Synthesis of Organofluorine Compounds

53

Takashi Koike

Contents

Abstract

This chapter describes representative examples of the photocatalytic fluorination and di- and trifluoromethylation of organic compounds mediated by metal complexes or metal oxides. These photocatalytic methods are useful for the synthesis of organofluorine compounds. The fundamental reaction design in each of the transformations is discussed, and general experimental procedures are included. Synthetic methodologies that involve defluorination processes or the incorporation of other fluorinated motifs are not considered in this chapter.

Keywords

Fluoroalkylation · Fluorination · Radical reaction · Redox reaction · C–H functionalization · Photocatalysis

53.1 Introduction

The installation of fluorine atom(s) or fluorinated groups in drug molecules often significantly improves their pharmacokinetics [1]. Therefore, the development of simple protocols for the synthesis of organofluorine compounds has attracted the attention of synthetic chemists [2, 3]. In particular, the late-stage installation of fluorine into various organic skeletons has become a promising approach for the rapid preparation and discovery of new drugs.

The use of radical species for late-stage bond formation is an attractive synthetic strategy due to the unique reactivities of radicals toward unactivated bonds and tolerance of various functional groups. In addition, recent progress in synthetic radical chemistry *via* photocatalysis, especially in photoredox catalysis [4–10] and photoinduced hydrogen atom transfer (HAT) [11–13] under mild conditions, has prompted many researchers to develop photocatalytic methodologies for the radical-mediated synthesis of a variety of organofluorine compounds [14–19]. In this chapter, processes for the photocatalytic di- and trifluoromethylation and fluorination of organic substrates by metal complexes or metal oxides are discussed. The introduction of other fluorinated groups and their synthesis through defluorination processes, as well as reactions associated with metal-free photocatalysis, are not considered. Before describing representative examples, the basic concepts are briefly explained.

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53.1.1 Basic Principles

Photoredox catalysis mediated by ruthenium polypyridyl complexes and iridium cyclometalated complexes (***M***) such as $[Ru(bpy)_3]^{2+}$ and *fac*-$[Ir(ppy)_3]$ (bpy: 2,2′-bipyridine; ppy: 2-pyridylphenyl) has become a useful redox tool in synthetic radical chemistry [4–10]. Fluoromethyl radicals ($\cdot\boldsymbol{R_F}$) can be generated from appropriate redox-active electron-accepting ($\boldsymbol{R_F}^+$) or electron-donating precursors ($\boldsymbol{R_F}^-$) by the action of $1e^-$-reduction and $1e^-$-oxidation processes, respectively. As a matter of course, the photocatalyst plays a pivotal role not only in the generation of $\cdot\boldsymbol{R_F}$ (step I) but also in the regeneration of the ground state catalyst (***M***) associated with the back $1e^-$-transfer process (step II), leading to the production of fluoromethylated compounds (P–$\boldsymbol{R_F}$), as shown in Fig. 53.1. The reaction sequence, which involves a series of single electron transfer (SET) processes, does not require sacrificial redox reagents, and therefore, is *redox-neutral*.

The discussion in the following sections will mostly focus on di- and tri-fluoromethylation through photoredox processes. In addition to fluoromethylation, photocatalytic fluorination *via* the generation of alkyl radicals (·**R**) followed by reaction with fluorine sources (F–LG) (Fig. 53.2) will be discussed.

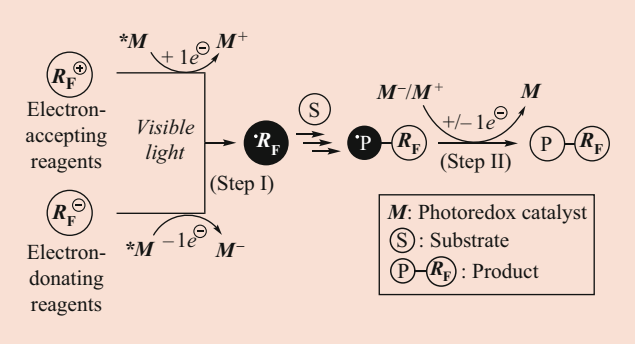


Fig. 53.1 General mechanistic illustration of the photoredox-catalyzed introduction of fluoromethyl groups highlighted in this chapter

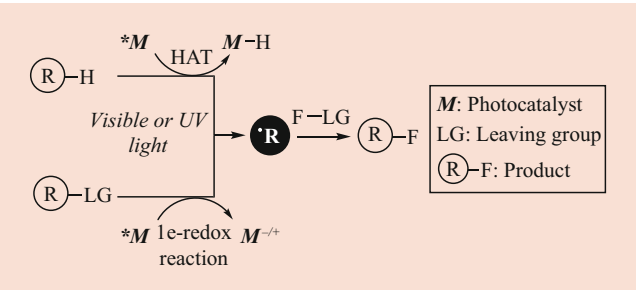


Fig. 53.2 General mechanism of photocatalytic fluorination highlighted in this chapter

Photoinduced HAT from aliphatic compounds (R–H) by metal oxides such as the decatungstate anion ($[W_{10}O_{32}]^{4-}$) or uranyl cation $[UO_2]^{2+}$, and redox reactions of appropriate radical precursors (R–LG) by photoredox catalysis are accessible to alkyl radicals (·**R**).

53.2 Trifluoromethylation Reactions

Trifluoromethylation by photoredox catalysis, leading to the synthesis of various CF_3-containing compounds, has been studied more extensively than methods for the introduction of other fluorinated groups. Radical trifluoromethylation with trifluoromethyl iodide (**1**) has been investigated since 1949, when Hazeldine discovered that **1** reacted with ethylene through the trifluoromethyl radical ($\cdot CF_3$) under relatively harsh conditions (e.g., heating at 250 °C or UV irradiation) [20, 21]. In photoredox reactions, the compounds shown in Fig. 53.3 have been frequently used as CF_3 sources. They can be classified as electron-accepting ($\boldsymbol{CF_3}^+$) or -donating ($\boldsymbol{CF_3}^-$) reagents. Examples of the former include **1**, CF_3SO_2Cl (**2**) [22], the Umemoto (**3**) [23], Yagupolskii-Umemoto (**4**) [24], and Togni (**5**) [25] reagents, and trifluoroacetic anhydride (**7**) [26]. Recently, the Umemoto II reagent (**6**) [27] was developed in response to the high cost of **3**. The Langlois reagent (**8**) [28] is an example of an electron-donating reagent ($\boldsymbol{CF_3}^-$).

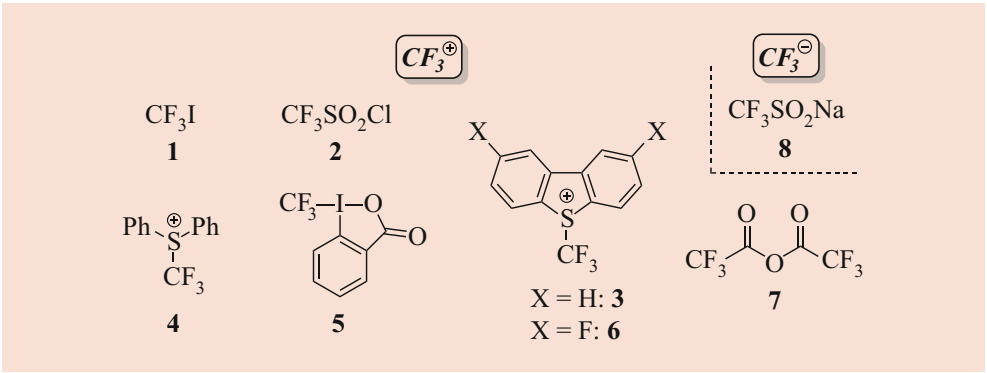
53.2.1 Trifluoromethylation of Olefins

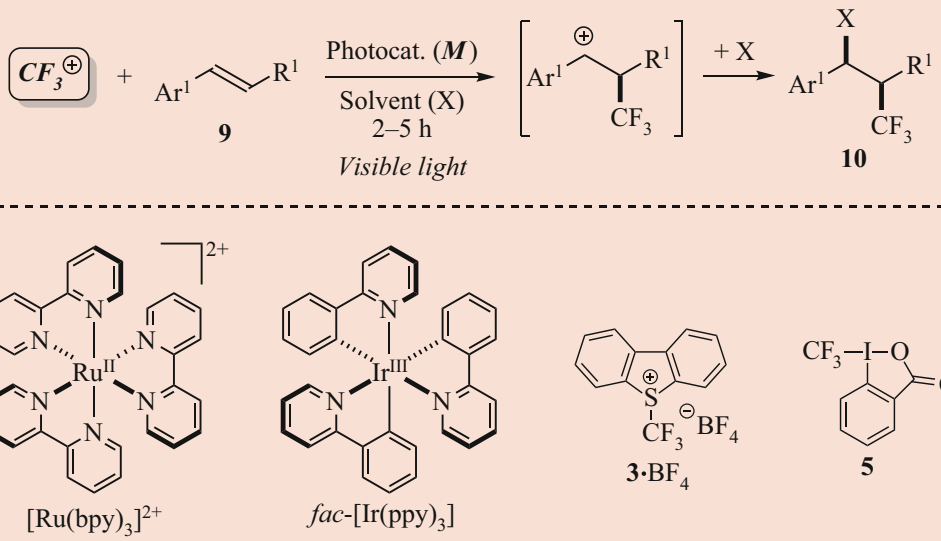
Synthesis of β-CF_3-Substituted Alcohols and Amines and α-CF_3-Substituted Ketones from Alkenes

Alkene difunctionalization is a straightforward strategy for the construction of vicinally substituted carbon frameworks in a single step. Although reactions involving the trifluoromethylation of olefins have historically been limited to halotrifluoromethylation [29], photoredox catalysis has recently realized the solvent-dependent, trifluoromethylative difunctionalization of aromatic alkenes (**9**) to produce oxy-, amino-, and keto-trifluoromethylated products (Fig. 53.4) [30–32]. Mechanistically, the processes involve solvolysis of a proposed CF_3-substituted carbocationic species to give trifluoromethylated difunctionalized products (**10**) such as β-CF_3-substituted alcohols and amines (*via* a Ritter-type reaction), or α-CF_3 substituted ketones (*via* Kornblum-type oxidation), as shown in Fig. 53.4.

Hydroxy-Trifluoromethylation: General Procedures [30]
A 20 mL Schlenk tube was charged with **3**•BF_4 (0.26–0.28 mmol), *fac*-$[Ir(ppy)_3]$ (0.5 mol%), styrene derivative **9** (0.25 mmol), acetone (4.5 mL), and H_2O (0.5 mL)

Fig. 53.3 Useful trifluoromethylating reagents [20, 22–28]





Selected examples of product **10**

Photocat.	CF_3^+	Solvent	Ar^1	R^1	X	Yield/%[a]
fac-$[Ir(ppy)_3]$ (0.5 mol%)	**3**•BF_4	Acetone/H_2O (9:1)	Ph	H	OH	88
fac-$[Ir(ppy)_3]$ (0.5 mol%)	**3**•BF_4	Acetone/H_2O (9:1)	Ph	Me	OH	88 (1:1 dr)
fac-$[Ir(ppy)_3]$ (0.5 mol%)	**3**•BF_4	CH_2Cl_2/EtOH (9:1)	Ph	H	OEt	75
fac-$[Ir(ppy)_3]$ (0.5 mol%)	**3**•BF_4	CH_2Cl_2/AcOH (9:1)	Ph	H	OAc	74
$[Ru(bpy)_3](PF_6)_2$ (0.5 mol%)	**3**•BF_4	MeCN[b]	Ph	H	NHAc	88
$[Ru(bpy)_3](PF_6)_2$ (0.5 mol%)	**3**•BF_4	MeCN[b]	Ph	Me	NHAc	87 (1.9:1 dr)
fac-$[Ir(ppy)_3]$ (2 mol%)	**5**	DMSO	Ph	H	=O	60
fac-$[Ir(ppy)_3]$ (2 mol%)	**5**	DMSO	Ph	Me	=O	87

[a]Isolated yields after chromatography [b]1 equiv. of H_2O with respect to **3** was added.

Fig. 53.4 Trifluoromethylative difunctionalization of alkenes by photoredox catalysis [30–32]

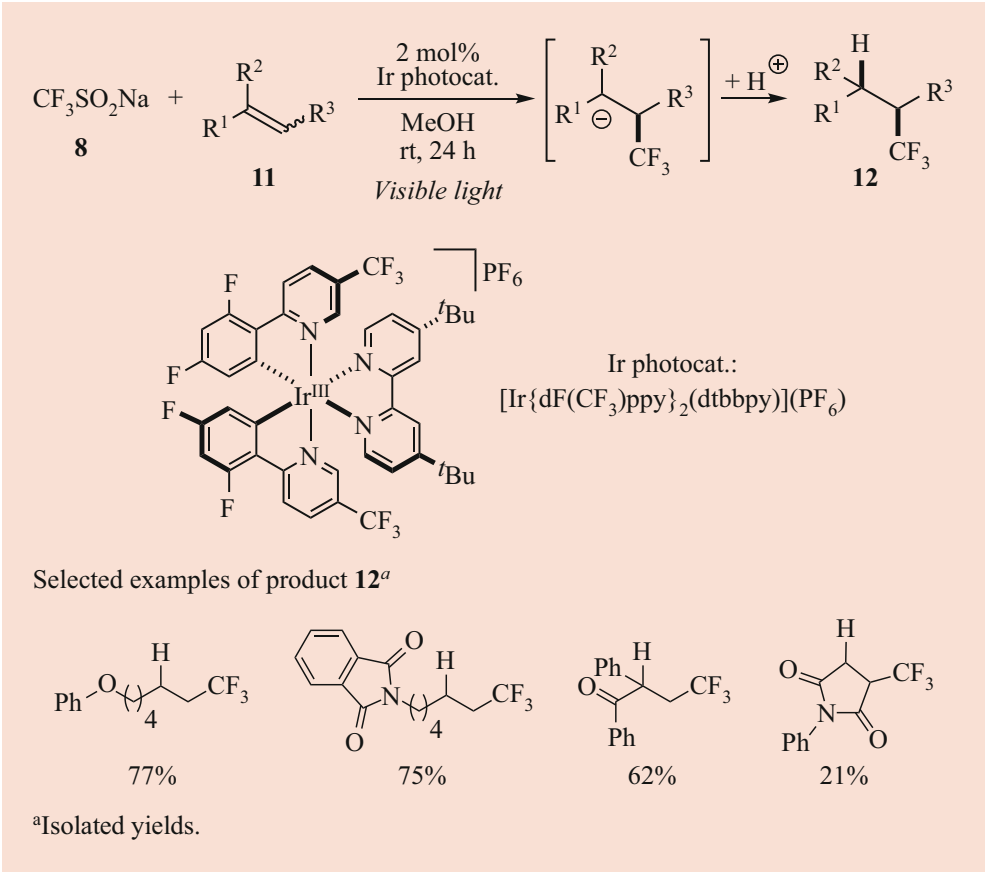


Fig. 53.5 Hydro-trifluoromethylation of alkenes [36]

under N_2. The tube was irradiated by two 3 W blue LED lamps (425 nm) placed at a distance of 2–3 cm. After reaction completion, the mixture was poured into aqueous Na_2SO_3 solution. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered. After concentration in *vacuo*, the residue was purified by chromatography on silica gel to afford product **10**.

Synthesis of CF_3-Alkanes from Olefins

The hydro-trifluoromethylation of alkenes allows access to alkanes containing a CF_3 group [33–35]. The electron-donating Langlois reagent ("$\boldsymbol{CF_3^-}$", **8**) reacts with aliphatic or electron-deficient alkenes (**11**) in the presence of a photoredox catalyst with high oxidizing power, [Ir{dF(CF_3)ppy}$_2$(dtbbpy)](PF_6), to produce an anionic intermediate that is protonated by MeOH to give product **12** (Fig. 53.5) [36, 37].

Hydro-Trifluoromethylation: General Procedures [36]

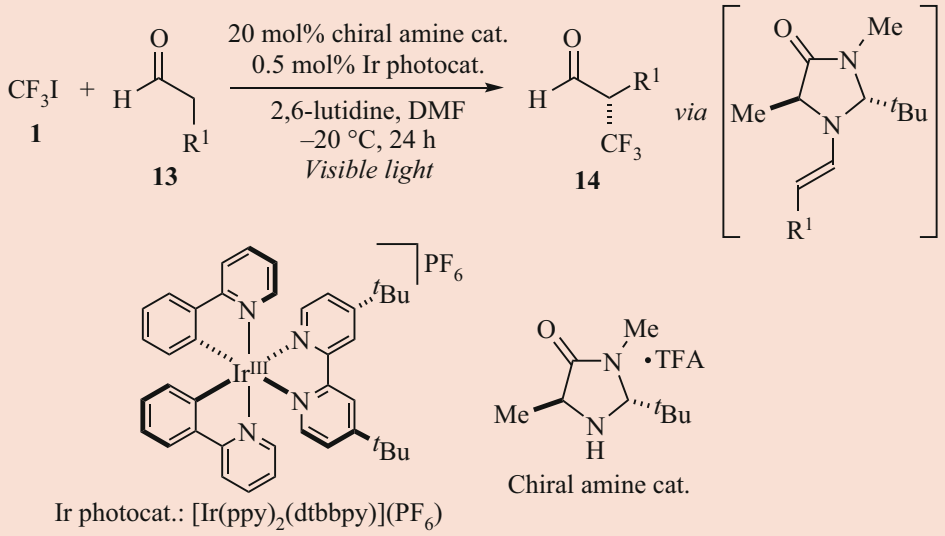
The alkene (**11**, 0.25 mmol), catalyst ([Ir{dF(CF_3)ppy}$_2$(dtbbpy)](PF_6), 2 mol%), and **8** (0.50 mmol) were placed in a Schlenk tube, to which MeOH (3 mL) was added under Ar atmosphere. The reaction mixture was stirred under irradiation by 36 W blue LEDs (distance from the lamp, ~3.0 cm) at room temperature. After 24 h, the mixture was quenched with water and extracted with ethyl acetate. The organic layers were combined and concentrated in *vacuo*. Product **12** was purified by flash column chromatography on silica gel.

Synthesis of Optically Active *α*-CF_3-Substituted Aldehydes

The electron-rich enamine intermediate formed by the condensation of an aldehyde (**13**) with a chiral amine catalyst was found to couple with the CF_3 radical in an enantioselective manner [38]. Photoredox catalysis with [Ir(ppy)$_2$(dtbbpy)](PF_6) was highly effective in generating the CF_3 radical from CF_3I (**1**) (Fig. 53.6).

Asymmetric Trifluoromethylation Followed by In Situ Reduction: General Procedures [38]

To an oven-dried borosilicate test tube equipped with a magnetic stir bar, the chiral amine catalyst ((2*R*,5*S*)-2-*t*-butyl-3,5-dimethylimidazolidin-4-one•TFA, 20 mol%) and [Ir(ppy)$_2$(dtbbpy)](PF_6) (0.5 mol%) photocatalyst were added. The tube was flushed with argon and cooled to −78 °C before DMF (2.53 mL) was added. The resulting yellow solution



Selected examples of product **14**

R^1	Yield/%[a]	ee/%[b]
$Me(CH_2)_5$–	79	99
$BnO(CH_2)_3$–	72	95
$EtO(CO)(CH_2)_3$–	86	97
Cy–	70	99
4-$MeOC_6H_4$–	61	93
Bn	75	97

[a]Isolated yields of the corresponding alcohols. [b]Enantiomeric excess, determined by chiral supercritical fluid chromatography (SFC) or HPLC analysis.

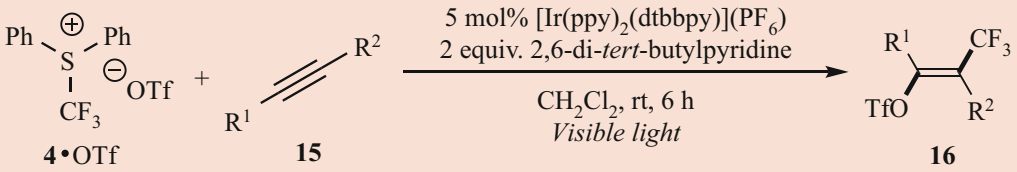
Fig. 53.6 Asymmetric α-trifluoromethylation of aldehydes by dual photoredox/chiral amine catalysis [38]

was further degassed at −78 °C and gaseous CF_3I (**1**) (~6.1 mmol) was then condensed into the tube. Subsequently, the aldehyde (**13**, 0.76 mmol) and 2,6-lutidine (0.84 mmol) were added. At −20 °C, the test tube was irradiated by a 26 W compact fluorescent light bulb placed at a distance of ~3 cm. After 7.5–8 h, the reaction mixture was transferred to a round-bottomed flask using CH_2Cl_2 (12 mL) at −78 °C. $NaBH_4$ (7.6 mmol) was added followed by cold MeOH (10 mL, −78 °C). The reaction mixture was stirred for 1 h at −78 °C before being quenched with saturated aqueous NH_4Cl solution. The resulting solution was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The residue was then purified by column chromatography on silica gel to furnish the desired alcohol product.

53.2.2 Trifluoromethylation of Alkynes

Stereoselective Synthesis of Tetrasubstituted CF_3-Alkenes from Alkynes

Multisubstituted CF_3-alkenes are useful structural motifs, especially for biologically active molecules and organic functional materials [39–41]. One straightforward synthetic method for the preparation of these compounds is the trifluoromethylation of alkynes [42, 43]. As shown in Fig. 53.7, the reaction of an internal alkyne (**15**) with **4**•OTf in the presence of the Ir catalyst, $[Ir(ppy)_2(dtbbpy)](PF_6)$, and a base, 2,6-di-*tert*-butylpyridine, selectively affords a *trans*-CF_3-alkenyl triflate (**16**), which undergoes Pd-catalyzed cross-coupling to give a tetrasubstituted CF_3-alkene with the retention of stereochemistry [44].



Selected examples of product **16**

R^1	R^2	Yield/%[a]	E/Z[b]
Ph	Me	74[c]	96:4
4-BrC_6H_4	Me	64	92:8
4-MeO(CO)C_6H_4	Me	73	91:9
4-MeO(CO)C_6H_4	^{n}Bu	52[d]	83:17
Ph	(CO)Me	63[e]	86:14
Ph	Ph	30	89:11

[a]Isolated yields. [b]The *E/Z* ratios were determined by ^{19}F NMR spectroscopy of the crude product mixtures.

[c]**4** and base (1.8 equiv. each). [d]**4** and base (2.8 equiv. each). [e]**4** and base (2.2 equiv. each).

Fig. 53.7 Stereoselective trifluoromethylation of alkynes [44]

Stereoselective Trifluoromethylation of Alkynes: General Procedures [44]

A 20 mL Schlenk tube was charged with $[Ir(ppy)_2(dtbbpy)](PF_6)$ (5 mol%), **4**•OTf (0.50 mmol), the alkyne (**15**, 0.25 mmol), 2,6-di-*tert*-butylpyridine (0.50 mmol), and dry CH_2Cl_2 (5 mL) under N_2. The tube was irradiated by two 3 W blue LED lamps (425 nm), placed at a distance of 2–3 cm, for 6 h at room temperature with stirring. Then, the reaction mixture was concentrated in *vacuo*. The residue was dissolved in Et_2O, and the solution was washed with 1 M HCl aq. and water, dried over Na_2SO_4, and filtered. The filtrate was concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel to afford **16**. When separation of the product from the diphenyl sulfide formed as a by-product was difficult, the latter was converted to its oxide by treatment with *meta*-chloroperbenzoic acid (*m*CPBA).

53.2.3 Synthesis of CF_3-Containing Heterocycles from Isocyanides

Heterocycles containing a CF_3 group as a ring substituent are important intermediates and building blocks for pharmaceuticals, agrochemicals, and functional materials. The trifluoromethylation of isocyanides (**17**) affords CF_3-substituted *N*-containing heteroaromatics (**18**) such as pyridines, isoquinolines, and phenanthridines through the intramolecular radical cyclization of the imidoyl radical intermediate (Fig. 53.8) [45–47].

Trifluoromethylation of Isocyanides: General Procedures [45]

A 10 mL round-bottomed flask equipped with a rubber septum was charged with **17** (0.20 mmol), **3**•BF_4 (0.30 mmol), the photocatalyst (1 mol%), and Na_2HPO_4 (0.30 mmol). The flask was evacuated and backfilled with argon three times. MeOH (2 mL) was added, and the mixture was irradiated with 5 W white LED strips. After the reaction was complete, the mixture was poured into a separatory funnel containing water and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo* after filtration. The residue was purified by flash chromatography on silica gel to afford product **18**.

53.2.4 Synthesis of CF_3-Aromatics Through C–H Trifluoromethylation of Arenes

The direct C–H trifluoromethylation of aromatics is the most step-economical synthetic strategy for trifluoromethylated aromatics when simple arenes are used as starting materials

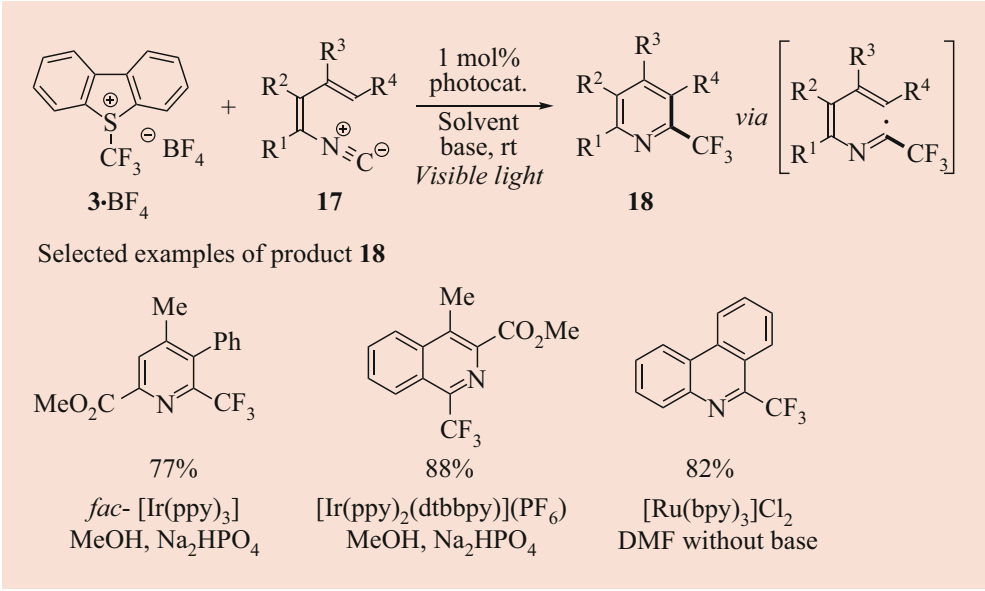


Fig. 53.8 Trifluoromethylation of isocyanides [45–47]

[48–50]. The reaction of CF_3SO_2Cl (**2**) with arenes and heteroarenes (**19**) in the presence of $[Ru(phen)_3]Cl_2$ or Ir $(Fppy)_3$ produces CF_3-arenes (**20**). Poor regio- and site-selectivities are occasionally noted (Fig. 53.9) [48].

Trifluoromethylation of Arenes: General Procedures [48] An oven-dried vial was charged with the photocatalyst (1–2 mol%), dry K_2HPO_4 (1.5 mmol), **19** (0.50 mmol), and MeCN (0.125 M), and degassed by alternating vacuum evacuation and argon backfill at −78 °C. Reagent **2** (0.502.0 mmol) was then added and the solution was irradiated by a 26 W compact fluorescent light bulb at room temperature. After 24 h, the reaction mixture was purified by column chromatography to furnish product **20**.

Several problems associated with large-scale photochemical reactions such as sluggishness and side reaction can be surmounted by the use of flow technology [51]. The photocatalytic trifluoromethylation reaction of inexpensive trifluoroacetic anhydride (**7**) with Boc-protected pyrrole (**19a**) in the presence of pyridine *N*-oxide (**21**) and $[Ru(bpy)_3]Cl_2$ (0.1 mol%) was applied on kilogram-scale under continuous flow conditions [50] (Fig. 53.10).

53.2.5 Synthesis of CF_3S Compounds from Thiols

A trifluoromethanesulfenyl group (CF_3S) can significantly enhance the lipophilicity of an organic molecule. In general, introducing a CF_3S group is superior to a CF_3 group with respect to lipophilicity. A CF_3S group can be formed by the trifluoromethylation of arene-, heteroarene-, and alkane thiols (**22**) with CF_3I (**1**) using the Ru photocatalyst, $[Ru(bpy)_3]Cl_2$ (Fig. 53.11) [52]. In addition, continuous microflow photoreactions are significantly more effective than batch photoreactions. On the other hand, photocatalytic trifluoromethylthiolation is also feasible with the appropriate choice of easy-to-handle electrophilic CF_3S reagents such as *N*-(trifluoromethylthio) pyrrolidine-2,5-dione, *N*-(trifluoromethylthio)phthalimide, and *N*-(trifluoromethylthio)saccharin [53–55].

Trifluoromethylation of Thiols: General Procedures [52] An oven-dried vial was charged with $[Ru(bpy)_3]Cl_2•6H_2O$ (1.0 mol%), **22** (1.0 mol), and MeCN (4 mL) (mixture A). The mixture was degassed by the freeze-pump-thaw method. A second mixture (mixture B) was prepared with triethylamine (1.1 mmol) dissolved in degassed MeCN (1 mL). Thereafter, a gas-tight syringe was filled with gaseous **1** (200 psi, ~4 mmol), which was subsequently added to reaction mixture A (i.e., bubbled through the mixture over 10 min), followed by the dropwise addition of mixture B. The reaction mixture was placed ~5 cm away from a 24 W compact fluorescent light bulb. After reaction completion, the reaction mixture was diluted with Et_2O and washed with 1 M aqueous HCl and then with aqueous $NaHCO_3$. The combined water layers were extracted with Et_2O, and the collected Et_2O layers were concentrated in *vacuo*. The crude mixture was purified by flash chromatography to give product **23**. When alkanenethiols were used as the substrate, PPh_3 (1.0 mmol) and H_2O (1.0 mmol) were added to mixture A prior to the addition of **1**.

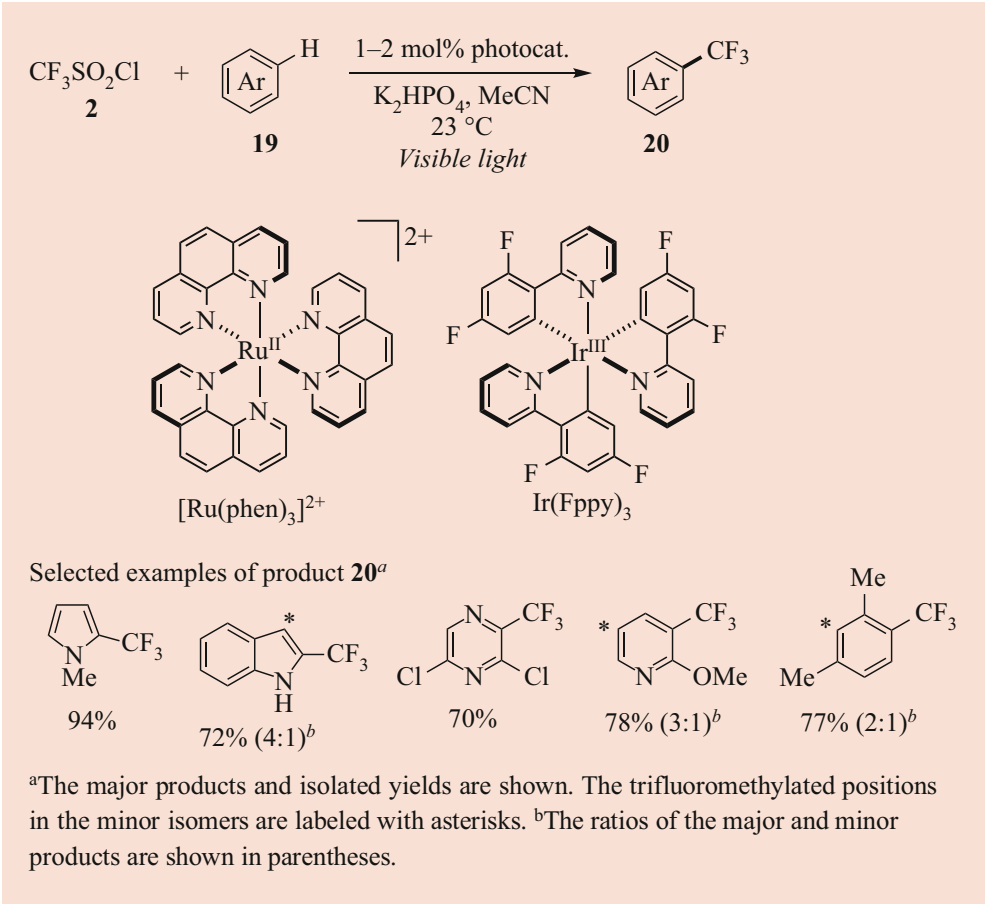


Fig. 53.9 Trifluoromethylation of arenes [48]

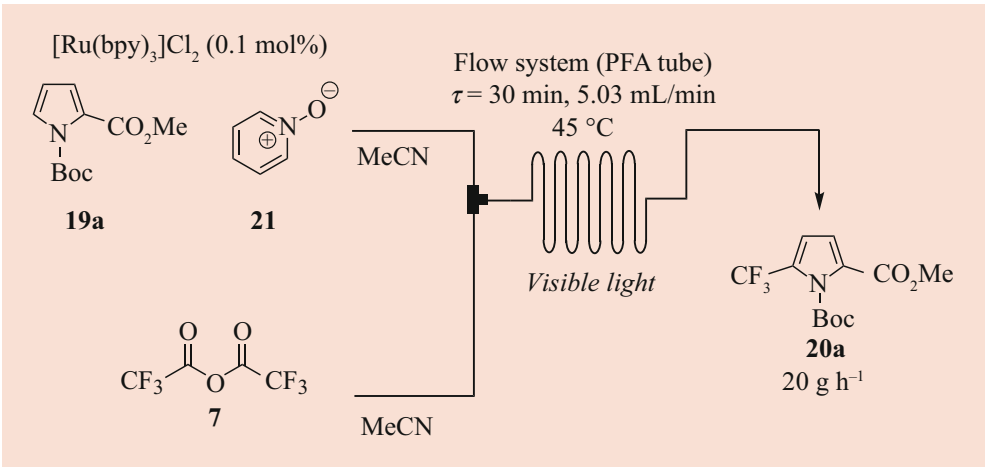


Fig. 53.10 Continuous-flow trifluoromethylation of an arene under visible light [50]

53.3 Difluoromethylation Reactions

The difluoromethyl (CF_2H) group is known to act as a bioisostere to hydroxyl and thiol units as well as a lipophilic hydrogen-bond donor. Thus, the CF_2H group has become an attractive target in the design of drugs and agrochemicals. Photocatalytic difluoromethylation requires a more elaborate reaction design because the corresponding precursors ($\boldsymbol{CF_2H^+}$ and $\boldsymbol{CF_2H^-}$) are more limited (Fig. 53.12). In particular, the 1e-reduction of the electrophilic CF_2H reagents ($\boldsymbol{CF_2H^+}$) turns out to be much more difficult than that of CF_3 reagents ($\boldsymbol{CF_3^+}$) because of the decrease in the number of electronegative F atoms. Therefore, the number of reaction variants has not yet

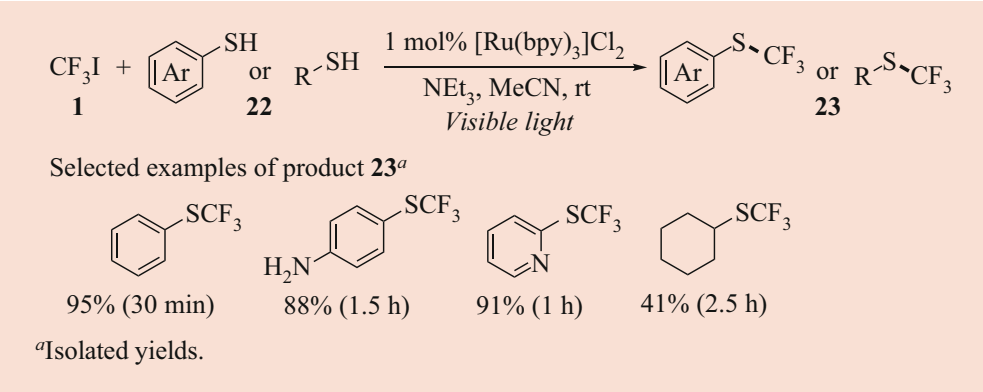


Fig. 53.11 Trifluoromethylation of thiols [52]

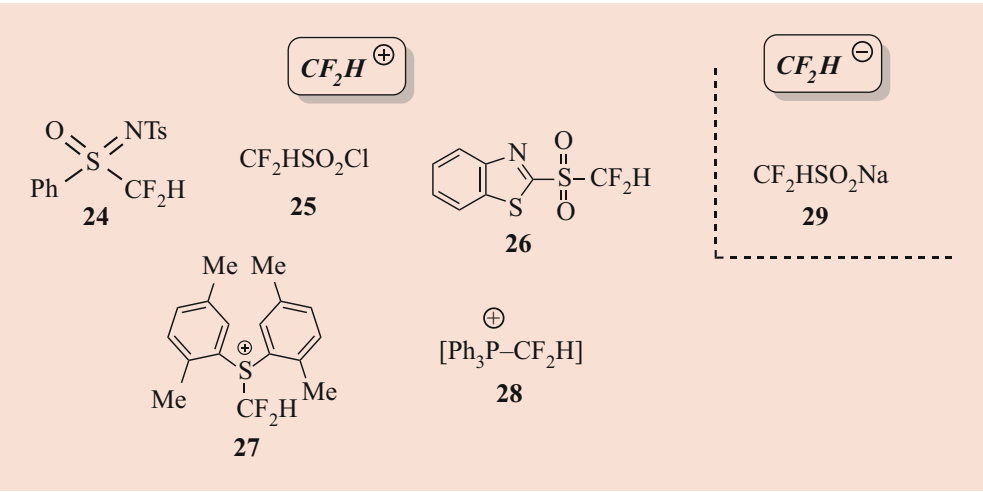


Fig. 53.12 Difluoromethylating reagents [56–61]

matched those of the aforementioned trifluoromethylation methods. In this section, the syntheses of (i) β-CF_2H substituted alcohols from alkenes and (ii) CF_2H-containing phenanthridines from isocyanides are illustrated.

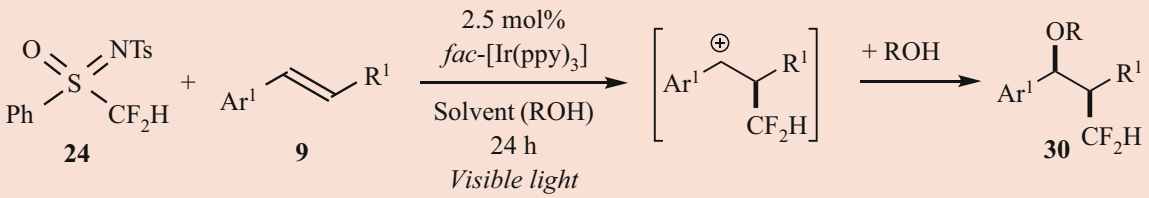
53.3.1 Synthesis of β-CF_2H Substituted Alcohol Derivatives from Alkenes

Known as a difluorocarbene source, the CF_2H reagent **24** [56] serves as a CF_2H radical precursor under reaction conditions similar to those described above for oxy-trifluoromethylation (Sect. 53.2.1), as shown in Fig. 53.13. In this case, CF_2H-substituted alcohol derivatives **30** are obtained [62].

Hydroxy-Difluoromethylation: General Procedures [62] A 20 mL Schlenk tube was charged with **24** (0.25–0.28 mmol), *fac*-[Ir(ppy)$_3$] (0.5–5 mol%), **9** (0.25–0.38 mmol), acetone (3.6 mL), and H_2O (0.4 mL) under N_2. The mixture was degassed by three freeze-pump-thaw cycles and refilled with N_2. The tube was irradiated by two 3 W blue LED lamps (425 nm) placed at a distance of 2–3 cm. After completion of the reaction, brine was added and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo* and the residue was purified by chromatography on silica gel to afford product **30**. Further purification by GPC was performed as required.

53.3.2 Synthesis of CF_2H-Containing Phenanthridines from Isocyanides

In a manner analogous to the trifluoromethylation of isocyanides described above (Sect. 53.2.3), the photocatalytic difluoromethylation of isocyanides (**17**) with CF_2H reagent



Selected examples of the reaction

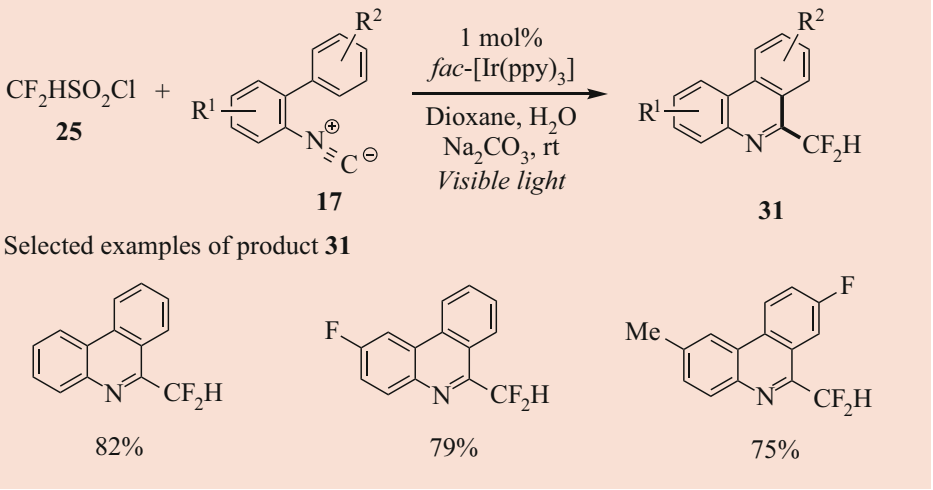
Solvent	Ar^1	R^1	R	Yield/%[a]
Acetone/H_2O (9:1)	Ph	H	H	72[b,c]
Acetone/H_2O (9:1)	4-MeC_6H_4	H	H	67[b,d]
Acetone/H_2O (9:1)	Ph	Me	H	43 (1.2:1 dr)[c,e]
CH_2Cl_2/EtOH (9:1)	4-MeC_6H_4	H	Me	69
CH_2Cl_2/AcOH (9:1)	4-MeC_6H_4	H	Ac	54

[a]Isolated yields after chromatography [b]0.5 mol% Ir cat. was used. [c]The ratio of **24** to **9** was 1:1.5.

[d]Reaction time = 2 h. [e]Reaction time = 36 h.

Fig. 53.13 Oxy-difluoromethylation of alkenes [62]

Fig. 53.14 Difluoromethylation of isocyanides [63]



25 affords CF_2H-substituted phenanthridines **31**, as shown in Fig. 53.14 [63]. Under similar reaction conditions, CF_2H reagent **26** can also be used [58].

Difluoromethylation of Isocyanides: General Procedures [63]

To an oven-dried borosilicate vial (8 mL) equipped with a magnetic stirrer, 2-isocyanobiphenyl **17** (0.2 mmol), *fac*-[Ir(ppy)$_3$] (0.002 mmol), and Na_2CO_3 (0.4 mmol) were added. To this mixture, dioxane (2 mL), deionized water and **25** (0.4 mmol) were introduced under nitrogen. The vial was sealed and stirred under visible light at room temperature for 18 h. Then, the dioxane was removed in *vacuo* and the residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (12:1). Product **31** was obtained as a white solid.

53.4 Fluorination Reactions

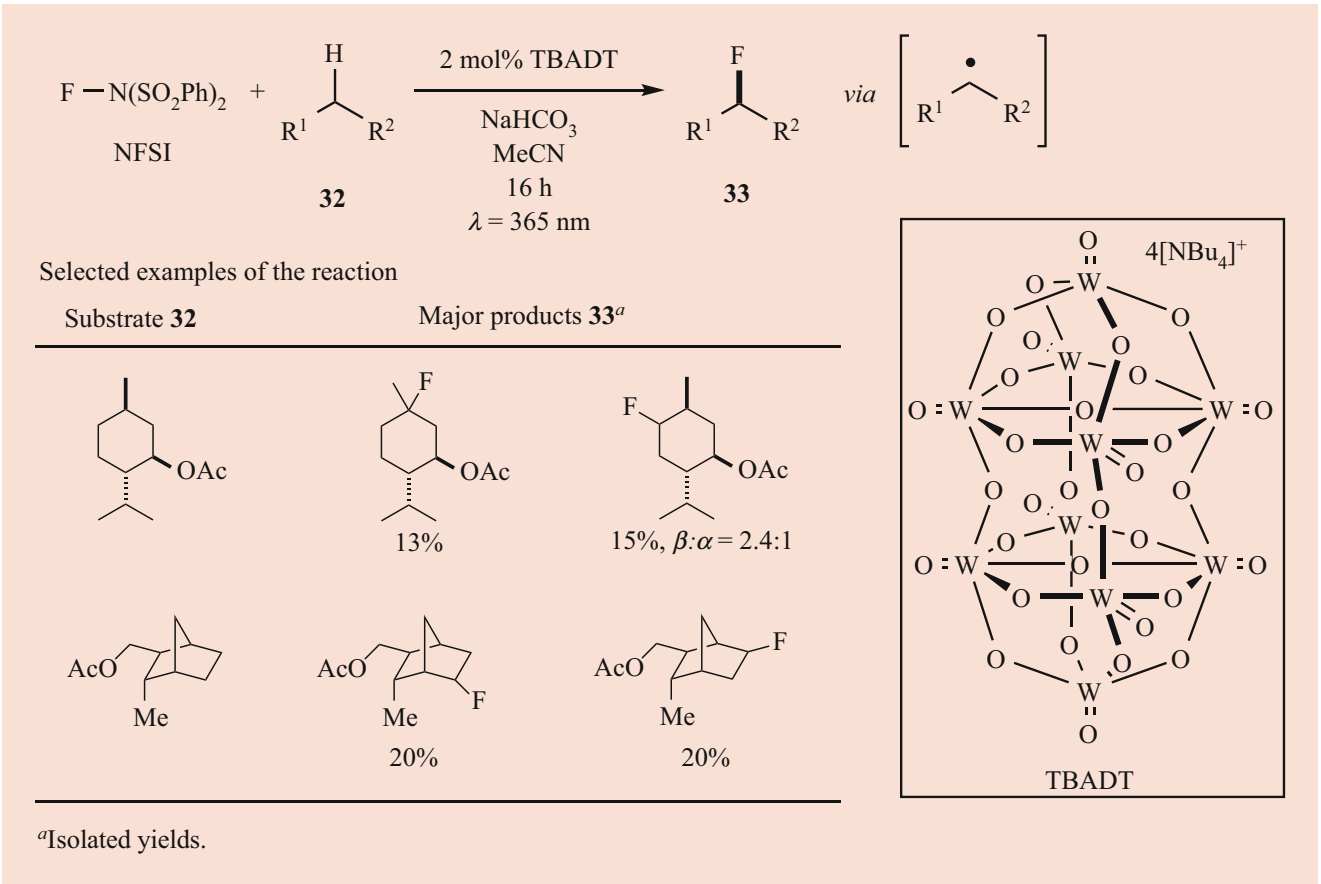
Photocatalysis is usually associated with the generation of carbon-centered radicals from appropriate precursors. The generated organic radicals react with fluorine sources such as *N*-fluorobenzenesulfonimide (NFSI) or Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), or F-TEDA) to give fluorinated products [64–70]. In this section, the fluorination of alkanes, carboxylic acids, and alcohols is described.

53.4.1 Fluorination of Aliphatic C(sp^3)–H Bonds

A well-characterized polyoxometalate photocatalyst, the tetrabutylammonium salt of decatungstate ($(NBu_4)_4[W_{10}O_{32}]$), TBADT), realizes the direct fluorination of unactivated C(sp^3)–H bonds in alkanes (**32**) with NFSI as a fluorine source under mild conditions. Because aliphatic groups are common units in organic compounds, this fluorination reaction can become a powerful tool for the introduction of a fluorine atom into organic molecules. However, product **33** is usually obtained as a mixture of isomers (Fig. 53.15) [64], and selectivity is a problem to be solved. Hydrogen abstraction from **32** by the photoexcited TBADT under UV irradiation is the key process for the generation of alkyl radicals. The metal oxide $[UO_2]^{2+}$ has also served as a photocatalyst in the direct fluorination of alkanes [65].

Photocatalytic Fluorination of Alkanes: General Procedures [64]

Substrate **32** (0.30 mmol) was dissolved in a solution of MeCN (2 M) in a sealable reaction vessel equipped with a magnetic stir bar, and TBADT (2 mol%), NFSI (0.36 mmol), and $NaHCO_3$ (10 mol%) were added. After sparging the resulting suspension with N_2 for 5 min, the reaction vessel was sealed, and the mixture was stirred and irradiated (two 15-W UVB-BLB lamps, centered at 365 nm) at room temperature overnight. The resulting blue solution was treated with saturated $NaHCO_3$ solution (1 mL) and extracted three times with CH_2Cl_2 (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The



[a]Isolated yields.

Fig. 53.15 Photocatalytic fluorination of C(sp^3)–H bonds [64]

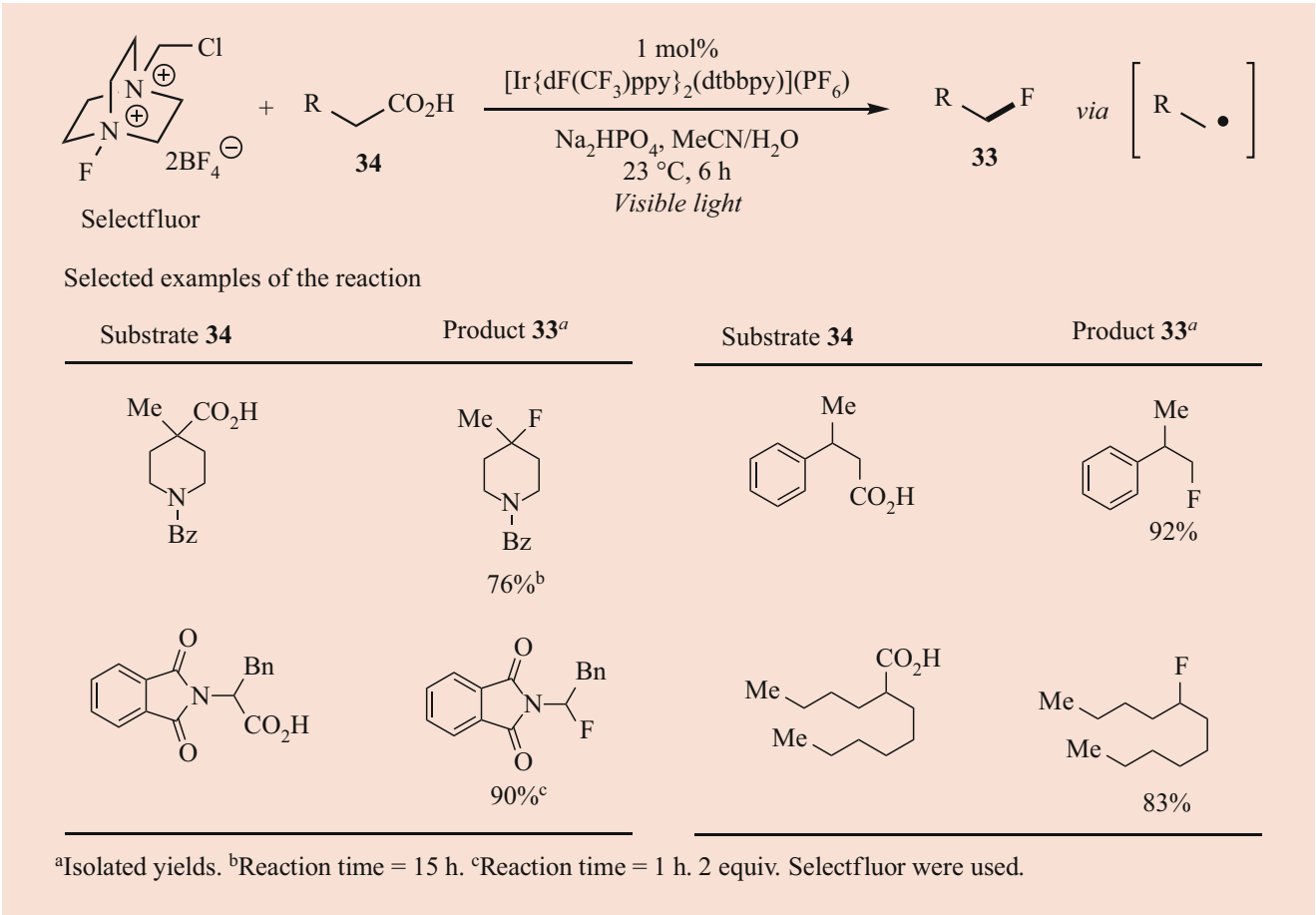


Fig. 53.16 Photocatalytic decarboxylative fluorination of aliphatic carboxylic acids [66]

crude product was purified by flash column chromatography to afford product **33**.

53.4.2 Decarboxylative Fluorination

A reliable method for the selective generation of organic radicals would solve the problem of non-regioselective fluorination. Photoredox catalysis enables the generation of organic radicals from carboxylic acids through decarboxylation [71, 72]. Thus, reactions of carboxylic acids **34** with Selectfluor in the presence of a photocatalyst proceed *via* selective fluorination at the position of carboxyl-group loss to afford fluorinated products **33** (Fig. 53.16) [66, 67].

Photocatalytic Decarboxylative Fluorination of Carboxylic Acids: General Procedures [66]

A solution of [Ir{dF(CF_3)ppy}$_2$(dtbbpy)](PF_6) (7.0 μmol, 1 mol%), carboxylic acid **34** (0.7 mmol), Na_2HPO_4 (1.40 mmol), and Selectfluor (2.10 mmol) in a mixture of MeCN/H_2O (1:1) was degassed by Ar sparging for 10 min, and then irradiated (at ~4 cm from the light source) with two 34 W blue LEDs. After the reaction was complete, the crude mixture was extracted with Et_2O, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in *vacuo*. Purification by flash chromatography on silica gel (5–10% Et_2O in pentane) afforded product **33**.

53.4.3 Deoxyfluorination of Alcohols

The concept of decarboxylative fluorination (Sect. 53.4.2) can be extended to the reaction of oxalates **35** [68–70]. Since oxalates **35** are easily prepared from alcohols **36**, the photocatalytic reaction leads to the formal deoxyfluorination of aliphatic alcohols (Fig. 53.17) [68]. Primary, secondary, and tertiary alcohols can be applied in the reaction.

Photocatalytic Deoxyfluorination of Oxalates: General Procedures [68]

A 40 mL glass vial equipped with a Teflon septum and magnetic stirring bar was charged with **35** (1 equiv), the Ir photocatalyst (1 mol%), Na_2HPO_4 or K_2HPO_4 (2.0 equiv), Selectfluor (1.1–4.5 equiv), and acetone/H_2O (4:1) or MeCN/

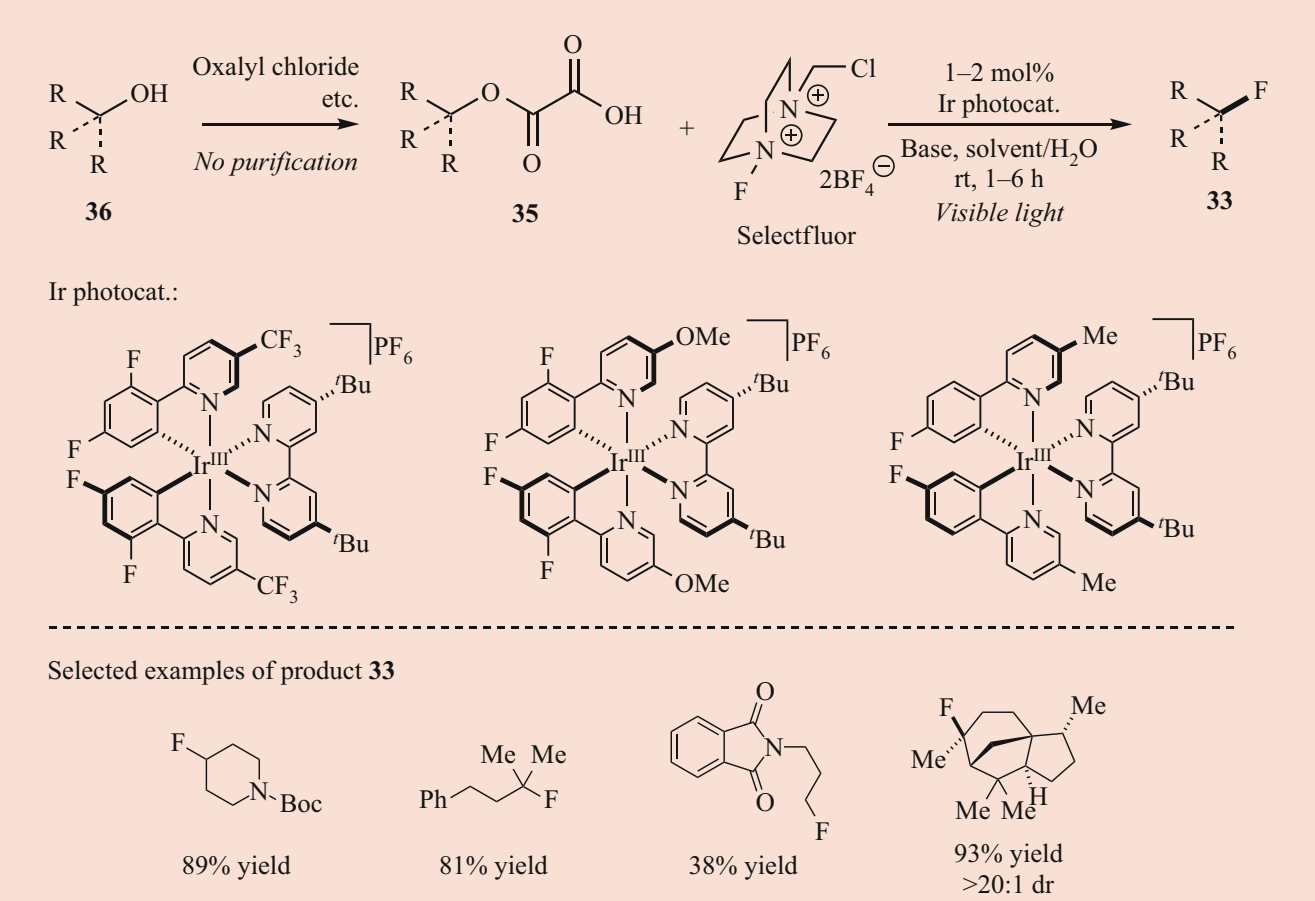


Fig. 53.17 Photocatalytic deoxyfluorination of alcohols [68]

H_2O (4:1). The resulting solution was then sparged with N_2 for 3 min. The vial was sealed and placed at ~1 inch from the lamp. After reaction completion, the reaction mixture was diluted with Et_2O or AcOEt and washed successively with water and brine. The combined aqueous washings were extracted with the appropriate organic solvent (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in *vacuo*. Purification by flash column chromatography over silica gel afforded product **33**.

53.5 Conclusion

The introduction of fluorine, the most electronegative of all elements, into organic compounds presents a synthetic challenge. In response, radical reaction systems associated with photocatalysis have emerged as key technologies for the installation of fluorine atom(s) or a fluorinated unit in organic molecules. The basic principles highlighted in this chapter are versatile approaches that are applicable in other photocatalytic fluoroalkylations, which were not covered here. The further development of novel metal-based and metal-free photocatalysts will increase the practicality of these already-useful photocatalytic systems.

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