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Study on Trifluoromethylation of Carbon–Carbon Unsaturated Bonds by Photoredox Catalysis

（フォトレドックス触媒による炭素－炭素不飽和結合のトリフルオロメチル化反応に関する研究）

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2016

Preface and Acknowledgements

The studies described in this thesis have been carried out under the supervision of Professor Dr. Munetaka Akita and Assistant Professor Dr. Takashi Koike from 2013 to 2015 at Chemical Resources Laboratory, Tokyo Institute of Technology. The studies are concerned with the development of new photocatalytic trifluoromethylation reactions.

First of all, the author wishes to express his sincerest gratitude to Professor Dr. Munetaka Akita for his kind guidance, constant support, hearty encouragement, and warm enthusiasm throughout this study.

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Chapter 1

General Introduction

Development of new methods for introduction of a trifluoromethyl group into various organic molecules is highly demanded. In particular, trifluoromethylation of unsaturated hydrocarbons, which are abundant and commonly used feedstocks, can produce highly functionalized trifluoromethylated compounds from simple substrates, but is still developing. The author expects radical trifluoromethylation by photoredox catalysis may pave the way for this goal.

In the first section of this Chapter, the author will briefly summarize general methods for trifluoromethylation according to the reaction types. Then the author will deal with recent advances in trifluoromethylation of carbon–carbon unsaturated bonds achieved by the action of electrophilic trifluoromethylating reagents, in particular, for oxy-trifluoromethylation. In the second section, the author will describe visible-light-driven photoredox catalysis. He will firstly mention principles of photoredox catalysis, and subsequently refer to pioneering works for organic reactions. Thirdly, the author will summarize photoredox-catalyzed trifluoromethylation. In the final section, the author will survey contents of this thesis.

1.1 Trifluoromethylation

1.1.1 Organofluorine Compounds

Organofluorine compounds continue to increase their importance in the fields of the pharmaceutical, agrochemical and functional material sciences.[1] A fluorine atom has a size similar to that of a hydrogen atom and C–F bond is the second shortest next to C–H bond. Therefore, replacement of the hydrogen atom of a C–H bond in a molecule by a fluorine atom hardly induces molecular dimension, resulting that living system takes a fluorinated molecule in a way similar to the non-fluorinated one (mimic effect). Additionally, C–F bond is stronger than C–H bond, so the replacement of the hydrogen by fluorine often improves chemical stability (block effect). On the other hand, because fluorine has the largest electronegativity among elements usually contained in organic compounds, introduction of fluorine atom(s) into organic molecules should significantly affect electronic properties of the molecules. Furthermore, low polarizability of fluorine reduces van der Waals interaction. Therefore, incorporation of fluorine atom(s) into drug compounds may lead to modulation of electrostatic interaction with a target structure and improvement of lipophilicity. Consequently, theses effects lead to better bioavailability, increases selectivity for a target organ, and lowers effective dose.[2] In 2011, there were 3 drugs among the best-selling 10 drugs and 7 drugs among the 35 newly approved drugs containing fluorine atoms.

1.1.2 Trifluoromethyl Group

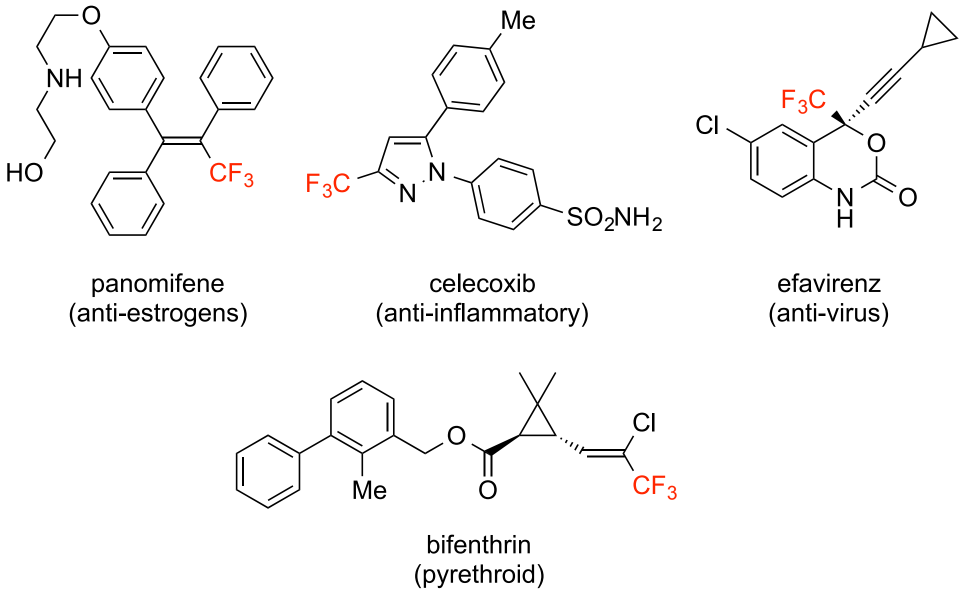
Among fluorinated functional groups, trifluoromethyl (CF_3) group has attracted significant attention as key components of drugs and materials. The trifluoromethyl group is a highly electron-withdrawing substituent, the Hammett constant of which is comparable to those of cyano group (Table 1.1).[1]

Table 1.1. Hammett constants and hydrophobicity

	Hammett constants		aliphatic compound hydrophobicity (π_R)[a]	aromatic compound hydrophobicity (π_R)[a]
substituent	σ_m	σ_p		
-COMe	0.38	0.50	-	-
$-CF_3$	0.43	0.54	0.06	0.88
-CN	0.56	0.66	–1.50	–0.57
$-NO_2$	0.72	0.78	–1.39	–0.28

a) π_R: hydrophobicity; $\pi_R = \log P_R - \log P_H$, P = partition coefficient between 1-octanol and water.

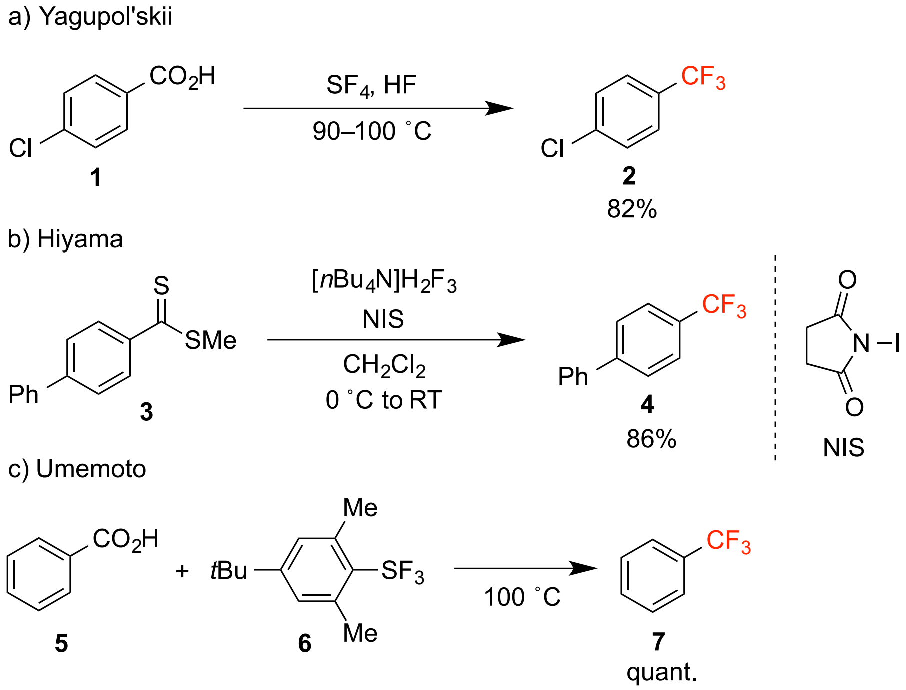
Therefore, CF_3 group affects acidity or basicity of neighboring groups and improves stability toward oxidation and electrophilic attack. While other electron-withdrawing groups such as cyano and carbonyl groups are susceptible to nucleophilic attack, CF_3 group is stable against the attack. In addition, CF_3 group shows high hydrophobicity in contrast to other electron-withdrawing groups, leading to an increase of membrane permeability. Furthermore, highly negative charge on CF_3 group affects molecular conformation and interaction with a target structure.[2b,c] Representative examples for drugs containing trifluoromethyl group are shown in Scheme 1.1.



Scheme 1.1. Representative examples for drugs containing CF_3 group

For the synthesis of organic compounds containing a trifluoromethyl group, fluorination of carboxylic acid derivatives is one of the useful methods. Classically, sulfur fluoride (SF_4) can transform a carboxylic acid to the CF_3 group (Scheme 1.2.a).[3a] But SF_4 is very reactive, corrosive and toxic. To overcome this problem, Hiyama et al. reported oxidative desulfurization-fluorination of dithiocarboxylates (Scheme 1.2.b).[3b] The reaction can be applied to various organosulfur compounds. More recently, Umemoto et al. reported a new fluorinating reagent, named Fluolead

(**6**),[3c] which is air- and moisture-stable solid, transforms a carboxylic acid group to the CF_3 group efficiently (Scheme 1.2.c).



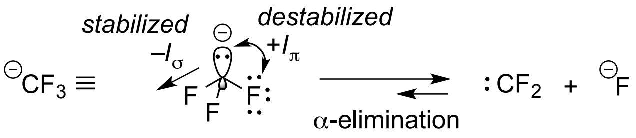
Scheme 1.2. Fluorination of carboxylic acids and thiocarboxylate

1.1.3 Trifluoromethylating Reagents

Another important trifluoromethylation method involves incorporation of a CF_3 unit into an organic molecule. Development of methodologies for highly efficient and selective incorporation of a CF_3 group into diverse molecular structures is an attractive and highly demanded research topic for synthetic chemists.[4] This research area has been developing along with advancement of trifluoromethylating reagents. Trifluoromethylating reagents are classified into nucleophilic, electrophilic and radical ones according to their properties.

1.1.3.1 Nucleophilic Trifluoromethylating reagents

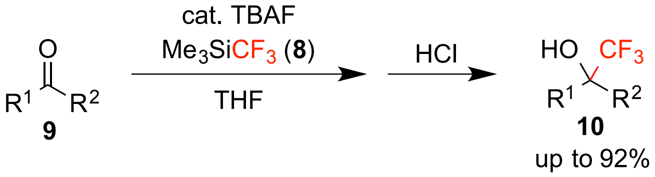
Free CF_3 anion ($^{-}CF_3$) is stabilized by the negative inductive effect of the fluorine atoms ($-I_\sigma$) but is concurrently destabilized by the electronic p–π repulsion between the anion on the carbon atom and the lone pair electrons of the fluorine atoms ($+I_\pi$) (Scheme 1.3). The CF_3 anion, therefore, easily undergoes α-elimination to generate difluorocarbene ($:CF_2$).[2d] Thus, using an appropriate CF_3 anion source is important.



Scheme 1.3. Property of the CF_3 anion

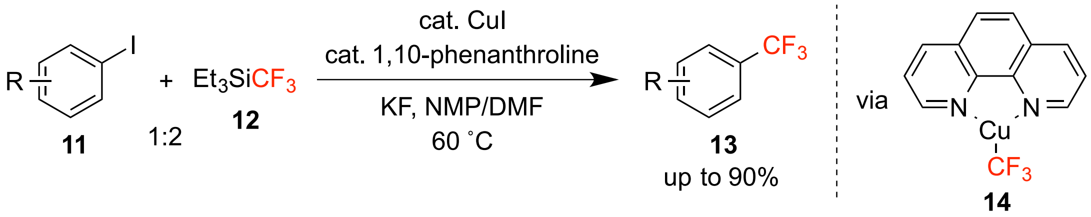
Trifluoromethylorganosilane (R_3SiCF_3, Ruppert-Prakash Reagents)

Trifluoromethyltrimethylsilane (Me_3SiCF_3, Ruppert-Prakash reagent) is the most widely used nucleophilic trifluoromethylating reagent. Me_3SiCF_3, which is stable and easy-handling liquid, was first synthesized by Ruppert et al. in 1984. In 1989, Prakash et al. reported the synthetic utility of the reagent for trifluoromethylation of carbonyl compounds (Scheme 1.4).[5] A catalytic amount of fluoride ion activates Me_3SiCF_3 (**8**) to begin the reaction.



Scheme 1.4. Trifluoromethylation of carbonyl compound with $TMSCF_3$

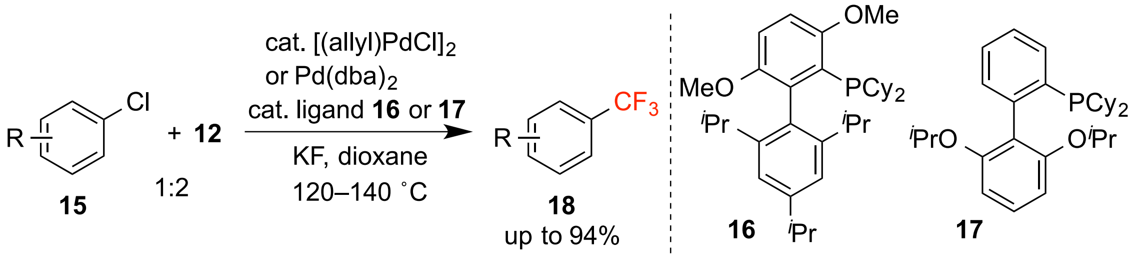
Hard-metal-CF_3 species such as Mg–CF_3 and Li–CF_3 is unstable.[2d] On the other hand, soft-metal-CF_3 species such as Cu–CF_3 is stable because of the covalent character of the metal–carbon bond and has been used for trifluoromethylation of aryl halide.[6] In 2009, Amii et al. reported the first copper-catalyzed trifluoromethylation of aryl iodides with Et_3SiCF_3 (**12**) (Scheme 1.5).[7] The combination of CuI and 1,10-phenanthroline ligand turns out to be effective for the catalytic reaction. Electron deficient aromatics and heteroaromatics are readily converted to the corresponding CF_3-aryl compounds in high yields by this catalytic system.



Scheme 1.5. Trifluoromethylation of aryl iodide with Cu–CF_3

In 2011, Hartwig et al. succeeded in isolation of (phen)$CuCF_3$ (**14**), which had been proposed to be the reactive species in the aromatic trifluoromethylation.[8] The copper reagent **14** is a stable solid, and exhibits a good performance for trifluoromethylation of various aryl iodides. It is highlighted that isolated **14** reacts with electron rich arenes efficiently and does not damage carbonyl groups such as ketone and aldehyde, which are not tolerable with the R_3SiCF_3 reagent.

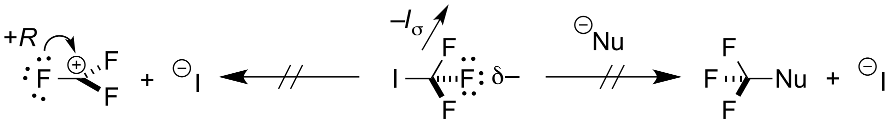
In terms of other metal, Buchwald et al. reported palladium-catalyzed trifluoromethylation of aryl chlorides with Et_3SiCF_3 (**12**) in 2010.[9] They achieved this elusive transformation by appropriate choice of bulky biaryl type ligands **16** or **17** (Scheme 1.6). This reaction can be applied to variety of aryl chlorides having functional groups.



Scheme 1.6. Palladium-catalyzed trifluoromethylation of aryl chlorides

1.1.3.2 Electrophilic Trifluoromethylating reagents

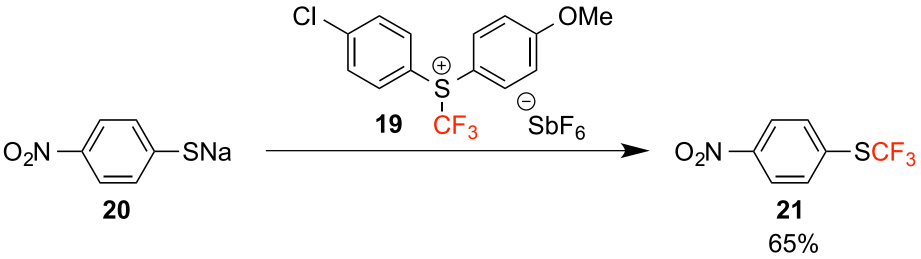
In contrast to non-fluorinated alkyl halides, trifluoromethyl iodide (CF_3I) does not undergo S_N2 type substitution reactions because of electrostatic repulsion between the lone pair electrons of the three fluorine atoms and the nucleophile. Furthermore, although trifluoromethyl cation is predicted as a stable species due to π-donation from the fluorines (+*R*), attempts to generate the species has never met with success due to the strong negative inductive effect of the fluorine atoms ($-I_\sigma$) (Scheme 1.7).[2d] Thus, development of an equivalent of the CF_3 cation has been needed.



Scheme 1.7. Reactivity of CF_3I with nucleophile

S-(Trifluoromethyl)diarylsulfonium Salt (Yagupolskii's Reagents)

In 1984, Yagpolskii et al. reported the first example of an electrophilic trifluoromethylating reagent, *S*-(trifluoromethyl)diarylsulfonium salt ($[Ar_2SCF_3]X$, Yaguplskii's reagent) **19**.[10] This reagent reacted with sodium 4-nitorophenylthiophenolate **20** to afford the corresponding trifluoromethyl sulfide **21** in 65% yield (Scheme 1.8).

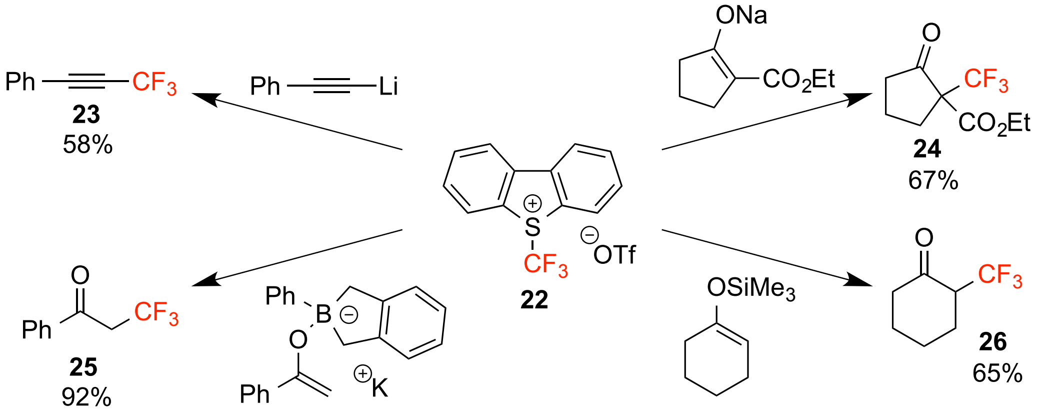


Scheme 1.8. Trifluromethylation of sodium thiophenoxide with Yaguploskii's reagent

S-(trifluoromethyl)dibenzothiophenium Salts (Umemoto's Reagents)

In 1990, Umemoto et al. reported *S*-(trifluoromethyl)dibenzothiophenium salt

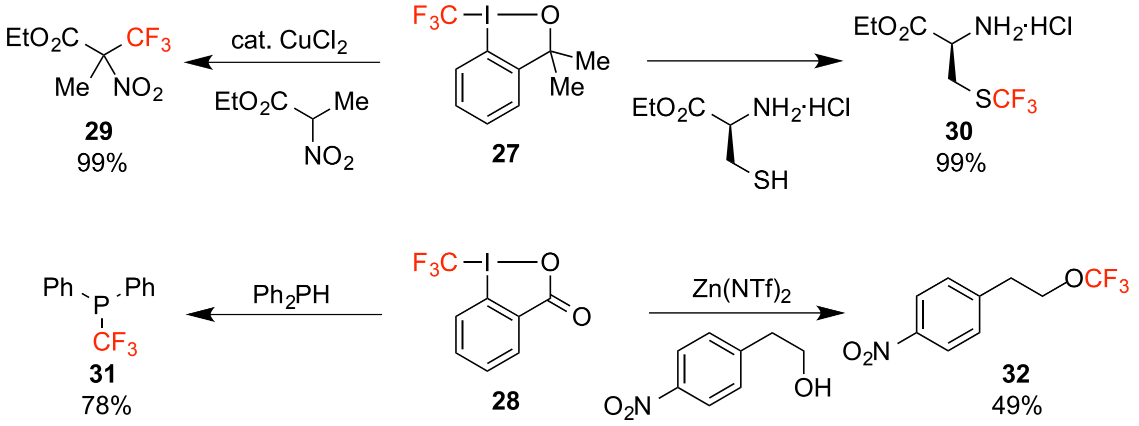
(Umemoto's reagent, **22**), which is a ring-fused derivative of Yaguploskii's regent.[11] A wide variety of nucleophiles such as carbanion, enamine, silyl enol ether, phenol, aniline, phosphine and thiolate reacted with Umemoto's reagent **22** to afford the trifluoromethylated products. Selected examples are shown in Scheme 1.9.



Scheme 1.9. Reaction examples of Umemoto's reagent

Trifluoromethyl Iodonium Salt (Togni's Reagents)

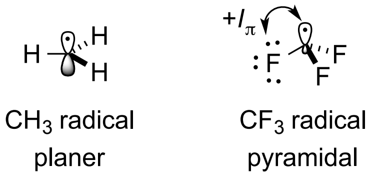
In 2006, Togni et al. reported a new family of electrophilic trifluoromethylating reagents containing a hypervalent iondine–CF_3 bond (Togni's reagents: 1-trifluoromethyl-3,3-dimethyl-1,2-benziodoxole (**27**), 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (**28**), Scheme 1.10).[12] Togni's reagents react with a wide variety of *C*, *S*, *P*, *O* and *N* nucleophiles, as shown below.



Scheme 1.10. Reaction examples of Togni's reagents

1.1.3.3 Radical Trifluoromethylating reagents

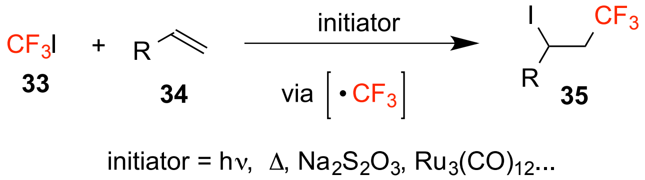
CF_3 radical is a pyramidal σ-radical in sharp contrast to the CH_3 radical, which is a trigonal planer π-radical (Scheme 1.11). This is because of a repulsion between the lone pair electrons of the fluorine atoms and the unpaired electron at the carbon atom.[13] The CF_3 radical has an electrophilic property due to the low-lying SOMO. Thus, electron-rich molecules act as a good acceptor for the CF_3 radical. In particular, radical trifluoromethylation works effectively for unsaturated hydrocarbons, which is the main subject of this thesis.



Scheme 1.11. CH_3 radical and CF_3 radical

Trifluoromethyl Iodide (CF_3I)

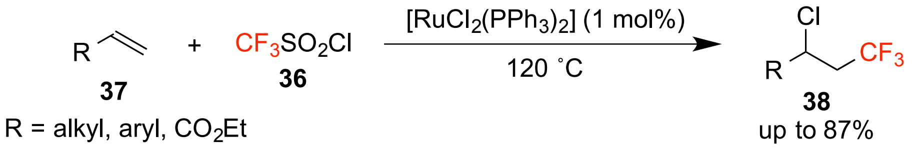
In the late 1940s, Haszeldine reported generation of CF_3 radical from CF_3I (**33**) through C–I bond homolysis induced by photolysis or thermolysis.[14a] In the presence of ethylene, he observed formation of 3-iodo-1,1,1-trifluoropropane as the major product, which resulted from an atom transfer radical addition (ATRA) type reaction (Scheme 1.12). CF_3 radical can be generated by the action of various radical initiators.[13] For example, sodium dithionite ($Na_2S_2O_4$)[14b] and a catalytic amount of transition metal species such as $[Ru_3(CO)_{12}]$[14c] initiated iodo-trifluoromethylation of alkenes.



Scheme 1.12. Iodo-trifluoromethylation of alkenes with CF_3I

Trifluoromethanesulfonyl Chloride (CF_3SO_2Cl)

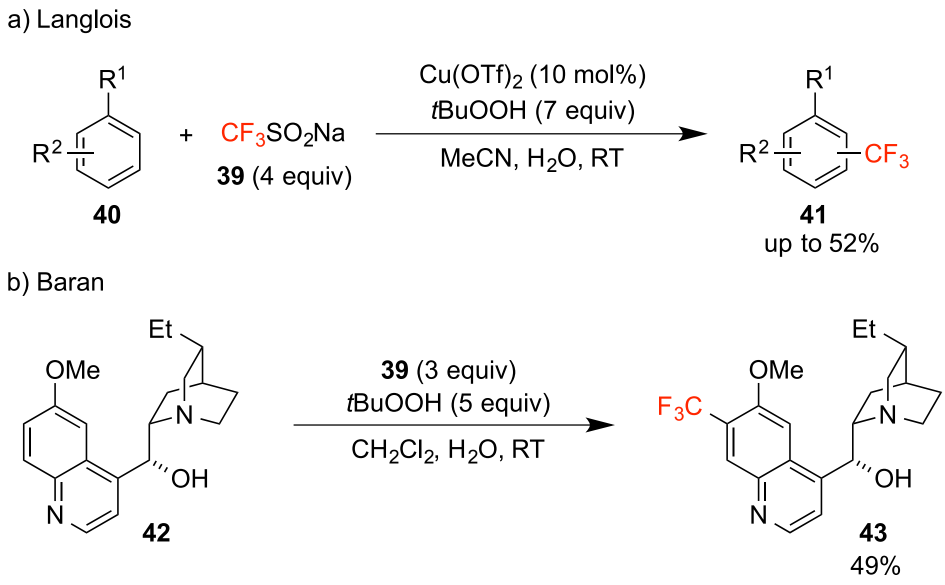
Gaseous CF_3I reagent is hard to handle. In contast, trifluoromethanesulfonyl chloride (CF_3SO_2Cl, **36**) is a liquid at room temperature (bp: 31 ˚C), although corrosive and moisture sensitive. Kamigata et al. reported [$RuCl_2(PPh_3)_2$]-catalyzed chloro-trifluoromethylation of alkenes using **36** (Scheme 1.13).[15] In this reaction, the Ru^{II} complex abstracts the chlorine atom from **36** to give a CF_3SO_2 radical, which undergoes SO_2 elimination to generate the CF_3 radical.



Scheme 1.13. Chloro-trifluoromethylation of alkenes with CF_3SO_2Cl

Sodium Trifluoromethanesulfinate (CF_3SO_2Na, Langlois Reagent)

Sodium trifluoromethanesulfinate (CF_3SO_2Na, Langlois reagent, **39**) is air and moisture stable solid. In 1991, Langlois et al. reported radical trifluoromethylation of electron-rich benzene derivatives by CF_3SO_2Na / *t*BuOOH / cat. $Cu(OTf)_2$ system (Scheme 1.14.a).[16] Recently, this pioneering study was shed light on by Baran et al. They brushed up this reaction for heteoaromatics. Various heteroarenes such as pyridines, pyrroles, indoles, pyrimidines, pyradines, phthalazines, quinoxalines, deazapurines, thiadiazoles, urasils, xanthines, and pyrazolinopyrimidines were successfully trifluoromethylated in moderate to good yields (33–96%).[17] It is highlighted that Baran's reaction can be applied to highly functionalized molecules such as dihydroquinine (**42**), meaning that it is powerful for late-stage trifluoromethylation (Scheme 1.14.b). In addition, Baran et al. extended this protocol to generation of other fluoroalkyl and non-fluoroalkyl radicals from the corresponding sodium or zinc sulfinate salts,[17b,c] and further developments are being continued.



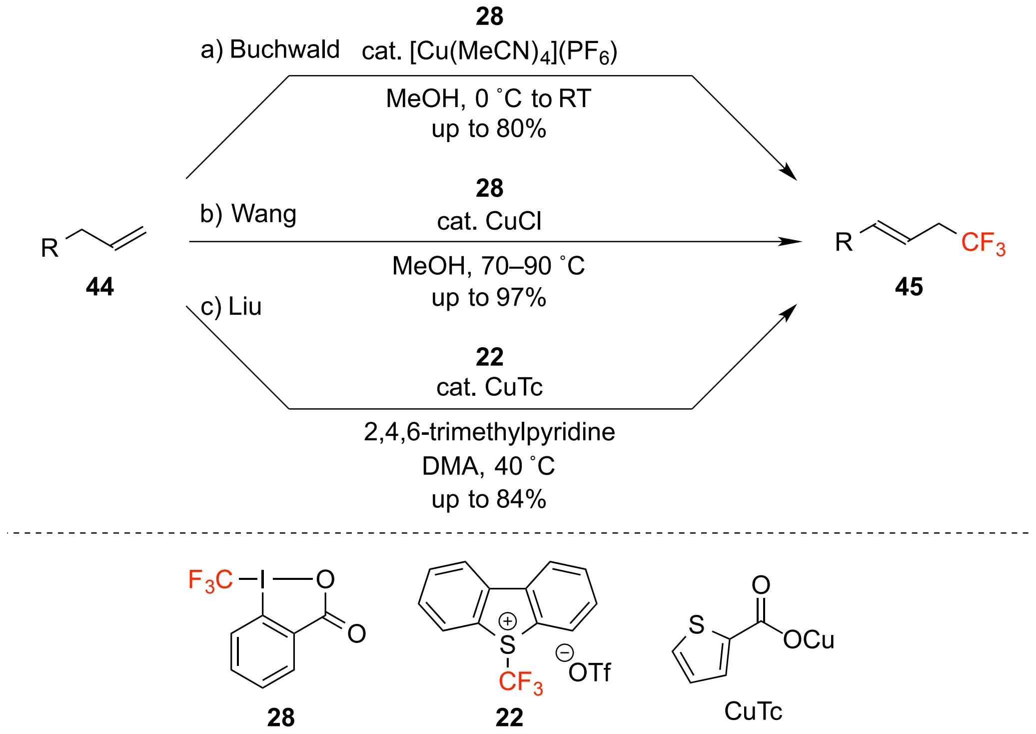
Scheme 1.14. Trifluromethylation of arenes with CF_3SO_2Na

1.1.4 Trifluoromethylation of Carbon–Carbon Unsaturated Bonds

As described above, polarized compounds, i.e. electrophile and nucleophile, can be trifluoromethylated by nucleophilic and electrophilic trifluoromethylating reagents, respectively. On the other hand, trifluoromethylation of non-polarized unsaturated hydrocarbons such as alkene and alkyne had been limited until recently. Hydrocarbons are abundant and commonly used feedstocks. Thus importance of synthesis of trifluoromethylated compounds from those easily accessible hydrocarbons is increasing. Radical trifluoromethylation may be a good way for this challenge, but most of CF_3 radical precursors are too hard to be handled to cause a delay of development. In recent years, development of shelf-stable electrophilic trifluoromethylating reagents such as Umemoto's reagent and Togni's reagents mentioned above have paved the way for development of new reaction systems.[18] Additionally, one of the powerful methods for trifluoromethylation is the reaction systems promoted by photoredox catalysis, which will be discussed in the following section.

1.1.4.1 Copper-catalyzed Allylic Trifluoromethylation of Terminal Alkenes

In 2011, Buchwald and Parson, Wang et al. and Liu et al. independently reported copper-catalyzed allylic trifluoromethylation of terminal alkenes (Scheme 1.15).[19] These reports had a common finding that a combination of a Cu(I) catalyst and an electrophilic trifluoromethylating reagent such as Togni's reagent **28** and Umemoto's reagent **22** is effective for alkene trifluoromethylation. Although detailed reaction mechanisms of these reactions are not yet clear, involvement of radical species or Cu(III) species is considered.

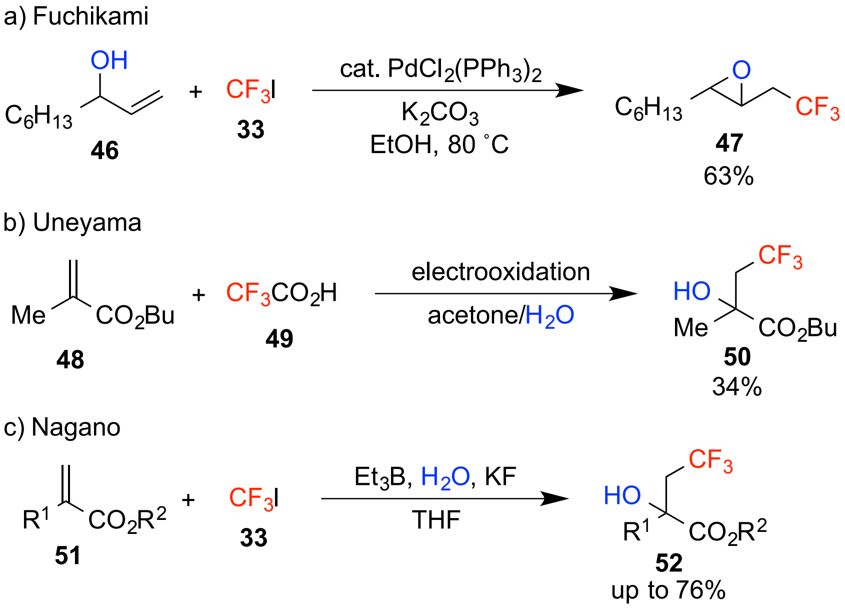


Scheme 1.15. Cu-catalyzed allylic trifluoromethylation of terminal alkenes

Stimulated by these reports, trifluoromethylation of alkenes has been studied intensively. In particular, trifluoromethylative difunctionalization is a promising approach for construction of complex trifluoromethylated molecules.

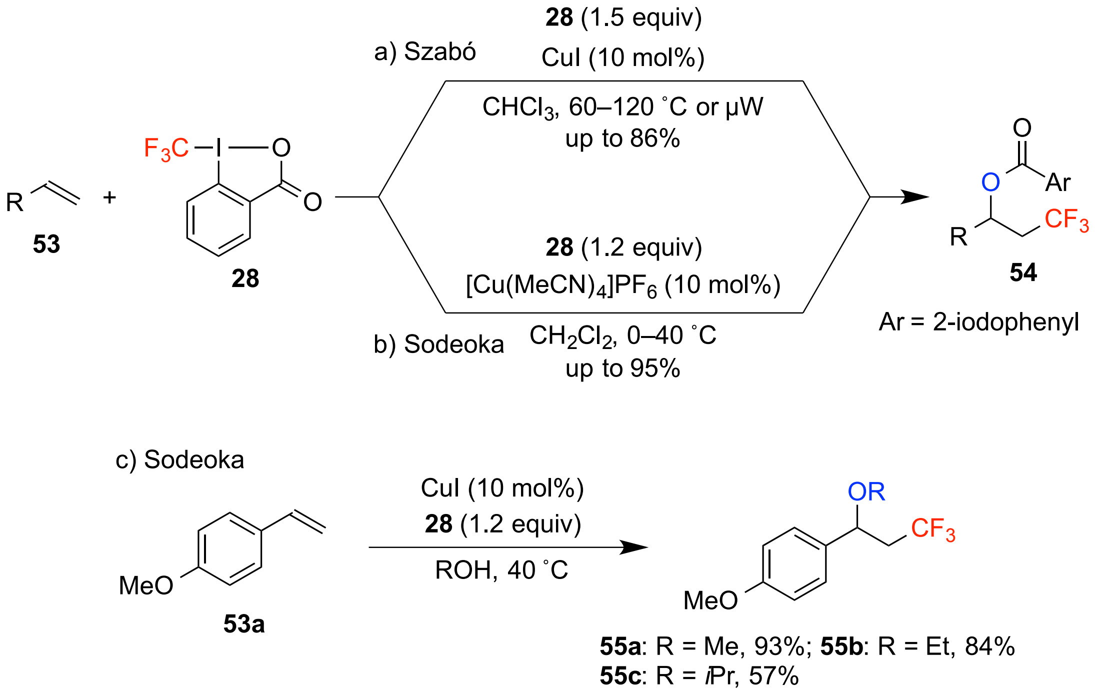
1.1.4.2 Oxy-Trifluoromethylation of Alkenes

Trifluoromethylation concomitant with introduction of an oxygen functional group (oxy-trifluoromethylation) has attracted attention among many researchers. Fuchikami et al. reported the pioneering oxy-trifluoromethylation in 1987.[20a] $PdCl_2(PPh_3)_2$ catalyst achieved trifluoromethylation of allylic alcohol **46** with CF_3I (**33**) followed by intramolecular cyclization to afford trifluoromethylated epoxide **47** (Scheme 1.16.a) but only one example was reported. Later on, Uneyama et al. reported hydroxy-trifluoromethylation of butyl 2-methacrylate (**48**) using electrooxidation of trifluoroacetic acid (**49**) (Scheme 1.16.b).[20b] In addition, Nagano et al. reported Et_3B induced radical hydroxy-trifluoromethylation of α,β-unsaturated ester **51** (Scheme 1.16.c).[20c,d]



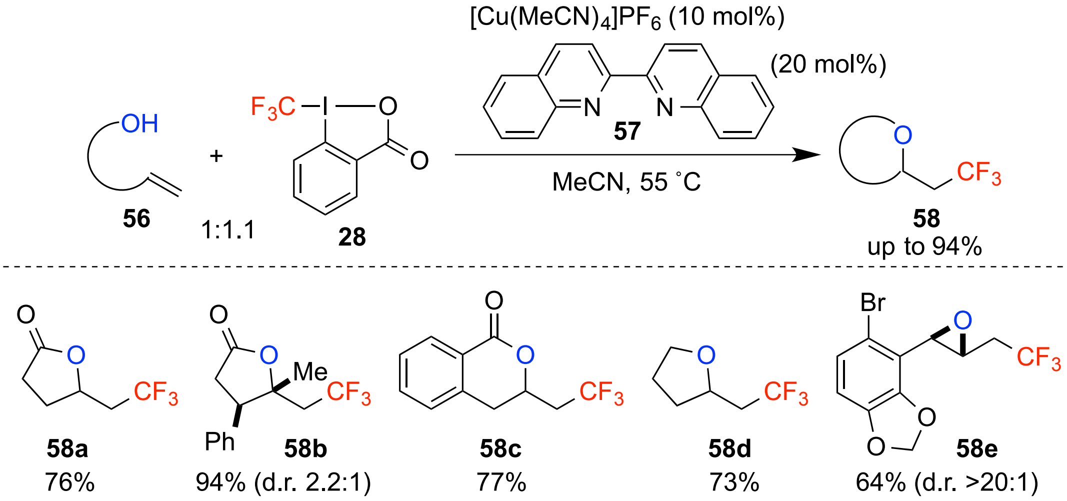
Scheme 1.16. Pioneering works for oxy-trifluoromethylation of alkenes

Almost at the same time in 2012, Szabó et al. and Sodeoka et al. reported Cu-catalyzed oxy-trifluoromethylation of terminal aromatic alkenes **53** with Togni's reagent **28** (Scheme 1.17.a and b).[21] In these reactions, the CF_3 group and 2-iodobenzyloxy group derived from **28** attach to the multiple bonds in a regioselective manner. Compared the two reports, the conditions of Sodeoka's report were milder and with a broader reaction scope, and the products yields were generally high. Furthermore, Sodeoka showed this reaction could be applied to trifluoromethylated ether synthesis when conducted in an alcohol solvent (Scheme 1.17.c).[21b]



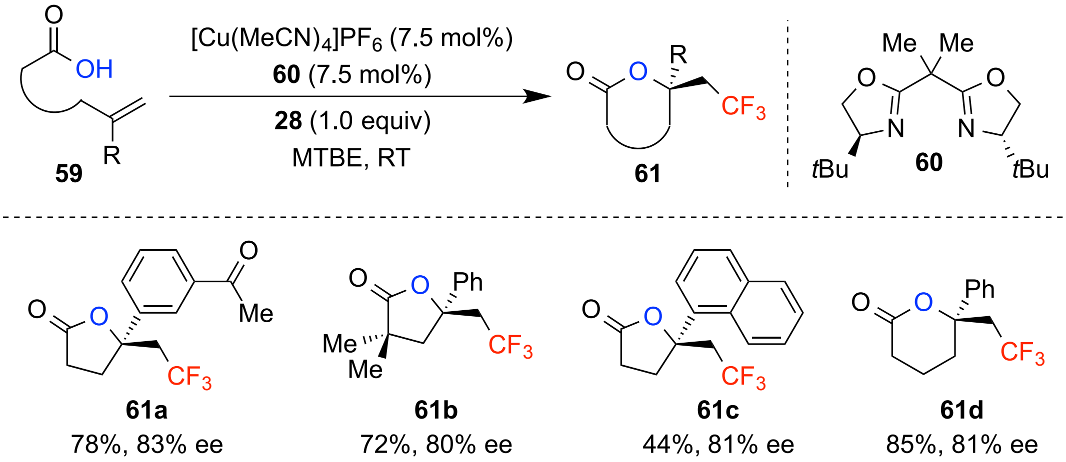
Scheme 1.17. Cu-catalyzed intermolecular oxy-trifluoromethylation of alkenes

Buchwald and Zhu reported intramolecular oxy-trifluoromethylation of alkenes bearing a nucleophilic pendant in 2012 (Scheme 1.18).[22a] They achieved suppression of formation of trifluoromethylated allyl compounds **45**[19a] and succeeded in the selective formation of cyclized products **58** by using MeCN as a solvent and 2,2'-biquinoline (**57**) as a ligand. This reaction allowed a variety of alkenes bearing carboxylic acid, alcohol and phenol functional groups to afford products with three-, four-, five- and six-membered rings.



Scheme 1.18. Cu-catalyzed intramolecular oxy-trifluoromethylation of alkenes

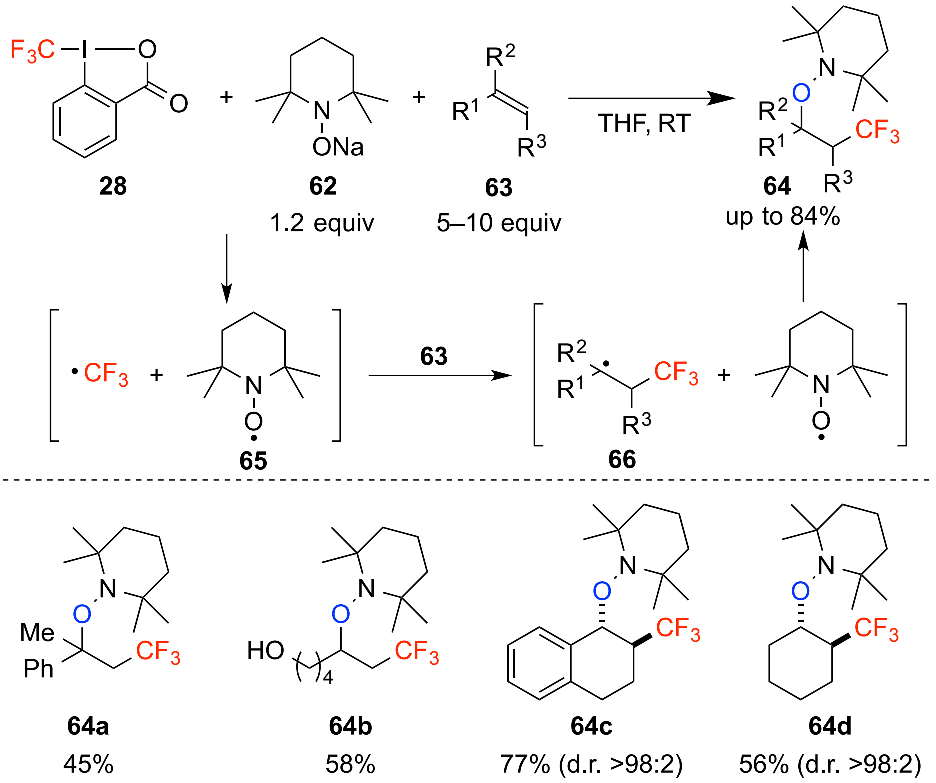
The same authors applied this oxy-trifluoromethylation to an asymmetric version (Scheme 1.19).[22b,c] Although the substrate scope was limited to styrene derivatives bearing carboxylic acid, the enantioselectivity was satisfactory.



Scheme 1.19. Asymmetric intramolecular oxy-trifluoromethylation of alkenes

In 2012, Studer and Li reported a unique approach for oxy-trifluoromethylation.[23] They used TEMPONa (**62**) as a single electron reductant for **28**. Resulting CF_3 radical added to alkene to give the alkyl radical intermediate **66**, which underwent radical coupling with TMEPO (**65**) to provide the aminoxy-trifluoromethylated product **64**

(Scheme 1.20). Although an excess amount of alkene was required, this reaction could be applied not only to terminal alkenes but also to internal alkenes including both conjugated and non-conjugated alkenes. In the case of cyclic alkenes, it is remarkable that the products were given in high diastereoselectively.

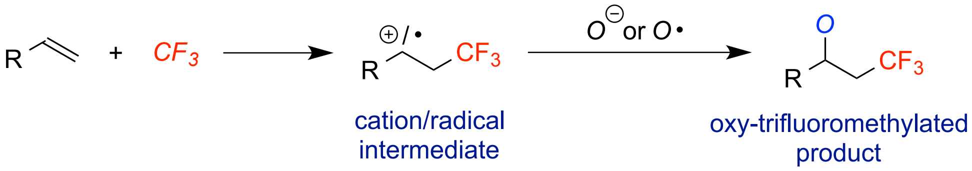


Scheme 1.20. Aminoxy-trifluoromethylation of alkenes with TEMPO

Qing and Jiang also reported the aminoxy-trifluoromethylation of alkenes using the Langlois reagent / *t*BuOOH / cat. Cu system and hydroxamic acid.[24]

As an other example, the oxy-trifluoromethylation methodology has been used for construction of heterocyclic structures bearing a CF_3 group in a way similar to the Buchwald's works.[22] As far as the author knows, synthesis of isoxazoline,[25a,b] oxazoline,[25c,44e] oxazine,[44e] and benzoxazine[25c,d] were reported.

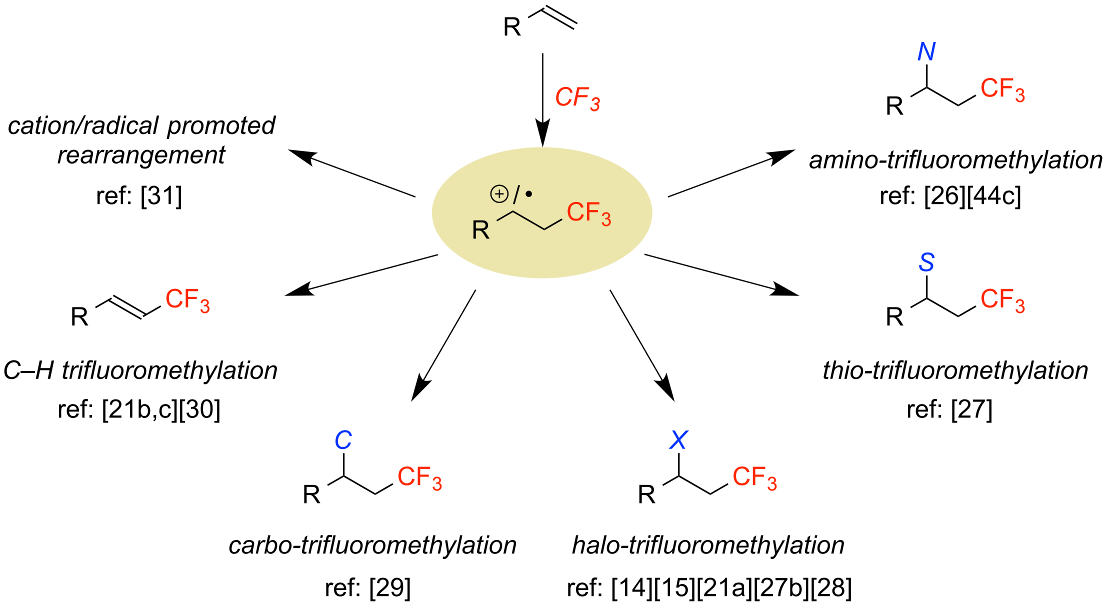
In most of the studies described above, reaction mechanisms were not discussed in detail. But some findings about substrate scopes and control experiments indicate involvement of a cationic or radical species as an intermediate. Subsequent nucleophilic attack or radical trapping may introduce the *O*-functionality (Scheme 1.21).



Scheme 1.21. Mechanistic Supposition

1.1.4.3 Other Trifluoromethylative Difunctionalizations of Alkenes

A wide variety of trifluoromethylative difunctionalizations were achieved by the strategies similar to oxy-trifluoromethylation. An overview is shown in Scheme 1.22 together with the references.

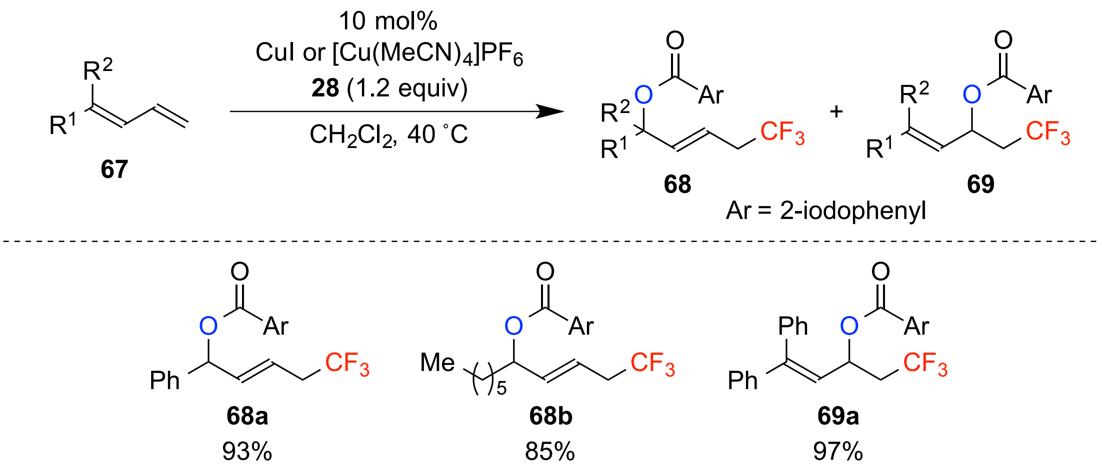


Scheme 1.22. Other trifluoromethylative difunctionalizations of alkenes

1.1.4.4 Oxy-Trifluoromethylation of Other Unsaturated Hydrocarbons

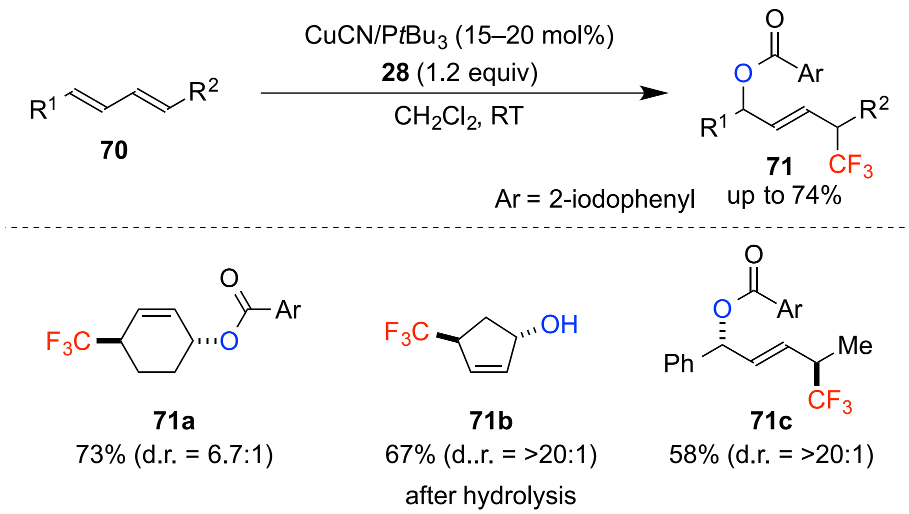
Few examples for trifluoromethylative difunctionalizations of unsaturated hydrocarbons other than alkenes have been reported. Among them, representative oxy-trifluoromethylations will be shown below.

Sodeoka et al. reported Cu-catalyzed oxy-trifluoromethylation of 1,3-dienes.[21b,c] They found 1-substituted dienes underwent 1,4-addition with Togni's reagent **28** to provide benzyloxy-trifluoromethylated products in high yields (**68a** and **68b** in Scheme 1.23). This reaction can be applied to aliphatic dienes. On the other hand, 1,1-disubstituted diene afforded the 1-trifluoromethyl-2-benzyloxylated product **69a** in a high yield.



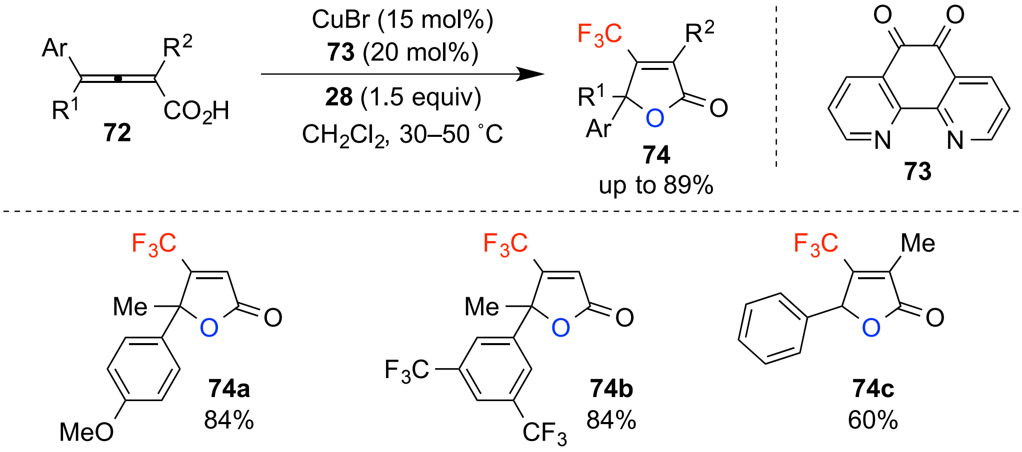
Scheme 1.23. Cu-catalyzed 1,2- or 1,4-oxy-trifluoromethylation of 1,3-dienes

Xu et al. also reported Cu-catalyzed benzyloxy-trifluoromethylation of 1,3-diene in 2013 (Scheme 1.24).[32] Compared to Sodeoka's report, this reaction could be applied to internal 1,3-dienes including cyclic dienes to afford 1,4-addition products, and proceeded in highly diastereoselective manner.



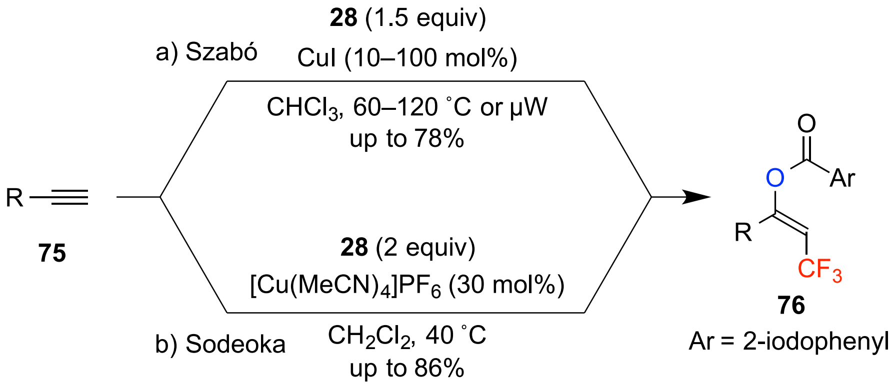
Scheme 1.24. Cu-catalyzed 1,4-oxy-trifluoromethylation of 1,3-dienes

In 2013, Ma and Yu reported oxy-trifluoromethylation of 2,3-allenoic acids providing trifluoromethylated butenolides.[33a] Trifluoromethylated butenolides having either an electron-rich or electron-deficient arene were obtained (Scheme 1.25). In 2014, Liu et al. Cu-catalyzed benzyloxy-trifluoromethylation of allenyl ethers, amines and sulfides with **28**.[33b]



Scheme 1.25. Cu-catalyzed intramolecular oxy-trifluoromethylation of allenes

Both of the groups of Szabó and Sodeoka mentioned Cu-catalyzed benzyloxy-trifluoromethylation of terminal alkynes in their reports about alkene trifluoromethylation.[21] They obtained tri-substituted CF_3-alkenes with high *E*-selectivity from terminal alkynes and Togni's reagent **28** (Scheme 1.26).



Scheme 1.26. Cu-catalyzed oxy-trifluoromethylation of terminal alkynes

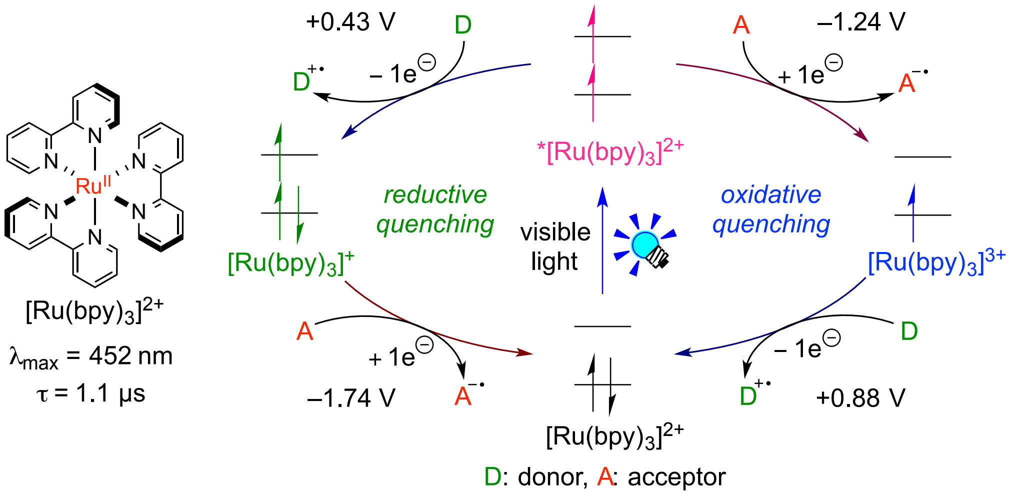
1.2 Photoredox Catalysis

1.2.1 Principles of Photoredox Catalysts

Radical reactions account for an important position in organic synthesis because radicals show characteristic reactivities distinct from those of ionic species, i.e. anion and cation. Conventional radical reactions often require precursors with weak bonds (e.g. tin reagent, azo compound and peroxide), which are frequently harmful and explosive. In addition, a high energy UV light source is required.

From this viewpoint, visible-light-induced radical reaction is an attractive approach for organic synthesis. Visible light, which is the main component of sunlight ($\lambda = 400$–700 nm), is non-toxic, abundant, and easy to handle by using household appliances such as fluorescent lamps and LED (light-emitting-diode) lamps. Even sunlight can be used as the light source. Most of organic molecules, however, are colorless and therefore cannot absorb visible light. In contrast, various inorganic and organometallic complexes have absorption bands in the visible light region. Among them, tris(bipyridyl)ruthenium (II) ($[Ru(bpy)_3]^{2+}$) and its derivatives, i.e. photoredox catalysts, have attracted attention because of their attracting behavior to cause single electron transfer (SET) processes.

The redox behavior of $[Ru(bpy)_3]^{2+}$ is illustrated in Scheme 1.25 as a representative example.[34] $[Ru(bpy)_3]^{2+}$ has an absorption maximum around 450 nm, indicating that this complex can be easily excited by visible light. The excitation derives from electron transfer from the dπ orbital of the ruthenium center to the π* orbital of the 2,2’-bipyridyl ligand (MLCT: metal-to-ligand charge transfer) and following intersystem crossing forms the luminescent triplet excited state, $*[Ru(bpy)_3]^{2+}$, which has a long emission lifetime (τ = approximately 1 μs) enough to be engaged in chemical reactions. The triplet $*[Ru(bpy)_3]^{2+}$ species with a hole and a high-energy electron causes single electron transfer reactions to/from external organic molecules, indicating that $*[Ru(bpy)_3]^{2+}$ can serve as either a one electron oxidant or reductant. The subsequent SET process regenerates the ground state, $[Ru(bpy)_3]^{2+}$ accompanying formation of another radical species.

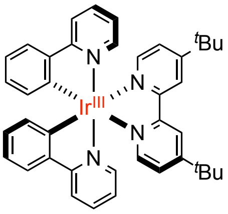
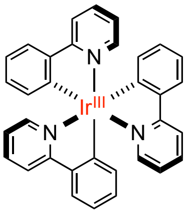
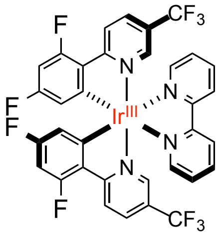


Scheme 1.27. Photoredox property of $[Ru(bpy)_2]^{2+}$ (redox potential = $E_{1/2}$ (vs. Cp_2Fe))

The photoredox catalysis can be divided into two types; one is *oxidative quenching cycle* and the other is *reductive quenching cycle*. The detailed mechanisms of them are described below. The oxidative quenching cycle begins with transfer of the excited electron to an external substrate to form the anionic radical of the substrate and an oxidized $[Ru(bpy)_3]^{3+}$ species. Because the Ru species is oxidized, this is called *oxidative quenching* but it should be noted that the external substrate is reduced. The oxidizing Ru(III) species causes one electron oxidation of an electron donor to result in regeneration of the ground state $[Ru(bpy)_3]^{2+}$ catalyst and formation of the cation radical of the donor. On the other hand, the reductive quenching cycle begins with single electron transfer from an external substrate to the hole to form the cation radical of the substrate and a reduced $[Ru(bpy)_3]^{+}$ species. Because the Ru species is reduced, this is called *reductive quenching*. The strong reductant, Ru(I) species, causes one electron reduction of an electron acceptor to result in regeneration of the ground state Ru catalyst and formation of the anionic radical of the acceptor.

Redox potential of the photoredox catalysts is one of the most important factors to design a visible-light-induced photoredox reaction. The redox potential is significantly affected by the kinds of the central metal, the ligand and the charge. Relevant cyclometalated iridium complexes, which are studied extensively as luminescent metal complexes, are also useful for photoredox catalysis.[35] Redox potentials of representative Ir species are shown in Table 1.2.

Table 1.2. Redox potentials of cyclometalated Ir complexes ($E_{1/2}$ (vs. Cp_2Fe))

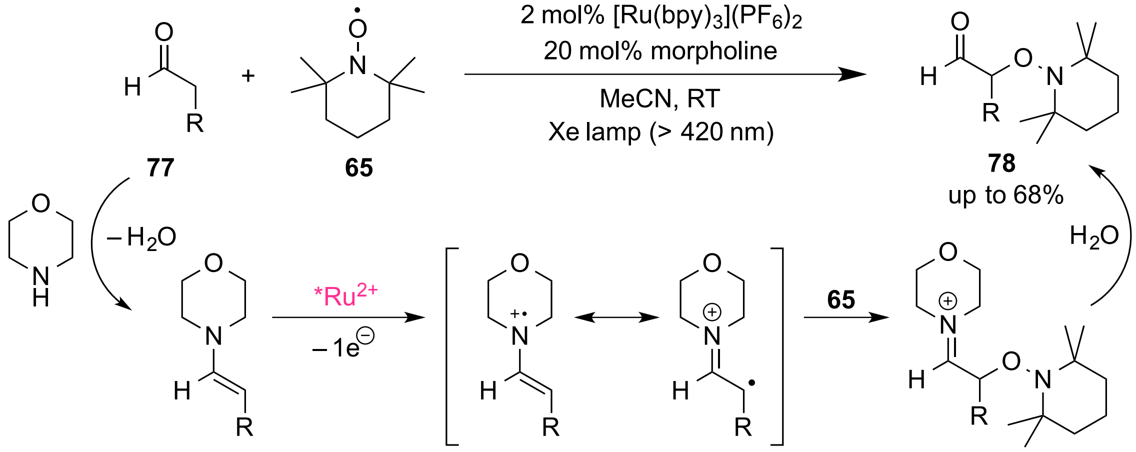
 $[Ir(ppy)_2(dtbbpy)]^+$	 *fac*-$[Ir(ppy)_3]$	 $[Ir(dF(CF_3)_2ppy)_2(dtbbpy)]^+$
oxidative quenching		
*Ir(III)/Ir(IV) = –1.37 V Ir(IV)/Ir(III) = +0.80 V	*Ir(III)/Ir(IV) = –2.14 V Ir(IV)/Ir(III) = +0.36 V	*Ir(III)/Ir(IV) = –1.41 V Ir(IV)/Ir(III) = +1.28 V
reductive quenching		
*Ir(III)/Ir(II) = +0.25 V Ir(II)/Ir(III) = –1.92 V	*Ir(III)/Ir(II) = –0.10 V Ir(II)/Ir(III) = –2.60 V	*Ir(III)/Ir(II) = +0.91 V Ir(II)/Ir(III) = –1.78 V

These complexes have been studied for the past several decades in inorganic chemistry to activate small inorganic molecules such as H_2O and CO_2. Such reaction systems promoted by sunlight may be called artificial photosynthesis. Recently, owing to the pioneering reports described below, the photoredox catalysis has attracted attention in organic synthesis.[36]

1.2.2 Pioneering Works of Photoredox Catalysis

Oxyamination of Aldehydes (Our Group)

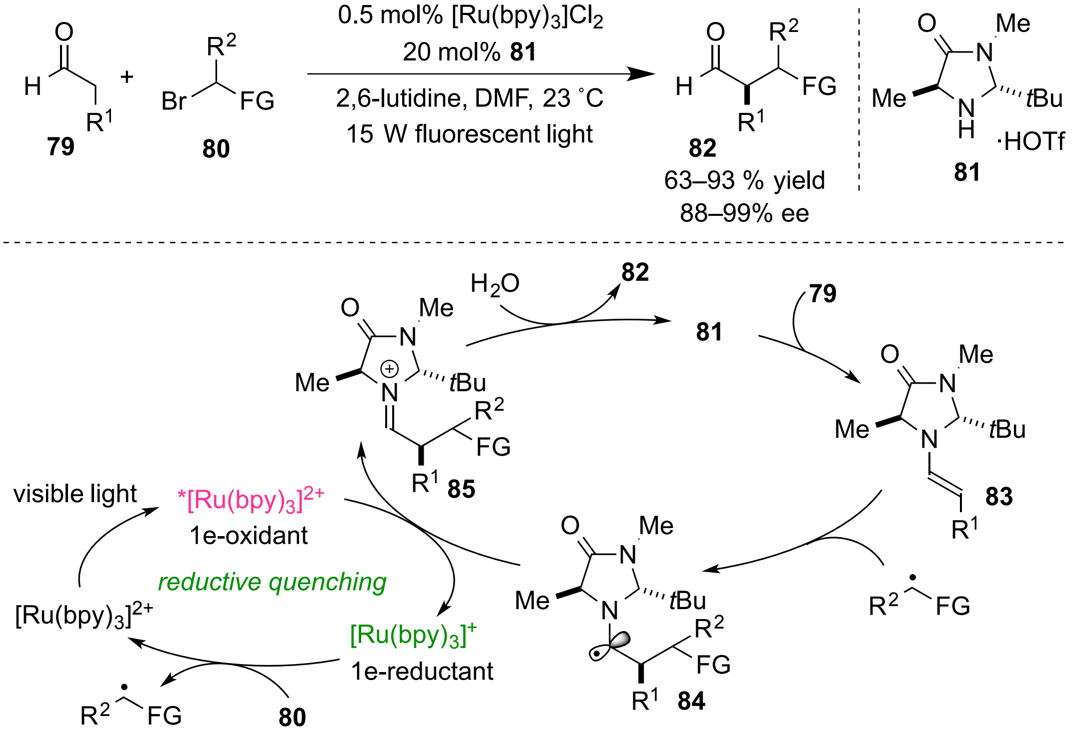
In 2009, Koike in our group found photo-induced oxyamination of aldehydes catalyzed by $[Ru(bpy_3)]^{2+}$ and morpholine (Scheme 1.28).[37] In this reaction, photoexcited $*[Ru(bpy)_3]^{2+}$ species causes SET oxidation of an enamine, which are generated by in-situ condensation between aldehyde **77** and morpholine. The resulting radical couples with TEMPO (**65**) to afford the oxyaminated product **78**.



Scheme 1.28. Photocatalytic oxyamination of aldehydes

Asymmetric α-Alkylation of Aldehydes

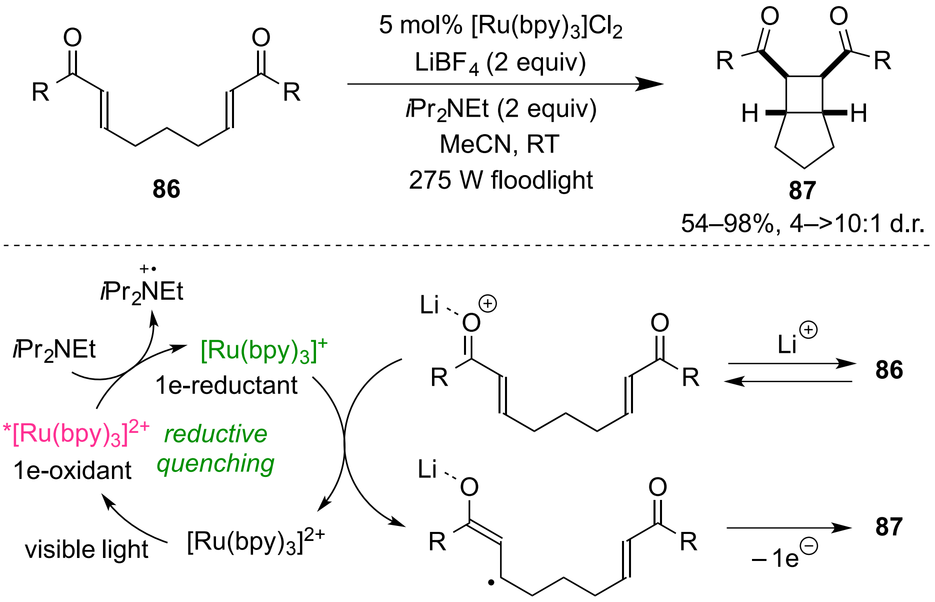
While our group was conducting the above-mentioned studies, MacMillan and Nicewicz reported asymmetric α-alkylation of aldehydes by a synergetic system of photoredox catalysis and organocatalysis (Scheme 1.29)[38]. In this catalysis, the photoexcited $*[Ru(bpy)_3]^{2+}$ species is reduced by enamine **83** derived from aldehyde **79** and the organocatalyst **81**. The resulting strong reductant, $[Ru(bpy)_3]^{+}$, undergoes SET to alkyl bromide **80** to lead to formation of alkyl radical and regeneration of the catalyst of the ground state, $[Ru(bpy_3)]^{2+}$. The alkyl radical reacts with the enamine **83** to give the radical intermediate **84**, the 1e-oxidation of which by the photoexcited Ru species affords the intermediate **85** and 1e-reductant, $[Ru(bpy)_3]^{+}$. Subsequent hydrolysis produces the enantio-enriched α-alkylated aldehyde **82**.



Scheme 1.29. Asymmetric α-alkylation of aldehydes promoted by photoredox catalysis

[2+2] Photocatalytic Cycloaddition of Bisenones

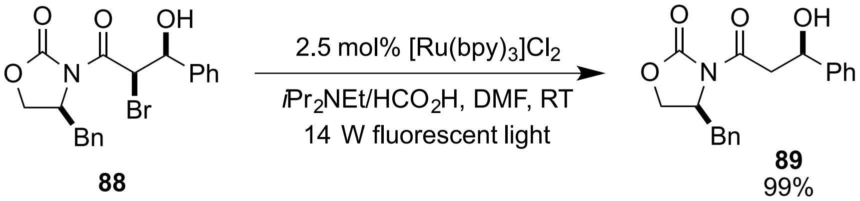
In 2008, Yoon et al. reported photo-induced intramolecular [2+2] cycloaddition of bisenones **86** (Scheme 1.30)[39]. In this reaction, the photoexcited $*[Ru(bpy)_3]^{2+}$ species is reduced by $i\mathrm{Pr}_2\mathrm{NEt}$. The resulting strong reductant, $[Ru(bpy)_3]^{+}$, undergoes SET to the enone **86** activated by $LiBF_4$ to lead to formation of the cyclized product **87** in a highly diastereoselective manner.



Scheme 1.30. Photocatalytic [2+2] cycloaddition of bisenones

Photocatalytic Reductive Dehalogenation of Alkyl Halides

In 2009, Stephenson et al. reported photocatalytic reductive dehalogenation of activated alkyl halides (Scheme 1.31)[40].



Scheme 1.31. Photocatalytic reductive dehalogenation of alkyl halides

1.2.3 Redox-neutral Transformation

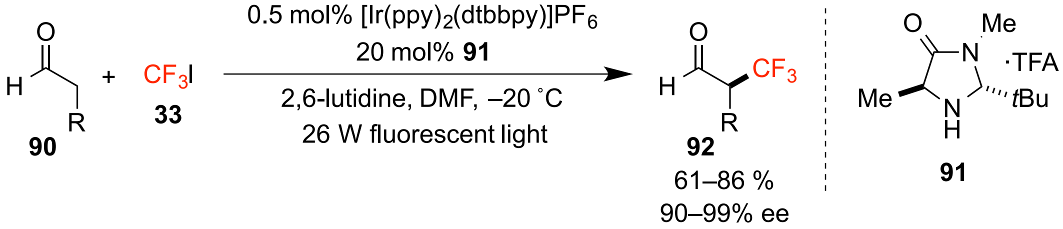
The author proposes the concept of *redox-neutral* transformation. The Yoon's reaction requires an excess amount of tertiary amine (iPr$_2$NEt) as a sacrificial reductant to generate the highly reducing [Ru(bpy)$_3$]$^+$ species. In contrast, the MacMillan's reaction proceeds without any sacrificial reagent due to the appropriate reaction design. *Redox-neutral* transformation is much preferred from the viewpoint of sustainability.

1.2.4 Trifluoromethylation by Photoredox Catalysis

In recent years, photoredox catalysis has been applied to a variety of transformations of organic molecules. In particular, the photoredox catalysis is compatible with radical trifluoromethylation. Representative trifluoromethylation reactions by photoredox catalysis will be explained below.

Asymmetric α-Trifluoromethylation of Aldehydes

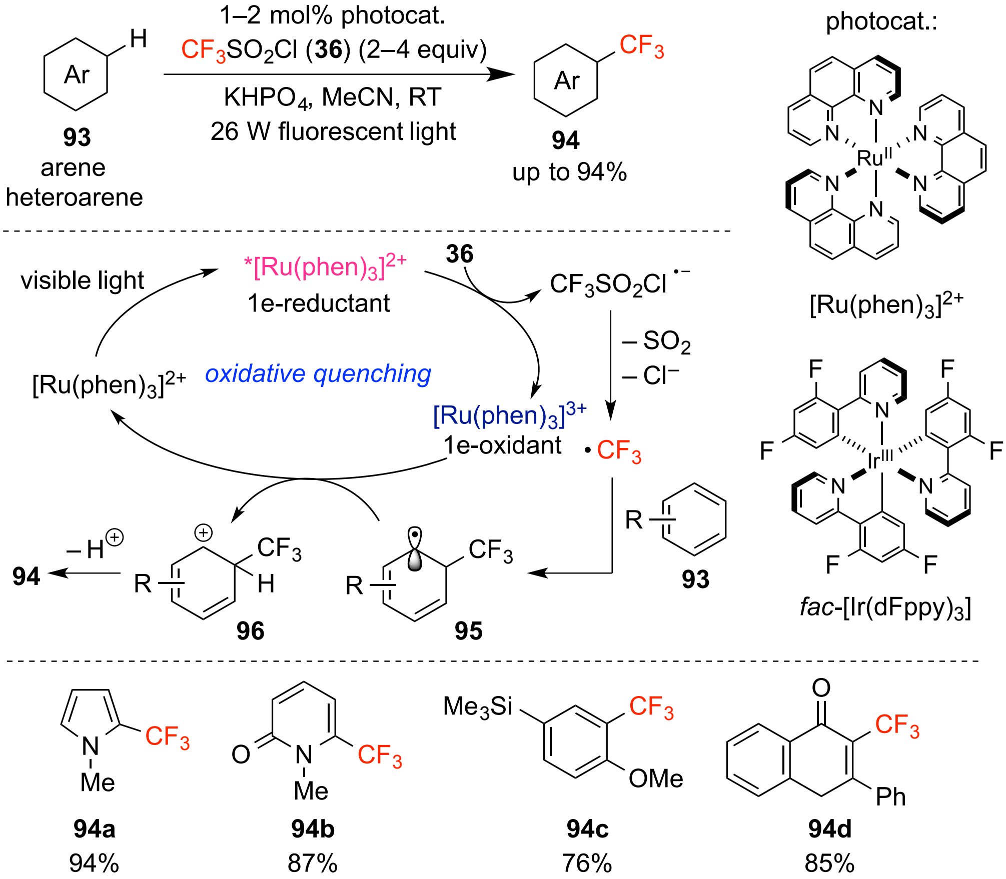
In 2009, MacMillan et al. applied their synergetic system of photoredox catalysis and organocatalysis to asymmetric α-trifluoromethylation of aldehydes with CF_3I (Scheme 1.32).[41] The reaction affords α-trifluoromethylated aldehydes highly enantio-selectively.



Scheme 1.32. Asymmetric α-trifluoromethylation of aldehydes promoted by photoredox catalysis

C–H Trifluoromethylation of Arenes

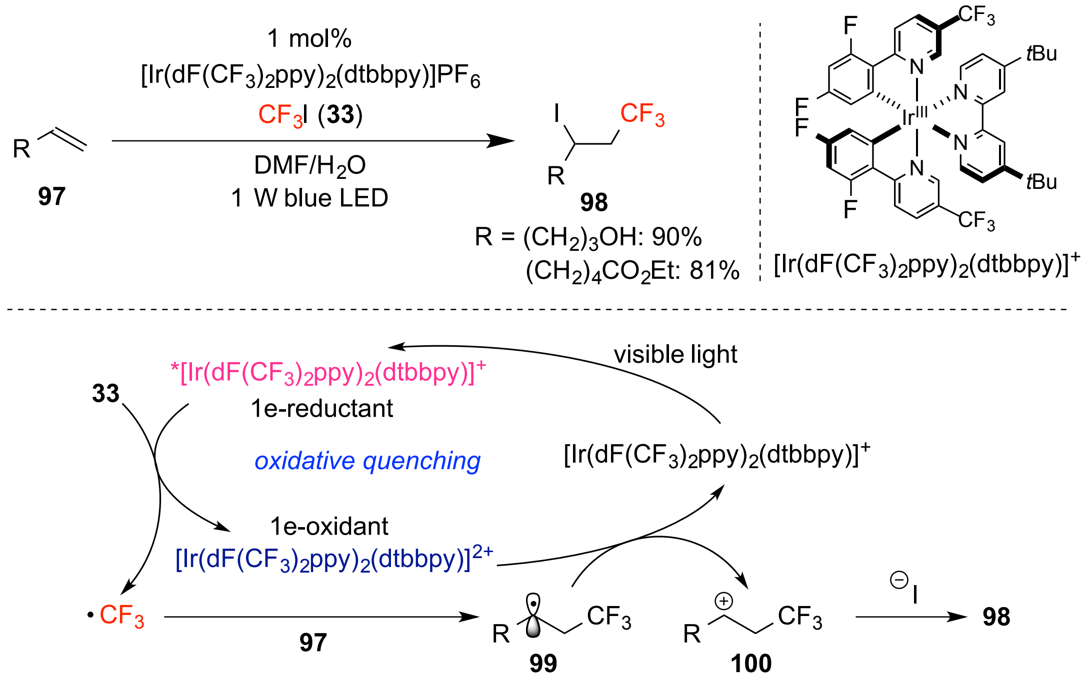
MacMillan and Nagib applied the photoredox catalysis to C–H trifluoromethylation of arenes.[42] They used CF_3SO_2Cl (**36**) as a CF_3 radical source and $[Ru(phen)_3]Cl_2$ (phen = 1,10-phenanthroline) or *fac*-$[Ir(dFppy)_3]$ (dF = 2-(2,4-difluorophenylpyrifyl)) as a photocatalyst (Scheme 1.33). This reaction system has a broad substrate scope and various five- and sixmembered arenes are allowed. A plausible reaction mechanism employing the Ru photocatalyst is detailed in Scheme 1.33. The photoexcited $*[Ru(phen)_3]^{2+}$ causes SET with CF_3SO_2Cl (**36**) to give the CF_3 radical and the highly oxidizing $[Ru(phen)_3]^{3+}$ species. The CF_3 radical reacts with arene **93** resulting in the radical intermediate **95**, which is oxidized by $[Ru(phen)_3]^{3+}$ to afford the cation intermediate **96** and $[Ru(phen)_3]^{2+}$. Deprotonation of the cation **96** produces the trifluoromethylated arene **94**.



Scheme 1.33. C–H trifluoromethylation of arenes promoted by photoredox catalysis

Iodo-Trifluoromethylation of Alkenes

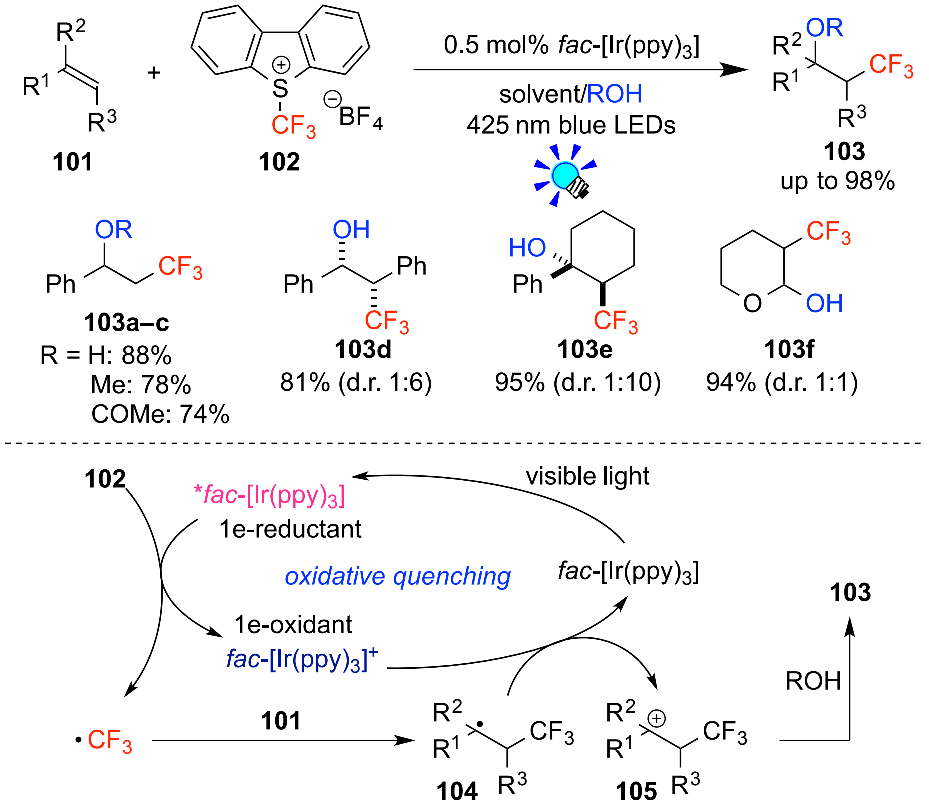
In 2011, Stephenson et al. reported iodo-trifluoromethylation of alkenes by photoredox catalysis (Scheme 1.34).[43] The photoexcited Ir catalyst, $*[Ir(dF(CF_3)ppy)_2(dtbbpy)]^+$, reduces CF_3I (**33**) to give the CF_3 radical and the highly oxidizing $[Ir(dF(CF_3)ppy)_2(dtbbpy)]^{2+}$ species. The CF_3 radical reacts with alkene **97** to give the α-trifluoromethylated radical intermediate **99**, which is oxidized by $[Ir(dF(CF_3)ppy)_2(dtbbpy)]^{2+}$ to afford the α-trifluoromethylated cation intermediate **100** and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]^+$. Final nucleophilic addition of iodide ion produces the iodo-trifluoromethylated product **98**. The authors remarked that involvement radical propagation pathway could not be excluded completely.



Scheme 1.34. Iodo-trifluoromethylation of alkenes promoted by photoredox catalysis

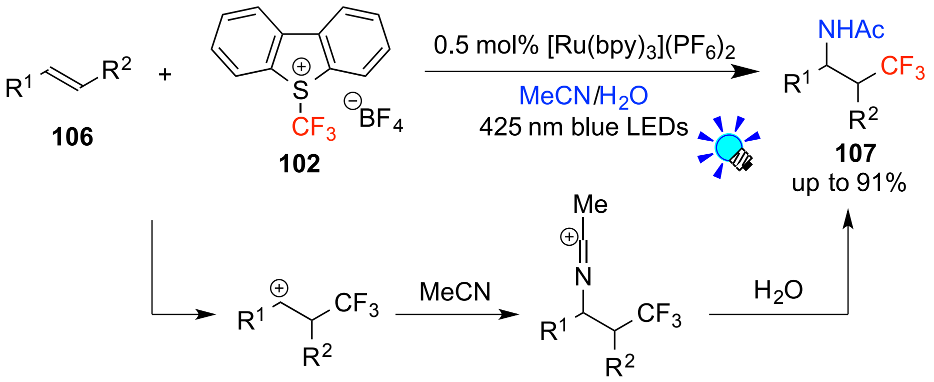
Oxy-Trifluoromethylation of Alkenes (Our Group)

In 2012, Yasu in our group found that the electrophilic trifluoromethylating reagent such as Umemoto's reagent **102** and Togni's reagent **28**, which are shelf-stable and easy-handling solids, act as an electron acceptor of the photoexcited catalyst to generate CF_3 radical. He then established oxy-trifluoromethylation of alkenes using Umemoto's reagent (Scheme 1.35).[44a] Although this reaction presumably proceeds in a mechanism similar to that of Stephenson's work shown in Scheme 1.34, the use of Umemoto's reagent makes it possible to extend the reaction to those with various nucleophiles such as H_2O, alcohols and carboxylic acids.

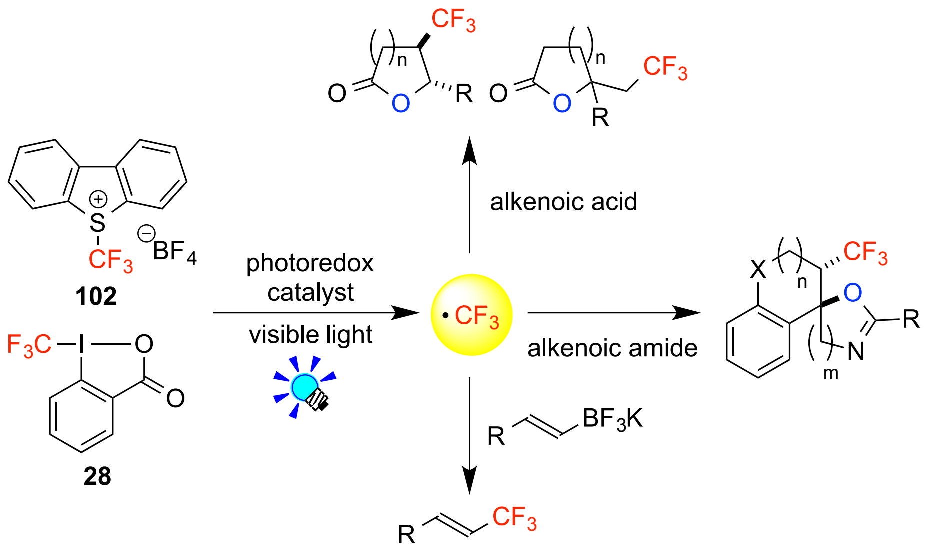


Scheme 1.35. Oxy-trifluoromethylation of alkenes promoted by photoredox catalysis

The combination of a photoredox catalyst and an electrophilic trifluoromethylating reagent has been expanded to various trifluoromethylative difunctionalizations of alkenes by our group. For example, this protocol can be applied to Ritter amination when the reaction is conducted in MeCN/H_2O (Scheme 1.36).[44c] Other examples reported by our group are shown in Scheme 1.37.[44]



Scheme 1.36. Amino-trifluoromethylation of alkenes promoted by photoredox catalysis



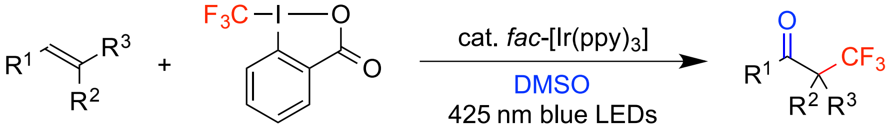
Scheme 1.37. Other trifluoromethylative difunctionalization of alkenes reported by our groups

1.3 Survey of This Thesis

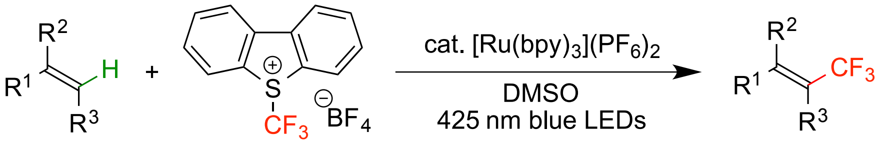
As described above, trifluoromethylation is an important, desired and intensively studied research field. In particular, trifluoromethylation of carbon–carbon unsaturated bonds to give highly functionalized trifluoromethyl compounds is an attractive synthetic method. So far, various kinds of trifluoromethylation of alkenes with concomitant introduction of additional functional groups have been reported. When the author started the study, however, the reactions of unsaturated hydrocarbons other than alkenes are not explored so much. In terms of oxy-trifluoromethylation, most of introduced oxygen functionalities are alcohols, ethers, esters and aminoxy groups. The author set up two issues to be solved, i.e. introduction of other oxygen functionalities and investigation of reactivity of unsaturated hydrocarbons other than alkenes. In particular, he thought a great deal of synthetic utility of the reaction product.

In this thesis, the author has developed various trifluoromethylation reactions of unsaturated hydrocarbons promoted by photoredox catalysis. The details are given in the following chapters.

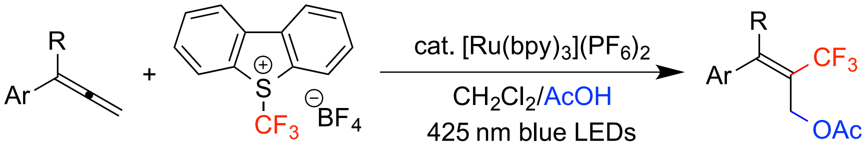
In Chapter 2, the author describes keto-trifluoromethylation of alkenes. In this reaction, DMSO acts as the key nucleophile and oxidant. A variety of aromatic alkenes are transformed into α-trifluoromethylated ketones in a single step.



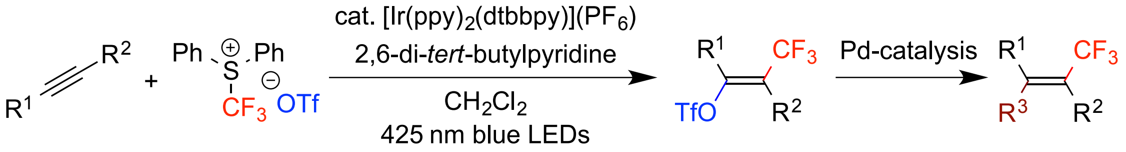
In Chapter 3, the author describes C–H trifluoromethylation of di- and tri-substituted alkenes. The reaction derives from the study described in Chapter 2, and an efficient synthetic method for tri- and tetrasubstituted trifluoromethyl alkenes from simple alkenes has been established.



In Chapter 4, the author describes the result of application of oxy-trifluoromethylation to allenes. The reaction intermediate is different that from alkenes. The reaction proceeds through an allyl radical/cation intermediate, which can be attacked by a nucleophile on the two terminal sites. But when AcOH is used as nucleophile, the reaction proceeded in a regio- and stereoselective manner. The product, allyl acetates, undergoes Pd-catalyzed allylic alkylation reaction.



In Chapter 5, the author establishes stereoselective sulfonyloxy-trifluoromethylation of internal alkynes. This reaction seems to proceed through an alkenyl radical/cation intermediate and a triflate ion, which is derived from an electrophilic trifluoromethylating reagent, adds to the intermediate from the side opposite to the CF_3 group. Products undergo Pd-catalyzed cross-couplings to afford various tertasubstituted trifluoromethyl alkenes.



Finally, summary and outlook will be shown in Chapter 6.

1.4 References

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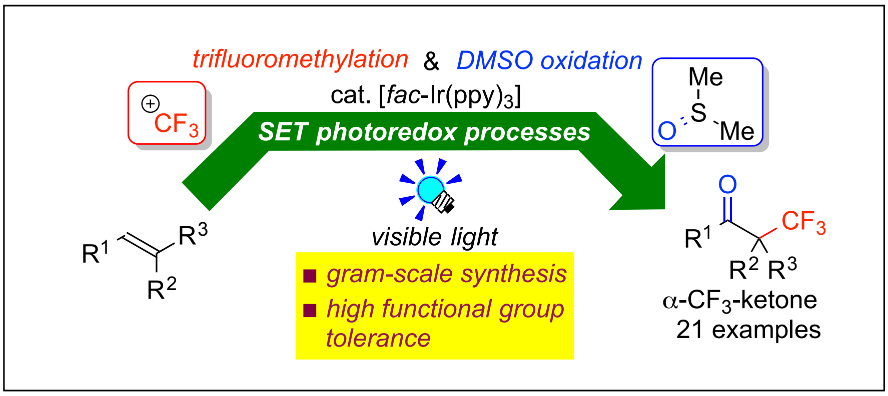
Chapter 2

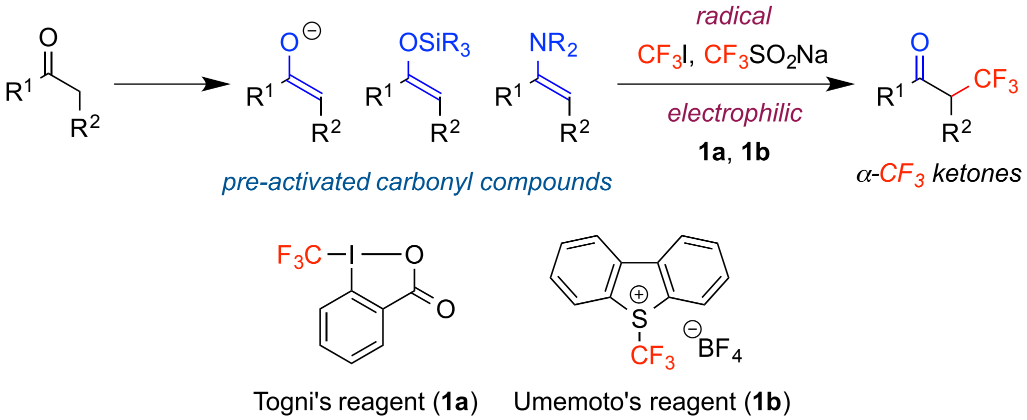
Combining Photoredox-Catalyzed Trifluoromethylation and Oxidation with DMSO: Facile Synthesis of α-Trifluoromethylated Ketones from Aromatic Alkenes

ABSTRACT: Trifluoromethylated ketones are useful building blocks for organic compounds with a trifluoromethyl group. A new and facile synthesis of ketones with a trifluoromethyl substituent in the α-position proceeds through a one-pot photoredox-catalyzed trifluoromethylation-oxidation sequence of aromatic alkenes. Dimethyl sulfoxide (DMSO) serves as a key and mild oxidant under these photocatalytic conditions. Furthermore, an iridium photocatalyst, *fac*-[Ir(ppy)$_3$], turned out to be crucial for the present photoredox process.



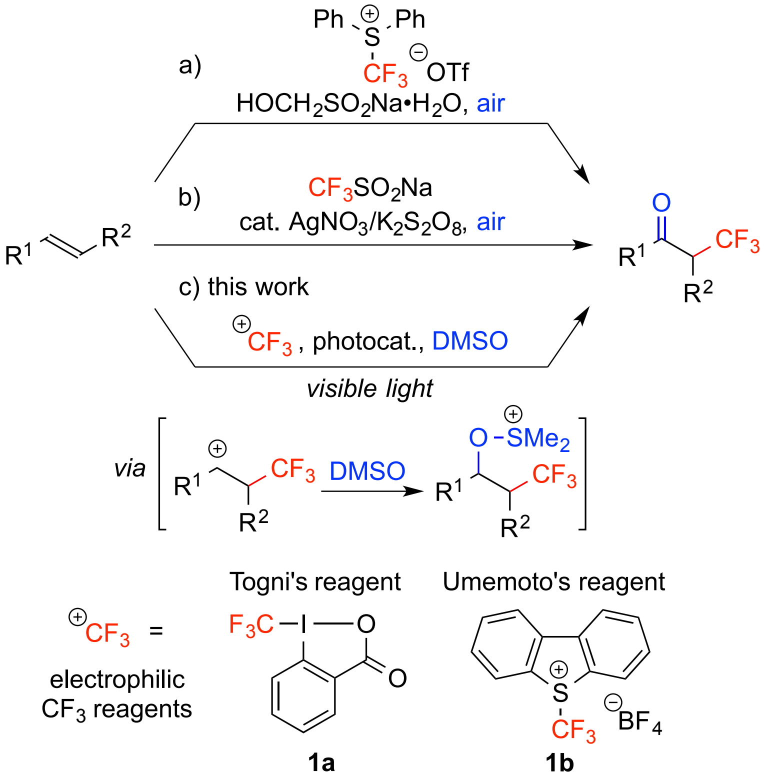
2.1 Introduction

As described in Chapter 1, the trifluoromethyl group prevails in pharmaceutical and agrochemical compounds as well as in functional organic materials.[1,2] Therefore, the development of new methods for efficient and selective incorporation of a CF_3 group into diverse molecular architectures has become an important research topic in the field of synthetic organic chemistry.[3] Trifluoromethylated carbonyl compounds are versatile building blocks for the synthesis of a wide variety of fluorinated compounds.[4] In general, electrophilic or radical trifluoromethylation of enolates, which are prepared from the corresponding carbonyl compounds in advance, provides accesses to valuable α-trifluoromethylated carbonyl compounds (Scheme 2.1).[5]



Scheme 2.1. General synthetic methods for α-CF_3-substituted ketones

A few other unique methods have also been reported[6–9], but examples of the “direct” oxidative trifluoromethylation (keto-trifluoromethylation) of alkenes, which are abundant and commonly used feedstocks, have been limited so far.[10] In 2011, Xiao et al. reported the keto-trifluoromethylation of styrenes with an *S*-(trifluoromethyl)diphenylsulfonium salt and air in the presence of an excess amount of the reducing agent, $HOCH_2SO_2Na$. However, the yields of the α-CF_3-substituted ketones were low (Scheme 2.2.a). In 2013, Maiti et al. described a catalytic system consisting of $AgNO_3$ and $K_2S_2O_8$, which is effective for the oxidative trifluoromethylation of alkenes with the Langlois reagent, CF_3SO_2Na, and air (Scheme 2.2.b). For both processes, involvement of a trifluoromethyl radical ($\cdot CF_3$) was proposed, and it was implied that the outcome of the reaction is significantly affected by the methods that are used for generation of the CF_3 radical and oxidation.



Scheme 2.2. Keto-trifluoromethylation of alkenes

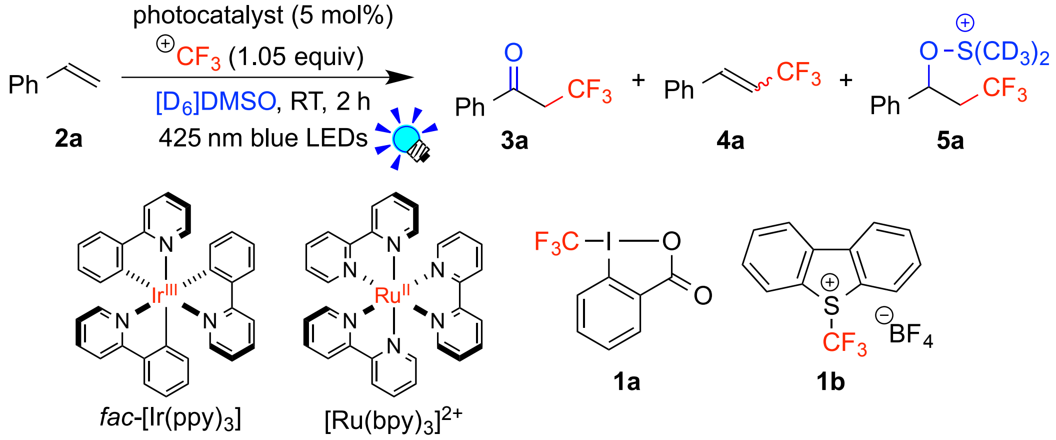
As mentioned in Chapter 1, our group has established the photoredox catalyzed trifluoromethylative difunctionalizations of C=C bonds[11] in the presence of electrophilic trifluoromethylating reagents (**$^+CF_3$**)[12], such as Togni's reagent **1a** and Umemoto's reagent **1b**. In these reactions, a key intermediate is the α-CF_3-substituted carbocation, which is generated from SET photoredox processes and undergoes subsequent nucleophilic attack to produce difunctionalized products. This is a powerful method for difunctionalization of alkenes without isolation of the intermediate. The author hypothesized that combining the photoredox-catalyzed trifluoromethylation and

Kornblum (DMSO) oxidation[13] of the α-CF_3-substituted carbocation would enable development of a facile and new approach to α-trifluoromethylated ketones by keto-trifluoromethylation (Scheme 2.2.c), which is the subject of the present chapter. The author's strategy provides an operationally simple procedure for a highly regioselective and efficient transformation. It has been revealed that an alkoxysulfonium species, which is a well-known intermediate in DMSO oxidation[14], smoothly produces an α-CF_3-sbustituted ketone without treatment with any base under photoredox reaction conditions.

2.2 Optimization of Keto-Trifluoromethylation of Styrene

The author initially examined the photocatalytic reaction of styrene (**2a**) with Togni's reagent **1a** (1.05 equiv) and the iridium photoredox catalyst *fac*-[Ir(ppy)$_3$][15] (5 mol%) in [D_6]DMSO under visible-light irradiation (blue LEDs: λ_{max} = 425 nm) for two hours. To our surprise, the α-CF_3-subsituted ketone **3a** was directly formed in 58% yield together with β-trifluoromethylstyrene (**4a**, 35% yield; entry 1, Table 2.1). When Umemoto's reagent **1b** was used in place of **1a**, a product mixture (**3a**: 59%, **4a**: 22%) similar to that of the reaction with Togni's reagent **1a** (entry 2) was obtained. The ruthenium photoredox catalyst [Ru(bpy)$_3$](PF$_6$)$_2$[16], in contrast, turned out to be sluggish for the present direct keto-trifluoromethylation (entries 3 and 4). The use of Togni's reagent **1a** resulted in low conversion (12%; entry 3). Remarkably, the use of Umemoto's reagent **1b** gave alkoxysulfonium salt **5a** in 76% yield instead of **3a** with concomitant formation of β-trifluoromethylstyrene **4a** in 20% yield (entry 4). When the salt **5a**, which is the key intermediate of the DMSO oxidation[14], was treated with NEt_3, the desired α-CF_3-substituted ketone **3a** was formed in 38% yield (entry 4). For entries 1 and 2, ketone **3a** was formed in the absence of a base, as is the case in the Kornblum oxidation. For confirmation, the author examined the reaction systems using other nucleophiles instead of DMSO (entries 5 and 6). But the combinations of *N*-oxides, 2,6-lutidine *N*-oxide or *N*-methylmorpholine *N*-oxide, with CD_3CN solvent were ineffective. On the basis of these results, the author have developed the direct keto-trifluoromethylation of alkenes using the iridium photocatalyst without addition of a base. Notably, product **3a** was not obtained either in the dark or in the absence of the photocatalyst (entries 5 and 6), strongly supporting that the photoexcited species of the photoredox catalyst plays key roles in the reaction.

Table 2.1. Optimization of the photocatalytic keto-trifluoromethylation of styrene (**2a**)



Entry	CF_3 reagent	Photocatalyst	Yield of **3a** [%][b]	Yield of **4a** [%][b]
1	**1a**	*fac*-[Ir(ppy)$_3$]	58	35
2	**1b**	*fac*-[Ir(ppy)$_3$]	59	22
3	**1a**	[Ru(bpy)$_3$](PF$_6$)$_2$	5	0
4	**1b**	[Ru(bpy)$_3$](PF$_6$)$_2$	76%(**5a**) (38[c])	20
5[d]	**1a**	*fac*-[Ir(ppy)$_3$]	8	0
6[e]	**1a**	*fac*-[Ir(ppy)$_3$]	0	0
7[f]	**1a**	*fac*-[Ir(ppy)$_3$]	0	0
8	**1a**	none	0	0

[a] For detailed reaction conditions, see the Experimental Section.

[b] Yields were determined by ^1H NMR spectroscopy using $SiEt_4$ as an internal standard. [c] The yield after treatment of the product mixture with NEt_3 (10 equiv). [d] 2,6-Lutidine *N*-oxide (2.0 equiv) and CD_3CN were used instead of [D$_6$]DMSO as nucleophile and solvent. [e] *N*-Methylmorpholine *N*-oxide (2.0 equiv) and CD_3CN were used instead of [D$_6$]DMSO. [f] In the dark.

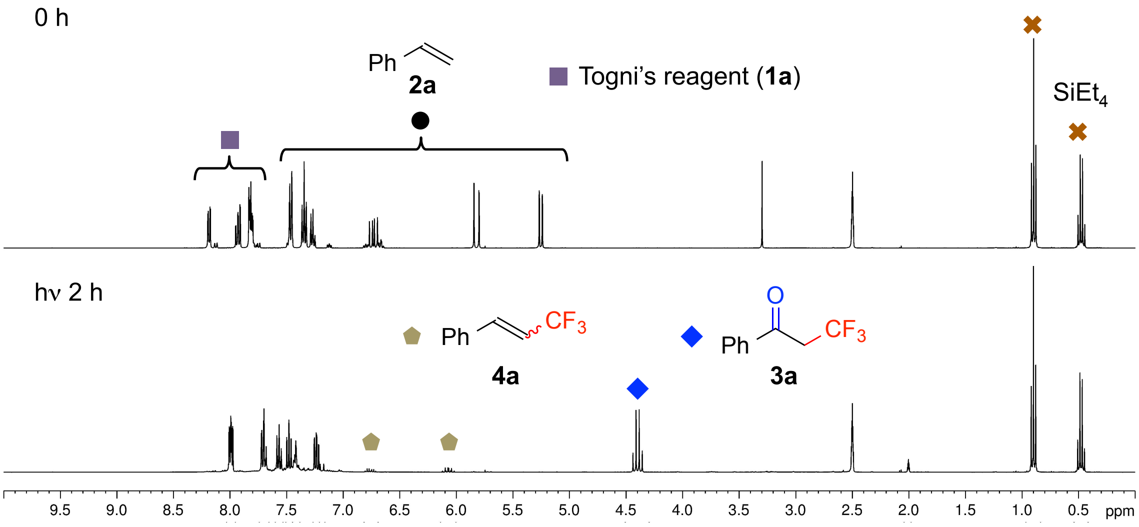


Figure 2.1. ^{1}H NMR spectra (400 MHz, [D$_6$]DMSO, rt) for entry 1 in Table 2.1

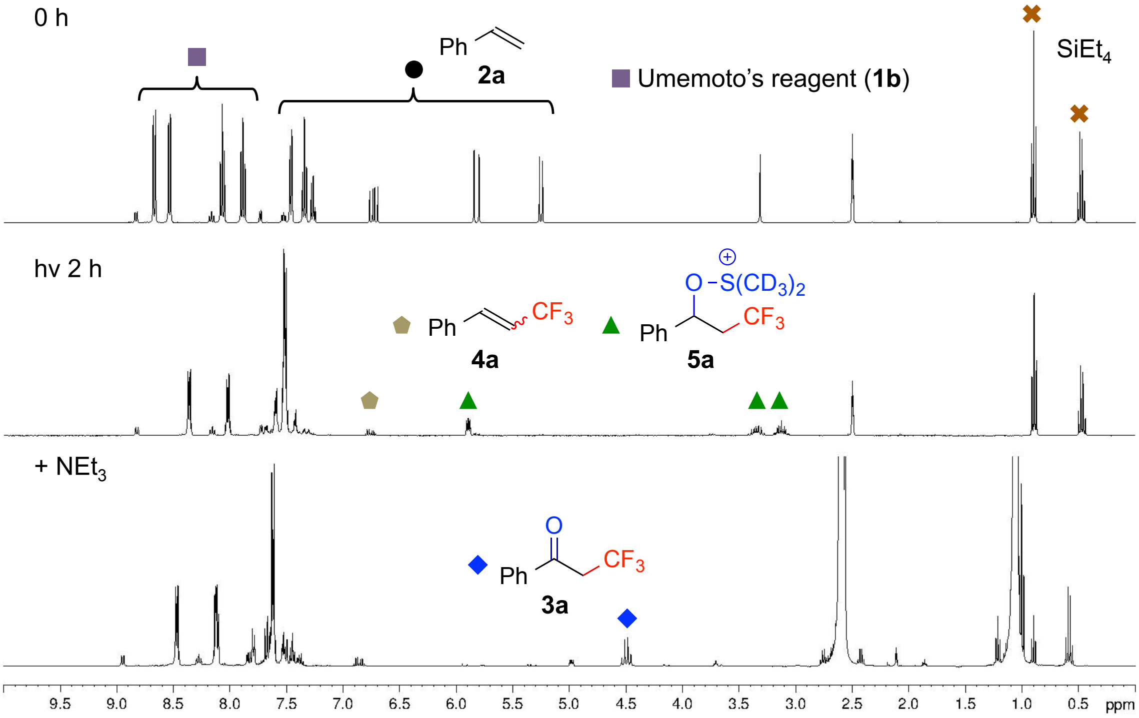


Figure 2.2. ^{1}H NMR spectra (400 MHz, [D$_6$]DMSO, rt) for entry 4 in Table 2.1

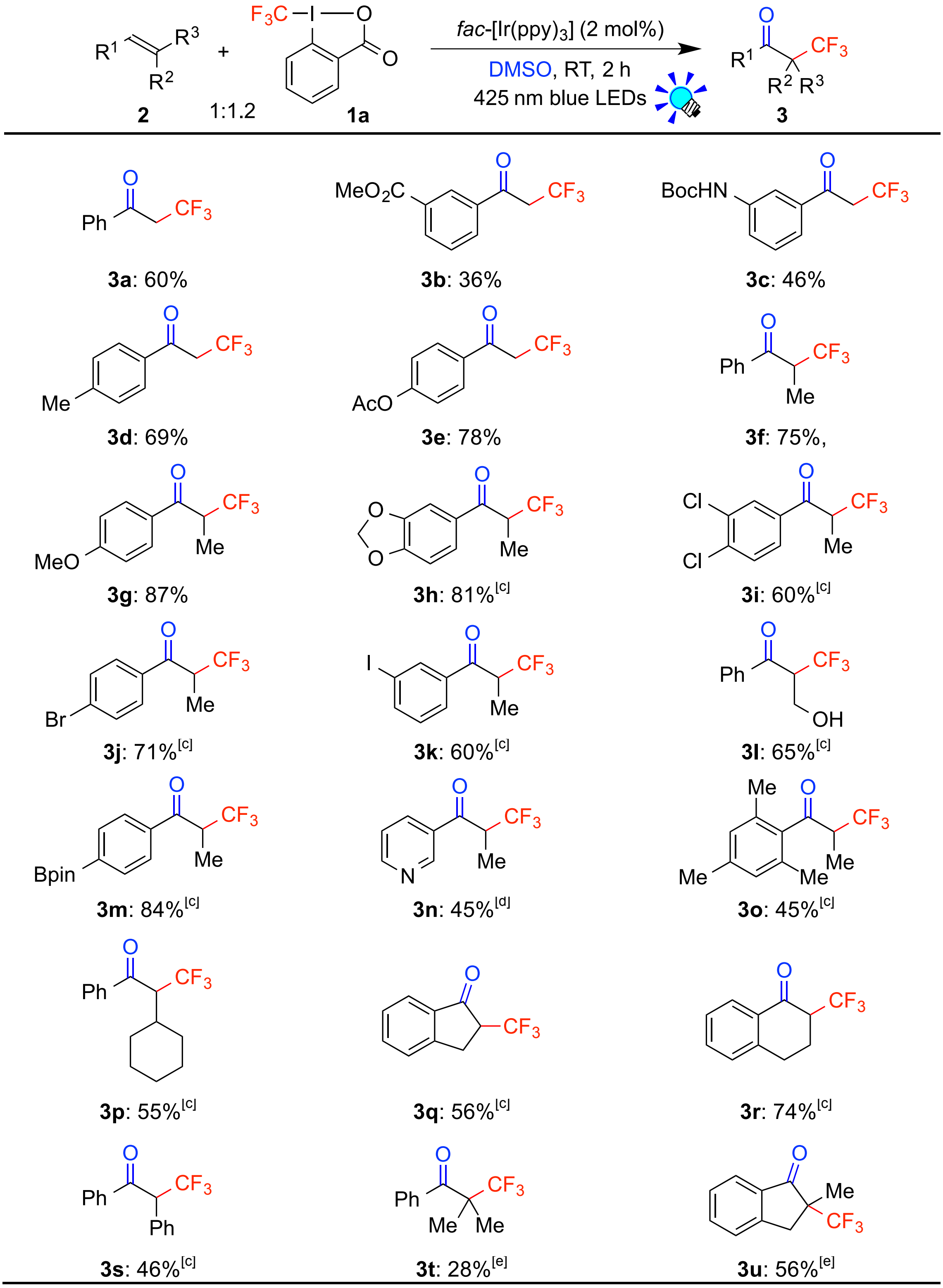
NMR spectra for the reaction course of entries 1 and 4 in Table 2.1 are shown in Figures 2.1 and 2.2. In Figure 2.1, the formation of the CF$_3$-ketone **3a** and the CF$_3$-alkene **4a** with consuming of the substrates **1a** and **2a** is observable after the irradiation of visible light. In Figure 2.2, the formation of the CF$_3$-alkene **4a** and the alkoxysulfonium ion **5a** is observed upon irradiation. Then, addition of NEt_3 caused disappearance of **5a** and formation of **3a**.

2.3 Scope of Substrates for Keto-Trifluoromethylation of Alkenes

The scope of the present photocatalytic keto-trifluoromethylation is summarized in Table 2.2. Styrene (**2a**) and styrene derivatives bearing CO_2Me (**2b**) and NHBoc groups (**2c**; Boc = *tert*-butoxycarbonyl) on the aryl ring produced the α-CF_3-substituted ketones (**3a**–**3c**) in moderate yields (36–60%) with concomitant formation of β-trifluoromethylstyrene derivatives **4**. In contrast, styrenes with electron-donating substituents, such as methyl (**2d**) and acetoxy groups (**2e**), and (*E*)-β-methylstyrene (**2f**) suppressed the formation of the side product **4** to a significant extent. As a result, the corresponding CF_3-substituted ketones were obtained in good yields (**3d**–**f**; 69–78%).

Furthermore, β-methylstyrene derivatives with electron-donating groups on the aromatic ring (**2g** and **2h**) smoothly afforded the corresponding products **3g** and **3h** in a regioselective fashion in 87% and 81% yields, respectively. Halogen (**2i**–**2k**), hydroxy (**2l**), boronic ester (Bpin; **2m**), and pyridyl groups (**2n**) did not hinder the reaction (45–84%). Alkenes with bulky mesityl or cyclohexyl substituents (**2o** and **2p**), cyclic alkenes (**2q** and **2r**), and *trans*-stilbene (**2s**) were also suitable substrates for this transformation (45–74%). Furthermore, the present catalytic system was amenable to the reaction of β-disubstituted alkenes (**2t** and **2u**). The corresponding α-CF_3-substituted ketones which bear a quaternary carbon atom were obtained in 28% and 56% yields, respectively (**3t** and **3u**). The reaction of some alkenes, such as 1-octene and vinylcyclohexane, resulted in an inseparable mixture of products. These results show that aromatic alkenes with a variety of functional groups, such as halogen, ester, acetal, boronic ester, hydroxy, and pyridyl groups, can be applied to the present photocatalytic keto-trifluoromethylation, leading to the corresponding α-CF_3-substituted ketones in a highly regioselective fashion.

Table 2.2. Scope of the photocatalytic keto-trifluoromethylation[a,b]



3a: 60%; **3b**: 36%; **3c**: 46%

3d: 69%; **3e**: 78%; **3f**: 75%,

3g: 87%; **3h**: 81%[c]; **3i**: 60%[c]

3j: 71%[c]; **3k**: 60%[c]; **3l**: 65%[c]

3m: 84%[c]; **3n**: 45%[d]; **3o**: 45%[c]

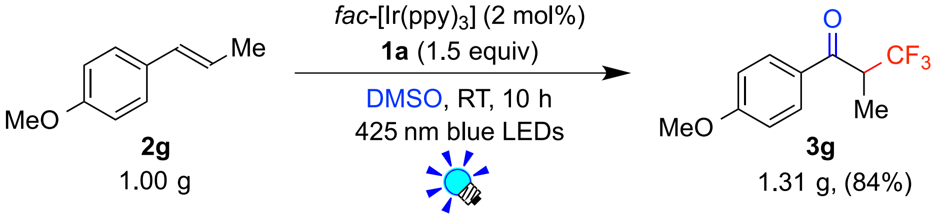
3p: 55%[c]; **3q**: 56%[c]; **3r**: 74%[c]

3s: 46%[c]; **3t**: 28%[e]; **3u**: 56%[e]

[a] For preparative reaction conditions, see the Experimental Section. [b] Isolated yields. [c] 1.30 equiv of **1a** was used. [d] 5 mol% Ir photocatalyst and 1.5 equiv of **1a** were used. [e] Ir photocatalyst (5 mol%), **1a** (2.0 equiv), reaction time = 5 h.

2.4 Gram-Scale Reaction

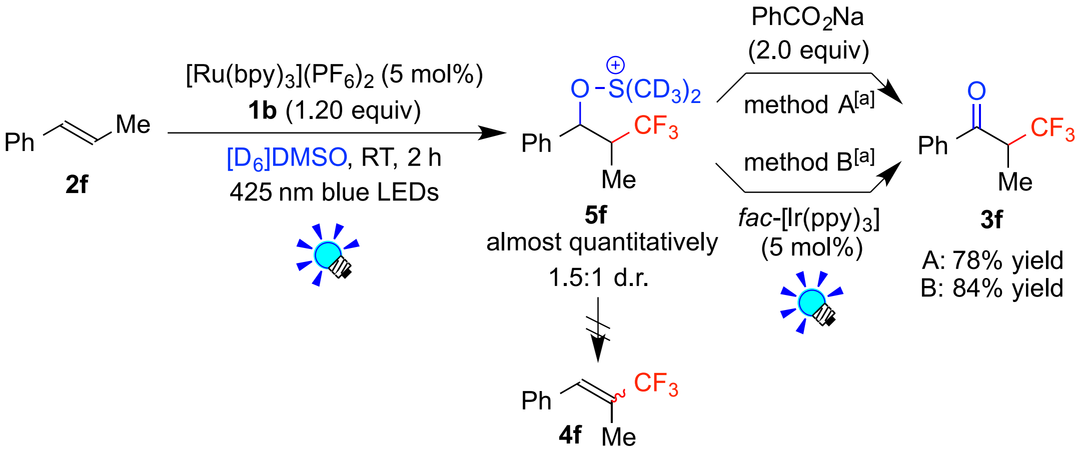
As a demonstration of scalability of the present photocatalytic reaction, the keto-trifluoromethylation of **2g** was carried out on a gram scale. As a result, the reaction proceeded in a way similar to the small scale reaction to give the product **3g** was obtained in 84% yield (1.31 g).



Scheme 2.3. Gram-scale synthesis of **3g.**

2.5 Studies to Obtain Mechanistic Insights

To gain insights into the reaction mechanism, the author conducted some control experiments. As mentioned above, the reaction of (*E*)-β-methylstyrene (**2f**) gave a yield better than that of styrene (**2a**) because formation of CF_3-substituted alkene **4** was suppressed. Therefore, the author conducted the reaction of **2f** with Umemoto's reagent **1b** in the presence of $[Ru(bpy)_3](PF_6)_2$ (5 mol%). As a result, quantitative formation of a diastereomeric mixture of alkoxysulfonium salt **5f** was observed by NMR spectroscopy (Scheme 2.4 and Figure 2.3). In light of these results, side product **4** is presumably formed prior to the formation of **5**. Subsequent treatment of **5f** with sodium benzoate (2.0 equiv; method A) or further photoreaction with addition of *fac*-[Ir(ppy)$_3$] (5 mol%; method B) provided **3f** in 78% and 84% yield, respectively (yields determined by NMR spectroscopy; Scheme 2.4, Figure 2.4 and 2.5). These results suggest that the action of benzoate or the iridium photocatalysis induces the formation of the corresponding ketones **3** from the alkoxysulfonium intermediate **5**. It is noteworthy that, for method A, the quintet ^{1}H NMR signal was observed around 2 ppm, whereas for method B, such a signal was not detected (Figures 2.4 and 2.5). The characteristic quintet signal was assigned to deuterated dimethylsulfide containing one proton, CHD_2SCD_3, and resulted from coupling with two D nuclei (I = 1).



Method A: Sodium benzoate (2 equiv) was added at RT, and the reaction mixture was left for 2 h. Method B: *fac*-[Ir(ppy)$_3$] (5 mol%) was added, and the reaction mixture was irradiated with visible light (425 nm blue LEDs) at RT for 1h.

Scheme 2.4. Control experiments.

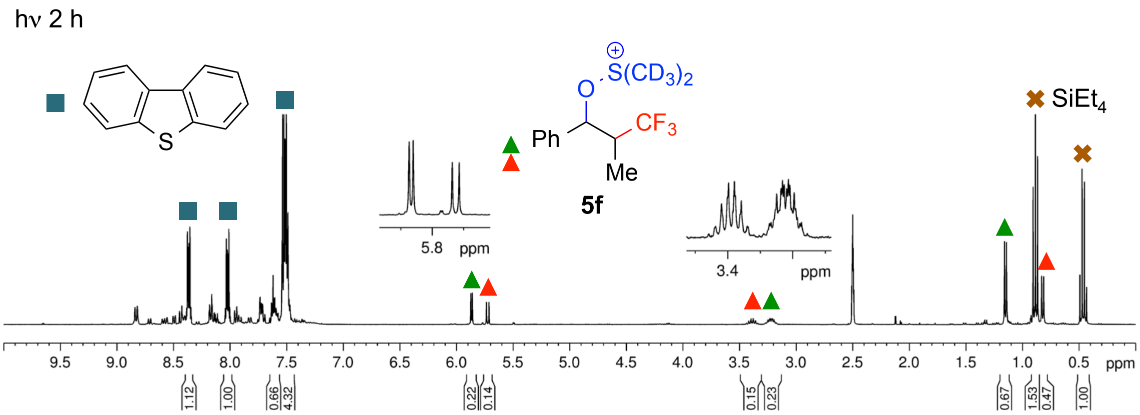


Figure 2.3. ^{1}H NMR spectrum (400 MHz, [D$_6$]DMSO, rt) for a reaction mixture containing **5f**

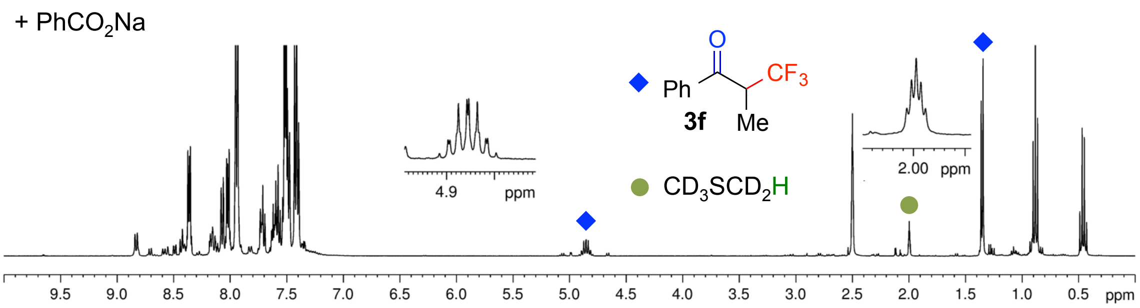


Figure 2.4. ^{1}H NMR spectrum (400 MHz, [D$_6$]DMSO, rt) for a sample after the treatment with $PhCO_2Na$

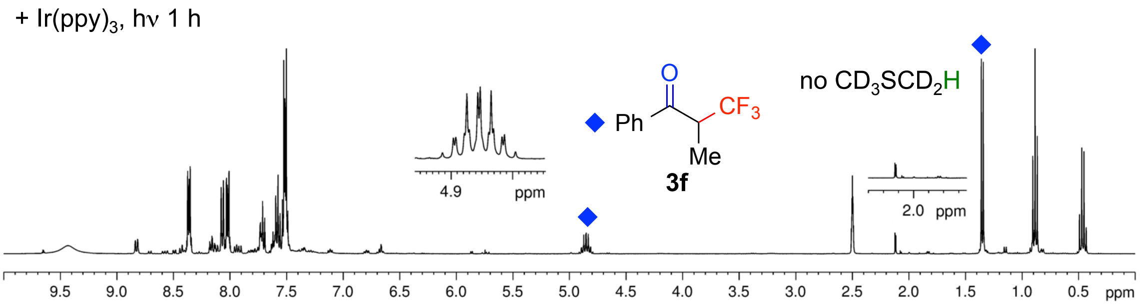
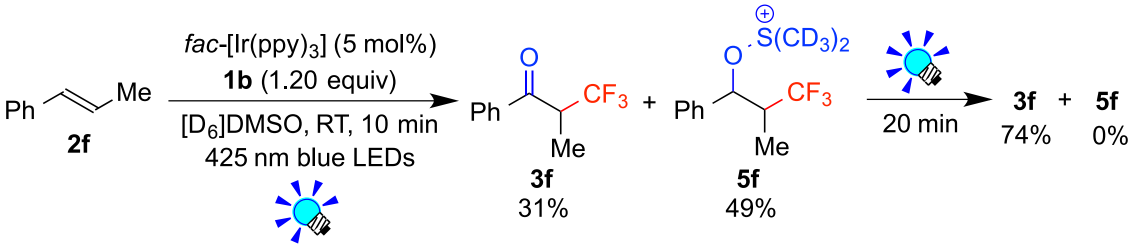


Figure 2.5. ^{1}H NMR spectrum (400 MHz, [D$_6$]DMSO, rt) for a sample after the further photoreaction with the Ir catalyst

When *fac*-[Ir(ppy)$_3$] (5 mol%) was added in the beginning of the reaction, a product mixture of **3f** (31% NMR yield) and **5f** (49% NMR yield) was obtained after ten minutes, and further irradiation (30 min) caused the formation of **3f** in 74% yield as a sole product (Scheme 2.6 and Figure 2.6).



Scheme 2.5. A time course experiment

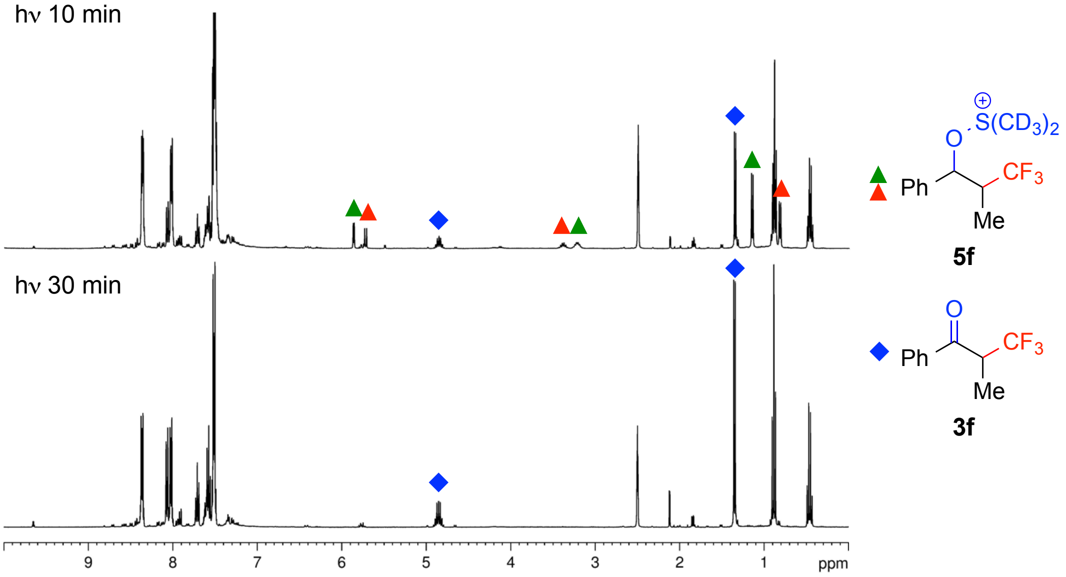
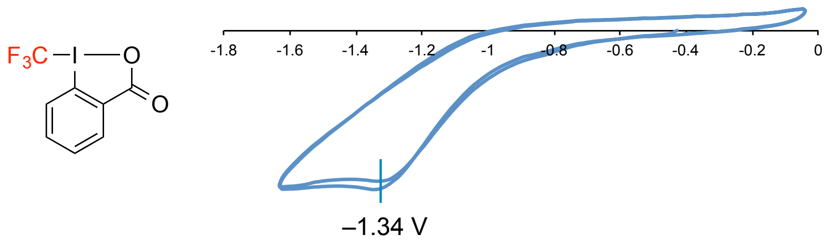


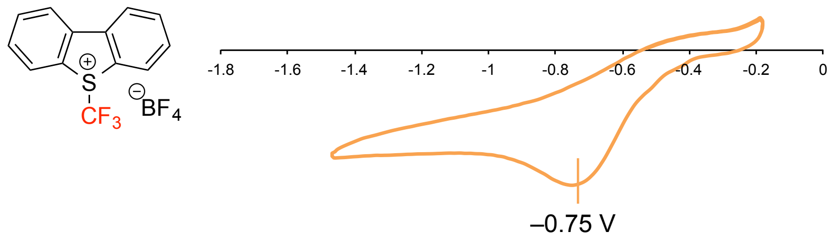
Figure 2.6. ^{1}H NMR spectra (400 MHz, [D$_6$]DMSO, rt) for the time course experiment

Cyclic voltammograms for Togni's reagent **1a** and Umemoto's reagent **1b** exhibited broad irreversible reduction waves at –1.34 V and –0.75 V (vs. [Cp$_2$Fe] in MeCN; Cp = cyclopentadienyl), respectively (Figures 2.7.a and b). The experimental results shown in Table 2.1 can be explained by these results as follows: the photoexcited *fac*-[Ir(ppy)$_3$] can easily reduce both **1a** and **1b**, while the photoexcited [Ru(bpy)$_3$]$^{2+}$ can easily reduce **1b** but not **1a**.[15,16] In addition, a cyclic voltammogram for the alkoxysulfonium salt **5f** exhibited a broad irreversible reduction wave at –1.07 V (Figure 2.7.c), which is close to the reduction potential of the photoexcited $[Ru(bpy)_3]^{2+}$, indicating that **5f** cannot be easily reduced by the photoexcited $[Ru(bpy)_3]^{2+}$, but only by the photoexcited *fac*-$[Ir(ppy)_3]$.

(a) CV of Togni's reagent (**1a**)



(b) CV of Umemoto's reagent (**1b**)



(c) CV of alkoxysulfonium intermediate (**5f**)

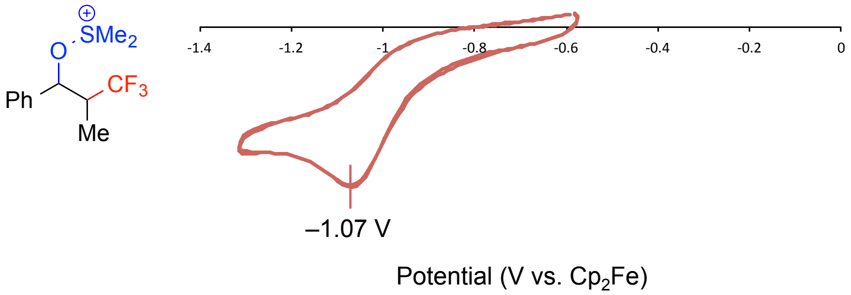


Figure 2.7. Cyclic voltammograms for **1a**, **1b** and **5f**

Furthermore, luminescence quenching experiments also gave insight for understanding the present photocatalytic reaction (Figure 2.8). Emission from the excited *fac*-$[Ir(ppy)_3]$ was efficiently quenched by the CF_3 reagents **1a** and **1b**. However, styrene (**2a**) could not quench the emission. These results support that the excited photocatalyst first undergo SET process with the trifluoromethylating reagent **1a** or **1b**.

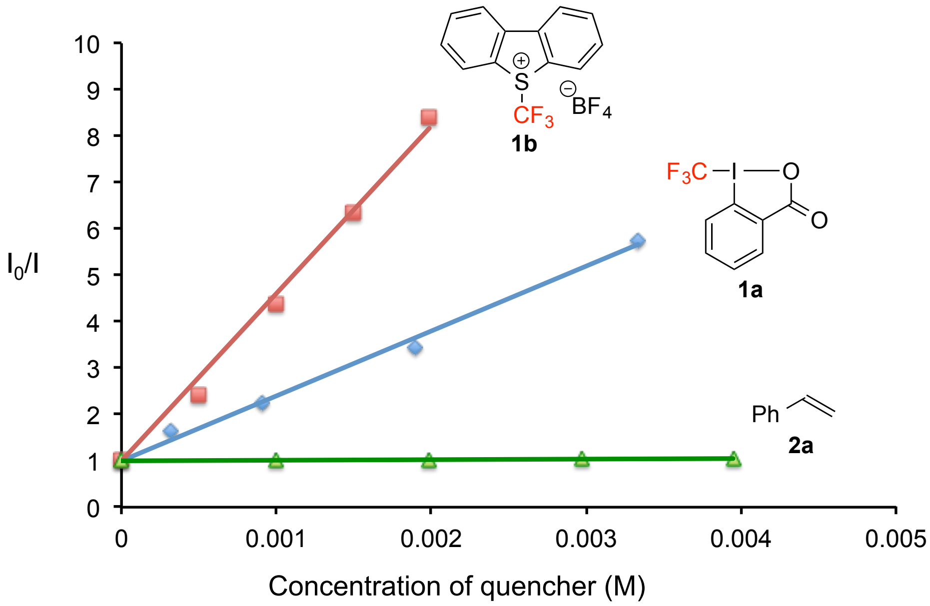
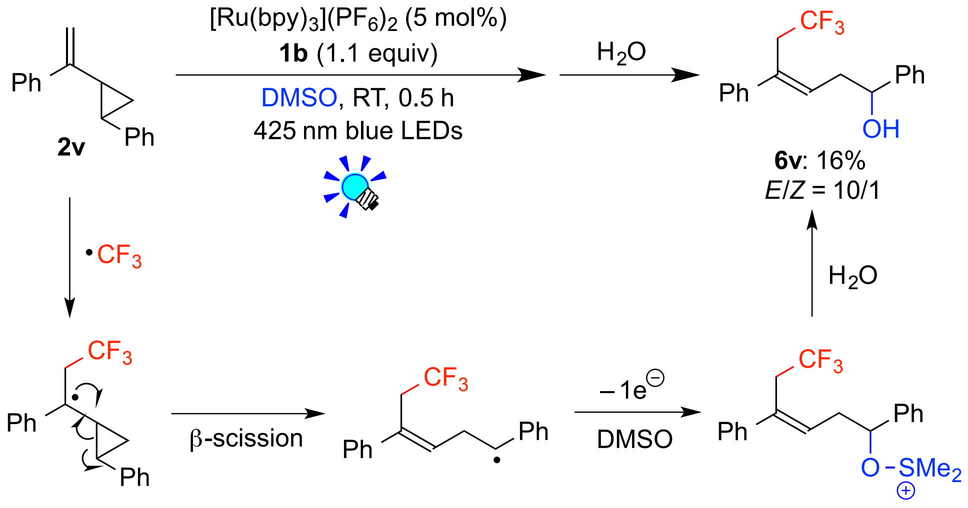


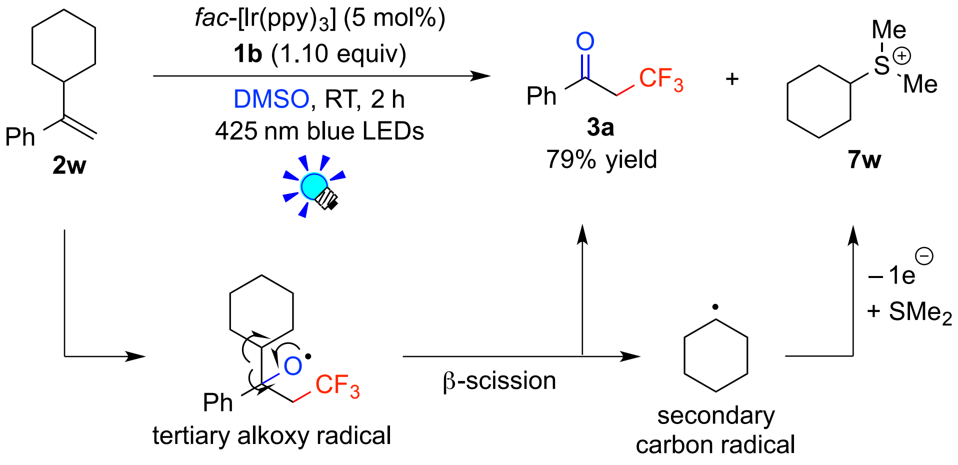
Figure 2.8. Stern-Volmer plots for **1a**, **1b** and **2a** with *fac*-[Ir(ppy)$_3$]

Next, the author examined the reaction of 1-phenyl-2-(1-phenylethenyl)cyclopropane (**2v**) with Umemoto's reagent **1b** in the presence of [Ru(bpy)$_3$](PF$_6$)$_2$ catalyst (Scheme 2.6). As a result, the photoreaction followed by work up with water afforded the trifluoromethylated alcohol **6v** in 16% isolated yield through a ring-opening process of the cyclopropane unit. This result suggests that radical intermediate is involved in the present photocatalytic reaction.



Scheme 2.6. Radical clock experiment

Furthermore, to our surprise, the reaction of α-substituted styrene derivatives, α-cyclohexylstyrene (**2w**) and α-methylstyrene (**2x**), with Umemoto's reagent **1b** afforded **3a** in 79% and 44% yield, respectively, resulting from a C–C bond cleavage process. In the case of the reaction of **2w**, the eliminated alkyl group was detected as the cyclohexyldimethylsulfonium salt **7w** (Scheme 2.6 and Figure 2.9). These remarkable C–C bond cleavage processes likely stem from β-scission of the tertiary alkoxy radical intermediate. These results suggest that photoredox catalysis is playing two crucial roles in the present photocatalytic keto-trifluoromethylation: 1) formation of the α-CF_3-substituted carbocation intermediate,[11] and 2) formation of the reactive alkoxy radical intermediate from the alkoxysulfonium intermediate **5**.



Scheme 2.7. Reaction of α-cyclohexylstyrene

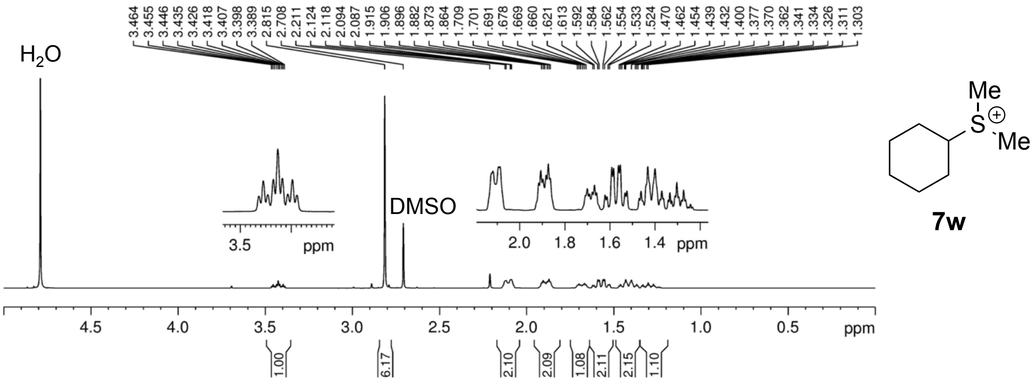
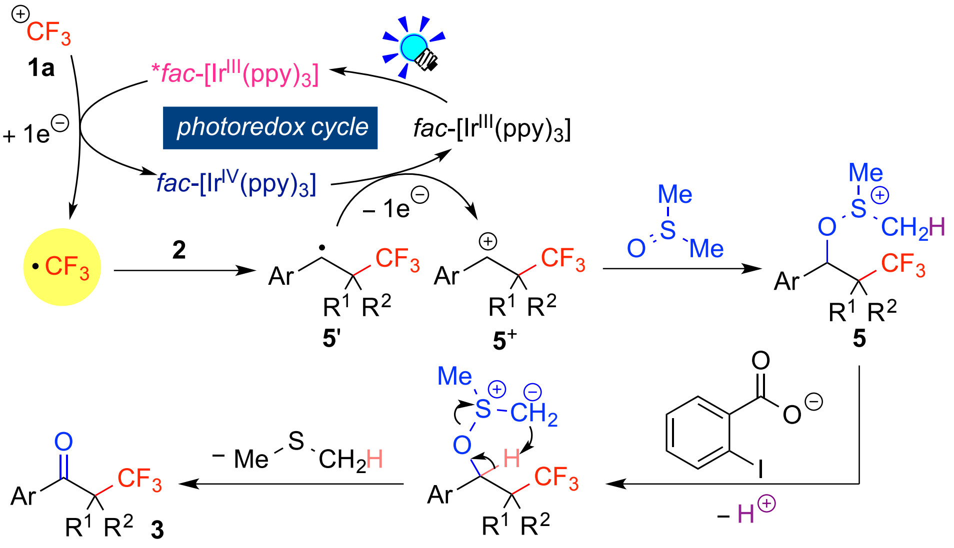


Figure 2.9. ^1H NMR (400 MHz, D_2O, rt) of **7w**

2.6 Plausible Reaction Mechanisms

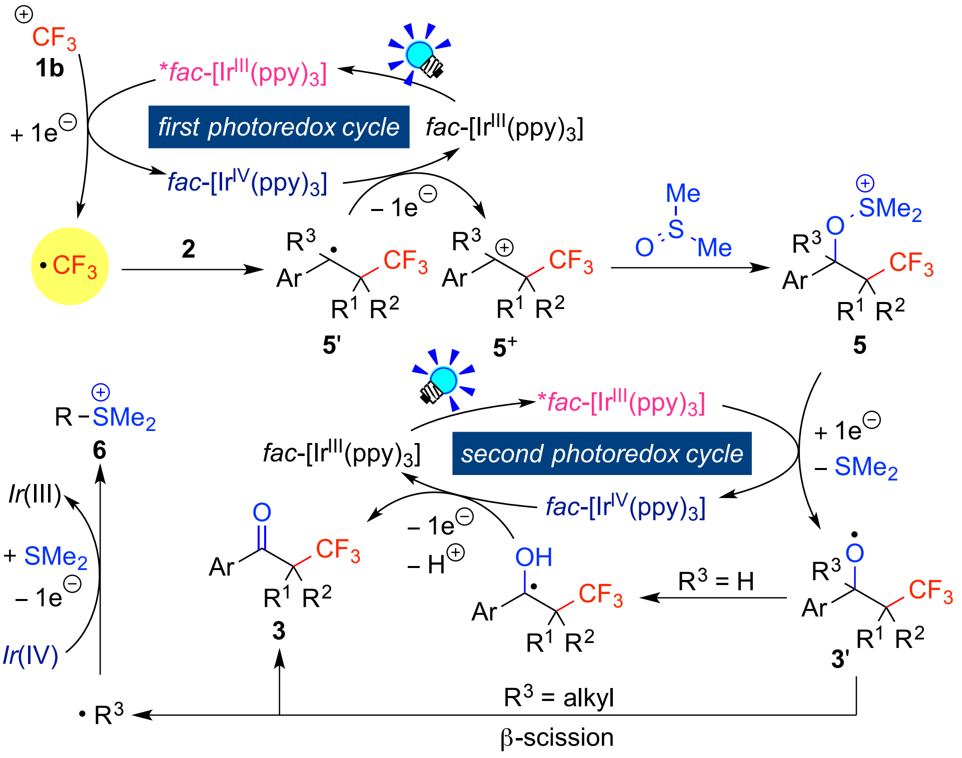
On the basis of these results, the author proposes two possible reaction mechanisms for the combined photoredox-catalyzed trifluoromethylation and oxidation of styrenes with DMSO (Scheme 2.7 and 2.8). First, when Togni's reagent **1a** is used, the photo-excited Ir catalyst, **fac*-[Ir(ppy)$_3$], undergoes SET reduction of the electrophilic trifluoromethylating reagent ($^{+}$**CF$_3$**) **1** to generate the CF$_3$ radical ($\cdot$CF$_3$), accompanied by formation of the strongly oxidizing *fac*-[Ir^{IV}(ppy)$_3$]$^{+}$ species. Addition of the CF$_3$ radical to alkene **2** proceeds regioselectively to form stabilized benzyl radical type intermediate **5'**. A second SET oxidation event from **5'** to *fac*-[Ir^{IV}(ppy)$_3$]$^{+}$ affords the *fac*-[Ir^{III}(ppy)$_3$] ground state, together with the α-CF$_3$-substituted carbocationic intermediate **5**$^{+}$. Nucleophilic attack of DMSO at **5**$^{+}$ affords alkoxysulfonium intermediate **5**. Then, *o*-iodobenzoate, which is the byproduct of the reduction of **1a**, should serve as the base. The reaction is similar to Kornblum oxidation to abstract an α-proton of a methyl group in **5** to give product **3** (Scheme 2.8).[17]



Scheme 2.8. A Plausible reaction mechanism using Togni's reagent **1a**

On the other hand, when Umemoto's reagent **1b** is used, similar processes occur up to the stage of the formation of **5**. The resultant strong reducing agent **fac*-[Ir(ppy)$_3$]

reduces **5**, leading to the formation of alkoxy radical **3'**. Subsequent SET oxidation followed by 1,2-hydrogen atom shift[18] or β-scission of the alkoxy radical **3'** furnishes the product **3** (Scheme 2.9). In the reactions of **2w** and **2x**, the alkyl groups (R) cannot be removed with the action of a base. This observation is therefore regarded as unequivocal evidence for the hypothesis that, at least, in the case of α-substituted styrene derivatives, the photoredox mechanism is operating for the conversion of **5** into **3** via **3'**.

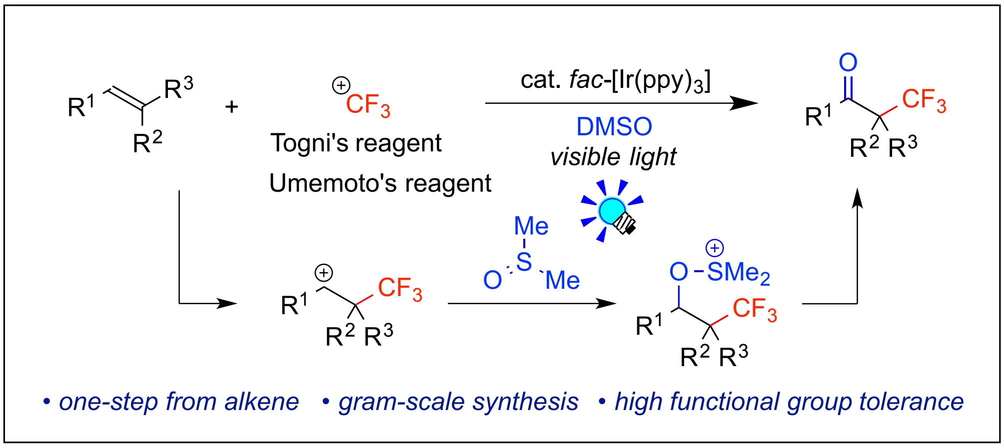


Scheme 2.9. Plausible reaction mechanism using Umemoto's reagent **1b**

2.7 Conclusion

In conclusion, the author has developed a new method for the synthesis of α-CF_3-substituted carbonyl compounds by combining photoredox-catalyzed trifluoromethylation and oxidation mediated by an alkoxysulfonium ion. The iridium photocatalyst, *fac*-[Ir(ppy)$_3$], which is a strong reducing agent, plays key roles in achieving the direct keto-trifluoromethylation of a C=C bond in a regioselective manner.

General synthetic methods for α-CF_3-ketones from carbonyl compounds require preparation of activated carbonyl groups in advance of trifluoromethylation. The present reaction can produce the α-CF_3-ketones in one-step from alkenes. In addition, the present method can be applied to alkenes with a wide variety of functional groups.



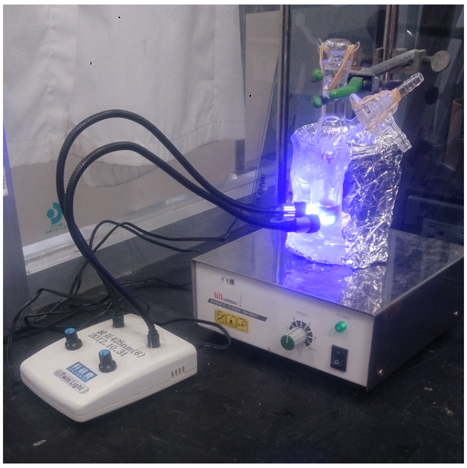
2.8 Experimental

Material and Methods

$[Ru(bpy)_3](PF_6)_2$[19a] and *fac*-$[Ir(ppy)_3]$[19b] were prepared according to the literature procedures. Togni's reagent **1a** was purchased from TCI. Umemoto's reagent **1b** was purchased from Aldrich. Alkenes **2b** and **2c** were prepared according to the literature procedures.[20a] Alkenes **2i**, **2j**, **2k**, **2m**, **2n**, **2o**, **2p**, **2v** and **2w** were prepared by Wittig reactions. Other alkenes were purchased and used as received. DMSO (super dehydrated grade) was purchased from Wako. $[D_6]$DMSO was dried over molecular sieve 4A, degassed and stored under N_2. Photocatalytic reactions were performed under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. Thin-layer chromatography was performed on Merck TLC plate with 60 F_{254}. Flash column chromatography was performed on silica gel 60N from Kanto Kagaku. Visible light irradiation was performed with Relyon LED lamp (3 W x 2; λ_{max} = 425 ± 15 nm). The NMR spectra were acquired on a Bruker AVANCE-400 spectrometer (400 MHz). NMR chemical shifts were referenced to the residual protio impurities in the deuterated solvents. ^{19}F NMR chemical shifts were referenced to external trifluoroacetic acid (–76.55 ppm in $CDCl_3$). HRMS spectra (ESI-TOF Mass spectra and EI Mass spectra) were obtained with Bruker micrOTOF II and JEOL JMS-700 mass spectrometers at Material Analysis Suzukake-dai Center, Technical Department, Tokyo Institute of Technology. Electrochemical measurements were recorded on a Hokutodenkou HZ-5000 analyzer (observed in 0.001 M MeCN; $[NBu_4PF_6]$ = 0.1 M; Ag/AgCl = electrode; reported with respect to the $[FeCp_2]/[FeCp_2]^+$ couple). Emission spectra were recorded on a SHIMADZU RF-5300PC spectrometer.

Reaction apparatus

Irradiation of visible light was performed with a Relyon LED lamp (3 W x 2; λ_{max} = 425 nm).



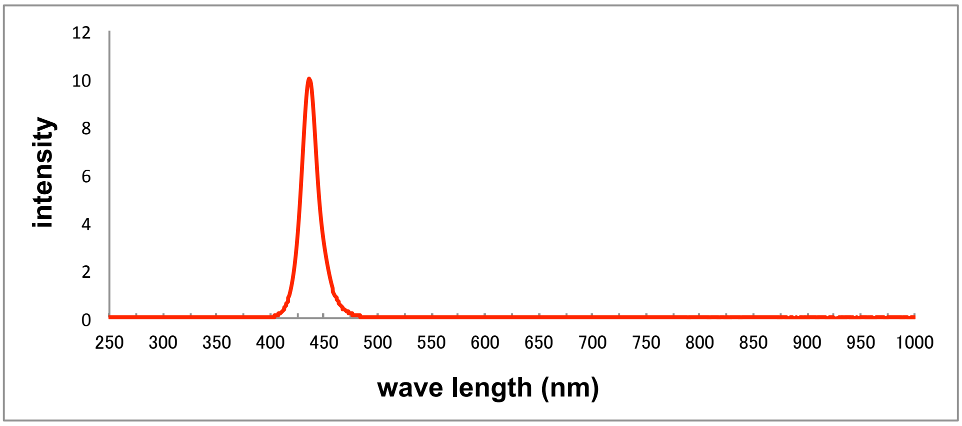
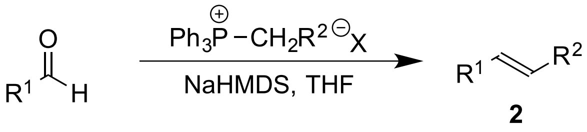


Figure 2.10. The emission spectrum of a Relyon LED lamp

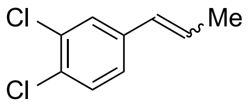
Synthesis of Substrates

General procedures for the synthesis of alkenes (2i, 2j, 2k, 2m, 2n, 2o, 2p, and 2w) by Wittig reaction



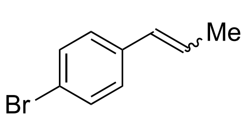
Under N_2, a two-neck 100 mL round-bottom flask was charged with an appropriate alkyl triphenyphosphonium salt (6 mmol) and dry THF (25 mL). Then sodium hexamethyldisilazide (1 M THF solution, 6 mL) was added into the solution and the resultant mixture was stirred at room temperature for 1 h. To the solution, carbonyl compound (5 mmol) was added and stirred at room temperature overnight. Et_2O was added into the reaction mixture, which was then filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to afford the product.

1-(3,4-Dichlorophenyl)propene (*E*/*Z* = 1/1) (2i)



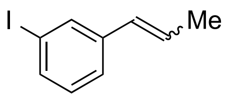
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.40–7.33 (m, 2H; Ar), 7.15–7.10 (m, 1H; Ar), 6.34–6.19 (m, 2H; ArC*H*=CH, CH=C*H*CH_3 in *E*-isomer), 5.85 (dq, *J* = 12, 7.2 Hz, 1H; CH=C*H*CH_3 in *Z*-isomer), 1.89–1.86 (m, 3H; CHC*H*$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 138.2, 137.8, 132.7, 132.3, 130.7, 130.5, 130.2, 129.0, 128.9, 128.3, 128.1, 127.8, 127.7, 125.2, 18.5, 14.7. **HRMS** (EI): calculated for $[C_9H_8Cl_2]^+$ requires 186.0003, found 186.0001.

1-(4-Bromophenyl)propene (*E*/*Z* = 1/1.9) (2j)



^{1}H NMR (400 MHz, $CDCl_3$, rt): *E*-isomer: δ 7.40 (d, *J* = 8.4 Hz, 2H; Ar), 7.18 (d, *J* = 10 Hz, 2H; Ar), 6.38–6.32 (m, 1H; ArC*H*=CH), 6.23 (dq, *J* = 16, 6.4 Hz, 1H; CH=C*H*CH_3), 1.87 (m, 3 H; CHC*H*$_3$); *Z*-isomer: δ 7.45 (d, *J* = 8.4 Hz, 2H; Ar), 7.16 (d, *J* = 8.4 Hz, 2H; Ar), 6.38–6.32 (m, 1H; ArC*H*=CH), 5.82 (dq, *J* = 12, 7.2 Hz, 1H; CH=C*H*CH_3), 1.87 (m, 3 H; CHC*H*$_3$). Spectral data were in agreement with the data reported in the literature.[20b]

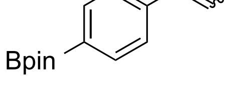
1-(3-Iodophenyl)propene (*E*/*Z* = 1/3.3) (2k)



E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.68 (s, 1H; Ar), 7.51 (d, *J* = 8.0 Hz, 1H; Ar), 7.28–7.24 (m, 1H; Ar), 7.01 (dd, *J* = 8.0, 8.0 Hz, 1H; Ar), 6.29 (d, *J* = 16 Hz, 1H; ArC*H*=CH), 6.22 (dq, *J* = 16, 6.0 Hz, 1H; CH=C*H*CH_3), 1.89–1.87 (m, 3H; CHC*H*$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 140.4, 135.7, 134.9, 130.2, 129.8, 127.5, 125.2, 94.8, 18.6.

Z-isomer: δ 7.64 (s, 1H; Ar), 7.55 (d, *J* = 7.6 Hz, 1H; Ar), 7.28–7.24 (m, 1H; Ar), 7.07 (dd, *J* = 8.0, 8.0 Hz, 1H; Ar), 6.34 (d, *J* = 12 Hz, 1H; ArC*H*=CH), 5.83 (dq, *J* = 12, 7.2 Hz, 1H; CH=C*H*CH_3), 1.89–1.87 (m, 3H; CHC*H*$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 139.9, 137.8, 135.5, 129.9, 128.6, 128.3, 128.1, 94.3, 14.7. **HRMS** (EI): calculated for $[C_9H_9I]^+$ requires 243.9749, found 243.9749.

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propene (*E*/*Z* = 1/3.3) (2m)

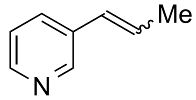


E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.73 (d, *J* = 8.0 Hz, 2H; Ar), 7.32 (d, *J* = 8.4 Hz, 2H; Ar), 6.41 (d, *J* = 15 Hz, 1H; ArC*H*=CH), 6.31 (dq, *J* = 16, 6.4 Hz, 1H; CH=C*H*CH_3), 1.89

(dd, *J* = 6.4, 1.2 Hz, 3H; CHC*H*$_3$), 1.34 (s, 12H; C(C*H*$_3$)$_2$). **^{13}C NMR** (100 MHz, CDCl$_3$, rt): δ 140.7, 135.0, 131.2, 126.8, 125.2, 83.6, 24.7, 18.5.

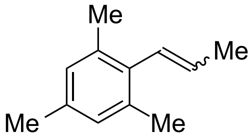
Z-isomer: **^{1}H NMR** (400 MHz, CDCl$_3$, rt): δ 7.78 (d, *J* = 8.0 Hz, 2H; Ar), 7.30 (d, *J* = 8.0 Hz, 2H; Ar), 6.44 (d, *J* = 12 Hz, 1H; ArC*H*=CH), 5.82 (dq, *J* = 12, 7.2 Hz, 1H; CH=C*H*CH$_3$), 1.90 (dd, *J* = 7.2, 2.0 Hz, 3H; CHC*H*$_3$), 1.35 (s, 12H; C(C*H*$_3$)$_2$). **^{13}C NMR** (100 MHz, CDCl$_3$, rt): δ 140.5, 134.6, 130.0, 128.1, 127.6, 83.7, 24.7, 14.6. **HRMS** (ESI-TOF): calculated for [$C_{15}H_{21}BO_2$+Na]$^+$ requires 267.1530, found 267.1526.

3-(1-Propenyl)pyridine (*E*/*Z* = 1/3.2) (2n)



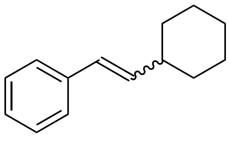
^{1}H NMR (400 MHz, CDCl$_3$, rt): *E*-isomer: δ 8.54 (s, 1H; Ar), 8.41 (dd, *J* = 4.8, 1.6 Hz, 1H; Ar), 7.63 (dt, *J* = 8.0, 2.0 Hz, 1H; Ar), 7.22–7.18 (m, 1H; Ar), 6.40–6.35 (m, 1H; ArC*H*=CH), 6.30 (dq, *J* = 16, 6.4 Hz, 1H; CH=C*H*CH$_3$), 1.91–1.88 (m, 3H; CHC*H*$_3$); *Z*-isomer: δ 8.54 (s, 1H; Ar), 8.44 (dd, *J* = 4.8, 1.6 Hz, 1H; Ar), 7.59 (dt, *J* = 8.0, 2.0 Hz, 1H; Ar), 7.27–7.24 (m, 1H; Ar), 6.40–6.35 (m, 1H; ArC*H*=CH), 5.92 (dq, *J* = 12, 7.2 Hz, 1H; CH=C*H*CH$_3$), 1.91–1.88 (m, 3H; CHC*H*$_3$). Spectral data were in agreement with the data reported in the literature.[20c]

1-Mesitylpropene (*E*/*Z* = 1.1/1) (2o)



^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 6.87 (s, 1H; Ar), 6.86 (s, 1H; Ar), 6.32 (d, *J* = 15 Hz, 1H; ArC*H*=CH in *Z*-isomer), 6.28 (d, *J* = 10 Hz, 1H; ArC*H*=CH in *E*-isomer), 5.82 (dq, *J* = 11, 6.8 Hz, 1H; ArC*H*=CH in *Z*-isomer), 5.67 (dq, *J* = 16, 6.4 Hz, 1H; ArC*H*=CH in *E*-isomer), 2.29 (s, 3H; ArC*H*$_3$), 2.26 (s, 3H; ArC*H*$_3$), 2.26 (s, 6H; ArC*H*$_3$), 2.17 (s, 6H; ArC*H*$_3$), 1.90 (dd, *J* = 6.4, 2.0 Hz, 3H; CHC*H*$_3$), 1.46 (dd, *J* = 6.4, 1.6 Hz, 3H; CHC*H*$_3$). Spectral data were in agreement with the data reported in the literature.[20d]

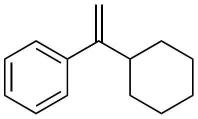
(2-Cyclohexylvinyl)benzene (*E*/*Z* = 6.7/1) (2p)



^{1}H NMR (400 MHz, CDCl$_3$, rt): *E*-isomer: δ 7.36–7.16 (m, 5H; Ar), 6.35 (d, *J* = 16 Hz, 1H; ArC*H*=CH), 6.18 (dd, *J* = 16, 6.8 Hz, 1H; C*H*Cy), 2.17-2.09 (m, 1H; Cy), 1.83–1.67 (m, 5H; Cy), 1.38–1.13 (m, 5H; Cy); *Z*-isomer: δ 7.36–7.16 (m, 5H; Ar), 6.31 (d, *J* =

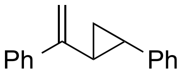
11 Hz, 1H; ArC*H*=CH), 5.49 (dd, *J* = 12, 10.4 Hz, 1H; C*H*Cy), 2.62–2.54 (m, 1H; Cy), 1.83–1.67 (m, 5H; Cy), 1.38–1.13 (m, 5H; Cy). Spectral data were in agreement with the data reported in the literature.[20e]

(1-Cyclohexylvinyl)benzene (2w)



^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.35–7.24 (m, 5H; Ar), 5.14 (s, 1H; C=C*H*H), 5.01 (s, 1H; C=CH*H*), 2.43 (t, *J* = 12 Hz, 1H; Cy), 1.86–1.70 (m, 5H; Cy), 1.39–1.25 (m, 5H; Cy). Spectral data were in agreement with the data reported in the literature.[20f]

1-Phenyl-1-(*trans*-2-phenylcyclopropyl)ethene (2w)



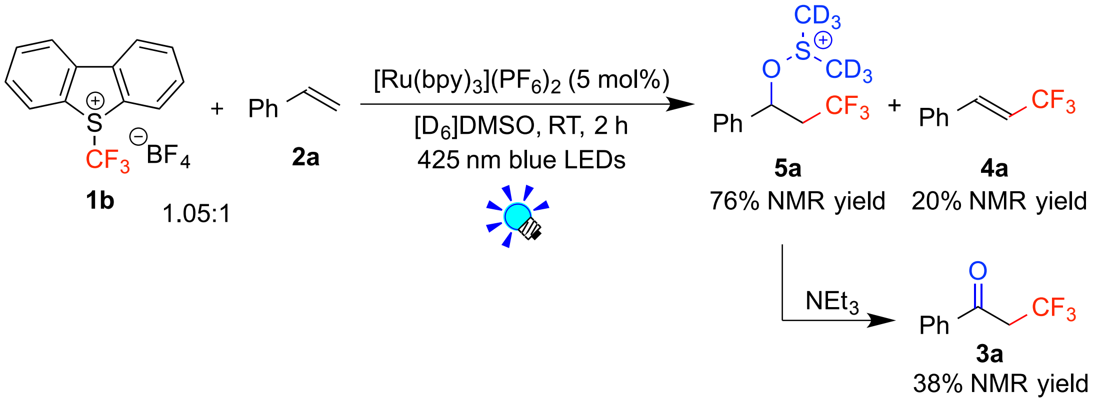
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.53 (dd, *J* = 8.2, 1.4 Hz, 2H; Ph), 7.33–7.25 (m, 5H; Ph), 7.22–7.16 (m, 2H; Ph), 5.38 (s, 1H; C=C*H*H), 5.06 (s, 1H; C=CH*H*), 2.05–1.95 (m, 2H; PhC*H*C*H*), 1.45 (m, PhCHC*H*H), 1.31 (m, 1H; PhCHCH*H*). Spectral data were in agreement with the data reported in the literature.[20g]

NMR experimental procedures and NMR spectra (Table 2.1)

The reaction using *fac*-[Ir(ppy)$_3$] catalyst and Togni's reagent 1a (entry 1 in Table 2.1)

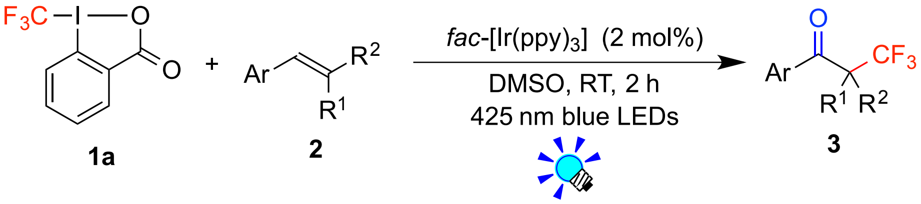
Under N_2, *fac*-[Ir(ppy)$_3$] (0.8 mg, 1 μmol), Togni's reagent **1a** (8.2 mg, 26 μmol), styrene (**2a**) (2.9 μL, 25 μmol), $SiEt_4$ (~1 μL; an internal standard), dry [D_6]DMSO (0.5 mL) were added to an NMR tube. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h at room temperature (in a water bath). The yields of the products were determined by ^{1}H NMR spectroscopy.

One-pot synthesis of 3a through treatment of 5a with NEt_3 (Entry 4 in Table 2.1)



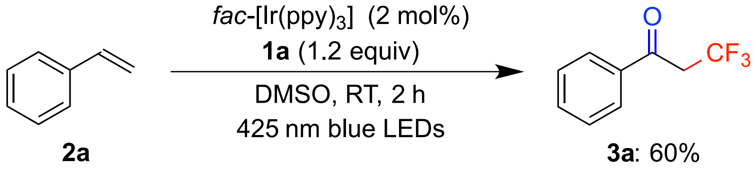
Under N_2, $[Ru(bpy)_3](PF_6)_2$ (1.1 mg, 1.3 µmol), Umemoto's reagent **1b** (8.8 mg, 26 µmol), styrene (**2a**) (2.9 µL, 25 µmol), $SiEt_4$ (~1 µL; an internal standard, dry $[D_6]DMSO$ (0.5 mL) were added to an NMR tube. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated at room temperature (in a water bath). After 2 h, NEt_3 (35 µL, 0.25 mmol) was added to the reaction mixture. The yields were determined by ^1H NMR spectroscopy.

General procedures for the keto-trifluoromethylation of alkenes (Table 2)



A 20 mL Schlenk tube was charged with *fac*-$[Ir(ppy)_3]$ (3.3 mg, 5 µmol), Togni's reagent (**1a**) (95 mg, 0.3 mmol), alkenes **2** (0.25 mmol) and dry DMSO (2.5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After of the reaction, aq. $NaHCO_3$ was added to the reaction mixture, and products were extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to afford keto-trifluoromethylated product **3**.

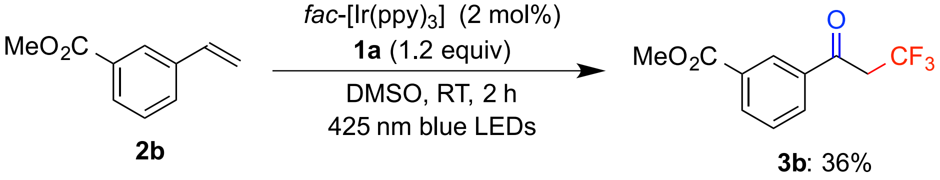
3,3,3-Trifluoro-1-phenylpropan-1-one (3a)



Following the general procedure, the title compound was synthesized from styrene (**2a**) (29 μL, 0.25 mmol). The product mixture was purified by silica gel column chromatography (pentane→pentane/Et_2O = 19/1) to afford **3a** (28 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.94 (d, *J* = 7.2 Hz, 2H; Ar), 7.64 (t, *J* = 7.4 Hz, 1H; Ar), 7.52 (t, *J* = 7.8 Hz, 2H; Ar), 3.80 (q, *J* = 10.0 Hz, 2H; CH_2CF_3). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –63.03 (t, *J* = 10.2 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[21a]

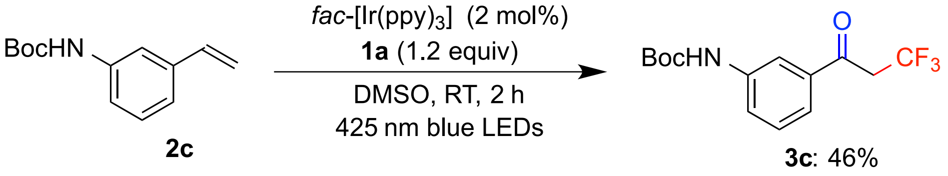
Methyl 3-(3,3,3-trifluoropropanoyl)benzoate (3b)



Following the general procedure, the title compound was synthesized from methyl 3-vinylbenzoate (**2b**) (41 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 9/1) to afford **3b** (22 mg, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.54 (dd, *J* = 1.6, 1.6 Hz, 1H; Ar), 8.29 (ddd, *J* = 7.6, 0.8, 0.8 Hz, 1H; Ar), 8.15 (ddd, *J* = 8.4, 0.8, 0.8 Hz, 1H; Ar), 7.61 (ddd, *J* = 7.8, 7.8, 0.4 Hz, 1H; Ar), 3.97 (s, 3H; CO_2CH_3), 3.84 (q, *J* = 9.9 Hz, 2H; CH_2CF_3). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 189.1, 166.0, 136.2, 135.0, 132.5, 131.3, 129.6, 129.4, 124.0 (q, *J* = 276 Hz), 52.7, 42.4 (q, *J* = 28.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –63.03 (t, *J* = 10.0 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{11}H_9F_3O_3+Na]^+$ requires 269.0396, found 269.0397.

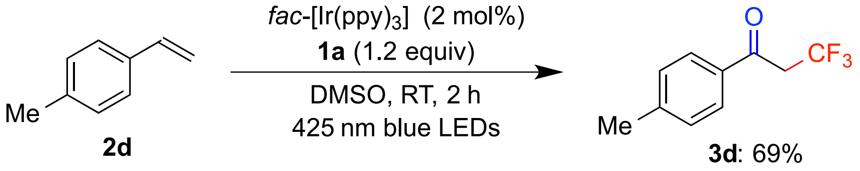
N-(*tert*-Butoxycarbonyl)-3-(3,3,3-trifluoropropanoyl)aniline (3c)



Following the general procedure, the title compound was synthesized from *N*-(*tert*-butoxycarbonyl)-3-vinylaniline (**2c**) (55 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/EtOAc = 9/1) to afford **3c** (35 mg, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.97 (s, 1H; Ar), 7.64 (d, *J* = 8.0 Hz, 1H; Ar), 7.60–7,57 (m, 1H; Ar), 7.42 (dd, *J* = 7.8, 7.8 Hz, 1H; Ar), 6.61 (br s, 1H; NH), 3.79 (q, *J* = 15 Hz, 2H; $C\mathit{H}_2CF_3$), 1.53 (s, 9 H; $C(C\mathit{H}_3)_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 189.7, 152.7, 139.5, 136.8, 129.7, 124.1 (q, *J* = 275 Hz), 124.0, 122.9, 118.0, 81.4, 42.3 (q, *J* = 28.1 Hz), 28.4. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –63.10 (t, *J* = 10.2 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{14}H_{16}F_3NO_3+Na]^+$ requires 326.0974, found 326.0978.

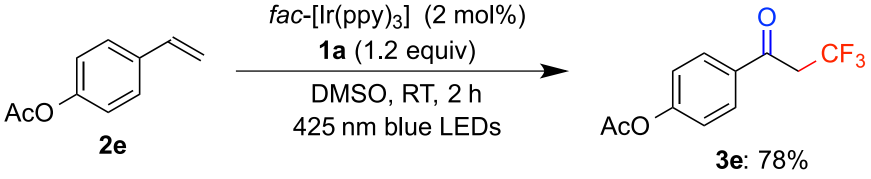
1-(4-Methylphenyl)-3,3,3-trifluoropropan-1-one (3d)



Following the general procedure, the title compound was synthesized from 4-methylstyrene (**2d**) (30 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3d** (35 mg, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.83 (dd, *J* = 6.8, 1.6 Hz, 2H; Ar), 7.30 (d, *J* = 8.0 Hz, 2H; Ar), 3.76 (q, *J* = 10 Hz, 2H; $C\mathit{H}_2CF_3$), 2.43 (s, 3 H; $ArC\mathit{H}_3$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –63.00 (t, *J* = 10.2 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[21a]

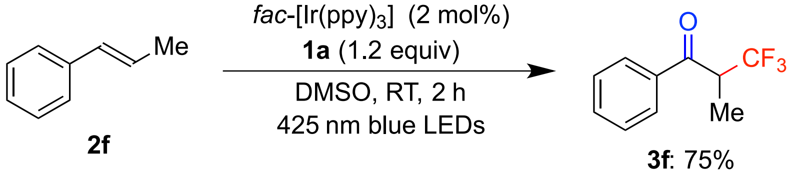
1-(4-Acetoxyphenyl)-3,3,3-trifluoropropan-1-one (3e)



Following the general procedure, the title compound was synthesized from 4-acetoxystyrene (**2e**) (41 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 9/1) to afford **3e** (48 mg, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.98 (d, J = 8.8 Hz, 2H; Ar), 7.25 (d, J = 9.2 Hz, 2H; Ar), 3.78 (q, J = 9.9 Hz, 2H; CH_2CF_3), 2.34 (s, 3H; CH_3CO). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 188.6, 168.7, 155.4, 133.5, 130.2, 124.1 (q, J = 275 Hz), 122.3, 42.3 (q, J = 28.2 Hz), 21.2. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –63.00 (t, J = 9.98 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{11}H_9F_3O_3+Na]^+$ requires 269.0396, found 269.0394.

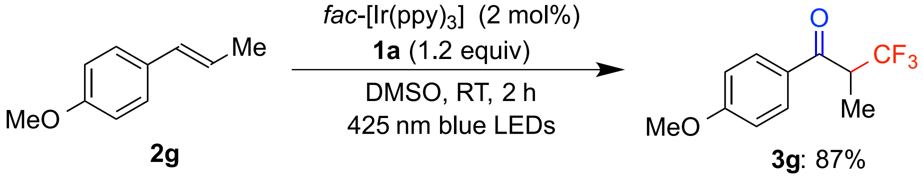
3,3,3-Trifluoro-2-methyl-1-phenylpropan-1-one (3f)



Following the general procedure, the title compound was synthesized from *trans*-β-methylstyrene (**2f**) (39 μL, 0.3 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3f** (45 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.97–7.94 (m, 2H; Ar), 7.65-7.61 (m, 1H; Ar), 7.51 (dd, J = 7.6, 7.6 Hz, 2H; Ar), 4.31–4.19 (m, 1H; CF_3CHCH_3), 1.48 (d, J = 7.2 Hz, 3H; $CHCH_3$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –69.27 (d, J = 8.28 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[21b]

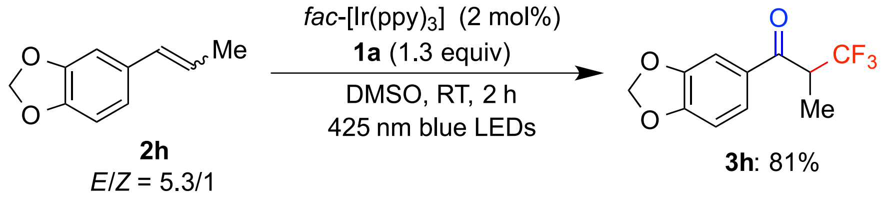
3,3,3-Trifluoro-1-(4-methoxyphenyl)-2-methylpropan-1-one (3g)



Following the general procedure, the title compound was synthesized from (*E*)-1-(4-methoxyphenyl)propene (**2g**) (59 mg, 0.4 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et$_2$O = 9/1) to afford **3g** (81 mg, 87% yield).

^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 7.94 (d, *J* = 8.8 Hz, 2H; Ar), 6.97 (d, *J* = 9.2 Hz, 2H; Ar), 4.19 (m, 1H; CF$_3$C*H*CH$_3$), 3.89 (s, 3H; C*H*$_3$O), 1.46 (d, *J* = 6.8 Hz, 3H; CHC*H*$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$, rt): δ 192.6, 164.3, 131.0, 128.8, 125.4 (q, *J* = 279 Hz), 114.1, 55.5, 43.9 (q, *J* = 26.3 Hz), 11.6. **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –69.29 (d, *J* = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for [C$_{11}$H$_{11}$F$_3$O$_2$+Na]$^+$ requires 255.0603, found 255.0601.

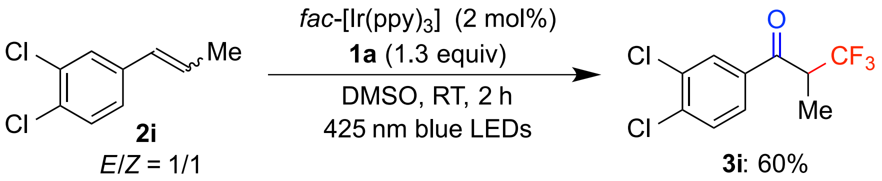
1-(Benzo[*d*][1,3]dioxol-5-yl)-3,3,3-trifluoro-2-methylpropan-1-one (3h)



Following the general procedure, the title compound was synthesized from isosafrole (**2h**) (41 mg, 0.25 mmol, *E*/*Z* = 5.3/1). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et$_2$O = 9/1) to afford **3h** (50 mg, 81% yield).

^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H; Ar), 7.44 (d, *J* = 2.0 Hz, 1H; Ar), 6.88 (d, *J* = 8.4 Hz, 1H; Ar), 6.07 (s, 2H; OC*H*$_2$O), 4.14 (m, 1H; CF$_3$C*H*CH$_3$), 1.45 (d, *J* = 7.2 Hz, 3H; CHC*H*$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$, rt): δ 192.4, 152.8, 148.8, 130.8, 125.5 (q, *J* = 279 Hz), 125.3, 108.5, 108.2, 102.3, 44.3 (q, *J* = 26.3 Hz), 11.9. **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –69.34 (d, *J* = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for [C$_{11}$H$_9$F$_3$O$_3$+Na]$^+$ requires 269.0396, found 269.0398.

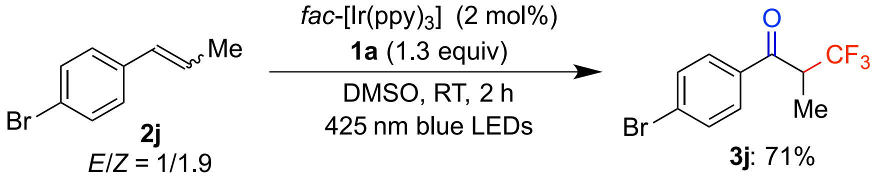
1-(3,4-Dichlorophenyl)-3,3,3-trifluoro-2-methylpropan-1-one (3i)



Following the general procedure, the title compound was synthesized from 1-(3,4-dichlorophenyl)propene (**2i**) (47 mg, 0.25 mmol, *E*/*Z* = 1/1). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3i** (41 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.03 (d, J = 2.0 Hz, 1H; Ar), 7.77 (dd, J = 8.4, 2.4 Hz, 1H; Ar), 7.60 (d, J = 8.4 Hz, 1H; Ar), 4.15 (m, 1H; $CF_3C\mathit{H}CH_3$), 1.47 (d, J = 7.2 Hz, 3H; $CHC\mathit{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 192.4, 139.0, 135.4, 134.0, 131.2, 130.7, 127.7, 125.1 (q, J = 279 Hz), 44.7 (q, J = 26.7 Hz), 11.6. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –69.15 (d, J = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{10}H_7Cl_2F_3O+Na]^+$ requires 292.9718, found 292.9721.

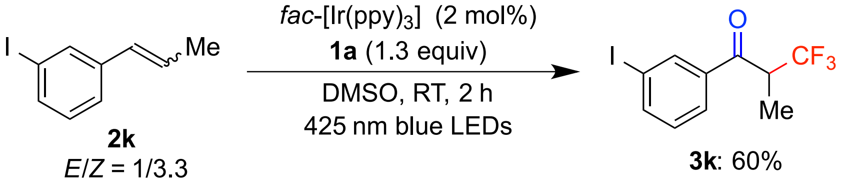
1-(4-Bromophenyl)-3,3,3-trifluoro-2-methylpropan-1-one (2j)



Following the general procedure, the title compound was synthesized from 1-(4-bromophenyl)propene (**2j**) (49 mg, 0.25 mmol, *E*/*Z* = 1/1.9). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3j** (50 mg, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.81 (d, J = 8.8 Hz, 2H; Ar), 7.66 (d, J = 8.8 Hz, 2H; Ar), 4.18 (m, 1H; $CF_3C\mathit{H}CH_3$), 1.47 (d, J = 6.8 Hz, 3H; $CHC\mathit{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 193.5, 134.6, 132.4, 130.2, 129.6, 125.3 (q, J = 278 Hz), 44.5 (q, J = 26.5 Hz), 11.7. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –69.20 (d, J = 7.91 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{10}H_8BrF_3+Na]$ requires 302.9603, found 302.9603.

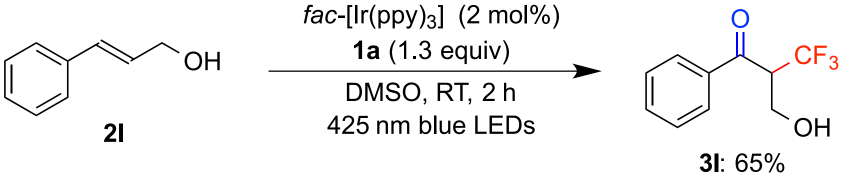
3,3,3-Trifluoro-1-(3-iodophenyl)-2-methylpropan-1-one (3k)



Following the general procedure, the title compound was synthesized from 1-(3-iodophenyl)propene (**2k**) (61 mg, 0.25 mmol, *E*/*Z* = 1/3.3). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3k** (49 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.27 (s, 1H; Ar), 7.96 (d, *J* = 8.0 Hz, 1H; Ar), 7.89 (d, *J* = 8.0 Hz, 1H; Ar), 7.26 (dd, *J* = 7.8, 7.8 Hz, 1H; Ar), 4.17 (m, 1H; CF_3CHCH_3), 1.47 (d, *J* = 7.2 Hz, 3H; $CHCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 193.2, 142.9, 137.6, 137.5, 130.7, 127.8, 125.2 (q, *J* = 279 Hz), 94.8, 44.6 (q, *J* = 26.5 Hz), 11.7. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –69.20 (d, *J* = 7.53 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{10}H_8F_3IO+Na]^+$ requires 350.9464, requires 350.9464.

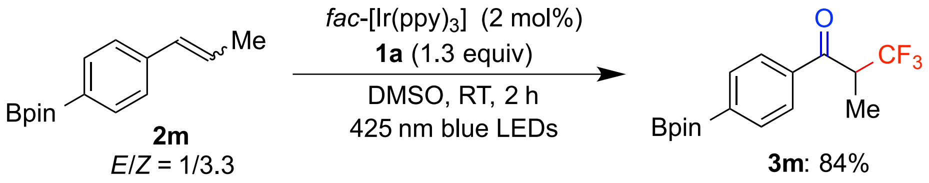
3,3,3-Trifluoro-2-(hydroxymethyl)-1-phenylpropan-1-one (3l)



Following the general procedure, the title compound was synthesized from (*E*)-cinnamylalcohol (**2l**) (34 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/EtOAc = 3/1) to afford **3l** (35 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.99 (d, *J* = 8.0 Hz, 2H; Ar), 7.65 (t, *J* = 7.4 Hz, 1H; Ar), 7.53 (t, *J* = 7.8 Hz, 2H; Ar), 4.51–4.42 (m, 1H; CF_3CHCH_2), 4.34–4.28 (m, 1H; CH_2OH), 4.17–4.12 (m, 1H; CH_2OH), 2.03 (t, *J* = 6.2 Hz, 1H; O*H*). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 193.6, 136.5, 134.3, 128.9, 128.8, 123.9 (q, *J* = 279 Hz), 59.3, 51.8 (q, *J* = 24.5 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –65.29 (d, *J* = 8.66 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{10}H_9F_3O_2+Na]^+$ requires 241.0447, found 241.0442.

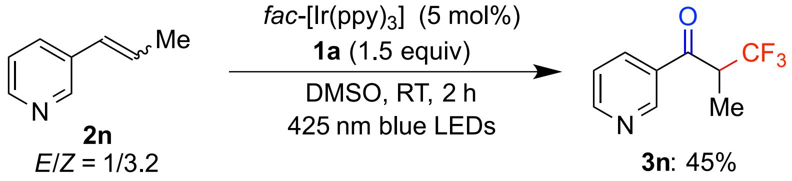
3,3,3-Trifluoro-2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-one (3m)



Following the general procedure, the title compound was synthesized from 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propene (**2m**) (61 mg, 0.25 mmol, *E*/*Z* = 1/3.3). The product mixture was purified by silica gel column chromatography (hexane→hexane/EtOAc = 9/1) to afford **3m** (69 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.92 (m, 4H; Ar), 4.24 (m, 1H; CF_3CHCH_3), 1.47 (d, J = 7.2 Hz, 3H $CHCH_3$), 1.36 (s, 12H; $C(CH_3)_2$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 194.8, 137.8, 135.3, 127.6, 125.5 (q, J = 278 Hz), 84.5, 44.7 (q, J = 26.5 Hz), 25.0, 11.8. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –69.26 (d, J = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{16}H_{20}BF_3O_3+Na]^+$ requires 351. 1353, found 351.1353.

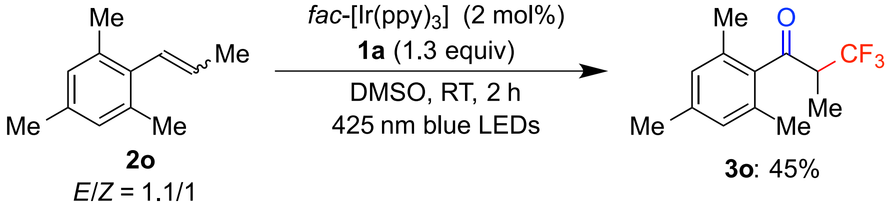
3,3,3-Trifluoro-2-methyl-1-(pyridin-3-yl)propan-1-one (3n)



Following the general procedure, the title compound was synthesized from 3-(1-propenyl)pyridine (**2n**) (30 mg, 0.25 mmol, *E*/*Z* = 1/3.2). The product mixture was purified by silica gel column chromatography (Et_2O) to afford **3n** (23 mg, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 9.16 (d, J = 1.6 Hz, 1H; Ar), 8.84 (dd, J = 4.8, 1.2 Hz, 1H; Ar), 8.26–8.23 (m, 1H; Ar), 7.49–7.46 (m, 1H; Ar), 4.27–4.15 (m, 1H; CF_3CHCH_3), 1.50 (d, J = 7.2 Hz, 3H; $CHCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 193.4, 154.4, 150.0, 136.1, 131.3, 125.1 (q, J = 278 Hz), 124.0, 45.1 (q, J = 26.7 Hz), 11.4. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –69.05 (d, J = 7.91 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_9H_8F_3NO+H]^+$ requires 204.0631, found 204.0636.

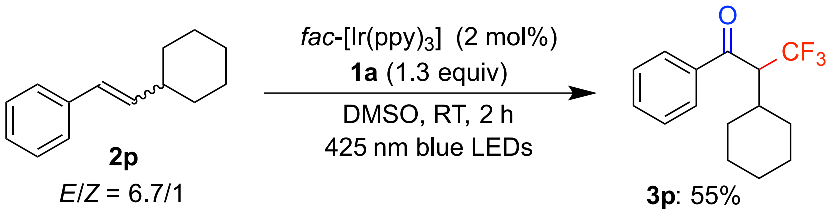
3,3,3-Trifluoro-1-mesityl-2-methylpropan-1-one (3o)



Following the general procedure, the title compound was synthesized from 1-mesitylpropene (**2o**) (64 mg, 0.4 mmol, *E*/*Z* = 1.1/1). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3o** (44 mg, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 6.87 (s, 2H; Ar), 3.74–3.62 (m, 1H; CF_3CHCH_3), 2.29 (s, 3H; $ArCH_3$), 2.23 (s, 6H; $Ar(CH_3)_2$), 1.41 (d, *J* = 7.2 Hz, 3H; $CHCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 203.0, 139.7, 137.5, 134.0, 129.2, 125.4 (q, *J* = 279 Hz), 51.1 (q, *J* = 25.3 Hz), 21.2, 19.6, 10.6. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –69.06 (d, *J* = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{13}H_{15}F_3O+Na]^+$ requires 267.0967, found 267.0965.

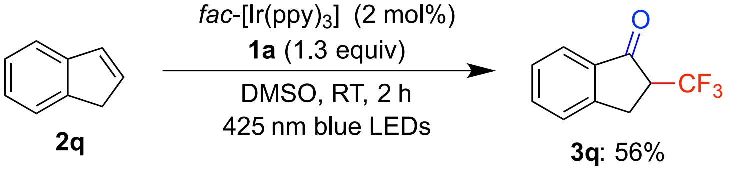
2-Cyclohexyl-3,3,3-trifluoro-1-phenylpropan-1-one (3p)



Following the general procedure, the title compound was synthesized from (2-cyclohexylvinyl)benzene (**2p**) (48 mg, 0.26 mmol, *E*/*Z* = 6.7/1). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3p** (39 mg, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.94 (d, *J* = 8.4 Hz, 2H; Ar), 7.62 (t, *J* =7.4 Hz, 1H; Ar), 7.51 (t, *J* = 7.6 Hz, 2H; Ar), 4.08–3.99 (m, 1H; $CHCHCF_3$), 2.27–2.17 (m, 1H; CH_2CHCH_2), 2.02–0.94 (m, 10H; Cy). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 195.7, 137.9, 133.9, 129.1, 128.6, 125.3 (q, *J* = 281 Hz), 54.9 (q, *J* = 23.9 Hz), 37.9, 31.3, 31.0, 26.1, 26.0. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –62.74 (d, *J* = 8.66 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{15}H_{17}F_3O+Na]^+$ requires 293.1124, found 293.1125.

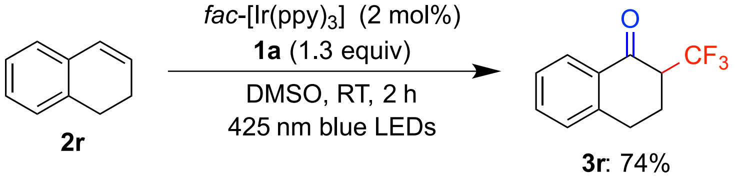
2-(Trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (3q)



Following the general procedure, the title compound was synthesized from indene (**2q**) (47 μL, 0.4 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 3/1) to afford **3q** (45 mg, 56% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.82 (d, *J* = 7.6 Hz, 1H; Ar), 7.66 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H; Ar), 7.52 (d, *J* = 7.6 Hz, 1H; Ar), 7.44 (dd, *J* = 7.6, 7.6 Hz, 1H; Ar), 3.49–3.30 (m, 3H; $ArCH_2CHCF_3$). ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –68.77 (d, *J* = 9.41 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[21b]

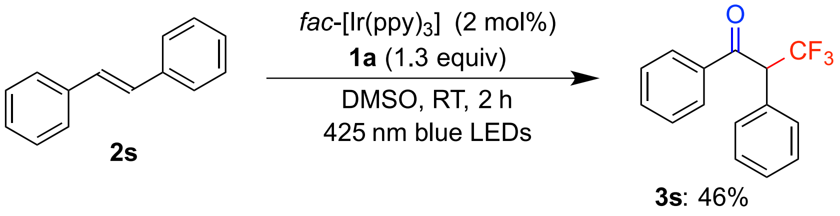
2-(Trifluoromethyl)-3,4-dihydronaphthalen-1(2*H*)-one (3r)



Following the general procedure, the title compound was synthesized from 1,2-dihydronaphthalene (**2r**) (39 μL, 0.3 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 4/1) to afford **3r** (47 mg, 74% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 8.07 (dd, *J* = 8.0, 1.2 Hz, 1H; Ar), 7.52 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H; Ar), 7.35 (dd, *J* = 7.6, 7.6 Hz, 1H; Ar), 7.27 (d, *J* = 8.0 Hz, 1H; Ar), 3.33–3.22 (m, 1H; $CHCF_3$), 3.12–3.07 (m, 2H; $ArCH_2$), 2.54–2.47 (m, 1H; $CHCH_2CH_2$), 2.35–2.23 (m, 1H; $CHCH_2CH_2$). ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –68.53 (d, *J* = 9.04 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[21b]

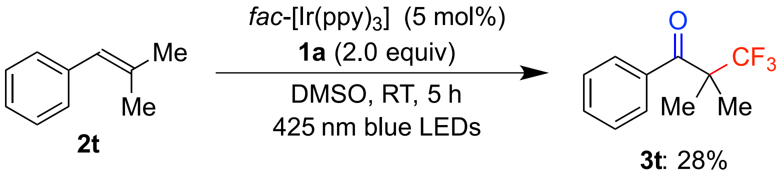
3,3,3-Trifluoro-1,2-diphenylpropan-1-one (3s)



Following the general procedure, the title compound was synthesized from *trans*-stilbene (**2s**) (45 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3s** (30 mg, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.90 (dd, J = 8.0, 1.6 Hz, 2H; Ar), 7.53 (dd, J = 7.2, 7.2 Hz, 1H; Ar), 7.47–7.37 (m, 7H; Ar), 5.28 (q, J = 8.4 Hz, 1H; C$H$$CF_3$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –67.53 (d, J = 8.28 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[21b]

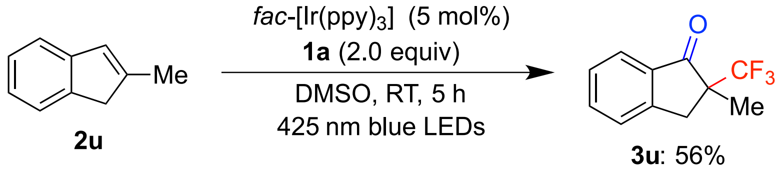
3,3,3-Trifluoro-2,2-dimethyl-1-phenylpropan-1-one (3t)



Following the general procedure, the title compound was synthesized from 2-methyl-1-phenylpropene (**2t**) (37 μL, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3t** (15 mg, 28% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.64 (d, J = 7.2 Hz, 2H; Ar), 7.51 (dd, J = 7.6, 7.6 Hz, 1H; Ar), 7.42 (dd, J = 8.0, 8.0 Hz, 2H; Ar), 1.57 (s, 6H; $C(CH_3)_2$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –73.66 (s, 3F). Spectral data were in agreement with the data reported in the literature.[21c]

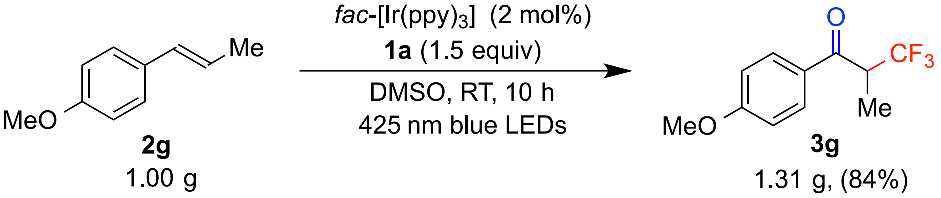
2-Methyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (3u)



Following the general procedure, the title compound was synthesized from 2-methyl-1*H*-indene (**2u**) (34 μL, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 9/1) to afford **3u** (30 mg, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.81 (d, J = 7.6 Hz, 1H; Ar), 7.66 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H; Ar), 7.49 (d, *J* = 7.6 Hz, 1H; Ar), 7.43 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H; Ar), 3.57 (d, *J* = 17.6 Hz, 1H; ArCH_2), 3.02 (d, *J* = 17.6 Hz, 1H; ArCH_2), 1.50 (s, 3H; CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –74.76 (s, 3F). Spectral data were in agreement with the data reported in the literature.[21d]

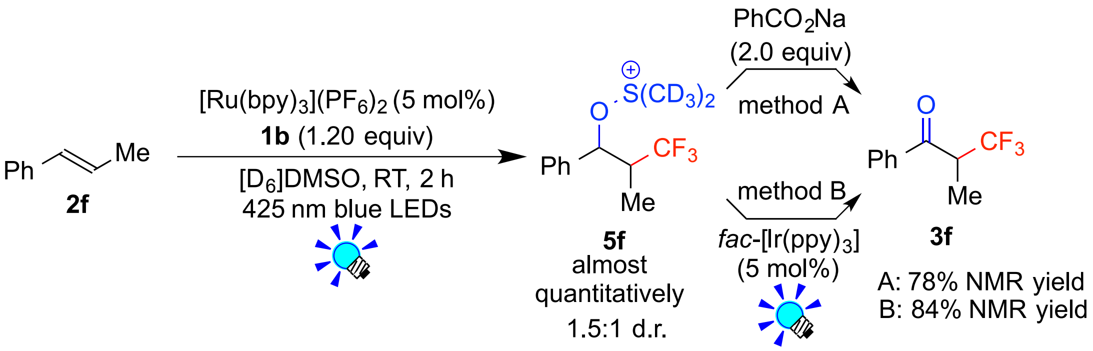
Procedure for the gram-scale synthesis for 3g (Scheme 2.3)



A 100 mL Schlenk tube was charged with *fac*-[Ir(ppy)$_3$] (88 mg, 0.14 mmol), Togni's reagent **1a** (2.56 g, 8.10 mmol), (*E*)-1-(4-methoxyphenyl)propene (**2g**) (1.00 g, 6.75 mmol) and dry DMSO (70 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 5 h with stirring at room temperature (in a water bath). TLC analysis indicated incomplete conversion of **2g**. After further addition of **1a** (0.64 g, 2.0 mmol) to the reaction mixture was conducted, the tube was irradiated by blue LED lamps for another 5 h. After the reaction, aq. $NaHCO_3$ was added to the reaction mixture, and products were extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane→hexane/Et_2O = 9/1) to afford **3g** (1.31 g, 84% yield).

Control experiments for insight on reaction mechanism (Scheme 2.4)

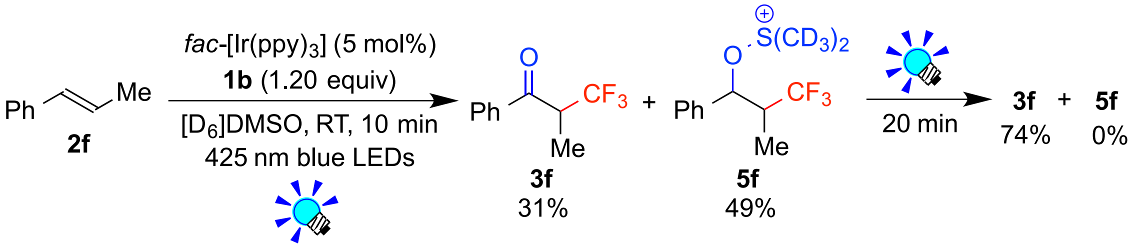
NMR experiments for generation of dimethyl(3,3,3-trifluoro-2-methyl-1-phenylpropoxy)sulfonium (5f) and transformation into 3,3,3-trifluoro-2-methyl-1-phenylpropan-1-one (3f)



Under N_2, $[Ru(bpy)_3](PF_6)_2$ (1.1 mg, 1.3 μmol), Umemoto's reagent **1b** (10 mg, 30 μmol), (*E*)-β-methylstyrene (**2f**) (3.3 μL, 25 μmol), $SiEt_4$ (~1 μL; an internal standard), dry [D$_6$]DMSO (0.5 mL) were added to an NMR tube. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h at room temperature (in a water bath). An NMR spectrum of the mixture revealed quantitative formation of a 1.5:1 diastereomeric mixture of dimethyl(3,3,3-trifluoro-2-methyl-1-phenylpropoxy)sulfonium (**5f**).

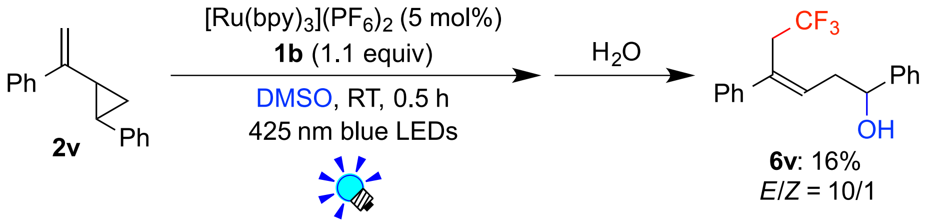
Method A: To the reaction mixture containing **5f**, sodium benzoate (7 mg, 50 μmol) was added at room temperature under N_2, and the NMR tube was shaken until sodium benzoate dissolved. The formation and yield of **3f** were determined by ^{1}H NMR.
Method B: To the reaction mixture containing **5f**, *fac*-[Ir(ppy)$_3$] (0.8 mg, 1 μmol) was added under N_2, and the NMR tube was irradiated by blue LED lamps for 1 h. The formation and yield of **3f** were determined by ^{1}H NMR.

The time course NMR experiment using the Ir photocatalyst and 1b



Under N_2, *fac*-[Ir(ppy)$_3$] (0.8 mg, 1.3 μmol), Umemoto's reagent **1b** (10 mg, 30 μmol), (*E*)-β-methylstyrene (**2f**) (3.3 μL, 25 μmol), $SiEt_4$ (~1 μL; an internal standard), dry [D$_6$]DMSO (0.5 mL) were added to an NMR tube. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated at room temperature (in a water bath).

The reaction of 1-phenyl-1-(*trans*-2-phenylcyclopropyl)ethene (2v) with Umemoto's reagent 1b and $[Ru(bpy)_3](PF_6)_2$ photocatalyst

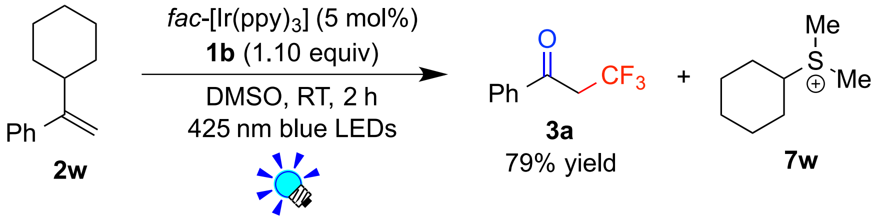


A 20 mL Schlenk tube was charged with [Ru(bpy$_3$)](PF$_6$)$_2$ (10 mg, 12 µmol), Umemoto's reagent **1b** (94 mg, 0.28 mmol), 1-phenyl-1-(*trans*-2-phenylcyclopropyl)ethene (**2v**) (56 mg, 0.25 mmol) and dry DMSO (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 0.5 h with stirring at room temperature (in a water bath). After the reaction, H_2O was added into the reaction mixture, and products were extracted with Et_2O. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to afford **6v** (13 mg, 16% yield). The *E*/*Z* ratio was determined to be 10/1 from the crude reaction mixture using ^{19}F NMR spectroscopy.

E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.40–7.25 (m, 10H; Ar), 6.05 (t, J = 7.2 Hz, 1H; C=C*H*), 4.85 (dd, J = 7.6, 5.6 Hz, 1H; C*H*OH), 3.32–3.21 (m, 2H; C*H*$_2$CF$_3$), 2.79–2.64 (m, 2H; C=CHC*H*$_2$), 2.02 (br s, 1H; O*H*). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 143.9, 141.9, 132.2 (q, J =2.4 Hz), 131.6, 128.7, 128.5, 128.0, 127.6, 126.5, 126.1 (q, J = 279 Hz), 125.9, 74.0, 39.0, 34.8 (q, J = 29.5 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –63.50 (t, J = 10.15 Hz, 3F).

Z-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.40–7.25 (m, 8H; Ar), 7.03 (dd, J = 8.4, 1.6 Hz, 2H; Ar), 5.81 (t, J = 7.2 Hz, 1H; C=C*H*), 4.73 (apparent t, J = 6.4 Hz, 1H; C*H*OH), 3.10 (q, J = 10 Hz, 2H; C*H*$_2$CF$_3$), 2.51–2.47 (m, 2H; C=CHC*H*$_2$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –64.49 (t, J = 10.90 Hz, 3F).

The reaction of α-cyclohexylstyrene (2w) with Umemoto's reagent 1b under the photocatalytic reaction condition



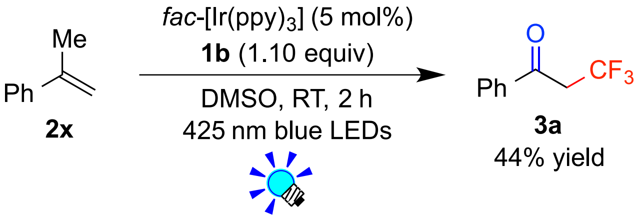
A 20 mL Schlenk tube was charged with *fac*-[Ir(ppy)$_3$] (8.2 mg, 13 µmol), Umemoto's reagent **1b** (94 mg, 0.28 mmol), α-cyclohexylstyrene (**2v**) (47 mg, 0.25 mmol) and dry DMSO (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, $CHCl_3$ (10 mL) and H_2O (10 mL) were added to the reaction mixture. Then, aqueous layer and organic layer were separated. Et_2O was added to the organic layer, and the resulting mixture was washed with H_2O. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel flash column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3a** (37 mg, 79% yield). The aqueous layer of the initial extraction was placed in EYELA FREEZE DRYER FD-1000 and removed H_2O and DMSO as far as possible under reduced pressure (~14 Pa).

Cyclohexyldimethylsulfonium ion (7w)

^{1}H NMR (400 MHz, D_2O, rt): δ 3.43 (tt, *J* = 11.4, 3.6 Hz, 1H; SC*H*), 2.13–2.09 (m, 2H), 1.92–1.86 (m, 2H), 1.71–1.66 (m, 1H), 1.62–1.52 (m, 2H), 1.46–1.36 (m, 2H), 1.33–1.23 (m, 1H). **^{13}C NMR** (100 MHz, D_2O, rt): δ 54.9, 27.3, 25.3, 24.9, 22.1. **HRMS** (ESI-TOF): calculated for $[C_8H_{17}S]^+$ requires 145.1045, found 145.1045.

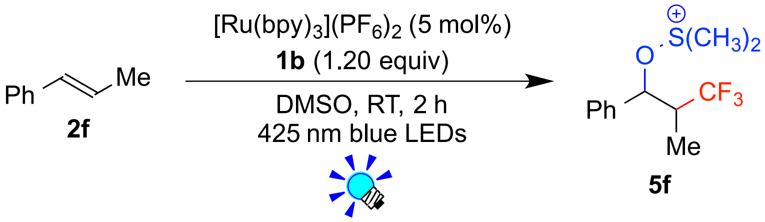
The ^{13}C NMR spectrum of **6w** was almost identical to the literature data,[22] which reported **^{13}C NMR** (dioxane/D_2O = 9/1): δ 54.6, 27.6, 25.6, 25.3, 22.0.

The reaction of α-methylstyrene (2x) with Umemoto's reagent 1b under the photocatalytic reaction condition



A 20 mL Schlenk tube was charged with *fac*-[Ir(ppy)$_3$] (8.2 mg, 13 μmol), Umemoto's reagent **1b** (94 mg, 0.28 mmol), α-methylstyrene (**2x**) (30 mg, 0.25 mmol) and dry DMSO (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, aq. $NaHCO_3$ was added to the reaction mixture, and products were extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel flash column chromatography (hexane→hexane/Et_2O = 19/1) to afford **3a** (21 mg, 44% yield).

The preparative experiment of alkoxysulfonium intermediate 5f



A 20 mL Schlenk tube was charged with $[Ru(bpy)_3](PF_6)_2$ (10 mg, 12 μmol), Umemoto's reagent **1b** (99 mg, 0.29 mmol), β-methylstyrene (**2f**) (31μL, 0.24 mmol) and dry DMSO (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, the tube was placed in an EYELA FREEZE DRYER FD-1000 and DMSO was removed as much as possible under reduced pressure (~14 Pa). The residue was dissolved in dry CH_2Cl_2 (2 mL), and dry Et_2O (8 mL) was added to the mixture to form precipitates. The solution was removed and the precipitate was dried under reduced pressure for several hours. The precipitates were determined to be **5f** as characterized by ^1H and ^{19}F NMR. The ^1H and ^{19}F NMR spectra for the precipitate were observed. The stereochemistry of **5f** was referred to the literature data[23] for 3,3,3-trifluoro-2-methyl-1-phenylpropanol. The spectral data indicated formation of **5f** as a mixture of diastereomers in addition to the residual $[Ru(bpy)_3]^{2+}$.

(1*R**,2*R**)-**5f**: **^{1}H NMR** (400 MHz, CD_2Cl_2, rt): δ 7.57–7.35 (m, 5H; Ar), 5.61 (d, *J* = 4.8 Hz, 1H; ArC*H*), 3.37 (s, 3H; $S(CH_3)_2$), 3.09 (s, 3H; $S(CH_3)_2$), 2.88–2.77 (m, 1H; C*H*CF_3), 1.29 (d, *J* = 7.2 Hz, 3H; CHCH_3). **^{19}F NMR** (376 MHz, CD_2Cl_2, rt): δ –70.41 (d, *J* = 8.28 Hz, 3F).

(1*R**,2*S**)-**5f**: **^{1}H NMR** (400 MHz, CD_2Cl_2, rt): δ 7.57–7.35 (m, 5H; Ar), 5.37 (d, *J* = 9.6 Hz, 1H; ArC*H*), 3.30 (s, 3H; $S(CH_3)_2$), 2.91 (s, 3H; $S(CH_3)_2$), 0.91 (d, *J* = 7.2 Hz, 3H; CHCH_3).**^{19}F NMR** (376 MHz, CD_2Cl_2, rt): δ –70.00 (d, *J* = 7.53 MHz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{12}H_{16}F_3OS]^+$ requires 265.0868, found 265.0841.

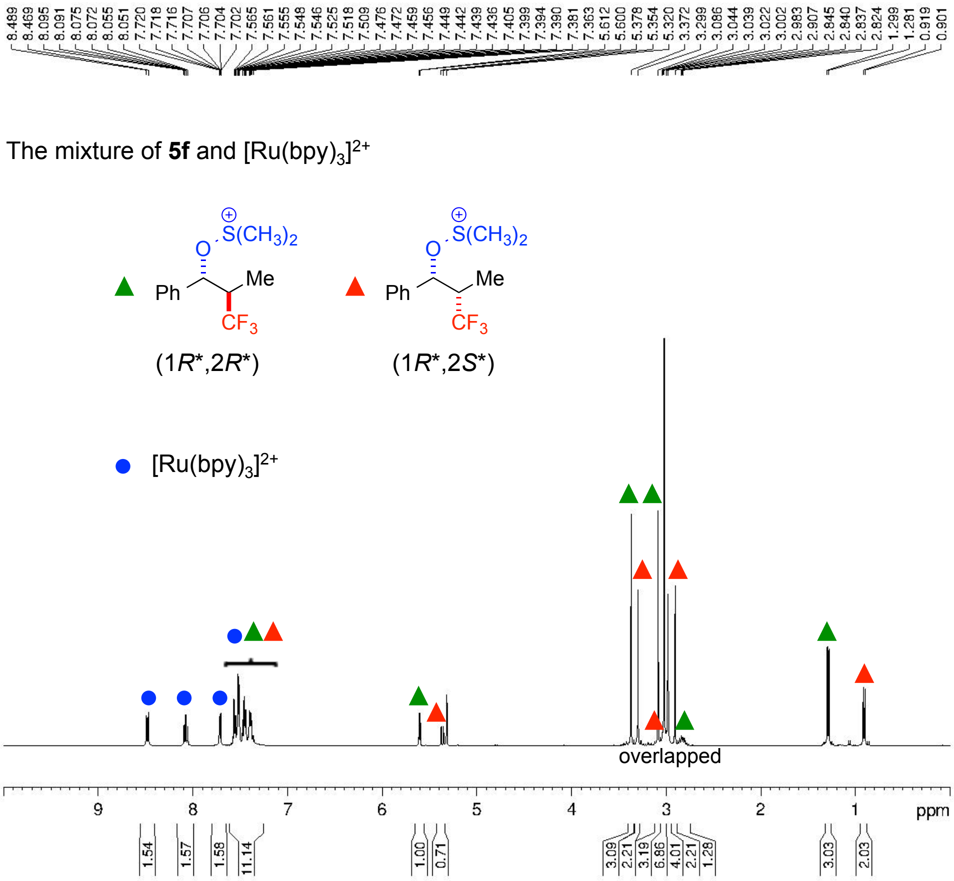


Figure 2.11. ^{1}H NMR spectrum (400 MHz, CD$_2$Cl$_2$, rt) of the mixture of **5f** and [Ru(bpy)$_3$]$^{2+}$

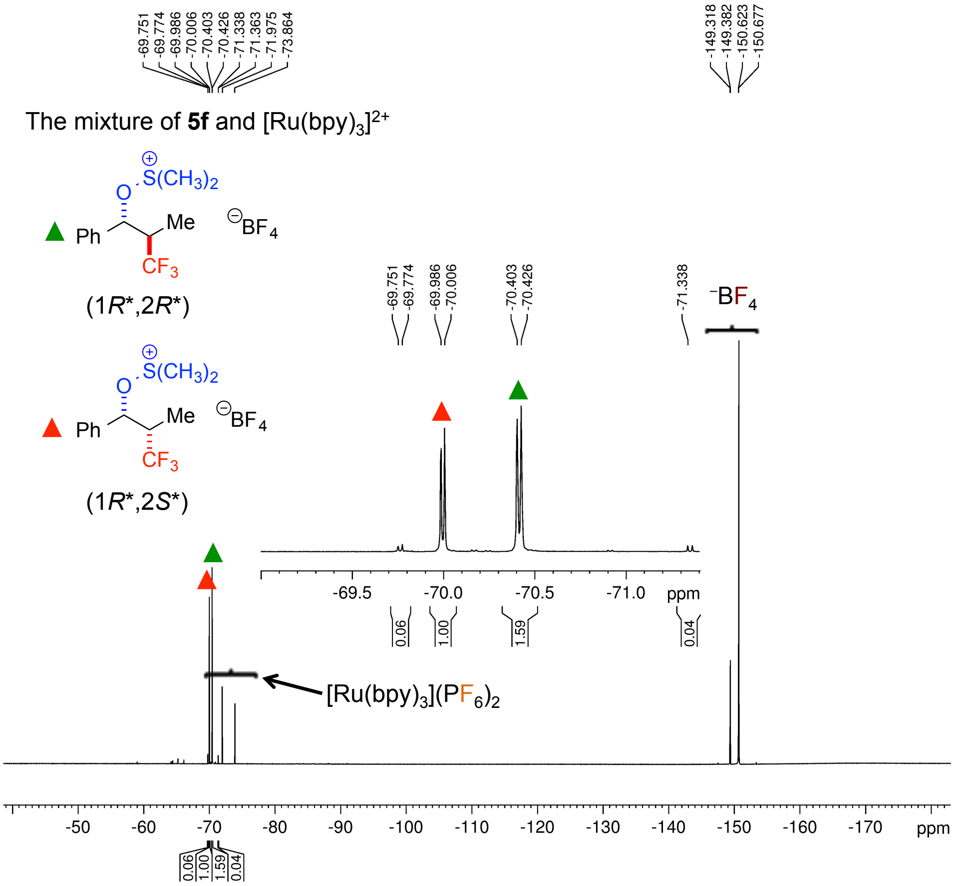


Figure S2.12. ^{19}F NMR spectrum (376 MHz, CD_2Cl_2, rt) of the mixture of **5f** and $[Ru(bpy)_3]^{2+}$

Cyclic voltammograms of CF_3 reagents (1a and 1b) and alkoxysulfonium intermediate 5f

Cyclic voltammetry were performed with a Hokutodenkou HZ-5000 analyzer under N_2 at room temperature (observed in 0.002 M MeCN; $[NBu_4PF_6]$ = 0.1 M; Ag/AgCl = electrode; reported with respect to the $[FeCp_2]/[FeCp_2]^+$ couple).

Luminescence quenching experiments

Emission spectra for the Ir catalyst in a deaerated solution whose concentration was adjusted so as to show the absorbance 0.1 at excitation wavelength were recorded at room temperature by a SHIMADZU RF-5300PC spectrometer. *fac*-$[Ir(ppy)_3]$ excited at 377 nm in DMSO exhibited emission band at 527 nm.

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[18] The reaction in the presence of **1b** (entry 2 in Table 2.1, method B in Scheme 2.3 and Scheme 2.5) can proceed through the pathway described in Scheme 2.8. We can not exclude other possibilities. This 1,2-H atom shift might be induced by adventitious H_2O or O_2 in DMSO, see: K. G. Konya, T. Paul, S. Lin, J. Lusztyk, K. U. Ingold, *J. Am. Chem. Soc*. **2000**, *122*, 7518–7527.

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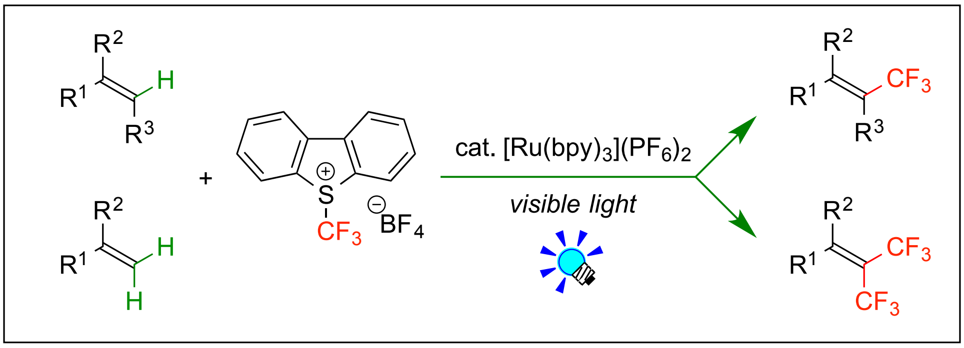
Chapter 3

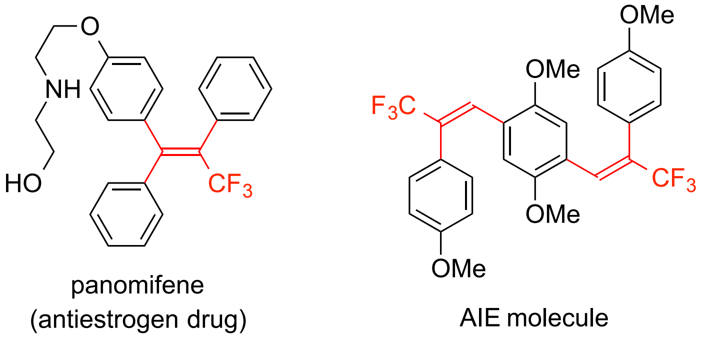
Direct C–H Trifluromethylation of Di- and Trisubstituted Alkenes by Photoredox Catalysis

ABSTRACT: Trifluoromethylated alkene scaffolds are known as useful structural motifs in drugs and materials. The photoredox reaction of di- and trisubstituted alkenes with Umemoto's reagent in the presence of $[Ru(bpy)_3]^{2+}$ catalyst affords the corresponding tri- and tetrasubstituted CF_3-alkenes via direct C–H trifluoromethylation. In addition, use of an excess amount of the CF_3 source induces double C–H trifluoromethylation to afford geminal bis(trifluoromethyl)alkenes.



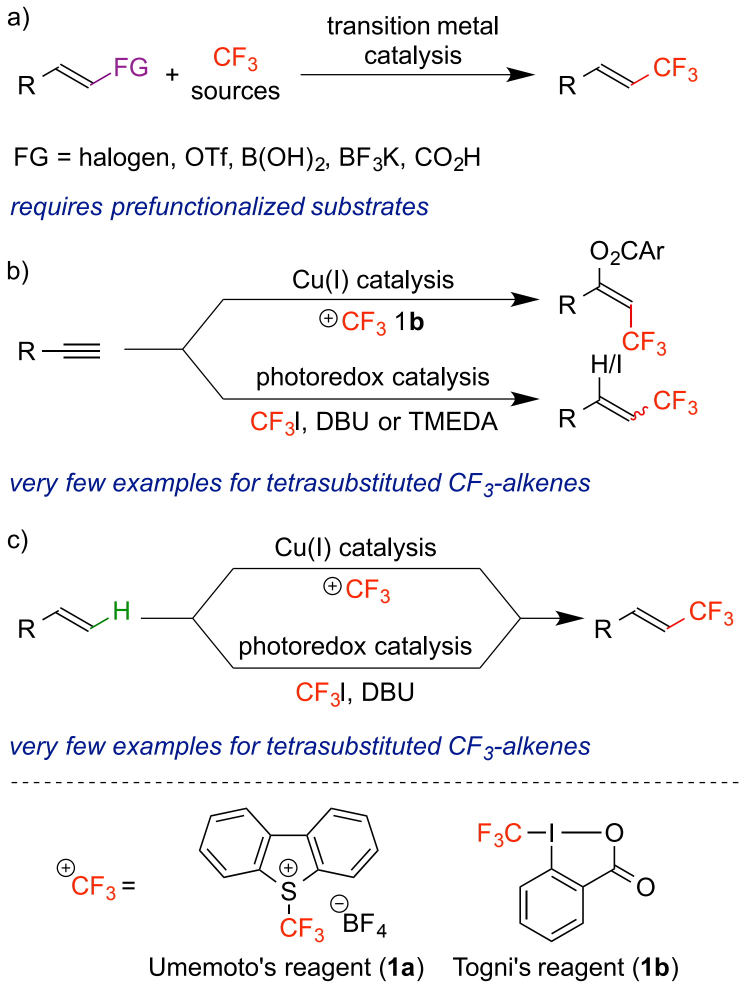
3.1 Introduction

Trifluoromethylated alkenes, especially multi-substituted CF_3-alkenes (3,3,3-trifluoropropene derivatives), have attracted our attention as fascinating scaffolds for agrochemicals, pharmaceuticals, and fluorescent molecules (Scheme 3.1).[1]



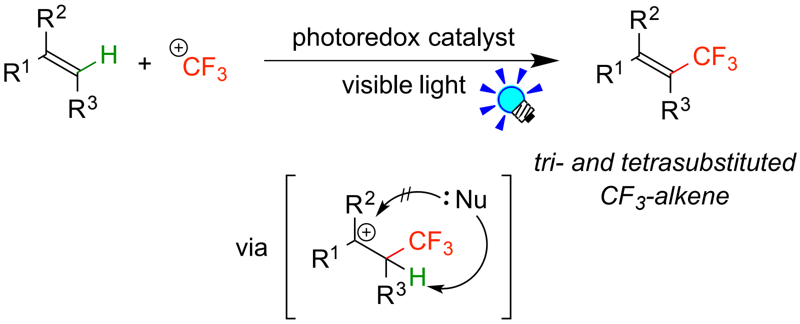
Scheme 3.1. Representative examples of multisubstituted CF_3-alkenes

Conventional approaches to CF_3-alkenes require multiple synthetic steps.[2] In contrast, “trifluoromethylation” is a promising protocol to obtain diverse CF_3-alkenes easily. Several catalytic synthetic methods via trifluoromethylation of alkenes have been developed so far.[3] Most of the reactions require prefunctionalized alkenes as a substrate (Scheme 3.2.a). Additionally, only a limited number of examples for synthesis of tri/tetra-substituted CF_3-alkenes have been reported so far. In 2012 and 2014, the groups of Szabó and Cho described trifluoromethylation of alkynes, leading to trifluoromethylated alkenes but the application to synthesis of tetrasubstituted CF_3-alkenes is not well addressed (Scheme 3.2.b).[4] Another straightforward approach is direct C–H trifluoromethylation of alkenes (Scheme 3.2.c). The groups of Loh, Besset, Cahard, Sodeoka and Xiao showed that copper catalysts can induce C–H trifluoromethylation of alkenes by electrophilic CF_3 reagents ($^+CF_3$).[5] In addition, Cho et al. reported trifluoromethylation of unactivated alkenes via base-induced E2 elimination of iodo-trifluoromethylated products of the alkenes obtained by photoredox-catalyzed reaction with CF_3I.[5f] To the best of our knowledge, however, development of synthetic methods for tri- and tetrasubstituted CF_3 alkenes through $C_{alkneyl}$–H trifluoromethylation of simple alkenes have been left to be explored.



Scheme 3.2. Catalytic synthesis of CF_3-alkenes via trifluoromethylation

As described in Chapter 2, the author established the keto-trifluoromethylation of aryl-alkenes by photoredox catalysis to afford the α-trifluoromethylated carbonyl compounds. In that reaction, the concomitant formation of β-trifluoromethylstyrenes from terminal styrene derivatives was observed. This result prompted him to explore the photoredox-catalyzed C–H trifluoromethylation of alkenes. The author hypothesized that if deprotonation from the α-CF_3-substituted carbocation intermediate occurs prior to the attack of a nucleophile, it can afford a CF_3-substituted alkene, selectively (Scheme 3.3). In this chapter, the author discloses a highly efficient direct C–H trifluoromethylation of di- and trisubstituted alkenes with Umemoto's reagent **1a** by visible-light-driven photoredox catalysis under mild conditions. The present photocatalytic protocol allows us easy access to a range of multi-substituted trifluoromethylated alkenes. In addition, his methodology can be extended to double trifluoromethylation of 1,1-disubstituted alkenes.

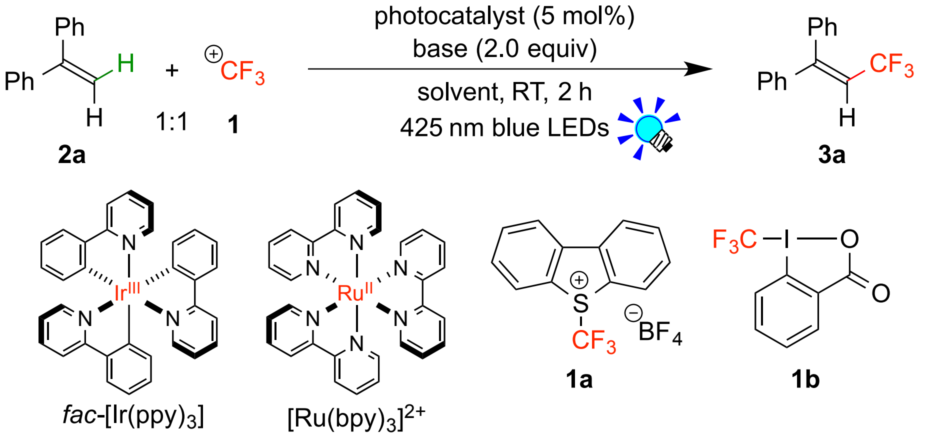


Scheme 3.3. Strategy for synthesis of CF_3-alkenes

3.2 Optimization of C–H Trifluoromethylation of 1,1-Diphenylethene

The results of optimization on the reaction conditions are summarized in Table 1. The author commenced examination of photocatalytic trifluoromethylation of 1,1-diphenylethene (**2a**) with 1 equivalent of Umemoto's reagent **1a** in the presence of 5 mol% *fac*-[Ir(ppy)$_3$] (the photocatalyst) and 2 equivalents of K_2HPO_4 (a base) in [D$_6$]DMSO under visible light irradiation (blue LEDs: λ_{max} = 425 nm) for 2 h. As a result, 3,3,3-trifluoro-1,1-diphenylpropene (**3a**) was obtained in an 82% NMR yield (entry 1, Table 3.1). The choice of the CF_3 reagent turned out to be crucial for the yield of **3a**. Togni's reagent **1b** gave **3a** in a lower yield (entries 2). The author also found that DMSO is a suitable solvent for the present reaction (entries 3–5). Other solvent systems gave substantial amounts of hydroxy-trifluoromethylated byproducts, which our group reported previously.[6] In addition, the present C–H trifluoromethylation proceeded even in the absence of a base (entry 6). Another photocatalyst, $[Ru(bpy)_3](PF_6)_2$, also promoted the present reaction, providing the product **3a** in an 85% NMR yield (entry 7). Because the Ru catalyst is less expensive than the Ir catalyst, the author chose the Ru photocatalyst for the experiments onward. Notably, product **3a** was obtained neither in the dark nor in the absence of the photocatalyst (entries 8 and 9), strongly supporting that the photoexcited species of the photoredox catalyst plays key roles in the reaction.

Table 3.1. Optimization of C–H trifluoromethylation of 1,1-diphenylthene **2a**.[a]



Entry	Photocatalyst	CF_3 reagent	Solvent	Base	Yield of **3a** [%][b]
1	*fac*-$[Ir(ppy)_3]$	**1a**	$[D_6]$DMSO	K_2HPO_4	82
2	*fac*-$[Ir(ppy)_3]$	**1b**	$[D_6]$DMSO	K_2HPO_4	17
3	*fac*-$[Ir(ppy)_3]$	**1a**	CD_3CN	K_2HPO_4	57
4	*fac*-$[Ir(ppy)_3]$	**1a**	CD_2Cl_2	K_2HPO_4	22
5	*fac*-$[Ir(ppy)_3]$	**1a**	$[D_6]$acetone	K_2HPO_4	29
6	*fac*-$[Ir(ppy)_3]$	**1a**	$[D_6]$DMSO	none	81
7	$[Ru(bpy)_3](PF_6)_2$	**1a**	$[D_6]$DMSO	none	85
8	none	**1a**	$[D_6]$DMSO	none	0
9[c]	$[Ru(bpy)_3](PF_6)_2$	**1a**	$[D_6]$DMSO	none	0

[a] For detailed reaction conditions, see the Experimental Section. [b] Yields were determined by ^1H NMR spectroscopy using $SiEt_4$ as an internal standard. [c] In the dark.

The NMR spectra for the reaction of entry 7 in Table 3.1 are shown below (Figure 3.1). It is observable that the efficient formation of the CF_3-alkene **3a** with consumption of the substrates **1a** and **2a** upon irradiation.

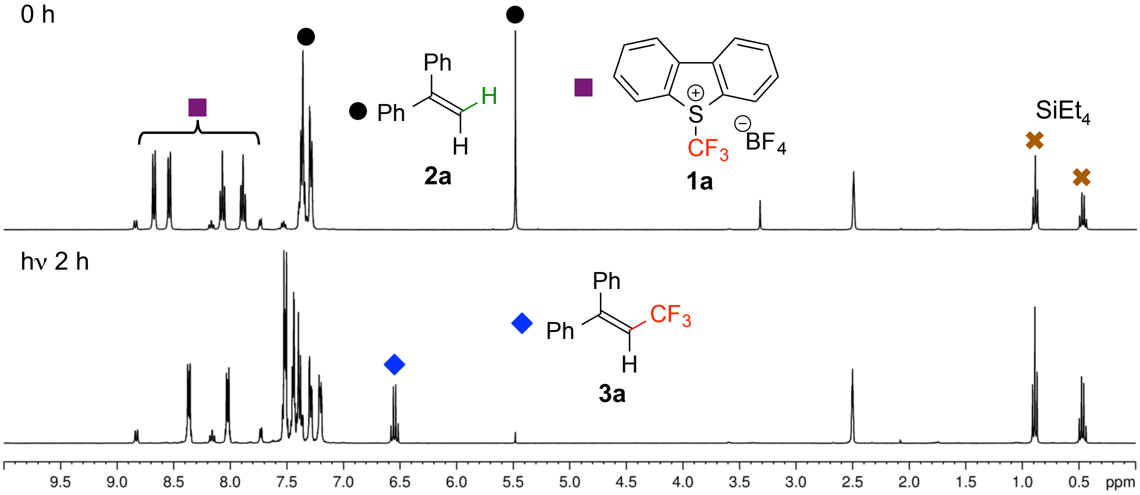


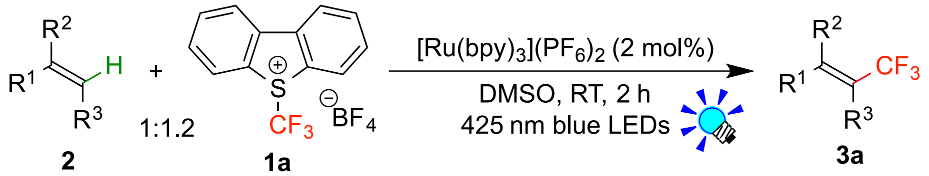
Figure 3.1. ^{1}H NMR spectra (400 MHz, [D_6]DMSO, rt) for the reaction of entry 7 in Table 3.1

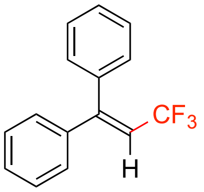
3.3 Scope of Substrates for C–H Trifluoromethylation of Alkenes

The scope and limitations of the present photocatalytic trifluoromethylation of alkenes are summarized in Table 3.2. 1,1-Diphenylethenes with MeO (**2b**), and halogens, Cl (**2c**) and Br (**2d**), smoothly produced the corresponding trisubstituted CF_3-alkenes (**3b**–**d**) in good yields. For the reactions of unsymmetrically substituted substrates (**2e**–**h**), products were obtained in good to moderate yields but consisted of mixtures of *E*- and *Z*-isomers. On the basis of the experimental results, the *E*/*Z* ratios are dependent on the electronic structure of the aryl substituent. The CF_3 groups in the major isomers obtained from substrates with electron-rich aryl substituent are located in trans with respect to the aryl groups. In addition, the present photocatalytic reaction was tolerant to the Boc-protected amino group (**2f**) or pyridine (**2h**). Moreover, a substrate with an alkyl substituent, 2,4-diphenyl-4-methyl-1-pentene (**2i**), was also applicable to this transformation, whereas the reaction of 1,2-disubstituted alkenes such as *trans*-stilbene provided complicated mixtures of products.

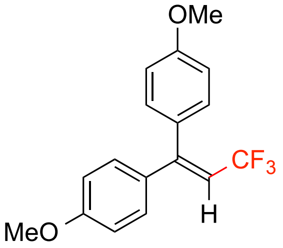
Next, the author extended the present C–H trifluoromethylation to trisubstituted alkenes. The reactions of 1,1-diphenylpropene derivatives **2j** and **2k** (*E*/*Z* = 1/1) afforded the corresponding tetrasubstituted CF_3-alkenes **3j** and **3k** in 82% and 59% (*E*/*Z* = 74/26) yields, respectively. Triphenylethenes **2l** and **2m** (only *E* isomer) were also applicable to this photocatalytic C–H trifluoromethylation. Remarkably, the *E*-isomer of **3m** is a key intermediate for the synthesis of panomifene, which is an antiestrogen drug.[7] These results show that the present protocol enables the efficient construction of a $C_{alkenyl}$–CF_3 bond through direct C–H trifluoromethylation of 1,1-disubstituted and trisubstituted aryl alkenes.

Table 3.2. The scope of the present trifluoromethylation of alkenes[a,b]

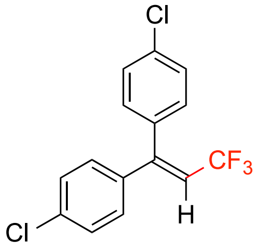




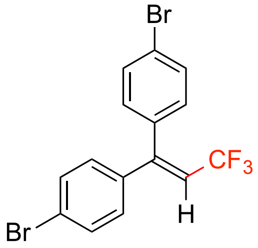
3a: 82%[c]



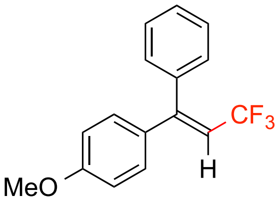
3b: 81%[c]



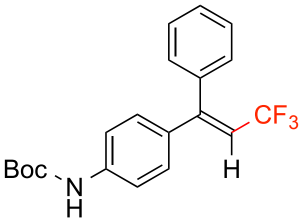
3c: 53%



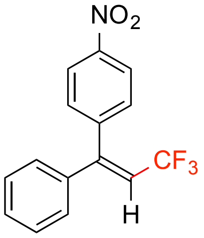
3d: 70%



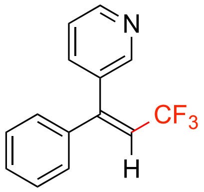
3e: 70%[c]
E/*Z* = 89/11[d]



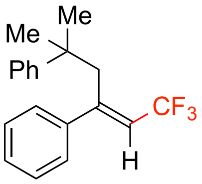
3f: 37%[e]
E/*Z* = 91/9[d]



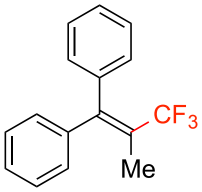
3g: 51%
E/*Z* = 17/83[d]



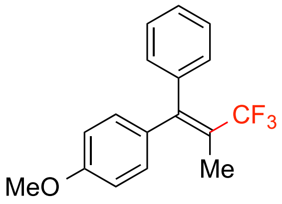
3h: 78%
E/*Z* = 33/67[d]



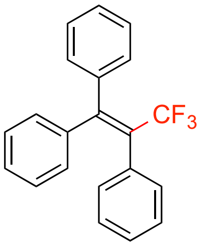
3i: 58%
E/*Z* = 88/12[d]



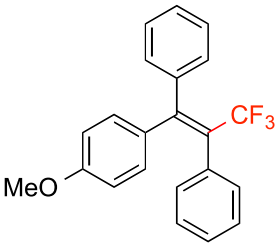
3j: 82%



3k: 59%
E/*Z* = 74/26[d]



3l: 65%

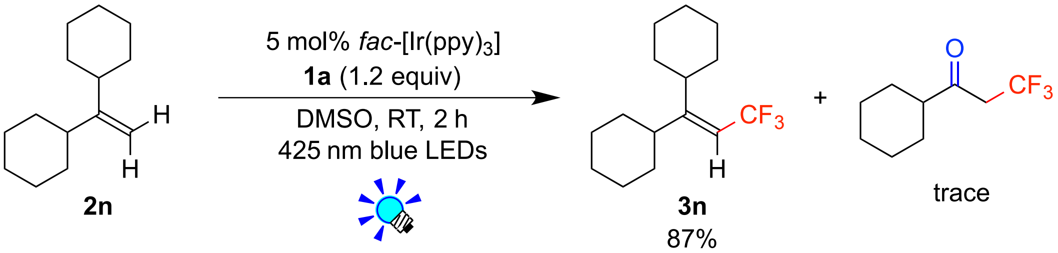


3m: 53%
E/*Z* = 88/12[d]

[a] For preparative reaction conditions, see the Experimental Section.

[b] Isolated yields. [c] NMR yields. [d] *E*/*Z* ratios were determined by ^{19}F NMR spectroscopy of crude product mixtures. [e] 2,6-lutidine (2 equiv.) was added as a base.

As described in Chapter 2, the photoreaction of α-cyclohexylstyrene with Umemoto's reagent in the presence of *fac*-[Ir(ppy)$_3$] photocatalyst in DMSO provided 3,3,3-trifluoro-1-phenylpropan-1-one and cyclohexyldimethylsulfonium salt efficiently (Scheme 2.7, Chapter 2). However, when 1,1-dicyclohexylethene (**2n**) was allowed to react under the same reaction conditions as those for Scheme 2.7, 1,1-dicyclohexyl-3,3,3-trifluoropropene (**3n**) was obtained in an 87% yield with a trace amount of 1-cyclohexyl-3,3,3-trifluoropropan-1-one (Scheme 3.4). This result implies that two bulky cyclohexyl groups block addition of DMSO to the carbocation intermediate, causing deprotonation to give the CF$_3$-alkene **3n**. In addition, this result suggests that the present C–H trifluoromethylation can be applied not only to aromatic alkenes but also to 1,1-dialkylethenes.

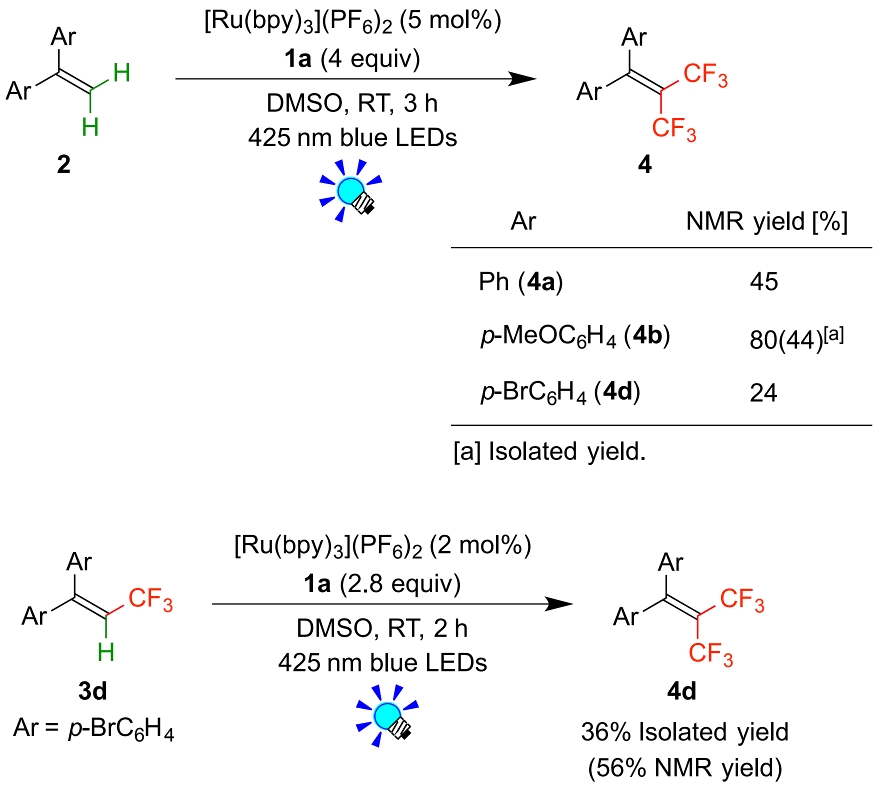


Scheme 3.4. The reaction of 1,1-dicyclohexylethene

3.4 Development of Double Trifluoromethylation

During the course of the author's study on the C–H trifluoromethylation of 1,1-diphenylethene **2**, he found that a detectable amount of bis(trifluoromethyl)alkenes **4** were formed through double C–H trifluoromethylation. In fact, the photocatalytic trifluoromethylation of **2a**,**b** and **d** with 4 equivalents of Umemoto's reagent **1a** in the presence of 5 mol% of [Ru(bpy)$_3$](PF$_6$)$_2$ for 3 h gave germinal bis(trifluoromethyl)ethenes (**4a**,**b** and **d**) in 45, 80 and 24% NMR yields, respectively (Scheme 3.5). Substituents on the benzene ring significantly affect the present double trifluoromethylation. Reaction of the electron-rich alkene **2b** afforded

1,1-anisyl-2,2-bis(trifluoromethyl)ethene (**4b**) in a yield better than those for other alkenes **2a** and **2d**. Additionally, the author found that photocatalytic trifluoromethylation of isolated CF_3-alkene **3d** in the presence of an excess amount of Umemoto's reagent **1a** produced bis(trifluoromethyl)alkene **4d** in a yield (56% NMR yield) better than the above-mentioned one-pot double trifluoromethylation of **2d**.



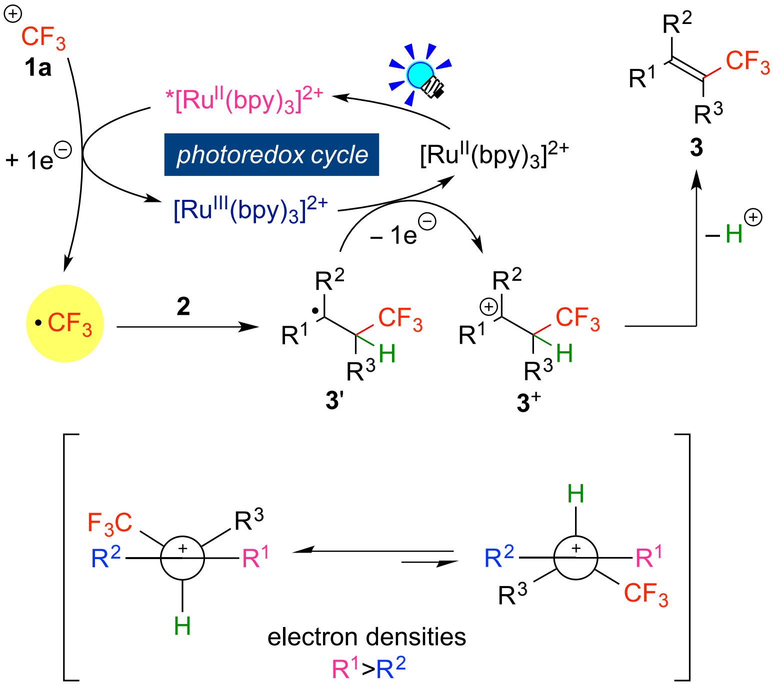
Ar	NMR yield [%]
Ph (**4a**)	45
p-$MeOC_6H_4$ (**4b**)	80(44)[a]
p-BrC_6H_4 (**4d**)	24

[a] Isolated yield.

Scheme 3.5. The double C–H trifluoromethylation of alkenes

3.5 Plausible Reaction Mechanism

A possible reaction mechanism based on SET photoredox processes is illustrated in Scheme 3.6. According to our previous photocatalytic trifluoromethylation,[6] the trifluoromethyl radical ($\cdot CF_3$) is generated from an one-electron-reduction of Umemoto's reagent **1a** by the photoactivated Ru catalyst, $*[Ru(bpy)_3]^{2+}$. The resultant $\cdot CF_3$ reacts with alkene **2** to give the benzyl radical-type intermediate **3'** in a regioselective manner. Subsequent one-electron-oxidation by the highly oxidizing Ru species, $[Ru^{III}(bpy)_3]^{3+}$, produces α-CF_3-substituted carbocation intermediate **3**$^+$. Finally, spontaneous elimination of the olefinic proton, which is made acidic by the action of the strongly electron-withdrawing CF_3 substituent, provides trifluoromethylated alkene **3**. In the case of unsymmetrical substrates, the isomer, where the CF_3 group and the electron-donating aryl group are arranged in *trans*-fashion, forms as the major product. The author's experimental results are consistent with the previous report,[7a] which described *E*-selective formation of the tetrasubstituted CF_3-alkene **3m** via a α-CF_3-substituted carbocation intermediate. These facts can be interpreted in terms of the stabilities of the rotational conformers of the α-CF_3-substituted carbocation intermediate **3**$^+$. In the presence of an excess amount of CF_3 reagent **1a**, further C–H trifluoromethylation of CF_3-alkene **3** proceeds to give bis(trifluoromethyl)alkene **4**.



Scheme 3.6. A plausible reaction mechanism

We cannot rule out a radical chain propagation mechanism, but the present transformation requires continuous irradiation of visible light (Figure 3.2), thus suggesting that chain propagation is not a main mechanistic component.

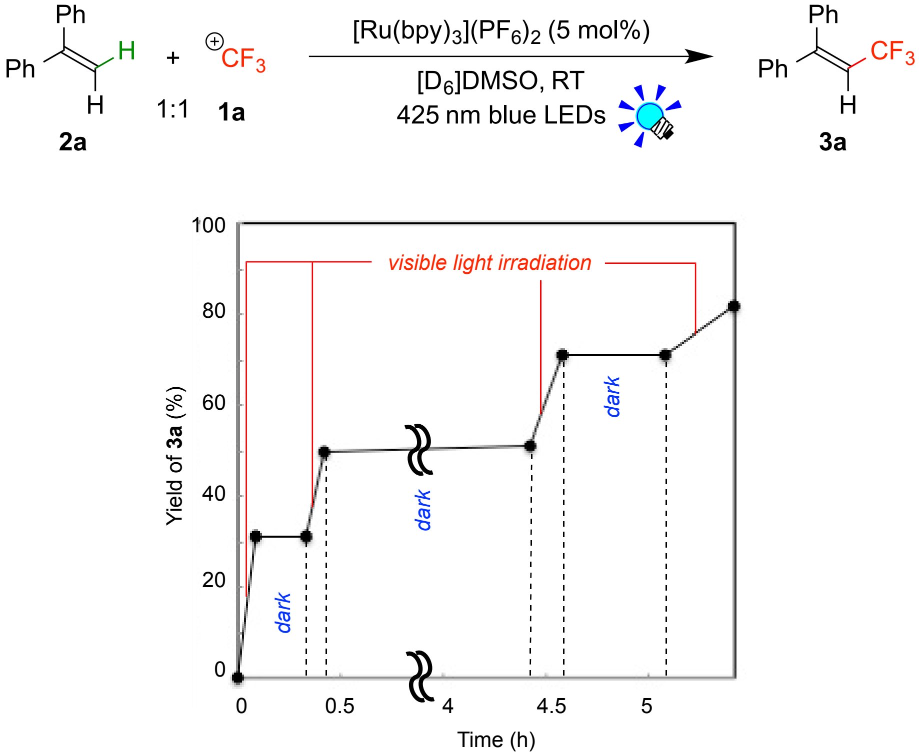
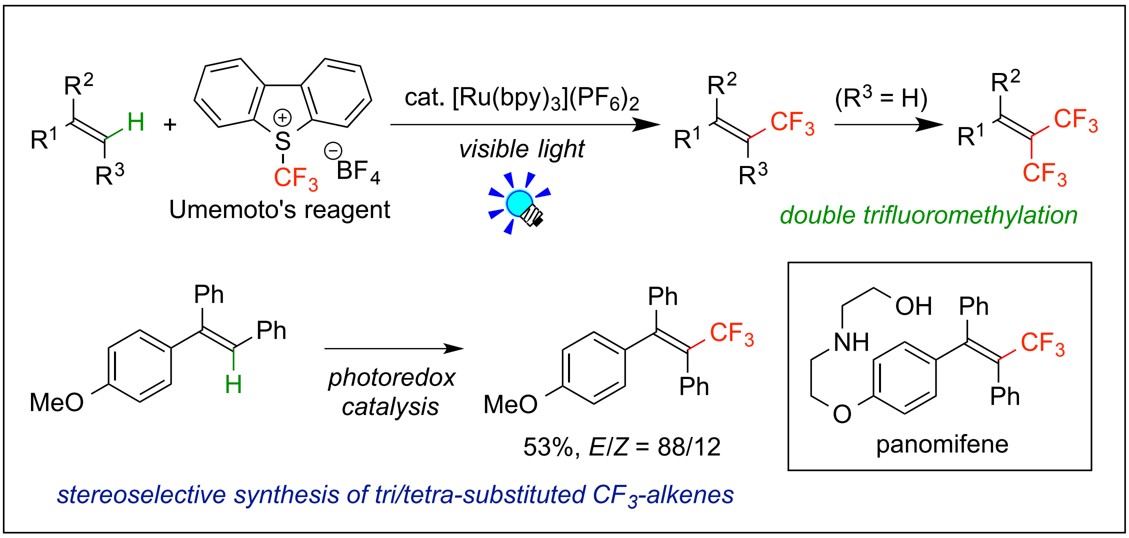


Figure 3.2. Time profile of the photocatalytic C–H trifluoromethylation of **2a**

3.6 Conclusion

The author have developed highly efficient C–H trifluoromethylation of alkenes using Umemoto's reagent as a CF_3 source by visible-light-driven photoredox catalysis. This reaction can be applied to multi-substituted alkenes, especially, 1,1-disubstituted and trisubstituted alkenes, leading to tri- and tetrasubstituted CF_3-alkenes. It is notable that the CF_3 group affects the stereoselective formation of CF_3-alkenes in the case of unsymmetrical substrates. The present straightforward method for the synthesis of multisubstituted CF_3-alkenes from simple aryl alkenes was reported for the first time. In addition, the author has extended the present photocatalytic system to double trifluoromethylation.


R1, R2, R3, H
+
CF3, BF4
Umemoto's reagent
cat. [Ru(bpy)3](PF6)2
visible light
(R3 = H)
double trifluoromethylation
Ph, Ph, H, MeO
photoredox catalysis
CF3
53%, E/Z = 88/12
OH, NH, O
panomifene
stereoselective synthesis of tri/tetra-substituted CF3-alkenes

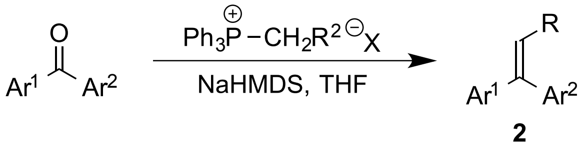
3.7 Experimental

Material and Methods

Alkenes **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2j**, **2k**, and **2n** were prepared by Wittig reactions. (*E*)-1,2-diphenyl-1-(4-methoxyphenyl)ethylene (**2m**) prepared according to the literature procedure.[8a] Catalytic reactions were performed under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. All solvents were dried over molecular sieves, degassed and stored under N_2. Visible light irradiation was performed with a Relyon LED lamp (3 W x 2; λ_{max} = 425 ± 15 nm). Japan Analytical Industry LC-9201 was utilized for recycling preparative HPLC (GPC).

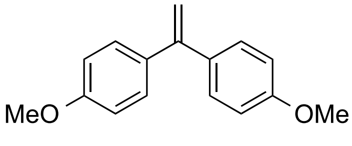
Synthesis of alkene 2

General procedure for the synthesis of alkenes (2b, 2c, 2d, 2e, 2g, 2h, 2j, 2k and 2n) by Wittig reaction



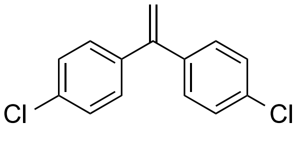
Under N_2, a two-necked 100 mL round-bottom flask was charged with an appropriate alkyl triphenyphosphonium salt (6 mmol) and dry THF (25 mL). Then sodium hexamethylldisilazide (1 M THF solution, 6 mL) was added into the solution and stirred at room temperature for 1 h. To the solution, benzophenone derivative (5 mmol) was added and stirred at room temperature overnight. Et_2O was added into the reaction mixture and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford the product.

1,1-Bis(4-methoxyphenyl)ethene (2b)



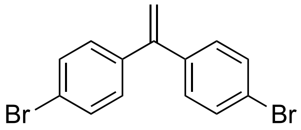
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.28 (d, J = 8.8 Hz, 4H; Ar), 6.86 (d, J = 8.8 Hz, 4H; Ar), 5.29 (s, 2H; C=CH_2), 3.83 (s, 6H; OCH_3). Spectral data were in agreement with the data reported in the literature.[8b].

1,1-Bis(4-chlorophenyl)ethene (2c)



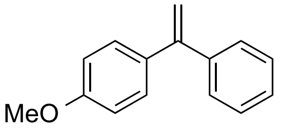
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.31 (d, J = 8.0 Hz, 4H; Ar), 7.24 (d, J = 8.0 Hz, 4H; Ar), 5.45 (s, 2H; C=CH_2). Spectral data were in agreement with the data reported in the literature.[8c].

1,1-Bis(4-bromophenyl)ethene (2d)



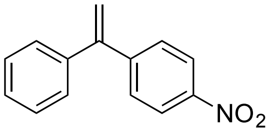
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.46 (d, *J* = 8.8 Hz, 4H; Ar), 7.18 (d, *J* = 8.8 Hz, 4H; Ar), 5.50 (s, 2H; C=C*H*$_2$). Spectral data were in agreement with the data reported in the literature.[8d].

1-(4-Methoxyphenyl)-1-phenylethene (2e)



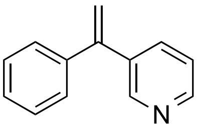
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.35–7.31 (m, 5H; Ph), 7.28 (d, *J* = 8.8 Hz, 2H; Ar), 6.87 (d, *J* = 8.8 Hz, 2H; Ar), 5.40 (s, 1H; C=C*H*H), 5.35 (s, 1H; C=CH*H*), 3.83 (s, 3H; OC*H*$_3$). Spectral data were in agreement with the data reported in the literature.[8e].

1-(4-Nitrophenyl)-1-phenylethene (2g)



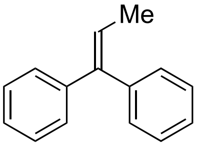
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.20 (d, *J* = 8.8 Hz, 2H; Ar), 7.50 (d, *J* = 8.8 Hz, 2H; Ar), 7.38–7.36 (m, 3H; Ph), 7.30–7.28 (m, 2H; Ph), 5.63 (s, 1H; C=C*H*H), 5.59 (s, 1H; C=CH*H*). Spectral data were in agreement with the data reported in the literature.[8f]

3-(1-Phenylvinyl)pyridine (2h)



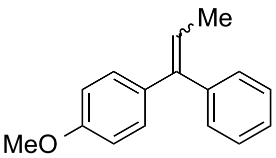
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.63 (dd, *J* = 2.4, 0.8 Hz, 1H; Py), 8.56 (dd, *J* = 4.8, 1.6 Hz, 1H; Py), 7.62 (ddd, *J* = 7.6, 2.0, 1.6 Hz, 1H; Py), 7.36–7.25 (m, 6H; Ar), 5.58 (d, *J* = 0.8 Hz, 1H; C=C*H*H), 5.51 (d, *J* = 0.8 Hz, 1H; C=CH*H*). Spectral data were in agreement with the data reported in the literature.[8g]

1,1-Diphenyl-1-propene (2j)



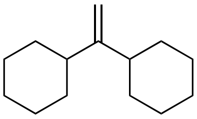
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.39 (t, *J* = 6.8 Hz, 2H; Ph), 7.34–7.19 (m, 8H; Ph), 6.20 (q, *J* = 7.2 Hz, 1H; C=C*H*), 1.78 (d, *J* = 7.2 Hz, 3H; C*H*$_3$). Spectral data were in agreement with the data reported in the literature.[8h].

1-(4-Methoxyphenyl)-1-phenyl-1-propene (2k) (*E*/*Z* = 1/1)



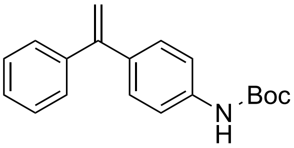
^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.39–7.10 (m, Ar), 6.92 (d, *J* = 8.4 Hz, 2H; Ar), 6.80 (d, *J* = 8.8 Hz, 2H; Ar), 6.13 (q, *J* = 6.8 Hz, 1H; C=C*H*), 6.09 (q, *J* = 7.2 Hz, 1H; C=C*H*), 3.84 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 1.78 (d, *J* = 6.8 Hz, 3H; CHCH_3), 1.74 (d, *J* = 7.2 Hz, 3H; CHCH_3). Spectral data were in agreement with the data reported in the literature.[8i].

1,1-Dicyclohexylethene (2n)



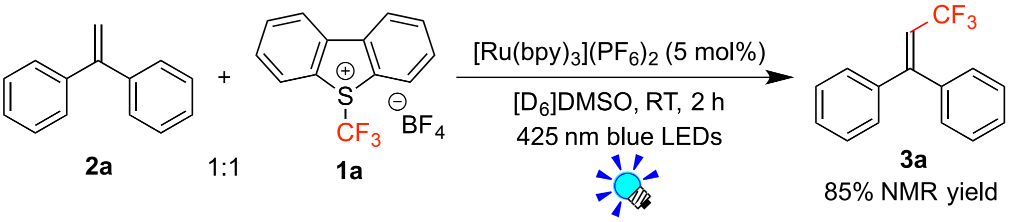
^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 4.79 (s, 2H; C=CH_2), 1.86–1.66 (m, 12H; Cy), 1.32–1.08 (m, 10H; Cy). Spectral data were in agreement with the data reported in the literature.[8j].

N-(*tert*-Butoxycarbonyl)-4-(1-phenylvinyl)aniline (2f)



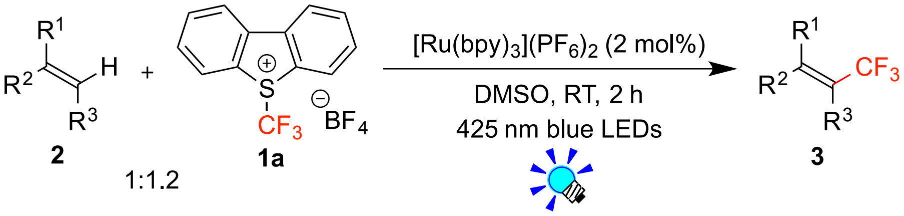
^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.34–7.26 (m, 9H, Ar), 6.48 (br s, 1H, N*H*), 5.41 (d, *J* = 1.2 Hz, 1H; C=C*H*H), 5.38 (d, *J* = 1.2 Hz, 1H; C=CH*H*), 1.53 (s, 9H, C(CH_3)$_3$). ^{13}**C NMR** (100 MHz, $CDCl_3$, rt): δ 152.8, 149.6, 141.7, 138.1, 136.4, 129.0, 128.4, 128.3, 127.8, 118.3, 113.6, 80.7, 28.5. **HRMS** (ESI-TOF): calculated for $[C_{19}H_{21}NO_2+Na]^+$ requires 318.1465, found 318.1464.

NMR experimental procedures (Entry 7 in Table 3.1) and NMR spectra



Under N_2, [Ru(bpy)$_3$](PF$_6$)$_2$ (1.1 mg, 1.3 μmol), Umemoto's reagent **1a** (8.5 mg, 25 μmol), 1,1-diphenylethylene (**2a**) (4.3 μL, 25 μmol), $SiEt_4$ (~1 μL; an internal standard), and [D$_6$]DMSO (0.5 mL) were added to an NMR tube. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h at room temperature (in a water bath). The yields were determined by ^{1}H NMR spectroscopy.

General procedures for the photocatalytic C−H trifluoromethylation of alkenes (Table 3.2, 3a−e, g−m)



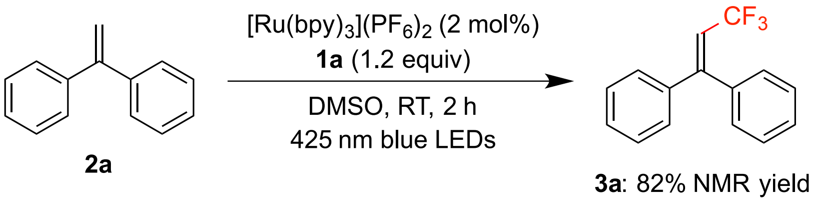
A 20 mL Schlenk tube was charged with Umemoto's reagent **1a** (102 mg, 0.3 mmol), $[Ru(bpy)_3](PF_6)_2$ (4.3 mg, 5 μmol), alkene **2** (0.25 mmol), and DMSO (2.5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, H_2O was added. Products were extracted with Et_2O, washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo.* The product was purified in two ways as described below.

For products **3b**, **3e**, **3g**, **3h**, **3k** and **3m**, the residues were purified by silica gel column chromatography to afford the corresponding products **3**.

For products **3a**, **3c**, **3d**, **3i**, **3j** and **3l**, the residues were treated by mCPBA (74 mg, ca. 0.3 mmol) in CH_2Cl_2 to convert dibenzothiophene, another reaction product, to sulfoxide, which was more easily separated from the products. After the mixture was stirred for 2 h at room temperature, an aqueous solution of $Na_2S_2O_3{\cdot}5H_2O$ was added to the solution, which was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to afford the corresponding product **3**.

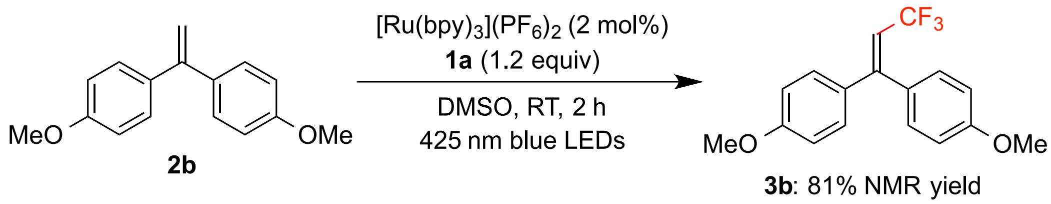
Further purification of **3c**, **3d** and **3m** by GPC provided pure **3c**, **3d** and **3m**.

3,3,3-Trifluoro-1,1-diphenyl-1-propene (3a)



Following the general procedure, the title compound was synthesized from 1,1-diphenylethene (**2a**) (46 mg, 0.26 mmol). The product mixture was purified by silica gel column chromatography (hexane) to afford **3a** including bis(trifluoromethyl)alkene **4a** (62 mg, **3a**: 82% NMR yield, **4a**: 5% NMR yield). The yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.40–7.23 (m, 10H; Ph), 6.13 (q, *J* = 8.4 Hz, 1H; $C\mathit{H}CF_3$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.62 (d, *J* = 8.27 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[9a]

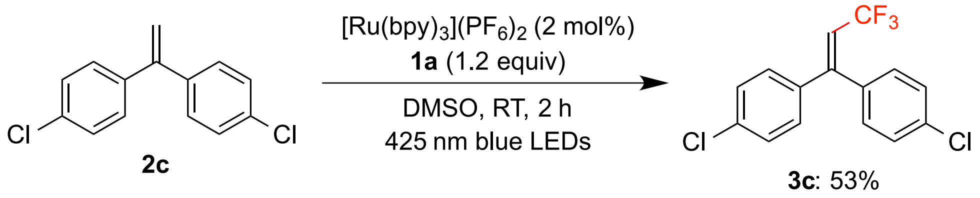
3,3,3-Trifluoro-1,1-bis(4-methoxyphenyl)-1-propene (3b)



Following the general procedure, the title compound was synthesized from 1,1-bis(4-methoxyphenyl)ethene (**2b**) (60 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 29/1) to afford **3b** including bis(trifluoromethyl)alkene **4b** (74 mg, **3b**: 81% NMR yield, **4b**: 18% NMR yield). The yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.19 (d, *J* = 8.4 Hz, 2H; Ar), 7.17 (d, *J* = 8.0 Hz, 2H; Ar), 6.91 (d, *J* = 8.4 Hz, 2H; Ar), 6.84 (d, *J* = 8.4 Hz, 2H; Ar), 5.98 (q, *J* = 8.4 Hz, 1H; $C\mathit{H}CF_3$), 3.85 (s, 3H; $OC\mathit{H}_3$), 3.82 (s, 3H; $OC\mathit{H}_3$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.08 (d, *J* = 8.27 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[10b]

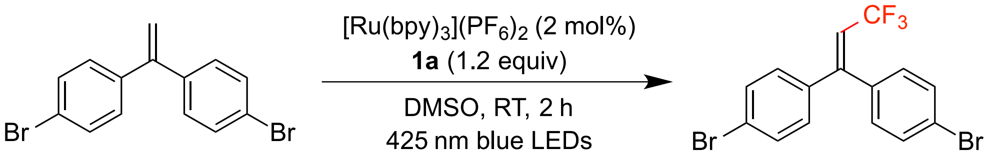
1,1-Bis(4-chlorophenyl) -3,3,3-trifluoro-1-propene (3c)



Following the general procedure, the title compound was synthesized from 1,1-bis(4-chlorophenyl)ethylene (**2c**) (62 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane) to afford **3c** including bis(trifluoromethyl)alkene **4c** (75 mg, **3c**: 82% NMR yield, **4c**: 8% NMR yield). The yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. Further purification by GPC provided pure **3c** (42 mg, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.38 (d, *J* = 8.8 Hz, 2H; Ar), 7.32 (d, *J* = 8.8 Hz, 2H; Ar), 7.16 (d, *J* = 8.4 Hz, 4H; Ar), 6.12 (q, *J* = 8.1 Hz, 1H; C=C*H*CF_3). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 150.4 (q, *J* = 5.4 Hz), 138.3, 136.1, 135.3, 135.2, 130.6, 129.3, 129.0, 128.7, 122.9 (q, *J* = 269 Hz), 116.5 (q, *J* = 33.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.76 (d, *J* = 7.91 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{15}H_9Cl_2F_3+Na]^+$ requires 338.9926, found 338.9967.

1,1-Bis(4-bromophenyl) -3,3,3-trifluoro-1-propene (3d)



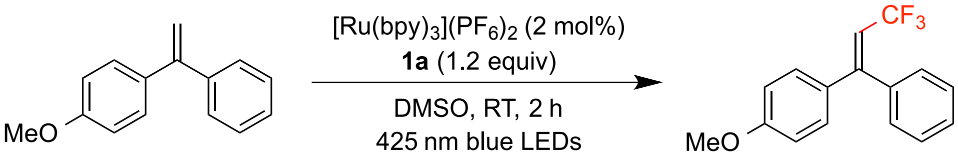
2d

3d: 70%

Following the general procedure, the title compound was synthesized from 1,1-bis(4-bromophenyl)ethylene (**2d**) (85 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane) to afford **3d** including bis(trifluoromethyl)alkene **4d** (90 mg, **3d**: 84% NMR yield, **4d**: 6% NMR yield). The yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. Further purification by GPC provided pure **3d** (71 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.54 (d, *J* = 8.4 Hz, 2H; Ar), 7.47 (d, *J* = 8.4 Hz, 2H; Ar), 7.10 (d, *J* = 8.4 Hz, 4H; Ar), 6.12 (q, *J* = 8.1 Hz, 1H; C=C*H*CF_3). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 150.4 (q, *J* = 5.4 Hz), 138.6, 135.7, 132.0, 131.7, 130.9, 129.6, 124.3, 123.4, 122.9 (q, *J* = 269 Hz), 116.5 (q, *J* = 34.0 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.72 (d, *J* = 7.91 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{15}H_9Br_2F_3+Na]^+$ requires 426.8915, found 426.9055.

3,3,3-Trifluoro-1-(4-methoxyphenyl)-1-phenyl-1-propene (3e)



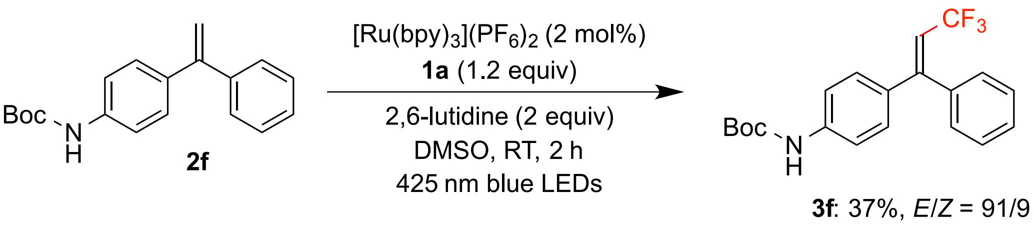
2e

3e: 70% NMR yield
E/*Z* = 89/11

Following the general procedure, the title compound was synthesized from 1-(4-methoxyphenyl)-1-phenylethene (**2e**) (53 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 89/11 from the crude reaction mixture using ^{19}F NMR spectroscopy. The product mixture was purified by silica gel column chromatography (hexane→ hexane/Et_2O = 29/1) to afford **3e** including bis(trifluoromethyl)alkene **4e** (54 mg, **3e**: 70% NMR yield (*E*/*Z* = 89/11), **4e**: 14% NMR yield). The yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard.

E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.40–7.38 (m, 3H; Ph), 7.25–7.22 (m, 2H; Ph), 7.18 (d, *J* = 8.8 Hz, 2H; Ar), 6.84 (d, *J* = 8.8 Hz, 2H; Ar), 6.06 (q, *J* = 8.4 Hz, 1H; C*H*CF_3), 3.81 (s, 3H; OC*H*$_3$). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.17 (d, *J* = 8.27 Hz, 3F). Spectral data were in agreement with the data reported in the literature.[9b]

N-(*tert*-Butoxycarbonyl)-4-(1-phenyl-3,3,3-trifluoropropenyl)aniline (3f)



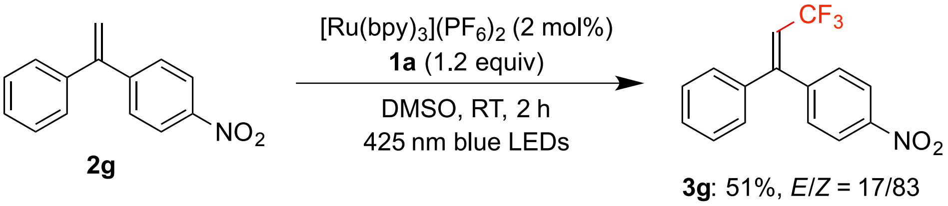
A 20 mL Schlenk tube was charged with Umemoto's reagent **1a** (102 mg, 0.3 mmol), $[Ru(bpy)_3](PF_6)_2$ (4.3 mg, 5 μmol), *N*-(*tert*-butoxycarbonyl)-4-(1-phenylvinyl)aniline (**2f**) (74 mg, 0.25 mmol), 2,6-lutidine (58 μL, 0.5 mmol) and DMSO (2.5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, H_2O was added. The resulting mixture was extracted with Et_2O, washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The *E*/*Z* ratio was determined to be 91/9 from the crude reaction mixture using ^{19}F NMR spectroscopy. The residue was purified by silica gel column chromatography (hexane→hexane/EtOAc = 9/1) to afford **3f** including bis(trifluoromethyl)alkene **4f** (60 mg, **3f**: 59% NMR yield, *E*/*Z* = 91/9, **4f**: 21% NMR yield). The yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. Further purification by GPC provided pure **3f** (33 mg, 37% yield, *E*/*Z* = 93/7). The stereochemistry was confirmed by ^{1}H-^{1}H NOESY NMR.

E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.38 (m, 3H; Ar), 7.32 (d, *J* = 8.8 Hz, 2H; Ar), 7.22 (m, 2H; Ar), 7.17 (d, *J* = 8.4 Hz, 2H; Ar), 6.53 (br s, 1H; N*H*), 6.08 (q, *J* = 8.4

Hz, 1H; C=C*H*CF$_3$), 1.52 (s, 9H; C(C*H*$_3$)$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$, rt): δ 152.6, 152.0 (q, *J* = 5.3 Hz), 139.8, 137.5, 134.7, 129.3, 128.9, 128.6, 128.1, 123.4 (q, *J* = 269 Hz), 118.32, 114.2 (q, *J* = 33.6 Hz), 81.1, 28.4. **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –55.32 (d, *J* = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for [C$_{20}$H$_{20}$F$_3$NO$_2$+Na]$^+$ requires 386.1338, found 386.1332.

Z-isomer: **^{1}H NMR** (400 MHz, CDCl$_3$, rt): δ 6.06 (q, *J* = 8.0 Hz, 1H; C=C*H*CF$_3$), 1.53 (s, 9H; C(C*H*$_3$)$_3$). **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –55.56 (d, *J* = 9.04 Hz, 3F).

3,3,3-Trifluoro-1-(4-nitrophenyl)-1-phenyl-1-propene (3g)



Following the general procedure, the title compound was synthesized from 1-(4-nitrophenyl)-1-phenylethylene (**2g**) (56 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 17/83 from the crude reaction mixture using ^{19}F NMR spectroscopy. The product mixture was purified by silica gel column chromatography (hexane→ hexane/Et$_2$O = 19/1) to afford **3g** (39 mg, 51% yield, *E*/*Z* = 17/83). The stereochemistry was confirmed by ^{1}H-^{1}H NOESY NMR.

Z-isomer: **^{1}H NMR** (400 MHz, CDCl$_3$, rt): δ 8.27 (d, *J* = 8.8 Hz, 2H; Ar), 7.45–7.35 (m, 5H; Ar), 7.21 (d, *J* = 8.0 Hz, 2H; Ar), 6.25 (q, *J* = 8.1 Hz, 1H; C=C*H*CF$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$, rt): δ 150.4 (q, *J* = 5.4 Hz), 148.2, 144.1, 138.7, 127.9, 123.5, 122.8 (q, *J* = 269 Hz), 117.1 (q, *J* = 34.0 Hz). Aromatic signals of *E*/*Z* isomers were overlapped around (130.3, 130.2, 129.3, 129.1, 129.0). **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –55.72 (d, *J* = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for [C$_{15}$H$_{10}$F$_3$NO$_2$+Na]$^+$ requires 316.0556, found 316.0553.

E-isomer: **^{1}H NMR** (400 MHz, CDCl$_3$, rt): δ 8.19 (d, *J* = 8.8 Hz, 2H; Ar), 7.45–7.35 (m, 5H; Ar), 7.21 (d, *J* = 8.0 Hz, 2H; Ar), 6.22 (q, *J* = 8.0 Hz, 1H; C=C*H*CF$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$, rt): δ 148.5, 146.4, 136.1, 128.6, 123.9, 118.6 (q, *J* = 33.8 Hz). Aromatic signals of *E*/*Z* isomers were overlapped around (130.3, 130.2, 129.3, 129.1, 129.0).

^{19}F NMR (376 MHz, CDCl$_3$, rt): δ –56.23 (d, *J* = 8.00 Hz, 3F).

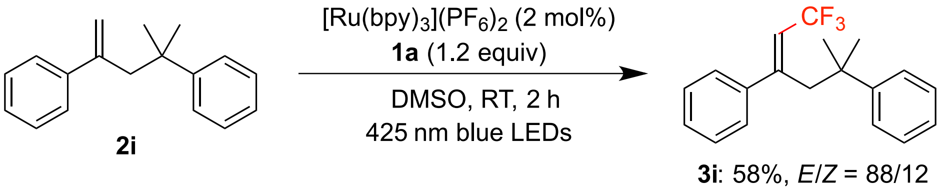
3,3,3-Trifluoro-1-phenyl-1-(3-pyridyl)-1-propene (3h)

Following the general procedure, the title compound was synthesized from 1-phenyl-1-(3-pyridyl)ethylene (**2h**) (45 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 33/67 from the crude reaction mixture using ^{19}F NMR spectroscopy. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 1/1) to afford **3h** (48 mg, 78% yield, *E*/*Z* = 32/68). The stereochemistry was confirmed by ^{1}H-^{1}H NOESY NMR.

Z-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 8.66 (dd, *J* = 4.8, 1.6 Hz, 1H; Ar), 8.52 (d, *J* = 1.6 Hz, 1H; Ar), 7.57 (d, *J* = 7.8 Hz, 1H; Ar), 7.42–7.33 (m, 3H; Ar), 7.28–7.22(m, 2H; Ar), 6.23 (q, *J* = 8.1 Hz, 1H; C=C*H*CF$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 149.9, 149.6, 149.1 (q, *J* = 5.3 Hz), 139.3, 136.6, 133.3, 128.9, 128.5, 128.0, 123.1, 122.9 (q, *J* = 269 Hz), 117.3 (q, *J* = 33.4 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.58 (d, *J* = 8.28 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{14}H_{10}F_3N+Na]^+$ requires 272.0658, found 272.0657.

E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 8.60 (dd, *J* = 4.8, 1.2 Hz, 1H; Ar), 8.56 (d, *J* = 2.0 Hz, 1H; Ar), 7.51 (d, *J* = 8.1 Hz, 1H; Ar), 7.42–7.33 (m, 3H; Ar), 7.28–7.22(m, 2H; Ar), 6.16 (q, *J* = 8.0 Hz, 1H; C=C*H*CF$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 150.5, 148.8, 136.3, 136.0, 135.4, 130.0, 129.1, 129.1, 123.4, 122.8 (q, *J* = 270 Hz), 116.9 (q, *J* = 33.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.99 (d, *J* = 8.28 Hz, 3F).

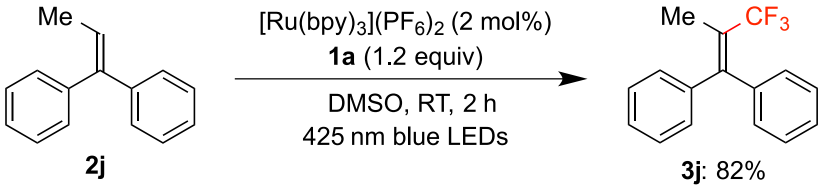
1,1,1-Trifluoro-3,5-diphenyl-5-methyl-2-hexene (3i)



Following the general procedure, the title compound was synthesized from 2,4-diphenyl-4-methyl-1-pentene (**2i**) (59 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 88/12 from the crude reaction mixture using ^{19}F NMR spectroscopy. The product mixture was purified by silica gel column chromatography (hexane) to afford **3i** (45 mg, 58% yield, *E*-isomer only). The stereochemistry was confirmed by ^{1}H-^{1}H NOESY NMR.

E-isomer: ^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.22–7.10 (m, 9H; Ar), 7.06 (t, *J* = 7.0 Hz, 1H; Ar), 5.66 (q, *J* = 8.8 Hz, 1H; C=C*H*CF_3), 3.09 (d, *J* = 1.2 Hz, 2H; CC*H*$_2$C), 1.21 (s, 6H; C*H*$_3$). ^{13}**C NMR** (100 MHz, $CDCl_3$, rt): δ 152.7 (q, *J* = 5.4 Hz), 149.3, 141.8, 128.3, 128.0, 127.0, 125.8, 125.7, 123.4 (q, *J* = 269 Hz), 119.6 (q, *J* = 33.1 Hz), 44.5, 38.4, 28.8. ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –55.96 (d, *J* = 9.41 Hz, 3F). **HRMS** (ESI-TOF): calculated for $[C_{19}H_{19}F_3+Na]^+$ requires 327.1331, found 327.1332.

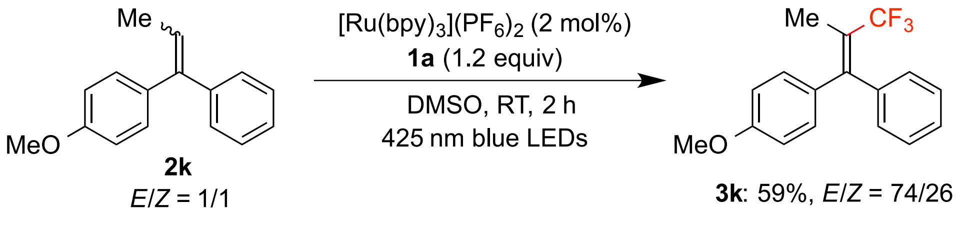
3,3,3-Trifluoro-1,1-diphenyl-1-propene (3j)



Following the general procedure, the title compound was synthesized from 1,1-diphenyl-1-propene (**2j**) (49 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane) to afford **3j** (54 mg, 82% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.35–7.28 (m, 6H; Ph), 7.18–7.13 (m, 4H; Ph), 1.93 (s, 3H; C*H*$_3$). ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –59.44 (s, 3F). Spectral data were in agreement with the data reported in the literature.[9c].

3,3,3-Trifluoro-1-(4-methoxyphenyl)-2-methyl-1-phenyl-1-propene (3k)

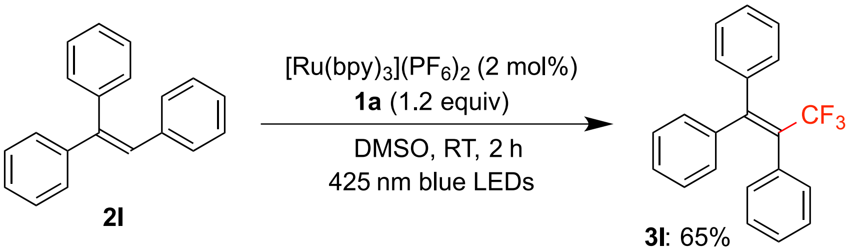


Following the general procedure, the title compound was synthesized from 1-(4-methoxyphenyl)-1-phenyl-1-propene (**2k**) (56 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 74/26 from the crude reaction mixture using ^{19}F NMR spectroscopy. The product mixture was purified by silica gel column chromatography (hexane→ hexane/Et_2O = 29/1) to afford **3k** (45 mg, 59% yield, *E*/*Z* = 74/26). The stereochemistry was confirmed by ^{1}H-^{1}H NOESY NMR.

E-isomer: ^{1}**H NMR** (400 MHz, CDCl$_3$, rt): δ 7.34–7.27 (m, 3H; Ar), 7.14 (d, *J* = 9.6 Hz, 2H; Ar), 7.05 (d, *J* = 8.8 Hz, 2H; Ar), 6.85 (d, *J* = 8.8 Hz, 2H; Ar), 3.80 (s, 3H; C*H*$_3$O), 1.96 (s, 3H; C*H*$_3$CCF$_3$). ^{13}**C NMR** (100 MHz, CDCl$_3$, rt): δ 159.3, 147.3, 141.4, 133.7, 130.5, 128.7, 128.4, 128.0, 127.6, 124.8 (q, *J* = 274 Hz), 123.0 (q, *J* = 27.9 Hz), 113.8, 55.4, 16.5. ^{19}**F NMR** (376 MHz, CDCl$_3$, rt): δ –59.23 (s, 3F). **HRMS** (ESI-TOF): calculated for $[C_{17}H_{15}F_3O+Na]^+$ requires 315.0967, found 315.0963.

Z-isomer: ^{1}**H NMR** (400 MHz, CDCl$_3$, rt): δ 7.34–7.27 (m, 3H; Ar), 7.12 (d, *J* = 8.4 Hz, 2H; Ar), 7.08 (d, *J* = 8.8 Hz, 2H; Ar), 6.82 (d, *J* = 8.8 Hz, 2H; Ar), 3.79 (s, 3H; C*H*$_3$O), 1.90 (s, 3H; C*H*$_3$CCF$_3$). ^{13}**C NMR** (100 MHz, CDCl$_3$, rt): δ 159.3, 147.3, 141.8, 133.4, 130.0, 129.0, 128.4, 127.8, 113.5, 55.3, 16.5. ^{19}**F NMR** (376 MHz, CDCl$_3$, rt): δ –59.36 (s, 3F).

3,3,3-Trifluoro-1,1,2-triphenyl-1-propene (3l)



Following the general procedure, the title compound was synthesized from triphenylethene (**2l**) (64 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane) to afford **3l** (53 mg, 65% yield).

^{1}**H NMR** (400 MHz, CDCl$_3$, rt): δ 7.38–6.92 (m, 15H; Ph). ^{19}**F NMR** (376 MHz, CDCl$_3$, rt): δ –55.76 (s, 3F). Spectral data were in agreement with the data reported in the literature.[9d]

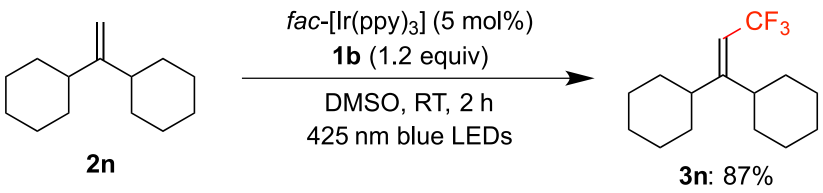
3,3,3-Trifluoro-1-(4-methoxyphenyl)-1,2-diphenyl-1-propene (3m)

Following the general procedure, the title compound was synthesized from

(*E*)-1-(4-methoxyphenyl)-1,2-diphenylethene (**2m**) (69 mg, 0.24 mmol). The *E*/*Z* ratio was determined to be 88/12 from the crude reaction mixture using ^{19}F NMR spectroscopy. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 29/1) followed by GPC to afford **3m** (46 mg, 53% yield, *E*/*Z* = 90/10).

^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.40–7.18 (m, 10H; Ar), 6.82 (d, J = 9.2 Hz, 2H; Ar), 6.56 (d, J = 8.8 Hz, 2H; Ar), 3.67 (s, 3H; OCH_3). ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –55.38 (s, 3F). Spectral data were in agreement with the data reported in the literature.[9d]

1,1-Dicyclohexyl-3,3,3-trifluoro-1-propene (3n)



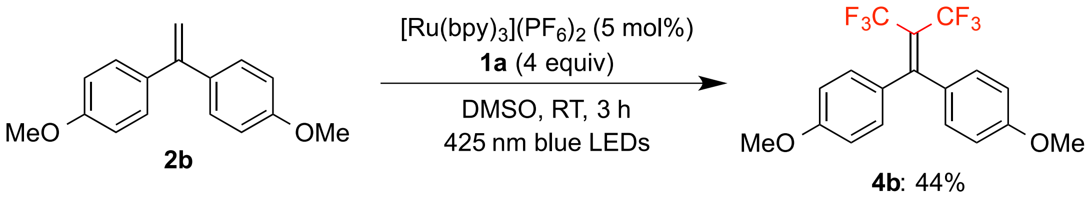
A 20 mL Schlenk tube was charged with Umemoto's reagent **1b** (102 mg, 0.3 mmol), *fac*-[Ir(ppy)$_3$] (8.2 mg, 13 μmol), 1,1-dicyclohexylethene (**2n**) (48 mg, 0.25 mmol), and DMSO (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, H_2O was added. The resulting mixture was extracted with Et_2O, washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo.*

The residue was treated by mCPBA (74 mg, ca. 0.3 mmol) in CH_2Cl_2 to convert the dibenzothiophene to sulfoxide. After the solution was stirred at room temperature for 2 h, an aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$ was added to the solution, which was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane) to afford **3n** (57 mg, 87% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 5.35 (q, J = 8.8 Hz, 1H; $CHCF_3$), 2.70 (m, 1H; Cy), 2.05 (tt, J = 12, 3.6 Hz, 1H; Cy), 1.77–1.65, 1.54–1.50, 1.38–1.07 (m, 20H; Cy). ^{13}**C NMR** (126 MHz, $CDCl_3$, rt): δ 166.4 (q, J = 5.3 Hz), 124.7 (q, J = 272 Hz), 112.8 (q, J = 33.4 Hz), 42.3, 39.8, 34.9, 30.2, 26.9, 26.2, 26.1, 26.1. ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –55.05 (d, J = 9.02 Hz, 3F). **HRMS** (EI): calculated for $[C_{15}H_{23}F_3]^+$ requires 260.1752, found 260.1753.

Procedures for the photocatalytic double C−H trifluoromethylation of alkenes

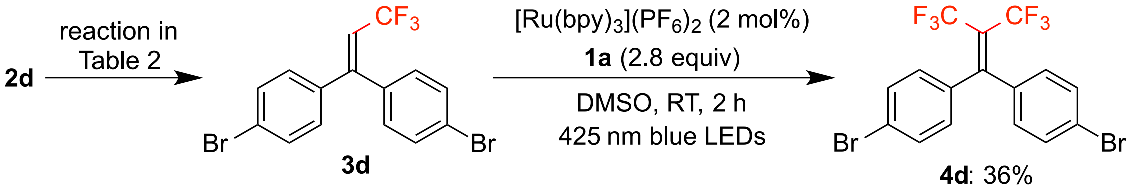
2-Trifluoromethyl-3,3,3-trifluoro-1-bis(4-methoxyphenyl)propene (4b)



A 20 mL Schlenk tube was charged with Umemoto’s reagent (**1a**) (340 mg, 1.0 mmol), $[Ru(bpy)_3](PF_6)_2$ (10.7 mg, 12 μmol), **2b** (60 mg, 0.25 mmol), and DMSO (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 3 h with stirring at room temperature (in a water bath). After the reaction, H_2O was added. Products were extracted with Et_2O, washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane→hexane/Et_2O = 29/1) to afford **4b** as a product mixture with **3b**. Further purification by GPC provided pure **4b** (44 mg, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.09 (d, J = 8.8 Hz, 4H; Ar), 6.87 (d, J = 8.8 Hz, 4H; Ar), 3.83 (s, 6H; CH_3O). **^{13}C NMR** (100 MHz, $CDCl_3$, rt): δ 161.3, 160.1, 132.3, 131.2, 122.3, (q, J = 273 Hz), 115.7 (q, J = 30.1 Hz), 113.7, 55.4. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –54.80 (s, 6F). **HRMS** (ESI-TOF): calculated for $[C_{18}H_{14}F_6O_2\text{+Na}]^+$ requires 399.0790, found 399.0795.

1-Bis(4-bromophenyl)-2-trifluoromethyl-3,3,3-trifluoropropene (4d)



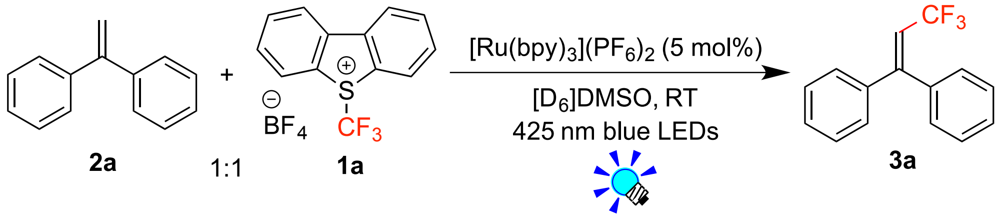
Two step reactions were conducted. Following the procedure in Table 2, **2d** (85 mg, 0.25 mmol) was converted into the mixture of **3d** and a small amount of **4d** (90 mg). To the mixture, Umemoto’s reagent **1a** (238 mg), $[Ru(bpy)_3](PF_6)_2$ (4.3 mg) and DMSO (5 mL) were added under N_2. The solution was placed at a distance of 2−3 cm from 3W blue LED lamp and irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, H_2O was added. Products were extracted with Et_2O, washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo.* The residue was treated by mCPBA (0.17 g, ca. 0.7 mmol) in CH_2Cl_2 to convert the dibenzothiophene to sulfoxide, which was more easily separated from the products. After the solution was stirred at room temperature for 2 h, an aqueous solution of $Na_2S_2O_3{\cdot}5H_2O$ was added to the solution, which was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane) to afford **4d** as a product mixture with **3d**. Further purification by GPC provided pure **4d** (42 mg, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.51 (d, J = 8.4 Hz, 4H; Ar), 7.01 (d, J = 8.4 Hz, 4H; Ar).

^{13}C NMR (100 MHz, $CDCl_3$, rt): δ 157.9, 137.7, 131.9, 130.3, 124.9, 121.5 (q, J = 276 Hz), 119.4 (q, J = 31.0 Hz), **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –55.31 (s, 6F). **HRMS** (ESI-TOF): calculated for $[C_{16}H_8Br_2F_6+Na]^+$ requires 474.8950, found 474.8953.

Time profile of the photocatalytic C−H trifluoromethylation of 2a (Figure 3.2)

The trifluoromethylation of **2a** was performed with repeating on-and-off irradiation of visible light irradiation. The time profile is shown in Figure 3.2. As a result, continuous irradiation of visible light is essential for efficient reaction. Furthermore, the result of this experiment suggests that radical chain propagation is not a main component in this reaction.



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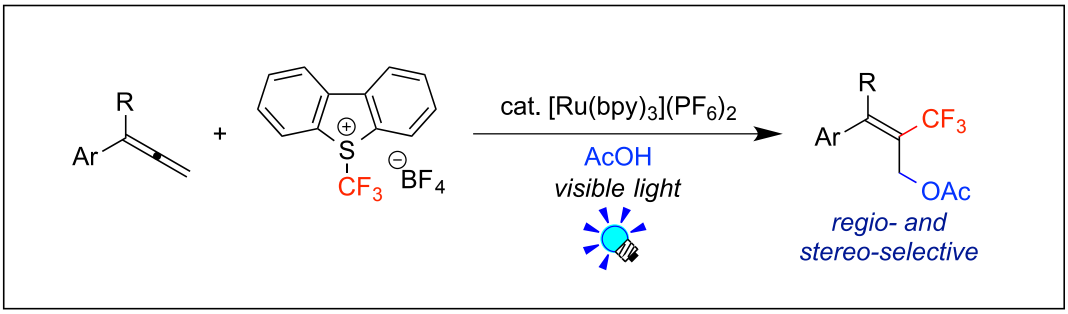
Chapter 4

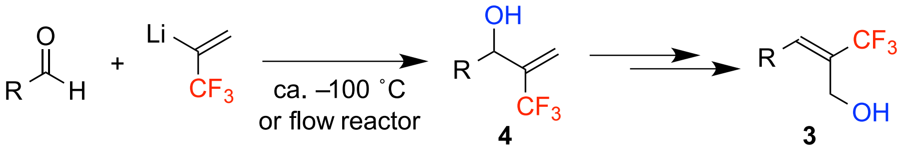
Oxy-Trifluoromethylation of Allenes by Photoredox Catalysis

ABSTRACT: Trifluoromethylated allylic alcohols are promising building blocks for synthesis of fluorinated compounds. Regio- and stereoselective synthesis of allylic acetates bearing tetrasubstituted CF_3-alkene moiety from 1,1-disubstituted allenes is achieved by photoredox-catalyzed SET processes. The products can be transformed into the corresponding allylic alcohol and applied to a palladium-catalyzed substitution reaction



4.1 Introduction

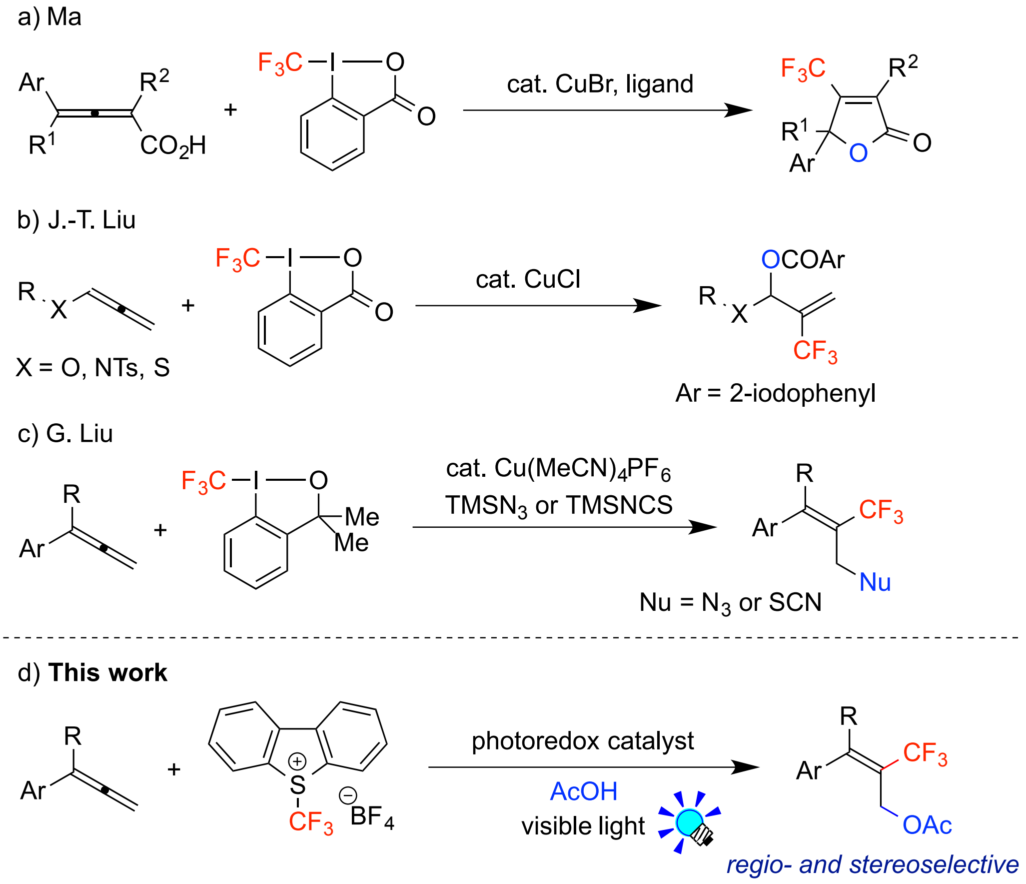
Allylic alcohols are highly useful building blocks for organic synthesis. A wide variety of organic reactions utilizes this functionality to obtain more complex molecules. Thus, allylic alcohol derivatives bearing trifluoromethylated (CF_3-) alkene moiety are regarded as key intermediates for fluorinated compounds.[1] Trifluoromethylated allylic alcohols **4** are classically synthesized by the reaction of aldehyde with α-(trifluoromethyl)vinyllithium prepared from 2-bromo-3,3,3-trifluoroprop-1-ene and following rearrangement gives a regioisomer **3** (Scheme 4.1).[1a,b,e,g,2] Because this lithium reagent, however, is very unstable, it should be prepared and reacted at extremely low temperature around –100 ˚C or requires a flow reactor.[2e] In addition, versatile synthetic methods for allylic alcohol derivatives bearing tetrasubstituted CF_3-alkene moiety are very limited so far.[3]



Scheme 4.1. Classical synthesis of trifluoromethylated allylic alcohols

In recent years, trifluoromethylation of alkenes has been studied extensively.[4] In contrast, there are few reports for trifluoromethylation of dienes. Sodeoka et al. and Xu et al. reported copper-catalyzed benzyloxy-trifluoromethylation of 1,3-dienes.[5] In terms of 1,2-diene, i.e. allene, the groups of Ma, J.-T. Liu and G. Liu separately reported Cu-catalyzed intra- or intermolecular trifluoromethylative difunctionalizations of allenes with electrophilic trifluoromethylating reagents, Togni's reagents (Scheme 4.2.a–c).[6]

As described in Chapter 2 and 3, the author has established trifluoromethylation of alkenes leading α-trifluoromethylated ketones and multisubstituted CF_3-alkenes by photoredox catalysis.[7] Motivated by these experiences, he attempted to expand the trifluoromethylation involving SET photoredox processes to allenes. In this chapter, a highly regio- and stereoselective acetoxy-trifluoromethylation of 1,1-disubstituted allenes will be described (Scheme 4.2.d). The present reaction gives us access to allylic acetates bearing tetrasubstituted CF_3-alkene moiety, which are precursors for trifluoromethylated allylic alcohols and substrates for further transformations.



Scheme 4.2. Trifluoromethylative difunctionalizations of allenes

4.2 Investigation of Oxy-Trifluoromethylation of Allene

Initially, the author examined photocatalytic hydroxyl-trifluoromethylation of an allene with reference to the hydroxyl-trifluoromethylation of alkenes.[7a] The reaction of 1-methyl-1-phenylallene (**2a**) with 1.0 equivalent of Umemoto's reagent **1a** was conducted in [D_6]acetone/D_2O (30/1) in the presence of [$Ru(bpy)_3$](PF_6)$_2$ (5 mol%) under visible-light irradiation (425 nm blue LEDs) for 1 h. As a result, the NMR spectra of the reaction mixture showed formation of trifluoromethylated allylic alcohols but as a mixture of the two allylic regio isomers **3a** (36% yield) and **4a** (37% yield) (Figure 4.1). This result indicates the reaction went through an allyl cation intermediate and water attacked both allylic terminals of the cation intermediate. Therefore, the author explored other systems, where the regio selectivity of the addition of a nucleophile can be controlled.

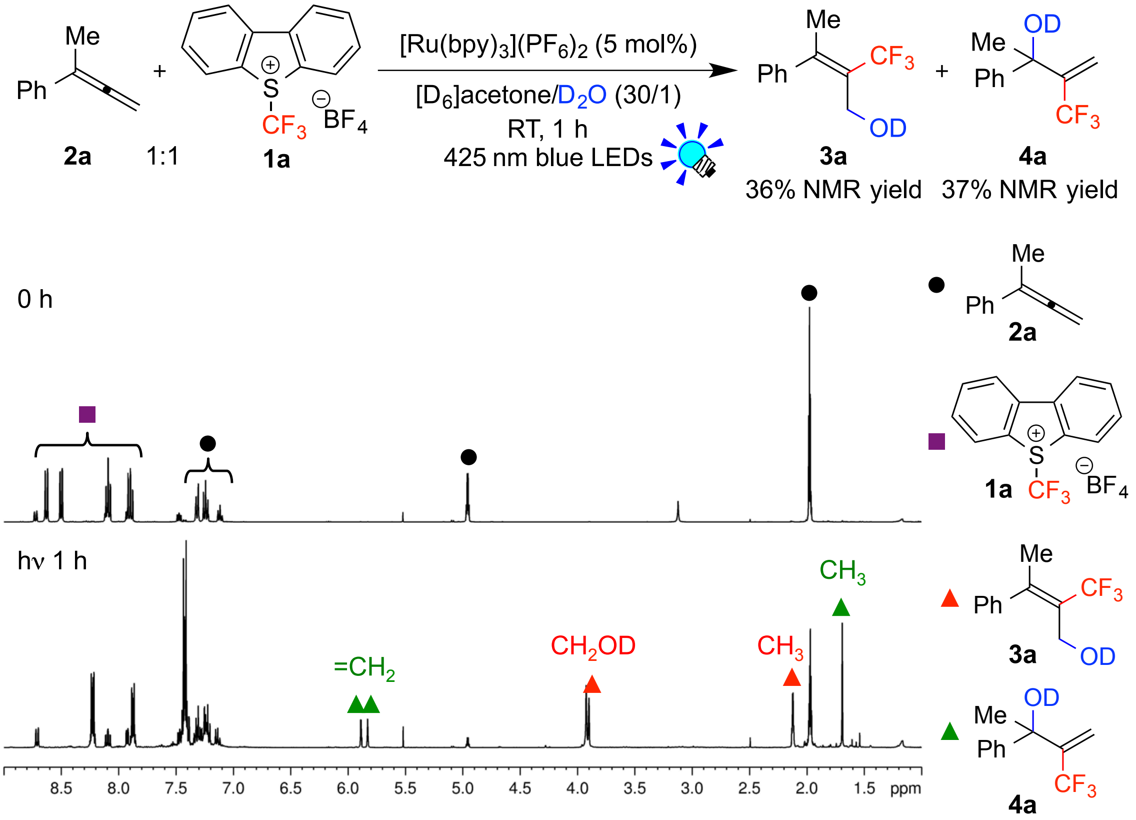


Figure 4.1. Photocatalytic hydroxy-trifluoromethylation of **2a** and its ^{1}H NMR spectra (400 MHz, CD_2Cl_2/CD_3CO_2D, rt)

To the author's delight, when he examined the reaction in a CD_2Cl_2/CD_3CO_2D (9/1) solvent system, an acetoxy-trifluoromethylated product **5a** was produced in a 63%

NMR yield in a highly regio- and stereoselective manner (Table 4.1, entry 1). As all of us know, allylic acetate is a useful building block for organic synthesis such as a precursor of allylic alcohol and a substrate for transition-metal-catalyzed allylic substitution reactions. Use of other trifluoromethylating reagents such as Yagupol'skii-Umemoto reagent **1b**[8] and Togni's reagent **1c** and combination of **1b** with the iridium photocatalyst, $[Ir(ppy)_2(dtbbpy)](PF_6)$,[9] lowered the yield and the regioselectivity of **5a** (entries 2–4). Other solvent systems, such as $[D_6]acetone/CD_3CO_2D$ and CD_3CN/CD_3CO_2D showed good regioselectivities but the yields of **5a** were lower (entries 5 and 6). Interestingly, the reaction in the presence of a larger amount of acetic acid (CD_2Cl_2/CD_3CO_2D = 3.5/1.5) lowered the regio selectivity of **5a**/**6a**, and addition of inorganic or organic base also lowered the regio selectivity (entries 7–9). Finally, irradiation with visible light and the photoredox catalyst were essential for the present reaction (entries 10 and 11). The NMR spectra for the reaction entry 1 in Table 4.1 show the selective formation of the CF_3-allylic acetate **5a** upon irradiation with consumption of the substrates **1a** and **2a** (Figure 4.2). The stereochemistry of **5a** was determined to be (*E*)-isomer by ^1H-^1H NOESY NMR spectrum of an isolated product.

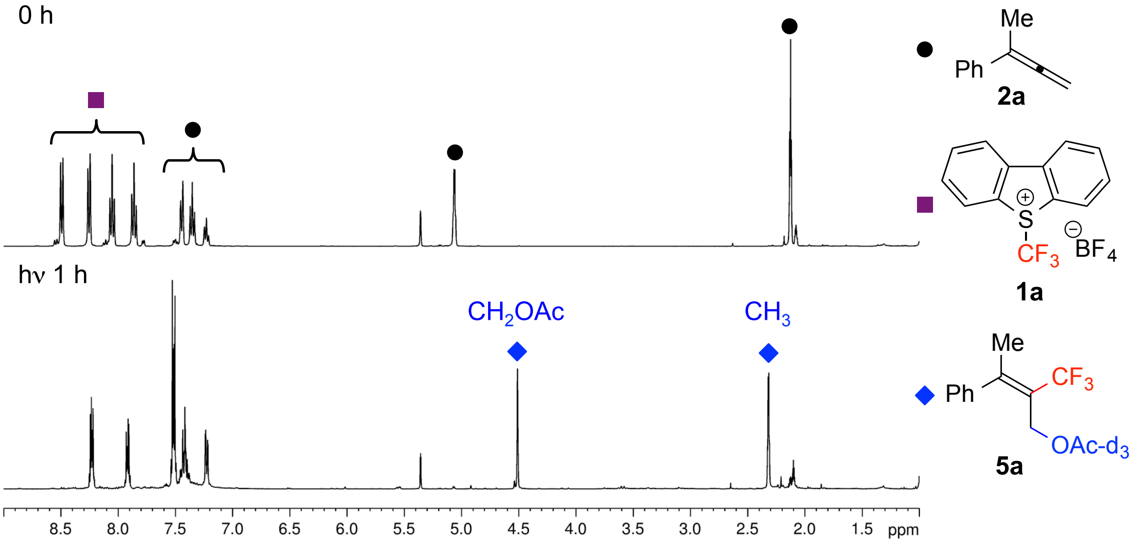
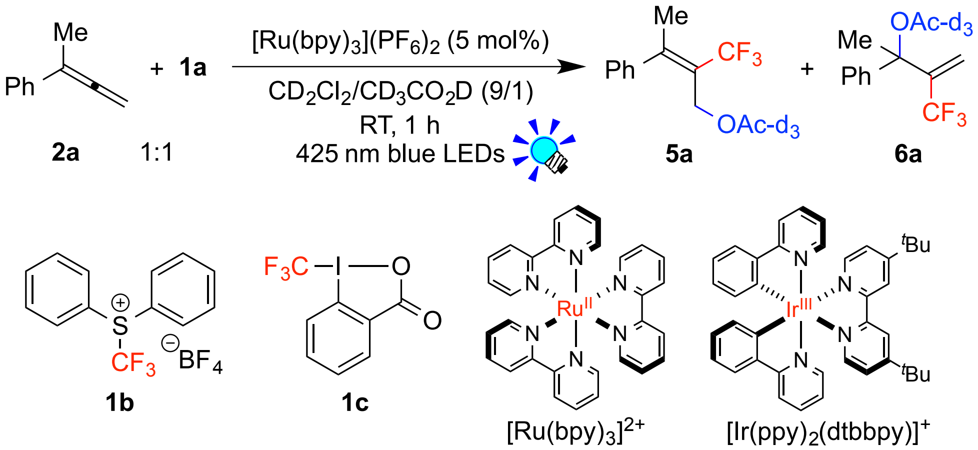


Figure 4.2. ^1H NMR spectra (400 MHz, CD_2Cl_2/CD_3CO_2D, rt) for entry 1 in Table 4.1

Table 4.1. Optimization of acetoxy-trifluoromethylation of **2a**



Entry	Deviations from the standard conditions[a]	Yield of **5a** [%][b]	Yield of **6a** [%][b]
1	-	63	0
2	**1b**, 4 h	11	4
3	**1c**, 6 h	6	2
4	**1b**, $[Ir(ppy)_2(dtbbpy)](PF_6)$	31	15
5	$[D_6]$acetone/CD_3CO_2D	34	0
6	CD_3CN/CD_3CO_2D	40	0
7	CD_2Cl_2/CD_3CO_2D (3.5/1.5)	39	17
8	NaOAc (2 equiv)	33	16
9	2,6-di-*tert*-butylpyridine (1.2 equiv)	38	17
10	In the dark	0	0
11	No photocatalyst	4	0

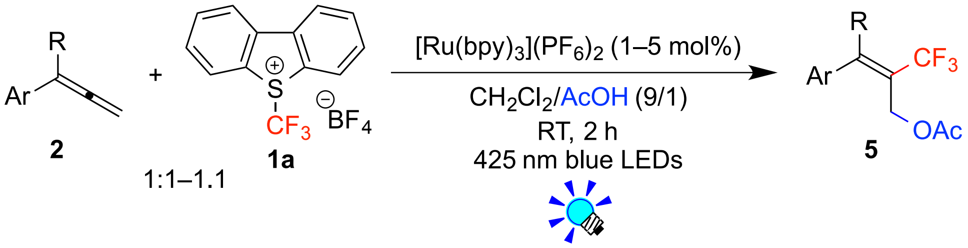
[a] For detailed reaction conditions, see the Experimental Section.

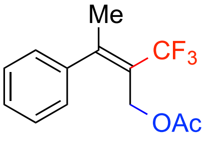
[b] Determined by ^1H NMR spectroscopy using $SiEt_4$ as an internal standard.

4.3 Scope of Substrates for Acetoxy-Trifluoromethylation of Allenes

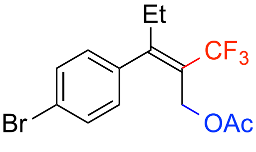
The scope of the present photocatalytic acetoxy-trifluoromethylation is summarized in Table 4.2. The acetoxy-trifluoromethylated product **5a** was obtained in 65% isolated yield from 1-phenyl-1-methylallene (**2a**). 1-Ethyl-1-phenylallene derivatives with bromine (**2b**), ester (**2c**) and cyano (**2d**) groups on the aryl ring were compatible with this reaction to give the desired products in good yields (**5b**–**5d**; 71–78%). Furthermore, 1-cyclohexyl-1-phenylallene (**2e**) could be applied to the present reaction to give the corresponding allylic acetate **5e** in 45% yield. In all cases, the reactions proceeded in a regio- and stereo-selective fashion and the yields were for the single isomers.

Table 4.2. Scope of the photocatalytic acetoxy-trifluoromethylation of allenes

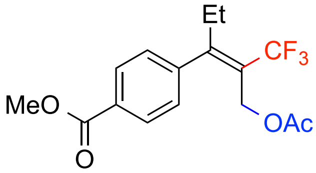




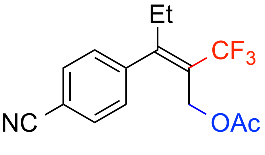
5a: 65%



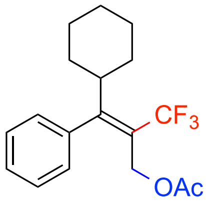
5b: 71%



5c: 78%



5d: 72%

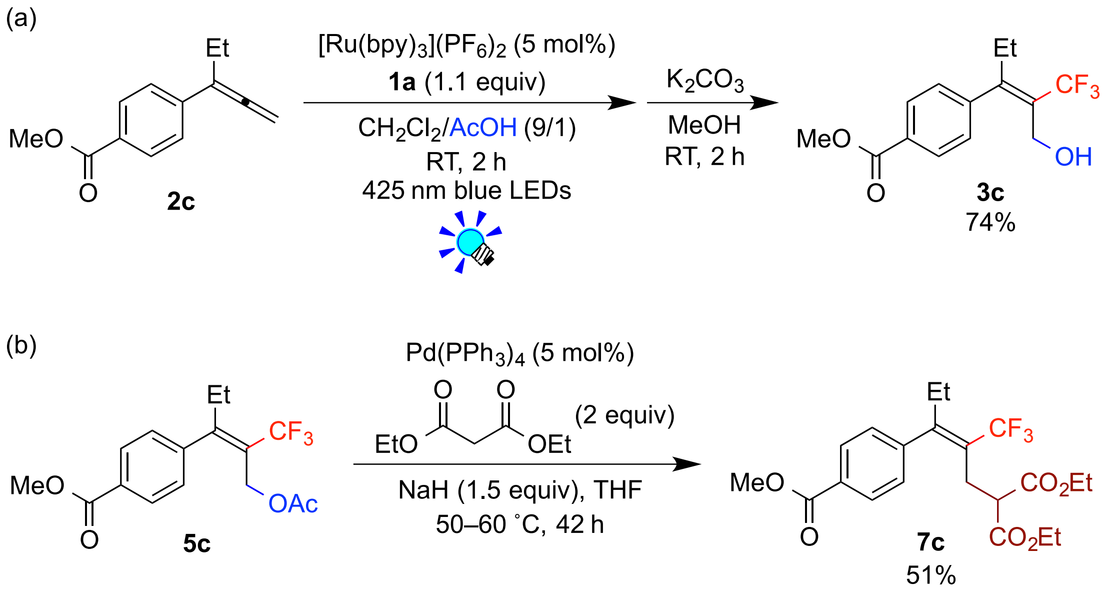


5e: 45%

[a] For detailed reaction conditions, see the Experimental Section.

4.4 Synthetic Applications of The Products

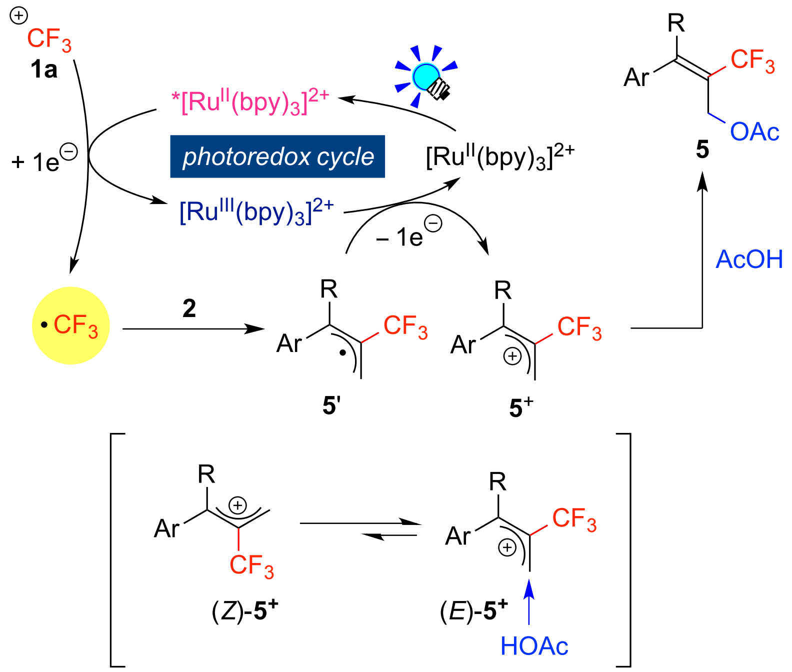
Allylic acetate is regarded as to be protected allylic alcohol. The trifluoromethylated allylic acetate **5c** was easily deprotected by treating with K_2CO_3/MeOH without purification to afford the allylic alcohol **3c** in 74% yield based on **2c** (Scheme 4.3.a). In addition, the trifluoromethylated allylic acetate could be applied to a palladium-catalyzed allylic alkylation reaction. The reaction of **5c** with sodium diethyl malonate in the presence of $Pd(PPh_3)_4$ catalyst provided the alkylated product **7c** in 51% yield in a highly stereoselective manner (Scheme 4.3.b).



Scheme 4.3. Synthetic applications of the CF_3-allylic acetate

4.5 Plausible Reaction Mechanism

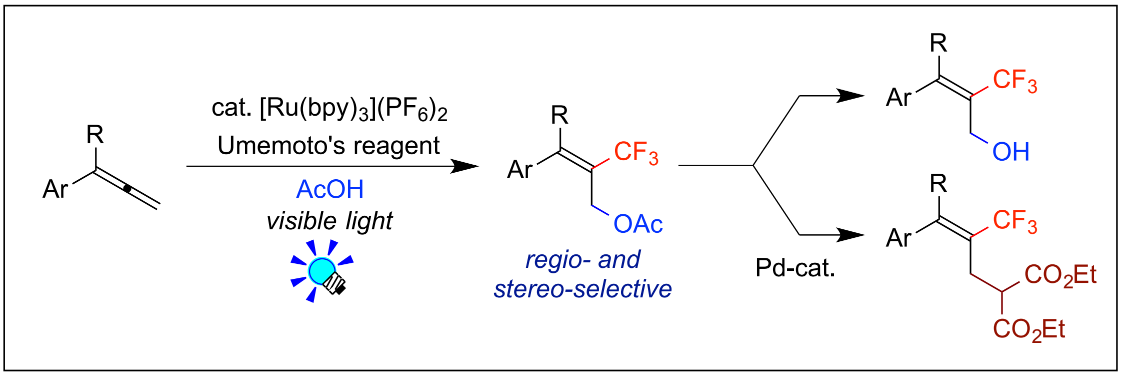
On the basis of the experimental results and our finding about alkene trifluoromethylations, a plausible reaction mechanism for the present reaction is illustrated in Scheme 4.4. Umemoto's reagent **1a** undergoes SET reduction by the photoexcited Ru catalyst, $*[Ru(bpy)_3]^{2+}$, to generate the CF_3 radical ($\cdot CF_3$) associated with formation of the highly oxidizing $[Ru(bpy)_3]^{3+}$ species. Addition of the CF_3 radical to allene **2** selectively proceeds at the central carbon atom of allene moiety to provide allyl radical intermediate **5'**, which is oxidized by $[Ru(bpy)_3]^{3+}$ to afford CF_3-substituted allyl cation intermediate $\mathbf{5}^+$. The allyl cation $\mathbf{5}^+$ has two geometric isomers, (*Z*)-$\mathbf{5}^+$ and (*E*)-$\mathbf{5}^+$. According to the experimental results, the isomer (*E*)-$\mathbf{5}^+$ is more favorable than the (*Z*)-$\mathbf{5}^+$. Finally, regioselective addition of AcOH to $\mathbf{5}^+$ affords the trifluoromethylated allylic acetate **5**.



Scheme 4.4. A plausible reaction mechanism

4.6 Conclusion

In conclusion, the author has developed the first highly regio- and stereo-selective synthesis of allylic acetates having tetrasubstituted CF_3-alkene moieties from allenes by visible-light driven photoredox catalysis. Using acetic acid in a low concentration is crucial for the high regioselectivity. The products can be transformed into the corresponding allylic alcohol and applied to the palladium-catalyzed substitution reaction.



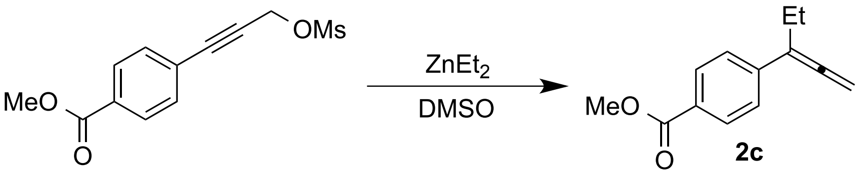
4.7 Experimental

Material and Methods

Allene **2a**,[10a] **2b**,[10b] and **2d**[10b] were prepared according to the literature procedures. Catalytic reactions were performed under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. CH_2Cl_2 was purified through the columns containing alumina and alumina-Cu catalyst and stored N_2 atmosphere. NMR solvents were dried over molecular sieves 3A, degassed and stored under N_2. Visible light irradiation was performed with a Relyon LED lamp (3 W x 2; λ_{max} = 425 nm). NMR spectra were acquired on a Bruker AVANCE-400 (400 MHz) and a Bruker AVANCE-500 spectrometer (500 MHz). HRMS spectra (EI Mass spectra and FAB Mass spectra) were a JEOL JMS-700 at Material Analysis Suzukake-dai Center, Technical Department, Tokyo Institute of Technology.

Synthesis of substrates

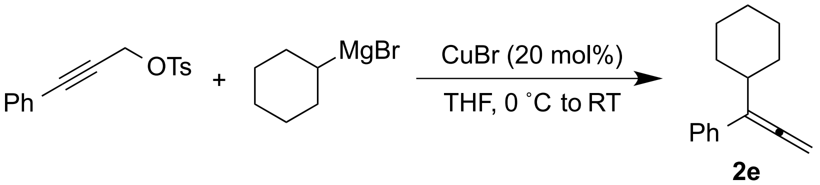
Methyl 4-(penta-1,2-dien-3-yl)benzoate (2c)



Under N_2, a 20 mL Schlenk was charged with methyl 4-(3-methylsulfonyloxyprop-1-yn-1-yl)benzoate (0.27 g, 1 mmol), dry DMSO (1.5 mL) and $ZnEt_2$ (1 M in hexane, 2 mL) and stirred for 24 h at room temperature. To the reaction mixture, sat. NH_4Cl aq. was added at 0 ˚C, and products were extracted with Et_2O. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/Et_2O = 20/1) to afford **2c** (0.15 g, 76%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.98 (d, J = 8.8 Hz, 2H; Ar), 7.47 (d, 8.8 Hz, 2H; Ar), 5.17 (t, J = 3.6 Hz, 2H; C=CH_2), 3.91 (s, 3H; OCH_3), 2.44 (m, 2H; CH_2CH$_3$), 1.16 (t, J = 7.2 Hz, 3H; CH$_2$CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 209.3, 167.2, 141.7, 129.8, 128.2, 125.9, 106.6, 79.5, 52.2, 22.3, 12.5. **HRMS** (EI): calculated for $[C_{13}H_{14}O_2]^+$ requires 202.0994, found 202.0994.

1-Cyclohexyl-1-phenylallene (2e)

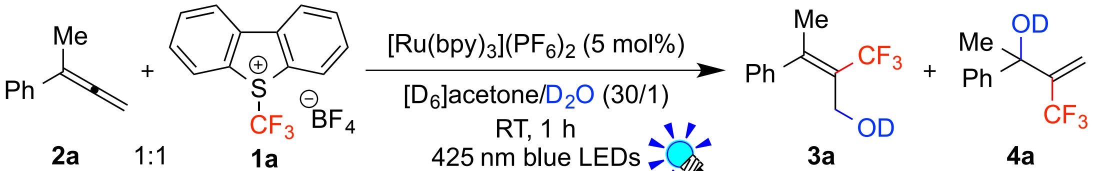


2e

Under N_2, a Schlenk tube was charged with Mg (0.30 g, 12 mmol) and stirred for several minutes at room temperature. Then, dry THF (5 mL), bromocyclohexane (1.0 g, 6.0 mmol) and I_2 was added to the tube and stirred at room temperature to generate Grignard reagent. Another Schlenk tube was charged with 3-phenyl-2-propenyl tosylate (1.4 g, 5.0 mml), CuBr (0.15 g, 1.0 mmol) and dry THF (10 mL) under N_2. The resulting Grignard reagent was added to the mixture at 0 ˚C and stirred at room temperature overnight. Saturated NH_4Cl aq. was added to the reaction mixture at 0 ˚C, and products were extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane) to afford **2e** (0.33 g, 33%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.39 (d, *J* = 7.6 Hz, 2H; Ph), 7.31 (t, *J* = 7.2 Hz, 2H; Ph), 7.19 (t, *J* = 7.2 Hz, 1H; Ph), 5.06 (d, *J* = 2.4 Hz, 2H; C=C*H*$_2$), 2.41 (m, 1H; Cy), 1.92–1.88 (m, 2H; Cy), 1.82–1.77 (m, 2H; Cy), 1.74–1.69 (m, 1H; Cy), 1.42–1.31 (m, 2H; Cy), 1.28–1.15 (m, 3H; Cy). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 208.3, 136.5, 128.5, 126.6, 126.6, 111.3, 78.8, 37.3, 32.8, 26.8, 26.5. **HRMS** (EI): calculated for $[C_{15}H_{18}]^+$ requires 198.1409, found 198.1411.

NMR experimental procedures for the hydroxy-trifluoromethylation of 2a (Figure 4.1)

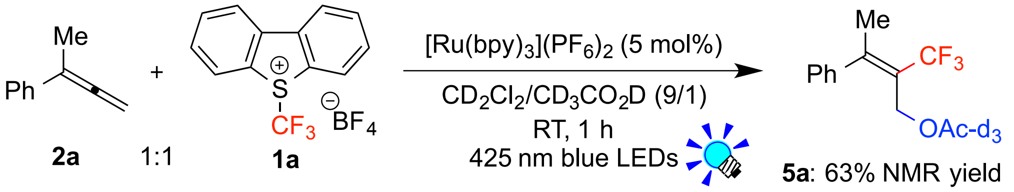


2a 1:1 **1a** **3a** **4a**

36% NMR yield 37% NMR yield

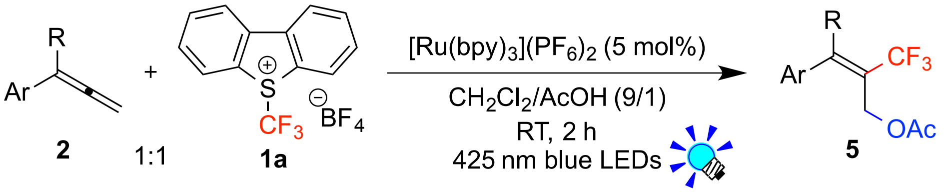
An NMR tube was charged with $[Ru(bpy)_3](PF_6)_2$ (1.2 mg, 1.4 μmol), Umemoto's reagent **1a** (85 mg, 25 μmol), 1-methyl-1-phenylallene (**1a**) (33 mg, 25 μmol), $SiEt_4$ (~1 μL; an internal standard), dry [D$_6$]acetone (0.45 mL) and D_2O (15 μL). The tube was degassed by three freeze-pump-thaw cycles and refilled with N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 1 h at room temperature (in a water bath). The yields of the products were determined by ^{1}H NMR spectroscopy.

NMR experimental procedures for the acetoxy-trifluoromethylation of 2a (entry 1 in Table 4.1)



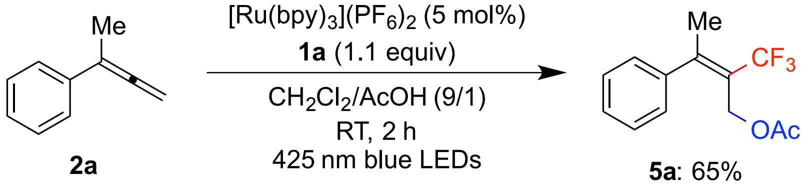
An NMR tube was charged with [Ru(bpy)$_3$](PF$_6$)$_2$ (1.1 mg, 1.3 µmol), Umemoto's reagent **1a** (85 mg, 25 µmol), 1-methyl-1-phenylallene (**1a**) (33 mg, 25 µmol), SiEt$_4$ (~1 µL; an internal standard), dry CD$_2$Cl$_2$ (0.45 mL) and CD$_3$CO$_2$D (50 µL). The tube was degassed by three freeze-pump-thaw cycles and refilled with N$_2$. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 1 h at room temperature (in a water bath). The yield of the product was determined by ^{1}H NMR spectroscopy.

General procedures for the photocatalytic acetoxy-trifluoromethylation of allenes



A 20 mL Schlenk tube was charged with [Ru(bpy)$_3$](PF$_6$)$_2$ (11 mg, 13 µmol), Umemoto's reagent **1a** (94 mg, 0.28 mmol), allene **2** (0.25 mmol), dry CH$_2$Cl$_2$ (4.5 mL) and AcOH (0.5 mL). The tube was degassed by three freeze-pump-thaw cycles and refilled with N$_2$. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 2 h with stirring at room temperature (in a water bath). After the reaction, aq. NaHCO$_3$ was added to the reaction mixture, and products were extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to afford acetoxy-trifluoromethylated product **5**. The stereochemistry was confirmed by ^{1}H-^{1}H NOESY NMR spectroscopy.

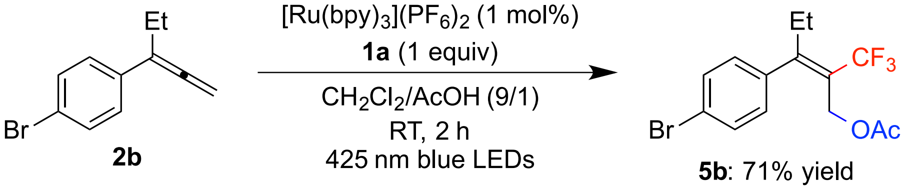
(*E*)-3-Phenyl-2-(trifluoromethyl)but-2-en-1-yl acetate (5a)



Following the general procedures, the title compound was synthesized from 1-methyl-1-phenylallene (**2a**) (33 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/EtOAc = 29/1) to afford **5a** (42 mg, 65% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.40–7.32 (m, 3H; Ar), 7.16 (dd, *J* = 8.0, 2.0 Hz, 2H; Ar), 4.48 (s, 2H; CH_2), 2.28 (q, *J* = 2.0 Hz, 3H; $C{=}CCH_3$), 2.04 (s, 3H; $COCH_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 170.5, 153.2 (q, *J* = 3.3 Hz), 140.9, 128.7, 128.5, 127.0, 124.3 (q, *J* = 276 Hz), 122.5 (q, *J* = 29.2 Hz), 61.1 (q, *J* = 2.3 Hz), 22.7 (q, *J* = 1.9 Hz), 20.9. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –59.95 (s, 3F). **HRMS** (FAB): calculated for $[C_{13}H_{13}F_3O_2]^+$ requires 258.0868, found 258.0868.

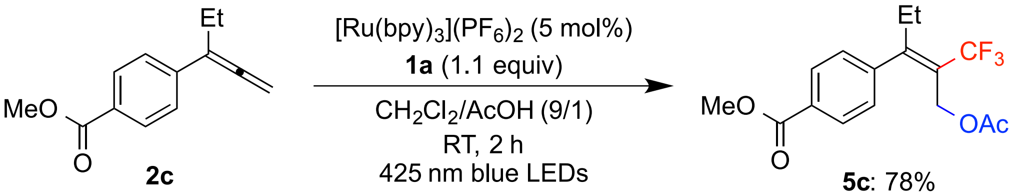
(*E*)-3-(4-Bromophenyl)-2-(trifluoromethyl)pent-2-en-1-yl acetate (5b)



Following the general procedures, the title compound was synthesized from 3-(4-bromophenyl)-1,2-pentadiene (**2b**) (56 mg, 0.25 mmol), $[Ru(bpy)_3](PF_6)_2$ (2.1 mg, 2.5 μmol), **1a** (85 mg, 0.25 mmol), dry CH_2Cl_2 (4.5 mL) and AcOH (0.5 mL). The product mixture was purified by silica gel column chromatography (hexane→hexane/EtOAc = 29/1) to afford **5b** (62 mg, 71% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.52 (d, *J* = 8.4 Hz, 2H; Ar), 7.02 (d, *J* = 8.4 Hz, 2H; Ar), 4.41 (s, 2H; CH_2OAc), 2.60 (m, 2H; CH_2CH_3), 2.04 (s, 3H; $COCH_3$), 0.93 (t, *J* = 7.6 Hz, 3H; CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 170.4, 157.7 (q, *J* = 3.0 Hz), 137.9, 131.8, 129.4, 124.1 (q, *J* = 277 Hz), 122.7, 122.4 (q, *J* = 29.5 Hz), 61.0 (q, *J* = 1.8 Hz), 28.9 (q, *J* = 1.1 Hz), 20.9, 12.3. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –59.51 (s, 3F). **HRMS** (FAB): calculated for $[C_{14}H_{14}BrF_3O_2]^+$ requires 350.0129, found 350.0138.

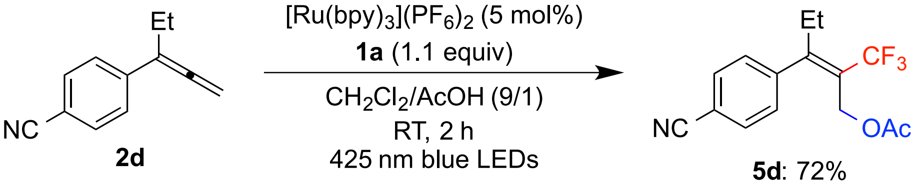
Methyl (*E*)-4-(2-(acetoxymethyl)-1,1,1-trifluoropent-2-en-3-yl)benzoate (5c)



Following the general procedures, the title compound was synthesized from methyl 4-(penta-1,2-dien-3-yl)benzoate (**2c**) (51 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane/Et_2O = 19/1→9/1) to afford **5c** (65 mg, 78% yield) as a colorless oil.

^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 8.06 (d, *J* = 8.4 Hz, 2H; Ar), 7.22 (d, *J* = 8.4 Hz, 2H; Ar), 4.39 (s, 2H; CH_2OAc), 3.93 (s, 3H; OCH_3), 2.64 (m, 2H; CH_2CH_3), 2.03 (s, 3H; $COCH_3$), 0.93 (t, *J* = 7.2 Hz, 3H; CH_2CH_3). ^{13}**C NMR** (126 MHz, $CDCl_3$, rt): δ 170.3, 166.6, 157.8 (q, *J* = 3.0 Hz), 143.7, 130.3, 129.9, 127.8, 124.1 (q, *J* = 277 Hz), 122.6 (q, *J* = 29.4 Hz), 60.9 (q, *J* = 1.9 Hz), 52.4, 28.8 (q, *J* = 1.3 Hz), 20.8, 12.2. ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –59.57 (s, 3F). **HRMS** (EI): calculated for $[C_{16}H_{17}F_3O_4]^+$ requires 330.1079, found 330.1082.

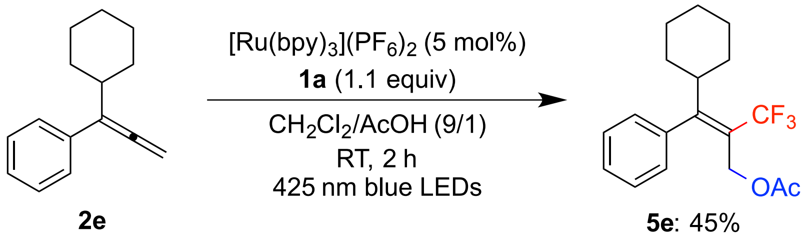
(*E*)-3-(4-cyanophenyl)-2-(trifluoromethyl)pent-2-en-1-yl acetate (5d)



Following the general procedures, the title compound was synthesized from 4-(penta-1,2-dien-3-yl)benzonitrile (**2d**) (42 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 4/1→3/1→2/1) to afford **5d** (54 mg, 72% yield) as a pale yellow oil.

^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.70 (d, *J* = 8.4 Hz, 2H; Ar), 7.27 (d, *J* = 8.4 Hz, 2H; Ar), 4.37 (s, 2H; CH_2OAc), 2.63 (m, 2H; CH_2CH_3), 2.03 (s, 3H; $COCH_3$), 0.94 (t, *J* = 7.6 Hz, 3H; CH_2CH_3). ^{13}**C NMR** (126 MHz, $CDCl_3$, rt): δ 170.2, 156.7 (q, *J* = 2.8 Hz), 143.8, 132.4, 128.6, 123.8 (q, *J* = 277 Hz), 123.3 (q, *J* = 29.6 Hz), 118.3, 112.6, 60.6 (q, *J* = 1.8 Hz), 28.7 (q, *J* = 1.4 Hz), 20.8, 12.2. ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –59.70 (s, 3F). **HRMS** (EI): calculated for $[C_{15}H_{14}F_3NO_2]^+$ requires 297.0977, found 297.0973.

(*E*)-3-Cyclohexyl-3-phenyl-2-(trifluoromethyl)allyl acetate (5e)

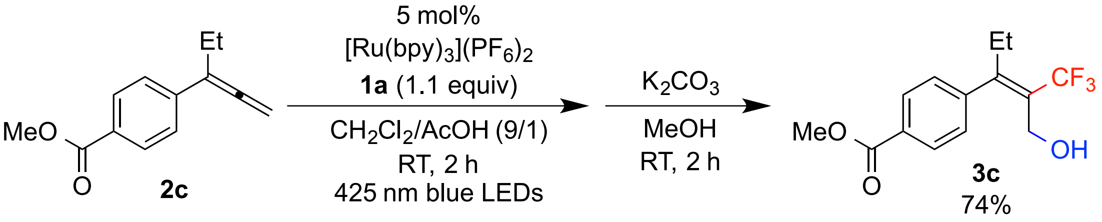


Following the general procedures, the title compound was synthesized from 1-cyclohexyl-1-phenylallene (**2e**) (50 mg, 0.25 mmol). The product mixture was purified by silica gel column chromatography (hexane→hexane/EtOAc = 29/1) to afford **5e** (37 mg, 45% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.36–7.32 (m, 3H; Ar), 7.00–6.98 (m, 2H; Ar), 4.28 (apparent d, J = 1.2 Hz, 2H; CH_2OAc), 2.93 (m, 1H; C=CCH), 1.99 (s, 3H; COCH_3), 1.72–1.59, 1.39–1.28, 1.09–0.90 (m, 10H; Cy). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 170.5, 161.9 (q, J = 3.2 Hz), 136.7, 128.0, 128.0, 127.8, 124.3 (q, J = 277 Hz), 122.4 (q, J = 29.0 Hz), 61.1 (q, J = 2.5 Hz), 42.5 (q, J = 1.4 Hz), 31.0, 26.1, 25.7, 20.9. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –58.42 (s, 3F). **HRMS** (FAB): calculated for $[C_{18}H_{21}F_3O_2+Na]^+$ requires 349.1391, found 349.1385.

Procedures for the synthesis of trifluoromethylated allylic alcohol 3c

Methyl (*E*)-4-(1,1,1-trifluoro-2-(hydroxymethyl)pent-2-en-3-yl)benzoate (3c)

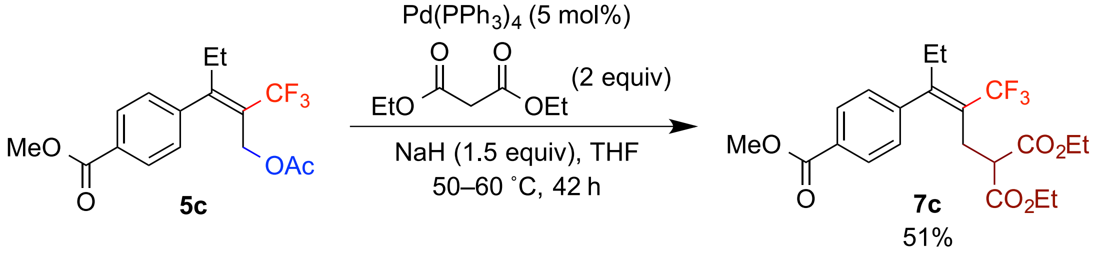


A 20 mL Schlenk tube was charged with $[Ru(bpy)_3](PF_6)_2$ (10 mg, 12 μmol), Umemoto's reagent **1a** (94 mg, 0.27 mmol), methyl 4-(penta-1,2-dien-3-yl)benzoate (**2c**) (51 mg, 0.25 mmol), dry CH_2Cl_2 (4.5 mL) and AcOH (0.5 mL). The tube was degassed by three freeze-pump-thaw cycles and refilled with N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated with stirring for 2 h at room temperature (in a water bath). After the reaction, aq. $NaHCO_3$ was added to the reaction mixture, and products were extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. Then, to the crude reaction mixture, MeOH (5 mL) and K_2CO_3 (0.14 g, 1.0 mmol) were added and stirred for 2 h at room temperature. H_2O was added to the reaction mixture, and products were 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 silica gel column chromatography (hexane/EtOAc = 9/1→5/1) to afford **3c** (53 mg, 74% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.07 (d, J = 8.4 Hz, 2H; Ar), 7.29 (d, J = 8.4 Hz, 2H; Ar), 3.98 (d, J = 4.8 Hz, 2H; CH_2OH), 3.94 (s, 3H; OCH_3), 2.61 (m, 2H; CH_2CH_3), 1.59 (br s, 1H; OH), 0.93 (t, J = 7.2 Hz, 3H; CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 166.8, 154.9 (q, J = 3.4 Hz), 144.2, 130.0, 129.8, 128.0, 126.7 (q, J = 27.3 Hz), 124.8 (q, J = 277 Hz), 59.4 (q, J = 2.3 Hz), 52.4, 28.5, 12.3. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –59.15 (s, 3F). **HRMS** (EI): calculated for $[C_{14}H_{15}F_3O_3]^+$ requires 288.0973, found 288.0976.

Procedures for the Pd-catalyzed allylic alkylation of 5c

Diethyl (*E*)-2-(3-(4-(methoxycarbonyl)phenyl)-2-(trifluoromethyl)pent-2-en-1-yl)-malonate (7d)



A 20 mL Schlenk tube was charged with **5c** (64 mg, 0.19 mmol), dry THF (5 mL), diethyl malonate (61 µL, 0.40 mmol), $Pd(PPh_3)_4$ (11 mg, 10 µmol) and NaH (13 mg; 60% dispersion in paraffin liquid) under N_2. The mixture was stirred for 18 h at 50 ˚C, and at 60 ˚C for 24 h. H_2O was added to the reaction mixture and products were 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 silica gel column chromatography (hexane/Et_2O = 19/1→9/1→5/1) to afford **7c** (42 mg, 51%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.05 (d, J = 8.4 Hz, 2H; Ar), 7.16 (d, J = 8.4 Hz, 2H; Ar), 4.08 (m, 4H; $CO_2CH_2CH_3$), 3.93 (s, 3H; CO_2CH_3), 3.36 (t, J = 7.6 Hz, 1H; CH_2CH), 2.69 (d, J = 7.6 Hz, 2H; CH_2CH), 2.53 (m, 2H; CCH_2CH_3), 1.17 (t, J = 7.2 Hz, 6H; $CO_2CH_2CH_3$), 0.88 (t, $J = 7.4$ Hz, 3H; CCH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 168.3, 166.8, 153.7 (q, $J = 3.3$ Hz), 144.8, 129.9, 129.7, 128.1, 124.6 (q, $J = 277$ Hz), 123.5 (q, $J = 28.2$ Hz), 61.6, 52.3, 50.7, 29.2, 28.3, 14.0, 12.3. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –58.15 (s, 3F). **HRMS** (EI): calculated for $[C_{21}H_{25}F_3O_6]^+$ requires 430.1603, found 430.1602.

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[9] The photoexcited $[\mathrm{Ir(ppy)_2(dtbbpy)}]^+$ species is stronger reductant ($E_{1/2} = -1.37$ V *vs* $\mathrm{Cp_2Fe}$) than the Ru photocatalyst, $[\mathrm{Ru(bpy)_3}]^{2+}$, see: M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, Jr., G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712–5719.

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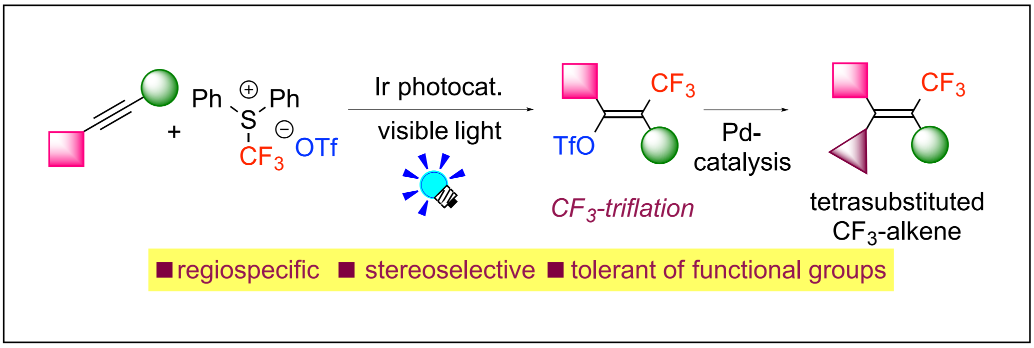
Chapter 5

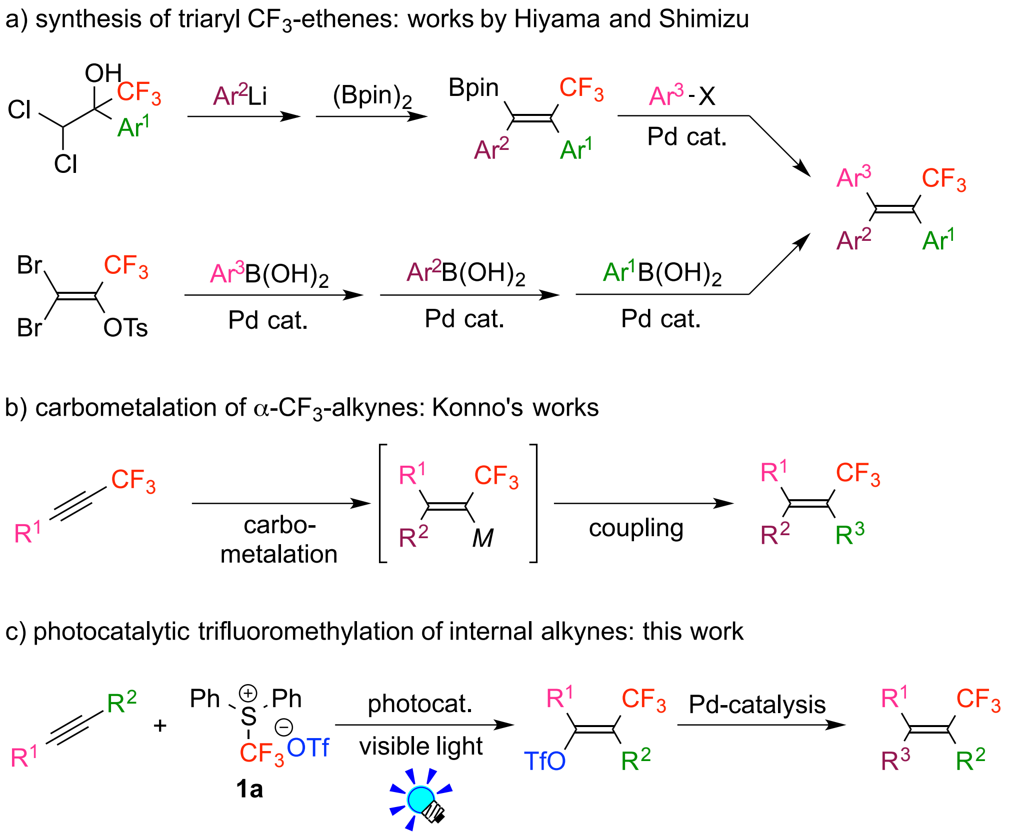
Photoredox-Catalyzed Stereoselective Conversion of Alkynes into Tetrasubstituted Trifluoromethylated Alkenes

ABSTRACT: The regio- and stereoselective simultaneous addition of trifluoromethyl and trifluoromethanesulfonate groups to alkynes is achieved by photoredox catalysis. Combining this process with the palladium-catalyzed cross-coupling reactions allows us to access to various tetrasubstituted trifluoromethylated alkenes from simple alkynes in a facile one-pot process.



5.1 Introduction

Tetrasubstituted alkenes represent a useful structural motif which is found in biologically active naturel products, drugs, and functional materials.[1] Therefore, the development of new and reliable methods for stereoselective synthesis of tetrasubstituted alkenes is in high demand.[2] In addition, owing to the unique properties of the trifluoromethyl group, CF_3-substituted alkenes (CF_3-alkenes) have great potential in the pharmaceutical, agrochemical, and material sciences.[3] Step-economic and versatile stereoselective synthetic methods towards tetrasubstituted CF_3-alkenes, however, have been extremely limited thus far.[4] Hiyama and Shimizu reported the synthesis of CF_3-substituted triarylethenes starting from CF_3-substituted dichlorohydrin and 1,1-dibromo-3,3,3-trifluoro-2-tosyloxypropene (Scheme 5.1.a). Konno et al. developed methods based on carbometalation of CF_3-substituted alkynes (Scheme 5.1.b). These excellent methods, however, require CF_3-substituted precursors, diminishing their versatility and simplicity. In contrast, the direct trifluoromethylation of alkynes is regarded as one of the most straightforward strategy for the synthesis of CF_3-alkenes. Nevertheless, highly stereoselective trifluoromethylation of simple internal alkynes still remains to be a great challenge in spite of the recent development of various trifluoromethylation methods.[5,6]



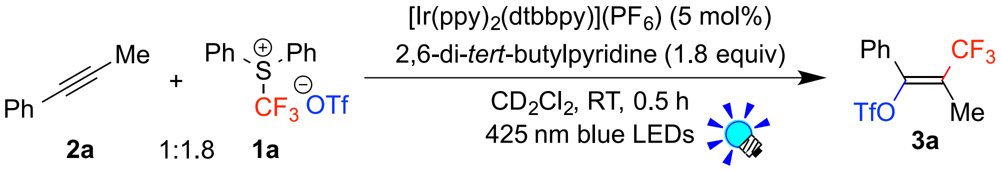
Scheme 5.1. Stereoselective synthesis of tetrasubstituted trifluoromethylalkenes

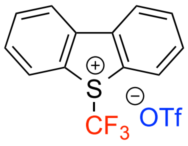
As described in Chapters 2–4, the author has developed trifluoromethylations of alkenes and allenes mediated by photoredox-catalysis.[7] The experience accumulated during these earlier projects prompted him to design a method for trifluoromethylating difunctionalization of alkynes through photoredox-mediated single electron transfer (SET) processes. In this chapter, the author describes a novel stereoselective sulfonyloxy-trifluoromethylation of internal unsymmetric alkynes promoted by visible-light photoredox catalysis. A shelf-stable and easy-to-use electrophilic CF_3 reagent, *S*-(trifluoromethyl)diphenylsulfonium trifluoromethanesulfonate (**1a**; Yagupol'skii–Umemoto reagent),[8] has been found to be a key compound for the difunctionalization of alkynes. The obtained trifluoromethylated alkenyl triflates may be readily converted into tetrasubstituted CF_3-alkenes in a stereocontrolled manner by the well-established Pd-catalyzed coupling reactions. This method thus enables facile one-pot synthesis of CF_3-alkenes bearing four different substituents (Scheme 5.1.c).

5.2 Optimization of Trifluoromethyl-Triflation of Alkyne

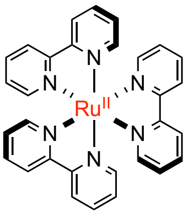
Initially, the author examined photocatalytic trifluoromethanesulfonyloxy-trifluoromethylation (trifluoromethyl-triflation) of 1-phenyl-1-propyne (**2a**), an unsymmetric internal alkyne, with the Yagupol'skii-Umemoto reagent **1a**. To his delight, the reaction of alkyne **2a** with 1.8 equivalents of **1a** in CD_2Cl_2 in the presence of an Ir photoredox catalyst, namely $[Ir(ppy)_2(dtbbpy)](PF_6)$ (5 mol%), and 2,6-di-*tert*-butylpyridine under visible-light irradiation (425 nm blue LEDs) for 0.5 h afforded the desired product **3a** in an NMR yield of 84% in a highly regio- and stereoselective manner (E/Z = 99/1). Shorter (10 min) or longer reaction times (2 h) did not lead to a significant deterioration of the stereoselectivity (Table 5.1, entries 1–3), indicating that an isomerization process is not involved in the present reaction as a major reaction pathway. Reducing the amount of **1a** led to a lower conversion of **2a** (entry 4). The use of Umemoto's reagent **1b** lowered the yield and the efficiency owing to the degradation of **1b** under the reaction conditions (entry 5). Other photocatalysts turned out to be inefficient (entries 6 and 7). Other solvent systems, such as CD_3CN and $[D_6]$acetone, gave complicated mixtures of products (entries 8 and 9). When the reaction was conducted without base or with the inorganic base (Na_2CO_3), a small amount of 1-phenylprop-1-en-1-yl trifluoromethanesulfonate formed as a byproduct (entries 11 and 12). Addition of a bulky organic base, 2,6-di-*tert*-butylpyridine, made the reaction cleaner to improve the yield of **3a**. Finally, irradiation of visible light and the photoredox catalyst were essential for the present reaction (entries 13 and 14).

Table 5.1. Optimization of photocatalytic trifluoromethyl-triflation of **2a**

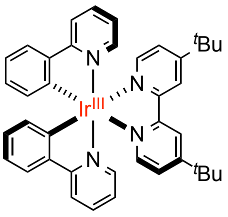




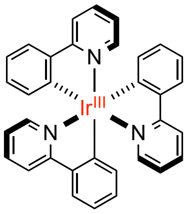
1b



$[Ru(bpy)_3]^{2+}$



$[Ir(ppy)_2(dtbbpy)]^{+}$



fac-$[Ir(ppy)_3]$

Entry	Deviations from the standard conditions[a]	Yield of **3a** [%][b]	*E*/*Z*[c]
1	-	84	99/1
2	10 min	74[d]	99/1
3	2 h	84	96/4
4	**1a** (1 equiv)	62[e]	98/2
5	**1b**, 1 h	75	94/6
6	$[Ru(bpy)_3](PF_6)_2$ 10 h	80	99/1
7	*fac*-$[Ir(ppy)_3]$, 2 h	70	99/1
8	CD_3CN	47	95/5
9	$[D_6]$acetone	13	-
10	2,6-lutidine	79	98/2
11	Na_2CO_3	77	98/2
12	no base	77	98/2
13	no light	0	-
14	no photocatalyst	0	-

[a] For detailed reaction conditions, see the Experimental Section.

[b] Determined by ^1H NMR spectroscopy using $SiEt_4$ as an internal standard. [c] Determined by ^{19}F NMR spectroscopy. [d] Unreacted **2a** (13%) was remained. [e] Unreacted **2a** (23%) was remained.

NMR spectra for the reaction of entry 1 in Table 5.1 are shown in Figure 5.1 and 5.2. According to the ^1H NMR spectra in Figure 5.1, irradiation of visible light causes formation of **3a** with consuming the substrates **1a** and **2a**. In addition, the ^{19}F NMR spectrum in Figure 5.2 shows two types of characteristic signals derived from the trifluoromethyl and the trifluoromethanesulfonyl groups in the products.

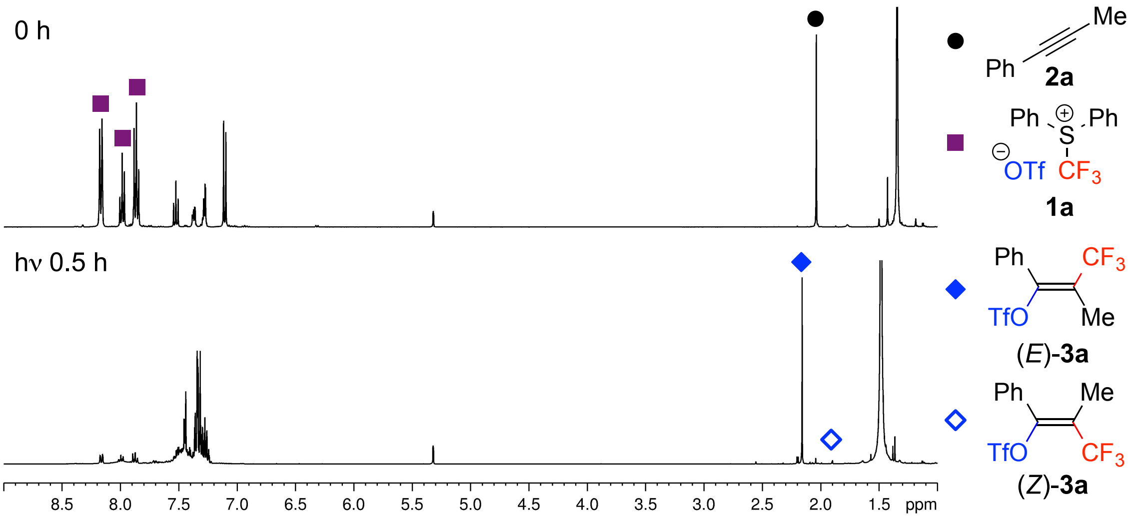


Figure 5.1. ^{1}H NMR spectra (400 MHz, CD_2Cl_2, rt) for entry 1 in Table 5.1

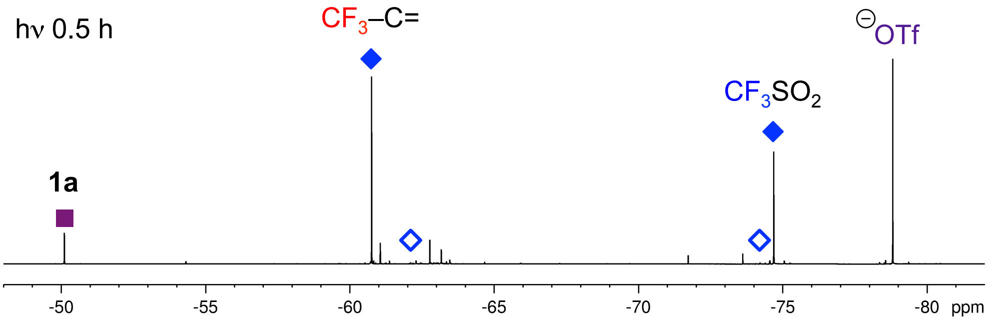


Figure 5.2. A ^{19}F NMR spectrum (376 MHz, CD_2Cl_2, rt) for entry 1 in Table 5.1

5.3 Scope of Substrates for Trifluoromethyl-Triflation of Alkynes

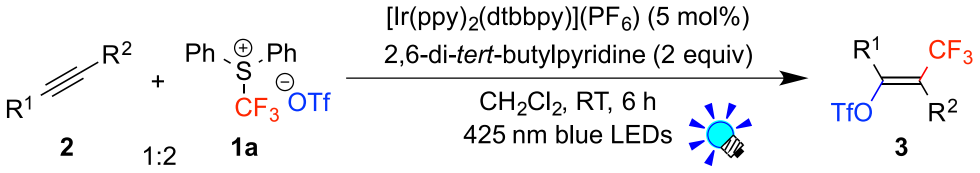
The tetrasubstituted CF_3-alkenyl triflates which were obtained through the present photocatalytic trifluoromethylation are shown in Table 5.2. The reactions of 1-phenyl-1-propyne (**2a**) and its various derivatives (**2b**–**2g**) afforded the corresponding CF_3-alkenyl triflates (**3a**–**3g**) in 49–86% yields in a highly stereoselective manner (*E*/*Z* = 86/14–96/4). Remarkably, the present reaction tolerates a variety of functional groups on the arene ring, such as halide (**2c**), ester (**2d**), primary amide (**2e**), nitrile (**2f**), and hydroxy (**2g**) groups. Furthermore, a substituent in the *ortho* position of the arene ring (**2h**) did not deteriorate the yield and stereoselectivity (**3h**: 76%, *E*/*Z* = 97/3).

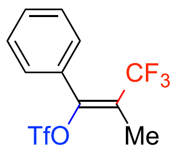
Aryl alkyl acetylenes (Ar–C≡C–R), such as **2i**, **2j**, and **2k**, can also be trifluoromethylated under these reaction conditions. Substrates with alkyl groups bulkier than methyl group, such as ethyl and *n*-butyl groups, still afforded the *E* stereoisomer selectively (**3i**: 67%, *E*/*Z* = 94/6; **3j**: 52%, *E*/*Z* = 83/17), while an even bulkier substituent, namely a cyclohexyl group, had a harmful effect on the efficiency and stereoselectivity (**3k**: 37%, *E*/*Z* = 61/39). The reactions of methyl 3-phenyl-2-propynoate (**2l**) and 4-phenyl-3-butyn-2-one (**2m**) also proceeded in a stereoselective manner to give useful α-CF_3-substituted enones (**3l**: 57%, *E*/*Z* = 85/15; **3m**: 63%, *E*/*Z* = 86/14).[6o] Furthermore, diaryl acetylenes (**2n** and **2o**) afforded the corresponding diaryl CF_3-alkenyl triflates in moderate yields and stereoselectivities (**3n**: 30%, *E*/*Z* = 89/11; **3o**: 30%, *E*/*Z* = 85/15). A simple aliphatic alkynes, 6-dodecyne, however, did not afforded the corresponding product. These results show that the present photocatalytic reaction can be used for the highly regio- and stereo-selective difunctionalization of aryl acetylenes with trifluoromethyl and triflate groups.

5.4 Assignment of Stereochemistry

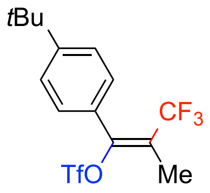
Both stereoisomers of **3d** can be separated and isolated. Figure 5.3 displays NMR spectra for assignment of the stereochemistry. A ^{1}H-^{19}F HOESY NMR spectrum of (*E*)-**3d**, which is the major isomer of the reaction, shows the correlation between the CF_3 group and the aromatic protons, indicating the stereochemistry is *E* (Figure 5.3.a). On the other hand, a ^{1}H-^{1}H NOESY NMR spectrum of (*Z*)-**3d** shows the correlation between the methyl protons and the aromatic protons, indicating the stereochemistry is *Z* (Figure 5.3.b). Additionally, in contrast to (*E*)-**3d**, a ^{19}F NMR spectrum of (*Z*)-**3d** shows characteristic quartet signals derived from a ^{19}F-^{19}F coupling (Figure 5.3.c and d). Thus, the author could assign the other products easily on the basis of this similar spectral features.

Table 5.2. Scope of photocatalytic trifluoromethyl-triflation of alkynes

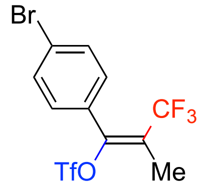




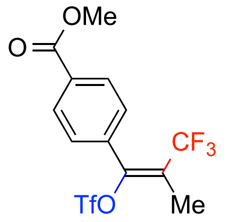
3a:[d] 74%, *E*/*Z* = 96/4



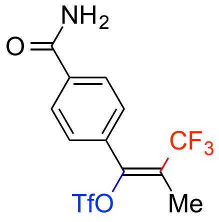
3b:[d] 86%, *E*/*Z* = 96/4



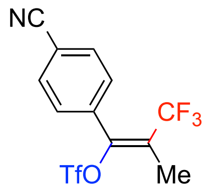
3c: 64%, *E*/*Z* = 92/8



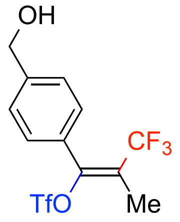
3d: 73%, *E*/*Z* = 91/9



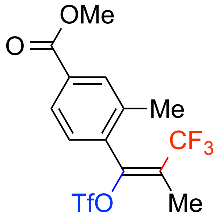
3e: 49%, *E*/*Z* = 86/14



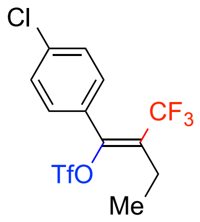
3f: 50%, *E*/*Z* = 88/12



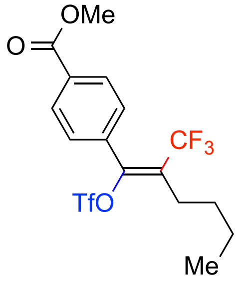
3g: 56%, *E*/*Z* = 94/6



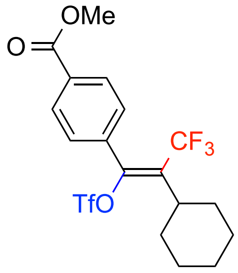
3h: 76%, *E*/*Z* = 97/3



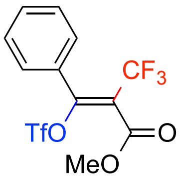
3i: 67%, *E*/*Z* = 94/6



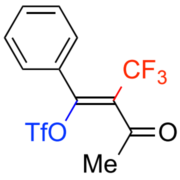
3j:[e] 52%, *E*/*Z* = 83/17



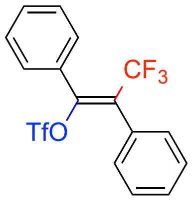
3k:[f] 37%, *E*/*Z* = 61/39



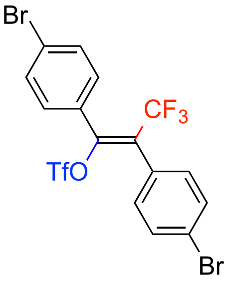
3l:[g] 57%, *E*/*Z* = 85/15



3m:[g] 63%, *E*/*Z* = 86/14



3n: 30%, *E*/*Z* = 89/11



3o: 30%, *E*/*Z* = 85/15

[a] For detailed reaction conditions, see the Experimental Section. [b] Yields of isolated products. [c] Determined by ^{19}F NMR spectroscopy of crude product mixtures. [d] **1a** and base (1.8 equiv each). [e] **1a** and base (2.8 equiv each). [f] **1a** and base (3.0 equiv each). [g] **1a** and base (2.2 equiv each).

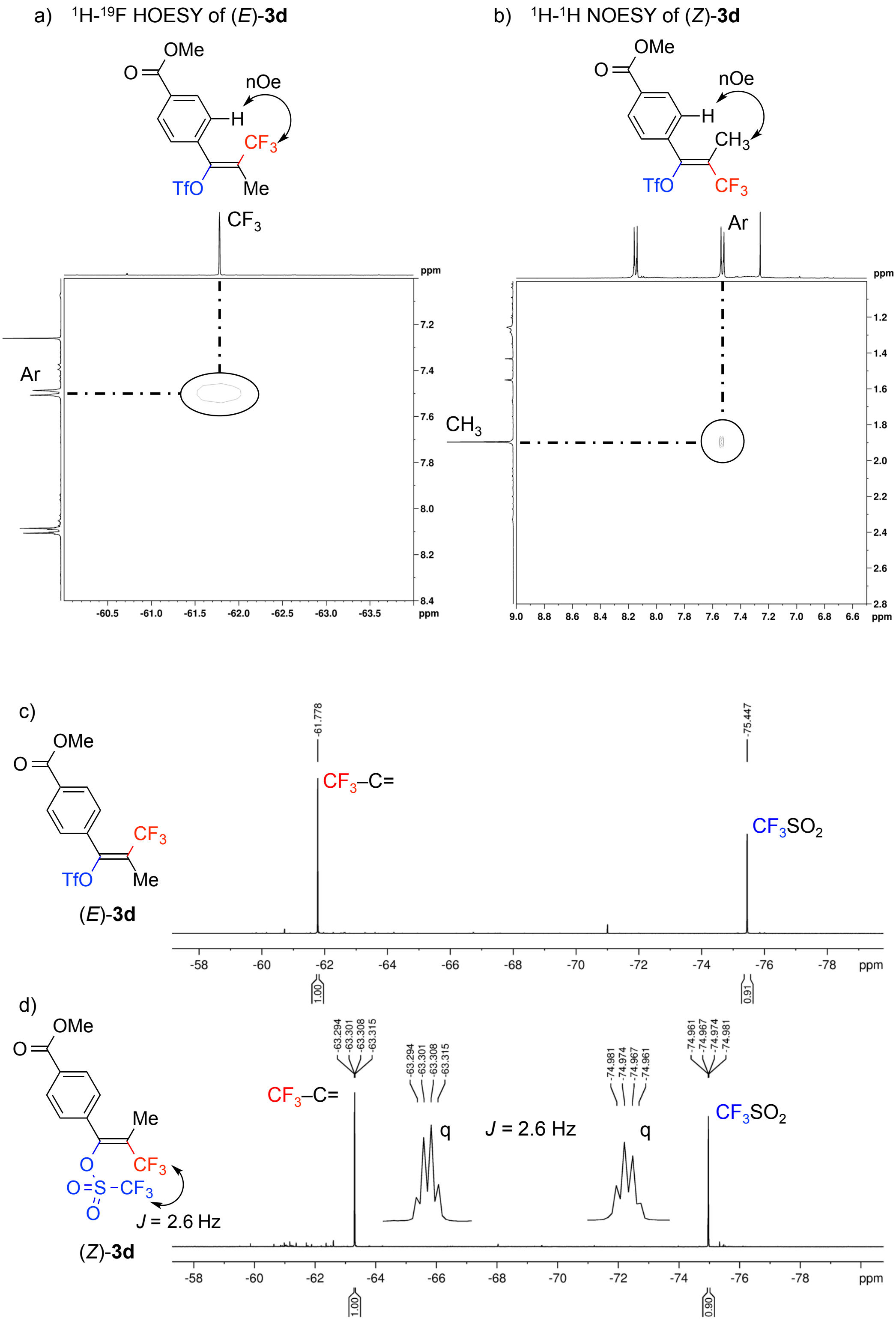
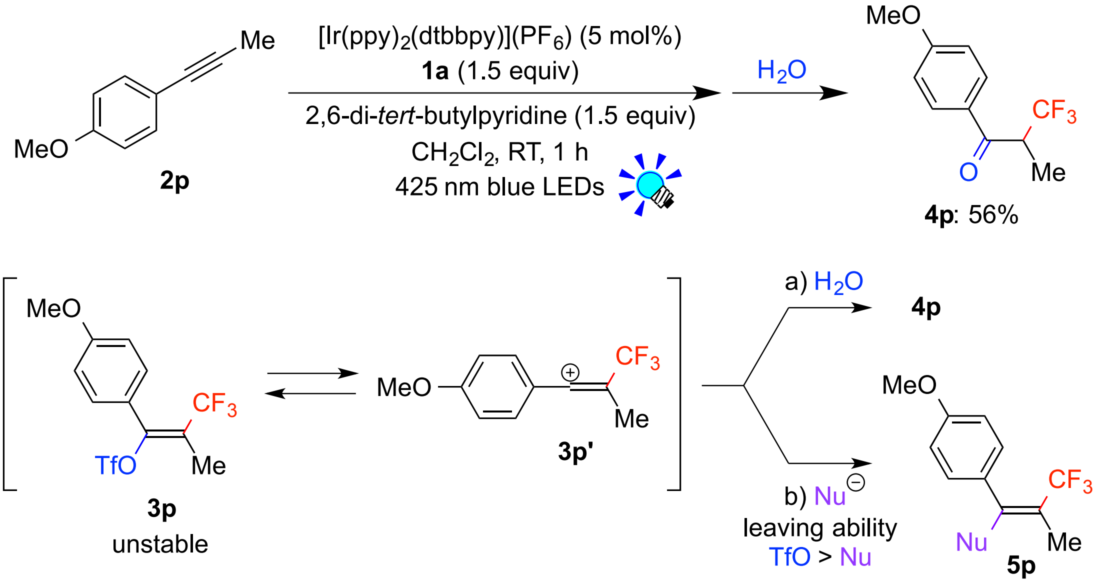


Figure 5.3. a) A ^{1}H-^{19}F HOESY NMR spectrum of (*E*)-**3d**; b) A ^{1}H-^{1}H NOESY NMR spectrum of (*Z*)-**3d**; c and d) ^{19}F NMR spectra of **3d**

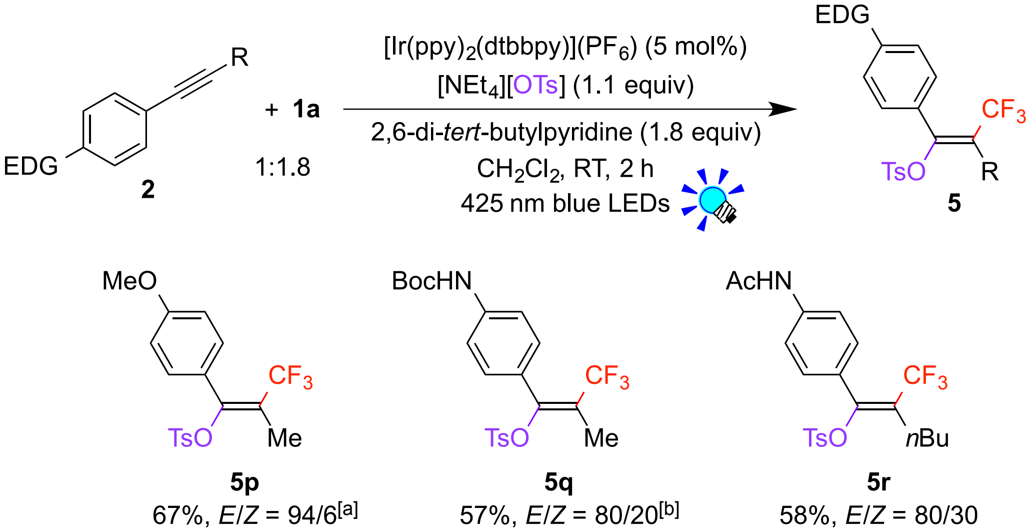
5.5 Trifluoromethyl-Tosylation of Alkynes

During the investigation of the scope of the reaction, the author found that the reaction products of 1-aryl-1-propynes bearing an electron-donating group (EDG) on the aryl ring could not be isolated presumably owing to their susceptibility to hydrolysis. Indeed, 1-(4-methoxyphenyl)-1-propyne (**2p**) reacted smoothly under the present photocatalytic reaction condition, but the product was easily hydrolyzed even by addition of water to afford an α-CF_3-substituted ketone **4p** in a 56% isolated yield (Scheme 5.2).



Scheme 5.2. Hydrolysis of alkenyl triflate **3p**

The reaction can be interpreted in terms of heterolysis of **3p**, which is trapped by H_2O (path a) to give **4p** after ketomigration. If the intermediate **3p'** can be trapped by a nucleophile Nu (path b), which is transformable for further reaction sequence, the resultant adduct **5p** would serve as a "stabilized" equivalent for the reactive triflates **3**. Then tosylate was chosen as the nucleophile, because its leaving ability is less than that of triflate. The author examined the reaction with a tetraalkylammonium tosylate (1.1 equiv), which yielded the corresponding CF_3-alkenyl tosylates **5** as isolable products. The tosylate system was amenable to the synthesis of anisylated and *N*-protected aminophenylated CF_3-alkenyl tosylates (**5p**: 67%, *E*/*Z* = 94/6; **5q**: 57%, *E*/*Z* = 80/20; **5r**: 58%, *E*/*Z* = 70/30). The tosylate system also exhibited a high stereoselectivity, as the trifluoromethyl and tosylate groups were added to the alkyne in a *trans* fashion (Scheme 5.3).



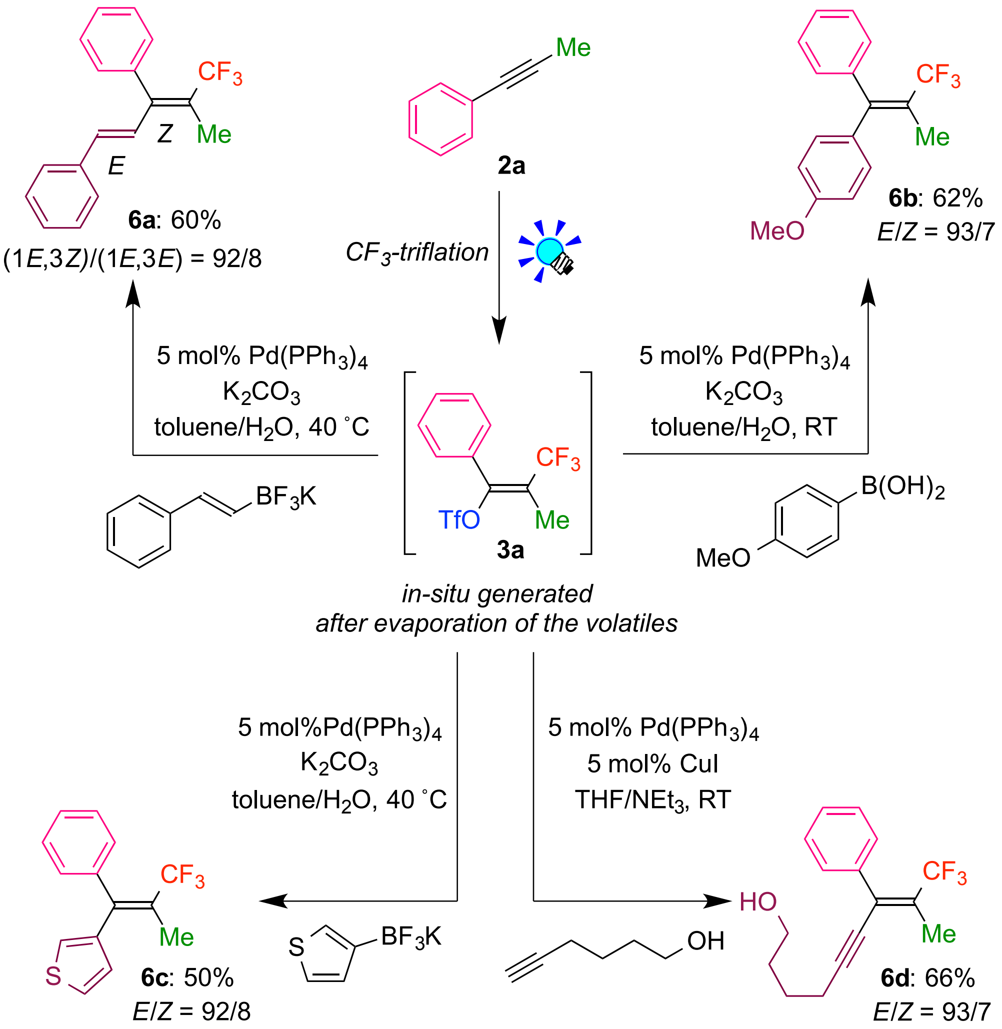
[a] **1a** and base (1.5 equiv each) were used. [b] [NMe$_4$][OTs] was used.

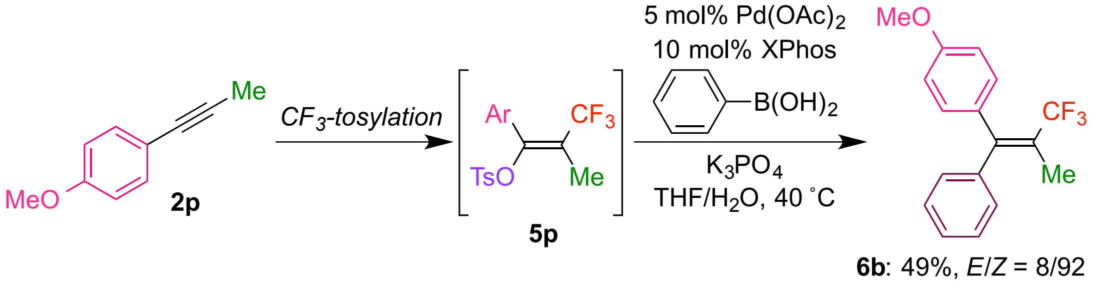
Scheme 5.3. Photocatalytic trifluoromethyl-tosylation of alkynes bearing an electron-donating group (EDG)

5.6 One-Pot Synthesis of Tetrasubstituted CF_3-Alkenes

Next, the author examined stereocontrolled synthesis of CF_3-alkenes bearing four different substituents through Pd-catalyzed coupling reactions of the CF_3-alkenyl triflates. As shown in Scheme 5.4, CF_3-alkenyl triflate **3a**, generated in situ by the photoredox-catalyzed reaction, was directly subjected to various Pd-catalyzed reactions without purification and after solvent exchange. As a result, the tetrasubstituted CF_3-alkene **6a** was obtained in a 60% yield in a highly stereoselective manner ((1*E*,3*Z*)/(1*E*,3*E*) = 92/8) in a one-pot process. The present, highly programmable strategy enabled the stereocontrolled synthesis of a variety of tetrasubstituted CF_3-alkenes **6a**–**6d** by facile one-pot reactions. It turned out that the stereochemistry of

3a was almost retained during the Pd-catalyzed reactions under mild conditions (RT – 40 ˚C). Furthermore, CF_3-alkenyl tosylate **5p** also underwent the Pd-catalyzed coupling with phenylboronic acid to afford **6b** (*E*/*Z* = 8/92) in 49% yield. The product **6b** is the same compound as **3k** in Chapter 3, which was synthesized from the trisubstituted alkene by C–H trifluoromethylation with moderate stereoselectivity (*E*/*Z* = 74/26, see Table 3.2 in Chapter 3). In contrast, it is notable that the present one-pot processes could produce both stereoisomers of **6b** with high stereoselectivities from the appropriate combination of alkynes and arylboronic acids.

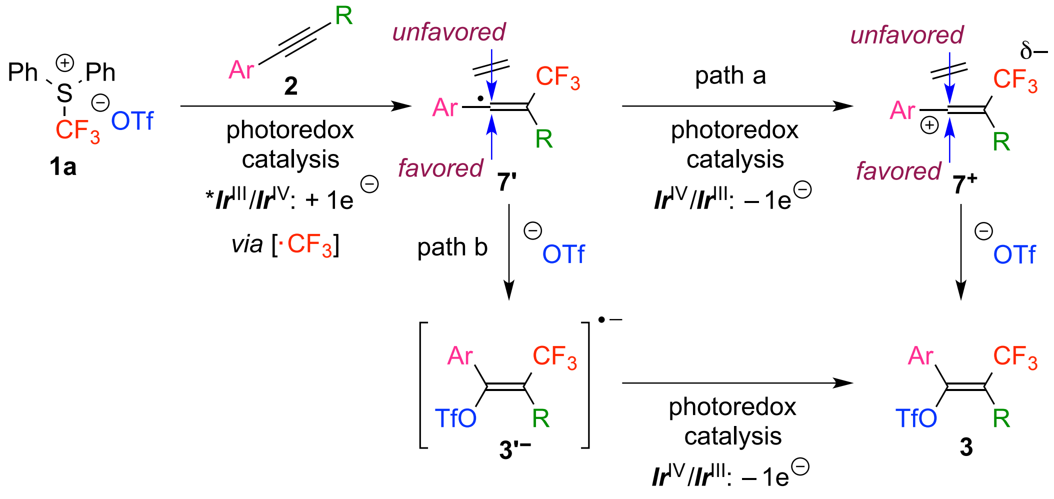




Scheme 5.4. One-pot stereocontrolled synthesis of tetrasubstituted trifluoromethylalkenes from alkynes (Yields are based on alkyne)

5.7 Plausible Reaction Mechanism

A plausible reaction mechanism for the photocatalytic sulfonyloxy-trifluoromethylation is illustrated in Scheme 5.5. Up to the stage of the regiospecific generation of the trifluoromethylated α-styryl radical **7'**, which is stabilized by delocalization over the π orbitals of the phenyl ring,[9a,c] the reaction should proceed through a mechanism similar to that of the previously reported photoredox-catalyzed trifluoromethylation of olefins.[7,10] Indeed, cyclic voltammogram for **1a** contains an irreversible reduction wave at –1.11 V vs. [Cp_2Fe] (Figure 5.4), indicating that **1a** is reduced by the photoexcited *[Ir(ppy)$_2$(dtbbpy)]$^+$ (****Ir*^{III}) (–1.37 V vs. [Cp_2Fe]). Key intermediate **7'** undergoes 1e-oxidation by the highly oxidizing Ir photocatalyst (***Ir***^{IV})[9b,10] to give trifluoromethylated alkenyl cation **7**$^+$ (path a). Nucleophilic attack of the triflate anion favors *trans* addition with respect to the CF_3 group owing to electrostatic repulsion between the strongly electronegative CF_3 group and the lone pair electrons of the nucleophile, as supported by the electrostatic potential map of **7a**$^+$ (Figure 5.5.a).[4a,11] The author also suggests another possible mechanism. The intermediate **7'** may undergo direct addition of the triflate ion to give a radical anion of CF_3-alkenyl triflate **3'**$^{•-}$ (path b) because Stephenson et al. mentioned that oxidation of a vinyl radical to a vinyl cation is thermodynamically unfavored.[12] The electrostatic potential map of **7a'** also supports that the triflate ion favors *trans* addition with respect to the CF_3 group (Figure 5.5.b). The radical anion intermediate **3'**$^{•-}$ is oxidized by the highly oxidizing Ir species (***Ir***^{IV}), leading to stereoselective production of **3**.



Scheme 5.5. A plausible reaction mechanism

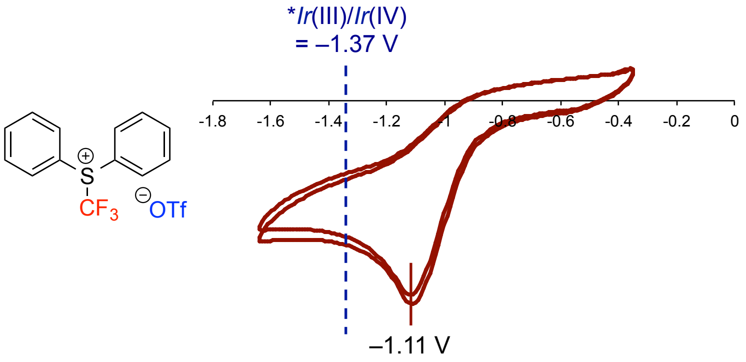


Figure 5.4. A cyclic voltammogram for **1a**

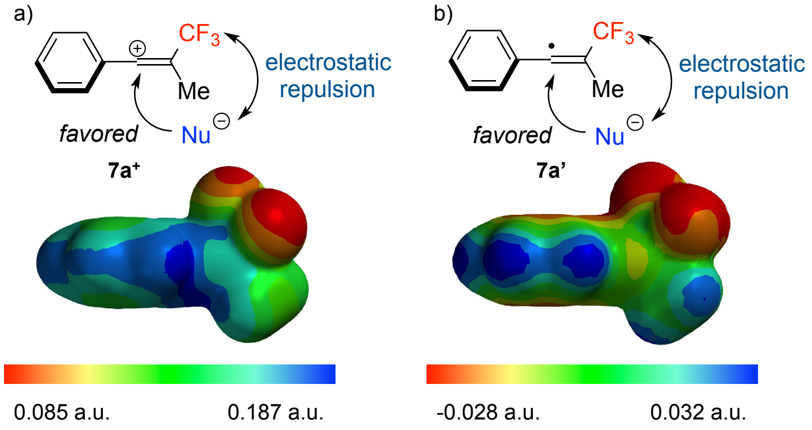
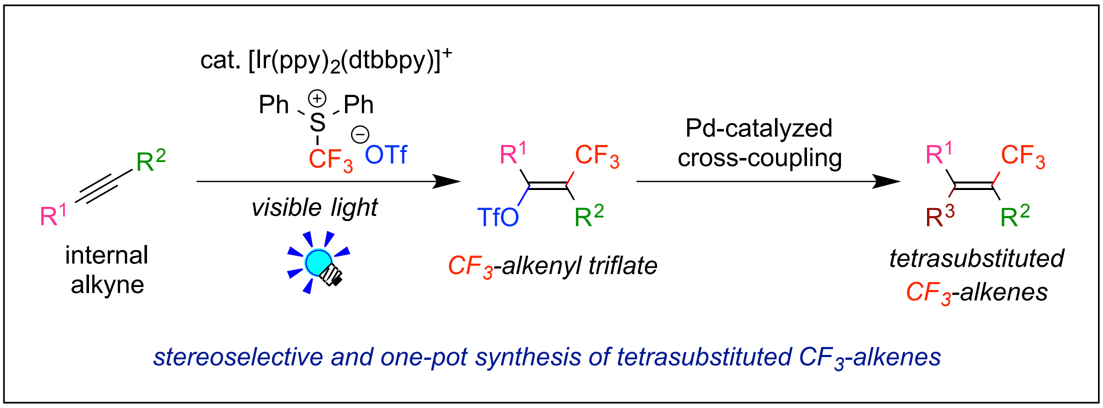


Figure 5.5. Electrostatic potential maps of **7a**$^{+}$ and **7a'**

5.8 Conclusion

The author has developed novel trifluoromethyl-triflation and -tosylation reactions of alkynes mediated by photoredox catalysis. The present photocatalytic system turns out to be powerful for the regio- and highly stereocontrolled synthesis of trifluoromethylated alkenyl triflates from simple alkynes bearing a wide variety of functional groups. Furthermore, by combining this process with the well-established palladium catalysis, various tetrasubstituted CF_3-alkenes are obtained in a highly stereoselective manner in a facile one-pot process. Compared to the previously reported synthetic methods for tertasubstituted CF_3-alkenes, the present protocol is able to achieve versatile structures step-economically from easily accessible alkynes.



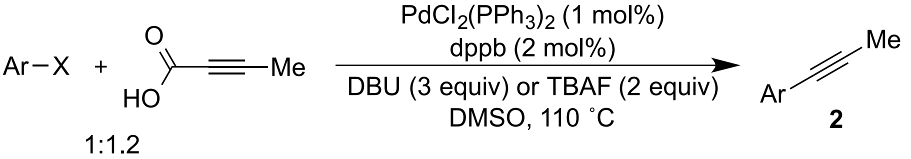
5.9 Experimental

Material and Methods

[Ir(ppy)$_2$(dtbbpy)](PF$_6$)[13], Yagupol'skii-Umemoto reagent **1a**[14], alkynes **2c**[15b] and **2p**[15c] were prepared according to the literature procedures. Alkynes **2a**, **2l**, **2m**, **2n**, and **2o** were purchased from Aldrich and TCI, and used as received. Catalytic reactions were performed under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. Visible light irradiation was performed with a Relyon LED lamp (3 W x 2; λ_{max} = 425 nm). DFT calculation was performed with Spartan '10 program package.

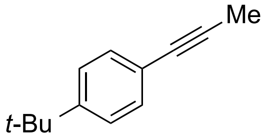
Synthesis of substrates

General procedures for synthesis of alkynes (2b, d, e, g, h, i, p, q)



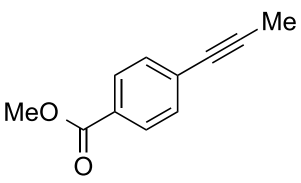
To a 50 mL Schlenk tube, PdCl$_2$(PPh$_3$)$_2$ (35 mg, 50 μmol), 1,4-bis(diphenylphosphino)butane (dppb) (43 mg, 0.10 mmol), 2-butynoic acid (0.50 g, 6.0 mmol), ArX (5.0 mmol), DMSO (15 mL), and DBU (2.2 mL, 15 mmol) or TBAF (1 M in THF, 10 mL, 10 mmol) were added. The tube was degassed under reduced pressure and refilled with N$_2$ three times. The solution was stirred for 12 h at 110 °C. After cooling to room temperature, sat. NH$_4$Cl aq. was added into the reaction mixture and products were extracted with CH$_2$Cl$_2$. The organic layer was washed with water, dried over Na$_2$SO$_4$, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to afford alkyne **2**.

1-(*tert*-Butyl)-4-(1-propynyl)benzene (2b)



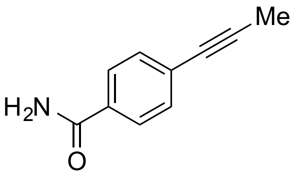
^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 7.33–7.28 (m, 4H; Ar), 2.04 (s, 3H; C≡CCH_3), 1.30 (s, 9H; *t*-Bu). Spectral data were in agreement with the data reported in the literature.[15a]

Methyl 4-(1-propynyl)benzoate (2d)



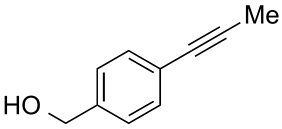
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.95 (d, *J* = 8.8 Hz, 2H; Ar), 7.43 (d, *J* = 8.4 Hz, 2H; Ar), 3.91 (s, 3H; OCH_3), 2.08 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 166.8, 131.6, 129.6, 129.0, 129.0, 89.5, 79.4, 52.3, 4.6. **HRMS** (ESI-TOF): calculated for $[C_{11}H_{10}O_2+Na]^+$ requires 197.0573, found 197.0573.

4-(1-Propynyl)benzamide (2e)



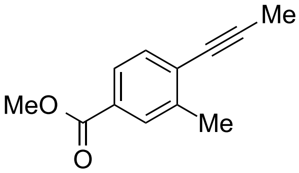
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.73 (d, *J* = 8.4 Hz, 2H; Ar), 7.45 (d, *J* = 8.4 Hz, 2H; Ar), 5.99 (br s, 1H; N*H*H), 5.57 (br s, 1H; NH*H*), 2.08 (s, 3H; CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 168.8, 132.1, 131.8, 128.2, 127.4, 89.2, 79.2, 4.6. **HRMS** (ESI-TOF): calculated for $[C_{10}H_9NO+Na]^+$ requires 182.0576, found 182.0576.

(4-(1-Propynyl)phenyl)methanol (2g)



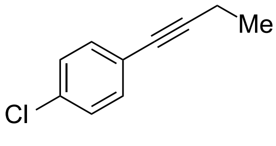
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.38 (d, *J* = 8.0 Hz, 2H; Ar), 7.27 (d, *J* = 8.0 Hz, 2H; Ar), 4.70 (d, *J* = 5.6 Hz, 2H; CH_2), 2.05 (s, 3H; CH_3), 1.72 (t, *J* = 5.8 Hz, 1H; O*H*). Spectral data were in agreement with the data reported in the literature.[15d]

Methyl 3-methyl-4-(1-propynyl)benzoate (2h)



^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.85 (d, *J* = 0.4 Hz, 1H; Ar), 7.76 (dd, *J* = 8.0, 1.2 Hz, 1H; Ar), 7.40 (d, *J* = 8.0 Hz, 1H; Ar), 3.90 (s, 3H; OCH_3), 2.44 (s, 3H; $ArCH_3$), 2.12 (s, 3H; $C\equiv CCH_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 167.0, 140.2, 131.9, 130.4, 128.9, 128.8, 126.7, 93.2, 78.3, 52.2, 20.7, 4.7. **HRMS** (ESI-TOF): calculated for $[C_{12}H_{12}O_2+Na]^+$ requires 211.0730, found 211.0732.

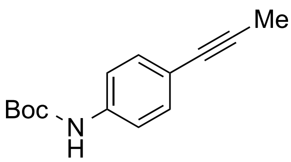
1-(1-Butynyl)-4-chlorobenzene (2i)



^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.31 (d, *J* = 8.8 Hz, 2H; Ar), 7.25 (d, *J* = 8.8 Hz, 2H; Ar), 2.41 (q, *J* = 7.6 Hz, 2H; CH_2CH_3), 1.23 (t, *J* = 7.4 Hz, 3H; CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 133.5, 132.9, 128.6, 122.7, 92.8, 79.0, 13.9, 13.2. **HRMS** (EI): calculated for

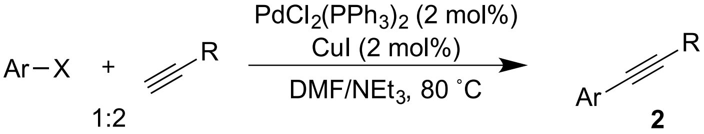
$[C_{10}H_9Cl]^+$ requires 164.0393, found 164.0394.

tert-Butyl (4-(1-propynyl)phenyl)carbamate (2q)



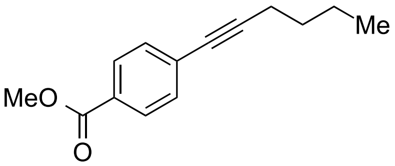
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.31 (d, *J* = 8.8 Hz, 2H; Ar), 7.27 (d, *J* = 9.2 Hz, 2H; Ar), 6.46 (s, 1H; N*H*), 2.03 (s, 3H; C≡CC*H*$_3$), 1.51 (s, 9H; *t*-Bu). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 152.6, 137.9, 132.3, 118.5, 118.2, 85.0, 80.9, 79.6, 28.4, 4.4. **HRMS** (ESI-TOF): calculated for $[C_{14}H_{17}NO_2+Na]^+$ requires 254.1151, found 254.1152.

General procedures for synthesis of alkynes (2j, k, r)



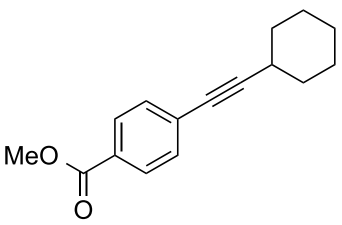
To a 50 mL Schlenk tube, ArX (5 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol), CuI (19 mg, 0.10 mmol), NEt_3 (10 mL), and DMF (10 mL) were added. The tube was degassed under reduced pressure and refilled with N_2 three times. Alkyne (10 mmol) was added to the tube. The solution was stirred for 12 h at 80 ˚C. After cooling to room temperature, water was added into the reaction mixture and products were extracted with Et_2O. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to afford **2**.

Methyl 4-(1-hexynyl)benzoate (2j)



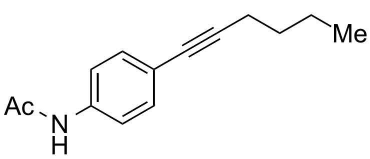
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.95 (d, *J* = 8.8 Hz, 2H; Ar), 7.44 (d, *J* = 8.4 Hz, 2H; Ar), 3.91 (s, 3H; OC*H*$_3$), 2.43 (t, *J* = 7.2 Hz, 2H; C≡CC*H*$_2$), 1.64–1.44 (m, 4H; C*H*$_2$C*H*$_2$CH$_3$), 0.95 (t, *J* = 7.4 Hz, 3H; CH$_2$C*H*$_3$). Spectral data were in agreement with the data reported in the literature.[15e]

Methyl 4-(cyclohexylethynyl)benzoate (2k)



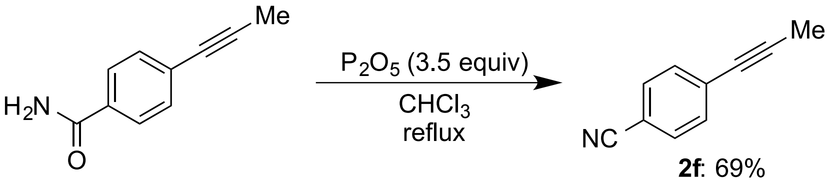
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.94 (d, *J* = 8.4 Hz, 2H; Ar), 7.44 (d, *J* = 8.4 Hz, 2H; Ar), 3.91 (s, 3H; OCH_3), 2.64–2.58 (m, 1H; Cy), 1.90–1.86 (m, 2H; Cy), 1.78–1.74 (m, 2H; Cy), 1.59–1.51 (m, 3H; Cy), 1.39–1.32 (m, 3H; Cy). Spectral data were in agreement with the data reported in the literature.[15f]

***N*-(4-(1-Hexynyl)phenyl)acetamide (2r)**



^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.43 (d, *J* = 8.4 Hz, 2H; Ar), 7.34 (d, *J* = 8.4 Hz, 2H; Ar), 7.19 (br s, 1H; N*H*), 2.39 (t, *J* = 7.0 Hz, 2H; CCH_2CH_2), 2.17 (s, 3H; $COCH_3$), 1.62–1.43 (m, 4H; $CH_2CH_2CH_3$), 0.94 (t, *J* = 7.3 Hz, 3H; CH_2CH_3). Spectral data were in agreement with the data reported in the literature.[15g]

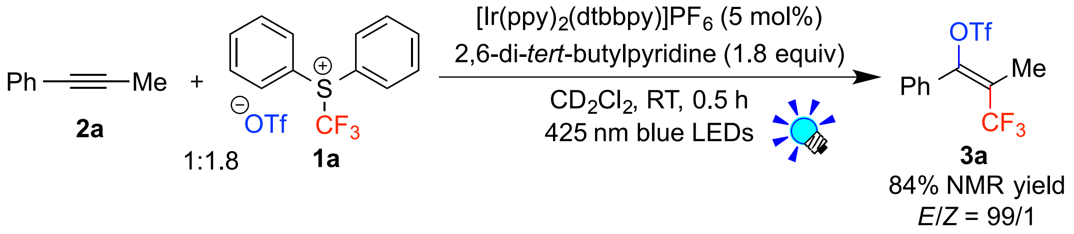
4-(1-Propynyl)benzonitrile (2f)



To a 20 mL Schlenk tube, 4-(1-propynyl)benzamide (**2e**) (0.16 g, 1.0 mmol), $CHCl_3$ (10 mL), and P_2O_5 (1.0 g, 3.5 mmol) were added under N_2. The solution was refluxed for 12 h. The reaction mixture was quenched by water at 0 °C, and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 3/1) to afford **2f** (97 mg, 69%) as a white solid. Spectral data were in agreement with the data reported in the literature.[15c]

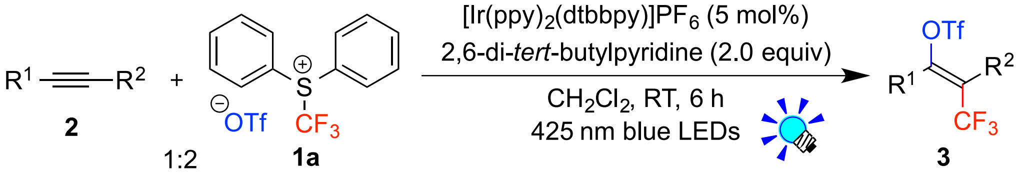
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.56 (d, *J* = 8.8 Hz, 2H; Ar), 7.45 (d, *J* = 8.4 Hz, 2H; Ar), 2.08 (s, 3H; CH_3).

NMR experimental procedures and NMR spectra



An NMR tube was charged with [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (1.1 mg, 1.2 μmol), Yagupol'skii-Umemoto reagent **1a** (18 mg, 45 μmol), 1-phenyl-1-propyne (**2a**) (3.1 μL, 25 μmol), 2,6-di-*tert*-butylpyridine (10 μL, 45 μmol), SiEt$_4$ (~1 μL; an internal standard), and dry CD$_2$Cl$_2$ (0.5 mL) under N$_2$. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 0.5 h at room temperature (in a water bath). The yield was determined by ^{1}H NMR spectroscopy.

General procedures for the photocatalytic trifluoromethanesulfonyloxy-trifluoromethylation of alkynes (CF$_3$-triflation)

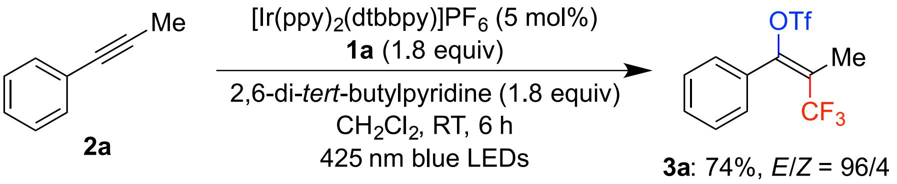


A 20 mL Schlenk tube was charged with [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (11 mg, 12 μmol), Yagupol'skii-Umemoto reagent **1a** (0.20 g, 0.50 mmol), alkyne (**2**) (0.25 mmol), 2,6-di-*tert*-butylpyridine (110 μL, 0.50 mmol), and dry CH$_2$Cl$_2$ (5 mL) under N$_2$. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated for 6 h with stirring at room temperature (in a water bath). The product was purified in two ways described as below. The stereochemistry was confirmed by ^{1}H-^{19}F HOESY NMR spectroscopy, and the *E*/*Z* ratios were determined by ^{19}F NMR spectra of the crude reaction mixture.

For products (**3d**, **e**, **f**, **g**, **h**, **j**, **k**, **l**, **m**), the reaction mixture was concentrated *in vacuo*. The residue was dissolved in Et$_2$O, and the solution was washed with 1 M HCl and H$_2$O, dried over Na$_2$SO$_4$, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the corresponding product **3**.

For products (**3a**, **b**, **c**, **i**, **n**, **o**), they could not be separated from sulfide (the side product from **1a**) by chromatography. The sulfide was converted to the oxide, which was separable by chromatography. mCPBA (0.14 g, ca. 0.55 mmol) was added to the reaction mixture and the solution was stirred at room temperature for 2 h. The reaction mixture was washed with aqueous solution of $Na_2S_2O_3 \cdot 5H_2O$ and then with H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. Then, the residue was dissolved in Et_2O and the solution was washed with 1 M HCl and H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. Finally, the residue was purified by silica gel column chromatography to afford the corresponding product **3**.

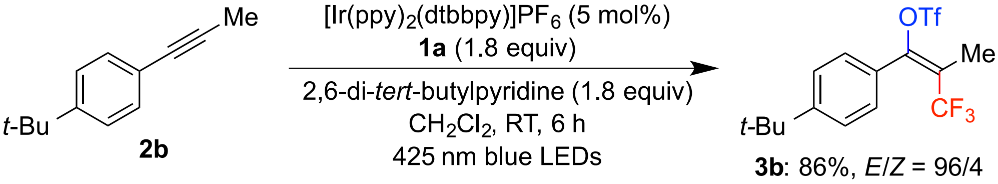
(*E*)-3,3,3-Trifluoro-2-methyl-1-phenyl-1-propenyl trifluoromethanesulfonate (3a)



Following the general procedures, the title compound was synthesized from 1-phenyl-1-propyne (**2a**) (31 μL, 0.25 mmol), **1a** (0.18 g, 0.45 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (11 mg, 12 μmol), 2,6-di-*tert*-butylpyridine (100 μL, 0.45 mmol) and dry CH_2Cl_2 (5 mL). The *E*/*Z* ratio was determined to be 96/4 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane) to afford **3a** (62 mg, 74% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.50–7.41 (m, 5H; Ar), 2.16 (s, 3H; C*H*$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 150.9, (q, *J* = 4.4 Hz), 131.2, 131.0, 129.6, 128.5, 122.9 (q, *J* = 274 Hz), 122.8 (q, *J* = 31.5 Hz), 118.1 (q, *J* = 321 Hz), 12.9 (q, *J* = 1.8 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –61.79 (s, 3F; C*F*$_3$), –75.59 (s, 3F; SO_2C*F*$_3$). **HRMS** (ESI-TOF): calculated for $[C_{11}H_8F_6O_3S+Na]^+$ requires 356.9991, found 356.9990.

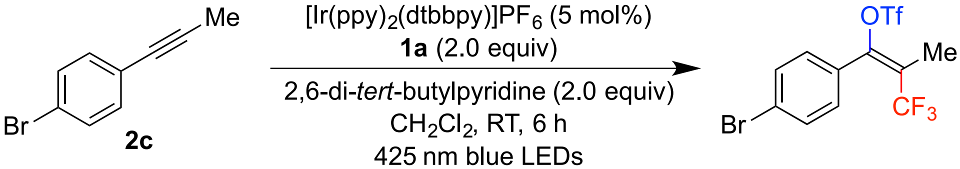
(*E*)-1-(4-(*tert*-Butyl)phenyl)-3,3,3-trifluoro-2-methyl-1-propenyl trifluoromethanesulfonate (3b)



Following the general procedures, the title compound was synthesized from 1-*tert*-butyl-4-(1-propynyl)benzene (**2b**) (43 mg, 0.25 mmol), **1a** (0.18 g, 0.45 mmol), [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (11 mg, 12 μmol), 2,6-di-*tert*-butylpyridine (100 μL, 0.45 mmol) and dry CH$_2$Cl$_2$ (5 mL). The *E*/*Z* ratio was determined to be 96/4 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane) to afford **3b** (84 mg, 86% yield, *E*/*Z* = 97/3) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 7.42 (d, *J* = 8.8 Hz, 2H; Ar), 7.33 (d, *J* = 8.4 Hz, 2H; Ar), 2.14 (s, 3H; C*H*$_3$), 1.33 (s, 9H; *t*-Bu). **^{13}C NMR** (126 MHz, CDCl$_3$, rt): δ 154.7, 151.3 (q, *J* = 4.2 Hz), 129.4, 128.0, 125.4, 123.0 (q, *J* = 274 Hz), 122.2 (q, *J* = 31.4 Hz), 118.1 (q, *J* = 321 Hz), 35.1, 31.2, 12.9 (q, *J* = 2.1 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –61.75 (s, 3F; C*F*$_3$), –75.62 (s, 3F; SO$_2$C*F*$_3$). **HRMS** (ESI-TOF): calculated for $[C_{15}H_{16}F_6O_3S+Na]^+$ requires 413.0617, found 413.0617.

(*E*)-1-(4-Bromophenyl)-3,3,3-trifluoro-2-methyl-1-propenyl trifluoromethanesulfonate (3c)

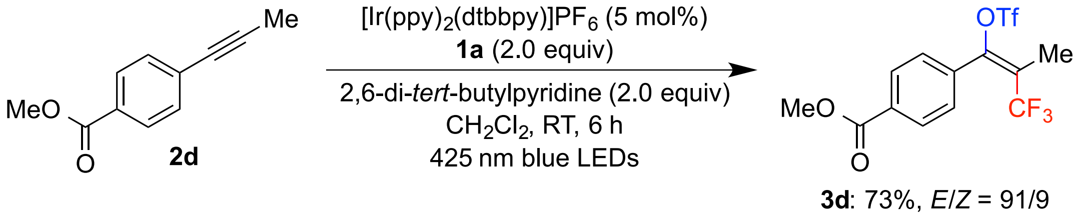


3c: 64%, *E*/*Z* = 92/8

Following the general procedures, the title compound was synthesized from 1-bromo-4-(1-propynyl)benzene (**2c**) (49 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 92/8 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane) to afford **3c** (66 mg, 64% yield) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 7.57 (d, *J* = 8.8 Hz, 2H; Ar), 7.28 (d, *J* = 8.4 Hz, 2H; Ar), 2.15 (s, 3H, C*H*$_3$). **^{13}C NMR** (126 MHz, CDCl$_3$, rt): δ 149.6 (q, *J* = 4.4 Hz), 131.9, 131.1, 129.9, 126.0, 123.7 (q, *J* = 31.6 Hz), 122.8 (q, *J* = 274 Hz), 118.1 (q, *J* = 321 Hz), 12.9 (q, *J* = 1.8 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –61.74 (s, 3F; C*F*$_3$), –75.46 (s, 3F; SO$_2$C*F*$_3$). **HRMS** (FAB): calculated for $[C_{11}H_7BrF_6O_3S]^+$ requires 411.9203, found 411.9199.

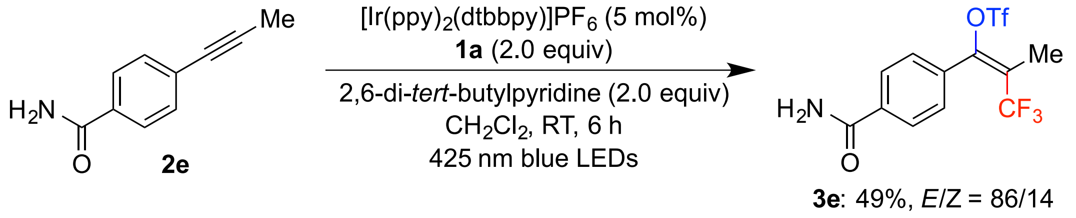
Methyl (*E*)-4-(3,3,3-trifluoro-2-methyl-1-(((trifluoromethyl)sulfonyl)oxy)-1-propenyl)benzoate (3d)



Following the general procedures, the title compound was synthesized from methyl 4-(1-propynyl)benzoate (**2d**) (44 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 91/9 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 49/1) to afford **3d** (71 mg, 73% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.10 (d, *J* = 8.4 Hz, 2H; Ar), 7.50 (d, *J* = 8.4 Hz, 2H; Ar), 3.95 (s, 3H; CH_3O), 2.18 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 166.2, 149.5 (q, *J* = 4.3 Hz), 135.1, 132.6, 129.7 (q, *J* = 1.4 Hz), 129.7, 124.1 (q, *J* = 31.5 Hz), 122.7 (q, *J* = 274 Hz), 118.1 (q, *J* = 321 Hz), 52.6, 12.9. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –61.78 (s, 3F; CF_3), –75.45 (s, 3F; SO_2CF_3). **HRMS** (ESI-TOF): calculated for $[C_{13}H_{10}F_6O_5S+Na]^+$ requires 415.0045, found 415.0043.

(*E*)-1-(4-Carbamoylphenyl)-3,3,3-trifluoro-2-methyl-1-propenyl trifluoromethanesulfonate (3e)

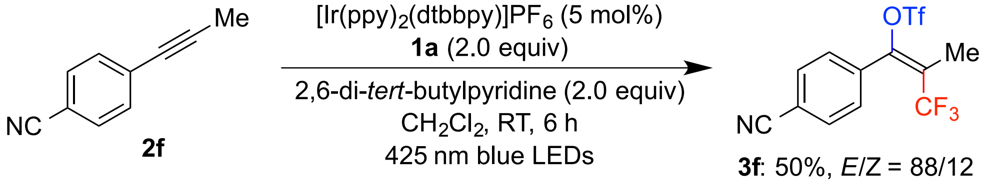


Following the general procedures, the title compound was synthesized from 4-(1-propynyl)benzamide (**2e**) (40 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 86/14 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane/EtOAc = 9/1→2/1→1/1) to afford **3e** (46 mg, 49% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.87 (d, *J* = 8.8 Hz, 2H; Ar), 7.51 (d, *J* = 8.4 Hz, 2H; Ar), 6.08 (br s, 1H; NH*H*), 5.87 (br s, 1H; N*H*H), 2.18 (s, 3H; CH_3). **^{13}C NMR** (126

MHz, $CDCl_3$, rt): δ 168.6, 149.4 (q, *J* = 4.3 Hz), 135.8, 134.3, 130.0, 127.5, 124.0 (q, *J* = 31.3 Hz), 122.7 (q, *J* = 270 Hz), 118.1 (q, *J* = 321 Hz), 12.9 (q, *J* = 1.8 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –61.72 (s, 3F; C*F*$_3$), –75.44 (s, 3F; SO_2C*F*$_3$). **HRMS** (ESI-TOF): calculated for $[C_{12}H_9F_6NO_4S+Na]^+$ requires 400.0049, found 400.0050.

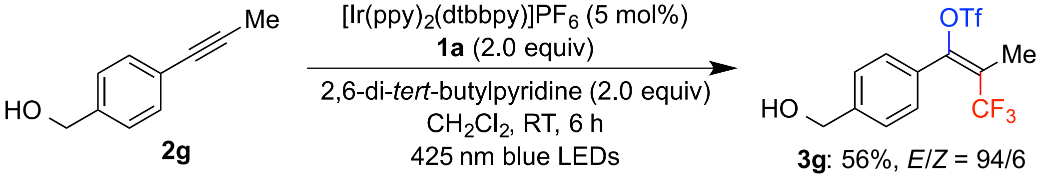
(*E*)-1-(4-Cyanophenyl)-3,3,3-trifluoro-2-methyl-1-propenyl trifluoromethanesulfonate (3f)



Following the general procedures, the title compound was synthesized from 4-(1-propynyl)benzonitrile (**2f**) (35 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 88/12 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/CH_2Cl_2 = 4/1) to afford **3f** (45 mg, 50% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.74 (d, *J* = 8.8 Hz, 2H; Ar), 7.54 (d, *J* = 8.0 Hz, 2H; Ar), 2.19 (s, 3H; C*H*$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 148.2 (q, *J* = 4.3 Hz), 135.2, 132.3, 130.4, 125.1 (q, *J* = 31.9 Hz), 122.5 (q, *J* = 275 Hz), 118.1 (q, *J* = 321 Hz), 117.8, 115.2, 13.0. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –61.72 (s, 3F; C*F*$_3$), –75.38 (s, 3F; SO_2C*F*$_3$). **HRMS** (ESI-TOF): calculated for $[C_{12}H_7F_6NO_3S+Na]^+$ requires 381.9943, found 381.9939.

(*E*)-3,3,3-Trifluoro-1-(4-(hydroxymethyl)phenyl)-2-methyl-1-propenyl trifluoromethanesulfonate (3g)

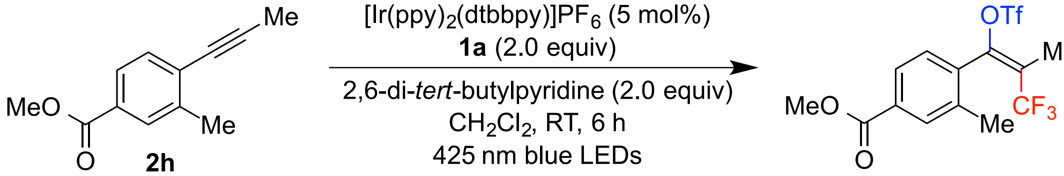


Following the general procedures, the title compound was synthesized from (4-(1-propynyl)phenyl)methanol (**2g**) (37 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 94/6 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane/Et_2O = 9/1

→hexane/EtOAc = 4/1) to afford **3g** (51 mg, 56% yield) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 7.44–7.40 (m, 4H; Ar), 4.77 (s, 2H; CH_2OH), 2.15 (s, 3H; CH_3), 1.88 (br s, 1H; OH). **^{13}C NMR** (126 MHz, CDCl$_3$, rt): δ 150.7 (q, J = 4.3 Hz), 144.1, 130.1, 129.8, 126.6, 122.9 (q, J = 274 Hz), 122.8 (q, J = 31.6 Hz), 118.1 (q, J = 321 Hz), 64.7, 12.9 (q, J = 1.6 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –61.72 (s, 3F; CF_3), –75.56 (s, 3F; SO$_2$CF_3). **HRMS** (ESI-TOF): calculated for $[C_{12}H_{10}F_6O_4S+Na]^+$ requires 387.0096, found 387.0096.

Methyl (*E*)-3-methyl-4-(3,3,3-trifluoro-2-methyl-1-(((trifluoromethyl)sulfonyl)oxy)-1-propenyl)benzoate (3h)

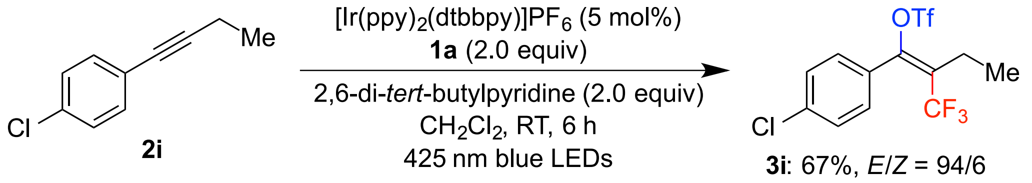


3h: 76%, *E*/*Z* = 97/3

Following the general procedures, the title compound was synthesized from methyl 3-methyl-4-(1-propynyl)benzoate (**2h**) (47 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 97/3 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane → hexane/Et$_2$O = 19/1) to afford **3h** (78 mg, 76% yield) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$, rt): δ 7.94 (s, 1H; Ar), 7.89 (d, J = 8.0 Hz, 1H; Ar), 7.40 (d, J = 8.0 Hz, 1H; Ar), 3.93 (s, 3H; OCH_3), 2.37 (s, 3H; ArCH_3), 2.19 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, CDCl$_3$, rt): δ 166.4, 149.4 (q, J = 4.3 Hz), 138.1, 134.4, 132.6, 131.4, 131.3 (q, J = 1.5 Hz), 126.8, 124.6 (q, J = 31.6 Hz), 122.7 (q, J = 274 Hz), 118.1 (q, J = 321 Hz), 52.5, 19.3, 12.6 (q, J = 1.5 Hz). **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –63.14 (s, 3F; CF_3), –75.79 (s, 3F; SO$_2$CF_3). **HRMS** (ESI-TOF): calculated for $[C_{14}H_{12}F_6O_5S+Na]^+$ requires 429.0202, found 429.0202.

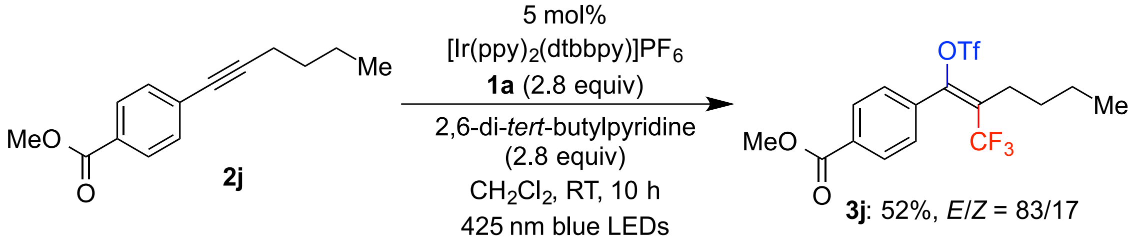
(*E*)-1-(4-Chlorophenyl)-2-(trifluoromethyl)-1-butenyl trifluoromethanesulfonate (3i)



Following the general procedures, the title compound was synthesized from 1-(1-butynyl)-4-chlorobenzene (**2i**) (41 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 94/6 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane) to afford **3i** (64 mg, 67% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.41 (d, *J* = 8.8 Hz, 2H; Ar), 7.36 (d, *J* = 8.4 Hz, 2H; Ar), 2.55 (q, *J* = 7.6 Hz, 2H; CH_2CH_3), 1.27 (t, *J* = 7.4 Hz, 3H; CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 149.8 (q, *J* = 4.3 Hz), 137.6, 131.0, 129.4, 129.2 (q, *J* = 30.1 Hz), 128.9, 123.1 (q, *J* = 275 Hz), 118.1 (q, *J* = 321 Hz), 21.1, 12.7. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –59.54 (s, 3F; CF_3), –75.49 (s, 3F; SO_2CF_3). **HRMS** (FAB): calculated for $[C_{12}H_9ClF_6O_3S]^+$ requires 381.9865, found 381.9862.

Methyl (*E*)-4-(2-(trifluoromethyl)-1-(((trifluoromethyl)sulfonyl)oxy)-1-hexenyl)-benzoate (3j)

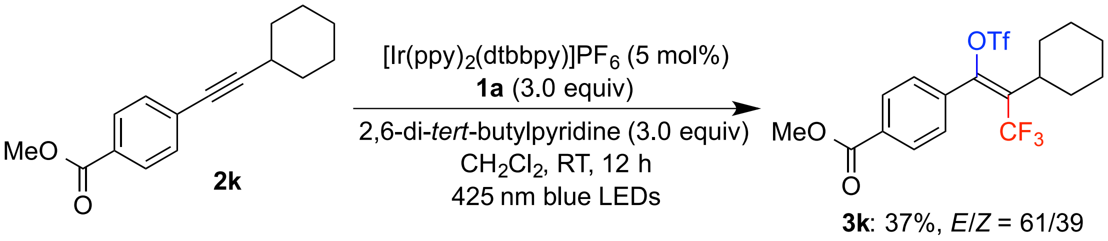


Following the general procedures, the title compound was synthesized from methyl 4-(1-hexynyl)benzoate (**2j**) (54 mg, 0.25 mmol), **1a** (0.28 g, 0.70 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (11 mg, 12 μmol), 2,6-di-*tert*-butylpyridine (154 μL, 0.70 mmol) and dry CH_2Cl_2 (5 mL). The *E*/*Z* ratio was determined to be 83/17 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 49/1) to afford **3j** (57 mg, 52% yield) as a pale brown oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.09 (d, *J* = 8.8 Hz, 2H; Ar), 7.50 (d, *J* = 8.4 Hz, 2H;

Ar), 3.95 (s, 3H; OC*H*$_3$), 2.52 (t, *J* = 8.2 Hz, 2H; CC*H*$_2$), 1.67–1.42 (m, 4H; C*H*$_2$C*H*$_2$CH$_3$), 0.99 (t, *J* = 7.2 Hz, 3H; CH$_2$C*H*$_3$). **^{13}C NMR** (126 MHz, CDCl$_3$, rt): δ 166.2, 149.8 (q, *J* = 4.5 Hz), 135.2, 132.5, 129.8, 129.6, 128.6 (q, *J* = 30.0 Hz), 123.0 (q, *J* = 276 Hz), 118.1 (q, *J* = 321 Hz), 52.6, 30.3, 27.5, 22.9, 13.8. **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –59.39 (s, 3F; C*F*$_3$), –75.50 (s, 3F; SO$_2$C*F*$_3$). **HRMS** (ESI-TOF): calculated for [C$_{16}$H$_{16}$F$_6$O$_5$S+Na]$^+$ requires 457.0515, found 457.0517.

Methyl 4-(2-cyclohexyl-3,3,3-trifluoro-1-(((trifluoromethyl)sulfonyl)oxy)-1-propenyl)benzoate (3k)



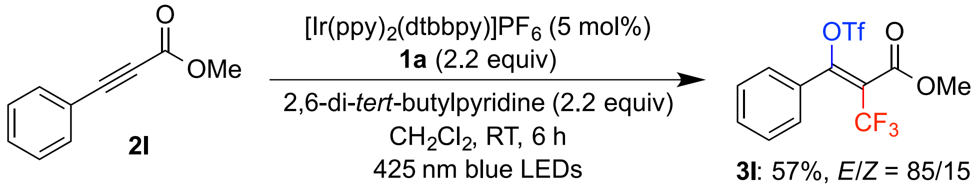
Following the general procedures, the title compound was synthesized from methyl 4-(cyclohexylethynyl)benzoate (**2k**) (60 mg, 0.25 mmol), **1a** (0.31 g, 0.76 mmol), [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (12 mg, 13 μmol), 2,6-di-*tert*-butylpyridine (165 μL, 0.75 mmol) and dry CH$_2$Cl$_2$ (5 mL). The *E*/*Z* ratio was determined to be 61/39 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et$_2$O = 39/1) followed by GPC to afford **3k** (43 mg, 37% yield, *E*/*Z* = 62/38) as a colorless oil.

E-isomer: **^{1}H NMR** (400 MHz, CDCl$_3$, rt): δ 8.08 (d, *J* = 8.8 Hz, 2H; Ar), 7.49 (d, *J* = 8.4 Hz, 2H; Ar), 3.94 (s, 3H; OC*H*$_3$), 2.93 (m, 1H; Cy), 1.89–0.96 (m, 10H; Cy). **^{13}C NMR** (126 MHz, CDCl$_3$, rt): δ 166.2, 149.5 (q, *J* = 5.4 Hz), 135.7, 132.4, 131.9 (q, *J* = 28.4 Hz), 129.8, 129.6, 123.3 (q, *J* = 277 Hz), 118.1 (q, *J* = 321 Hz), 52.6, 39.7, 30.1, 26.7, 25.7. **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –55.52 (s, 3F; C*F*$_3$), –75.40 (s, 3F; SO$_2$C*F*$_3$). **HRMS** (ESI-TOF): calculated for [C$_{18}$H$_{18}$F$_6$O$_5$S+Na]$^+$ requires 483.0671, found 483.0671.

Z-isomer: **^{1}H NMR** (400 MHz, CDCl$_3$, rt): δ 8.15 (d, *J* = 8.8 Hz, 2H; Ar), 7.51 (d, *J* = 8.0 Hz, 2H; Ar), 3.97 (s, 3H; OC*H*$_3$), 2.17 (m, 1H; Cy), 1.89–0.96 (m, 10H; Cy). **^{13}C NMR** (126 MHz, CDCl$_3$, rt): δ 166.1, 147.4 (q, *J* = 4.2 Hz), 135.2, 132.7, 130.4 (q, *J* = 28.2 Hz), 130.1, 129.6, 122.9 (q, *J* = 278 Hz), 118.1 (q, *J* = 321 Hz), 52.7, 41.1, 30.3, 26.4, 25.4. **^{19}F NMR** (376 MHz, CDCl$_3$, rt): δ –57.71 (s, 3F; C*F*$_3$), –75.08 (s, 3F;

SO_2CF_3).

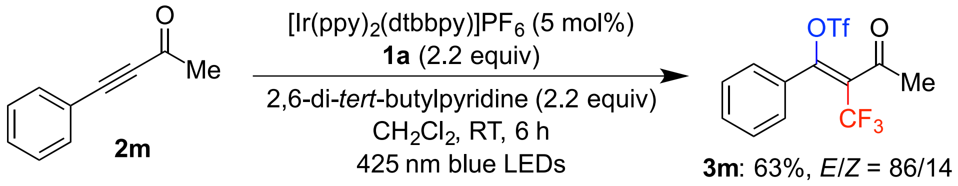
Methyl (*E*)-3-phenyl-2-(trifluoromethyl)-3-(((trifluoromethyl)sulfonyl)oxy)acrylate (3l)



Following the general procedures, the title compound was synthesized from methyl 3-phenylpropiolate (**2l**) (40 mg, 0.25 mmol), **1a** (0.22 g, 0.55 mmol), [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (11 mg, 12 μmol), 2,6-di-*tert*-butylpyridine (120 μL, 0.55 mmol) and dry CH_2Cl_2 (5 mL). The *E*/*Z* ratio was determined to be 85/15 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 29/1) to afford **3l** (54 mg, 57% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.60–7.46 (m, 5H; Ar), 3.96 (s, 3H; OCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 160.5 (q, J = 1.4 Hz), 155.8 (q, J = 4.2 Hz), 132.5, 129.3, 129.3, 128.8, 120.7 (q, J = 275 Hz), 120.6 (q, J = 34.4 Hz), 118.0 (q, J = 321 Hz), 53.7. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –57.68 (s, 3F; CF_3), –75.33 (s, 3F; SO_2CF_3). **HRMS** (ESI-TOF): calculated for $[C_{12}H_8F_6O_5S+Na]^+$ requires 400.9889, found 400.9894.

(*E*)-3-Oxo-1-phenyl-2-(trifluoromethyl)-1-butenyl trifluoromethanesulfonate (3m)

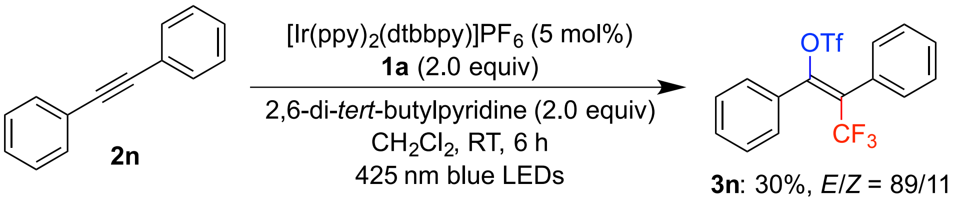


Following the general procedures, the title compound was synthesized from 4-phenyl-3-butyn-2-one (**2m**) (35 μL, 0.25 mmol), **1a** (0.22 g, 0.55 mmol), [Ir(ppy)$_2$(dtbbpy)]PF$_6$ (11 mg, 12 μmol), 2,6-di-*tert*-butylpyridine (120 μL, 0.55 mmol) and dry CH_2Cl_2 (5 mL). The *E*/*Z* ratio was determined to be 86/14 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 29/1) to afford **3m** (57 mg, 63%

yield) as a pale brown oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.59–7.46 (m, 5H; Ar), 2.57 (s, 3H; C*H*$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 193.0, 152.8 (q, *J* = 4.9 Hz), 132.4, 129.2, 129.2, 128.8, 127.2 (q, *J* = 32.6 Hz), 121.0 (q, *J* = 275 Hz), 118.0 (q, *J* = 322 Hz), 31.1. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –56.96 (s, 3F; C*F*$_3$), –75.11 (s, 3F; SO_2C*F*$_3$). **HRMS** (ESI-TOF): calculated for $[C_{12}H_8F_6O_4S+Na]^+$ requires 384.9940, found 384.9935.

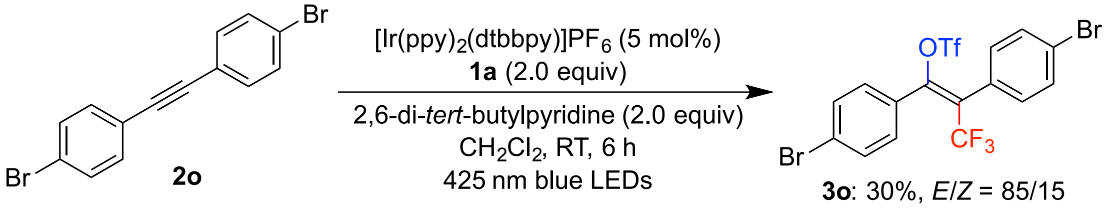
(*E*)-3,3,3-Trifluoro-1,2-diphenyl-1-propenyl trifluoromethanesulfonate (3n)



Following the general procedures, the title compound was synthesized from diphenylacetylene (**2n**) (44 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 89/11 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane) to afford **3n** (30 mg, 30% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.60–7.42 (m, 10H; Ar). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 151.8 (q, *J* = 3.8 Hz), 131.6, 130.8, 129.8, 129.6, 129.6, 129.5, 128.8, 128.6, 127.5 (q, *J* = 32.4 Hz), 122.4 (q, *J* = 275 Hz), 117.8 (q, *J* = 321 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –58.59 (s, 3F; C*F*$_3$), –76.06 (s, 3F; SO_2C*F*$_3$). **HRMS** (FAB): calculated for $[C_{16}H_{10}F_6O_3S]^+$ requires 396.0255, found 396.0247.

(*E*)-1,2-Bis(4-bromophenyl)-3,3,3-trifluoro-1-propenyl trifluoromethanesulfonate (3o)



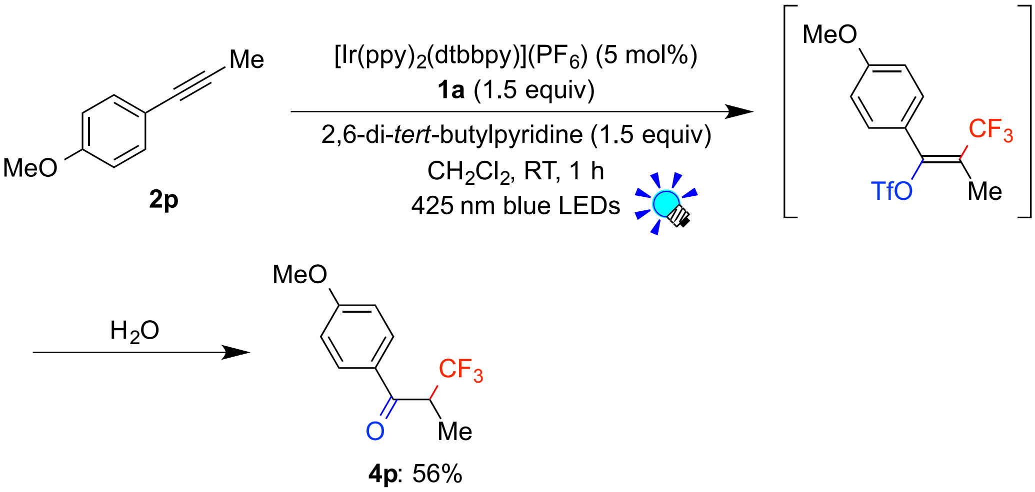
Following the general procedures, the title compound was synthesized from bis(4-bromophenyl)acetylene (**2o**) (84 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 85/15 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane) to afford **3o** (41 mg, 30%

yield, *E*/*Z* = 85/15) as a colorless solid.

E-isomer: ^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.66–7.63 (m, 4H; Ar), 7.44 (d, *J* = 8.4 Hz, 2H; Ar), 7.29 (d, *J* = 8.4 Hz, 2H; Ar). ^{13}**C NMR** (126 MHz, $CDCl_3$, rt): δ 150.9 (q, *J* = 3.8 Hz), 132.3, 132.2, 131.1, 131.0 (q, *J* = 1.4 Hz), 129.4, 128.0, 127.1 (q, *J* = 32.5 Hz), 126.7, 124.6, 122.0 (q, *J* = 275 Hz), 117.8 (q, *J* = 321 Hz). ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –58.51 (s, 3F; CF_3), –75.73 (s, 3F; SO_2CF_3). **HRMS** (FAB): calculated for $[C_{16}H_8Br_2F_6O_3S]^+$ requires 551.8465, found 551.8461.

Z-isomer: ^{1}**H NMR** (400 MHz, $CDCl_3$, rt): δ 7.44–7.03 (m, 4H; Ar), 7.09 (d, *J* = 8.4 Hz, 2H; Ar), 7.01 (d, *J* = 8.4 Hz, 2H; Ar). ^{13}**C NMR** (126 MHz, $CDCl_3$, rt): δ 132.3, 132.1, 132.0, 131.2. ^{19}**F NMR** (376 MHz, $CDCl_3$, rt): δ –60.07 (q, *J* = 3.0 Hz, 3F; CF_3), –74.69 (q, *J* = 2.3 Hz, 3F; SO_2CF_3).

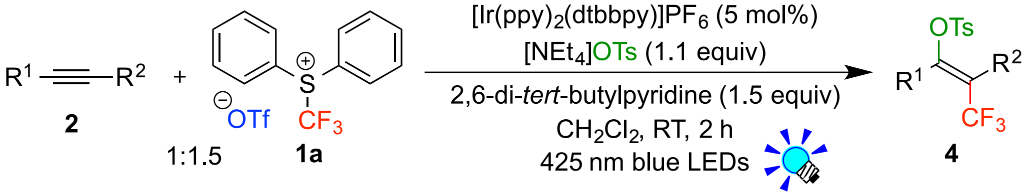
The synthesis of α-trifluoromethylated ketone 4p through CF_3-triflation and hydrolysis (Scheme 5.2)



A 20 mL Schlenk tube was charged with $[Ir(ppy)_2(dtbbpy)]PF_6$ (11 mg, 12 μmol), Yagupol'skii-Umemoto reagent **1a** (0.15 g, 0.38 mmol), 1-(4-methoxyphenyl)-1-propyne (**2p**) (37 mg, 0.25 mmol), 2,6-di-*tert*-butylpyridine (110 μL, 0.50 mmol), and dry CH_2Cl_2 (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated with stirring for 1 h at room temperature (in a water bath). Then, H_2O was added to the reaction mixture, and products were extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. ^{1}H and ^{19}F NMR spectra of the crude reaction mixture showed formation of **4p**. The residue was dissolved in Et_2O and the solution was washed with 1 M HCl and H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane → hexane/Et_2O = 9/1) to afford 3,3,3-trifluoro-1-(4-methoxyphenyl)-2-methylpropan-1-one (**4p**) (33 mg, 56% yield) as a pale yellow oil.

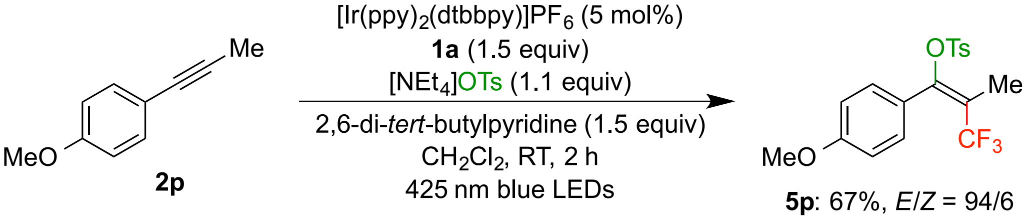
^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.94 (d, J = 9.2 Hz, 2H; Ar), 6.97 (d, J = 9.2 Hz, 2H; Ar), 4.19 (m, 1H; C*H*CF_3), 3.89 (s, 3H; OC*H*$_3$), 1.46 (d, J = 7.2 Hz, 3H; CHC*H*$_3$). Spectral data were in agreement with the data reported in the literature.[7d]

General procedures for the photocatalytic *p*-toluenesulfonyloxytrifluoromethylation of alkynes (CF_3-tosylation)



A 20 mL Schlenk tube was charged with $[NEt_4]OTs$ (83 mg, 0.28 mmol) and dried with a heat gun under reduced pressure. After refilled with N_2, the tube was charged with $[Ir(ppy)_2(dtbbpy)]PF_6$ (11 mg, 12 μmol), Yagupol'skii-Umemoto reagent **1a** (0.15 g, 0.38 mmol), alkyne **2** (0.25 mmol), 2,6-di-*tert*-butylpyridine (82 μL, 0.38 mmol), and dry CH_2Cl_2 (5 mL). The tube placed at a distance of ~3 cm from blue LED lamps was irradiated with stirring for 2 h at room temperature (in a water bath). The reaction mixture was concentrated *in vacuo*. The residue was dissolved in Et_2O and the solution was washed with 1 M HCl and H_2O, 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 the corresponding product **5**.

(*E*)-3,3,3-Trifluoro-1-(4-methoxyphenyl)-2-methyl-1-propenyl 4-methylbenzene-sulfonate (5p)

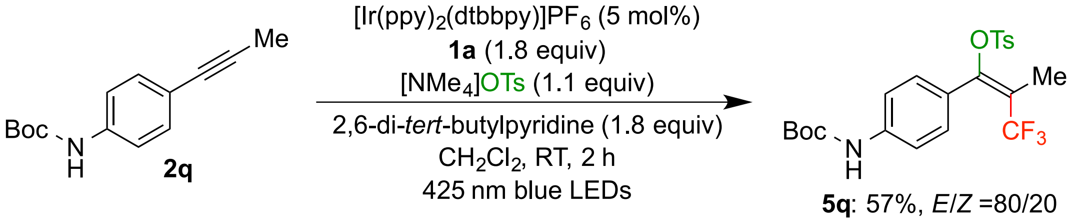


Following the general procedures, the title compound was synthesized from 1-methoxy-4-(1-propynyl)benzene (**2p**) (37 mg, 0.25 mmol). The *E*/*Z* ratio was determined to be 94/6 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane → hexane/Et_2O = 9/1→4/1) to afford **5p** (65 mg, 67% yield, *E*/*Z* = 94/6) as a pale yellow solid.

E isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.38 (d, *J* = 8.4 Hz, 2H; Ar), 7.10 (d, *J* = 8.8 Hz, 2H; Ar), 7.10 (d, *J* = 8.8 Hz, 2H; Ar), 6.65 (d, *J* = 8.8 Hz, 2H; Ar), 3.80 (s, 3H; OCH_3), 2.37 (s, 3H; $ArCH_3$), 2.06 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 160.8, 150.8 (q, *J* = 4.3 Hz), 144.8, 134.3, 131.2 (q, *J* = 1.5 Hz), 129.5, 127.9, 124.3, 123.8 (q, *J* = 274 Hz), 119.7 (q, *J* = 30.5 Hz), 113.2, 55.4, 21.7, 12.8 (q, *J* = 1.7 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –61.09 (s, 3F). **HRMS** (ESI-TOF): calculated for $[C_{18}H_{17}F_3O_4S+Na]^+$ requires 409.0692, found 409.0692.

Z isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.43 (d, *J* = 8.4 Hz, 2H; Ar), 7.11–7.09 (overlap with *E*, 4H; Ar), 6.71 (d, *J* = 8.8 Hz, 2H; Ar), 3.80 (s, 3H; OCH_3), 2.37 (s, 3H; $ArCH_3$), 1.83 (s, 3H; CCH_3). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –62.56 (s, 3F).

(*E*)-1-(4-((*tert*-Butoxycarbonyl)amino)phenyl)-3,3,3-trifluoro-2-methyl-1-propenyl 4-methylbenzenesulfonate (5q)



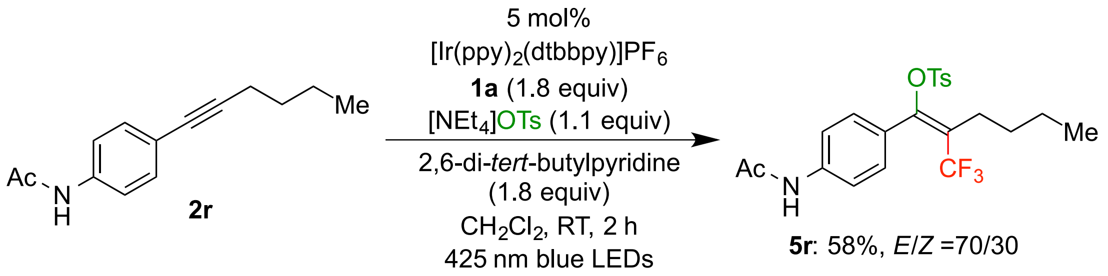
Following the general procedures, the title compound was synthesized from *tert*-butyl (4-(1-propynyl)phenyl)carbamate (**2q**) (58 mg, 0.25 mmol), **1a** (0.18 g, 0.45 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (12 mg, 13 μmol), 2,6-di-*tert*-butylpyridine (100 μL, 0.45 mmol), $[NMe_4]OTs$ (68 mg, 0.28 mmol) and dry CH_2Cl_2 (5 mL). The *E*/*Z* ratio was determined to be 80/20 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/Et_2O = 9/1 →hexane/EtOAc = 9/1) to afford **5q** (67 mg, 57% yield, *E*/*Z* = 83/17) as a yellow solid.

E-isomer: **^{1}H NMR** (500 MHz, $CDCl_3$, rt): δ 7.38 (d, *J* = 8.0 Hz, 2H; Ar), 7.14–7.07 (m, 6H; Ar), 6.49 (s, 1H; N*H*), 2.36 (s, 3H; $ArCH_3$), 2.06 (s, 3H; CCH_3), 1.52 (s, 9H; *t*-Bu).

^{13}C NMR (126 MHz, $CDCl_3$, rt): δ 152.4, 150.5 (q, *J* = 4.4 Hz), 145.0, 140.0, 134.1, 130.6 (q, *J* = 1.5 Hz), 129.6, 127.9, 126.2, 123.8 (q, *J* = 274 Hz), 120.0 (q, *J* = 30.6 Hz), 117.1, 81.1, 28.4, 21.7, 12.8 (q, *J* = 2.1 Hz). **^{19}F NMR** (471 MHz, $CDCl_3$, rt): δ –61.05 (s, 3F). **HRMS** (ESI-TOF): calculated for $[C_{22}H_{24}F_3NO_5S+Na]^+$ requires 494.1219, found 494.1218.

Z-isomer: **^{1}H NMR** (500 MHz, $CDCl_3$, rt): δ 7.43 (d, *J* = 8.5 Hz, 2H; Ar), 7.20 (d, *J* = 8.5 Hz, 2H; Ar), 7.14–7.07 (overlap with *E*, 4H; Ar), 6.53 (s, 1H; N*H*), 2.38 (s, 3H; ArCH_3), 1.82 (s, 3H; CCH_3), 1.53 (s, 9H; *t*-Bu). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 152.4, 145.0, 140.1, 134.1, 130.7, 129.4, 128.1, 125.7, 117.5, 81.1, 28.3, 21.7, 13.8. **^{19}F NMR** (471 MHz, $CDCl_3$, rt): δ –62.60 (s, 3F).

1-(4-Acetamidophenyl)-2-(trifluoromethyl)-1-hexenyl 4-methylbenzenesulfonate (5r)



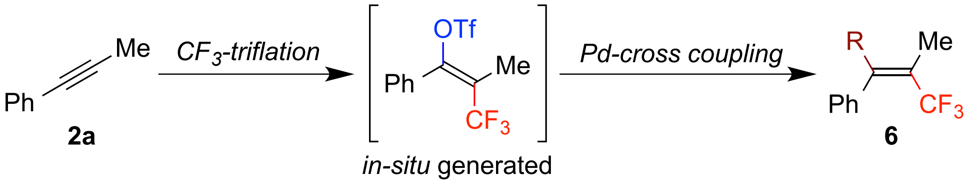
Following the general procedures, the title compound was synthesized from *N*-(4-(1-hexynyl)phenyl)acetamide (**2r**) (54 mg, 0.25 mmol). **1a** (0.18 g, 0.45 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (11 mg, 12 μmol), 2,6-di-*tert*-butylpyridine (100 μL, 0.45 mmol), $[NEt_4]OTs$ (83 mg, 0.28 mmol) and dry CH_2Cl_2 (5 mL). The *E*/*Z* ratio was determined to be 70/30 from a ^{19}F NMR spectrum of the crude reaction mixture. The product mixture was purified by silica gel column chromatography (hexane→hexane/EtOAc = 9/1→4/1) to afford **5r** (66 mg, 58% yield, *E*/*Z* = 75/25) as a yellow solid.

E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.38 (d, *J* = 8.4 Hz, 2H; Ar), 7.31 (d, *J* = 8.4 Hz, 2H; Ar), 7.14 (d, *J* = 8.4 Hz, 2H; Ar), 7.11 (d, *J* = 8.0 Hz, 2H; Ar), 2.43 (t, *J* = 8.0 Hz, 2H; CCH_2), 2.36 (s, 3H; ArCH_3), 2.17 (s, 3H; COCH_3), 1.60–1.34 (m, 4H; CH_2CH_2CH_3), 0.94 (t, *J* = 7.2 Hz, 3H; CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 169.0, 150.9 (q, *J* = 4.5 Hz), 145.3, 139.7, 133.9, 130.5, 129.6, 127.7, 127.5, 124.5 (q, *J* = 29.2 Hz), 124.0 (q, *J* = 275 Hz), 118.6, 30.6, 27.2, 24.6, 22.9, 21.6, 13.8. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –58.65 (s, 3F). **HRMS** (ESI-TOF): calculated for

$[C_{22}H_{24}F_3NO_4S+Na]^+$ requires 478.1270, found 478.1271.

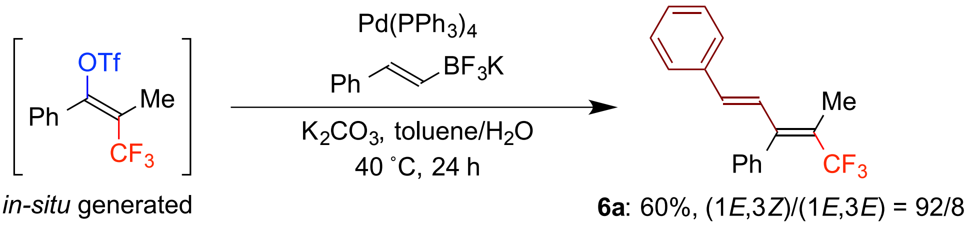
Z-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$, rt): δ 7.45 (d, *J* = 8.4 Hz, 2H; Ar), 7.40–7.37 (overlap with *E*, 2H; Ar), 7.15–7.12 (overlap with *E*, 2H; Ar), 7.19 (d, *J* = 8.4 Hz, 2H; Ar), 2.38 (s, 3H; $ArCH_3$), 2.19 (s, 3H; $COCH_3$), 2.12 (t, *J* = 7.8 Hz, CCH_2), 1.42–1.12 (m, 4H; $CH_2CH_2CH_3$), 0.76 (t, *J* = 7.4 Hz, 3H; CH_2CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 169.0, 149.0, 145.3, 140.0, 133.8, 130.3, 129.5, 127.9, 126.7, 118.9, 31.1, 27.5, 22.3, 21.6, 13.6. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –60.54 (s, 3F).

Procedures for one-pot synthesis of tetrasubstituted CF_3-alkenes



A 20 mL Schlenk tube was charged with $[Ir(ppy)_2(dtbbpy)]PF_6$ (11 mg, 12 µmol), Yagupol'skii-Umemoto reagent **1a** (0.18 g, 0.45 mmol), **2a** (31 µL, 0.25 mmol), 2,6-di-*tert*-butylpyridine (100 µL, 0.45 mmol) and dry CH_2Cl_2 (5 mL) under N_2. The tube placed at a distance of ~3 cm from blue LED lamps was irradiated with stirring for 6 h at room temperature (in a water bath). The volatiles were removed *in vacuo*. Then, palladium-catalyzed cross coupling reaction was conducted without further purification. The stereochemistry of coupling products were assigned by ^{1}H-^{1}H NOESY NMR spectroscopy, and the *E*/*Z* ratio were determined by ^{19}F NMR spectrum of the crude reaction mixture.

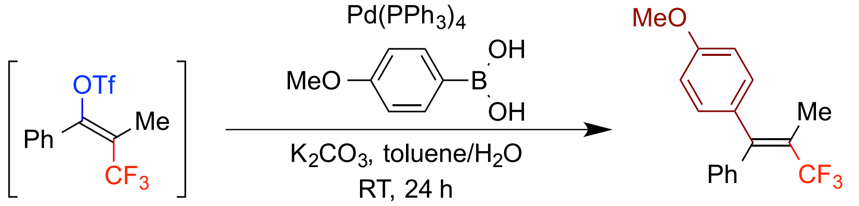
(1*E*,3*Z*)-5,5,5-Trifluoro-4-methyl-1,3-diphenyl-1,3-pentadiene (6a)



Following the general procedures, CF_3-alkenyl triflate **3a** was generated from **2a** (31 µL, 0.25 mmol). To the crude **3a** in the 20 mL Schlenk tube, toluene (5 mL), H_2O (1 mL), K_2CO_3 (0.10 g, 0.75 mmol), potassium *trans*-styryltrifluoroborate (80 mg, 0.38 mmol) and $Pd(PPh_3)_4$ (15 mg, 13 µmol) were added. The tube was degassed by three freeze-pump-thaw cycles and refilled with N_2. Then, the tube was stirred for 24 h at 40 °C. To the reaction mixture, Et_2O was added. The solution was washed with 1 M HCl and H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The (1*E*,3*Z*)/(1*E*,3*E*) ratio was determined to be 92/8 from a ^{19}F NMR spectrum of the crude reaction mixture. The residue was roughly purified by silica gel column chromatography (hexane) and further purification was conducted by GPC to afford **6a** (44 mg, 60% yield, (1*E*,3*Z*)/(1*E*,3*E*) = 91/9) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.38–7.23 (m, 11H; C_6H_5, $C_6H_5CH{=}CH$), 6.10 (d, J = 15.6 Hz, 1H; PhC*H*=CH), 2.18 (s, 3H; CH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 143.2 (q, J = 3.9 Hz), 138.0, 137.9, 136.7, 129.3 (q, J = 1.5 Hz), 128.8, 128.6, 127.9, 127.6, 127.4, 127.1, 124.7 (q, J = 275 Hz), 123.2 (q, J = 27.9 Hz), 13.8 (q, J = 2.9 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –60.08 (s, 3F). **HRMS** (EI): calculated for $[C_{18}H_{15}F_3]^+$ requires 288.1126, found 288.1120.

(*E*)-1-Methoxy-4-(3,3,3-trifluoro-2-methyl-1-phenyl-1-propenyl)benzene (6b)



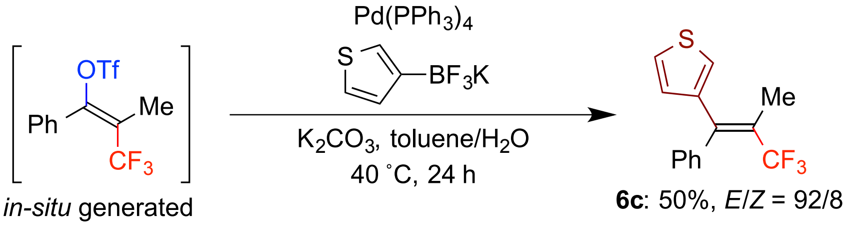
in-situ generated

6b: 62%, *E*/*Z* = 93/7

A 20 mL Schlenk tube was charged with K_2CO_3 (0.10 g, 0.74 mmol), H_2O (1 mL), 4-methoxyphenylboronic acid (57 mg, 0.38 mmol), toluene solution (5 mL) of the crude **3a**, and $Pd(PPh_3)_4$ (15 mg, 13 μmol). Then, the tube was degassed by three freeze-pump-thaw cycles and refilled with N_2. The tube was stirred for 24 h at room temperature. To the reaction mixture, Et_2O was added. The solution was washed with 1 M HCl and H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The *E*/*Z* ratio was determined to be 93/7 from a ^{19}F NMR spectrum of the crude reaction mixture. The residue was purified by silica gel column chromatography (hexane→hexane/Et_2O = 29/1) to afford **6b** (46 mg, 62% yield, *E*/*Z* = 92/8) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.33–7.26 (m, 3H; Ar), 7.14 (dd, J = 8.0, 2.4 Hz, 2H; Ar), 7.05 (d, J = 8.8 Hz, 2H; Ar), 6.85 (d, J = 8.8 Hz, 2H; Ar), 3.80 (s, 3H; OCH_3), 1.95 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 159.3, 147.0 (q, J = 3.8 Hz), 141.3, 133.6, 130.5, 128.7, 128.0, 127.6, 124.8 (q, *J* = 276 Hz), 122.9 (q, *J* = 28.4 Hz), 113.8, 55.4, 16.6. **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –60.55 (s, 3F). **HRMS** (EI): calculated for $[C_{17}H_{15}F_3O]^+$ requires 292.1075, found 292.1082.

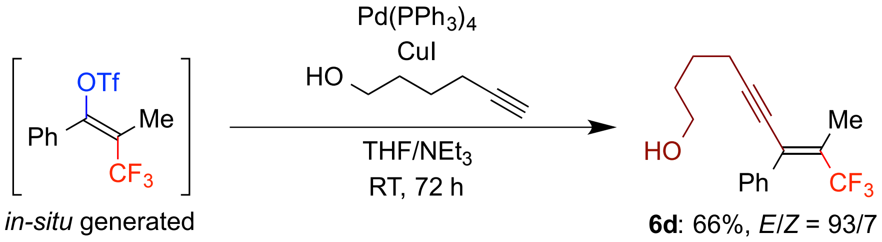
(*E*)-3-(3,3,3-Trifluoro-2-methyl-1-phenyl-1-propenyl)thiophene (6c)



A 20 mL Schlenk tube was charged with K_2CO_3 (0.11 g, 0.76 mmol), H_2O (1 mL), potassium 3-thiophenetrifluoroborate (72 mg, 0.38 mmol), toluene solution (5 mL) of the crude **3a**, and $Pd(PPh_3)_4$ (15 mg, 13 μmol). Then, the tube was degassed by three freeze-pump-thaw cycles and refilled with N_2. The tube was stirred for 24 h at 40 ˚C. To the reaction mixture, Et_2O was added. The solution was washed with 1 M HCl and H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The *E*/*Z* ratio was determined to be 92/8 from a ^{19}F NMR spectrum of the crude reaction mixture. The residue was roughly purified by silica gel column chromatography (hexane) and further purification was conducted by GPC to afford **6c** (33 mg, 50% yield, *E*/*Z* = 95/5) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.33-7.28 (m, 3H; Ar), 7.26 (dd, *J* = 5.2, 2.8 Hz, 1H; thiophenyl), 7.17–7.15 (m, 2H; Ar), 7.07 (dd, *J* = 2.8, 1.2 Hz, 1H; thiophenyl), 6.85 (dd, *J* = 4.8, 1.2 Hz, 1H; thiophenyl), 2.06 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 142.1 (q, *J* = 3.7 Hz), 141.2, 140.9, 128.7, 128.6 (q, *J* = 2.1 Hz), 128.0, 127.7, 125.4, 125.3, 124.6 (q, *J* = 276 Hz), 123.5 (q, *J* = 28.5 Hz), 16.6 (q, *J* = 2.5 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –60.56 (s, 3F). **HRMS** (EI): calculated for $[C_{14}H_{11}F_3S]^+$ requires 268.0534, found 268.0528.

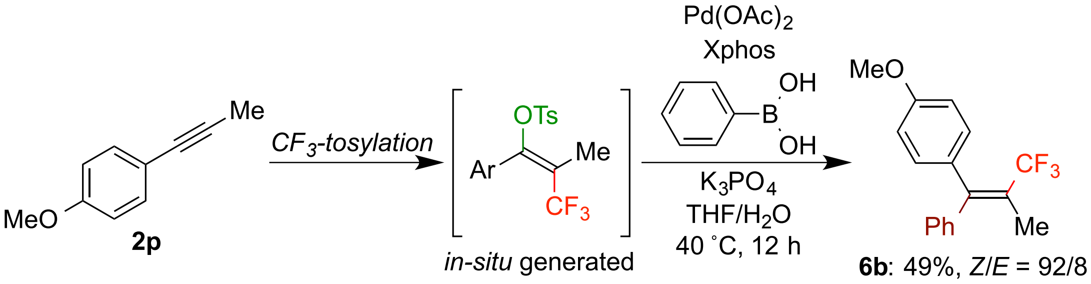
(*E*)-9,9,9-Trifluoro-8-methyl-7-phenylnon-7-en-5-yn-1-ol (6d)



A 20 mL Schlenk tube was charged with CuI (3 mg, 13 µmol), Pd(PPh_3)$_4$ (14 mg, 13 µmol), THF solution (2.5 mL) of the crude **3a**, NEt_3 (2.5 mL), and 5-hexyn-1-ol (37 mg, 0.38 mmol). Then, the tube was degassed by three freeze-pump-thaw cycles and refilled with N_2. The tube was stirred for 72 h at room temperature. The reaction mixture was concentrated *in vacuo*. The *E*/*Z* ratio was determined to be 93/7 from a ^{19}F NMR spectrum of the crude reaction mixture. The residue was purified by silica gel column chromatography (hexane→hexane/EtOAc = 9/1→2/1) to afford **6d** (47 mg, 66% yield, *E*/*Z* = 94/6) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.34–7.30 (m, 3H; Ar), 7.28–7.25 (m, 2H; Ar), 3.66 (t, *J* = 6.2 Hz, 2H; C*H*$_2$OH), 2.43 (t, *J* = 6.2 Hz, 2H; CC*H*$_2$), 2.20 (s, 3H; CC*H*$_3$), 1.69–1.62 (m, 4H; C*H*$_2$C*H*$_2$CH$_2$OH). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 138.1, 130.4 (q, *J* = 29.3 Hz), 129.6 (q, *J* = 4.2 Hz), 128.1, 128.1, 128.0, 124.2 (q, *J* = 275 Hz), 101.3, 80.3, 62.4, 31.9, 24.9, 19.7, 17.0 (q, *J* = 1.6 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –60.39 (s, 3F). **HRMS** (ESI-TOF): calculated for [$C_{16}H_{17}F_3O$+Na]$^+$ requires 305.1124, found 305.1124.

(*Z*)-1-Methoxy-4-(3,3,3-trifluoro-2-methyl-1-phenyl-1-propenyl)benzene (6b)

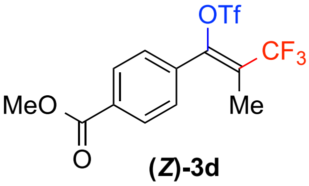


A 20 mL Schlenk tube was charged with [NEt_4]OTs (85 mg, 0.28 mmol) and dried with a heat gun under reduced pressure. After refilled with N_2, the tube was charged with [Ir(ppy)$_2$(dtbbpy)]PF_6 (11 mg, 12 µmol), **1a** (0.15 g, 0.38 mmol), **2p** (37 mg, 0.25 mmol), 2,6-di-*tert*-butylpyridine (82 µL, 0.38 mmol) and dry CH_2Cl_2 (5 mL). The tube placed at a distance of ~3 cm from blue LED lamps was irradiated with stirring for 2 h at room temperature (in a water bath). The reaction mixture was concentrated *in vacuo*. Then, the palladium-catalyzed cross coupling reaction was conducted without further purification.

A 20 mL Schlenk tube was charged with Xphos (14 mg, 29 μmol), $Pd(OAc)_2$ (3.3 mg, 15 μmol) and THF (1 mL) under N_2 and the mixture was stirred for 15 min at room temperature. To the solution, K_3PO_4 (0.16 g, 0.74 mmol), phenylboronic acid (46 mg, 0.38 mmol), THF solution (4 mL) of the crude **5p**, and H_2O (0.5 mL) were added. Then, the tube was degassed by three freeze-pump-thaw cycles and refilled with N_2. The tube was stirred for 12 h at 40 °C. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in Et_2O. The solution was washed with 1 M HCl and H_2O, dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The *Z*/*E* ratio was determined to be 92/8 from a ^{19}F NMR spectrum of the crude reaction mixture. The residue was purified by silica gel column chromatography (hexane→hexane/Et_2O = 29/1) to afford **5b** (36 mg, 49% yield, *Z*/*E* = 91/9) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 7.33 (dd, *J* = 7.2, 7.2 Hz, 2H; Ar), 7.27 (dd, *J* = 7.6, 7.2 Hz, 1H; Ar), 7.12 (d, 6.8 Hz, 2H; Ar), 7.08 (d, *J* = 8.8 Hz, 2H; Ar), 6.82 (d, *J* = 8.8 Hz, 2H; Ar), 3.79 (s, 3H; OCH_3), 1.90 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 159.2, 147.2, 141.7, 133.3, 130.0, 129.0, 128.4, 127.8, 124.8 (q, *J* = 275 Hz), 123.1 (q, *J* = 28.5 Hz), 113.4, 55.3, 16.6 (q, *J* = 2.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –60.67 (s, 3F). **HRMS** (EI): calculated for $[C_{17}H_{15}F_3O]^+$ requires 292.1075, found 292.1072.

Isolation of the minor stereoisomer of 3d and assignment of the stereochemistry



(*Z*)-3d

(*Z*)-3d was isolated from the reaction of methyl 4-(1-propynyl)benzoate (**2d**) in 8% yield. The stereochemistry was determined by ^{1}H-^{1}H NOESY NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$, rt): δ 8.15 (d, *J* = 8.4 Hz, 2H; Ar), 7.53 (d, *J* = 8.4 Hz, 2H; Ar), 3.96 (s, 3H; OCH_3), 1.90 (s, 3H; CCH_3). **^{13}C NMR** (126 MHz, $CDCl_3$, rt): δ 166.0, 146.1 (q, *J* = 3.5 Hz), 134.9, 132.7, 130.1, 129.7, 122.3 (q, *J* = 276 Hz), 121.8 (q, *J* =

31.5 Hz), 118.1 (q, *J* = 321 Hz), 52.7, 14.3 (q, *J* = 2.3 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$, rt): δ –63.30 (q, *J* = 2.6 Hz, 3F; CF_3), –74.97 (q, *J* = 2.6 Hz, 3F; SO_2CF_3). **HRMS** (ESI-TOF): calculated for $[C_{13}H_{10}F_6O_5S+Na]^+$ requires 415.0045, found 415.0047.

Cyclic voltammogram for Yagupol'skii-Umemoto reagent (1a) (Figure 5.4)

CV measurement was performed using a Hokutodenkou HZ-5000 analyzer under N_2 at room temperature (observed in 0.002 M CH_2Cl_2; $[NBu_4PF_6]$ = 0.1 M; Ag/AgCl = electrode; reported with respect to the $[FeCp_2]/[FeCp_2]^+$ couple).

Electrostatic potential maps of alkenyl cation 6a$^+$ and alkenyl radical 6a' (Figure 5.5)

Electrostatic potential map was calculated using Spartan '10.[16] Geometry optimization was performed with DFT calculation by using the B3LYP/6-31G(d).

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[10] A Cyclic voltammogram for **1a** contained an irreversible reduction wave at –1.11 V vs. [Cp_2Fe], indicating that **1a** is reduced by the photoexcited [$Ir^{III}(ppy)_2(dtbbpy)]^+$ (***Ir***^{III}) (–1.37 V vs. [Cp_2Fe]). In addition, the highly oxidizing Ir species (***Ir***^{IV}: [$Ir^{IV}(ppy)_2(dtbbpy)]^{2+}$) exhibits high oxidation potential at +0.80 V vs. [Cp_2Fe] compared to $Mn(OAc)_3$, see: M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, Jr., G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712–5719.

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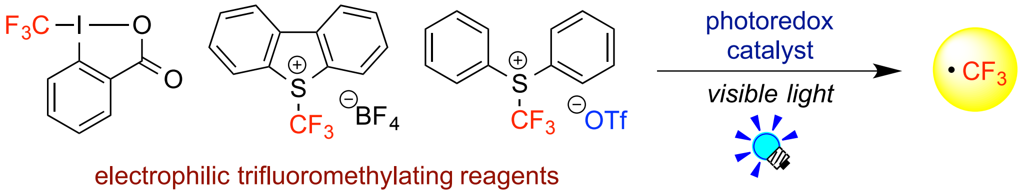
Chapter 6

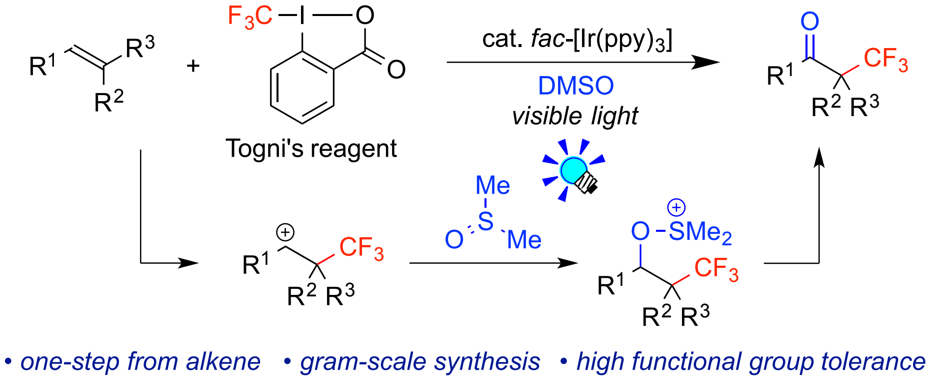
Summary and Outlook

Through this thesis, the author has developed novel trifluoromethylation reactions of carbon–carbon unsaturated bonds by visible-light-induced photoredox catalysis involving generation of the CF_3 radical from electrophilic trifluoromethylating reagents (Scheme 6.1). The over view is given below.



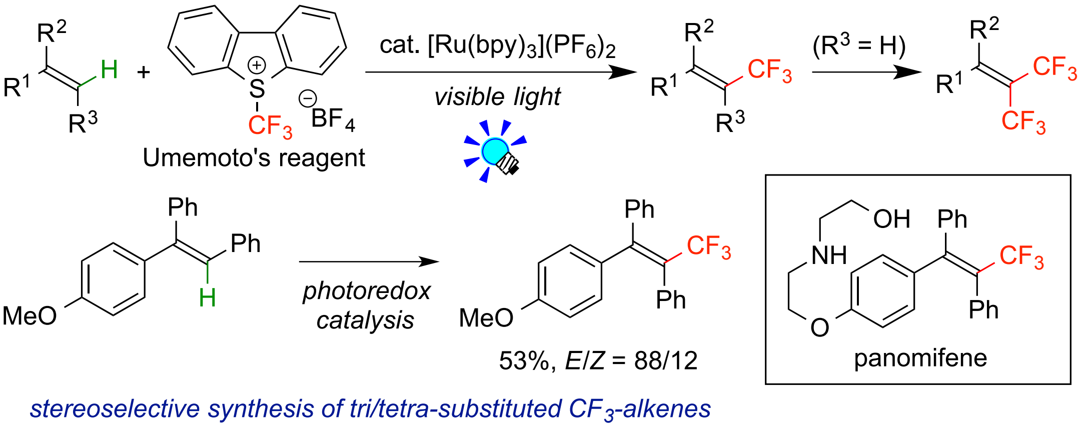
Scheme 6.1. Generation of CF_3 radical by photoredox catalysis

In Chapter 2, the author has developed photoredox-catalyzed keto-trifluoromethylation of alkenes. He found dimethylsulfoxide (DMSO) serves as a key nucleophile and oxidant to achieve direct synthesis of α-trifluoromethylated ketones from alkenes (Scheme 6.2). The reaction can be carried out on a gram scale, and be applied to aromatic alkenes having a wide variety of functional groups.



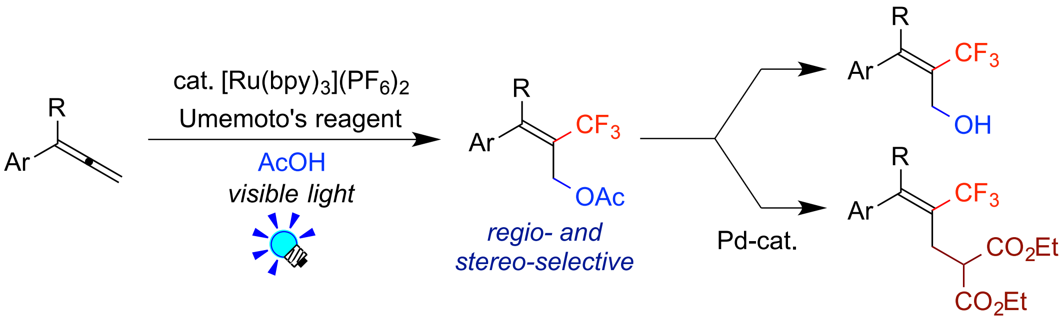
Scheme 6.2. Keto-trifluoromethylation of alkenes

In Chapter 3, the author has established C–H trifluoromethylation of di- and trisubstituted alkenes. He found this reaction as a side reaction of the reaction described in Chapter 2, and has made it into a synthetically useful reaction. The reaction proceeds in a stereoselective manner in the case of unsymmetric substrates owing to the CF_3 group (Scheme 6.3). The precursor for anti-estrogen drug, panomifene, can be synthesized in a stereoselective manner by this reaction. Additionally, use of an excess amount of Umemoto's reagent affords bis(trifluoromethyl)alkenes.



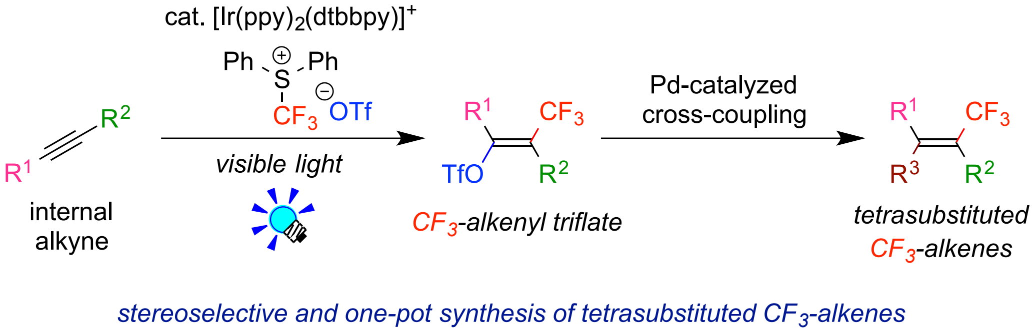
Scheme 6.3. C–H trifluoromethylation of alkenes

In Chapter 4, the author has expanded the photoredox-catalyzed trifluoromethylation to another unsaturated hydrocarbon, allene. The reaction proceeds through the allyl cation intermediate, which is different from that for the reaction of alkenes. It is noteworthy that the use of AcOH as the nucleophile is crucial for the high regioselectivity. The products, CF_3-allylic acetates, can be easily transformed into the corresponding allylic alcohol and can be subjected to palladium-catalyzed substitution reaction.



Scheme 6.4. Acetoxy-trifluoromethylation of allenes

In Chapter 5, the author has developed sulfonyloxy-trifluoromethylation of internal alkynes by photoredox catalysis. The reaction proceeds in a highly stereoselective manner, which is attributed to the electrostatic repulsion between the CF_3 group and the triflate anion in the nucleophilic addition step to the cation intermediate. In addition, facile one-pot synthesis of tetrasubstituted CF_3-alkenes can be achieved by combining the photoredox catalysis and the palladium catalysis.



Scheme 6.5. One-pot synthesis of tetrasubstituted CF_3-alkenes through photoredox and palladium catalysis

In conclusion, the author has developed four types of trifluoromethylation reactions of molecules with carbon–carbon unsaturated bonds by photoredox catalysis. The author has achieved expansion of CF_3 radical acceptors to alkyne and allene, reactions of which go through intermediates different from those for the reaction of alkene and produce the unique products. The author also investigates oxygen nucleophiles and reveals the utility of using DMSO and triflate ion as nucleophile for access to ketone and alkenyl triflate. In addition, the author has demonstrated the stereoselective reactions affected by a trifluoromethyl group, especially the synthesis of multisubstituted CF_3-alkenes. This thesis reveals that electronic abnormal CF_3 group has a power to dominate reaction selectivities. The author expects that these findings have led to exploration of valuable compounds containing CF_3 group and discovery of new useful reactions.

In the fields of trifluoromethylation and photoredox catalysis, there are still demands for developments. For example, (1) direct trifluoromethylation of aliphatic C–H bonds, (2) asymmetric introduction of a CF_3 group into various substrates, (3) inexpensive and efficient reagent, (4) highly reactive catalyst (it has high oxidation/reduction potentials) opens up new reaction types, (5) scalable reaction system and apparatus, and more. The author believes that further study to make these demands come true contributes to development of the organic chemistry and industry.

List of Publications

Chapter 2

Combining Photoredox-Catalyzed Trifluoromethylation and Oxidation with DMSO: Facile Synthesis of α-Trifluoromethylated Ketones from Aromatic Alkenes

R. Tomita, Y. Yasu, T. Koike, M. Akita, *Angew. Chem. Int. Ed.* **2014**, *53*, 7144–7148.

Chapter 3

Direct C–H trifluoromethylation of di- and trisubstituted alkenes by photoredox catalysis

R. Tomita, Y. Yasu, T. Koike, M. Akita, *Beilstein J. Org. Chem.* **2014**, *10*, 1099–1106.

Chapter 4

Oxy-Trifluoromethylation of Allenes by Photoredox Catalysis

R. Tomita, T. Koike, M. Akita, *in preparation*

Chapter 5

Photoredox-Catalyzed Stereoselective Conversion of Alkynes into Tetrasubstituted Trifluoromethylated Alkenes

R. Tomita, T. Koike, M. Akita, *Angew. Chem. Int. Ed.* **2015**, *54*, 12923–12927.

Other Publications

1. Homogeneous Pd-catalyzed Transformation of Terminal Alkenes to Primary Allylic Alcohols and Derivatives
   R. Tomita, K. Mantani, A. Hamasaki, T. Ishida, M. Tokunaga, *Chem. Eur. J.* **2014**, *20*, 9914–9917.

2. Highly Regio- and Diastereoselective Synthesis of CF_3-Substituted Lactones via Photoredox-Catalyzed Carbolactonization of Alkenoic Acids
   Y. Yasu, Y. Arai, **R. Tomita**, T. Koike, M. Akita, *Org. Lett.* **2014**, *16*, 780–783.

3. Trifluoromethylation of aromatic alkenes by visible-light-driven photoredox catalysis: Direct conversion of alkenes to 3-trifluoromethyl-1-propenyl and 1,3-bis(trifluoromethyl)- 1-propenyl derivatives
   M. Asano, **R. Tomita**, T. Koike, M. Akita, *J. Fluorine Chem.* **2015**, *179*, 83–88.

4. Oxydifluoromethylation of Alkenes by Photoredox Catalysis: Simple Synthesis of CF_2H-Containing Alcohols
   Y. Arai, **R. Tomita**, G. Ando, T. Koike, M. Akita, *Chem. Eur. J.* **2016**, *22*, 1262–1265.