

Addition of CF₃ across unsaturated moieties: a powerful functionalization tool

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In the last few years, the efficient introduction of trifluoromethyl groups in organic molecules has become a major research focus. This review highlights the recent developments enabling the incorporation of CF₃ groups across unsaturated moieties, preferentially alkenes, and the mechanistic scenarios governing these transformations. We have specially focused on methods involving the simultaneous formation of C–CF₃ and C–C or C–heteroatom bonds by formal addition reactions across π -systems, as such difunctionalization processes hold valuable synthetic potential.

Introduction

The presence of C–F bonds in organic molecules has a profound effect on properties such as lipophilicity, permeability and metabolic stability so that more than 20% of the current approved drugs contain at least one fluorine atom.^{1,2} Thus, in the past few years, the efficient introduction of fluorine atoms or fluorine containing groups in pharmaceuticals, agrochemicals and functional materials has turned into a major research focus

for synthetic chemists.^{3–10} Transition metal catalyzed trifluoromethylation reactions are the most popular route to introduce CF₃ groups into common building blocks, although recently, metal-free processes have also been described to carry out this transformation under alternative, and sometimes even complementary, conditions. In this context, double bonds can be considered privileged starting materials, as they are easily accessible and robust feedstocks, but are also amenable to flexible functionalization. This review highlights the recent developments enabling the incorporation of CF₃ groups across unsaturated moieties and the mechanistic scenarios governing these transformations. We have preferentially focused on alkenes as

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starting materials, with special attention on methods that involve the simultaneous formation of C–CF₃ and C–C or C–heteroatom bonds by formal addition reactions across π -systems.

1. Alkene trifluoromethylation

Pioneering studies describing the electrochemical hydrotrifluoromethylation of alkenes were reported in the late 80's.^{11,12} Aliphatic trifluoromethylated compounds could be efficiently prepared by electrochemical oxidation of trifluoroacetic acid, as TFA is one of the most economic and easily available sources of CF₃.¹³ Fumaronitrile **1** and related activated olefins were transformed into the 2-trifluoromethylsuccinyl derivatives by oxidation of trifluoroacetic acid in platinum electrodes in a mixture of acetonitrile and water at 50–55 °C (Scheme 1).¹⁴ The trifluoromethyl radicals generated in the anode recombined with the succinyl radicals produced at the cathodic site, leading to the formation of products **2**.

In 2002, Langlois *et al.* showed the hydrotrifluoromethylation of unactivated alkenes with CF₃SO₂Na by electrochemical oxidation albeit with low chemoselectivity.¹⁵ Later, the hydrotrifluoromethylation of α,β -unsaturated ketones in the presence of RhCl(PPh₃)₃ and Et₂Zn was reported. In this reaction, CF₃I was employed as a trifluoromethyl source and α -trifluoromethylated carbonyl compounds were obtained in moderate yields.¹⁶ The authors proposed the formation of a rhodium hydride complex by reaction of RhCl(PPh₃)₃ and Et₂Zn. The oxidative addition of CF₃I occurred on the rhodium enolate, which furnished the product by reductive elimination. In contrast, the reaction of α,β -unsaturated acyl-oxazolidinones **3** in the presence of Et₃B under oxidative conditions (O₂) enabled the synthesis of chiral β -trifluoromethylated amino acids (Scheme 2).¹⁷ The proposed mechanism involves the generation of a CF₃-radical, which undergoes Michael addition to form a diethylboron enolate whose *in situ* hydrolysis led to the observed product **4** with complete β -regioselectivity but no diastereoselectivity.

In contrast to the previously described methods, the hydrotrifluoromethylation reaction of unactivated olefins remained, until recently, much less explored. The groups of Qing,¹⁸



Scheme 1 Hydrotrifluoromethylation of fumaronitrile **1**.



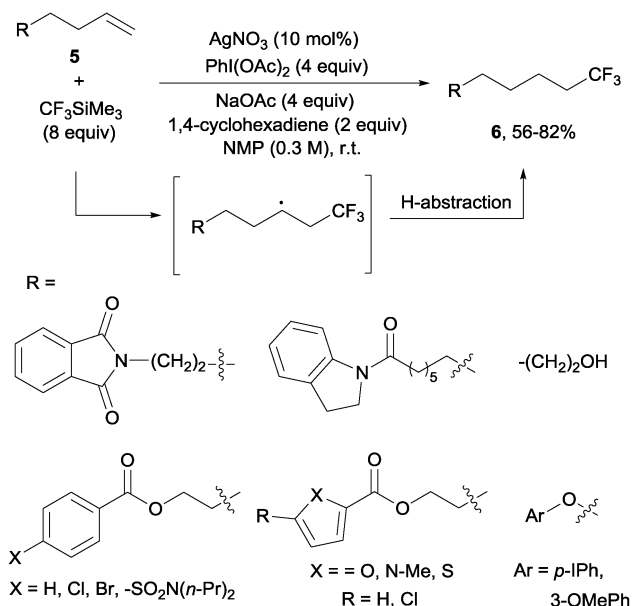
R = H, Me, Et, *n*-hexyl, -(CH₂)₂Ph, cyclohexyl, -(CH₂)₃OBn, -(CH₂)₄CO₂Et

Scheme 2 Trifluoromethylation of acyl-oxazolidinones.

Gouverneur¹⁹ and Nicewicz²⁰ described, almost simultaneously, the hydrotrifluoromethylation of unactivated alkenes. The reactions, operating under mild conditions, enabled a net “fluoroform” addition across alkenes and alkynes in a regioselective manner obtaining exclusively in most cases anti-Markovnikov regioisomers. Qing's protocol required AgNO₃ as a catalyst, CF₃SiMe₃ as a trifluoromethylating agent and PhI(OAc)₂ as an oxidant. These conditions were amenable to monosubstituted alkenes **5** which produced trifluoromethyl alkanes **6** at room temperature (Scheme 3). Preliminary control experiments seemed to point towards the formation of CF₃ radical species under the above-mentioned conditions. Upon addition of the CF₃ radical to the double bond, hydrogen is likely abstracted from 1,4-cyclohexadiene to give the observed products.

Gouverneur's hydrotrifluoromethylation of unactivated terminal and geminally disubstituted alkenes (Scheme 4) and alkynes (Scheme 5) could also be carried out at room temperature using visible-light-activated Ru(bpy)₃Cl₂·6H₂O, Umemoto's reagent (**7**) as a CF₃ source and methanol as a hydrogen donor according to the mechanism proposed in Scheme 4.¹⁹

Nicewicz developed a metal-free photoredox process for the hydrotrifluoromethylation of unactivated mono-, di- and trisubstituted alkenes shortly thereafter.²⁰ The Langlois reagent (CF₃SO₂Na) was used as a CF₃ source and *N*-methyl-9-mesityl



Scheme 3 Silver-catalyzed hydrotrifluoromethylation of unactivated alkenes.





Scheme 8 Trifluoromethylation of 2-substituted allylsilanes.



Scheme 9 Copper-catalyzed synthesis of trifluoromethylated vinylsilanes.

of alkenes. A pioneering example was reported by Liu's group in 2012. A palladium-catalyzed intramolecular oxidative aryltrifluoromethylation of activated alkenes was developed so that CF_3 -substituted oxindoles **13** could be obtained in excellent yields.²⁶ Upon π -activation of the olefin by the metal and cyclization with the aromatic ring, the Pd(II) intermediate was oxidized to Pd(IV) in the presence of $\text{PhI}(\text{OAc})_2$. The system $\text{CsF}/\text{TMSCF}_3$ worked as a nucleophilic source of CF_3 , triggering the ligand exchange on the Pd(IV) intermediate **12** prior to the reductive elimination, furnishing the new $\text{Csp}^3\text{-CF}_3$ bond (Scheme 10).

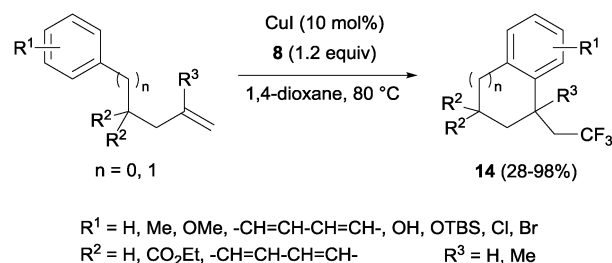
Later, Sodeoka's group reported the combination of CuI and Togni reagent **8** to access trifluoromethylated oxindoles in excellent yields from similar acrylanilide starting materials.²⁷ The use of Langlois' reagent ($\text{CF}_3\text{SO}_2\text{Na}$) and TBHP in the presence of Cu(II) in aqueous media at room temperature also furnished this type of compounds through a radical process.²⁸ The recycling of the aqueous medium was possible at least 5 times with only a slight decrease in the isolated yields. A similar process but in a mixture of organic solvents was also developed.²⁹

The combination of copper salts and Togni reagent **8** enabled Sodeoka's group to synthesize trifluoromethylated carbo- (**14**, Scheme 11) and heterocycles (**15**, Scheme 12) in the first examples of aryltrifluoromethylations on unactivated olefins.³⁰ In this case, the six membered ring formation seemed to be faster than the five membered ring one, an acceleration that could be explained by a more favourable orbital interaction between the aryl ring and alkene in the transition state for the former case.

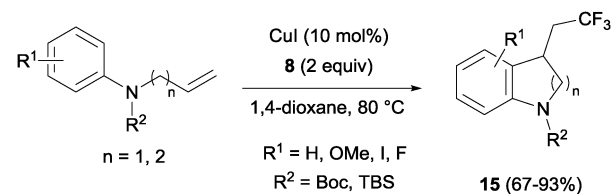
Trifluoromethylated 1,2-benzothiazinane dioxide derivatives **16** could be obtained by a similar tandem trifluoromethylation-annulation reaction with *N*-allyl-*N*-sulfonyl amines as substrates also in the presence of copper and Togni reagent **8** (Scheme 13).³¹



Scheme 10 Synthesis of oxindoles by Pd-catalyzed aryltrifluoromethylation of alkenes.



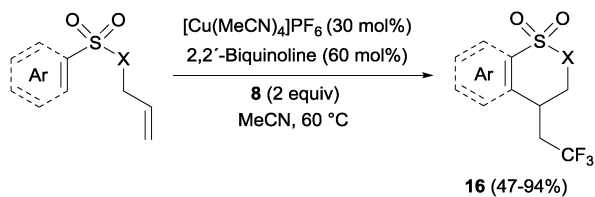
Scheme 11 Synthesis of carbocycles by trifluoromethylation of alkenes.

Scheme 12 Copper-catalyzed carbotrifluoromethylation of *N*-protected allyl- and homoallylaniline derivatives.

In the presence of catalytic amounts of copper and Togni reagent **8**, 1,6-enynes **17** delivered substituted hydrofurans, tetrahydropyranes, piperidines and pyrrolidines as a result of a tandem trifluoromethylation-cyclization process (Scheme 14).³² Upon addition of 2-iodo benzoic acid released from Togni's reagent, the triple bond seemed to work here as a nucleophile generating 5- or 6-*exo-dig* carbo- and heterocycles in a highly regioselective manner.

Recently, Nevado's group described an aryltrifluoromethylation of alkenes in which the reactivity of acrylamides **18** was modulated by the substituent on the nitrogen atom.³³ *N*-Alkyl substituted substrates furnished trifluoromethylated oxindoles

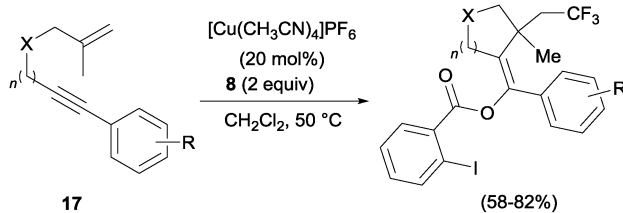




Ar = Ph, *o*-MePh, *m*-MePh, *p*-MePh, *p*-OMePh, TsN
p-BrPh, *p*-NO₂Ph, 2-thienyl, 3-pyridyl

X = *N*-*i*Pr, *N*-Et, *N*-Me, *N*-H, *N*-(CH₂)₂OH,
N-(CH₂)₂Br, *N*-(CH₂)₂NHTs, *N*-SO₂Ph, CH₂, *N*-CH₂

Scheme 13 Trifluoromethylation-cyclization on *N*-allyl-*N*-sulfonylamines.

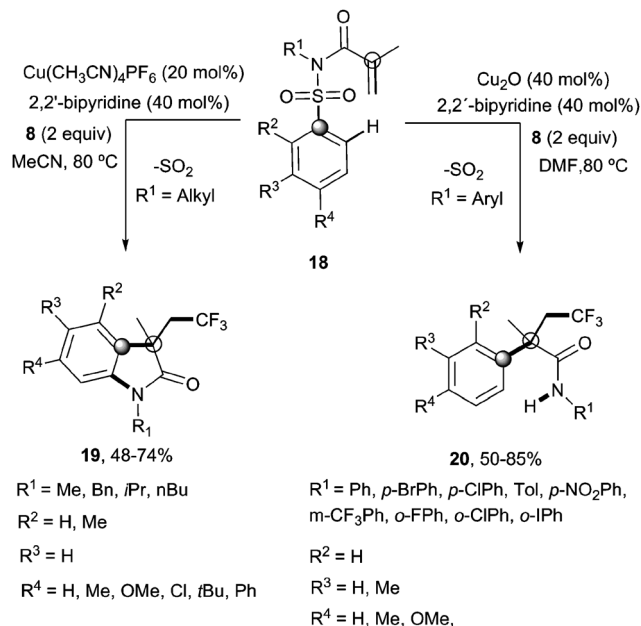


X = NH, O, -CH(CO₂Et)₂

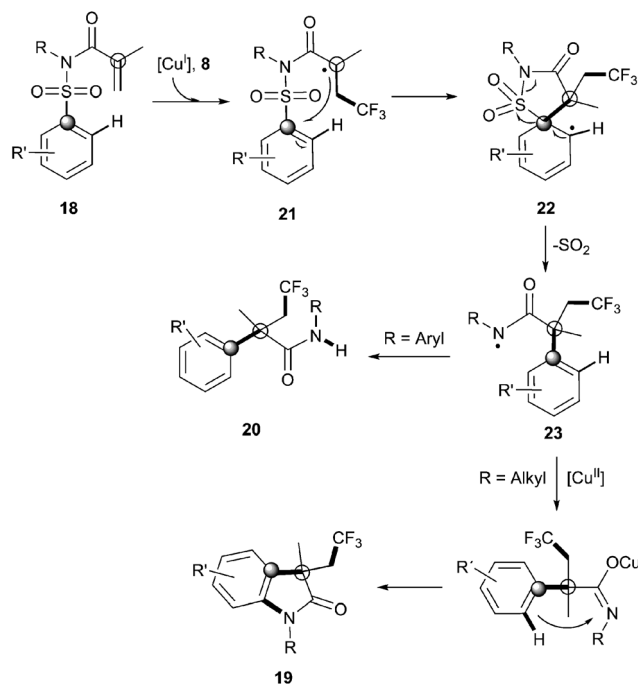
R = H, *m*-Me, *p*-Me, *o*-OMe, *p*-OMe, *o*-F, *m*-F, *p*-F, *p*-Cl, *p*-CO₂Me, *o*-CN

Scheme 14 Trifluoromethylation-cyclization of enynes.

19 in 48–74% yield when [Cu(MeCN)₄]PF₆ was used as a catalyst and 2,2'-bipyridine as a ligand in acetonitrile at 80 °C in the presence of trifluoromethylating agent **8**. In contrast, α -aryl- β -trifluoromethylamides bearing a quaternary stereocenter **20** were obtained with Cu₂O as a catalyst when an aromatic ring was attached to the nitrogen atom (Scheme 15). Both transformations



Scheme 15 Copper-catalyzed aryltrifluoromethylation-desulfonylation cascade on acrylamides **18**.



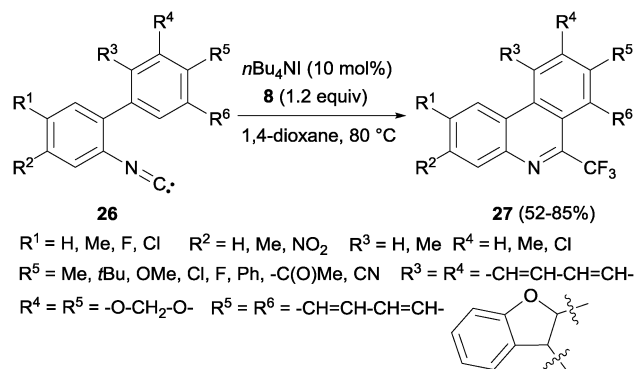
Scheme 16 Mechanism of the copper-catalyzed aryltrifluoromethylation-desulfonylation cascade.

could be rationalized on the basis of a mechanism involving the trifluoromethylation of the activated alkene to give an alkyl radical intermediate **21** as shown in Scheme 16. Upon cyclization with the arylsulfonyl moiety, a spirocyclic intermediate **22** was formed. Re-aromatization accompanied by desulfonylation delivered an amidyl radical **23** which could either undergo protonation to give the corresponding amides **20** or, alternatively, form a new C(sp²)-N bond in the *ortho* relative position to the original sulfonyl group explaining oxindoles **19**. In both processes, a copper-catalyzed one-pot trifluoromethylation, 1,4-aryl migration and desulfonylation cascade seemed thus to be operating.

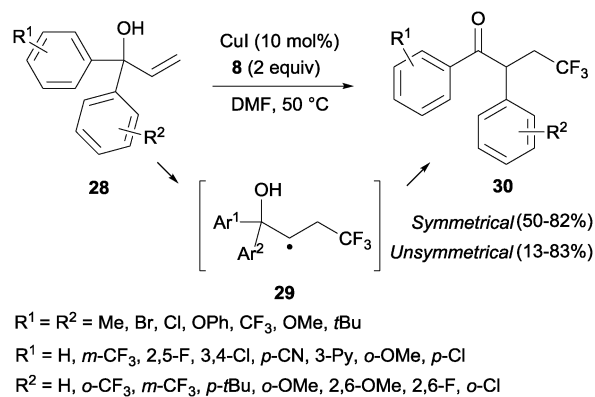
The same group also described the first example of a metal-free alkene aryltrifluoromethylation.³⁴ Tetrabutylammonium iodide could activate Togni reagent **8** forming highly active iodine(III) species, which seem to easily release the CF₃ group. Trifluoromethylated isoquinolinediones **24**, oxindoles **19**, spirocycles **25** and α -aryl- β -trifluoromethylamides **20** could be obtained by this procedure with excellent yields in a highly regioselective fashion (Scheme 17). Preliminary mechanistic studies seemed to rule out a radical mechanism for these transformations. An alternative metal-free aryltrifluoromethylation of alkenes was also recently described using inexpensive TMSCF₃, PhI(OAc)₂ and KF as additives likely involving radical intermediates.³⁵

Interestingly, a metal-free synthesis of phenanthridines **27** from isonitriles **26** was previously described by Studer's group using tetrabutylammonium iodide as an activator of Togni reagent **8** in a radical process (Scheme 18).³⁶ A new phenyl ring is formed after trifluoromethylation reaction. Also Zhou's group described the synthesis of phenanthridines by oxidative cyclization of 2-isocyanobiphenyls with PhI(OAc)₂ and CF₃SiMe₃.³⁷



Scheme 17 Metal-free trifluoromethylation reaction of methacryloyl benzamides and α,β -unsaturated amides.

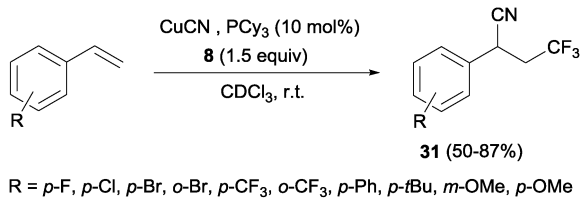
Scheme 18 Metal-free synthesis of 6-trifluoromethyl-phenanthridines.

Scheme 19 Copper-catalyzed trifluoromethylation and radical 1,2-aryl migration in α,α -diaryl allylic alcohols.

The trifluoromethylation of α,α -diaryl allylic alcohols **28** provided trifluoromethyl ketones **30** through a 1,2-aryl migration in intermediate **29** upon addition of a CF₃ radical to the double bond (Scheme 19).³⁸ Aromatic rings bearing electron-withdrawing groups migrated preferentially over electron-rich aryl groups in line with the radical mechanism proposed for this transformation. Sodeoka's group showed that iron acetate in the presence of base (K₂CO₃) also led to the formation of substituted trifluoromethylated carbonyl compounds starting from diaryl allyl alcohols in very good yields.³⁹

Other interesting example that combined alkene trifluoromethylation with the formation of a new C-C bond was described by Szabó's group.⁴⁰ Styrenes, in the presence of CuCN as the cyanide source and bulky phosphines or B₂pin₂ as additives, delivered cyanotrifluoromethylated aromatic compounds **31** in a highly regioselective manner in a one-pot trifluoromethylation/C-C bond formation (Scheme 20). This protocol was limited to styrenes with electron-withdrawing *para* and *ortho* substituents. However, this reaction was also described with aliphatic and





Scheme 20 Trifluoromethylation–cyanation of styrene derivatives.

ortho, *meta* and *para*-substituted aromatic substrates with good yields using Cu(OTf)₂ as a catalyst, **8** as a trifluoromethylating agent and TMSCN as a cyanide source.⁴¹

3. Alkene trifluoromethylation and C–heteroatom bond formation

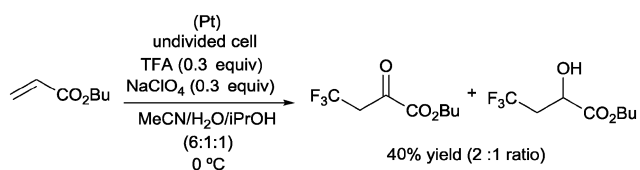
3.1 Alkene trifluoromethylation and C–O bond formation.

As discussed in Section 1, the electrooxidation of trifluoroacetic acid was an efficient way to generate CF₃ radicals *in situ*. Thus, pioneering examples of alkene oxotrifluoromethylations were reported under these reaction conditions. In a representative example, the reaction of butyl acrylate, under controlled electrooxidation conditions, furnished 4,4,4-trifluoro-2-oxobutanoate and butyl 4,4,4-trifluoro-2-hydroxybutanoate in a 2:1 ratio and 40% overall yield (Scheme 21).⁴²

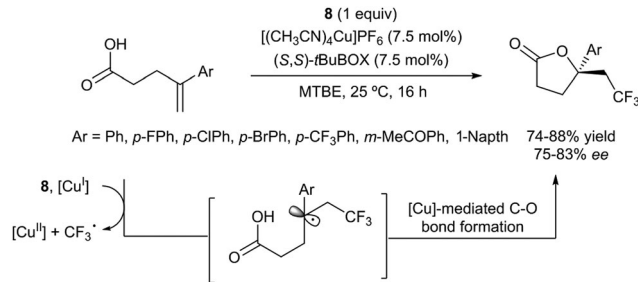
The first examples of oxotrifluoromethylation in unactivated alkenes were reported by Buchwald and co-workers in 2012. Based on the [Cu(MeCN)₄PF₆]/2,2'-biquinoline catalytic system and in the presence of Togni reagent **8**, the intramolecular nucleophilic attack of various oxygenated species such as carboxylic acids, alcohols and phenols following trifluoromethyl addition to the double bond could be carried out. A broad array of functional groups including amides, epoxides, aryl bromides and β-lactones were compatible with the reaction conditions.⁴³ In addition, an enantioselective version of this transformation was described by the same group using (*S,S*)-*t*BuBOX as a chiral ligand for copper.⁴⁴ The mechanistic proposal involved a metal C–O bond formation *via* a carbon radical intermediate as shown in Scheme 22.

Trifluoromethyl-substituted isoxazolines could also be obtained by cyclization of oximes after C–CF₃ bond formation using 20 mol% of CuCl and Togni's reagent.⁴⁵ A related protocol using CuBr and 1,10-phenanthroline-5,6-dione **33** was described by Ma and co-workers for the efficient oxotrifluoromethylation of 2,3-allenoic acids **32**. β-Trifluoromethylated butenolides **34** could be obtained in moderate to high yields (Scheme 23).⁴⁶

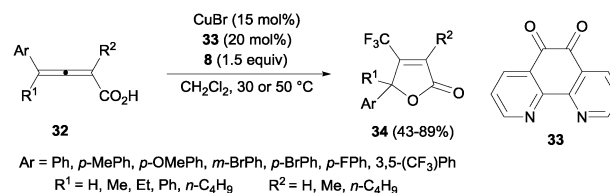
The combination of copper salts and Togni reagent **8** was also successfully applied to the oxotrifluoromethylation of



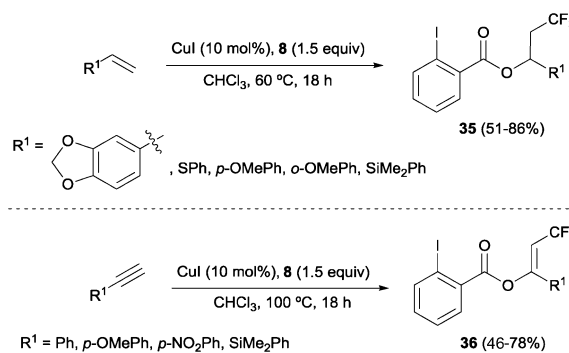
Scheme 21 Electrooxidative alkene oxotrifluoromethylation.



Scheme 22 Copper-catalyzed enantioselective oxotrifluoromethylation of unactivated olefins.



Scheme 23 Oxotrifluoromethylation of 2,3-allenoic acids.

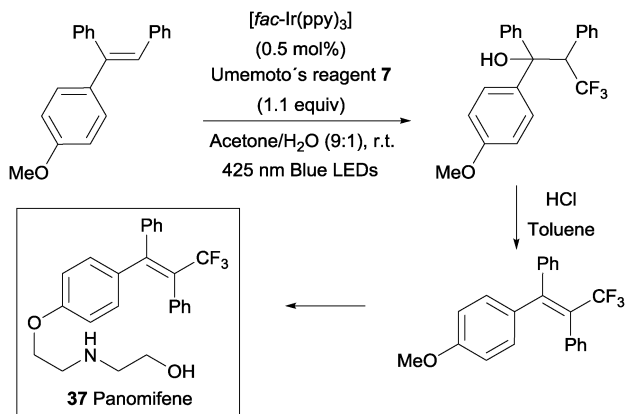


Scheme 24 Oxotrifluoromethylation of styrene and aryl alkene derivatives.

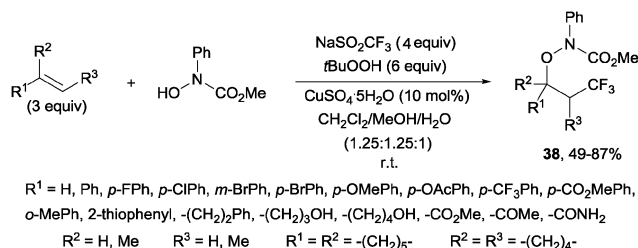
styrenes and arylalkynes as reported by Szabó and co-workers.⁴⁷ In these reactions, the 2-iodo benzoic acid generated upon transfer of the trifluoromethyl group from **8** reacted as an external nucleophile, delivering the corresponding trifluoromethylated vinyl or alkyl benzoates **35** and **36**, respectively (Scheme 24). Direct formation of β-trifluoromethylstyrene derivatives from the corresponding styrene starting material was also achieved by Sodeoka's group under closely related reaction conditions upon addition of a Bronsted acid.⁴⁸ An oxotrifluoromethylation of enamides was also reported in the presence of the CuCl/Togni's reagent system in MeOH as a solvent.⁴⁹

An intermolecular oxotrifluoromethylation of alkenes was also developed taking advantage of photoredox catalysis in a three component reaction using Umemoto's reagent **7** as a trifluoromethyl source. The reaction is highly regioselective and different O functionalities could be introduced in the styrene substrates.⁵⁰ This methodology was applied in the synthesis of panomifene **37**, a compound with antiestrogenic activity used in the treatment of breast cancer (Scheme 25).^{51,52}





Scheme 25 Synthesis of panomifene.

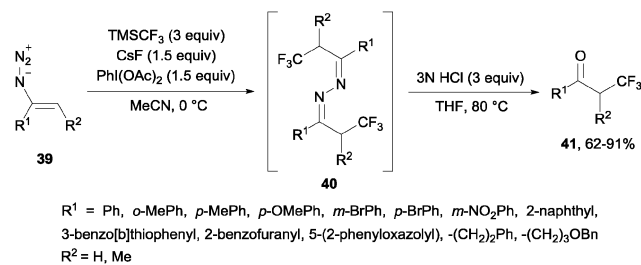
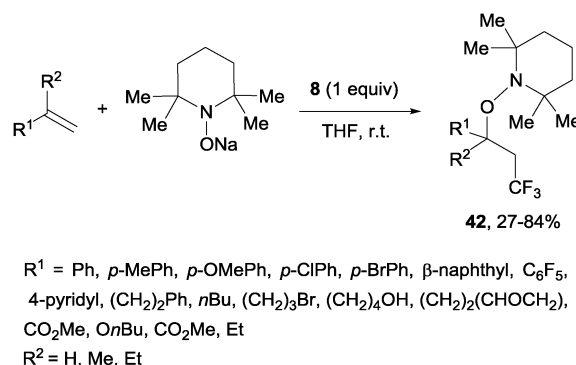


Scheme 26 Oxytrifluoromethylation of alkenes using Langlois' reagent.

An additional three-component oxytrifluoromethylation of alkenes was reported by Qing and co-workers using hydroxyl amines, Langlois reagent (NaSO_2CF_3), $t\text{BuOOH}$ and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$. This reaction is regioselective and a radical mechanism is proposed to explain the formation of the observed products **38** (Scheme 26).⁵³

Alternatively, the oxidative trifluoromethylation of unactivated olefins with the system $\text{CF}_3\text{SO}_2\text{Na}/\text{AgNO}_3/\text{K}_2\text{S}_2\text{O}_8$ at room temperature provided a straightforward access to α -trifluoromethyl ketones in good yields with O_2 as an ultimate oxygen source.⁵⁴ α -Trifluoromethylated ketones could also be obtained by reaction of styrenes and Umemoto's reagent **7** in the presence of $\text{Na}_2\text{S}_2\text{O}_4$ or $\text{NaSO}_2\text{CH}_2\text{OH}$. Following the same principle as in the previous case, these reagents could reduce the sulfonium salt to generate a CF_3 radical which reacted with styrene so that after oxidation with air, trifluoromethylated ketones were generated in moderate yields (21–39%).⁵⁵ α -Trifluoromethyl azines **40** could be obtained by radical trifluoromethylation of vinyl azides **39** using TMSCF_3 . These compounds could be transformed by simple methods into α -trifluoromethyl ketones **41**, β -trifluoromethyl amines and 5-fluoropyrazoles (Scheme 27).⁵⁶

A novel metal-free trifluoromethylaminoxylation of alkenes was reported by Studer's group using TEMPONa .⁵⁷ This reagent was formed from TEMPO and sodium, whereas CF_3 radicals could be released from Togni reagent **8** as shown in Scheme 28. The diastereoselectivity of the process was excellent when cyclic alkenes were used as starting materials (Scheme 29). The products (**42**) could be reduced with Zn/AcOH delivering synthetically useful β -trifluoromethylated secondary alcohols.

Scheme 27 Synthesis of α -trifluoromethyl ketones **41**.

Scheme 28 Metal-free trifluoromethylaminoxylation of terminal alkenes.



Scheme 29 Diastereoselective trifluoromethylation of internal alkenes.

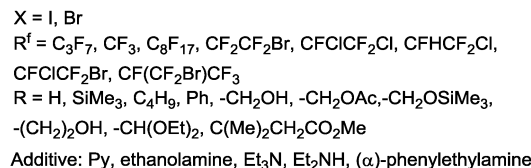
3.2 Alkene trifluoromethylation and C–N bond formation. In contrast to the numerous studies dealing with the oxytrifluoromethylation of alkenes, the concomitant formation of C–N and C– CF_3 bonds has been much less developed. Sodeoka and co-workers described one of the first examples of this type of transformations. Allyl amines react with CuI and Togni's reagent **8** to give aziridines **43** in high yields by trifluoromethylation and intramolecular C–N bond formation (Scheme 30).⁵⁸ One pot reactions including the ring-opening of the aziridine in the presence of various nucleophiles set the path for the efficient synthesis of β -trifluoromethylamines, which are important building blocks for bioactive compounds.

An intermolecular aminotrifluoromethylation of terminal alkenes by photoredox catalysis was also described using $[\text{Ru}(\text{bpy})_3]^{2+}$ under

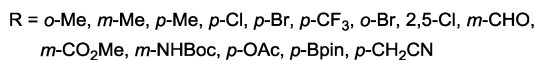




Scheme 30 Aminotrifluoromethylation of allylamines.



Scheme 34 Reaction of polyfluoroalkyl halides with alkenes and alkynes.



Scheme 31 Aminotrifluoromethylation of terminal alkenes.



Scheme 32 Products of aminotrifluoromethylation of internal alkenes.

visible light irradiation with Umemoto's reagent 7 as a precursor of CF₃ radicals leading to α-trifluoromethylamines **44** (Scheme 31). Good levels of stereoselectivity were obtained in the reactions of internal alkenes (Scheme 32).⁵⁹

3.3 Alkene trifluoromethylation and C-S bond formation. β-Sulfanyl-(trifluoromethyl)-alkanes **47** could be obtained by photolysis of trifluoromethanethiosulfonates **45** or trifluorothioacetates **46**. The trifluoromethyl radicals generated under UV radiation could then be trapped by the double bond, although yields remained moderate and products **48**, resulting from a formal hydrotrifluoromethylation reaction, could also be detected in the reaction media. This process is highly regioselective so that the product stemmed from the addition of the CF₃ radical on the less hindered carbon of the alkene (Scheme 33).⁶⁰

3.4 Alkene trifluoromethylation and C-halogen bond formation. Formally, the one-pot trifluoromethylation and



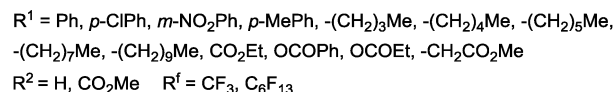
Scheme 33 Photolysis of trifluoromethanethiosulfonate and trifluorothioacetate in the presence of alkenes.

C-halogen bond formation across double bonds were first described in the 50's when olefin polymerizations were carried out in the presence of iodotrifluoromethane.⁶¹ Thus, the reaction of iodotrifluoromethane with tetrafluoroethylene enabled the synthesis of short-chain tetrafluoroethylene polymers with general formula CF₃-(CF₂-CF₂)_n-I (*n* = 1-10).

Decades later, the reaction of polyfluoroalkyl halides with alkenes and alkynes catalyzed by iron, cobalt and ruthenium complexes produced the corresponding addition products **49** in moderate to excellent yields (Scheme 34).⁶² Other metals such as platinum,⁶³ nickel⁶³ or palladium^{64,65} could also be used to catalyze this reaction.

Trifluoromethanesulfonyl chloride⁶⁶ and perfluoroalkanesulfonyl chlorides⁶⁷ could also be incorporated into alkenes in a reaction catalyzed by a ruthenium(II) complex as shown in Scheme 35.

Addition of CF₂Br₂, CF₃I and (CF₃)CFI to allylbenzenes could be carried out by sodium dithionite in a H₂O:MeCN mixture through a simple chain radical mechanism (Scheme 36).⁶⁸ The reaction of CF₂Br₂ and CF₃I with allylbenzenes had to be performed in a closed system because of the volatility of the



Scheme 35 Reaction of perfluoroalkanesulfonyl chlorides with alkenes.

Scheme 36 Sodium dithionite initiated addition of CF₂Br₂, CF₃I and (CF₃)₂CFI to allylbenzenes.



Scheme 37 Iodotrifluoromethylation of alkynes.



Scheme 38 Iodotrifluoromethylation of arynes.

former whereas the addition of (CF₃)₂CFI was carried out in the presence of NaHCO₃ as a HI scavenger.

Recently, alkynes in the presence of [Ru(phen)₃]Cl₂ and TMEDA under visible-light irradiation produced trifluoromethylated alkenyl iodides **50** in an *E*-selective manner (Scheme 37).⁶⁹

Trifluoromethylation and iodination of arynes were also described using AgCF₃ (generated *in situ* by mixing TMSCF₃ and AgF) in the presence of 2,2,6,6-tetramethylpiperidine, which accelerated the iodination and suppressed the undesired protonation yielding by-product **52** (Scheme 38).⁷⁰

Conclusions

As a result of the growing interest in the efficient synthesis of fluorinated molecules, alkenes have aroused as highly valuable building blocks for the construction of C-CF₃ bonds. In this review, we have aimed to show the latest progress in the incorporation of CF₃ groups across C=C π-systems: from the formal addition of HCF₃ to the simultaneous formation of C-C/X and C-CF₃ bonds to produce X-C-C-CF₃ moieties, we have showcased the most synthetically useful methodologies and the corresponding mechanistic manifolds operating in this rapidly evolving field.

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