HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2020 August 12.

Published in final edited form as:

Angew Chem Int Ed Engl. 2019 August 12; 58(33): 11171–11181. doi:10.1002/anie.201902243.

Synthesis of Tri- and Difluoromethoxylated Compounds by Visible Light Photoredox Catalysis

Johnny W. Lee[a], **Katarzyna N. Lee**[a], **Ming-Yu Ngai**[a]

[a]Department of Chemistry and Institute of Chemical Biology and Drug Discovery, Stony Brook University, Stony Brook, NY 11794, USA

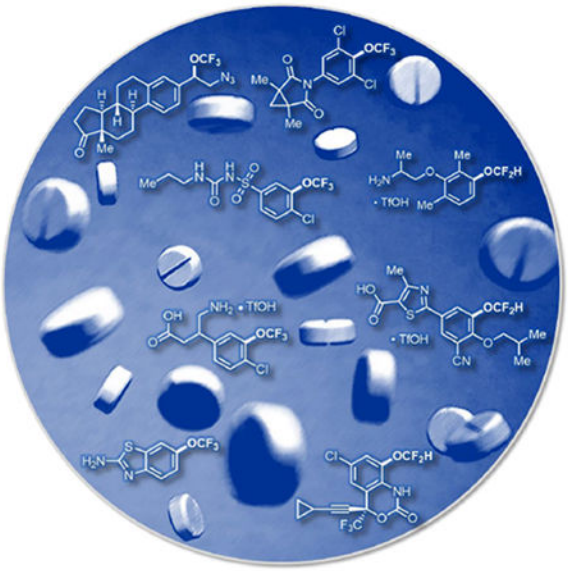
Abstract

The trifluoromethoxy (OCF_3) and difluoromethoxy (OCF_2H) groups are fluorinated structural motifs that exhibit unique physicochemical characteristics. Incorporation of these substituents into organic molecules is a highly desirable approach used in medicinal chemistry and drug discovery processes to alter the properties of a parent compound. Recently, tri- and difluoromethyl ethers have received increasing attention and several innovative strategies to access these valuable functional groups have been developed. In this mini-review, we focus on visible-light photoredox catalysis for the synthesis of tri- and difluoromethyl ethers which also includes recent photocatalytic strategies for the formation of O–CF_3, C–OCF_3, O–CF_2H, and C–OCF_2H bonds as well as other transformations leading to the construction of OR_F groups.

Graphical Abstract

Shine Light on the OCF_2H and OCF_3 Groups: Tri- and difluoromethyl ethers are privileged moieties in the realm of medicinal chemistry and are found in marketed pharmaceuticals and agrichemicals. Recent advances in the visible light photocatalytic synthesis of these moieties would likely render them to be routinely considered during the drug design and discovery processes.

ming-yu.ngai@stonybrook.edu.



Keywords

photoredox catalysis; difluoromethoxylation; trifluoromethoxylation; drug discovery; organofluorine compounds; visible light

1. Introduction

Fine-tuning of physicochemical properties of a drug candidate is a pivotal aspect of any drug development process. A common approach to modify the physicochemical properties of a drug candidate involves incorporation of fluorinated functional groups, such as the trifluoromethoxy (OCF_3) and difluoromethoxy (OCF_2H) groups, into the parent compound.[1] Since addition of these groups into organic molecules may result in an enhancement of the efficacy of drug candidates by impacting the biological activities such as increasing their metabolic stability, enhancing their cellular membrane permeability, and improving their pharmacokinetic properties, they are often viewed as privileged functional groups in the realm of medicinal chemistry and are routinely considered during design and development processes of successful drugs.[2]

The OCF_3 and OCF_2H groups have a combination of several unique properties that are distinct from other functional groups.[3] For example, the OCF_3 group has high electronegativity (χ = 3.7 according to the Pauling's electronegativity scale)[4] and excellent lipophilicity (π_x = +1.04).[5] In addition, the OCF_3 moiety lies in the plane orthogonal to the aromatic ring in aryl trifluoromethyl ethers (Figure 1a).[6] This peculiar conformation is due to the steric interaction between the CF_3 group and the *ortho*-hydrogen atoms of the aromatic ring and the negative hyperconjugation ($n_o \rightarrow \sigma^*_{C-F}$). These interactions significantly weaken the tendency of the oxygen lone pair electrons to delocalize into the aromatic ring and, as a consequence, the OCF_3 group is allowed to rotate freely to adopt a more stable conformation where the dihedral angle (θ) of the C=C–O–CF_3 bond is close to 90°. Due to this conformation, compounds containing an aryl trifluoromethyl ether may have

additional binding affinity in an active site of a target. [2b, 6] On the other hand, molecules containing the OCF_2H group exhibit dynamic lipophilicity (π_x = +0.2–0.6) where they can alter their lipophilicity according to their surrounding chemical environment by a simple bond rotation around the O–CF_2H bond ($\Delta G^{\neq}$ = 0.45 kcal mol^{-1}).[7] In addition, the OCF_2H group could serve as a hydrogen bond donor to enrich molecular interactions with residues in binding pockets. As a result, the OCF_3 and OCF_2H groups are installed into pharmaceuticals and agrochemicals to fine-tune their *in vivo* adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties.[3, 8]

Although a number of currently prescribed pharmaceutical agents bear either the OCF_3 or OCF_2H motif in their aromatic systems, for example Sonidegib® (anti-cancer drug),[9] Riluzole® (anticonvulsant drug)[10] Pantoprazole® (anti-inflammatory drug),[11] and Roflumilast® (anti-inflammatory drug)[12] (Figure 1b), access to these analogs often requires installation of the OCF_3[13] and OCF_2H[14] groups at an early stage of a multi-step synthetic sequence.[15] The lack of late-stage tri- and difluoromethoxylation strategies results in laborious synthetic efforts for the preparation of a handful of structurally-related analogs and limits the number of derivatives for structure-activity-relationship studies.[16] Thus, synthetic methods that enable an easy introduction of the OCF_3 and OCF_2H groups at a late stage of synthesis are highly desired.

Over the past few decades, visible light photoredox catalysis has emerged as an important synthetic tool.[17] A great number of novel C–C and C–X bond forming reactions have been developed and employed in the preparation of molecules which would be otherwise difficult or impossible to access. These photoredox-catalyzed transformations proceed via radical intermediates that are generated under mild reaction conditions. In contrast to traditional chemical methods involving single electron transfer processes, photocatalytic strategies do not require radical initiators and stoichiometric amounts of strong oxidizing or reducing agents.[18] More recently, several innovative and promising photoredox-based approaches to form tri- and difluoromethoxylated compounds have been reported. The purpose of this review is to provide an overview of the recent developments of photoredox-catalyzed reactions for the synthesis of tri- and difluoromethoxylated compounds. The O–R_F and the C–OR_F bond-forming reactions as well as other transformations leading to the construction of OCF_3- and OCF_2H-molecules are discussed herein. Non-photoredox strategies for the introduction of the tri- and difluoromethoxy groups are out of the scope of this review but have been summarized in other excellent reviews.[13], [14]

2. Synthesis of Trifluoromethoxylated Compounds

The incorporation of the OCF_3 group into (hetero)aromatic substrates has long been known as a daunting task in synthesis, and until recently there has been a scarcity of synthetic methods for the introduction of this functional group into organic molecules.[13d, 19] The most common approach towards trifluoromethyl ethers is based on nucleophilic trifluoromethoxylation strategies, which employ reagents capable of releasing the OCF_3 anion ($^{-}OCF_3$). Over the years, however, the development of these reactions has been hindered due to the instability of the $^{-}OCF_3$ anion which is the result of its facile decomposition to the more stable fluorophosgene and fluoride anion.[20] On the other side of

the spectrum, strategies that utilize the trifluoromethoxy radical (•OCF_3), an underexplored species, have been extremely rare.[19] Nevertheless, over the past few years, several innovative approaches utilizing $^{-}OCF_3$ and •OCF_3 for the synthesis of trifluoromethyl ethers have been reported in the literature.[13d]

2.1. Anionic Trifluoromethoxylation

In 2017, Ngai and colleagues reported the first synthesis of trifluoromethyl aryl ethers utilizing *N*-(hetero)aryl-*N*-hydroxylamides and commercially available and inexpensive CF_3I as starting materials (Scheme 1).[21] Based on their previous reports,[22] the authors envisioned that selective O–CF_3 bond formation was feasible if *N*-hydroxyl and trifluoromethyl radicals were generated simultaneously. Instead of using expensive Togni's Reagents (e.g., Togni's reagent **I** costs \$55,980 mol^{-1}),[23] Ngai and coworkers used trifluoromethyl iodide, which costs \$83 mol^{-1},[23] and $Ru(bpy)_3(PF_6)_2$ [tris(2,2'-bipyridine)ruthenium(II) hexafluorophosphate] to form the CF_3 radical upon irradiation with blue LED light. Under the optimized reaction conditions, alkyl or halide substituted as well as more structurally elaborate (hetero)aryl-*N*-hydroxylamides were successfully *O*-trifluoromethylated and underwent OCF_3-migration to afford the desired products. A major advantage of this strategy is its applicability to the synthesis of other polyfluoroalkoxylated arenes and heteroarenes using readily available polyfluoroalkyl iodides such as perfluoroisopropyl iodide, perfluoro-*sec*-butyl iodide, and *n*-perfluorohexyl iodide as coupling partners.

Stern–Volmer quenching experiments indicated that the deprotonated *N*-phenyl-*N*-hydroxylamide (**2.1**, $E_{1/2}^{red}$ = +0.62 V vs SCE)[24] quenched *$Ru(bpy)_3^{2+}$ efficiently (k_q = 7.84×10^9 M^{-1} s^{-1}), while there was no observable quenching with *N*-phenyl-*N*-hydroxylamide **2.2** and perfluoroisopropyl iodide (**2.3**) (Scheme 2a). Furthermore, Ngai and co-workers observed that the OR_F migration was slower when electron deficient aromatic substrates were used, which was consistent with their previous observations and proposal of an ionic OR_F-migration pathway.[22c] Based on these data, a reductive quenching photocatalytic cycle for selective O–R_F bond formation and the subsequent OR_F-migration were proposed as outlined in Scheme 2b. Excitation of $Ru(bpy)_3^{2+}$ with visible light produces a long-lived photoexcited *$Ru(bpy)_3^{2+}$ ($t_{1/2}$ = 1.10 μs)[24], which is reductively quenched by **2.1** to give *N*-hydroxyl radical **2.4** and $Ru(bpy)_3^{+}$. Subsequently, R_FI engages in a SET with $Ru(bpy)_3^{+}$ to form the polyfluoroalkyl radical (•R_F) and regenerate the ground state $Ru(bpy)_3^{2+}$. Next, radical-radical coupling between **2.4** and •R_F affords the *O*-polyfluoroalkylated *N*-phenyl-*N*-hydroxylamide **2.5**. It is noteworthy that Ngai *et al.* did not detect any aryl C-H polyfluoroalkylated side products even though such a reaction has been developed under similar conditions.[25] Presumably, this is due to the persistent radical effect,[26] where the coupling of the persistent *N*-hydroxyl radical and transient •R_F is more favorable than the addition of the •R_F to a (hetero)arene. Once the *O*-polyfluoroalkylated *N*-phenyl-*N*-hydroxylamide is formed, it undergoes: (i) heterolytic N–OR_F bond cleavage, (ii) recombination of the resulting short-lived ion pair **2.6** to give **2.7**, and (iii) tautomerization of **2.7** to produce the desired polyfluoroalkoxylated (hetero)arene product **2.8**.

In 2018, Tang and coworkers accomplished the first azidotrifluoromethoxylation of styrenes by combining visible-light mediated photoredox catalysis and silver catalysis (Scheme 3).[27] In this transformation, $Ru(bpy)_3(PF_6)_2$ was used as a photoredox catalyst, Zhdankin reagent was employed as an azide radical ($\bullet N_3$) precursor and trifluoromethyl arylsulfonate as the trifluoromethoxide source. The reactive $AgOCF_3$ species was formed *in situ* from aryl trifluoromethyl sulfonate and silver(I) fluoride salt. Tang's azidotrifluoromethoxylation procedure was applicable to a wide range of electron-rich and deficient styrenes with yields ranging from 28% to 72%. Also heteroaromatics such as benzothiophene and quinolone derivatives could react and afford the corresponding products in moderate to high yields.

Tang *et al.* performed a series of Stern-Volmer luminescence quenching experiments and observed that only the Zhdankin reagent (**4.1**) quenched $*Ru(bpy)_3^{2+}$. Furthermore, the quantum yield of the reaction was determined to be 0.55, which indicates a closed catalytic cycle (Scheme 4a). Moreover, radical trapping experiments with TEMPO (2,2,6,6-Tetramethyl-1-piperidinyloxy) resulted in the formation of the TEMPO/N_3 adduct **4.2** isolated in 6% yield, which corroborated the formation of the putative $\bullet N_3$ (Scheme 4b). In addition, under standard conditions, both (*E*) and (*Z*)-styrene derivatives gave the same diastereoselectivities (3:2) and analogous yields, which suggests the intermediacy of a benzyl radical species resulting from the addition of $\bullet N_3$ to styrenes. Based on these observations, a possible mechanism for the azidotrifluoromethoxylation of styrenes is displayed in Scheme 4c. Photo-generated $*Ru(bpy)_3^{2+}$ is oxidatively quenched by **4.1** generating the highly oxidizing $Ru(bpy)_3^{3+}$ and the azide radical, $\cdot N_3$ (**4.3**). Subsequently, addition of $\cdot N_3$ to styrene (**4.4**) affords benzylic radical **4.5**, which is then oxidized to benzylic carbocation **4.6** by $Ru(bpy)_3^{3+}$. Concurrently, the *in situ* generated silver(I) trifluoromethoxide (**4.7**) from trifluoromethyl 4-methyl benzenesulfonate and AgF is trapped by the benzylic carbocation **4.6**, affording the desired product **4.8**. The azidotrifluoromethoxylation of styrenes is the first example of synergistic trifluoromethoxylation reaction using sliver and photoredox catalysis.

2.2. Radical Trifluoromethoxylation

In early 2010s, Arguello and Navarrini reported the use of $F_3CO–OCF_3$ and $F–OCF_3$ (based on the pioneering work of Barton and Hesse in 1968),[28] respectively, as precursors for the generation of the $\bullet OCF_3$ radical, which adds onto simple thiophenes and arenes to form trifluoromethoxylated (hetero)arenes (Figure 2a).[29] Although these strategies provided an access to the $\bullet OCF_3$ radical, the use of difficult-to-handle, highly reactive, and toxic gaseous reagents and the requirement of specialized reaction apparatus have limited their application in preparation of (heteroaryl)aryl trifluoromethyl ethers. It was not until 2018 when Ngai's and Togni's groups independently reported three distinct photo- or redox-active trifluoromethoxylating reagents, which are easy-to-handle and bench stable species capable of generating the $\bullet OCF_3$ radical at room temperature (Figure 2b).

In early 2018, Ngai and co-workers reported the first photoactive radical trifluoromethoxylating reagent **I** that liberates the OCF_3 radical under irradiation with violet LED light at room temperature (Scheme 5).[19, 30] This benzimidazole reagent (**I**), readily prepared in two steps from commercially available building blocks, enabled the first

catalytic intermolecular aryl C(sp^2)–H trifluoromethoxylation of (hetero)arenes. Exposure of reagent **I** to 10 equivalents of (hetero)arenes in the presence of a redox-active catalyst such as $Ru(bpy)_3(PF_6)_2$ (0.03 mol%) in MeCN under irradiation with violet LED light (λ_{max} = 402 nm) at room temperature afforded (hetero)aryl trifluoromethyl ethers in good yields. An excess amount of (hetero)arene (10 equiv) was needed to prevent bis-trifluoromethoxylation of the substrate. This procedure was amenable to simple arenes containing common functional groups including halides, carboxylic acids, ketones, esters, ethers, nitriles, carbonates, and phosphine oxides. Furthermore, substrates with benzylic moieties as well as heteroarenes such as pyridine, pyrimidine, and thiophene were all well tolerated. Moreover, structurally complex compounds, including derivatives of fructose and *trans*-androsterone were successfully trifluoromethoxylated using only 1 equivalent of substrate. Due to its radical reactivity, the $\bullet OCF_3$ adds to different reaction sites of aryl substrates to form a mixture of regioisomers. This is beneficial from a drug discovery perspective because it allows rapid access to different regioisomers without labor-intensive, parallel multi-step analogue synthesis.[31] It also increases the efficiency of structure-activity relationship (SAR) studies of OCF_3 analogues and can conveniently produce promising new candidates that might have never been evaluated otherwise.

Ngai *et al.* conducted a series of mechanistic studies to delineate the reaction mechanism. Interestingly, DFT calculations showed that a direct electron transfer from excited $*Ru(bpy)_3^{2+}$ to reagent **I** to form a radical anion is energetically unfavorable. Even if the radical anion of reagent **I** was formed, it would preferentially undergo mesolytic cleavage of the N–O bond to generate the *N*-centered benzimidazole radical ($\bullet NR^1R^2$) and the OCF_3 anion, rather than the desired $\bullet OCF_3$ radical.[30] An experiment in which the reaction was performed using a bandpass filter (λ_{max} = 488 ± 2 nm) suggested that reagent **I** is photoexcited to **I*** under irradiation with violet LED light and then fragments to form the $\bullet OCF_3$ (**6.1**) and $\bullet NR^1R^2$ **6.2** (Scheme 6a). Additional studies and computations indicated that the $\bullet OCF_3$ reacts with arenes faster than the benzimidazole radical (**6.2**) to form the cyclohexadienyl radical (**6.3**) (Scheme 6b). Redoxactive catalysts such as $Ru(bpy)_3^{2+}$ facilitate a SET between **6.2** and **6.3** to afford benzimidazole anion **6.4** and carbocation **6.5**, respectively. Deprotonation of **6.5** liberates the desired aryl trifluoromethyl ether **6.6**.

Despite the success of Ngai's first-generation reagent, the reaction is complicated by the formation of 3–10% yield of *N*-arylated side product and the requirement of a high energy violet light. Also, the formation of the $\bullet OCF_3$ from imidazole reagent **I** is not catalytic and selective. In order to overcome these limitations, Liu and Ngai reported a second-generation, redox-active, cationic trifluoromethoxylating reagent **II** that can liberate $\bullet OCF_3$ in a controllable, catalytic and selective manner under visible light-mediated photocatalytic conditions at room temperature (Scheme 7).[32] Reagent **II** showed a broader substrate scope than their first generation trifluoromethoxylating reagent. Although 10 equivalents of simple arenes and heteroarenes were still needed to prevent formation of bis-trifluoromethoxylated side products, 7.9–9.2 equivalents of aromatic substrates could be recovered at the end of the reaction, which is important for valuable substrates. More importantly, a number of biorelevant compounds could be used as limiting reagents, for example, Metronidazole®, Chlorpropamide®, Baclofen® derivatives were successfully converted into their

trifluoromethoxylated analogs. Notably, the reaction can proceed under air atmosphere and/or in the presence of water without diminished yields.

DFT calculations indicate that a SET from *Ru(bpy)$_3^{2+}$ to **II** is thermodynamically favorable (ΔG = –20.9 kcal mol^{-1}) and the resulting neutral radical **8.1** readily undergoes β-scission (ΔG = –43.3 kcal mol^{-1}) to generate the •OCF$_3$ **8.3** (Scheme 8a). In addition, a cyclic voltammetry (CV) measurement of reagent **II** (E_p = +0.140 V, vs SCE in MeCN) shows that a single electron reduction by *Ru(bpy)$_3^{2+}$ ($E_{½}^{red}$ = −0.81 V vs SCE in MeCN) is thermodynamically favorable (Scheme 8a). Once the •OCF$_3$ is formed, the following reactions such as trapping of the OCF$_3$ radical by an arene (ΔG = −52.5 kcal mol^{-1}) and oxidation of the resulting cyclohexadienyl radical **8.3** by Ru(bpy)$_3^{3+}$ to afford cyclohexadienyl cation **8.4** (ΔG = −64.5 kcal mol^{-1}) are both exergonic processes (Scheme 8b). Deprotonation of **8.4** gives the desired trifluoromethoxylation product **8.5**. It is noteworthy that neutral radical **8.1** forms the OCF$_3$ radical more favorably than the benzotriazole *N*-radical ($\Delta\Delta G$ = −8.8 kcal mol^{-1}). As a result, such energetic preference prevents formation of *N*-arylated side products.

In the same year, Togni and co-workers independently developed and disclosed an elegant work on photocatalytic radical trifluoromethoxylation of (hetero)arenes using pyridinium-based trifluoromethoxylating reagent **III** (Scheme 9).[33], [34] **III** can be synthesized in one-step in 63% yield via trifluoromethylation of 4-cyanopyridine *N*-oxide using Togni's Reagent I and TMSNTf$_2$ (*N*-trimethylsilyl-bis(trifluoromethanesulfonyl)imide). Under the optimal conditions: arene (5 equiv), Ru(bpy)$_3$(PF$_6$)$_2$ (5.0 mol%), and upon irradiation with 350 W blue LEDs, trifluoromethoxylation of a wide range of arenes and heteroarenes was achieved in 21–66% yields. Again, due to the reactivity of the OCF$_3$ radical, the addition of an excess amount of (hetero)aromatic substrate was necessary to prevent the formation of over trifluoromethoxylated side products. The reaction tolerated a broad array of common functional groups such as halides, aldehydes, ketones, esters, benzylic moieties, and imides. Also, it was applicable to a late-stage functionalization of biorelevant molecules including Femara® (a breast cancer drug), Metalaxyl (an acylalanine fungicide), Phenytoin (an anti-seizure medication), and Procymidone (a fruit fungicide).

Extensive spin-trapping experiments using advanced-pulse EPR measurements at cryogenic temperature (–80 °C) in the presence of a 0.1 W blue laser with the radical trap α-(4-pyridyl *N*-oxide)-*N*-*tert*-butylnitrone (POBN) successfully provided the first preliminary evidence of the involvement of the OCF$_3$ radical (Scheme 10a). Other common nitrone spin traps such as 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and *N*-tert-butyl-α-phenylnitrone (PBN) failed in trapping the reactive •OCF$_3$. DFT calculations and cyclic voltammetry measurements showed that single electron reduction of **III** by the excited *Ru(bpy)$_3^{2+}$ to form the neutral radical is favorable. They also revealed that the subsequent β-scission of **10.1** to produce the desired trifluoromethoxy radical **10.2** and the neutral pyridine is slightly more favorable than the generation of a trifluoromethoxide and a pyridinium radical cation ($\Delta\Delta G$ = –3.1 kcal mol^{-1}). This small energy difference accounts for the formation of <15% of aryl-pyridinium side products. On the basis of this mechanistic evidence, it was proposed that the reaction begins with the photoexcitation of Ru(bpy)$_3^{2+}$ to *Ru(bpy)$_3^{2+}$ (Scheme 10b). Subsequently, *Ru(bpy)$_3^{2+}$ is oxidatively quenched by the pyridinium cationic reagent **III** (E_p = –0.14 vs

SCE in MeCN) to afford $Ru(bpy)_3^{3+}$ and 4-cyanopyridinium radical **10.1**. β-Scission of **10.1** produces the neutral pyridine and the trifluoromethoxy radical that adds to an arene, forming the cyclohexadienyl radical **10.3**. Oxidation of **10.3** by $Ru(bpy)_3^{3+}$ followed by deprotonation affords the desired trifluoromethoxylated product **10.4**.

Overall, the radical approach towards direct trifluoromethoxylation of (hetero)arenes developed by Ngai and Togni has enabled photocatalytic C–H trifluoromethoxylation of (hetero)aromatic substrates and the late-stage functionalization of complex molecules at room temperature (Figure 2). Although these novel reagents still have their limitations such as the requirement of an excess amount of substrates, the formation of multiple regioisomeric products, and HPLC aided separation of the regioisomers, the ability to access the reactive OCF_3 radical and catalytically convert arenes to their OCF_3 analogues without prefunctionalization and under unprecedentedly mild conditions renders this radical approach highly valuable in the field of discovery chemistry.

3. Synthesis of Difluoromethoxylated Compounds

The most common approach towards preparation of difluoromethyl ethers is based on the reaction of oxygen nucleophiles and difluorocarbene (Figure 3a).[14, 35] A range of procedures and reagents for generation of difluorocarbene such as sodium chlorodifluoroacetate (Hazeldine),[36] diethyl bromodifluoromethylphosphonate (Zafrani and Segall),[35c] trifluoromethyl silane (Hu, Olah, and Prakash),[37] difluoromethyl triflate (Hartwig),[35g] and fluoroform (Dolbier)[35h] have been developed over the past few decades (Figure 3b). *O*-Difluoromethylation reactions using these reagents provide access to a wide array of simple OCF_2H-containing compounds. Nevertheless, some of the reagents used for the synthesis of difluoromethyl ethers are commercially unavailable chemicals, gaseous compounds, or ozone-depleting molecules such as HCF_2Cl (Freon 22). Also, reactions using some of the difluorocarbene sources require special reaction apparatus, elevated temperatures, or strong bases. To alleviate some of these limitations and establish milder reaction conditions, visible light photoredox catalysis has been used for the generation of the difluorocarbene intermediate.[35m] More recently, Ngai *et al.* reported a distinct and complementary photocatalytic radical aryl C–H difluoromethoxylation strategy using a redox-active cationic difluoromethoxylating reagent (**IV**) (Figure 3b).[38] This reagent can be synthesized in gram scale from commercially available starting materials with 41% overall yield and exhibits favorable physical and chemical properties (Figure 3c). More importantly, it enables the first catalytic and selective liberation and utilization of the OCF_2H radical at room temperature (*vide infra*).

3.1. Photocatalytic Difluorocarbene Protocol

In 2017, Fu and co-workers reported a strategy that enabled preparation of aromatic difluoromethyl ethers under visible-light photocatalytic conditions (Scheme 11).[35m] The difluorocarbene species, $:CF_2$, was generated *in situ* from commercially available and easy-to-handle difluorobromoacetic acid ($BrCF_2CO_2H$) in the presence of *fac*-$Ir(ppy)_3$ at room temperature upon irradiation with visible light. Under the optimized reaction conditions,

phenols and heteroaryl alcohols bearing halides, cyano, nitro, acetyl, alkyl, ester, ether groups underwent *O*-difluoromethylation reaction in 48-95% yield.

To investigate the reaction mechanism, Fu *et al.* subjected compound **12.1** to standard reaction conditions, but they could not detect any desired product (Scheme 12a) Thus, oxy-difluoroacetic acids such as **12.1** are unlikely reaction intermediates under the reported conditions. Furthermore, Stern–Volmer quenching of photoexcited *fac*-Ir(ppy)$_3$ revealed that only $BrCF_2COOCs$ quenches the excited Ir(ppy)$_3$. On the basis of these results, Fu and coworkers postulated that the reaction begins with photoexcitation of *fac*-Ir(ppy)$_3$ (Scheme 12b). Cesium carboxylate **12.2** (E_p = −1.29 V vs SCE)[35m] is then reduced by the photoexcited **fac*-Ir(ppy)$_3$ ($E_{1/2}^{IV/*III}$ = −1.73 V vs SCE)[39] to afford α-carbonyl radical **12.3**. Subsequently, a SET oxidation of **12.3** by *fac*-Ir(ppy)$_3^+$ regenerates the ground state *fac*-Ir(ppy)$_3$ and liberates difluorocarbene intermediate **12.4**, which is trapped by phenoxide **12.5** and then protonated to afford the desired aryl difluoromethyl ether **12.6**.

3.2. Radical Difluoromethoxylation

In 2019, Ngai *et al.* reported a distinct radical approach for catalytic C–H difluoromethoxylation of (hetero)arenes using an unprecedented difluoromethoxylating reagent **IV** (Scheme 13).[38] In analogy to their trifluoromethoxylating reagent **II**, **IV** enables the first catalytic and selective formation of the OCF_2H radical (•OCF_2H) at room temperature. Under the optimized reaction conditions, the OCF_2H radical can add to a wide range of arenes and heteroarenes affording difluoromethoxylated (hetero)aromatic compounds. The reaction tolerates common functional groups such as halides, aldehydes, ketones (with or without enolizable protons), carboxylic acids, esters, amides, and carbonates. Substrates bearing weak benzylic C−H bond (BDE ≈ 88 kcal/mol), benzylic halides, unprotected alcohols, or phenols are proved compatible and afford the desired products in good yields. Notably, the reaction is amenable to late-stage functionalization of bio-relevant molecules such as Febuxostat® (anti-hyperuricemic), Mexiletine® (anti-arrhythmic), Efavirenz® (an anti-retroviral drug for treating HIV).

With regard to the reaction mechanism, Ngai *et al.* showed that the quantum yield of the reaction was 0.52, which suggested a closed catalytic cycle (Scheme 14a). A radical probe experiment using 1,4-cyclohexadiene as the substrate afforded difluoromethoxylated benzene (**14.2**), indicating the formation of the OCF_2H radical (Scheme 14b). On the basis of these and additional results from other mechanistic studies including DFT calculations, CV measurements, Stern-Volmer luminescence quenching studies, radical trap as well as competition experiments, Ngai and coworkers proposed a catalytic cycle that begins with photoexcitation of Ru(bpy)$_3^{2+}$ followed by single electron transfer from the resulting excited *Ru(bpy)$_3^{2+}$ to reagent **IV** (ΔG = −17.0 kcal mol^{-1}), forming a neutral radical **14.3** (Scheme 14c). This radical readily undergoes β-scission to release benzotriazole **14.4** and the desired •OCF_2H radical (ΔG = −42.4 kcal mol^{-1}), which adds favorably to an arene to form cyclohexadienyl radical **14.5** (ΔG = −44.9 kcal mol^{-1}) rather than undergoes decomposition to fluorophosgene and hydrogen atom (ΔG = −36.5 kcal mol^{-1}). Subsequently, oxidation of **14.5** by Ru(bpy)$_3^{3+}$ ($E_{1/2}^{red}$ = +1.28 V, versus SCE in MeCN) and deprotonation of the

resulting cyclohexadienyl cation **14.6** ($\Delta G = -61.6$ kcal mol^{-1}) give the desired product **14.2**.

3. Conclusion

In summary, recent advances in visible light photoredox catalysis have enabled development of novel synthetic strategies towards preparation of tri- and difluoromethoxylated compounds. Several new O–R_F and the C–OR_F bond-forming reactions as well as other radical transformations leading to the construction of OCF_3 and OCF_2H groups have provided access to numerous valuable OCF_3 and OCF_2H-bearing molecules. The use of photocatalytic SET processes allows the synthesis of tri- and difluoromethoxylated molecules in moderate to good yields under mild conditions. New photo- and redox-active reagents for the direct tri- and difluoromethoxylation of unactivated arenes and heteroarenes through a radical-mediated mechanism were developed and successfully applied in late-stage functionalization of biologically-relevant molecules. The radical (hetero)aryl tri- and difluoromethoxylation has offered a possibility of generating multiple OCF_3- and OCF_2H-analogues in a single operation, thus greatly accelerating synthesis of compounds needed for thorough SAR studies. Due to the growing interest in OCF_3- and OCF_2H- substituted compounds as well as the rapid progress in the area of visible light photoredox catalysis, one might anticipate further breakthroughs in the field. In addition, improved access to tri- and difluoromethyl ethers is likely to facilitate the discovery and development of novel functional molecules for medicinal and material applications.

Acknowledgments

We are grateful for NIGMS (R35GM119652) in support of this work. We greatly appreciate the helpful comments and suggestions provided by the referees.

Biographies

Johnny W. Lee was born in New York, United States. In 2015, he obtained his B.Sc. in chemistry from Stony Brook University. In the same year, he began his PhD degree at Stony Brook University under the supervision of Prof. Ngai. His research focuses on development of novel fluorination strategies utilizing photoredox catalysis, with a specific interest in tri- and difluoromethoxylation reactions.

Dr. Katarzyna N. Lee was born in Warsaw, Poland. In 2011, she completed her M.S with honors in chemistry from the University College London. She continued her studies at Harvard University and received her M.A. in chemistry in 2013. Subsequently, she competed her Ph.D. in chemistry (2013–2017) at the Stony Brook University under the supervision of Prof. Ming-Yu Ngai.

Prof. Dr. Ming-Yu Ngai was born in Fuching, China. He received his B.Sc. degree from the University of Hong Kong in 2003 and his Ph.D. degree from the University of Texas at Austin (2004–2008). He then worked as the Croucher postdoctoral fellow (2009–2011) at Stanford University and a postdoctoral associate at Harvard University (2011–2013). In 2013, he was appointed as an Assistant Professor in the Department of Chemistry at Stony Brook University. His research focuses on photoredox catalysis and creating new functional molecules with a specific interest in fluorinated compounds and exploring their properties as well as applications in the fields of chemistry, biology, and materials science.

References

[1]. a) Purser S, Moore PR, Swallow S, Gouverneur V, Chem. Soc. Rev 2008, 37, 320; [PubMed: 18197348] b) Ojima I, Fluorine in Medicinal Chemistry and Chemical Biology, Blackwell Publishing Ltd, 2009;c) Liang T, Neumann CN, Ritter T, Angew. Chem. Int. Ed 2013, 52, 8214;Angew. Chem 2013, 125, 8372;d) Wang J, Sánchez-Roselló M, Aceña JL, del Pozo C, Sorochinsky AE, Fustero S, Soloshonok VA, Liu H, Chem. Rev 2014, 114, 2432; [PubMed: 24299176] e) Zhou Y, Wang J, Gu Z, Wang S, Zhu W, Aceña JL, Soloshonok VA, Izawa K, Liu H, Chem. Rev 2016, 116, 422. [PubMed: 26756377]

[2]. a) Leroux F, Jeschke P, Schlosser M, Chem. Rev 2005, 105, 827; [PubMed: 15755078] b) Muller K, Faeh C, Diederich F, Science 2007, 317, 1881; [PubMed: 17901324] c) Jeschke P, Baston E, Leroux FR, Mini-Rev. Med. Chem 2007, 7, 1027; [PubMed: 17979805] d) Landelle G, Panossian A, Leroux FR, Curr. Top. Med. Chem 2014, 14, 941. [PubMed: 24484423]

[3]. Xing L, Blakemore DC, Narayanan A, Unwalla R, Lovering F, Denny RA, Zhou H, Bunnage ME, ChemMedChem 2015, 10, 715. [PubMed: 25755132]

[4]. Mcclinton MA, Mcclinton DA, Tetrahedron 1992, 48, 6555.

[5]. Hansch C, Leo A, Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley, New York, 1979.

[6]. Federsel D, Herrmann A, Christen D, Sander S, Willner H, Oberhammer H, J. Mol. Struct 2001, 567, 127.

[7]. a) Müller K, Chimia 2014, 68, 356; [PubMed: 25198745] b) Huchet QA, Trapp N, Kuhn B, Wagner B, Fischer H, Kratochwil NA, Carreira EM, Müller K, J. Fluorine Chem 2017, 198, 34.

[8]. a) Waring MJ, Expert Opin. Drug Discov 2010, 5, 235; [PubMed: 22823020] b) Gaulton A, Bellis LJ, Bento AP, Chambers J, Davies M, Hersey A, Light Y, McGlinchey S, Michalovich D, Al-Lazikani B, Overington JP, Nucleic Acids Res 2012, 40, D1100. [PubMed: 21948594]

[9]. Burness CB, Drugs 2015, 75, 1559. [PubMed: 26323341]

[10]. Milane A, Vautier S, Chacun H, Meininger V, Bensimon G, Farinotti R, Fernandez C, Neurosci. Lett 2009, 452, 12. [PubMed: 19146924]

[11]. Dias LM, Clin. Drug. Investig 2009, 29, 3.

[12]. Chong J, Leung B, Poole P, Cochrane Database Syst. Rev 2017, 10.1002/14651858.CD002309.pub5.

[13]. Selected recent reviews on trifluoromethoxylation reactions:a) Lee KN, Lee JW, Ngai M-Y, Synlett 2016, 27, 313; [PubMed: 27872511] b) Besset T, Jubault P, Pannecoucke X, Poisson T, Org. Chem. Front 2016, 3, 1004;c) Tlili A, Toulgoat F, Billard T, Angew. Chem. Int. Ed 2016, 55, 11726;Angew. Chem 2016, 128, 11900;d) Lee KN, Lee JW, Ngai M-Y, Tetrahedron 2018, 74, 7127; [PubMed: 30906076] e) Zhang P. XT, Sci. Chi. Chem 2019, 62, 10.1007/s11426-018-9402-x.

[14]. Ni C, Hu J, Synthesis 2014, 46, 842.

[15]. Leroux F, Jeschke P, Schlosser M, Chem. Rev 2005, 105, 827. [PubMed: 15755078]

[16]. Zhou Y, Wang J, Gu Z, Wang S, Zhu W, Aceña JL, Soloshonok VA, Izawa K, Liu H, Chem. Rev 2016, 116 , 422. [PubMed: 26756377]

[17]. Selected reviews on photoredox catalysis:a) Prier CK, Rankic DA, MacMillan DWC, Chem. Rev 2013, 113, 5322; [PubMed: 23509883] b) Karkas MD, Porco JA Jr., Stephenson CR, Chem. Rev 2016, 116, 9683; [PubMed: 27120289] c) Romero NA, Nicewicz DA, Chem. Rev 2016, 116, 10075; [PubMed: 27285582] d) Skubi KL, Blum TR, Yoon TP, Chem. Rev 2016, 116, 10035; [PubMed: 27109441] e) Matsui JK, Lang SB, Heitz DR, Molander GA, ACS Catal 2017, 7, 2563. [PubMed: 28413692]

[18]. Schultz DM, Yoon TP, Science 2014, 343, 985.

[19]. Sahoo B, Hopkinson MN, Angew. Chem. Int. Ed 2018, 57, 7942;Angew. Chem 2018, 130, 8070.

[20]. a) Redwood ME, Willis CJ, Can. J. Chem 1965, 43, 1893;b) Farnham WB, Smart BE, Middleton WJ, Calabrese JC, Dixon DA, J. Am. Chem. Soc 1985, 107, 4565;c) Nishida M, Vij A, Kirchmeier RL, Shreeve JM, Inorg. Chem 1995, 34, 6085;d) Christe KO, Hegge J, Hoge B, Haiges R, Angew. Chem. Int. Ed 2007, 46, 6155;Angew. Chem 2007, 119, 6267.

[21]. a) Lee JW, Spiegowski DN, Ngai M-Y, Chem. Sci 2017, 8, 6066; [PubMed: 28989637] b) Swager TM, Yoshinaga K, Synfacts 2017, 13, 1142.

[22]. a) Hojczyk KN, Feng PJ, Zhan CB, Ngai MY, Angew. Chem. Int. Ed 2014, 53, 14559;Angew. Chem 2014, 126, 14787;b) Feng PJ, Lee KN, Lee JW, Zhan CB, Ngai MY, Chem. Sci 2016, 7, 424; [PubMed: 27857834] c) Lee KN, Lei Z, Morales-Rivera CA, Liu P, Ngai MY, Org. Biomol. Chem 2016, 14, 5599. [PubMed: 27043815]

[23]. Beatty JW, Douglas JJ, Cole KP, Stephenson CRJ, Nat. Commun 2015, 6, 7919. [PubMed: 26258541]

[24]. Juris A, Balzani V, Belser P, von Zelewsky A, Helv. Chim. Acta 1981, 64, 2175.

[25]. a) Studer A, Angew. Chem. Int. Ed 2012, 51, 8950;Angew. Chem 2012, 124, 9082;b) Nappi M, Bergonzini G, Melchiorre P, Angew. Chem. Int. Ed 2014, 53, 4921;Angew. Chem 2014, 126, 5021.

[26]. a) Studer A, Chem. - Eur. J 2001, 7, 1159; [PubMed: 11322540] b) Fischer H, Chem. Rev 2001, 101, 3581. [PubMed: 11740916]

[27]. Cong F, Wei Y, Tang P, Chem. Commun 2018, 54, 4473.

[28]. Barton DHR, Godinho LS, Hesse RH, Pechet MM, Chem. Commun. (London), 1968, 0, 804.

[29]. a) Pelaez WJ, Arguello GA, Tetrahedron Lett 2010, 51, 5242;b) Venturini F, Navarrini W, Famulari A, Sansotera M, Dardani P, Tortelli V, J. Fluorine Chem 2012, 140, 43.

[30]. Zheng W, Morales-Rivera CA, Lee JW, Liu P, Ngai MY, Angew. Chem. Int. Ed 2018, 57, 9645;Angew. Chem 2018, 130, 9793.

[31]. a) Nagib DA, MacMillan DW, Nature 2011, 480, 224; [PubMed: 22158245] b) Cernak T, Dykstra KD, Tyagarajan S, Vachal P, Krska SW, Chem. Soc. Rev 2016, 45, 546. [PubMed: 26507237]

[32]. Zheng W, Lee JW, Morales-Rivera CA, Liu P, Ngai M-Y, Angew. Chem. Int. Ed 2018, 57, 13795;Angew. Chem 2018, 130, 13991.

[33]. OCF_3-pyridinium salt was first synthesized by Umemoto and Hu for trifluoromethoxylation of electron rich arenes in the absence of photoredox catalyst, see:Umemoto T. ZM, Hu J, Vol. CN105017143A (Ed.: CN FZS), China, 2015.

[34]. Application of OCF_3-pyridinium salts for radical trifluoromethoxylation of (hetero)arenes under photoredox-catalysed conditions, see:Jelier BJ, Tripet PF, Pietrasiak E, Franzoni I, Jeschke G, Togni A, Angew. Chem. Int. Ed 2018, 57, 13784;Angew. Chem 2018, 130, 13980.

[35]. Synthesis of aryl difluoromethyl ethers from phenols: for selected examples of stoichiometric reactions, see:a) Zhang L, Zheng J, Hu J, J. Org. Chem 2006, 71, 9845; [PubMed: 17168605] b) Zheng J, Li Y, Zhang L, Hu J, Meuzelaar GJ, Federsel H-J, Chem. Commun 2007, 5149;c) Zafrani Y, Sod-Moriah G, Segall Y, Tetrahedron 2009, 65, 5278;d) Wang F, Huang W, Hu J, Chin. J. Chem 2011, 29, 2717;e) Wang F, Zhang L, Zheng J, Hu J, J. Fluorine Chem 2011, 132, 521;f) Sperry JB, Sutherland K, Org. Process Res. Dev 2011, 15, 721;g) Fier PS, Hartwig JF, Angew. Chem. Int. Ed 2013, 52, 2092;Angew. Chem 2013, 125, 2146;h) Thomoson CS, Dolbier WR Jr, J. Org. Chem 2013, 78, 8904; [PubMed: 23931184] i) Li L, Wang F, Ni C, Hu J, Angew. Chem. Int. Ed 2013, 52, 12390;Angew. Chem 2013, 125, 12616;for examples of other indirect, multi-step strategies, see:j) Hagooly Y, Cohen O, Rozen S, Tetrahedron Lett 2009, 50, 392;k) Dolbier WR Jr, Wang F, Tang X, Thomoson CS, Wang L, J. Fluorine Chem 2014, 160, 72;for examples of catalytic O-CF_2H bond forming reactions, see:l) Levchenko K, Datsenko OP, Serhiichuk O, Tolmachev A, Iaroshenko VO, Mykhailiuk PK, J. Org. Chem 2016, 81, 5803; [PubMed: 27150198] m) Yang J, Jiang M, Jin Y, Yang H, Fu H, Org. Lett 2017, 19, 2758. [PubMed: 28480711]

[36]. Birchall JM, Cross GE, Haszeldine RN, Proc. Chem. Soc., London 1960, 81.

[37]. Wang F, Luo T, Hu J, Wang Y, Krishnan HS, Jog PV, Ganesh SK, Prakash GKS, Olah GA, Angew. Chem. Int. Ed 2011, 50, 7153;Angew. Chem 2011, 123, 7291.

[38]. Lee JW, Zheng W, Morales-Rivera CA, Liu P, Ngai MY, Chem. Sci 2019, 10, 3217. [PubMed: 30996904]

[39]. Flamigni L, Barbieri A, Sabatini C, Ventura B, Barigelletti F, Top. Curr. Chem 2007, 281, 143.

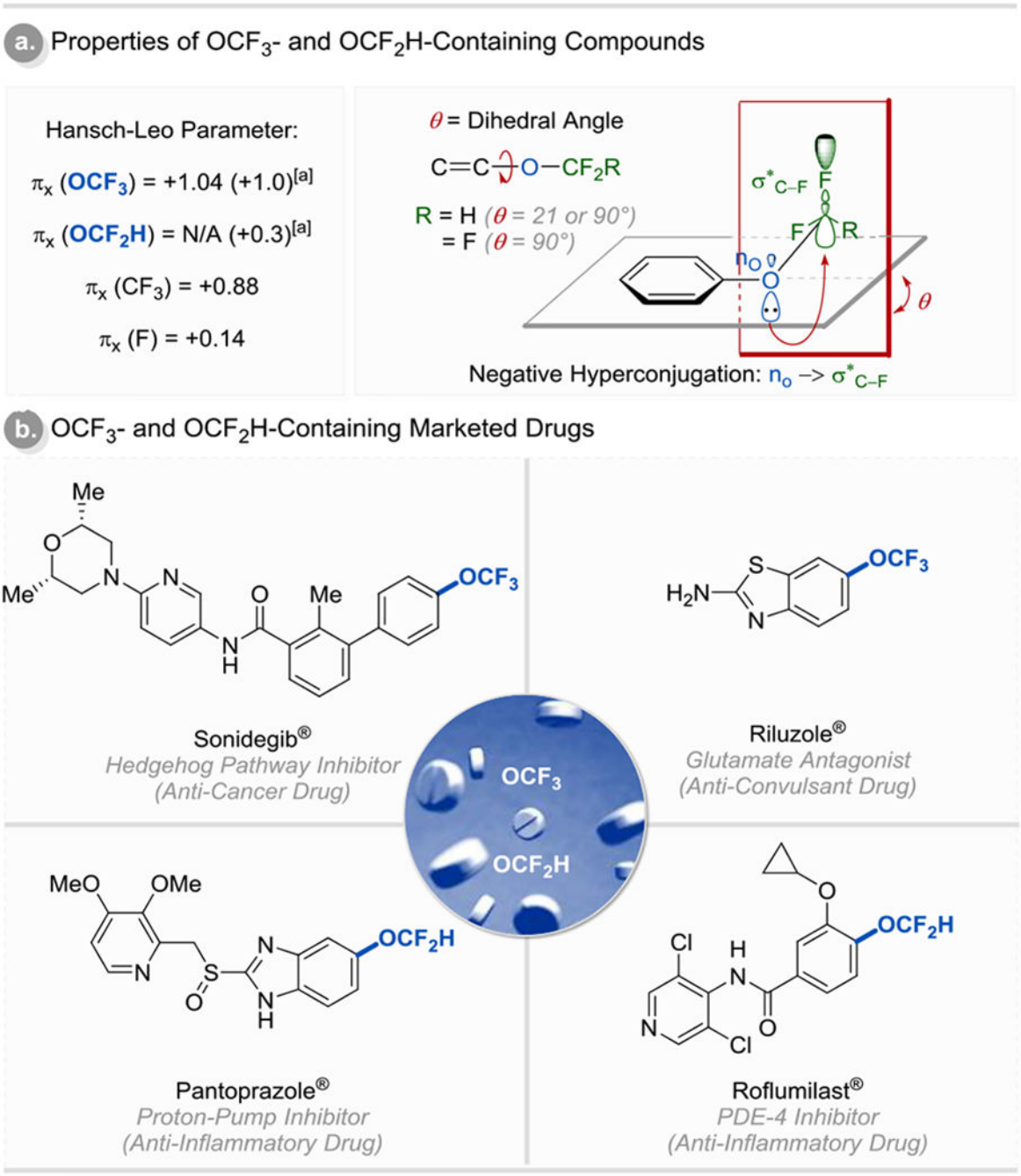
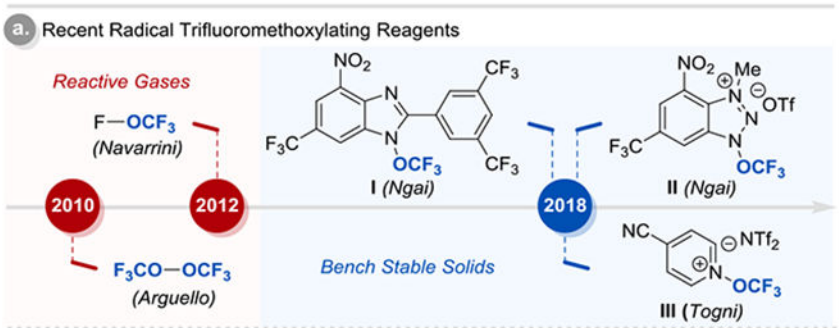


Figure 1.

(a) Properties of OCF_3- and OCF_2H-containing compounds (b) OCF_3- and OCF_2H-containing marketed drugs.



b. Comparison of Reagents **I**, **II**, and **III**

	I *(Ngai)*	II *(Ngai)*	III *(Togni)*
Synthesis of Reagent			
# Steps from Commercially Available Materials	2	3	1
Overall Yield	46%	32%	63%
Reaction Condidtions			
Mode of Activation	Direct Excitation *(Photolysis)*	SET *(β-scission)*	SET *(β-scission)*
Light Source	10 W Purple LEDs (λ_{max} = 402 nm)	10 W Blue LEDs (λ_{max} = 447 nm)	350 W Blue LEDs (λ_{max} = 450 nm)
$Ru(bpy)_3^{2+}$ Loading *Photoredox Catalyst*	0.03 mol%	1.00 mol%	5.00 mol%
Equivalents of (Hetero)Arenes	1 or 10	1 or 10	5
Reaction Time	16 h	16 h	1 h
Oxygen Sensitivity	None	None	None
Water Sensitivity	–	With 100 equiv of Water Yield Dropped by <4%	With 10 equiv of Water Yield Dropped by <30%[a]
Physical Properties			
Cyclic Voltammetry *vs SCE in MeCN*	–	E_p = +0.14 V *(irreversible)*	E_p = +0.14 V *(irreversible)*
Formation of $•OCF_3$ vs $•NR_1R_2$ via SET $\Delta\Delta G$ *(kcal mol-1)*	–	−8.8	−3.1
N-Arylated Side Product from $•NR_1R_2$	<10%	<1%	<15%
$•OCF_3$ Addition to Reagent By Product	<5%	<1%	<5%
Differential Scanning Calorimetry (DSC) On-Set	130 °C[b] *(endothermic)*	185 °C *(exothermic)*	115 °C *(exothermic)*

Figure 2.

(a) Recent developments in direct trifluoromethoxylation reagents. (b) Comparison of reaction conditions and physical properties of bench stable trifluoromethoxylating reagents **I**, **II**, and **III**.

[a]Decomposition to pyridone was observed [b]on-set of melting curve.

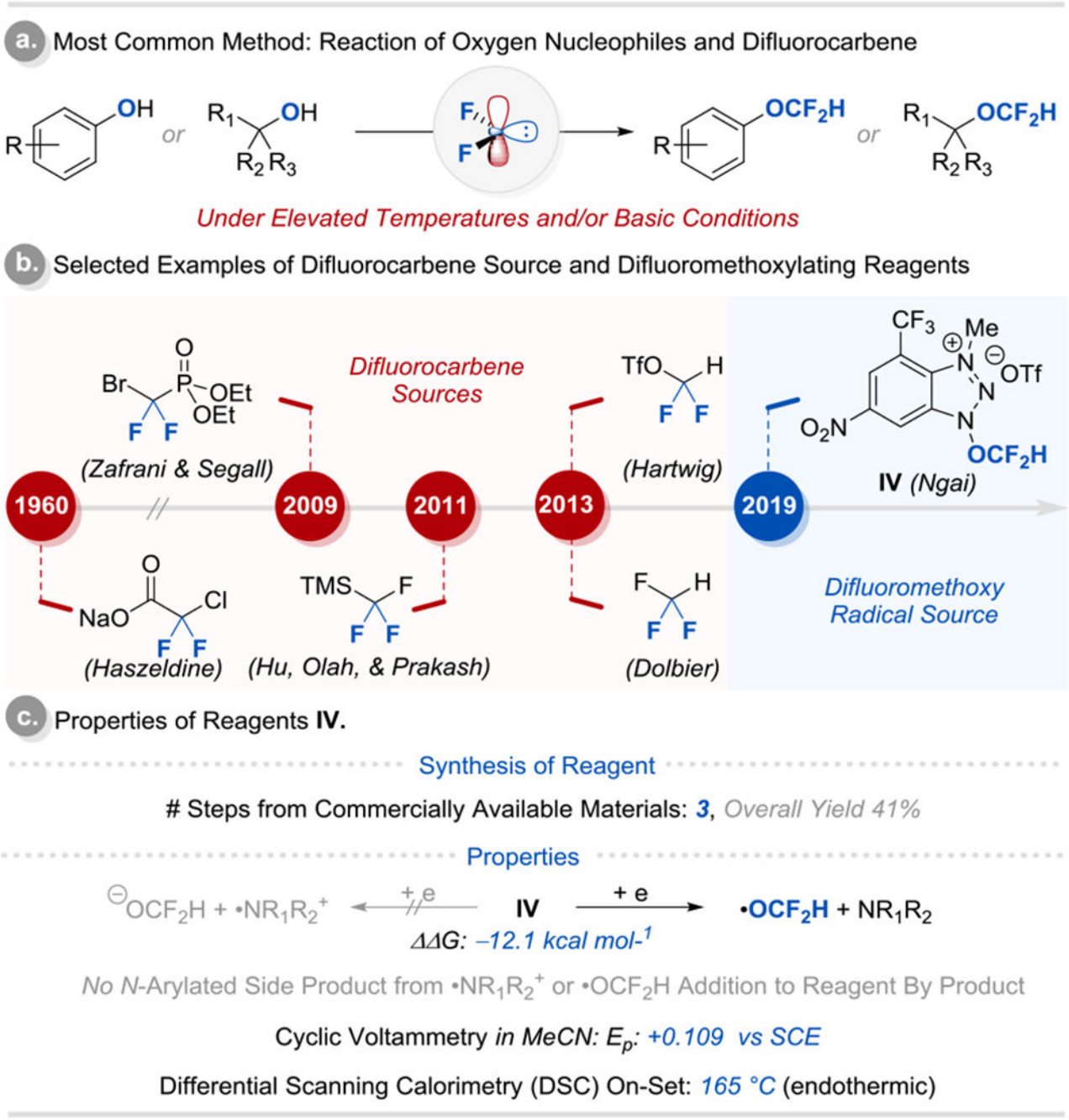
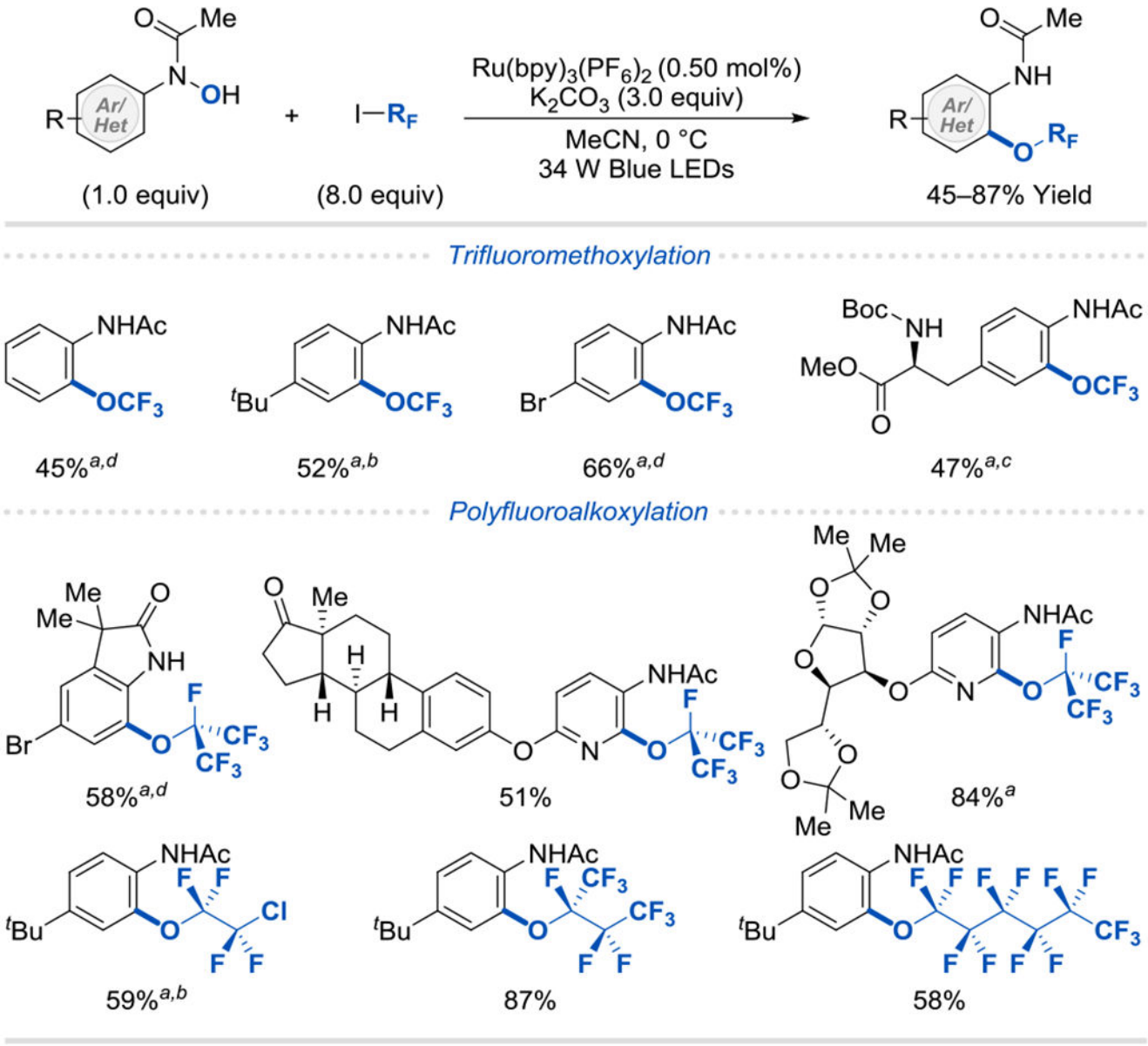


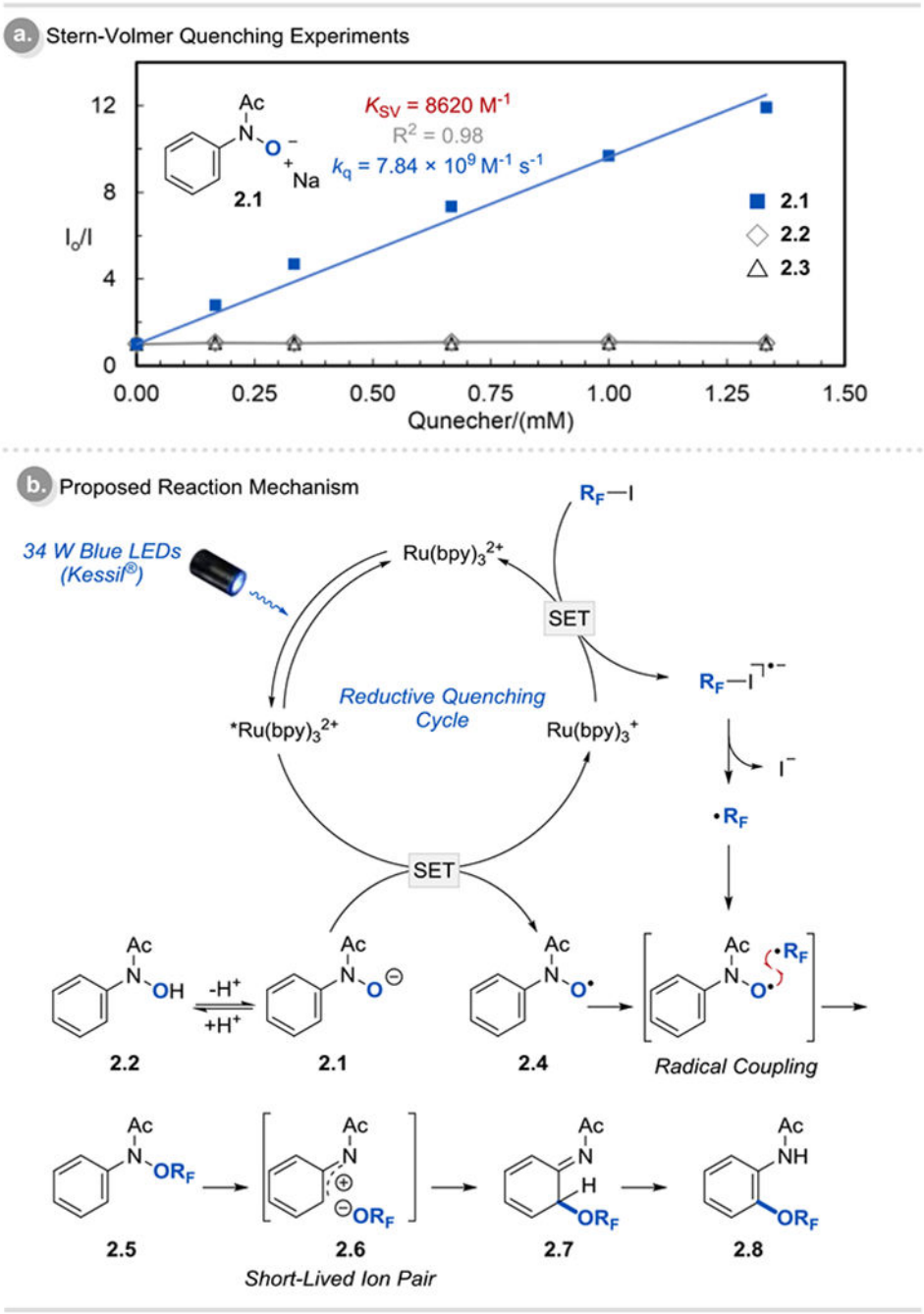
Figure 3.

(a) Synthesis of difluoromethyl ethers based on the reaction of oxygen nucleophiles with difluorocarbene. (b) Selected examples of reagents used as difluorocarbene sources and difluoromethoxylating reagents. (c) Properties of reagent **IV**.



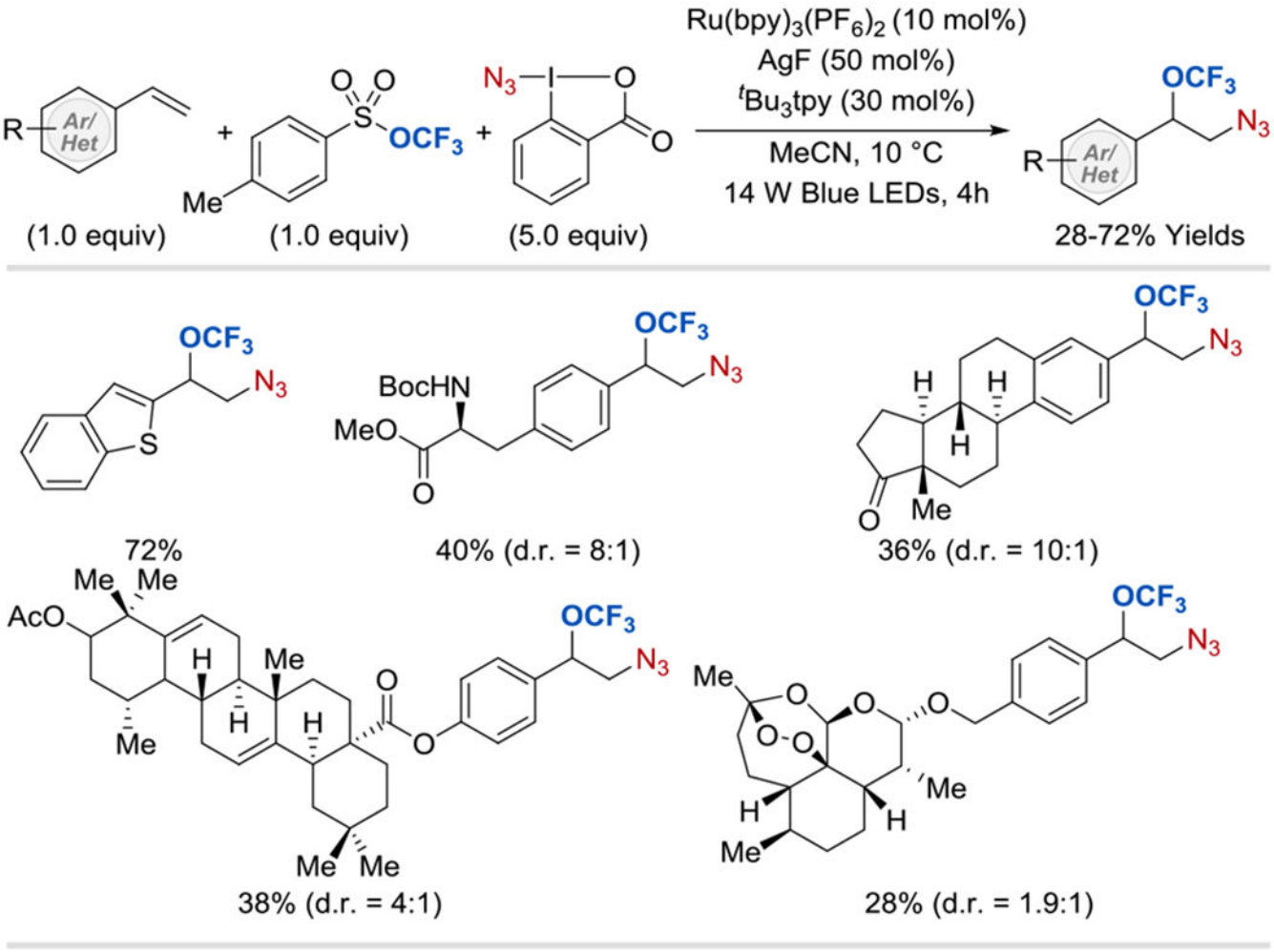
Scheme 1.

Selective C–O bond formation via a photocatalytic radical coupling strategy: access to perfluoroalkoxylated (OR_F) (hetero)arenes. [a]–40 °C. [b]After 12 h the reaction mixture was heated to 40 °C. [c]After 12 h the reaction mixture was concentrated, and the residue was dissolved in MeCN and heated to 40 °C. [d]After 12 h the reaction mixture was filtered, concentrated, and the residue was dissolved in MeCN and heated to 80 °C.

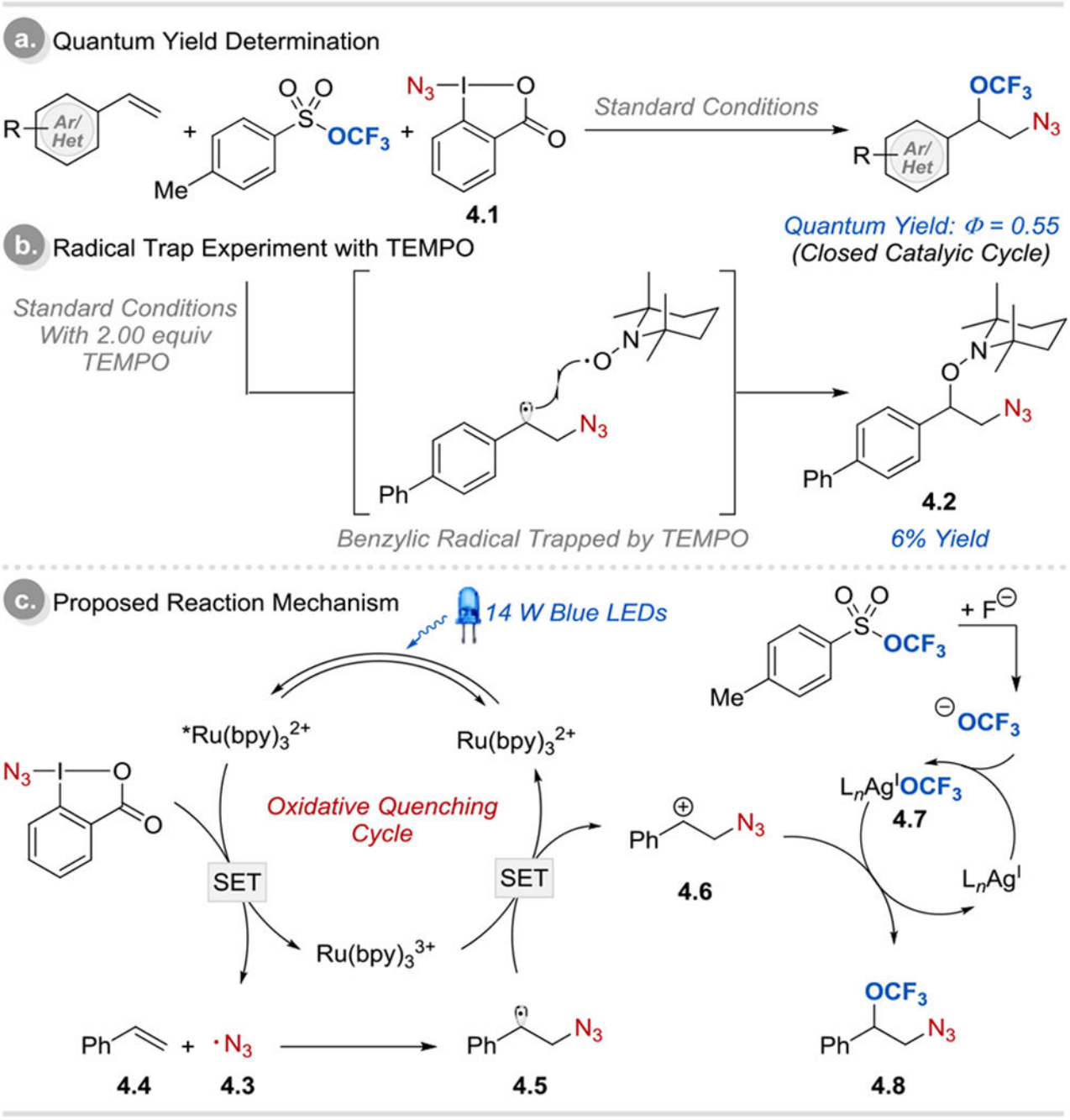


Scheme 2.

(a) Stern–Volmer quenching experiments. (b) Proposed catalytic cycle and the subsequent ionic rearrangement. Adapted with permission from reference.[21a] © 2017 Royal Society of Chemistry.

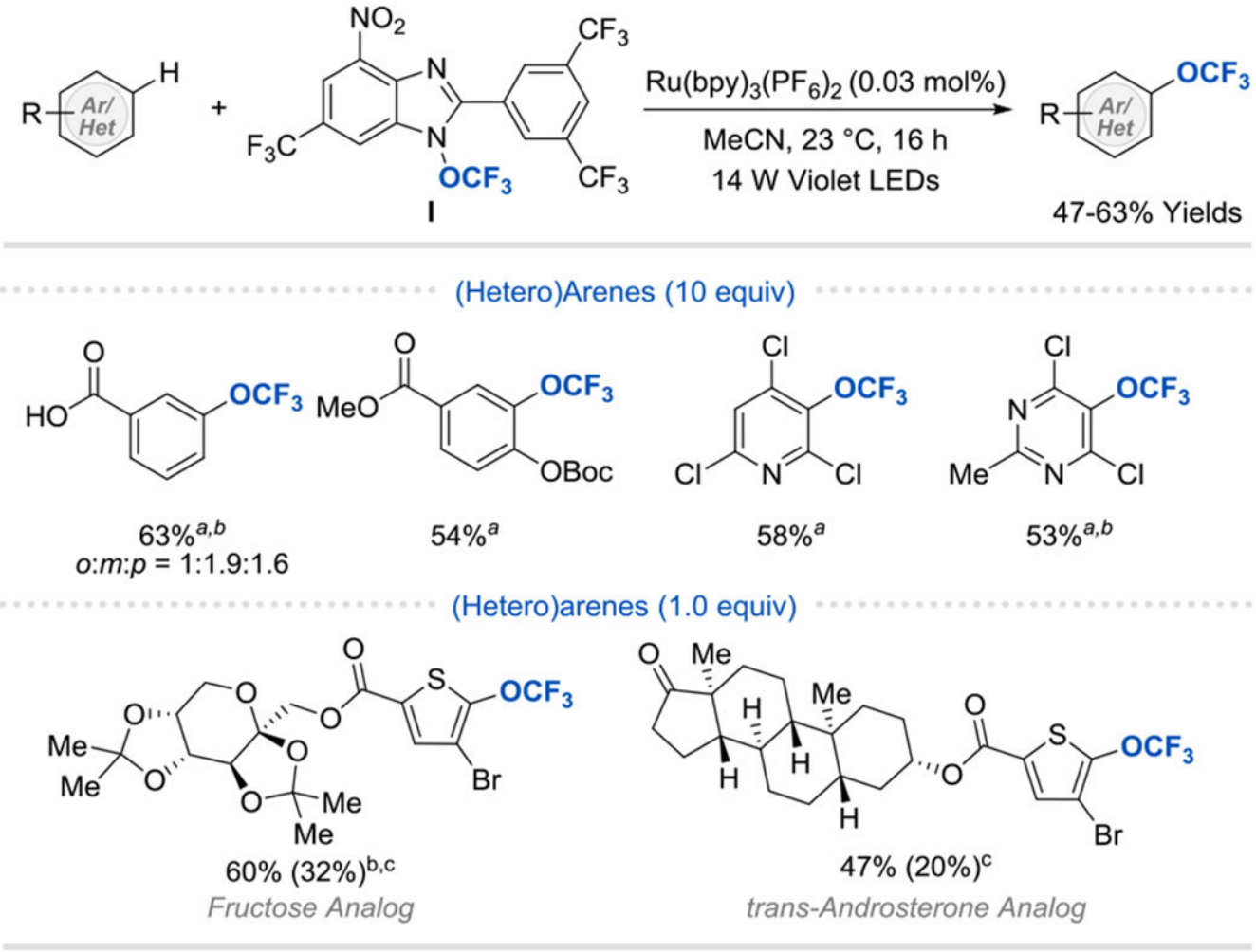


Scheme 3.
Azidotrifluoromethoxylation of styrenes via photoredox and silver catalysis.



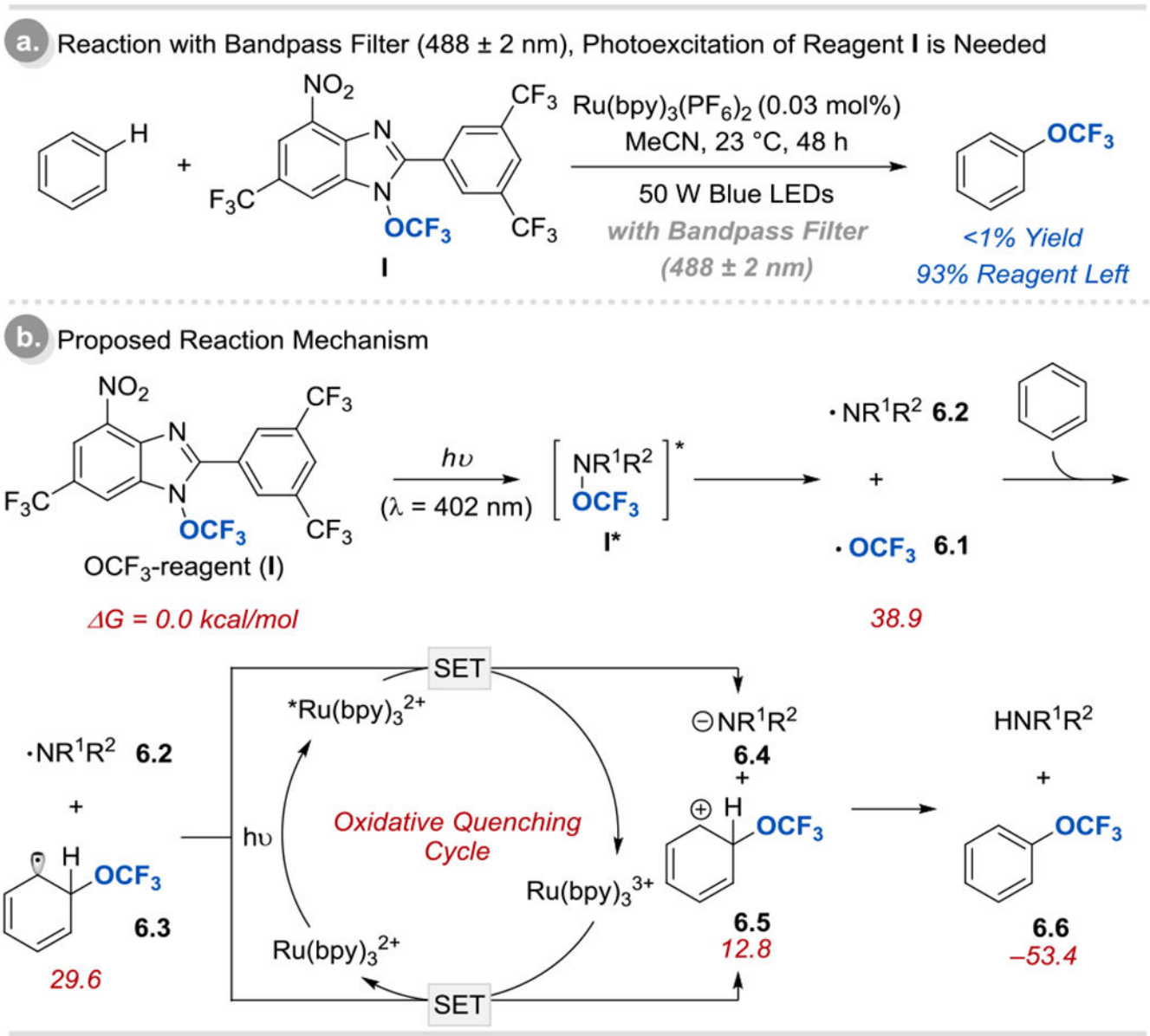
Scheme 4.

(a) Quantum yield of the reaction. (b) Radical trapping with TEMPO under standard conditions. (c) Proposed mechanism for the azidotrifluoromethoxylation of styrenes via photoredox and silver catalysis.



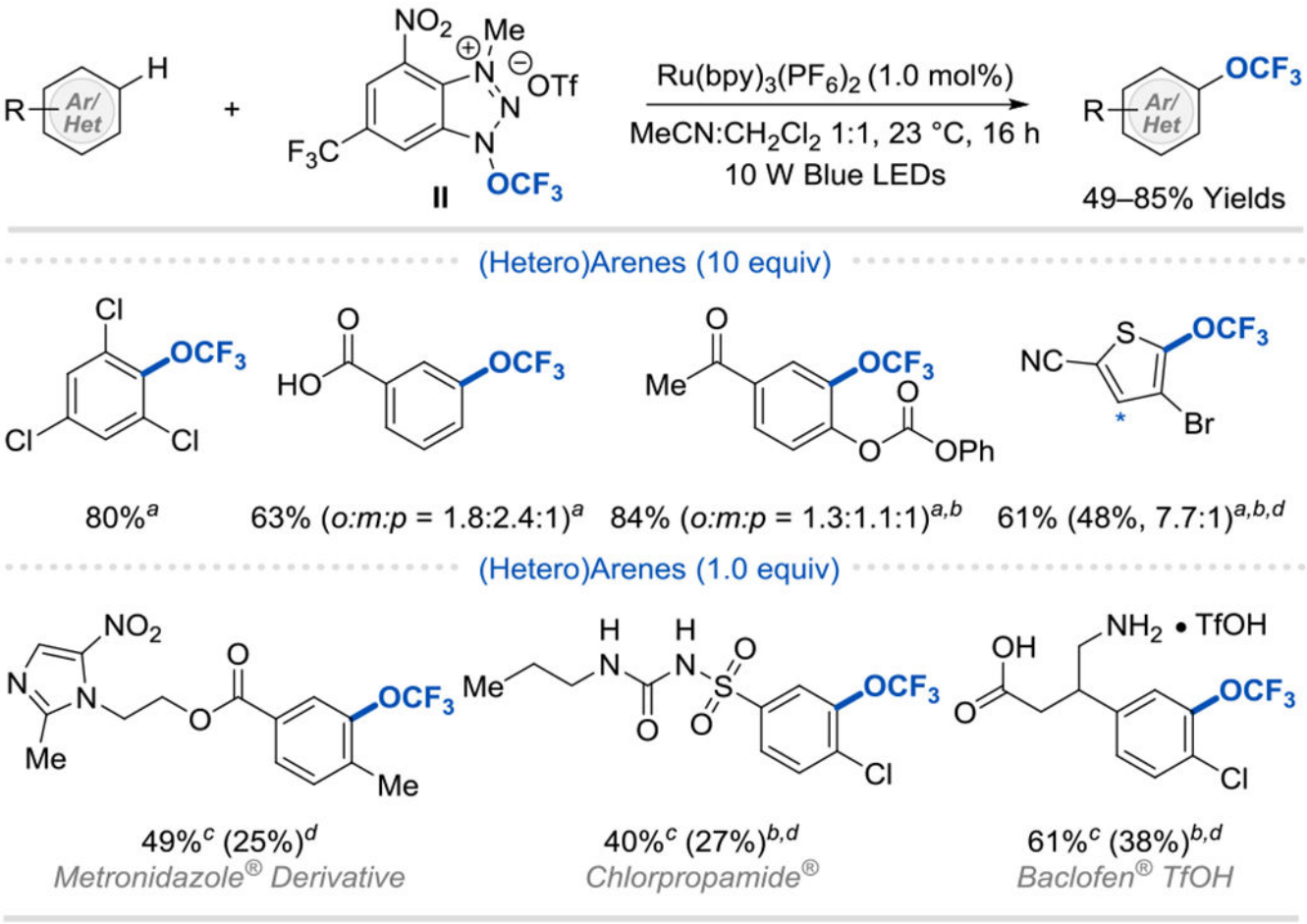
Scheme 5.

Catalytic C–H trifluoromethoxylation of (hetero)arenes with reagent **I**. [a]Yields and regioselectivity were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [b]Reaction was performed at 40 °C. [c] Yield of isolated product based on the recovered starting material, yield in parenthesis is the yield of isolated product.



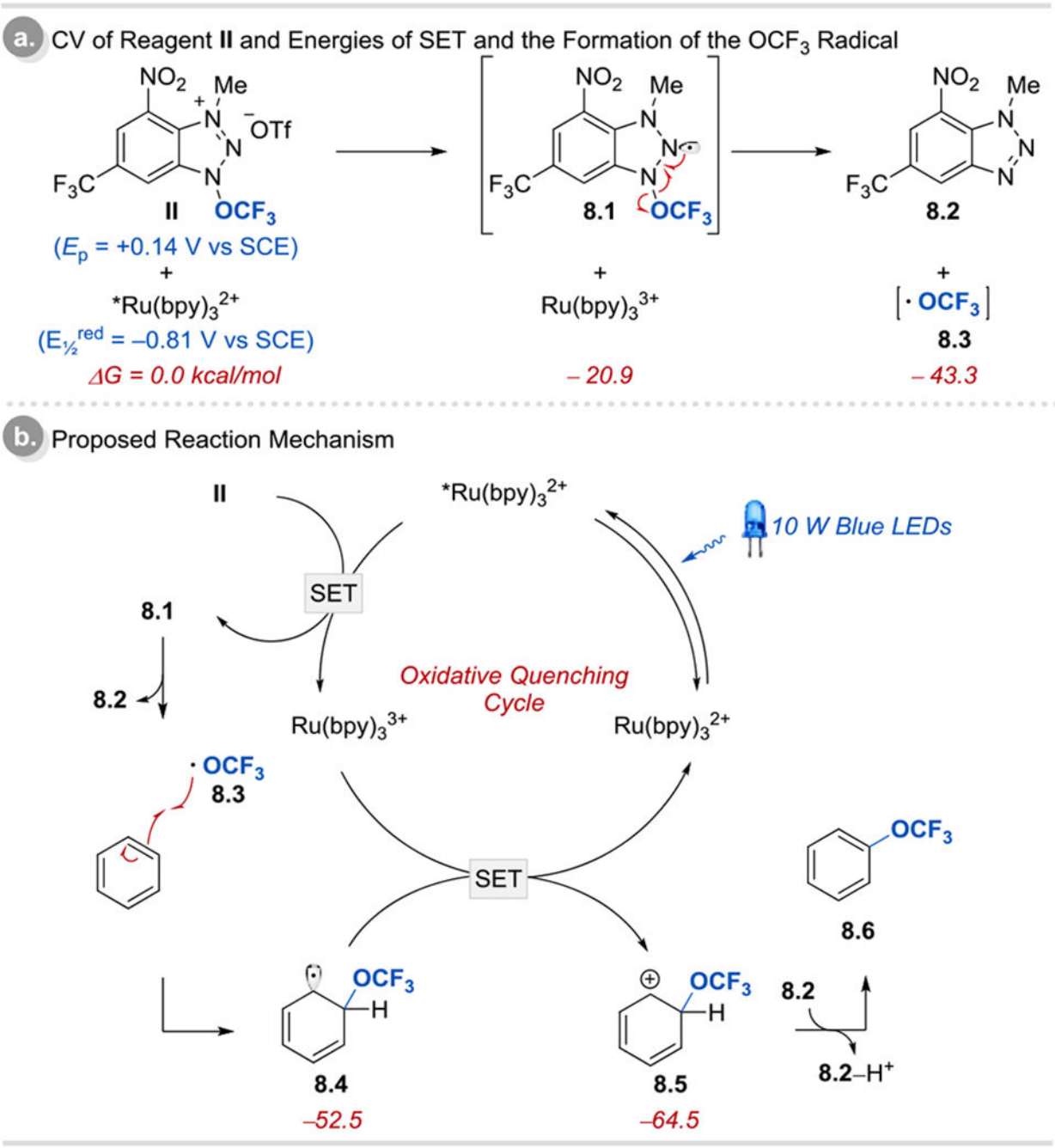
Scheme 6.

(a) Reaction with a 488 ± 2 nm bandpass filter. (b) Proposed mechanism for the trifluoromethoxylation of (hetero)arenes.



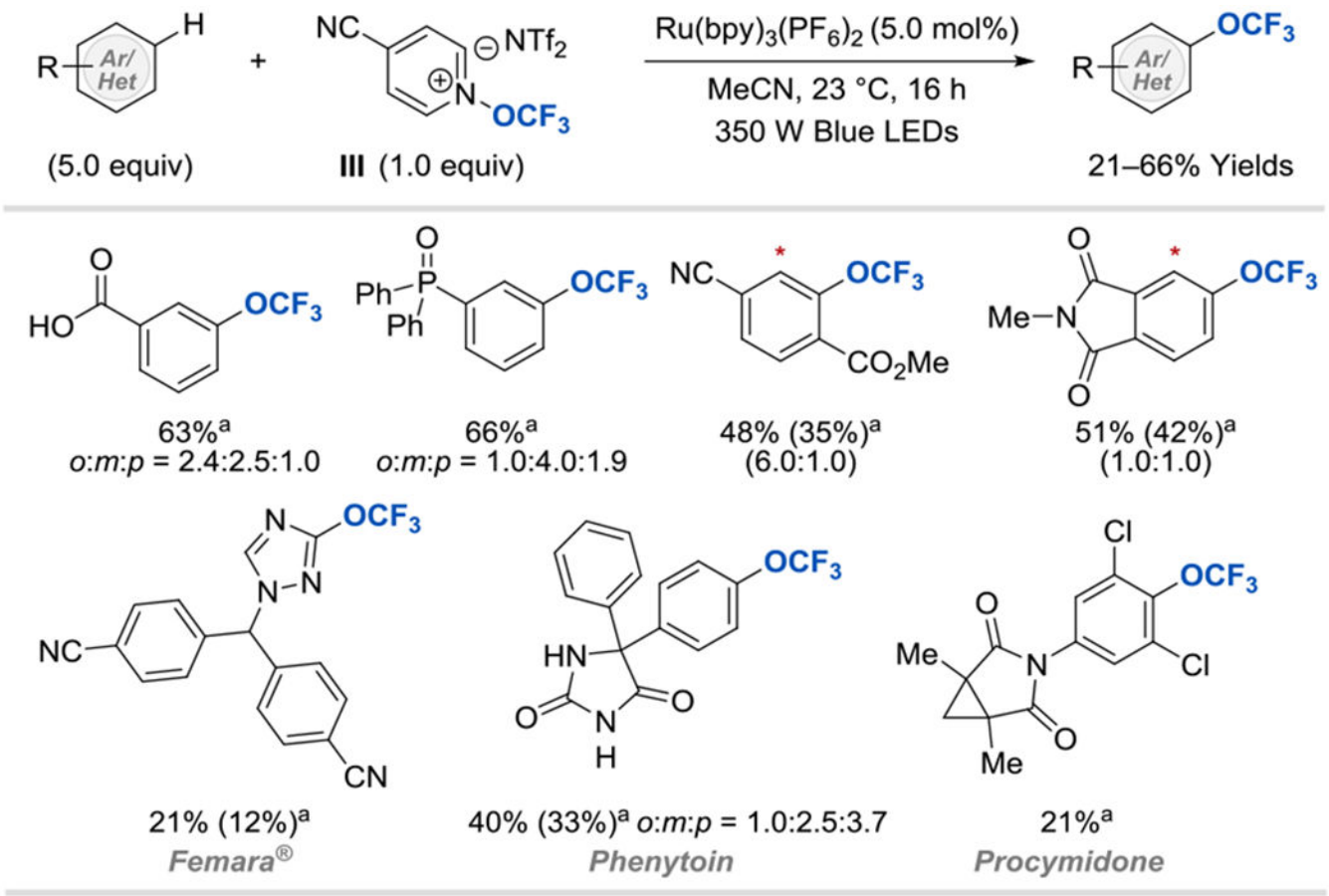
Scheme 7.

Photoredox-catalyzed intermolecular C–H trifluoromethoxylation of (hetero)arenes with reagent **II**. [a]Yields and regioselectivity were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. [b]MeCN was used as the solvent. [c]Reactions were performed using 1 equivalent of substrates and 2 equivalents of reagent **II**. The isolated yield based on the recovered starting material. [d]Yield in parenthesis is of isolated yield.



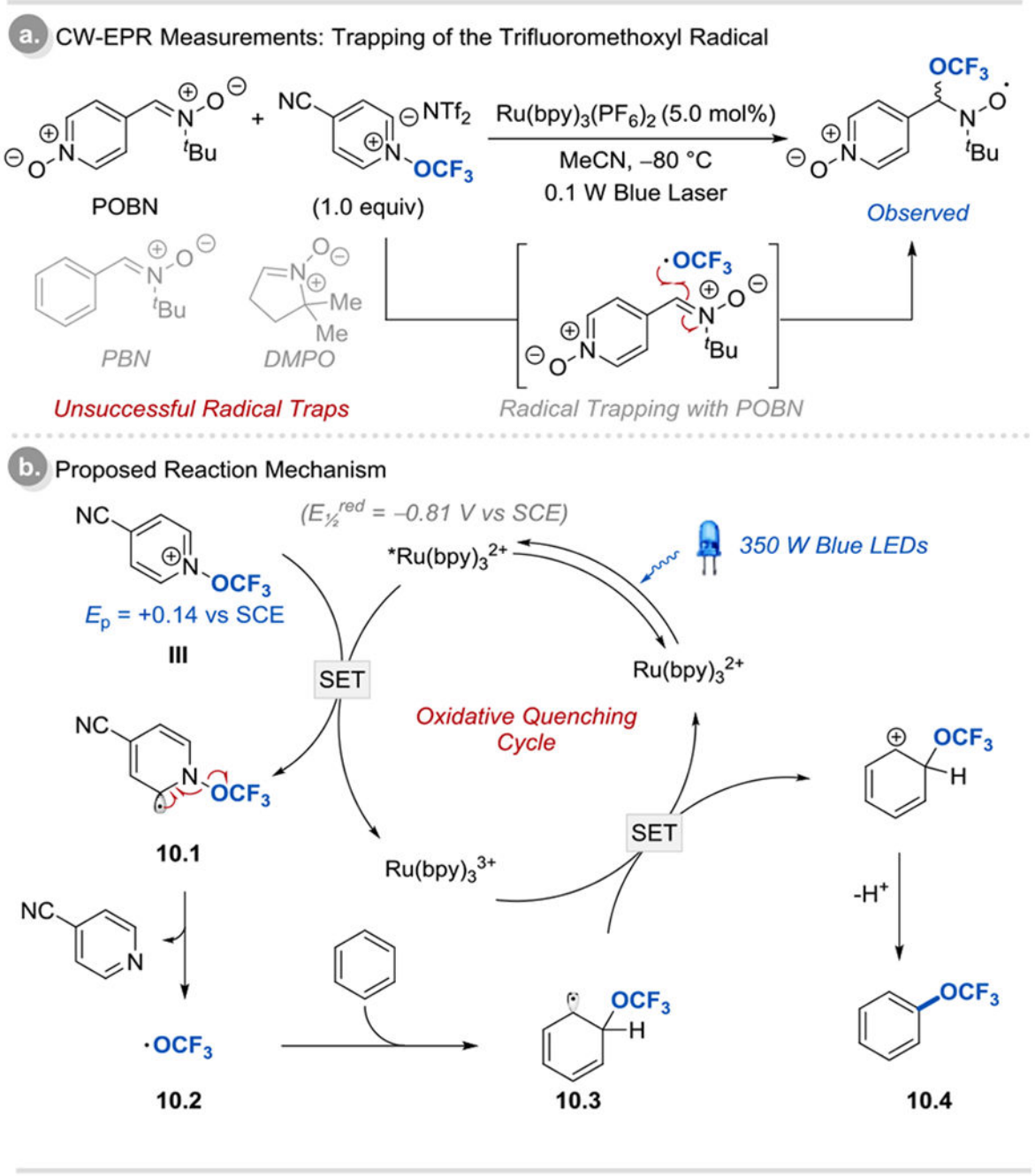
Scheme 8.

(a) CV and Energies of SET and the formation of •OCF_3 radical from Reagent **II**. (b) Proposed mechanism for the photoredox-catalyzed C–H trifluoromethoxylation of arenes with reagent **II**.



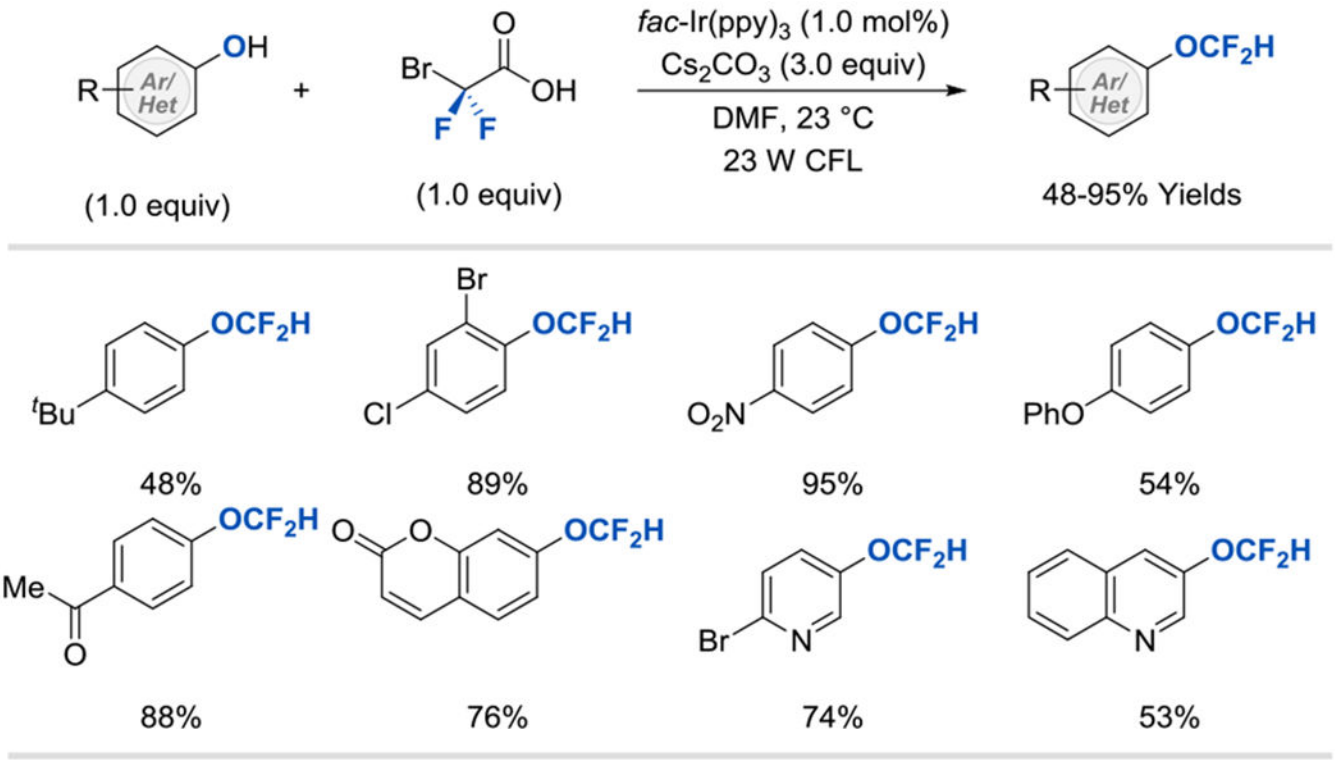
Scheme 9.

Visible light photoredox-catalyzed intermolecular C–H trifluoromethoxylation of arenes with **III**. [a]Yields and regioselectivity were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. Yield in parenthesis is of isolated product.



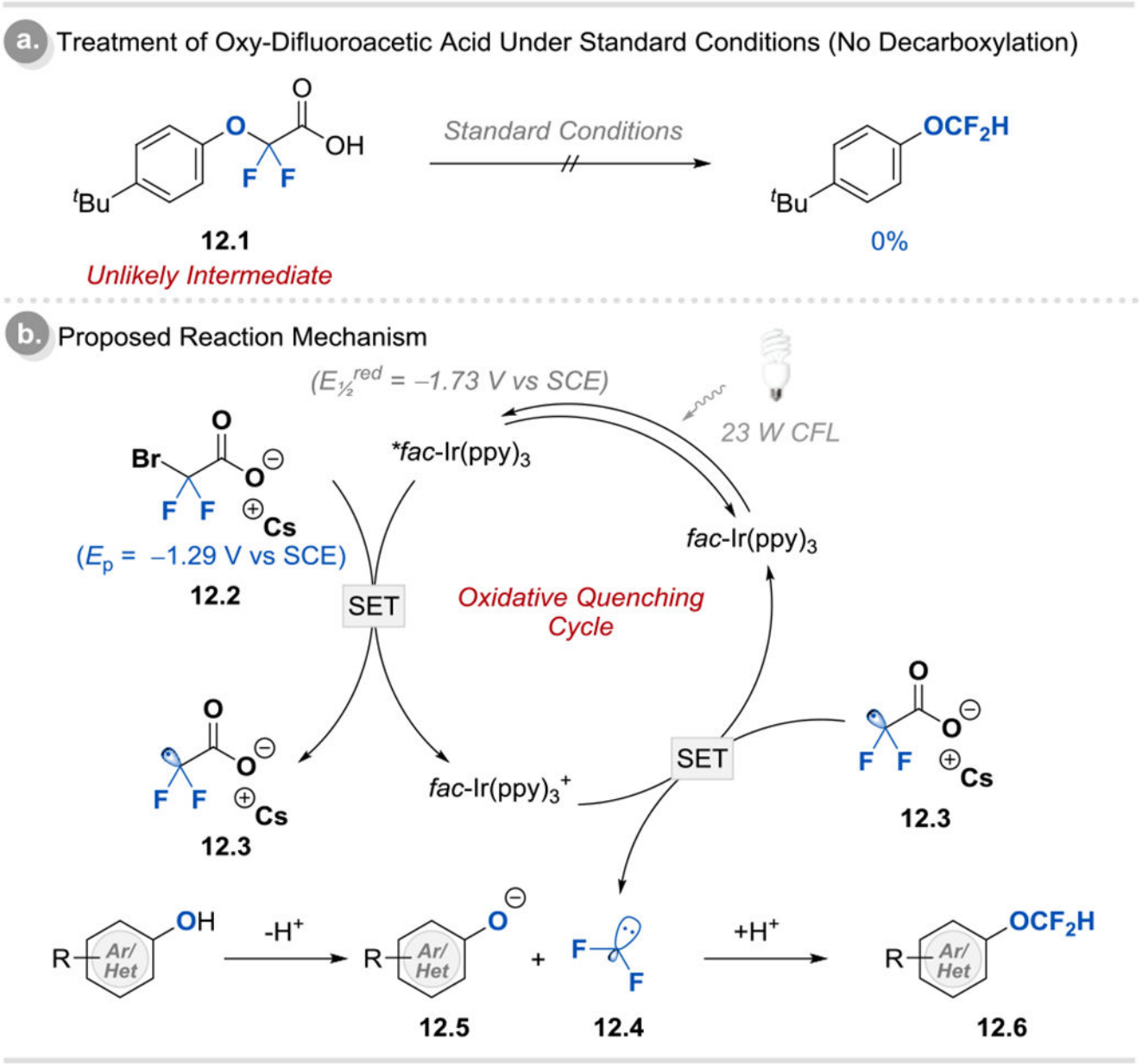
Scheme 10.

(a) CW-EPR studies. (b) Proposed catalytic cycle for trifluoromethoxylation of arenes with reagent **III** under visible light photoredox conditions.[34]



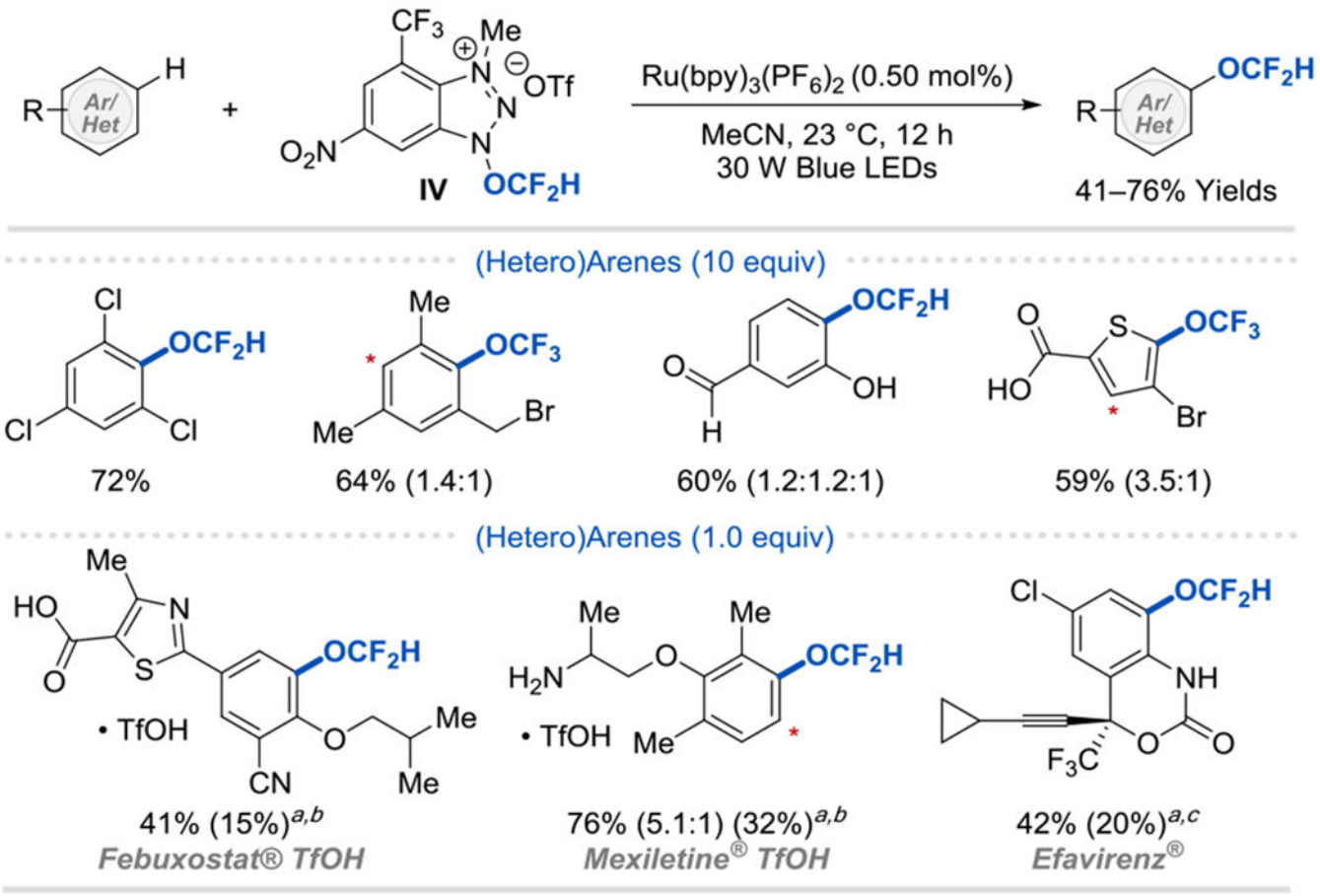
Scheme 11.

Difluoromethylation of phenols with difluorobromoacetic acid under visible-light photoredox catalysis.



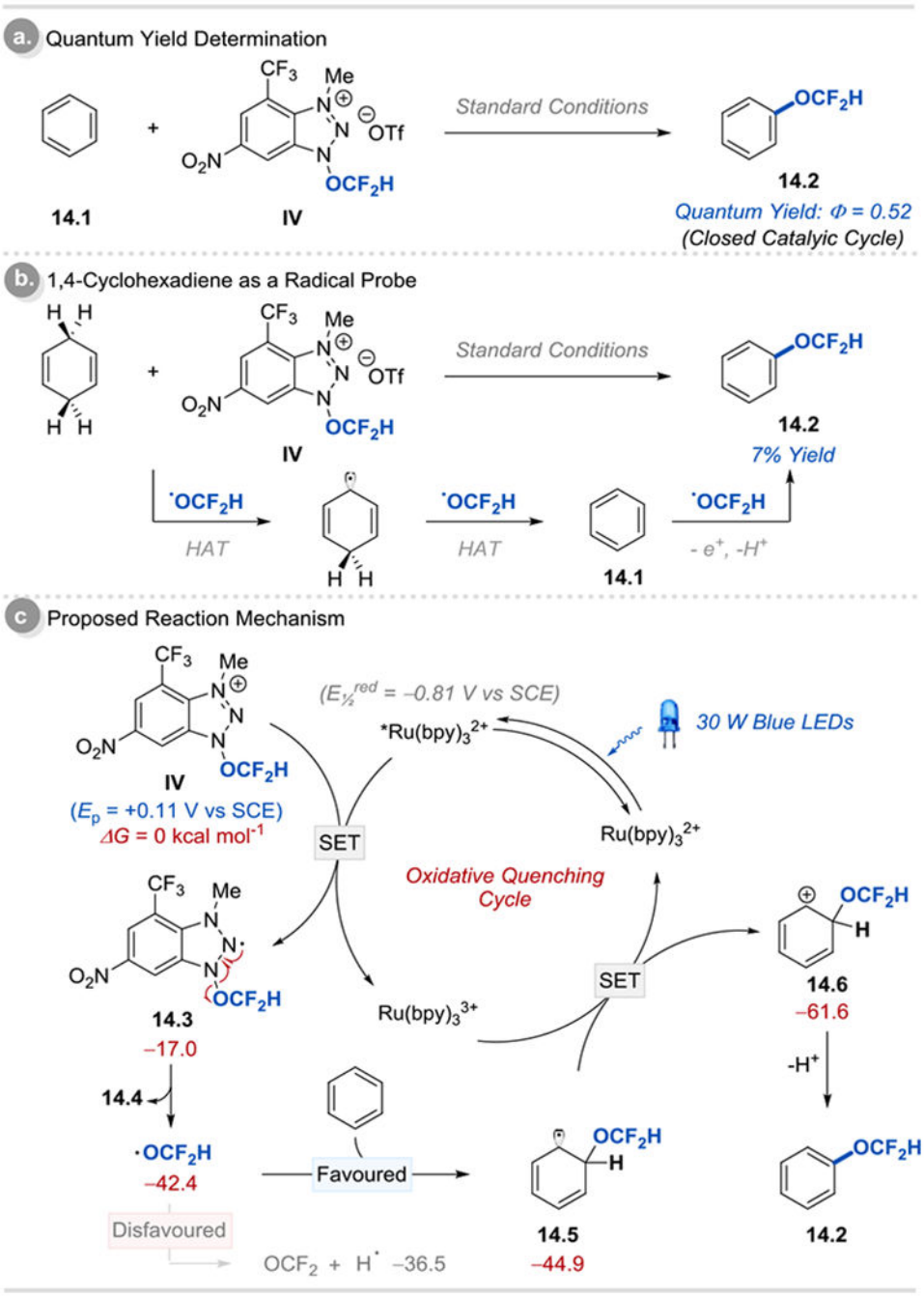
Scheme 12.

(a) Treatment of oxy-difluoroacetic acid under standard conditions. (b) Proposed catalytic cycle for difluoromethylation of phenols under photocatalytic conditions.



Scheme 13.

Catalytic Radical Difluoromethoxylation of Arenes and Heteroarenes. *a*Reactions were performed using 1 equivalent of substrates and 2 equivalents of reagent **IV**. Yields were determined based on the recovered starting material. The yield in parentheses is the isolated yield. The asterisk (*) denotes functionalization of a minor regioisomeric product. *b*Reaction performed with 1.0 equivalent of TfOH. *c*1.0 equivalent of K_2CO_3.



Scheme 14.

(a) Quantum yield determination. (b) Trapping experiments with 1,4-cyclohexadiene as a radical probe. (c) Proposed catalytic cycle for difluoromethoxylation of (hetero)arenes under photocatalytic conditions.