Université des Sciences et Techniques du Languedoc (USTL) in Montpellier with Prof. R. J. P. Corriu and E. Colomer, she returned to UAB where she became Associate Professor in 1991 and Full Professor of Organic Chemistry in 2004. She has been assistant coordinator of the degree in Chemistry, Vice-Dean of the Faculty of Sciences and coordinator of the PhD program in Materials Science.

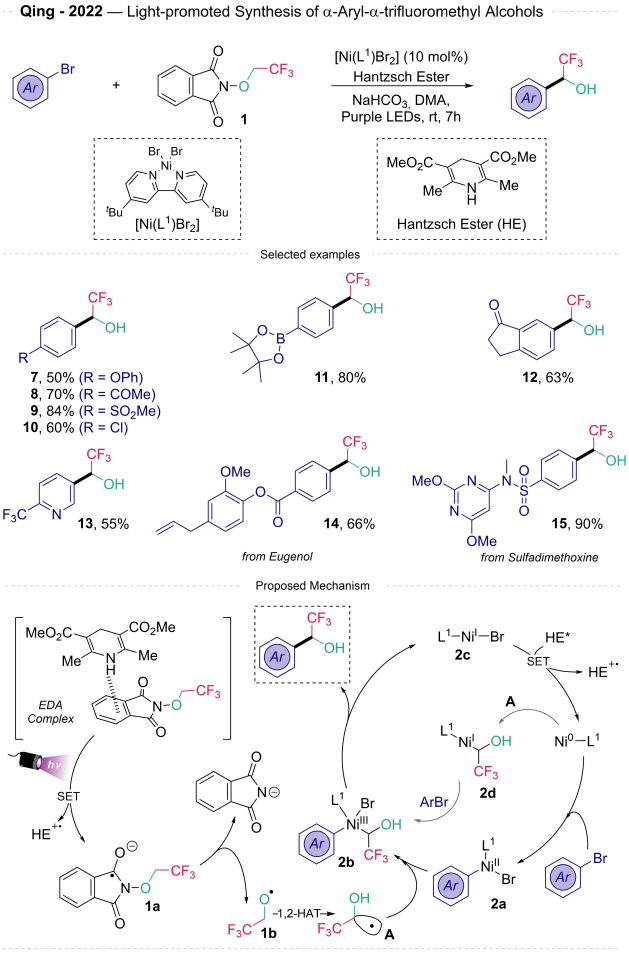
Dr. Carolina Gimbert-Suriñach obtained her PhD at UAB under the supervision of Prof. A. Vallribera. After one year as assistant professor at the same university, she moved to UNSW to undertake postdoctoral research with Prof. S. B. Colbran. Then she worked at ICIQ in Prof. A. Llobet group as postdoctoral fellow and research group coordinator. After a short stay at UB as Serra Húnter professor, she started as Ramón y Cajal fellow and co-leader of CatSy-NanoMat group at UAB in 2021. She was promoted to Associate Professor of Organic Chemistry in 2023.

Prof. Adelina Vallribera received her PhD in Chemistry in 1993 from the UAB under the supervision of Prof. J. Marquet. After a post-doctoral stay at the Laboratoire de Chimie Organique de Synthese in Belgium in the group of Prof. L. Ghosez, she joined the group of Prof. M. Moreno-Mañas in the UAB. She became assistant professor in 1997 in the unit of Organic Chemistry at the Department of Chemistry of the UAB and Full Professor in 2017.

Dr. Albert Granados received his MSc in Electrochemistry, Science and Technology in 2014. Then, he joined the Vallribera group at UAB, where he received his PhD with a special award in 2018. Subsequently, he pursued postdoctoral studies with Prof. R. Pleixats and Prof. A. Vallribera at UAB. In 2021, he began another postdoctoral stint in the Molander group at University of Pennsylvania (UPenn) working on novel photoinduced organic transformations. He started his current position as a Lecturer in Organic Chemistry at CatSyNanoMat group at UAB early 2023.



Scheme 1. Synthesis of benzyl 4-trifluoromethyl-4-hydroxy-2-methylenepentanoate **6** via photoredox generation of radical synthon **A** using Ir(ppy)$_3$ photocatalyst HE=Hantzsch Ester.



Scheme 2. Visible-light mediated preparation of α-aryl-α-trifluoromethyl alcohols. Radical synthon **A** generated from a new EDA-complex and captured by a nickel complex.

benzyl for the C(sp^3)–H allylation from allyl sulfones under reductive quenching photoredox catalysis. This reaction operates via single-electron reduction of **1** to the corresponding radical anion species **1a** by Ir(II) species. Then, **1a** undergoes N–O bond scission, yielding the oxygen-centered radical **1b**. The use of polar protic methanol as solvent proved to be key for the generation of the carbon-centered radical **A**. Computational studies indicated that methanol assists the 1,2-HAT step by decreasing the corresponding activation energy.[22] Finally, alkyl radical **A** reacts with the alkyl sulfone to yield **6** in 39% yield. The regioselective outcome was hypothesized to benefit from solvent effect. This unprecedented reactivity represented a new avenue for the preparation of free alcohol containing organic entities.

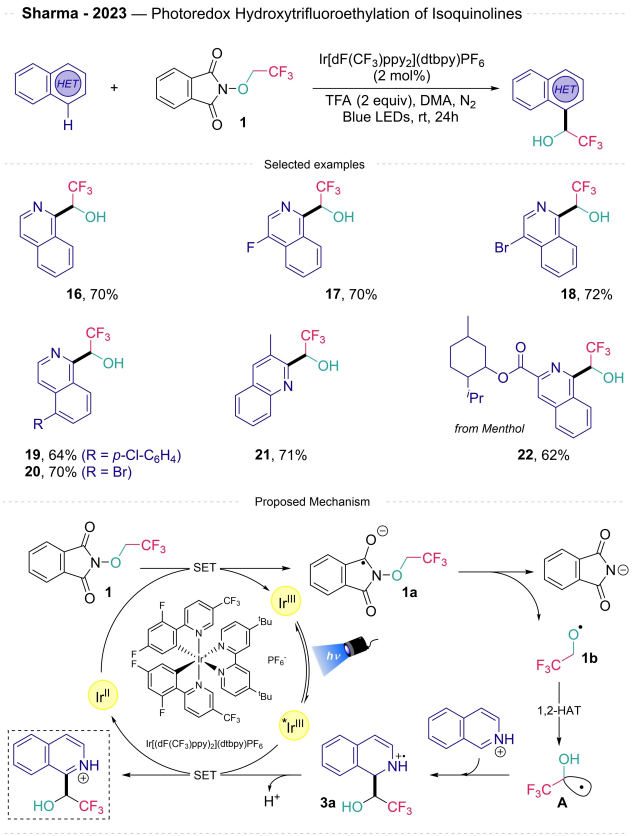
In late 2022, the Qing group presented an efficient cross-coupling method to access α-aryl-α-trifluoromethyl alcohols from aryl bromides and redox-active species **1** (Scheme 2).[23] This C(sp^3)–C(sp^2) cross-coupling reaction is enabled by the synergy of a nickel catalytic process and the charge transfer event of an electron donor-acceptor (EDA) complex between **1** and Hantzsch Ester (HE). The key step that allows the synthesis of the trifluoromethylated benzyl alcohols is the formation of the alkyl radical **A** via 1,2-HAT event. Of note, this method does not mandate the use of exogenous photocatalyst or stoichiometric metal reductant. The substrate scope is suitable for a wide range of aryl bromides bearing electron-donating (**7**), electron-neutral and electron-withdrawing groups (**8**–**10**). In general, electron-deficient substituents provided the desired product in higher yield. Of note, ketone, sulfone, nitrile, boronate (**11**) and vinyl groups could be tolerated under the reaction conditions, which offer opportunities for post-functionalization. This method was successfully applied for late-stage functionalization of relevant biomolecules, such as antimicrobial Eugenol (**14**) or Sulfadimethoxine (**15**). The operative mechanism of this transformation is driven by a dual system based on the photoactivation of an EDA complex and a nickel catalytic process. First, the association of HE and fluorinated **1** generates a molecular aggregate in the ground state, which undergoes SET after purple LED irradiation to generate HE$^{\bullet+}$ and radical anion **1a** species. Subsequently, a homolysis event from **1a** provides phthalimido anion and trifluoroethoxyl radical **1b**, which undergoes 1,2-HAT yielding the hydroxytrifluoroethyl radical **A**. An electron paramagnetic resonance (EPR) experiment with 5,5-dimethylpyrroline *N*-oxide evidenced the involvement of both radical species in the mechanism. Moving forward to the nickel cycle, first oxidative addition of the corresponding aryl halide to Ni(0) forms the Ni(II) intermediate **2a**, which then captures the fluorinated alkyl radical **A** to accomplish the high-valence Ni(III) intermediate **2b**. Then, reductive elimination of the Ni(III) species occurs yielding the final cross-coupled α-aryl-α-trifluoromethyl alcohol and Ni(I) intermediate **2c**, which is reduced back to Ni(0) ($E_{red}^{Ni(I)/Ni(0)} = -1.17$ V vs SCE) by the potent reductant photoexcited HE* ($E_{red}^{HE*/HE^{\bullet+}} = -2.28$ V vs SCE). Although the alkyl radical species **A** can be captured by Ni(0) and form Ni(I) intermediate **2d** followed by oxidative addition with aryl bromide to yield **2b**, control experiments indicate that

this Ni(0)/Ni(I)/Ni(III) catalytic cycle is an unlikely process in this transformation.

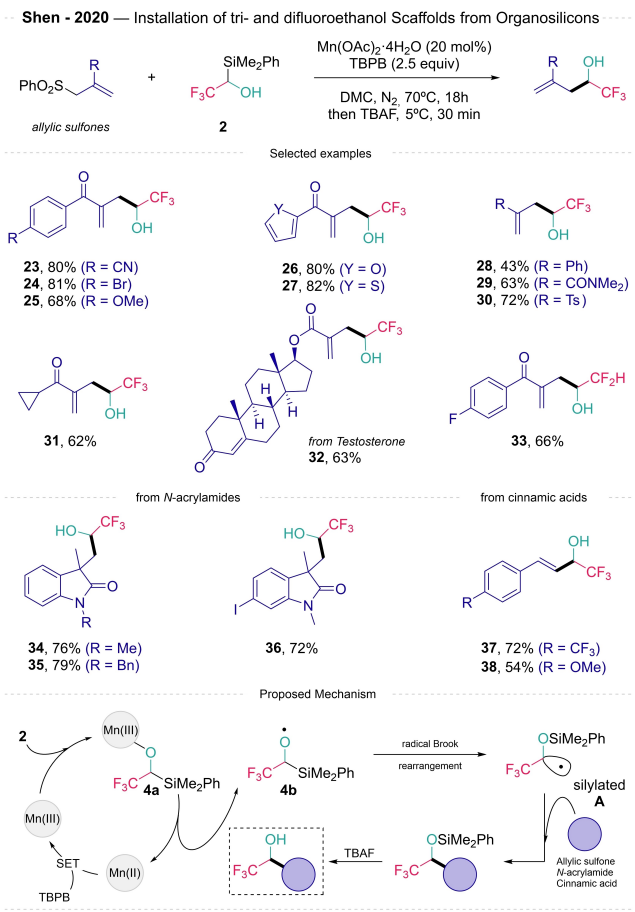
The Sharma group recently reported a Minisci-type C–H hydroxytrifluoroethylation process under a photoinduced net-neutral radical/polar crossover approach harnessing medicinally-relevant isoquinolines as radical acceptors and reagent **1** (Scheme 3).[24] This reaction mandates isoquinoline activation with trifluoroacetic acid (TFA) and using iridium-based photocatalyst in dimethylacetamide (DMA) as solvent. The substrate scope of the trifluoroethylated heteroarenes is amenable to fluoro (**17**), bromo (**18**) and ester substituents in the C4-position. Next, alkylation of C5-substituted isoquinolines was also feasible under the optimal conditions (**19** and **20**). Then, 3-methyl (**21**) and 4-methyl substituted quinoline also delivered the desired compounds in good chemical yields. Finally, a menthol-derived isoquinoline (**22**) proved to be a suitable core for this transformation. The involvement of radicals in the reaction mechanism was proved with radical-trapping experiments with TEMPO and 3,5-di-*tert*-4-butylhydroxytoluene. The crux of this net-neutral radical/polar crossover approach is a series of well-orchestrated, single-electron reduction and oxidation steps. Initially, the authors indicate that the reduced Ir(II) species is formed by sacrificial amounts of isoquinoline. Then, Ir(II) reduces the ($E_{1/2}^{Ir(III)/Ir(II)} = -1.37$ V vs SCE) fluorinated reagent **1** ($E_{p/2}^{red} = -1.24$ V vs SCE) to afford the radical anion species **1a** and Ir(III). Subsequently, species **1a** undergoes N–O bond cleavage to deliver the oxygen-centered radical **1b**. Computational findings support that this species undergoes exergonic rearrangement (−16 kcal/mol) to form the carbon-centered radical **A** through a 1,2-HAT process as proposed in Scheme 1. Afterwards, the reaction follows a Minisci-type alkylation where the radical **A** is trapped with protonated isoquinolines furnishing intermediate **3a**, which delivers the desired product upon deprotonation and oxidation events via single-electron transfer with the long-lived *Ir(III) species.

2.2. Via Transition Metal Complexes

In 2020, Shen and coworkers presented a novel silicon-based reagent (**2**) for hydroxytrifluoroethylation of organic molecules (Scheme 4).[25] The authors designed the generation of the carbon-centered α-alkoxy radical via C–Si bond cleavage using Mn(II)/Mn(III) metal catalysis. The generated fluorinated radical was trapped with allylic sulfones, giving access to α-trifluoromethylated homoallylic alcohols. This protocol is amenable to a wide variety of allylic sulfones with yields that range from 40 to 96%. Of note, this method allows retention of halide handles in sp^2 hybridized carbons (**24**), which along with ketones, esters,



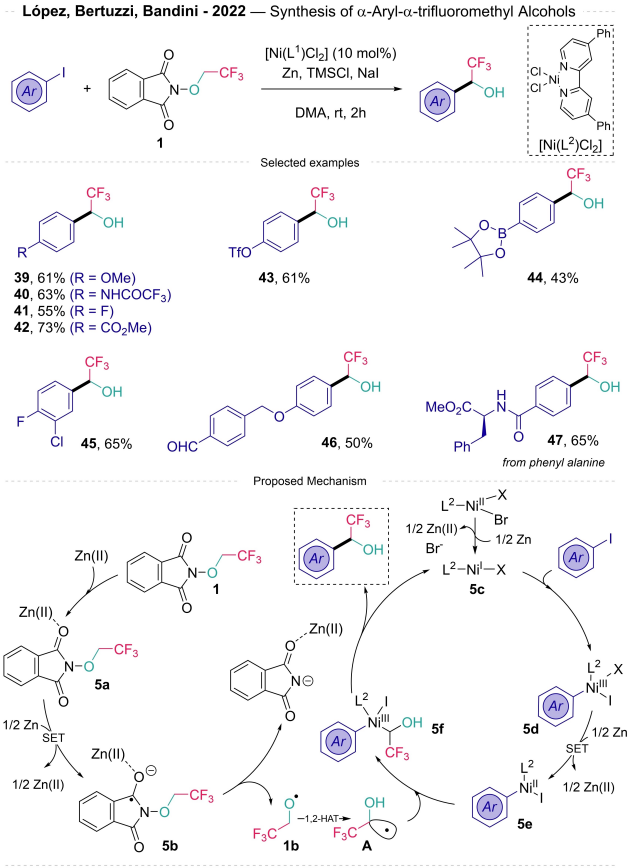
Scheme 3. Synthesis of hydroxytrifluoroethyl isoquinolines mediated by the photochemical generation of radical synthon **A** using an iridium photocatalyst.



Scheme 4. Installation of hydroxytrifluoroethyl group on allylic sulfones, *N*-acrylamides and cinnamic acids via silylated radical synthon **A** generated by Mn(II)/Mn(III) catalysis.

nitro, amides (**29**), sulfones (**30**), alcohols, aldehydes, and relevant biomolecules (**32**) demonstrate the high functional group tolerance. The insertion of the hydroxydifluoroalkyl moiety is also possible using the optimized reaction conditions (**33**). On the other hand, the same approach can be efficiently extended to *N*-acrylamides and cinnamic acids as organic substrates, providing hydroxytrifluoroethylated oxindoles (**34**–**36**) and α-trifluoromethylcinnamyl alcohols (**37**–**38**) from moderate to excellent yields. Importantly, the synthesis of the relevant antitumor agent Z (Figure 1) can be addressed through this strategy. The mechanism of this reaction is governed by the involvement of a catalytic cycle and a radical Brook rearrangement as key events. The authors indicate that stoichiometric $Mn(OAc)_3 \cdot 2H_2O$ could promote the desired reaction without external oxidant, revealing that the Mn(III) species is the active catalyst. First, ligand exchange between the Mn(III) and **2** generated the intermediate **4a**. Subsequently, this intermediate after homolysis delivers the alkoxy radical **4b** and Mn(II) species, which can be oxidized by *tert*-butyl peroxybenzoate (TBPB) via SET. Radical Brook rearrangement takes place to form the carbon centered radical silylated **A** from **4b**. Finally, trapping the radical with the desired organic host yields the silylated intermediate, that upon a desilylation event using TBAF provides the hydroxytrifluoroethylated organic molecule.

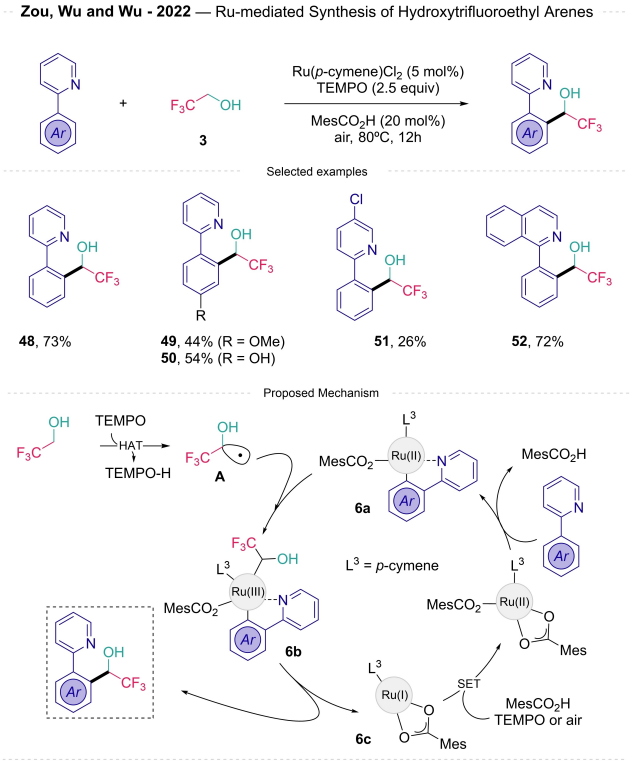
Access to α-aryl-α-trifluoromethyl alcohols is feasible from aryl iodides and reagent **1** through a nickel catalyzed cross-electrophile coupling process. This approach reported by López, Bertuzzi, and Bandini proved to be effective when using 10 mol% of a bipyridine nickel(II) complex in the presence of Zn as reductant and DMA as solvent (Scheme 5).[26] The use of NaI and TMSCl ensures better efficacy, reproducibility, and shorter reaction time. In contrast to Friedel-Crafts-like methods employing trifluoroacetaldehyde, where only electronically rich arenes are amenable, the documented nickel catalyzed process allows the preparation of a wide range of α-trifluoromethyl alcohols possessing electron-donating (OMe, OAc or NBn_2), but also electron-withdrawing groups (F, Cl, CF_3, CO_2Me) in the aromatic position. Of note, the Csp^2–Br bond could be moved forward during this metal process, showing a notable Br/I selectivity. As a bonus, the method was tolerant to important sensitive groups, such as triflate (**43**), Bpin (**44**), or TMS-protected alkynyl moieties. Aldehyde functional group was kept under the optimized reaction conditions as well (**46**). Finally, a series of iodoarene-containing bioactive molecules (**47**) were subjected to the alkylation process with yields that ranged 32–65%. The operative mechanism of this transformation was investigated experimentally and computationally. Metallic Zn undergoes a series of coordination and single-electron transfer events (**5a** to **5b**) with **1** to deliver the fluorinated alkoxy radical **1b**. Importantly, Zn species facilitates the N–O bond scission of the phthalimide backbone **5b**, ensuring a facile deliver of the alkoxy radical **1b**, that furnishes the key alkyl-centered radical **A** after solvent promoted 1,2-HAT event. The role of Zn is also essential in the nickel catalytic cycle forming the active Ni(I) species **5c** via SET from Ni(II) precatalyst. This active intermediate coordinates the aryl iodide instead of reagent **1** because the latter is



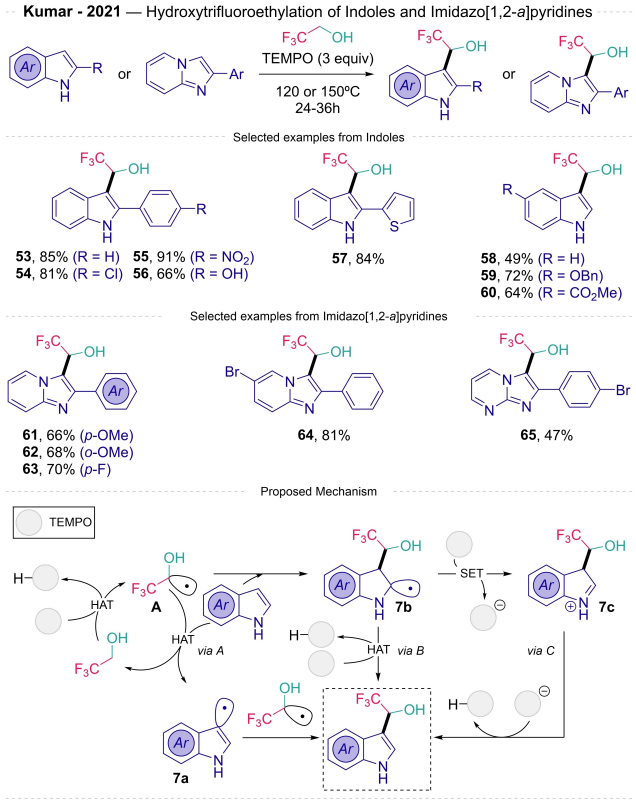
Scheme 5. Preparation of α-aryl-α-trifluoromethyl alcohols via cross-electrophile coupling. Radical synthon (**A**) generated by metallic zinc species and captured by nickel.

an energy demanding step as suggested by calculations. After coordination, oxidative addition occurs (**5d**) and another SET with Zn deliver the Ar–Ni(II)-(L^2)I intermediate **5e**. This species traps the carbon-centered radical **A** yielding the Ni(III) species **5f**, which upon reductive elimination provide access to the desired α-aryl-α-trifluoromethyl alcohol.

The selective *ortho* C–H hydroxyfluoroalkylation of arenes can be accessed under ruthenium catalysis. This method reported by Zou, Wu and Wu operates using trifluoroethanol **3** as radical precursor and involves an irreversible C–H bond metalation and an irreversible oxidative addition of radical synthon **A** (Scheme 6).[27] The method is amenable to a wide range of electron-rich (**49**–**50**) and electron-poor (**51**) 2-phenylpyridine derivatives with moderate yields. However, the method is limited to 2-phenylpyridines due to the synergy with the metal center in the metalation process. The reaction is ineffective to other heteroaromatics. Other fluorinated alcohols also proved to be competent under the standard reaction conditions. Interestingly, non-fluorinated alcohols failed to provide the C–H alkylated products, thus showing the importance of the radical's synthon **A** electronic character. The authors presented a plausible mechanism based on an irreversible C–H bond metalation and a radical addition of **A** as key steps. First, radical **A** is yielded after a HAT event from



Scheme 6. Ruthenium-mediated synthesis of hydroxytrifluoroethylated arenes via synthon **A** generated by TEMPO promoted HAT.



Scheme 7. Hydroxytrifluoroethylation of indoles and imidazo[1,2-*a*]pyridines under thermal conditions via generation of radical synthon **A** generated by TEMPO promoted HAT.

trifluoroethanol and TEMPO. Subsequently, **A** reacts with the activated Ru species **6a** that hosts the 2-phenylpyridine substrate, obtaining intermediate **6b**. Then, a reductive elimination event occurs leading to the formation of the desired product and intermediate **6c**, which is further oxidized via SET with TEMPO or O_2 with subsequent ligand addition to restore **6a**.

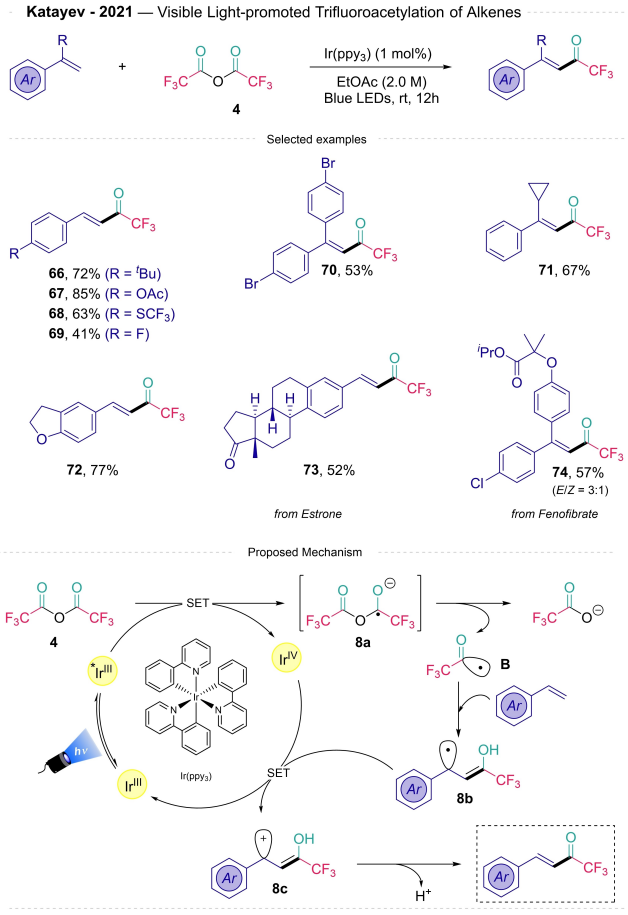
2.3. Via Metal-free Single-Electron Transfer

In 2021, the Kumar group reported an efficient metal-free hydroxytrifluoroalkylation of indoles and imidazo[1,2-*a*]pyridines using trifluoroethanol as fluorinating agent. This transformation proceeds via cross-dehydrogenation coupling mediated by TEMPO as oxidant and under thermal conditions (Scheme 7).[28] The substrate scope is applicable to unprotected 2-arylindoles bearing both electron-withdrawing and electron-donating groups (**54**–**56**). Importantly, the method is not only limited to 2-arylindoles, but also C2-unsubstituted substrates (**58**–**60**) reacted with yields that ranged from 49 to 72%. *N*-alkylated indoles are also competent substrates in this transformation. Subsequently, the authors extended this hydroxytrifluoroethylation method to imidazo[1,2-*a*]pyridines with electron-donating and electron-withdrawing groups (**61**–**65**). Of note, the optimized reaction conditions were extended for general hydroxyfluoroalkylation using pentafluoropropan-1-ol and heptafluorobutan-1-ol as fluorinated precursors. The usefulness of the method is highlighted in the late-stage functionalization of the gastroprotective Zolimidine, as well as in the post-functionalization of the prepared hydroxyfluoroalkylated products to aza-heterocycles. The mechanism of this transformation is governed by the generation of the carbon-centered radical **A** after a HAT event from TEMPO and trifluoroethanol. The generated radical **A** can undergo HAT with the heterocyclic substrate yielding the indole radical **7a** (via A). Subsequently, recombination of both radical species provides the final hydroxytrifluoroethylated indole. However, another two possible mechanistic pathways are considered by the authors (via B and C). The generated radical **A** can be trapped by the heterocyclic substrate to provide radical species **7b**. Herein, this species can produce the desired product via HAT with TEMPO (via B) or can meet with TEMPO to give rise to a SET event to form the cationic intermediate **7c**, which upon deprotonation give access to the desired indole (via C).

3. Radical-mediated Trifluoroacetylation

3.1. Via Photoinduced Methods

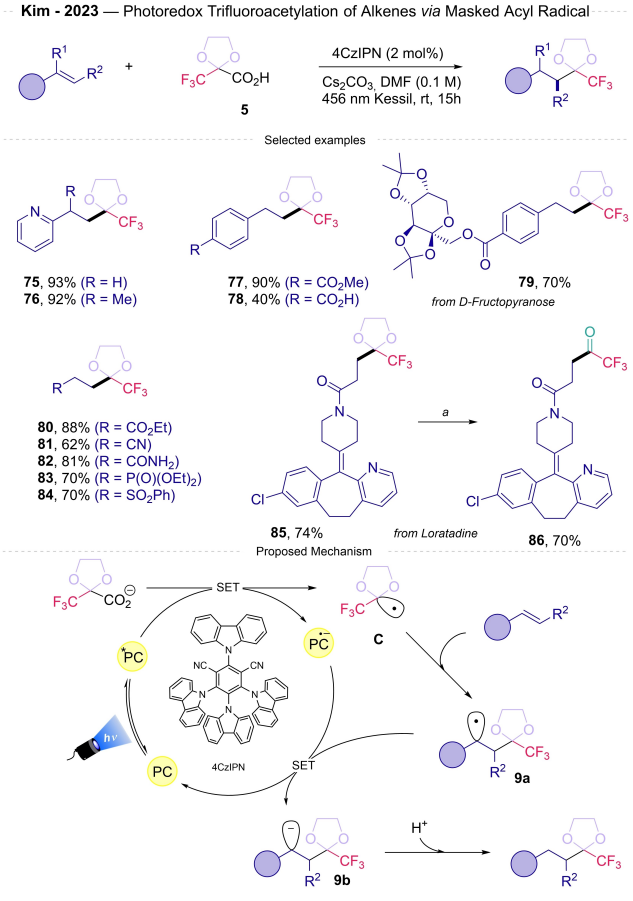
The trifluoroacetylation of alkenes can be addressed under visible-light conditions and using trifluoroacetic anhydride **4** (TFAA) as feedstock (Scheme 8).[29] The Katayev group exploited



Scheme 8. Trifluoroacetylation of alkenes mediated by the photochemical formation of radical synthon **B**.

the well-known electrochemistry of **4** to generate the desired radical through photoredox catalytic process. The incorporation of the radical into a variety of alkene derivatives is accomplished through a catalytic cycle based on the readily accessible $Ir(ppy)_3$ under blue light irradiation without extra additives, which makes this method operationally simple. The presented method is amenable to a wide number of styrenes bearing electronically rich and electron-withdrawing groups and heterocyclic alkenes (**72**), obtaining chemical yields from 30 to 94%. Interestingly, a critical parameter of the protocol is the reagents concentration. It was noticed that the fragmentation of radical **B** ($CF_3CO^{\bullet}$) into CO and $^{\bullet}CF_3$ is a thermodynamically favored process, thus a high concentration of the reagents favors the Giese addition to the alkene over its fragmentation. Moreover, if the reaction is performed under CO atmosphere, the fragmentation of radical **B** could be almost suppressed. The trifluoroacetyl moiety can be installed in a large number of organic backbones with different functionalities, including aromatic halides (**69**), esters and medicinally relevant molecules (**73**). However, the scope of the reaction is limited to notably electron-rich substrates since the electrophilic character of the acyl radical could lead to polarity-mismatched reactivity between reagents. After mechanistic investigations including experimental electrochemical, photophysical, H/D scrambling and computational experiments, the operative mechanistic pathway of this synthetic method is based on a classical photocatalytic cycle via an oxidative quenching. Photoexcitation of $Ir(ppy)_3$ under blue LEDs irradiation generates a highly reducing excited state *Ir(III) ($E_{1/2}$*Ir(III)/Ir(IV) = −1.73 V vs SCE) which reduces TFAA (**4**) ($E_{1/2}^{4/4\bullet-}$ = −1.20 V vs SCE) to intermediate **8a**. After C–O bond fragmentation, trifluoroacetoxy anion and trifluoroacetyl radical **B** are formed. The generated electrophilic radical reacts with the alkene yielding the radical intermediate **8b** ($E_0^{[8b]}$ = 0.43 V vs SCE), which after SET with the oxidized Ir(IV) ($E_0^{Ir(IV)/Ir(III)}$ = 0.77 V vs SCE) deliver the cationic intermediate **8c** and Ir(III) is recovered. Finally, tautomerization of intermediate **8c** followed by deprotonation furnish the desired product.

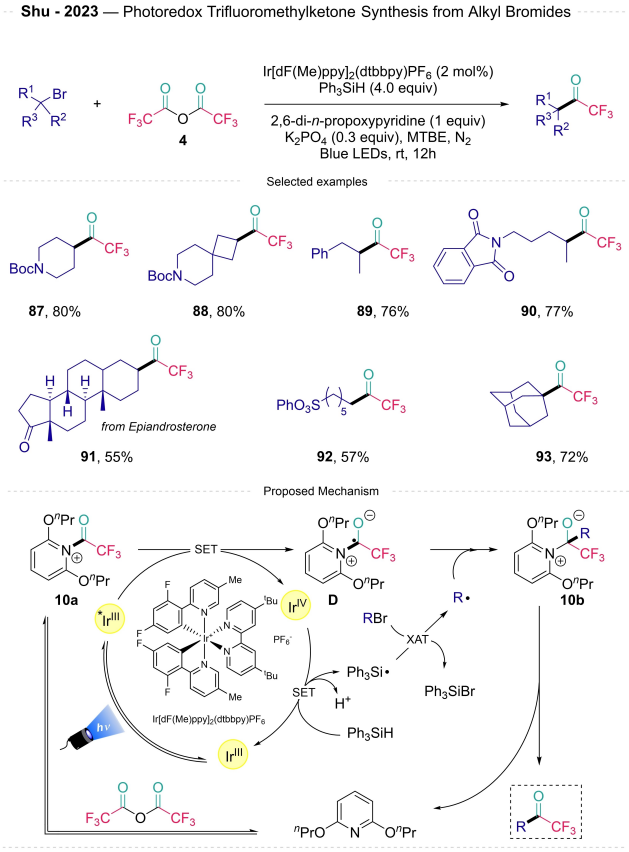
In 2023, the Kim group designed a photoredox method for the trifluoroacetylation of alkenes through a masked acyl radical **C** (**5** in Scheme 9).[30] This work reports a unique cyclic acetal-based trifluoromethylated radical precursor, which is considered a masked acyl radical. This original radical would own a totally opposed electronic character compared to the trifluoroacetyl radical. This nucleophilic like radical represents a dramatic change of reactivity and opens a new scenario for chemists. Moreover, the addition of the protecting group greatly



Scheme 9. Indirect trifluoroacetylation of alkenes via metal-free photo-induced generation of acetal-protected radical synthon **C**. [a] BBr_3 (3 equiv), DCM, 0 °C, 2 h.

enhances the stability of the formed radical, thus avoiding the decarbonylation process that ultimately forms $^{\bullet}CF_3$ and leads to competing reactions. The masked trifluoroacetyl moiety is tethered to electron deficient alkenes as organic architectures using the radical precursor **5** and operated by 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) as organophotocatalyst. The method is amenable to a wide range of heteroaromatics (**75**–**76**), styrenes (**77**–**78**), and Michael acceptors (**80**–**84**) with moderate to excellent yields (28–94%). Moreover, it exhibits excellent functional group tolerance such as esters (**77**), carboxylic acids (**78**), free amides (**82**), phosphonates (**83**), sulfones (**84**), among others. Importantly, the masked acyl group can be later deprotected to obtain the true trifluoromethylketone (**86** from **85**), which has interesting features in organofluorous chemistry as discussed above. Although the acetal deprotection step presented several drawbacks, the authors found greater ease of deprotection using alternative heterocyclic protecting groups, such as oxazolidine. Finally, a photoredox cycle governed by a reductive quenching is proposed as a mechanistic scenario. First, deprotonation of compound **5** ($E_{1/2}^{5\bullet/5^-} = 1.33$ V vs SCE) favors an oxidation event via SET with the excited state of the organic photocatalyst ($E_{1/2}$*4CzIPN/4CzIPN$^{\bullet-}$ = 1.35 V vs SCE), followed by a decarboxylation to form radical intermediate acetal **C**. Then, acetal **C** undergoes Giese addition in a regulated fashion yielding intermediate **9a**, which lately undergoes SET with reduced 4CzIPN$^{\bullet-}$ to restore the photocatalyst and form the anionic species **9b**. Finally, the masked trifluoroacetylated compound is obtained after protonation of the anionic intermediate.

Very recently, the Shu group accessed alkyl trifluoromethylketones from TFAA and alkyl bromides under photoredox conditions (Scheme 10).[31] This transformation operates through a dual system formed by an iridium photocatalytic cycle along with a halogen atom transfer (XAT) event promoted by Ph_3SiH. Of note, the addition of a pyridine derivative proved to show better efficacy to the formation and stabilization of the trifluoroacetyl radical. The transformation is amenable to tertiary, secondary and primary alkyl halides in moderate to good yields. Furthermore, protected amines (**87**–**88**), esters, imides (**90**), sulfonates (**92**), *N*-H amides, aromatic halides, among other functional groups are well tolerated. Remarkably, this photoinduced protocol is synthetically useful for late-stage functionalization of biologically active compounds such as Epiandrosterone (**91**). The standard conditions can be applied to other perfluorinated anhydrides in moderate yields. The formation of a stable trapped trifluoroacetyl radical intermediate (**10a** in Scheme 10) was detected by luminescence quenching experiments. Although, TFAA showed a significant quenching, the pyridine/TFAA mixture showed a much more intense quenching, thus suggesting that *N*-trifluoroacetyl pyridinium salt **10a** is more likely the redox-active species operating in this mechanism. Further experiments along with the luminescence quenching studies provided mechanistic insights for this transformation. First, TFAA and the pyridine derivative react to form the redox-active pyridinium salts **10a**, which undergoes SET with excited Ir(III) to generate the zwitterionic intermediate **D** and the oxidized Ir(IV). Then, Ir(IV) species provides one electron

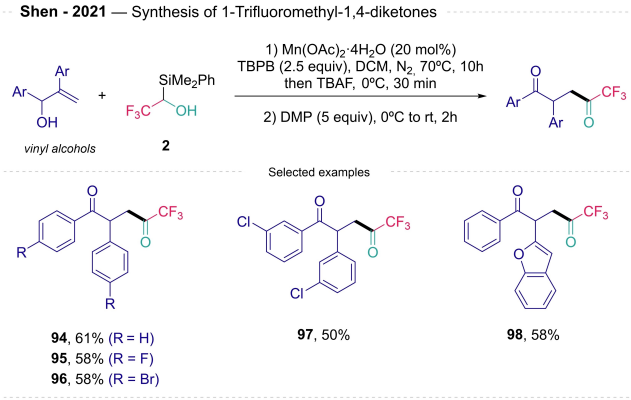


Scheme 10. Visible-light mediated synthesis of trifluoromethylketones from alkyl bromides and TFAA.

($E_{1/2}^{Ir(III)/Ir(IV)} = 1.94$ V *vs* SCE) to triphenylsilane ($E_{1/2}^{Ox} = 0.81$ V *vs* SCE) yielding the corresponding silyl radical species with concomitant proton loss and the photocatalyst ground state. The obtained radical undergoes XAT with the corresponding alkyl bromide, obtaining the desired radical that subsequently reacts with the zwitterionic species **D** to generate **10b** in a regulated fashion. Finally, elimination of the pyridine derivative furnishes the final trifluoromethylketone organic compound.

3.2. Via Transition Metal complexes

The Shen group utilized the silicon-based reagent **2** for the preparation of 1-trifluoromethyl-1,4-diketones via manganese-catalysis (Scheme 11).[32] This reaction operates via single-electron process in a similar way as described for the preparation of α-trifluoromethyl-containing homoallylic alcohols (Scheme 4). The desired 1-trifluoromethyl 1,4-diketones are produced after a two-step process consisting of a manganese-catalyzed reaction followed by an oxidation step using Dess-Martin periodinane (DMP) reagent. Aryls bearing alkyl and halide (**94**–**96**) groups are amenable substrates to this transformation, as well as benzofuran derivative (**98**).



Scheme 11. Mn(II)/Mn(III) catalyzed preparation of 1-trifluoromethyl-1,4-diketones *via* silyl-protected radical synthon **A**.

4. Summary and Outlook

While hydroxytrifluoroethylated and trifluoroacetylated organic skeletons have been widely used in pharmaceuticals and agrochemicals over the last years, the direct introduction of these fluorinated moieties is recently becoming more popular given their unique properties, including their bioisosteric character. New ways of exploiting their chemical synthesis are receiving great attention via single-electron transfer processes as key modes of reactivity. In this regard, the renaissance of radical chemistry has proved to be competent for the chemical synthesis of these relevant molecules.

Many of the hydroxytrifluoroethylation protocols via radical synthon **A** aim the functionalization of sp^2-hybridized carbons from aryl halides and allylic sulfones. Additional challenges for the future include extending the range of radical acceptors, further designing processes for difunctionalization or multi-component reactions for novel chemical space exploration. Development of novel synthetic methods using greener solvents and avoiding transition metals will also be of great interest. Although direct trifluoroacetylation of organic backbones from radical synthons **B** and **C** is still in its infancy, they have proved to be very effective under photoinduced conditions. However, protocols avoiding the use of iridium-based photocatalysts would represent an improvement of sustainability. In addition, exploring further organic hosts for radical synthons **B** and **C** beyond styrenes, electron-deficient alkenes and alkyl bromides will be of interest for synthetic organic and medicinal chemists.

In summary, the direct introduction of the hydroxytrifluoroethyl and trifluoroacetyl groups into organic entities has emerged as a tailor-made methodology for the exploitation of single-electron transfer processes. This includes photoredox, HAT and transition metal chemistry. The direct accessibility of such fluorinated functional moieties will lend itself to the future development of general processes of broad synthetic scope.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: trifluoroacetylation · hydroxytrifluoroethylation · single-electron transfer · trifluoromethyl alcohols · trifluoromethyl ketones

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