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Perspective

New Opportunities to Access Fluorinated Molecules Using Organophotoredox Catalysis via C(sp^3)−F Bond Cleavage

Sourav Roy* and Tatiana Besset*

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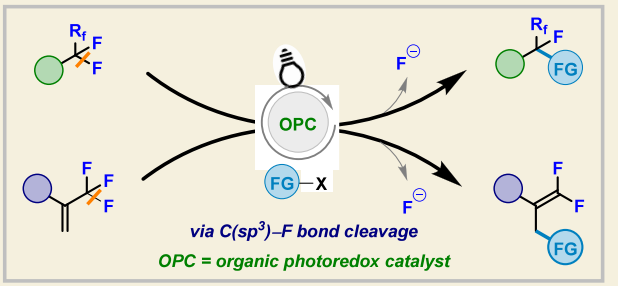
ABSTRACT: Fluorinated molecules are of paramount importance because of their unique properties. As a result, the search for innovative approaches to the synthesis of this class of compounds has been relentless over the years. Among these, the combination of photocatalysis and organofluorine chemistry turned out to be an effective partnership to access unattainable fluorinated molecules. This Perspective provides an overview of the recent advances in synthesizing fluorinated molecules via an organophotoredox-catalyzed defluorination process from trifluoromethylated compounds. It encompasses the preparation of difluoromethylated (hetero)arenes, amides, and esters as well as *gem*-difluoroalkene derivatives using C(sp^3)−F bond activation or *β*-fragmentation. This Perspective will highlight remaining challenges and discuss future research opportunities.



KEYWORDS: *Photocatalysis, Organic dyes, Single C(sp^3)−F bond cleavage, Synthetic methodology, Difluoromethylated motifs*

1. INTRODUCTION

The field of organofluorine chemistry is a vibrant area of research, with steady progress in the quest for straightforward synthetic development to reach high-valued organofluorine compounds.[1−14] From molecules with a single fluorine atom to those substituted with a large diversity of fluorinated groups, fluorine-containing molecules are prevalent in materials science, pharmaceutical, and agrochemical industries.[15−20] Indeed, the installation of a fluorinated residue can drastically change the physical properties of the corresponding products.[21] Due to the importance of these compounds and to address contemporary concerns, the continuous search for innovative synthetic pathways drives scientists to make significant advances in the field.[22−27] Among the different strategies, radical chemistry and more recently light driven photoredox catalysis[28−36] allowed the synthesis of fluorinated molecules (Scheme 1(i)) via (1) direct fluoroalkylation and fluorination reactions using a suitable fluorinating reagent (e.g., Selectfluor, iodonium and sulfonium salts, perfluoroalkyl halides)[37−45] and (2) valorization of fluorinated feedstocks to construct high-value-added fluorinated molecules through C−F bond functionalization,[46−51] the last approach being still in its infancy. With the selective single C(sp^3)−F bond cleavage of readily available CF_3-containing precursors, useful CF_2-containing compounds[52,53] will be produced without needing any specific fluorinating reagents. However, this is a challenging task given the redox potential of the targeted fluorinated molecules (Scheme 1(ii)) along with possible polydefluorination as side reactions.[54]

In this context, precious transition metal based photoredox catalysts based on ruthenium and iridium complexes have been extensively used. They can trigger reactions by undergoing either a single electron transfer (SET) or energy transfer (E_nT) mechanism. However, to reduce reliance on precious transition metal catalysts and promote sustainable synthetic chemistry, in recent years, organic photoredox catalysts (OPCs)[55−63] have emerged as a potent class of photocatalysts (Scheme 2). They have demonstrated several advantages such as (i) being easy to synthesize or commercially available, (ii) being less toxic, and (iii) having redox properties that can be fine-tuned by structural modifications. Moreover, a key advantage of OPCs is their highly oxidizing nature, which enables them to reduce strong bonds, such as the C−F bond (BDE(C−F) ≈ 130 kcal·mol^{-1}). Hence, the synthesis of unattainable fluorinated molecules was possible by photochemical synthetic strategies, which generally proceeded via single C−F bond cleavage or *β*-fluoride elimination starting from fluorinated feedstocks.

This Perspective will focus on the groundbreaking advances made to build up diversely substituted fluorinated molecules by organophotoredox-catalyzed single C−F bond functionaliza-

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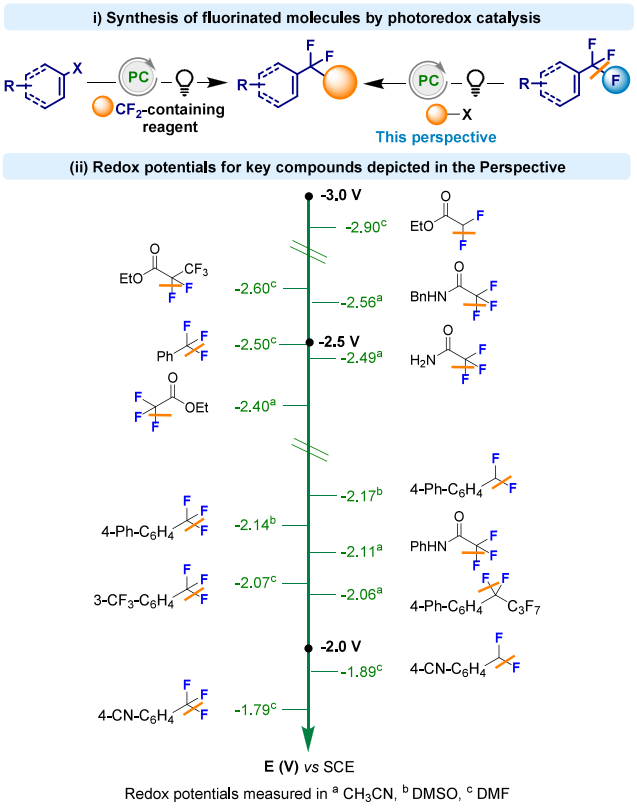
Scheme 1. (i) Main Synthetic Pathways to Synthesize Fluorinated Molecules by Photoredox Catalysis and (ii) Redox Potentials of the Key Compounds Depicted in This Perspective Based on Previous Literature[82,83,101,102,104−112,114−116,119,120]



tion. From direct C−F bond cleavage (section 2) to β-fragmentation (section 3), trifluoromethylated (hetero)arenes, carbonyl derivatives, and trifluoromethylated alkenes have been straightforwardly functionalized to offer high-value-added fluorinated compounds. Note that transformations based on transition metal catalysis are out of the scope of this Perspective.[64−69]

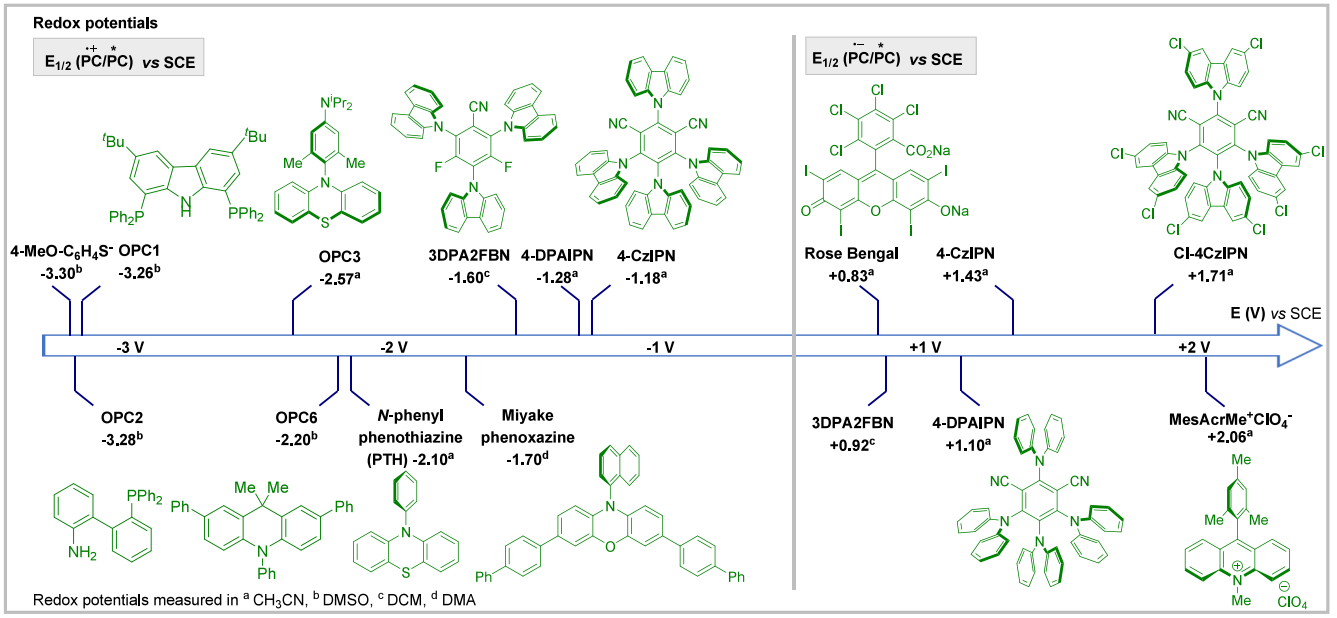
2. STRATEGY BASED ON SINGLE C−F BOND ACTIVATION FOR THE SYNTHESIS OF DIFLUOROMETHYLATED MOLECULES

Over the last years, strategies for the synthesis of difluoromethylated derivatives from CF_3-containing molecules by selective single C(sp^3)−F bond cleavage have emerged as a powerful tool (Scheme 3(i)). In this section, the major advances that have been made using (1) organophotoredox catalysis and (2) dual catalysis including processes merging organophotoredox catalysis with HAT or transition metal catalysis are covered. The selectivity issue is the main obstacle associated with the reduction of trifluoromethylated molecules as undesired over-defluorination reactions might compete with the targeted transformation, resulting in a mixture of partially or fully defluorinated products.

Organophotoredox catalyzed defluorination of trifluoromethylated compounds through direct single C(sp^3)−F bond activation could follow both oxidative and reductive quenching pathways (Scheme 3(ii)). In the oxidative quenching pathway, the ground state photocatalyst (PC) was excited under light irradiation to reach its excited state (PC*). This latter (PC*) then reduced **1** via a single electron transfer (SET) process to generate the corresponding radical anion intermediate **I**. After a mesolytic cleavage, the resulting difluoromethylated radical **II** reacted with a suitable coupling partner **2** to deliver the product **3** in the subsequent steps. The photocatalyst was regenerated after a SET process in the presence of a suitable electron donor species (**D**).

On the other hand, the reductive quenching pathway was initiated by the reduction of the excited state photocatalyst (PC*) by any electron donor species (**D**). In the next step, the reduced photocatalyst ($PC^{\bullet-}$) reacted with the fluorinated

Scheme 2. Overview of the Organophotoredox Catalysts Depicted in This Perspective (Structures and Redox Properties)[70−73,102,104,106,115]



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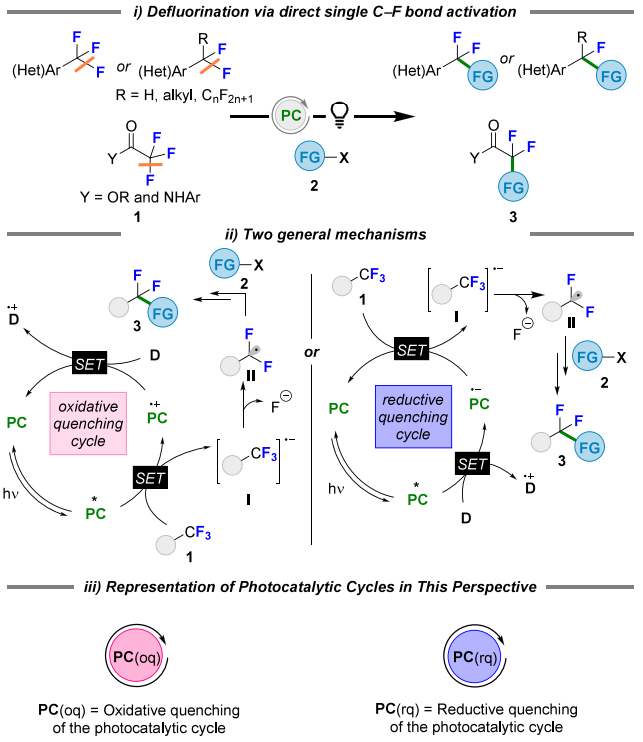
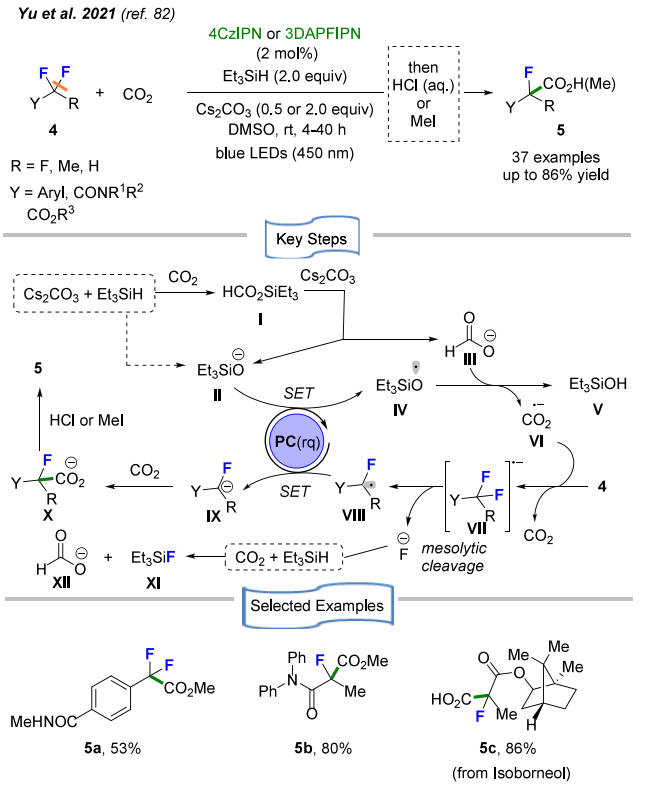
Scheme 3. Organophotoredox-Catalyzed Defluorination via a Single C−F Bond Activation



Scheme 4. Carboxylation of C(sp^3)−F Bonds with CO_2 under Photoredox Catalysis



molecule **1**, resulting in the formation of the difluoromethyl radical **II** via the intermediate **I** and regenerating the photocatalyst. In the final step, the intermediate **II** was functionalized to deliver the expected product **3**.

2.1. Using Organophotoredox Catalysis

Starting from groundbreaking research by König *et al.*,[74] several research groups have employed photocatalysts based on transition metals for C−F bond cleavage, which has been thoroughly documented in several review articles.[75−81] At the same time, organophotoredox catalysis has emerged as a powerful strategy for activating single C−F bonds, as highlighted by the developments discussed in this section.

2.1.1. Using Organic Dyes as Photocatalysts. In 2021, Yu's group investigated the organophotoredox-catalyzed carboxylation of versatile fluorinated compounds **4** using CO_2 as a nontoxic, abundant C1 source. This methodology demonstrated the dual role of CO_2 as both electron carrier and electrophile, thus resulting in the valuable fluorinated carboxylic acid derivatives **5**, conventionally known as bioisosteres of aryl acetic acids (Scheme 4).[82] Based on mechanistic studies and DFT calculations, it appeared that the fluorinated substrates **4** were not directly activated by the reduced photocatalyst. Instead, the mechanism followed a stepwise pathway. First, *in situ* generated silicate ion **II** was oxidized by the excited photocatalyst via a stepwise outer-sphere single-electron transfer to form the corresponding siloxyl-radical **IV**. This latter reacted with the *in situ* generated formate **III** to deliver Et_3SiOH **V** and the CO_2 radical anion **VI** after a single electron transfer (SET). Reduction of **4** by $CO_2^{\bullet-}$ led to the species **VII**. After a mesolytic cleavage of the C−F bond, the resulting carbon radical **VIII** further underwent a SET-reduction process with the reduced PC to give the corresponding carbanion **IX**. This latter would further react with CO_2 to give the desired carboxylate **X**, which after protonation or methylation would afford **5**. Note that the expelled fluoride ion in this process participated in the formation of fluorosilane **XI**, and formate **XII** in the presence of CO_2 and triethylsilane (Scheme 4).

Most of the photoredox catalyzed C(sp^3)−F activation methods require reducing conditions or fluoride scavengers.[46−51] In 2023, Zhang and co-workers reported a fluoride-scavenger-free protocol where alkene-selective insertion into a benzylic C−F bond occurred under visible-light photoredox catalysis (Scheme 5). An organic photocatalyst, the Miyake phenoxazine, was able to trigger the reaction between **6** and the alkene **7**, where $Et_3N{\cdot}3HF$ acted as a fluoride source to furnish the desired product **8**. This method was also applicable to some complex molecules of biological relevance.[83] As depicted in Scheme 5, the photocatalytic cycle started with the reduction of **6** with the exited photoredox catalyst to generate the benzylic radical intermediate **II** after fluoride release. Next, trapping of radical **II** with alkene **7** led to intermediate **III**, which underwent a photocatalytic radical polar crossover (RPC) path to generate the carbocation intermediate **IV**. Finally, after the reaction of carbocation **IV** with $Et_3N{\cdot}3HF$, the desired product **8** was obtained (Scheme 5).

Although major developments have been achieved for the construction of C−C/C−H bonds, only a few methods exist to forge carbon−heteroatom (C−Het) bonds by selective C−F bond cleavage. To fill this gap, in 2023, Xu and co-workers came up with an interesting study where an OPC had been utilized to synthesize difluoromethyl ethers [$-CF_2X-$ (X = O, S, Se)] via single C(sp^3)−F bond activation of trifluoromethylated arenes (Scheme 6). Notably, difluoromethyl ether motifs have appeared as prominent mimetics of biologically active esters in

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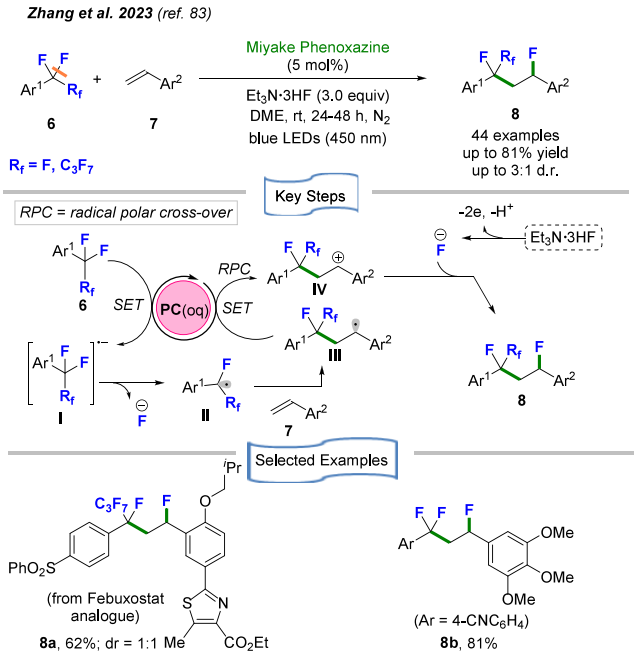
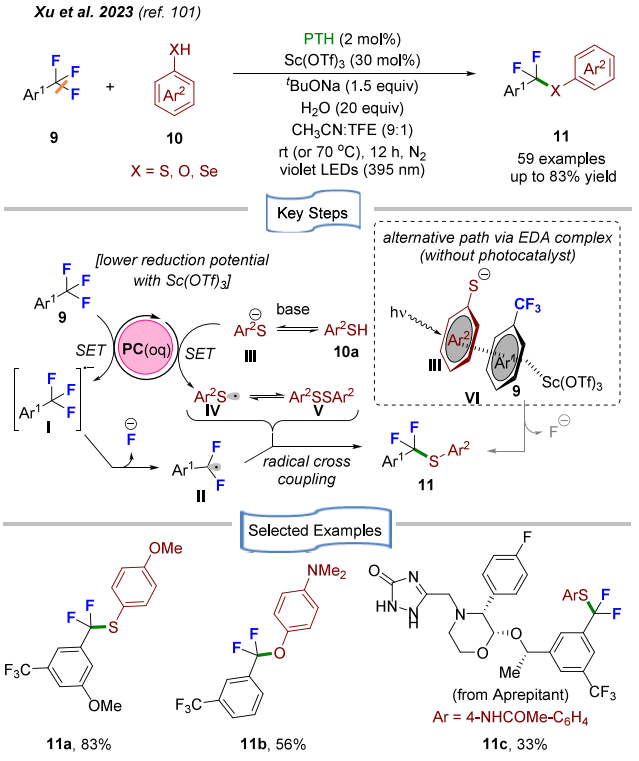
Scheme 5. OPC-Catalyzed Formal Insertion of Alkenes into a Benzylic C−F Bond



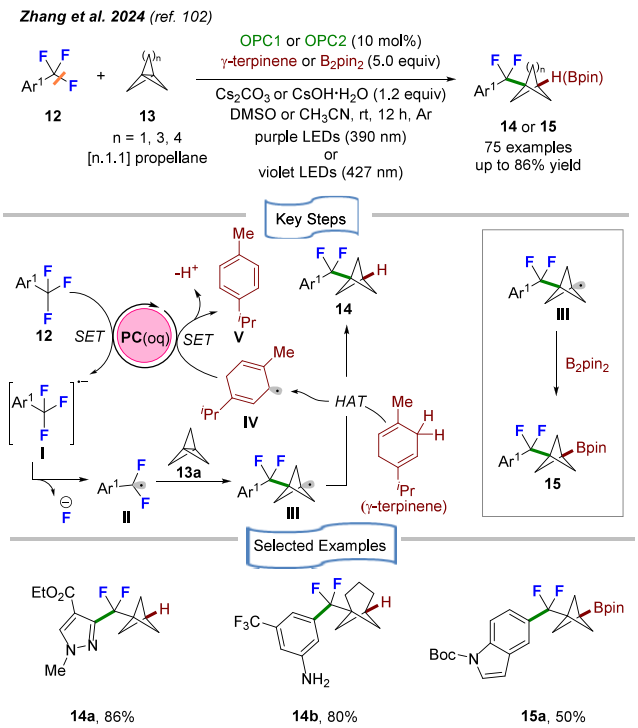
Scheme 6. Lewis Acid-Assisted Construction of C−X (X = S, O, Se) Bonds via C−F Bond Activation



drug development.[84−90] As a complementary approach compared to the existing routes,[91−100] this method allowed the direct functionalization of readily available trifluoromethyl arenes **9** and thiophenols (or phenols, selenols) **10** to construct the corresponding difluoromethyl ethers **11** (or − CF_2X− (X = S, Se) without any need for preactivation steps.[101] To favor and control the quenching of the *in situ* generated difluoromethyl radical via a HAT, the astute combination of phenylthiohydantoin (PTH) as an OPC and $Sc(OTf)_3$ as a Lewis acid, enabled lowering of the reduction potential of trifluoromethyl arenes, which was the key to ensure high efficiency of the reaction (Scheme 6). Note that the addition of water (20 equiv) played a significant role in solubilizing the *in situ* generated thiolate and in promoting the formation of dynamic H−F hydrogen bonds with the radical anion intermediate **I** to facilitate the fluoride anion elimination. This method was tolerant of various thiols, phenols, and selenols (**10**) as nucleophiles. In addition, its synthetic utility was further illustrated by the late-stage functionalization of several CF_3-containing pharmaceuticals. Two possible mechanisms were suggested based on either a photocatalytic single electron-transfer (SET) or an electron donor−acceptor (EDA) process. For the photoredox pathway, $Sc(OTf)_3$ can lower the reduction potential of **9** (ΔE = 0.11 V). Therefore, the excited PTH easily reduced the trifluoromethylated compound **9** to its radical anion **I**. After mesolytic cleavage of fluoride from intermediate **I**, the corresponding difluorobenzylic radical **II** was generated. Besides, the thiolate anion **III** was oxidized from the photocatalytic cycle to produce the nucleophilic radical **IV** or disulfide compound **V**. Then, an open shell radical−radical cross-coupling between radicals **IV** and **II** delivered the desired product **11**. A complementary path via an EDA-guided mechanism would imply the formation of a colored EDA complex **VI** between the thiolate anion **III** and the trifluoromethylarene **9** assisted by $Sc(OTf)_3$ to furnish the product **11** after radical−radical cross-coupling (Scheme 6).

Recently, Zhang and co-workers[102] disclosed that a light-driven C−F bond activation strategy can also be employed over strain-release of sp^3-hybridized small-ring cage hydrocarbons (Scheme 7). The bicyclo[1.1.1]pentane (BCP) was selected as a reaction partner due to its ability to enhance the pharmacokinetic properties of organic molecules and because it is

Scheme 7. Synthesis of Aryldifluoromethyl Bicyclopentanes Enabled by C−F Bond Activation



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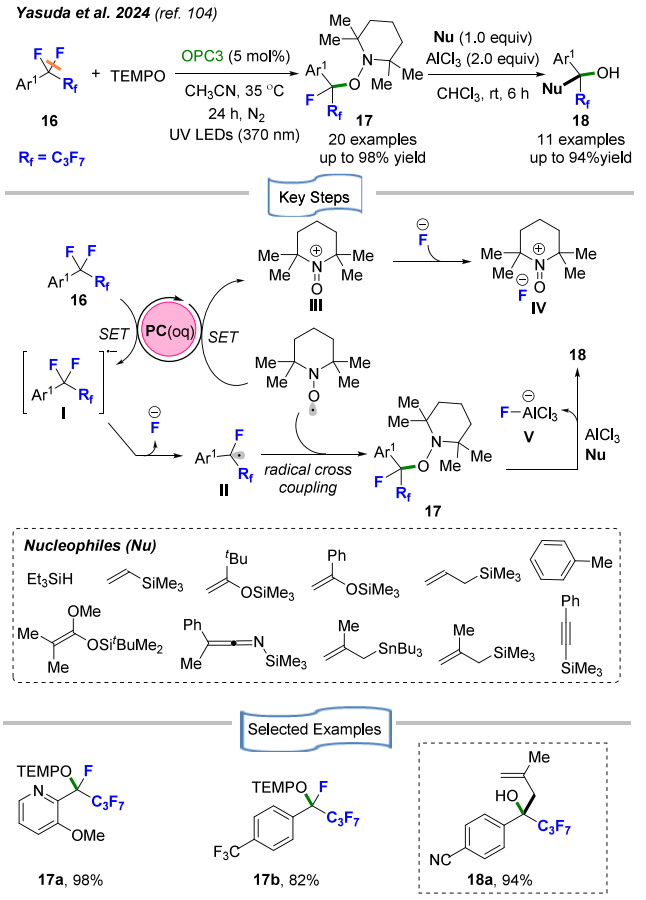
considered an attractive bioisostere for benzene rings. In this respect, various [1.1.1]propellane, [3.1.1]heptane, and [4.1.1]-octane strain ring systems **13** were reacted with trifluoromethyl arenes **12**, whereas γ-terpinene was chosen as a hydrogen atom donor to achieve diversifiable $ArCF_2$−BCP synthetic linchpin **14**.[102] Notably, the main advantage of Zhang's report relied on the valorization of readily available $ArCF_3$ derivatives over $ArCF_2Br$ analogs.[103] It is worth mentioning that the synthesized aryl difluoromethyl bicyclopentane can also act as a bioisostere of the benzophenone core. This is a challenging transformation, as evidenced by several identified hurdles to overcome, such as (i) overfunctionalization of the resulting difluoromethylated product, (ii) propellane oligomerization, and (iii) deleterious quenching of *in situ* generated difluorobenzylic radicals by a hydrogen atom. Using the carbazole- or phosphine-based organic photocatalyst (**OPC1** or **OPC2**), which displayed a high reduction potential, a wide variety of fluorinated compounds **14** including complex drug derivatives were prepared. Mechanistic studies suggested that the defluorination of the trifluoromethyl arene derivative **12** generated the corresponding difluoromethyl radical **II**, which was rapidly intercepted by [1.1.1]propellane **13a** to form the resulting BCP radical **III**. The electrophilic radical **III** then underwent a hydrogen atom transfer (HAT) process with γ-terpinene, thus providing product **14** and the corresponding cyclohexadienyl radical **IV**. Finally, after a single-electron transfer (SET), the photocatalyst was regenerated along with the formation of *p*-cymene **V** via a deprotonation step. To introduce more versatility into $ArCF_2$−BCP frameworks, this protocol was further applied to the synthesis of $ArCF_2$−BCP boronates **15** using B_2pin_2 as a radical trap (Scheme 7).

The above-mentioned protocols mainly focused on C−F bond activation from trifluoromethyl arenes. However, performing a similar reaction with perfluoroalkyl-containing molecules is still underexplored. This year, the group of Yasuda developed a method combining photoredox catalysis and Lewis acid mediation to transform the CF_2 unit in perfluoroalkyl groups **16** into complex fluoroalkylated compounds **18** through sequential cleavage of two C−F bonds (Scheme 8).[104] First, by use of the phenothiazine-based organocatalyst **OPC3** under visible light irradiation, the synthesis of aminoxylated products **17** was possible thanks to the defluoroaminoxylation of perfluoroalkylarenes with (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl (TEMPO). Synthesized products **17** were further reacted with nucleophiles in the presence of $AlCl_3$ as a Lewis acid to promote the second defluorination reaction, furnishing highly functionalized perfluoroalkyl alcohols **18**. The mechanistic studies suggested that the generation of benzyl radical **II** was crucial. An excess of TEMPO was required to regenerate the photocatalyst along with the formation of the *N*-oxo-ammonium cation **III** as a byproduct, which acted as a fluoride scavenger to trap the *in situ* generated fluoride to form the *N*-oxoammonium fluoride **IV** (Scheme 8). In the same vein, Kang and co-workers were able to defluorinate polyfluoroalkyl and perfluoroalkyl substances (PFASs) by using a carbazole-cored super-photoreductant. This method illustrates the conversion of several oligomeric PFASs such as perfluorinated compounds (PFCs), polyfluorooctanoic acid (PFOA), and perfluorooctane sulfonic acid (PFOS) derivatives into their corresponding carbonate, oxalate, formate, and trifluoroacetate compounds via defluorination under mild reaction conditions.[105]

2.1.2. Using Thiol/Disulfides as Photocatalysts. Over the years, thiol derivatives have proven to be efficient catalysts to

Scheme 8. Organophotoredox-Catalyzed Aminoxylation of Perfluoroalkylarenes with TEMPO



trigger single C−F bond cleavage under photochemical conditions. A pioneering example was reported by the group of Shang in 2022.[106] Under visible-light irradiation, the 4-methoxybenzenethiol can act as both a highly reducing electron-donating redox catalyst and a HAT catalyst to promote the catalytic C−F bond activation of trifluoromethyl substrates **19**. The choice of the thiols was important as aliphatic thiols and electron-demanding group substituted thiophenols were less efficient in triggering this reaction. It was postulated that the photoexcited thiolate **II** reduced the fluorinated substrates **19**. This feature rises as, in thiolate **I**, a direct HOMO to LUMO transition occurs for which the LUMO is situated on the π^*-orbital of the benzene ring. The HOMO is mostly positioned on the sulfur p-orbital and benefits from the conjugated π-orbitals of the 4-methoxybenzenethiol. As depicted by the authors, excited thiolate was reducing enough to convert **19** into the radical intermediate **IV** via fluoride elimination. Trapping of radical intermediate **IV** by alkene **20** led to intermediate **V**. Meanwhile, *in situ* generated thiyl radical **III** could participate in a HAT process with lithium formate to afford either the thiol or its dimer **VII** under visible light. Alternatively, thiol could participate in an HAT process with intermediate **V** to furnish disulfide **VII** and the desired product compound **21**. Finally, formate radical **VI** regenerated the catalyst via a SET process. Note that radical intermediate **IV** could also be obtained via a SET process with **VI**. This methodology was applicable over a wide variety of fluorinated derivatives **19** and alkenes **20**, providing a new platform to explore arene thiolates as inexpensive photocatalysts (Scheme 9).

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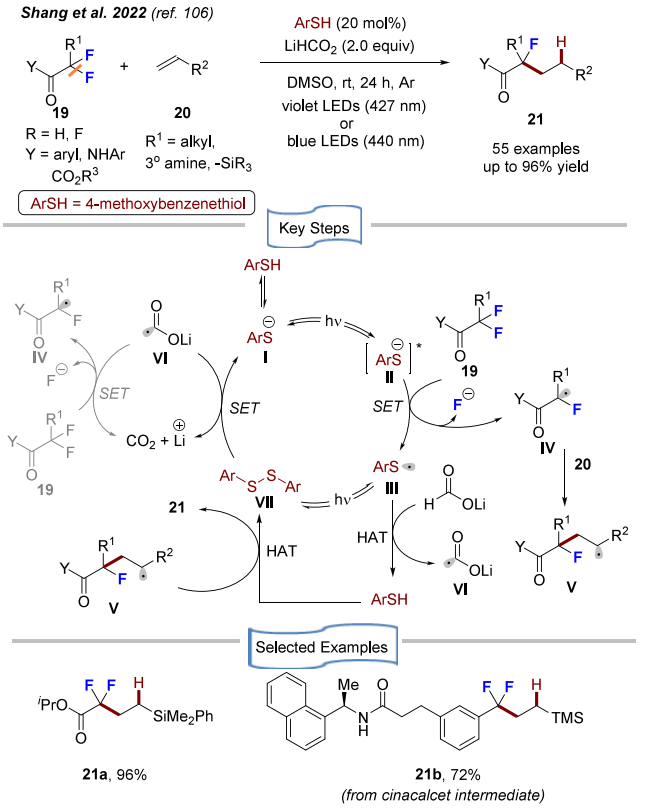
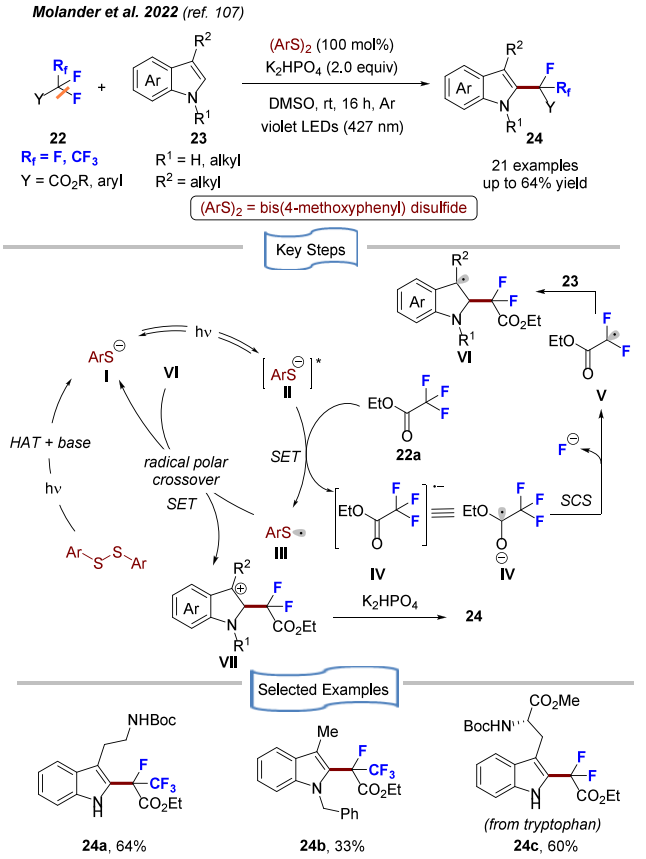
Scheme 9. Defluoroalkylation of Trifluoromethylated Carbonyl Derivatives Using 4-Methoxybenzenthiol as a Dual Function Catalyst



Scheme 10. Aryldisulfide Catalyzed Difluoroalkylation of Indoles



Following this, two back-to-back reports from the Molander group appeared. The first one dealt with the bis(4-methoxyphenyl) disulfide promoted synthesis of *gem*-difluoroalkylindoles **24** by C−F bond activation of the trifluoromethyl group.[107] In the same vein as Shang's report,[106] the generation of the thiolate ion **I** from the disulfide was crucial. Photoactive species **II** participated in a SET process with **22a** to generate the radical intermediate **V** via a spin center shift. This latter reacted with the indole **23** resulting in the radical intermediate **VI**, which was then oxidized to the corresponding carbocationic intermediate **VII** and after a final deprotonation step furnished **24** (Scheme 10).

Then, the same group reported the conversion of *N*-arylmethacrylamides **26** into difluorinated oxindoles **27** thanks to 4-methoxybenzenethiol catalyzed selective C−F bond activation followed by a cascade reaction (Scheme 11).[108] The following mechanism was suggested. The excited aryl thiolate **II** reduced the C−F bond present in **25a** to generate the corresponding radical anion **VI**. This latter followed a spin-center shift (SCS) process to afford the *gem*-difluoro radical intermediate **IX** via the intermediates **VII** and **VIII**. Finally, *in situ* generated radical intermediate **X**, resulting from the radical addition of **IX** to **26**, underwent a radical cyclization followed by a HAT process to deliver the desired oxindoles **27**. It is worth mentioning that the formate radical **V** was important to regenerate the active catalyst **I** after a SET (Scheme 11). This protocol was robust, as the reaction could be carried out under air.

2.2. Using Dual Catalysis

Previously discussed reports highlight the use of an organic photoredox catalyst (OPC) for single C(sp^3)−F bond activation. As a complementary strategy, several groups reported straightforward transformations based on dual catalysis especially combining organophotoredox and HAT or organophotoredox and transition metal catalysis.

2.2.1. Using Organophotoredox/HAT Dual Catalysis. *2.2.1.1. Difluoroalkylation Reaction.* Merging of the OPC and HAT catalysts, groundbreaking research was reported by Jui and co-workers in 2018 (Scheme 12). Using the highly reducing organic photoredox catalyst *N*-phenylphenothiazine (PTH), they accomplished the intermolecular defluorinative coupling of trifluoromethyl arenes **28** with unactivated alkenes **29**.[109] Similar to the previously discussed C(sp^3)−F bond activation, a photocatalytic-assisted generation of the difluoromethylated radical **III** remained crucial for this transformation. Then, an intermolecular radical addition to alkene **29** led to the formation of radical **IV**, which afforded **30** after a hydrogen atom transfer with cysteine (CySH). Finally, a subsequent HAT process with sodium formate regenerated CySH and radical species **I**. This latter (**I**) regenerated the OPC via a SET and released sodium fluoride and carbon dioxide as the sole stoichiometric byproducts (Scheme 12). However, the authors did not rule out the possibility of a radical chain process involving formate radical anion **I** as a propagating reductant. The year after, the same group reported a complementary approach. Whereas their previous report mainly focused on the generation of difluoromethyl radicals from the trifluoromethyl arenes substituted with electron-withdrawing groups (e.g., $-CF_3$,

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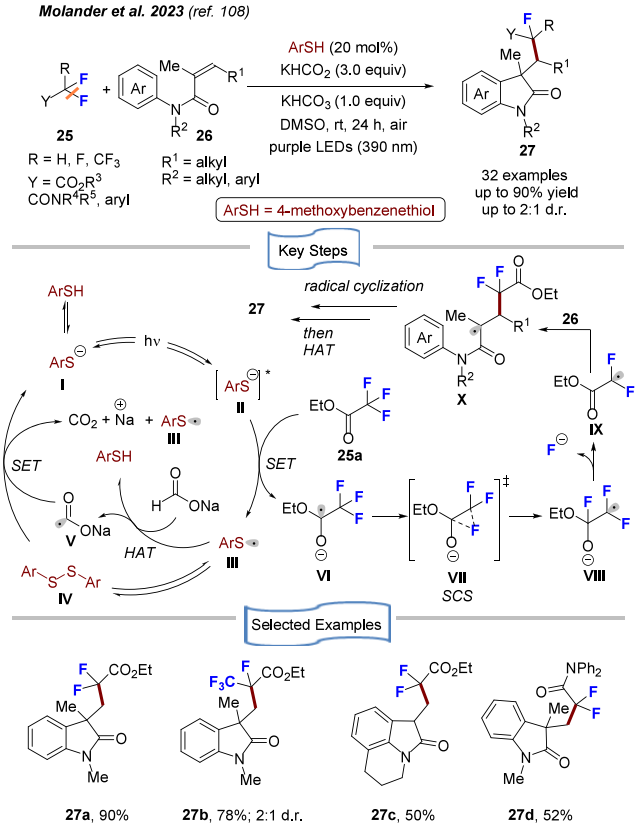
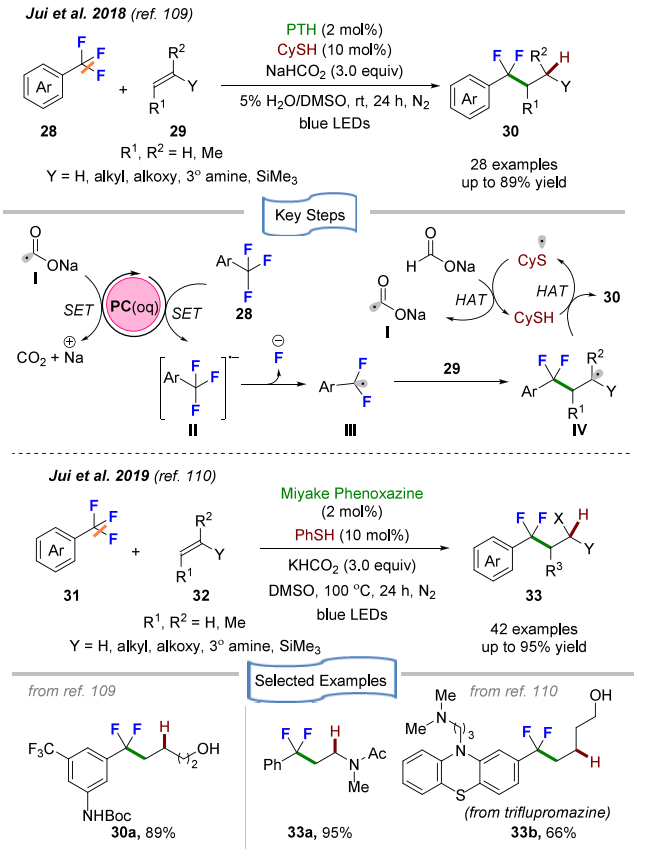
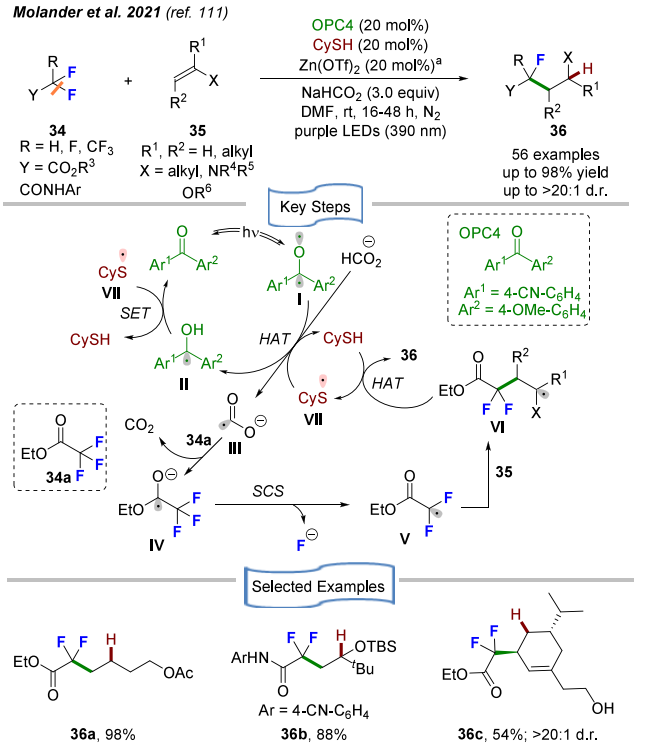
Scheme 11. Thiol-Catalyzed Synthesis of Difluoromethylated Oxindoles



Scheme 12. OPC-HAT Dual-Catalyzed Defluoroalkylation of Trifluoromethylated Arenes



Scheme 13. HAT-Initiated Defluoroalkylation of Trifluoromethyl-Acetates and -Acetamides



$-CN$, $-SO_2NH_2$), in this report, they have generalized the protocol by using a wide array of unactivated trifluoromethyl arenes **31**.[110] Their success relies on the use of the Miyake phenoxazine catalyst ($E_{1/2}^* = -1.70$ *vs* SCE) possessing high intersystem crossing (ISC) efficiency with a long-lived triplet excited state ($\tau_{max} = 480\ \mu S$), which is much higher than other conventional photocatalysts (PCs). This protocol is mechanistically interesting as photocatalyst PTH ($E_{1/2}^* = -2.10$ *vs* SCE) was less effective to trigger this transformation, although it is more reducing in nature than the Miyake phenoxazine. Thus, the mesolytic C−F cleavage event to generate the crucial difluorobenzylic radical intermediate is most likely thermodynamically driven (Scheme 12).

Whereas reports by Jui and co-workers demonstrated the use of π-conjugated organic dyes as PCs to access benzylic *gem*-difluorinated scaffolds, the group of Molander utilized the inexpensive diaryl ketone **OPC4** as a photoactive species to cleave the C−F bond present in trifluoroacetates and -acetamides **34**. A wide variety of alkenes **35** were used as coupling partners to afford diverse fluorinated compounds **36** (Scheme 13).[111] Photoexcited diaryl ketone catalyst **I** is in its triplet state, possessed diradical character, and participated in a HAT with sodium formate to form $CO_2^{\bullet-}$. The highly reductive nature of $CO_2^{\bullet-}$ **III** ($E_{1/2} = -2.2$ V *vs* SCE) allowed the reduction of the α-trifluoromethylcarbonyl **34a**, resulting in formation of radical anion **IV** and CO_2. After a spin-center shift, radical intermediate **IV** led to *gem*-difluoromethyl radical **V**, after a defluorination step. The Giese addition of **V** to alkene **35** led to product **36**, after a HAT process with CySH. *In situ* generated thiyl radical **VII** then allowed regeneration of the photocatalyst via a SET process. Alternatively, thiyl radical **VII** underwent a

[a]$Zn(OTf)_2$ was used in the case of acetamides.

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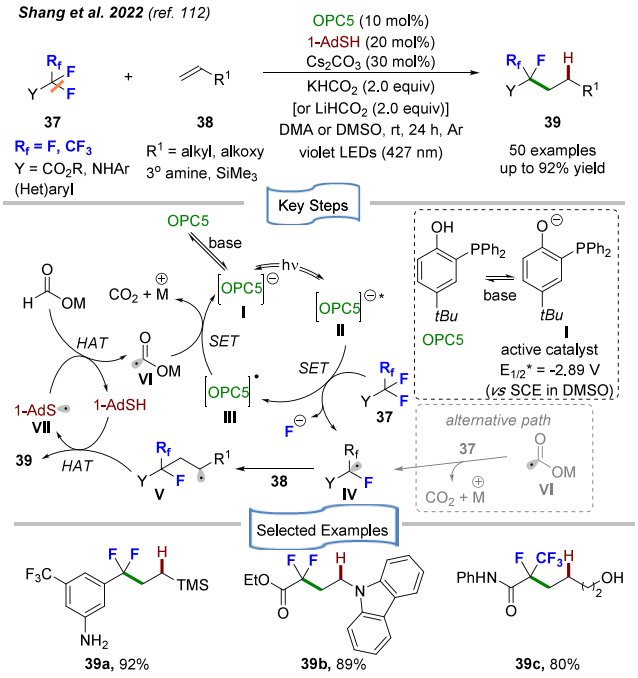
HAT with sodium formate to initiate the radical chain process (Scheme 13).

In 2022, Shang and co-workers investigated the anionic phenolate (**I**) as an OPC for the C−F functionalization of a versatile range of trifluoromethylated feedstocks such as trifluoroacetamides, trifluoroacetates, and trifluoromethyl (hetero)arenes **37** (Scheme 14).[112] Mechanistic investigations

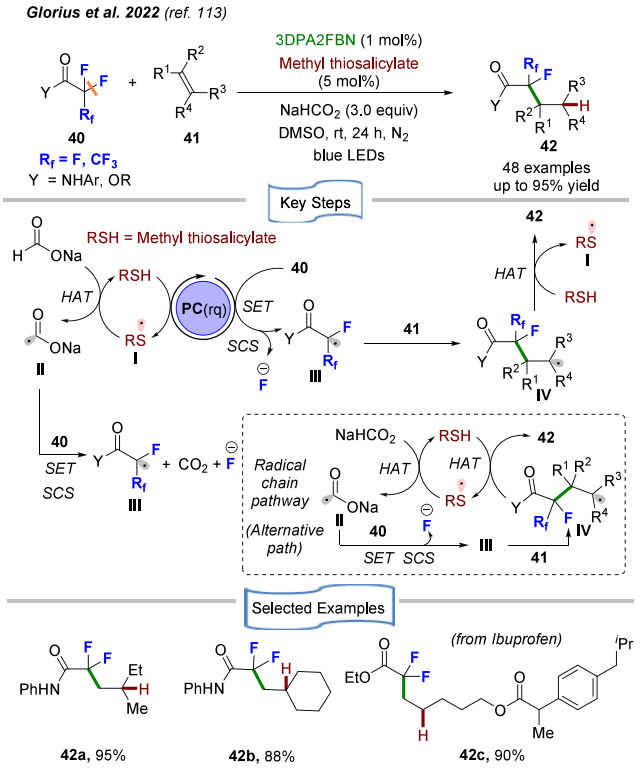
Scheme 14. *o*-Phosphinophenolate-Catalyzed Defluoroalkylation of Trifluoromethylated Compounds



revealed that **I** (deprotonated **OPC5**) acts as an active photocatalyst ($E_{1/2}^*$ = −2.89 V *vs* SCE). The presence of the *ortho*-diphenylphosphino substituent in **OPC5** was crucial to ensure the catalyst efficiency: (i) bathochromic shifting of absorption of the ground state anion **I** from the ultraviolet to visible light range, (ii) the heavy atom effect of phosphine allowing intersystem crossing (ISC) to reach the triplet state and prolonging its lifetime for effective photoelectron transfer with substrates, (iii) the oxophilicity of the phosphine helping interaction with oxygen radicals and thus smooth photoelectron transfer in the anionic excited state **II**, and (iv) also providing stability to the radical **OPC5** (**III**). This dual PC−HAT catalytic system follows a mechanistic path similar to the one described in Scheme 12. This transformation is highly air-sensitive as air can quench the excited triplet state of **I** and can also oxidize the thiol (1-AdSH), hence inhibiting HAT catalysis (Scheme 14).

The same year, the group of Glorious reported the defluorofunctionalization of polyfluorinated aliphatic esters and amides **40** by using 2,4,6-tris(diphenylamino)-3,5-difluorobenzonitrile (3DPA2FBN) as the OPC and methyl thiosalicylate as the hydrogen atom transfer (HAT) catalyst (Scheme 15).[113] Whereas previously discussed methods relied on oxidative quenching of the photocatalytic cycle, in this report, the authors proposed a reductive quenching cycle, in which the excited photocatalyst was reduced by the thiolate anion to generate a thiyl radical **I** along with the reduced photocatalyst. Note that the thiyl radical can be regenerated by sodium formate and readily converted into intermediate **II**. Fluorinated aliphatic

Scheme 15. Defluoroalkylation of Polyfluorinated Aliphatic Amides and Esters



esters and amides **40** were easily reduced by either the reduced photocatalyst or carbon dioxide radical anion **II**. Finally, trapping of fluorinated carbon radical **III** by alkenes **41** followed by a HAT led to the formation of products **42**. Interestingly, the reaction proceeded without photocatalyst at a slower reaction rate involving an innate chain process in a parallel manner.

In 2023, Dilman and co-workers utilized the photocatalytic ability of 3DPA2FBN for the hydrofluoroalkylation of alkenes **44** with fluorinated carbonyl derivatives **43** in combination with *t*BuSH as a HAT catalyst.[114] In this protocol, the authors used trimethyltriazinane (TA) as a stoichiometric reducing agent and KI as a fluoride scavenger. Thanks to the strong reductive ability of triazinane (TA), a diamino-substituted alkyl radical **II** was formed via the intermediate **I**. Alkyl radical **II** then activated **43** to generate difluorinated radical **V** along with triazinyl fluoride **III**, which then participated in a potassium-cation-mediated labile heterolytic C−F bond cleavage to deliver highly stabilized amidinium cation **IV**. Finally, radical **V** was trapped over olefin **44** to deliver intermediate **VI**, which abstracts one hydrogen atom either from the HAT catalytic cycle or from triazinane (TA) to furnish the desired product **45**. Alternatively, the difluorinated radical **V** could be obtained via a fluoride elimination from the radical intermediate **VIII**, itself generated from the intermediate **VII** after a spin-center shift (SCS) (Scheme 16).

The same year, Xu's group showed that the dihydroacridine derivatives can be used as an OPC to functionalize the C−F bond of **46** with diverse alkenes **47** under mild reaction conditions (Scheme 17).[115] Several dihydroacridine derivatives were screened to promote this transformation, with the dihydroacridine based organic photocatalyst **OPC6** being the most efficient one. In this process, CySH was used as a HAT catalyst and $NaBH(OAc)_3$ acted as a potential hydrogen atom

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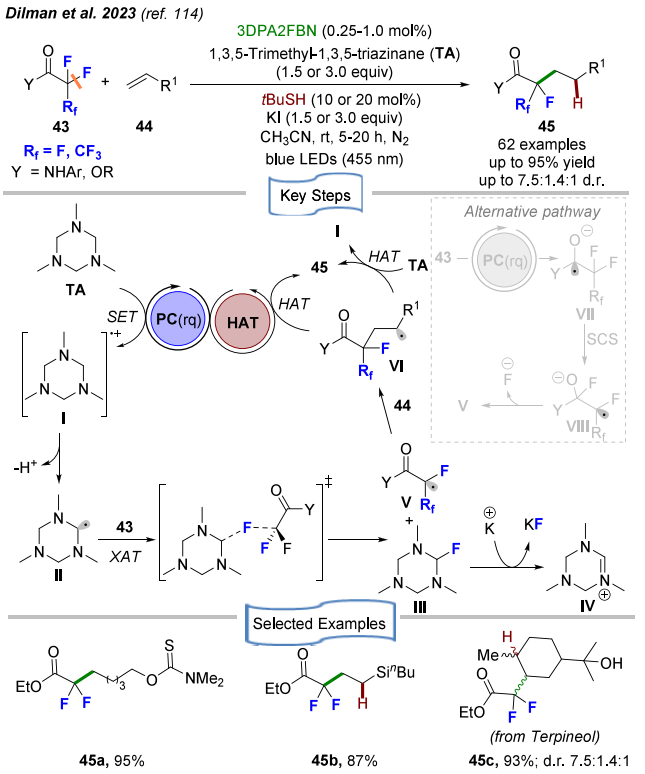
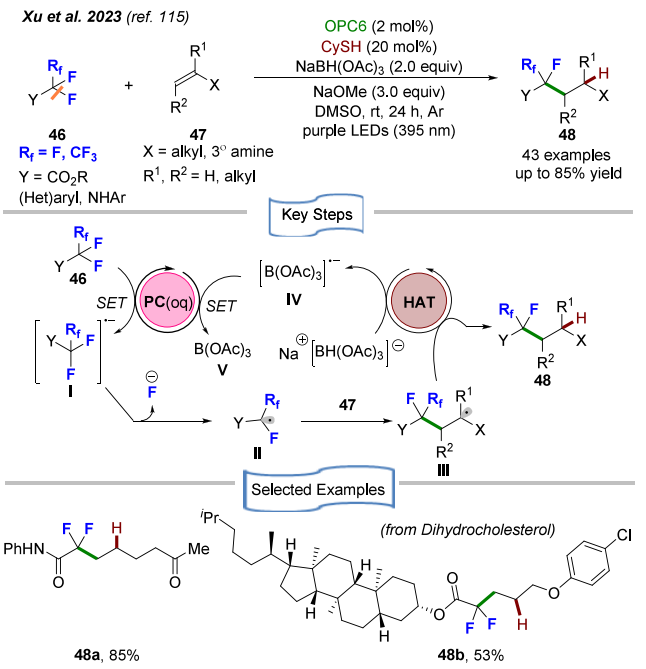
Scheme 16. Defluoroalkylation of Fluorinated Esters Enabled by Photocatalytically Generated Diaminoalkyl Radical



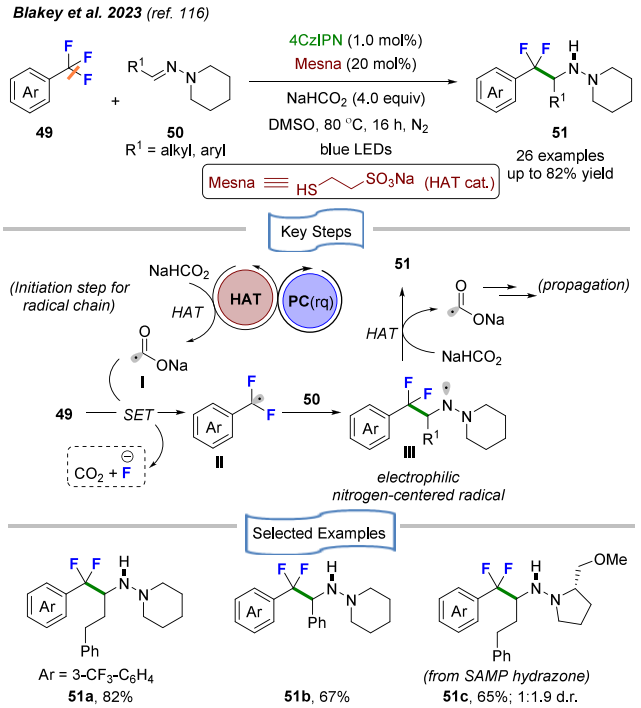
Scheme 17. Dihydroacridine-Catalyzed Selective Defluoroalkylation of Trifluoromethylated Molecules



donor in the HAT cycle to produce $B(OAc)_3^{\bullet-}$ (**IV**). Intermediate **IV** was crucial in regeneration of the photocatalyst.

Although reactions between the photochemically generated difluoromethyl radicals and alkenes have been well studied, the use of imines as a coupling partner C−N remain underexplored. As a result, Blakey and co-workers studied the reactivity of aldehyde-derived *N*,*N*-dialkylhydrazones **50** with trifluoromethyl arenes **49** in a defluoroalkylation event.[116] This approach is challenging because of the electrophilic nature of both imines and the *in situ* formed difluorobenzylic radical **II**. This issue was resolved thanks to the nucleophilic aza-enamine character of *N*,*N*-dialkylhydrazones **50**. A radical chain-based mechanism was most likely involved. The radical process was initiated by the formation of the highly reducing $CO_2^{\bullet-}$ **I** ($E_{1/2}$ = −2.21 V *vs* SCE), which in subsequent steps generated the pivotal difluorobenzylic radical **II**. The radical chain was propagated by a HAT process between the electronically *N*-centered radical intermediate **III** and $NaHCO_2$ and produced the desired *β*-difluoroarylhydrazines **51** (Scheme 18). These latter can easily

Scheme 18. Photochemical Defluoroalkylation of Trifluoromethylarenes with Hydrazones



be converted to pharmaceutically relevant benzylic difluoroarylethylamine scaffolds. Note however that this protocol is mainly restricted to the use of electron-poor trifluoromethyl arenes **49** and electron-rich hydrazones **50**.

2.2.1.2. Hydrodefluorination Reaction. Considering the large diversity of CF_3-containing molecules, building value-added fluorinated molecules from these readily available feedstocks is an appealing strategy. In particular, access to CF_2H-containing molecules[117,118] has inspired several research groups to elaborate innovative solutions.

In this context, the group of Gouverneur developed the organophotoredox-catalyzed hydrofluorination of trifluoromethyl arenes **52** under OPC/HAT dual catalysis using 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (4-DPAIPN) and 4-hydroxythiophenol as catalysts (Scheme 19).[119] A panel of difluoromethylated compounds **53** have been synthesized. Although the method showcased a large functional group tolerance to various functional groups and pharmacophores, it was restricted to electron-demanding trifluoromethyl arene derivatives **52**. As suggested by the authors, the transformation proceeded as follows. Under basic conditions, 4-hydroxythiophenol reduced the excited photocatalyst to generate the thiyl

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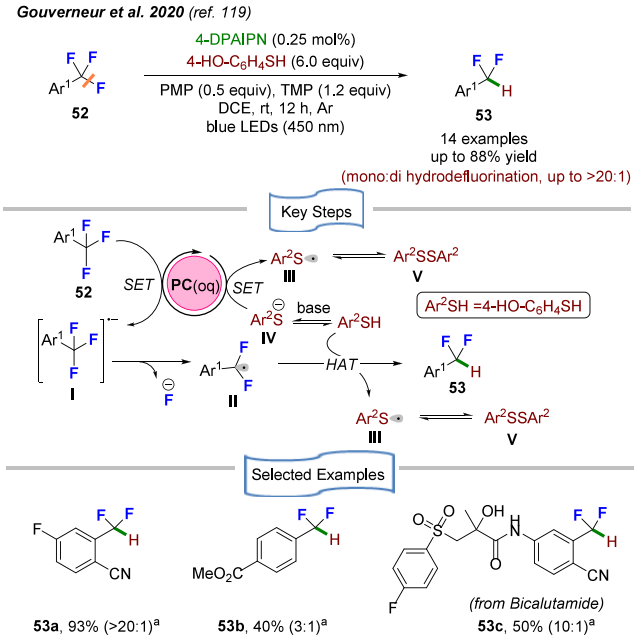
Scheme 19. Hydrodefluorination via Reductive Defluorination



[a]CF_2H/CH_2F ratio determined by ^{19}F NMR spectroscopy using the 4-fluoroanisole as an internal standard.

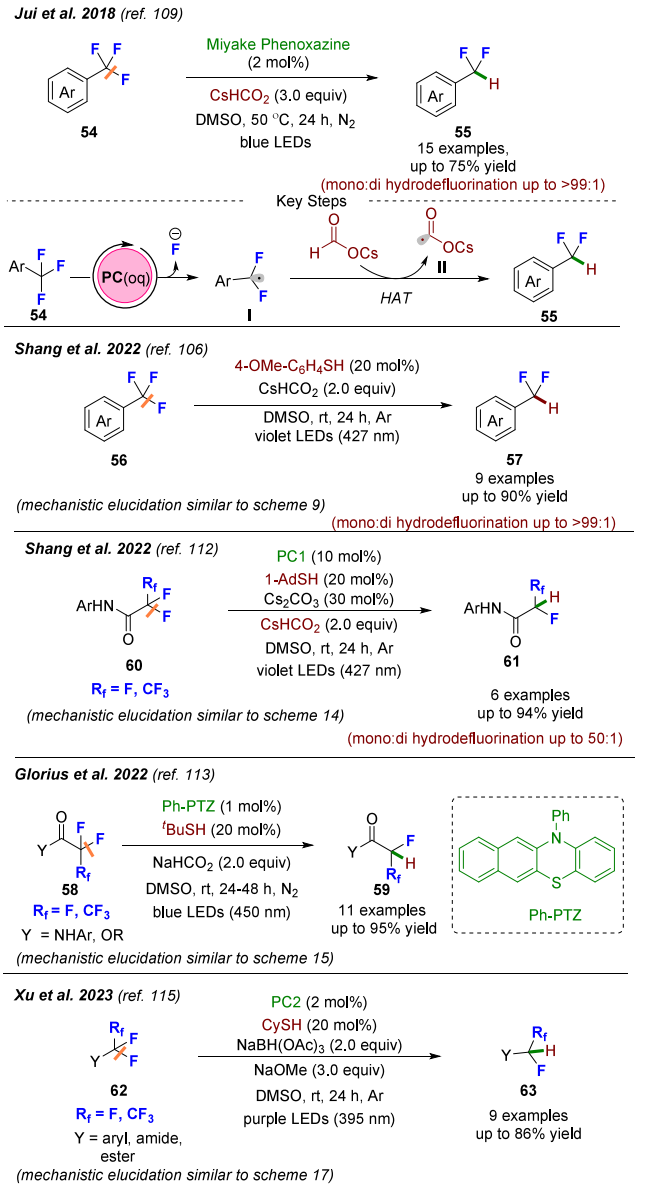
radical **III**. The reduced photocatalyst then was able to cleave the C−F bond from trifluoromethylated arenes **52** to form the corresponding difluoromethyl radical **II**. Finally, a HAT process between **II** and 4-hydroxythiophenol led to the desired product **53** and **III** (Scheme 19). In the same vein, Jui,[109] Shang,[106,112] Glorius,[113] and Xu,[115] independently, further explored the potential of OPCs for the synthesis of CF_2H- and CR_fFH-containing derivatives, as depicted in Scheme 20.

2.2.2. Using Organophotoredox/Transition Metal Dual Catalysis. Combining photoredox catalysis and copper catalysis is challenging due to the possible competitive quenching of the photoexcited reducing photocatalysts by the Cu(II) salts. In 2024, Chu and co-workers developed a metallaphotoredox-mediated defluorinative strategy to access synthetically useful *γ-gem*-difluoroalkyl boronates **67** by reacting trifluoromethyl arenes and trifluoroacetamides **64** with various nonactivated terminal and internal alkenes **65**. The use of the bis(pinacolato)diboron (B_2pin_2) **66** as the borylating agent and KOH and NaI as additives were essential for this reaction,[120] the latter presumably being important to increase the solubility of the excess base. Therefore, it was suggested that the *in situ* generated **64**/[HO-B_2pin_2] species **I** was the active species responsible for the oxidation of the excited photocatalyst, which then would generate the difluoroalkyl radical **III**. After addition to alkenes **65**, the nucleophilic alkyl radical **IV** was formed and readily reacted with the *in situ* generated electrophilic Cu(II)-Bpin **VI** to deliver the Cu(III) species **VII**. Finally, a reductive elimination step was responsible for the formation of the expected product **67** as well as Cu(I) regeneration (Scheme 21).

3. SYNTHESIS OF *GEM*-DIFLUOROALKENES VIA *β*-FLUORIDE ELIMINATION

An alternative approach relies on the defluoroalkylation of trifluoromethyl-substituted alkenes to provide *gem*-difluoroalkenes via *β*-fluoride elimination. The *gem*-difluoroalkene

Scheme 20. Various OPC-Catalyzed Hydrodefluorination Reactions



scaffolds are recognized as widespread building blocks found in compounds of interest, Seletracetam being a flagship derivative.[121] Due to their excellent metabolic stability, and electronic and steric similarity to aldehydes, ketones, and esters, *gem*-difluoroalkenes are often considered as carbonyl bioisosteres in drug development.[122]

This section outlines the major advances that have been made to provide access to *gem*-difluoroalkenes. Building on the pioneering work by Zhou and co-workers,[123] several beneficial protocols have emerged over the past few years. Interestingly, a wide variety of alkenes and radical precursors were available as coupling partners with this approach. A general mechanism for the *β*-fluoride elimination strategy under photochemical conditions is shown in Scheme 22. This process mainly followed a reductive quenching pathway. Upon irradiation and in the presence of a photocatalyst, addition of the *in situ* generated radical intermediate **I** to the trifluoromethyl-substituted alkenes led to the radical intermediate **II**. This latter was further reduced by the reduced photocatalyst ($PC^{\bullet-}$) to produce the anionic

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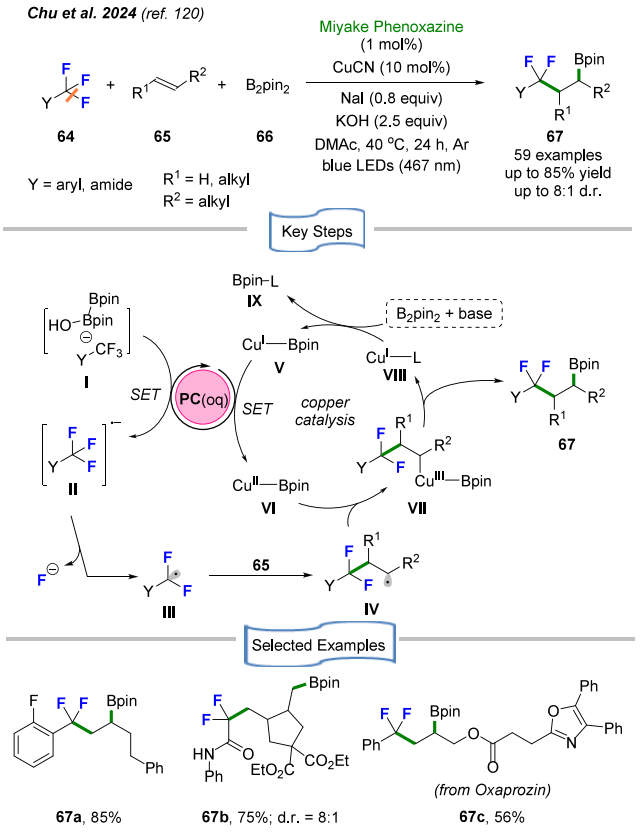
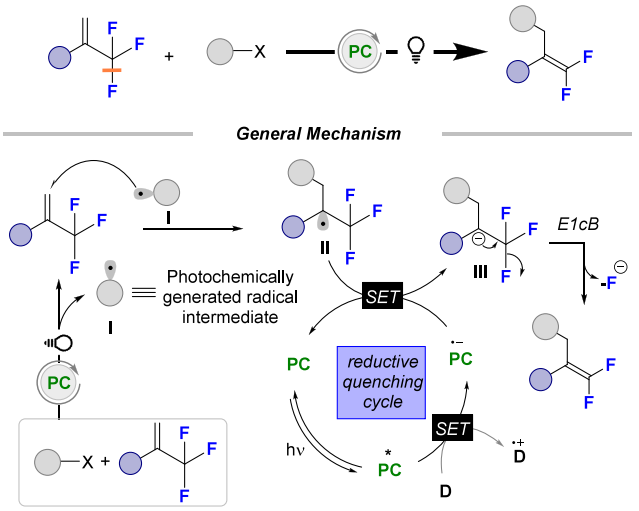
Scheme 21. Dual Photoredox- and Copper-Catalyzed Defluorinative Alkylboration of Alkenes



Scheme 22. Cleavage of C−F Bonds via β-Fluoride Elimination



derivative **III**. Finally, the latter underwent an elimination (unimolecular) conjugate base (E1cB)-type fluoride elimination to deliver the *gem*-difluoroalkene.

3.1. C−C Bond Formation via C-Centered Radical Formation

The construction of C−C bonds through 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN)- or 4DPAIPN-catalyzed defluoroalkylation of trifluoromethyl-substituted alkenes via β-fluoride elimination has been steadily investigated over the years. In this context, various radical precursors used in these transformations are summarized in Figure 1.[124−138] A selection of representative examples is detailed in this section.

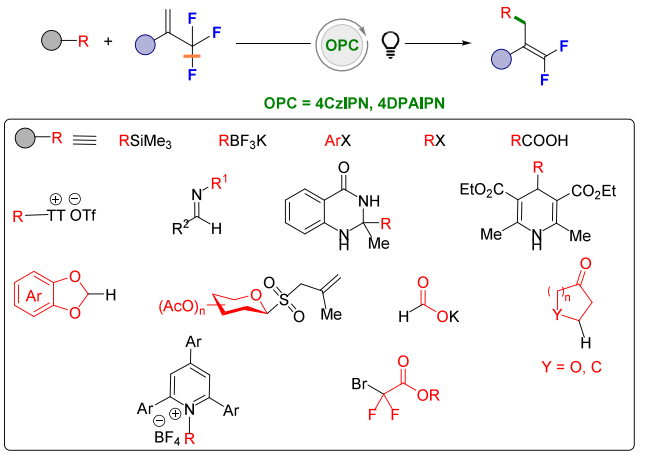
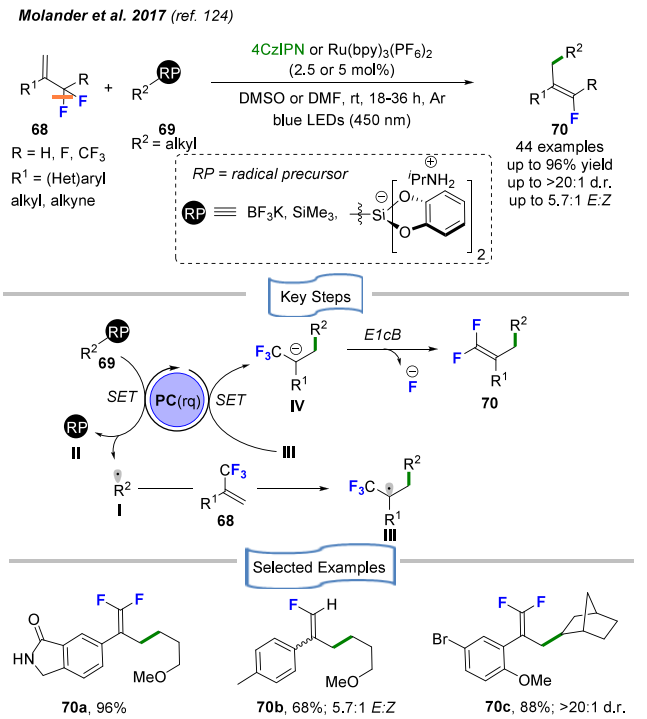


Figure 1. Overview of main radical precursors used in defluoroallylation of trifluoromethyl alkenes under 4CzIPN and 4DPAIPN catalysis.

In 2017, Molander and co-workers developed a method for the synthesis of alkylated *gem*-difluoroalkenes **70** using 4CzIPN as a catalyst. Trifluoromethyl-substituted alkenes **68** were functionalized with various classes of carbon radical precursors (R^2RP, **69**): potassium organotrifluoroborates and alkylbis(catecholato)silicates being very efficient in this reaction (Scheme 23).[124] After oxidation of the carbon radical precursor **69** by the excited photocatalyst, the radical intermediate **I** reacted with the trifluoromethylated alkene **68** to afford the corresponding α-CF_3 radical **III**. Its reduction by a SET process afforded the carbanion **IV** via a radical-polar crossover event and regenerated the photocatalyst. Finally, after E1cB-type fluoride

Scheme 23. Construction of 1,1-Difluoroalkenes via the Generation of Carbon-Centered Radicals



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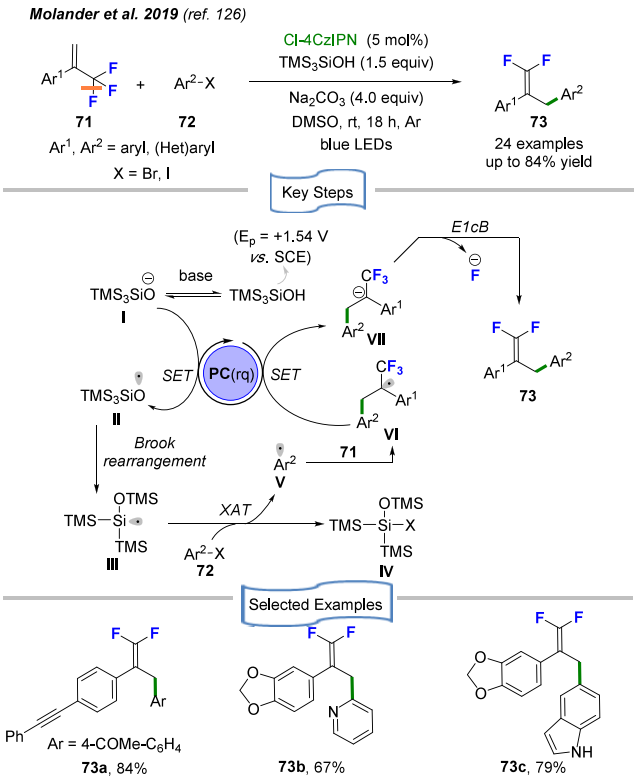
elimination, the *gem*-difluoroalkene was obtained (Scheme 23). Important to note that the byproduct (RP) **II** generated in the course of the transformation can efficiently trap the fluoride ion released during the last step. Later in 2019, a similar defluorinative alkylation strategy was developed by the same group by using silicates, dihydropyridines, and amino acids as alkyl radical precursors to functionalize a DNA-encoded library (DEL) under Ni/OPC dual catalysis.[125]

Aiming to develop a unified strategy using not only alkyl but also aryl radicals, the same group showed that aryl halides **72** can be used as an aryl radical precursor when activated with tris(trimethylsilyl)silanol (Scheme 24).[126] A diverse range of

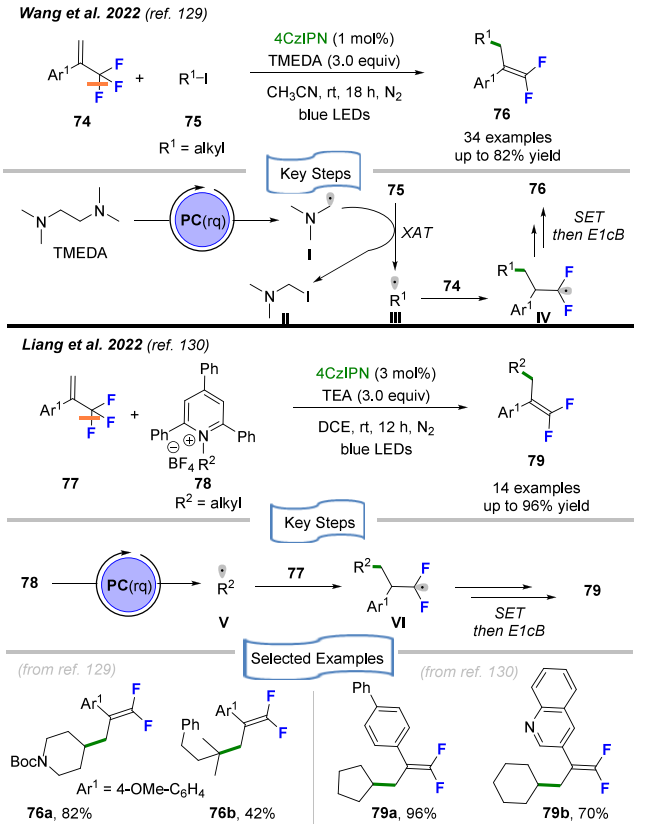
Scheme 24. Defluorinative Arylation of Trifluoromethyl Alkenes under OPC Catalysis



gem-difluoroalkenes **73** were produced via *β*-fragmentation with moderate to good yields. Mechanistically, the deprotonated silanol reduced the excited OPC to afford the corresponding siloxyl radical **II**. Next, a radical Brook rearrangement converted **II** into the silyl radical **III**, which allowed the generation of the aryl radical **V** from the corresponding aryl halides **72** via a halogen atom transfer (XAT) process. The aryl radical **V** underwent a defluorinative arylation with *α*-trifluoromethyl alkenes **71**. The final steps are similar to those shown in Scheme 23 for the formation of **73** from **VI**. The XAT process was further utilized by Glorius *et al.* for a defluorinative ketyl−olefin coupling reaction by using 4CzIPN as an OPC.[128]

In 2022, a similar strategy was employed by the groups of Wang[129] and Liang[130] (Scheme 25). The method developed by the group of Wang allowed the functionalization of **74** with primary, secondary, and tertiary alkyl halides **75**. The generation of alkyl radicals **III** proceeded via a halogen-atom transfer (XAT) in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Note, however, that allyl, benzyl, and aryl iodides remained reluctant coupling partners in this reaction.

Scheme 25. Visible Light Driven Allylic Difluoroallylation of Alkyl Iodides via C−F Bond Cleavage



Liang's group developed photoredox catalytic radical addition/defluoroalkylation reactions between *α*-trifluoromethyl alkenes **77** and various amines **78** to produce difluoroalkenes **79** (Scheme 25). The generation of the primary and secondary alkyl radicals occurred via a C−N bond cleavage by using the Katritzky salts **78**.

3.2. C−C Bond Formation via a 1,5-HAT Process

The remote C−H functionalization of aliphatic amides and amines via a 1,5-HAT process has emerged as a potent strategy to access original fluorinated compounds.[14]

In this context, Pan and co-workers reported the *δ*-selective C(sp^3)−H *gem*-difluoroallylation of aliphatic amine derivatives **81**. The process involved the generation of an amidyl radical intermediate **II** (Scheme 26).[139] Intermediate **II** was obtained after the oxidation of deprotonated amine **I** by a SET process under blue LED irradiation using 4CzIPN as a catalyst. Then, the carbon centered radical **III** was selectively generated at the *δ*-position after a 1,5-hydrogen atom transfer (HAT) process and reacted with the trifluoromethylated alkene **80** to provide, after a reduction/*β*-fluoride elimination, the desired product **82**. This protocol features a broad substrate scope with high chemoselectivity and great functional group tolerance, which was further illustrated with the late-stage functionalization of more complex architectures. In the same vein, Yuan and co-workers reported the photocatalyzed C(sp^3)−H *gem*-difluoroallylation of carboxylic acid derivative **84** via 1,5-HAT (Scheme 26).[140] The reaction was initiated by the oxidation of carboxylic acid **84** by the excited photocatalyst to produce *N*-centered radical **VI** with the extrusion of acetone and CO_2, which remained the pivotal step for this process.

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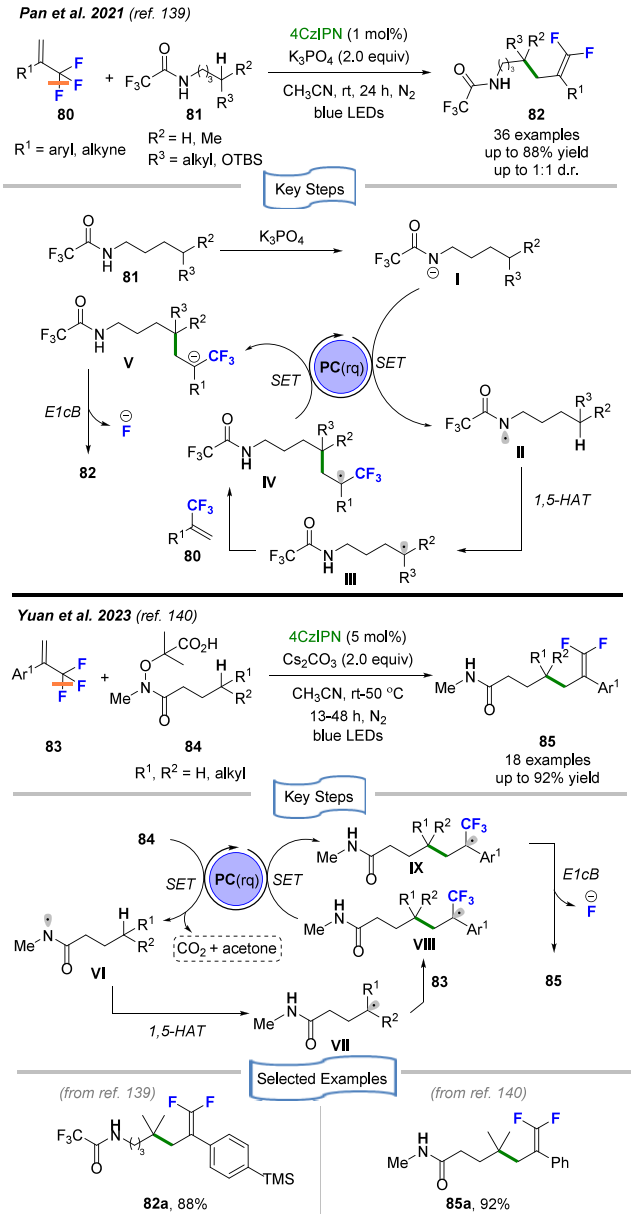
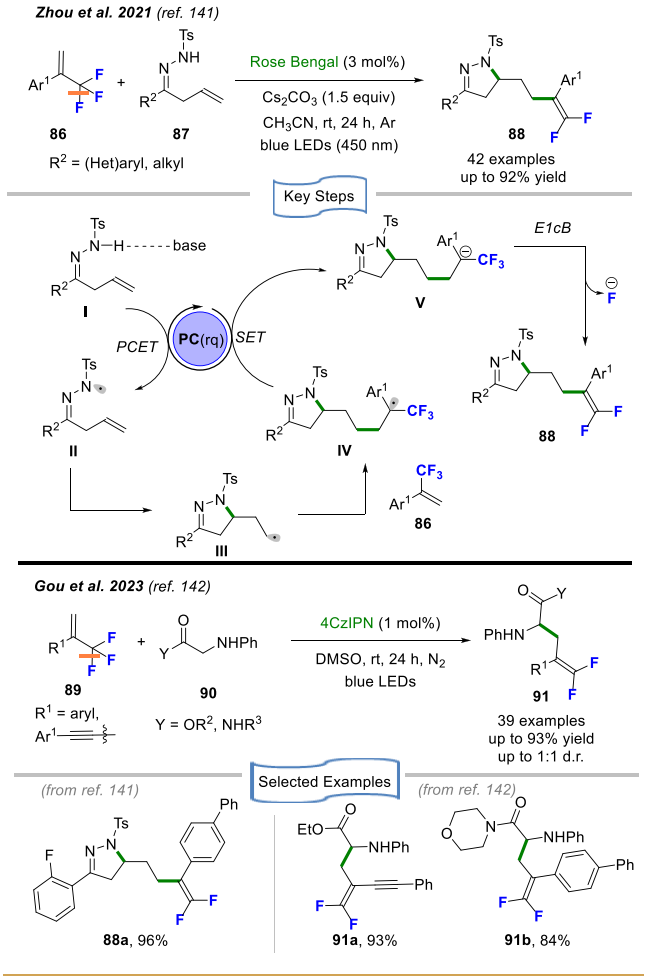
Scheme 26. Difluoroallylation of Remote C(sp^3)−H Bonds via a 1,5-HAT Process



3.3. C−C Bond Formation via the Generation of a *N*-Centered Radical Intermediate

In 2021, Zhou and co-workers were able to generate *N*-centered radicals from *β*,*γ*-unsaturated hydrazones **87** using Rose Bengal as the OPC to perform a tandem radical cyclization/defluorinated alkylation with *α*-trifluoromethyl alkenes **86**.[141] A base-mediated PCET (proton-coupled electron transfer) was crucial to generating the *N*-centered radical **II**, which was involved in an intramolecular cyclization to deliver diversely functionalized dihydropyrazoles **88** in subsequent steps (Scheme 27). As a follow-up, in 2023, the Guo group reported the *gem*-difluoroallylation of glycine derivatives **90** with trifluoromethyl alkenes and trifluoromethyl 1,3-enynes **89** (Scheme 27).[142] The construction of not only fluorinated amino acids but also fluorinated dipeptides was possible. The key step of the process relied on the carbon-centered radical formation at the *α*-position of the carbonyl group via an *N*-centered radical intermediate. In the same line, in 2024, Chen *et al.* were able to perform C(sp^3)−H functionalization of glycine derivatives and glycine derived dipeptides to furnish *gem*-difluoroalkene-containing unnatural amino acids.[143]

Scheme 27. Redox-Neutral Difluoroallylation via *N*-Centered Radical Formation



3.4. C−C Bond Formation via *β*-Scission

This epoch-making defluorination technique was further extended by Wu and co-workers with the regioselective synthesis of ketones bearing a *gem*-difluoroalkene moiety **94** at a remote position via the ring-opening functionalization of unstrained tertiary cycloalkanols **93** (Scheme 28).[144] Herein, the authors utilized acridine photocatalyst **OPC7** which, in its excited state, performed a SET with the electron-rich *para*-methoxyphenyl group (PMP) of the tertiary alcohol **93a** to form the corresponding arene radical cation **I**. Then, a base-mediated intramolecular PCET delivered the alkoxyl radical **II**. After a *β*-scission and ring opening, the remote carbon-centered radical **III** was trapped by alkene **92** to form the desired product **94** in subsequent steps. The use of the quaternary ammonium cation *N*-butyl-*N*-methylpyrrolidinium hexafluorophosphate ([C_4MPr]$^+PF_6^-$) was important for the *β*-fluoride elimination step (Scheme 28). In the same year, Teng and co-workers were also able to install an alkyl radical generated from *β*-scission of nonstrained cyclic alcohols to *α*-(trifluoromethyl)styrenes to provide remote *gem*-difluoroalkenyl ketones under OPC catalysis.[145]

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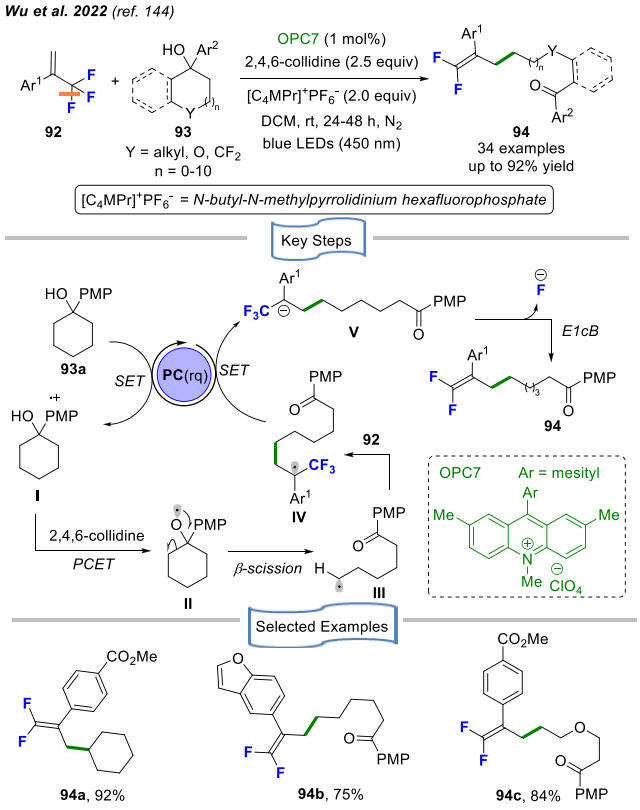
Scheme 28. Difluoroallylation via Ring-Opening of Nonstrained Cycloalkanols



3.5. C–C Bond Formation via Decarboxylation

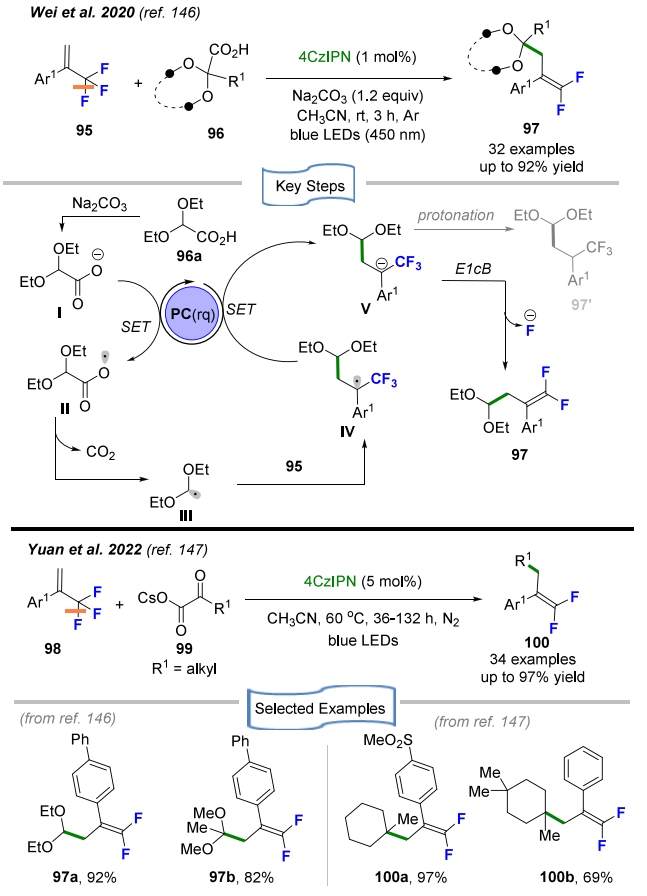
As a complementary pathway, photochemical decarboxylation can efficiently produce valuable alkyl radical intermediates. In this regard, the group of Wei reported the defluoroacetalation of α-trifluoromethyl alkenes **95** with glyoxylic acid acetals **96** (considered as a formyl-radical equivalent) to furnish versatile masked γ,γ-difluoroallylic aldehydes **97** with good yields (Scheme 29).[146] Aliphatic and aromatic α-ketal acids **96** were smoothly converted into the targeted products **97**. According to the proposed mechanism, excited 4CzIPN oxidized the deprotonated carboxylic acid **I** to form the radical **II**, which after decarboxylation delivered the alkyl radical **III**. This latter was converted into the expected product **97** after the following steps: radical addition to alkene **95**, SET, and β-fluoride elimination. This method possesses good functional group tolerance; thus the late-stage functionalization of diverse biologically active molecules was carried out successfully. Two years later, Yuan and co-workers developed a similar approach (Scheme 29).[147] In their study, cesium alkyl oxalates **99** were employed as a tertiary radical precursor to construct all-carbon quaternary center *gem*-difluoroallylated products **100**.

3.6. C–C Bond Formation via a Three-Component Reaction

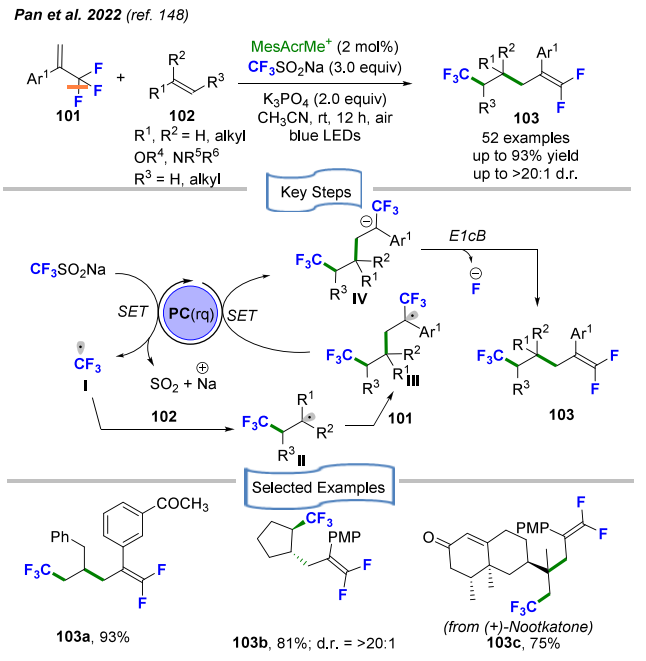
In 2022, the group of Pan developed a three-component reaction for the trifluoromethylation–difluoroallylation of unactivated alkene **102** (Scheme 30).[148]

In the presence of the excited Fukuzumi acridinium salt ($MesAcrMe^+$), a single-electron oxidation of Langlois' reagent ($NaSO_2CF_3$) led to the formation of the CF_3 radical **I**. After addition to unactivated alkene **102**, the corresponding alkyl radical intermediate **II** reacted with α-trifluoromethyl alkene **101** to furnish radical intermediate **III**. After a single electron

Scheme 29. Selective C–F Bond Cleavage via Decarboxylation



Scheme 30. OPC-Catalyzed Three-Component Trifluoromethylation-Difluoroallylation of Unactivated Alkenes



reduction and a β-fluoride elimination step, various trifluoromethyl-substituted *gem*-difluoroalkene derivatives **103** were

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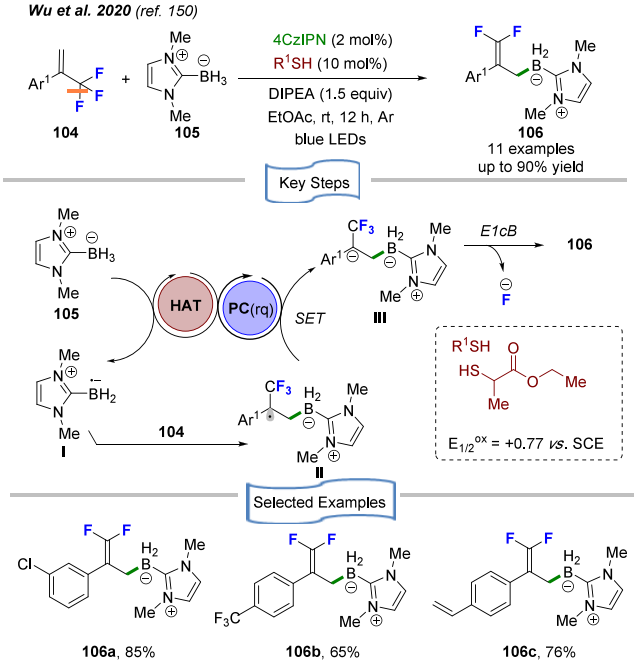
obtained in moderate to good yields. Another example of a three component reaction was showcased by Zhang and co-workers where 1,3-bromodifluoroallylation of [1.1.1]propellane was performed by using α-trifluoromethylalkenes and inexpensive KBr salts as bromine radical precursors.[149]

3.7. C−B and C−Si Bond Formation

So far, various strategies for forming a C−C bond have been discussed, with the synthesis of *gem*-difluoroalkenes. Meanwhile, a great deal of interest has been devoted to the formation of C−B and C−Si bonds using a defluorofunctionalization process. As fluorinated organic boranes are useful synthetic handles to access more complex molecules, there is a need to develop tools to obtain fluorinated organic borane building blocks. However, the strong affinity of boron reagents for fluoride anions is a significant synthetic hurdle. To meet this challenge, the Wu group developed a dual OPC−HAT catalyzed defluoroborylation of trifluoromethylalkenes **104** by using NHC−BH_3 complexes **105** (Scheme 31).[150] In this transformation, a wide

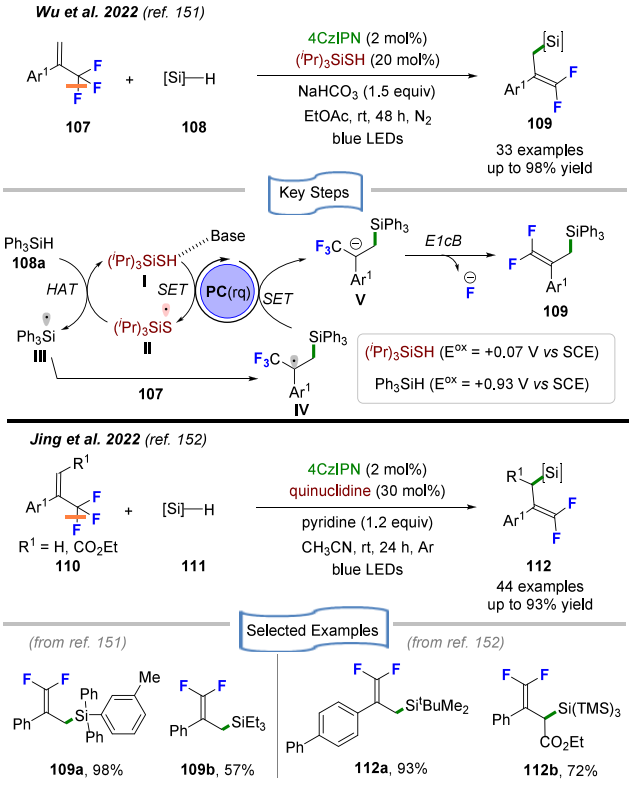
Scheme 31. Defluoroborylation of Trifluoromethyl Alkenes via Direct B−H Activation of NHC Boranes



variety of *gem*-difluoroallylboranes **106** were prepared. Following their mechanistic studies, the authors suggested that the kinetically favored polarity-matched HAT-induced generation of nucleophilic NHC−boryl radical **I** remained crucial for the allylation reactions. Indeed, the addition of NHC−boryl radical **I** to α-trifluoromethyl alkene **104** and then the generation of the following carbanion **III** after a SET process followed by a β-fluoride elimination step led to the desired *gem*-difluoroallylboranes **106**.

Considering the indispensable importance of organosilane compounds in synthetic and medicinal chemistry, Wu and coworkers developed a defluorosilylation reaction of trifluoromethylalkenes **107** using 4CzIPN and $(^i\mathrm{Pr})_3$SiSH as OPC and HAT catalyst, respectively, (Scheme 32).[151] Through HAT−PC dual catalysis, both aryl and alkyl silanes **108** were suitable for this transformation. Mechanistic investigations suggested that the oxidative potential of triphenylsilane ($E_{1/2}^{ox}$ = +0.93 V *vs* SCE in

Scheme 32. Defluorosilylation of Trifluoromethyl Alkenes under OPC Catalysis



EtOAc) was much higher than that of $(^i\mathrm{Pr})_3$SiSH ($E_{1/2}^{ox}$ = +0.07 V *vs* SCE in EtOAc). Therefore, the excited photocatalyst was more efficiently quenched by $(i\mathrm{Pr})_3$SiSH than silanes **108**. The quenching ability of $(^i\mathrm{Pr})_3$SiSH was even intensified in the presence of $NaHCO_3$ as a base. According to these observations, the authors suggested a plausible mechanism: Upon irradiation, the excited photocatalyst was quenched by $(^i\mathrm{Pr})_3$SiSH to produce thiyl radical intermediate **II**, which upon a HAT process with **108a** liberated silyl radical intermediate **III**. This latter was trapped by the alkene **107** to afford the radical intermediate **IV**. Finally, after SET and β-fluoride elimination steps, the silyl *gem*-difluoroalkenes **109** were afforded. A similar defluorosilylation protocol was reported by Jing *et al.* in the same year using quinuclidine as a HAT catalyst to initiate the photocatalytic cycle.[152] The mechanistic details are similar to Wu's report.

3.8. OPC-Catalyzed Functionalization of 2-Bromo-3,3,3-trifluoropropene (BTP)

The above-mentioned protocols primarily utilize α-trifluoromethylstyrenes as a fluorinated source, whereas the bulk industrial chemical 2-bromo-3,3,3-trifluoropropene (BTP) remains underexplored in this direction. To fill this gap, the group of Zhou reported two back-to-back reports where photocatalytic C−F bond cleavage and activation of the C(sp^2)−Br bond sequentially took place using a single photocatalyst. The first example dealt with the synthesis of 4-(difluoromethylidene)-tetrahydroquinolines **115** by reacting *N*-aryl amino acids **114** and BTP **113** (Scheme 33).[153] It turned out that the generation of α-amino alkyl radical **III** from **I** via an oxidative decarboxylation process remained crucial. Next, the addition of **III** to BTP **113**, followed by a SET reduction of **IV** and a β-fluoride elimination step led to the targeted *gem*-difluoroalkene **VI**. Following this, a SET reduction of **VI** resulted in *gem*-

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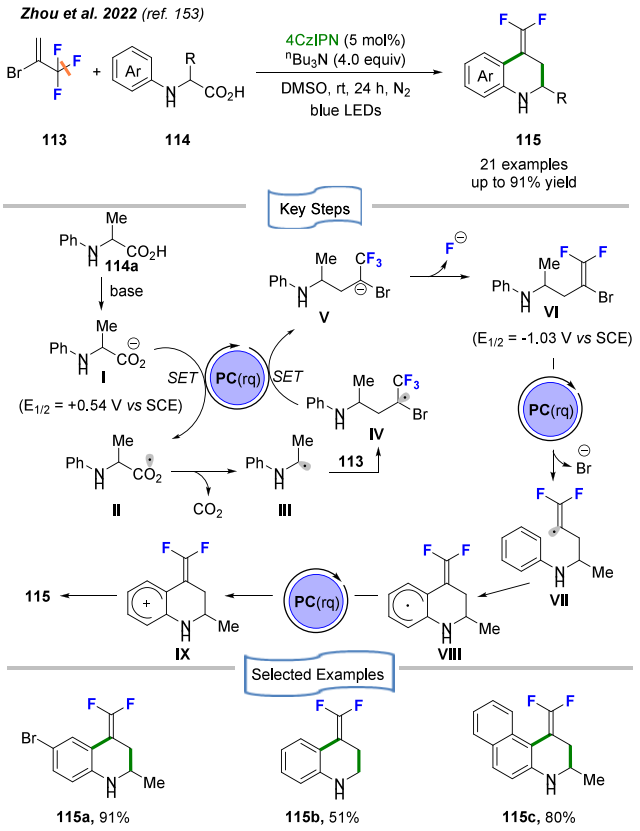
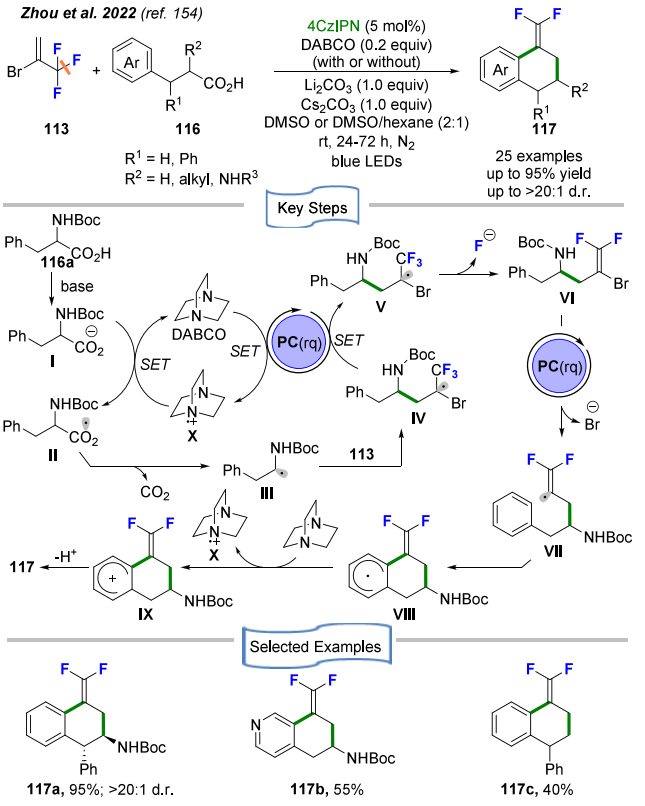
Scheme 33. Defluorosilylation of Trifluoromethyl Alkenes under OPC Catalysis



Scheme 34. Synthesis of 4-(Difluoromethylidene)-tetrahydroquinolines under OPC Catalysis



difluoro vinyl radical **VII**. This latter underwent a radical cyclization and a SET oxidation followed by a deprotonation step to deliver the desired product **115** (Scheme 33).

The second report highlighted the synthesis of the *gem*-difluoromethyl substituted tetralins **117**.[154] A wide variety of *N*-Boc protected arylalanines and 3-aryl propanoic acids **116** were used as radical precursors. Note that a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) acted as a reductive quencher. Similarly to the mechanism depicted in Scheme 33, the *in situ* generated alkyl radical **III** was added to BTP **113** to form the intermediate **IV**, which, in subsequent steps, was converted into the products **117** (Scheme 34).

4. CONCLUSION AND PERSPECTIVES

This Perspective provides an overview of the significant advancements in selective single C−F bond cleavage under organophotoredox catalysis. The valorization of fluorinated feedstocks offers promising opportunities for the synthesis of a wide range of difluoromethylated architectures. Various elegant methodologies proved to be selective toward the targeted C−F bond to be cleaved in the case of derivatives bearing several fluorinated groups or perfluoroalkylated compounds. Nevertheless, considerable opportunities and several challenges remain that can be systematically addressed to further advance and enrich this flourishing field. In particular, the strategy based on the cleavage of a single C−F bond is limited to a trifluoromethyl group directly linked to a π-system (e.g., aryl, vinyl, and carbonyl). Consequently, there is an urgent need to develop and design synthetic methods for the photocatalyzed functionalization of aliphatic fluorinated feedstocks through C−F bond activation. Furthermore, it is essential to expand and diversify the range of fluorinated moieties that can be used in this approach. To overcome these limitations, research efforts should be directed toward the development of innovative synthetic routes for the functionalization of inaccessible fluorinated molecules, thanks to the rapid and impressive advances in transition metal catalysis and single electron processes via photoredox or electrochemistry. Finally, the design of organophotoredox-catalyzed enantioselective transformations via C(sp^3)−F bond cleavage is still underexplored. Given the steady demand for fluorinated chemicals, we believe that these advances will not only impact chemical synthesis but also inspire the design of future technologies for the synthesis of organofluorine compounds in a more sustainable and cost-effective manner.

AUTHOR INFORMATION

Corresponding Authors

Sourav Roy − *INSA Rouen Normandie, Univ Rouen Normandie, CNRS, Normandie Univ, COBRA UMR 6014, F-76000 Rouen, France*; Email: sourav.roy@univ-rouen.fr

Tatiana Besset − *INSA Rouen Normandie, Univ Rouen Normandie, CNRS, Normandie Univ, COBRA UMR 6014, F-76000 Rouen, France*; Email: tatiana.besset@insa-rouen.fr

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.4c01158

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Sourav Roy** writing - original draft,

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writing - review & editing; **Tatiana Besset** conceptualization, resources, supervision, writing - review & editing.

Notes

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