CF$_3$SO$_2$X (X = Na, Cl) as reagents for trifluoromethylation, trifluoromethylsulfenyl-, -sulfinyl- and -sulfonylation.
Part 1: Use of CF$_3$SO$_2$Na

Hélène Guyon, Hélène Chachignon and Dominique Cahard[*]

Abstract

Sodium trifluoromethanesulfinate, CF$_3$SO$_2$Na, and trifluoromethanesulfonyl chloride, CF$_3$SO$_2$Cl, are two popular reagents that are widely used for the direct trifluoromethylation of a large range of substrates. Further, these two reagents are employed for the direct trifluoromethylsulfenylation and trifluoromethylsulfinylation, the introduction of the SCF$_3$ and the S(O)CF$_3$ group, respectively. In addition to the aforementioned reactions, the versatility of these two reagents is presented in other reactions such as sulfonylation and chlorination. This first part is dedicated to sodium trifluoromethanesulfinate.

Introduction

In organofluorine chemistry, the CF$_3$ group occupies a place of choice as privileged structural motif in the development of multifaceted catalysts and ligands for organic synthesis as well as in the design of pharmaceuticals, agrochemicals and specialty materials [1-4]. The trifluoromethyl group is most of the time linked to a carbon atom but can also be encountered with chalcogens (S, Se, O) and nitrogen. The CF$_3$S motif, which was till recently considered as an emerging substituent, is henceforth a tamed substituent as a result of abundant literature describing methods to prepare CF$_3$S-featuring molecules [5]. Its oxidised congeners CF$_3$S(O) and CF$_3$SO$_2$ are also well-de-

veloped as structural units in biologically active compounds, catalysts for synthesis, and functional materials. The chemistry of CF$_3$Se derivatives is less developed but basically shares the same synthetic approaches with CF$_3$S analogues [6,7]. The CF$_3$O group is also of high interest but difficulties still exist to easily introduce this motif directly onto organic molecules [8]. The reasons behind such massive interest for the CF$_3$ group are due to the specific physical and chemical properties of the compounds that contain it. The CF$_3$ group has a large van der Waals volume somewhere between those of the iPr and the *t*-Bu groups [9]. Its electronegativity is comparable to that of oxygen

(4.0 versus 3.5 on the Pauling scale) and its hydrophobicity is large (0 for H, 0.51 for Me, and 1.07 for CF$_3$) [10]. In this respect, judicious installation of CF$_3$ group(s) in catalysts or ligands is an effective tool to tune their reactivity and selectivity in synthesis. As a pharmacophore, CF$_3$ substantially improves the catabolic stability, lipophilicity, and transport rate. In association with chalcogens (OCF$_3$, SCF$_3$, SeCF$_3$), the CF$_3$ group imparts enhanced lipophilicity of aromatic compounds in comparison with aryl–CF$_3$ analogues (Hansch's hydrophobic parameter π(SCF$_3$) = 1.44; π(OCF$_3$) = 1.04 versus π(CF$_3$) = 0.88). Trifluoromethyl sources are manifold displaying nucleophilic, electrophilic or radical reactivities [11]. The most popular nucleophilic trifluoromethylating reagent is certainly the trifluoromethyltrimethylsilane, CF$_3$SiMe$_3$, known as the Ruppert–Prakash reagent discovered in 1984 by Ruppert and applied for trifluoromethylation in 1989 by Prakash and Olah. More recently, renewed investigation on the use of fluoroform, CF$_3$H, as an ideal source of trifluoromethide offered new horizons for atom-economical, low-cost trifluoromethylation reactions. With regard to electrophilic CF$_3$ donors, *S*-(trifluoromethyl)sulfonium salts developed by Yagupolskii and Umemoto and hypervalent iodine(III)-CF$_3$ reagents developed by Togni are widely employed in a variety of trifluoromethylation reactions [12]. Traditional radical CF$_3$ sources include the gaseous trifluoroiodomethane CF$_3$I and trifluorobromomethane CF$_3$Br. More conveniently, the liquid trifluoromethanesulfonyl chloride CF$_3$SO$_2$Cl and the solid sodium trifluoromethanesulfinate CF$_3$SO$_2$Na that are commercially available at reasonable prices, are easy-to-handle sources of trifluoromethyl radicals. Remarkably, CF$_3$SO$_2$Na and CF$_3$SO$_2$Cl are multi-purpose reagents since they not only act as CF$_3$ donors by extrusion of SO$_2$, but also, under certain reaction conditions, the sulfur atom is retained for trifluoromethylsulfenylation (also named trifluoromethylthiolation), trifluoromethylsulfinylation, or trifluoromethylsulfonylation reactions. Typically, CF$_3$SO$_2$Na reacts under oxidative conditions whereas CF$_3$SO$_2$Cl requires reductive conditions. The advent of a new dynamism and the versatility of these two reagents have been recently demonstrated through several creative research articles; hence, this review aims to collect the recent progresses in the diverse uses of CF$_3$SO$_2$Na and CF$_3$SO$_2$Cl reagents. A special emphasis is placed on mechanistic studies. The review is divided in Part 1 and Part 2 that are published back-to-back. The literature is comprehensively covered through July 2017.
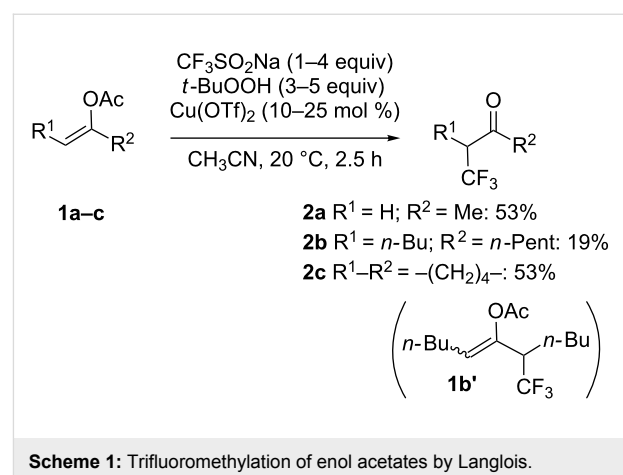
Review

Sodium trifluoromethanesulfinate (alternate names: sodium triflinate, trifluoromethanesulfinic acid sodium salt, Langlois reagent), CAS No. 2926-29-6, MW 156.06, is a stable white solid (mp 350 °C) soluble in water and slightly soluble in acetonitrile, methanol and acetone [13]. Although this reagent was
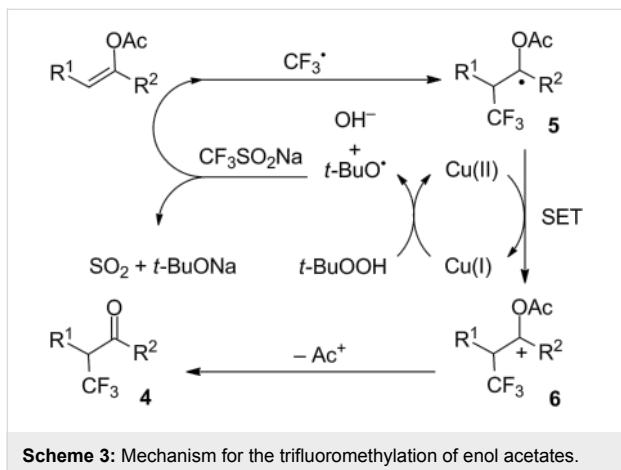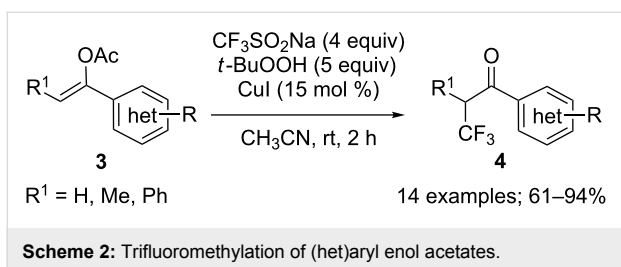
prepared in 1955 by Haszeldine [14] and in 1976 by Roesky [15], it is only in 1991 that Langlois reported the trifluoromethylation of aromatic compounds under oxidative conditions [16]. Since then, the use of CF$_3$SO$_2$Na has grown considerably for the creation of C$_{sp3}$–CF$_3$, C$_{sp2}$–CF$_3$ and C$_{sp}$–CF$_3$ bonds [17-19]. This reagent is also conveniently used in trifluoromethylsulfinylation and trifluoromethylsulfonylation reactions. More recently, from 2015, CF$_3$SO$_2$Na has found a new application as source of SCF$_3$ for direct trifluoromethylsulfenylation.

1 Trifluoromethylation
C$_{sp3}$–CF$_3$ bond-forming reactions

Synthesis of α-trifluoromethyl ketones from alkenes: After their original reports on the trifluoromethylation of aromatics (see later in the text, Scheme 34) [16] and disulfides (Scheme 69) [20], Langlois and co-workers demonstrated that enol acetates **1a–c** were converted into the corresponding α-trifluoromethyl ketones upon treatment with CF$_3$SO$_2$Na with *tert*-butyl hydroperoxide (TBHP) and a catalytic amount of copper(II) triflate (Scheme 1) [21]. The scope was rather narrow and yields were moderate to poor. In particular, enol acetate **1b**, prepared from symmetrical undecan-6-one, gave a mixture of the desired α-CF$_3$ ketone and two isomeric enol acetates **1b'**. In 2014, Li, Duan and co-workers applied the conditions described by Langlois to a series of enol acetates **3** derived from aryl and heteroaryl ketones featuring a single enolizable position (Scheme 2) [22]. Notably, it was found that Cu(II) and Cu(I) salts gave similar yields. A radical trifluoromethylation was suggested for this transformation. The CF$_3$•, which was generated by reaction of *tert*-butyl hydroperoxide with CF$_3$SO$_2$Na in the presence of copper(I), reacted at the more electron-rich carbon atom of the C=C double bond to give the radical species **5** that was oxidised by copper(II) into the corresponding cationic intermediate **6** via a single electron transfer (SET). Finally, the acetyl cation was eliminated to provide the α-CF$_3$ carbonyl compound **4** (Scheme 3).

Scheme 1: Trifluoromethylation of enol acetates by Langlois.

Scheme 2: Trifluoromethylation of (het)aryl enol acetates.

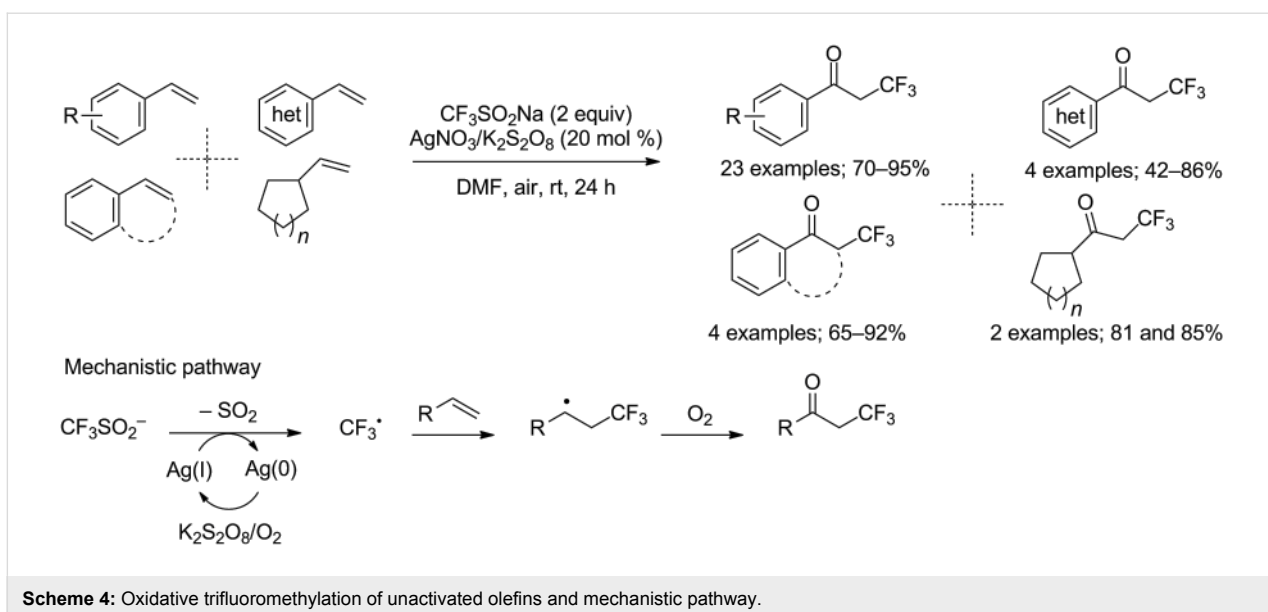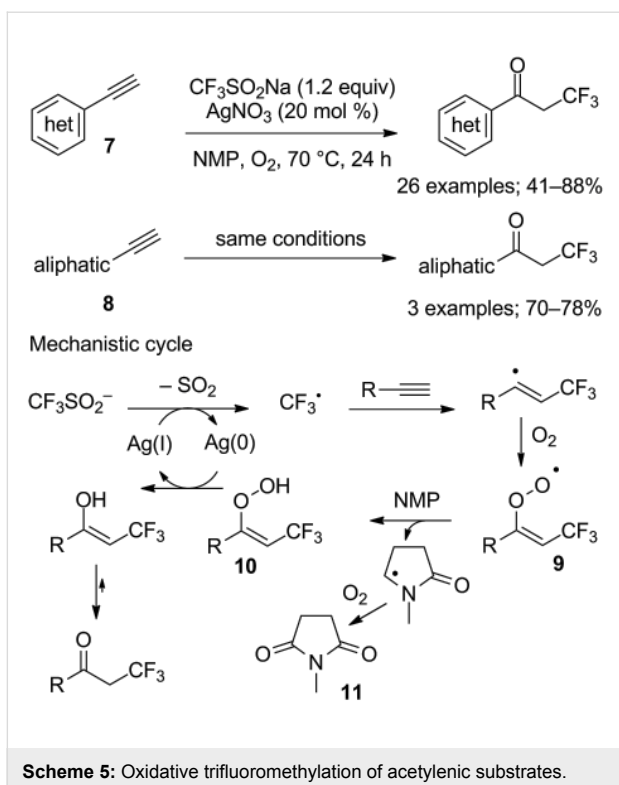**Scheme 3:** Mechanism for the trifluoromethylation of enol acetates.

Unactivated olefins are widely available substrates prone to be transformed into α-trifluoromethyl carbonyl compounds under oxidative trifluoromethylation as first reported by Maiti and co-workers in 2013. The reaction is operationally simple, conducted under air at room temperature and presents a predictable reactivity pattern as well as a wide functional group tolerance. The substrate scope was evaluated on 33 styrenes, β-substituted styrenes, heteroaromatic olefins and vinyl cycloalkanes

(Scheme 4). The trifluoromethyl radical was generated from CF$_3$SO$_2$Na by means of an oxidative system comprising catalytic amounts of silver(I) nitrate and potassium persulfate K$_2$S$_2$O$_8$. Both atmospheric oxygen and K$_2$S$_2$O$_8$ can be the source of the oxygen atom of the ketone moiety. A series of experiments that include the formation of TEMPO–CF$_3$ (TEMPO: 2,2,6,6-tetramethylpiperidine 1-oxyl), the detection of Ag(0) by X-ray photoelectron spectroscopy, the retardation of the reaction in absence of air and an ^{18}O-labeling reaction led the authors to propose the mechanism described in Scheme 4 [23].

Because some limitations appeared with heterocycles such as quinolone, indole, pyrimidine, thiophene, etc. the Maiti group reported an alternative approach toward α-trifluoromethyl ketones starting from (hetero)arylacetylenes **7** and also aliphatic terminal alkynes **8** (Scheme 5) [24]. The trifluoromethyl radical was generated from CF$_3$SO$_2$Na as indicated earlier, oxygen from air was the source of the oxygen atom, and *N*-methylpyrrolidine (NMP) acted as solvent and source of the hydrogen atom to convert the peroxo intermediate **9** to its hydroperoxo form **10**. As proof of the mechanism, *N*-methylsuccinimide (**11**) was identified in all these reactions.

Simultaneously to Maiti's work, Luo and co-workers reported a metal-free protocol for the trifluoromethylation of styrenes with CF$_3$SO$_2$Na, *tert*-butyl hydroperoxide and benzoquinone (BQ) as oxidant. The reactions were run at 80 °C for 16 h to give mixtures of α-trifluoromethyl ketones **12** and the corresponding alcohols **13** (Scheme 6) [25]. The scope was limited to simple substituted styrenes and yields were only moderate although super-stoichiometric amounts of reagents were used. The ratio **12**/**13** ranged from 31:69 to 66:34 but a subsequent reduction or

Scheme 4: Oxidative trifluoromethylation of unactivated olefins and mechanistic pathway.

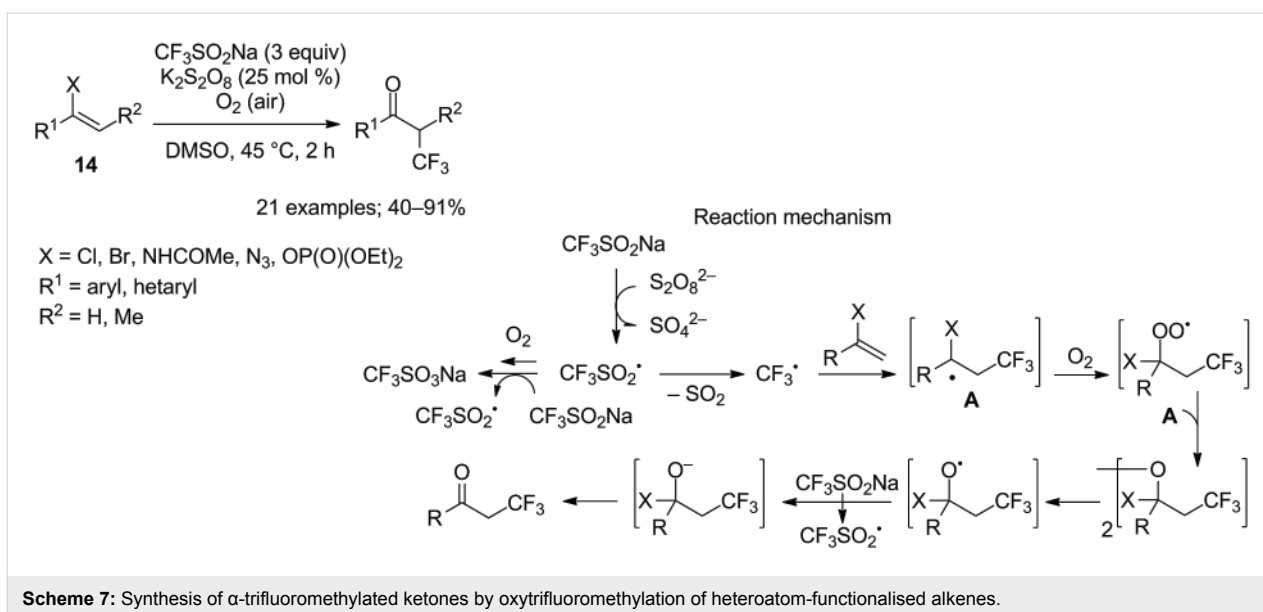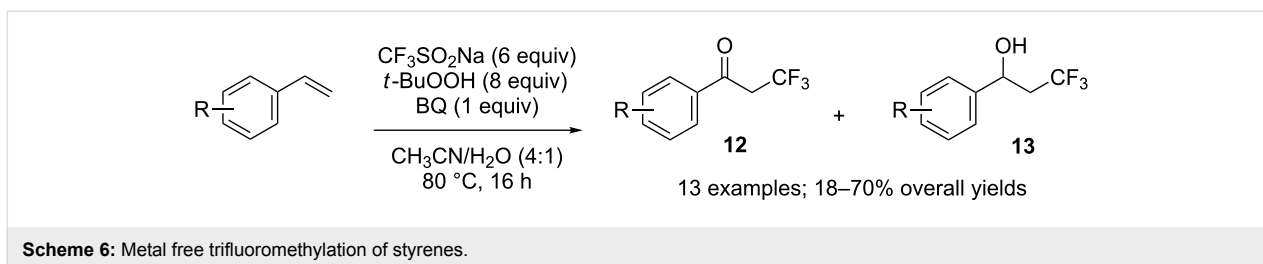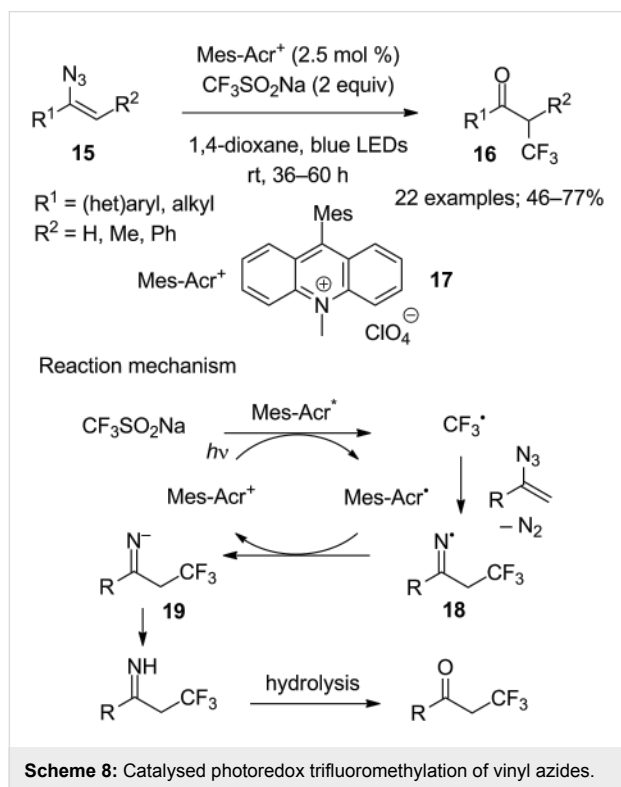**Scheme 5:** Oxidative trifluoromethylation of acetylenic substrates.

oxidation allowed to access either the alcohol or the ketone exclusively.

The use of transition metal catalysts and/or a large excess of organic oxidants can be obstacles to production. In a quest for ideal conditions, Lei and co-workers exposed heteroatom-functionalised alkenes **14** to aerobic C_{vinyl}–heteroatom bond oxygenation under metal-free conditions, where oxygen from air worked in concert with a catalytic amount of potassium persulfate to activate CF_3SO_2Na (Scheme 7) [26]. The heteroatom must be a good leaving group or part of it (X = Br, Cl, $NHCOMe$, N_3, $OP(O)(OEt)_2$). A mechanistic investigation demonstrated the role of oxygen: 93% isotopic purity of the ketone product was obtained when using $^{18}O_2$; no reaction occurred under N_2 instead of O_2; $K_2S_2O_8$ rather than O_2 served as initiator; the radical CF_3SO_2• could either extrude SO_2 to CF_3• or react with O_2 to re-initiate the radical chain process (Scheme 7).

Vinyl azides were used by Liu and co-workers as precursors of α-trifluoromethylated ketones by reaction of CF_3SO_2Na under photoredox catalysis. The substrate scope was broad and the reaction proceeded with high functional group tolerance;

Scheme 6: Metal free trifluoromethylation of styrenes.

Scheme 7: Synthesis of α-trifluoromethylated ketones by oxytrifluoromethylation of heteroatom-functionalised alkenes.

indeed, aryl-, alkyl-, hetero-functionalised terminal as well as non-terminal vinyl azides **15** were compatible with the reaction conditions. In the presence of the organic photocatalyst *N*-methyl-9-mesitylacridinium (**17**), CF_3SO_2Na was converted into $CF_3^{\bullet}$ upon visible-light irradiation. The $CF_3^{\bullet}$ radical reacted with the vinyl azide to give the iminyl radical **18** that was reduced by Mes-Acr$^{\bullet}$ (Mes-Acr: 9-mesityl-10-methylacridinium) into the iminyl anion **19**. After protonation and hydrolysis of the imine function, the α-trifluoromethylated ketones **16** were obtained in moderate to good yields (Scheme 8) [27].

Scheme 8: Catalysed photoredox trifluoromethylation of vinyl azides.

Alkenyl MIDA (*N*-methylimidodiacetic) boronates **20**, as functionalised alkenes, were transformed into α-trifluoromethyl-α-boryl ketones **21** by oxidative trifluoromethylation with CF_3SO_2Na. In that case, 2-iodoxybenzoic acid (IBX) was used as the oxidant to generate the trifluoromethylated radical **22** and atmospheric oxygen was the oxygen source to form the ketone (Scheme 9) [28].

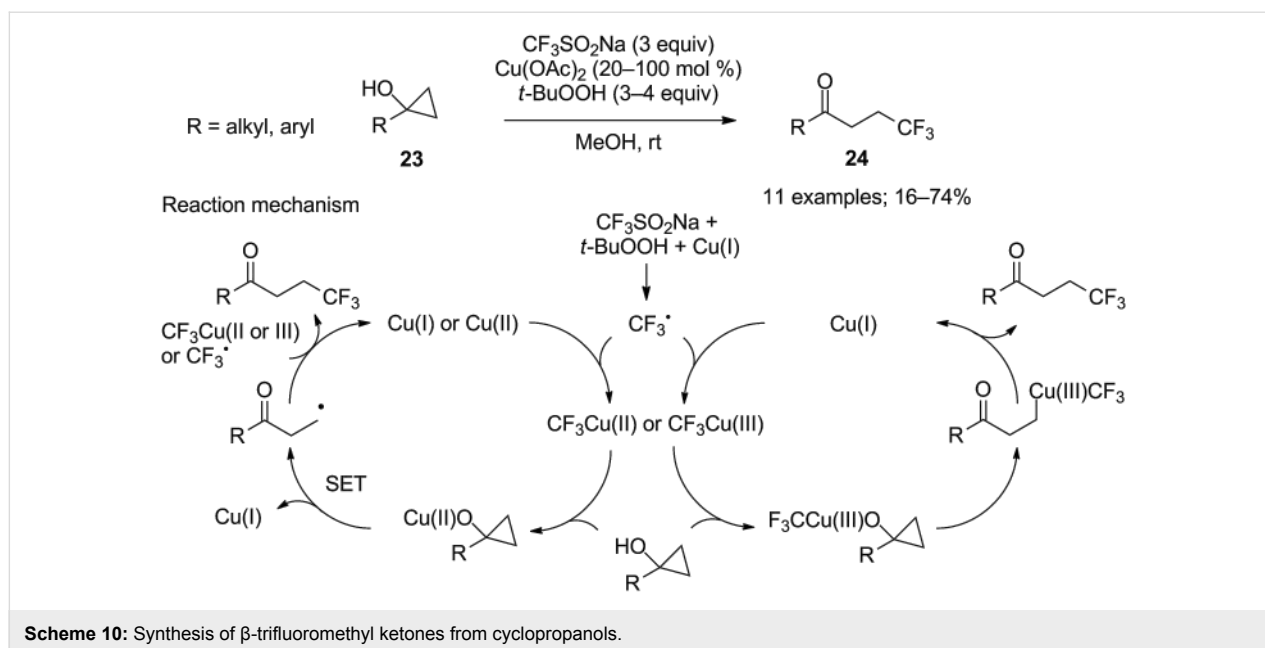**Synthesis of β-trifluoromethyl ketones from cyclopropanols:** Moving away the CF_3 group by one carbon atom further from the carbonyl function would provide the corresponding β-trifluoromethyl ketones. For this aim, distally trifluoromethyl ketones were synthesised by the ring-opening of cyclopropanol derivatives by means of per- or polyfluorinated sulfonates, including CF_3SO_2Na. Kananovich and co-workers demonstrated that sodium triflinate, under Langlois' conditions, served as a

**Scheme 9:** Oxidative difunctionalisation of alkenyl MIDA boronates.
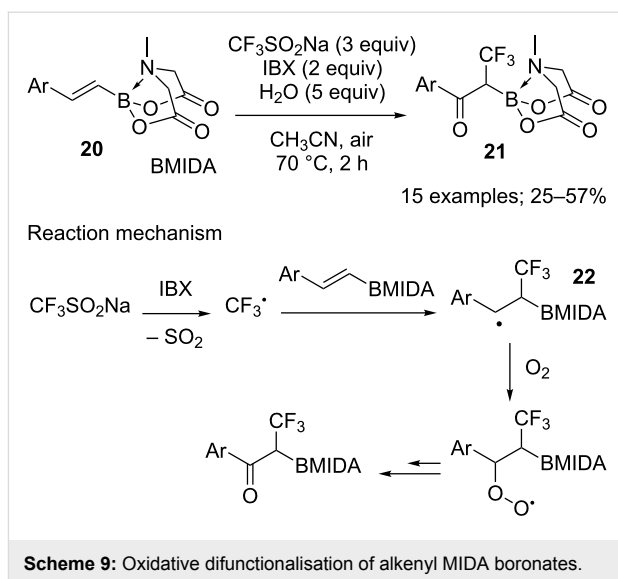
precursor of trifluoromethyl copper species that were involved in the ring-opening trifluoromethylation of tertiary cyclopropanols **23** (Scheme 10) [29]. The substrate scope was broad allowing access to various β-trifluoromethyl ketones **24** featuring aryl, alkyl, functionalised alkyl, alkenyl, acetal, silylated alcohol, pyran, and piperidine functionalities (R group in **24**). Mechanistic studies by ^{19}F NMR allowed to identify CF_3 complexes of copper(I) and copper(III) and the predominance of an electrophilic pathway (versus SET pathway) was suggested by regioselective trifluoromethylation of a case substrate. Although Cu(II) acetate was used, the authors mentioned that Cu(I) can be formed in situ by reduction with MeOH or the cyclopropanol. Concomitant mechanisms are depicted in Scheme 10.

β-Trifluoromethyl ketones could also be obtained from allylic alcohols **25** by a cascade trifluoromethylation/1,2-aryl migration. Yang, Xia and co-workers employed sodium triflinate under metal-free conditions with ammonium persulfate as the oxidant that was necessary to generate the CF_3 radical (Scheme 11) [30].

Amino- and azotrifluoromethylation of alkenes: Alkene trifluoromethylation was applied to the construction of indole, pyrazole and pyridazinone moieties via a multicomponent cascade reaction developed by Antonchick and Matcha in 2014 [31]. The method was based on the reaction between simple alkenes, sodium triflinate and diazonium salts. The CF_3 radical was produced from CF_3SO_2Na by oxidation with H_2O_2 in the presence of silver nitrate. Then, $CF_3^{\bullet}$ was added to the terminal position of the alkene to give radical **26** that was trapped by the arenediazonium salt to form the radical cation **27**, which was reduced into **28** prior to be converted into nitrogen heterocycles
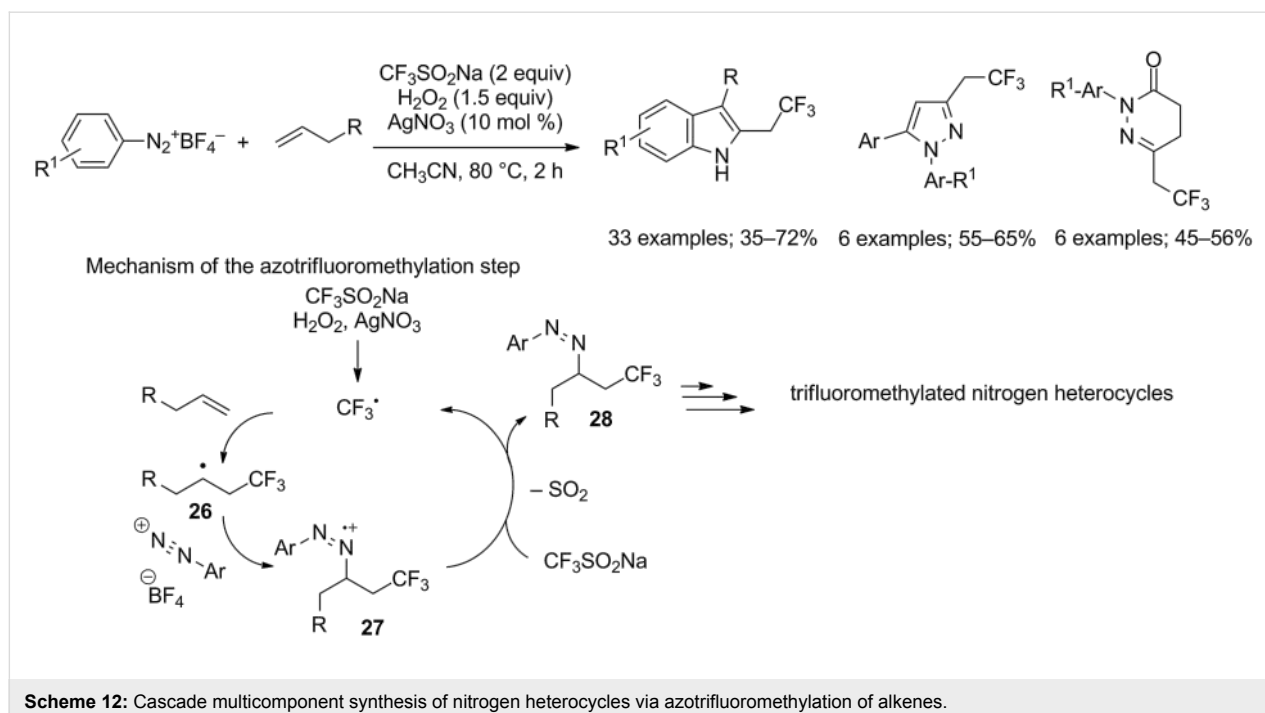
Scheme 10: Synthesis of β-trifluoromethyl ketones from cyclopropanols.
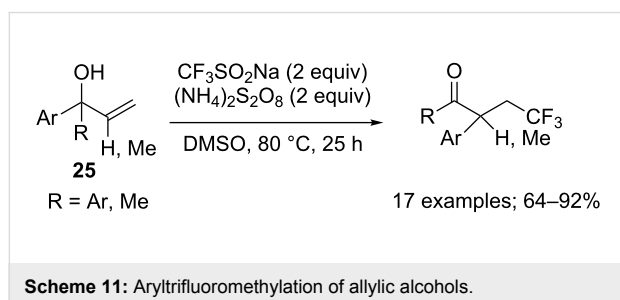
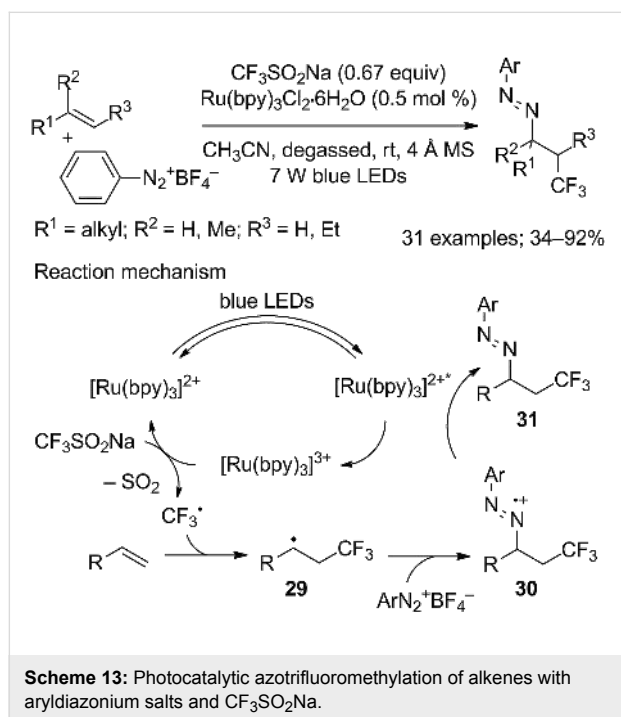**Scheme 11:** Aryltrifluoromethylation of allylic alcohols.

via [1,3]-hydride shift and cyclisation steps (Scheme 12). The reaction was regioselective and had a broad scope. This application of alkene trifluoromethylation provided a convenient entry to trifluoromethylated nitrogen heterocycles.

Subsequently, a photoredox-catalysed azotrifluoromethylation of unactivated alkenes was developed by Chen, Xiao and co-workers [32]. The scope was broad for a variety of unactivated alkenes, functionalised or not, and aryldiazonium salts


Scheme 12: Cascade multicomponent synthesis of nitrogen heterocycles via azotrifluoromethylation of alkenes.

(Scheme 13). Interestingly, the method did not require stoichiometric amounts of oxidant and further transformation of the azotrifluoromethyl products allowed a Fisher indole synthesis. From a mechanistic point of view, the excited photocatalyst was oxidised by the aryldiazonium salt to produce $[Ru(bpy)_3]^{3+}$ (bpy: 2,2'-bipyridine) as the oxidant to generate the CF_3 radical from CF_3SO_2Na with extrusion of SO_2. Then, $CF_3^{\bullet}$ underwent a radical addition to the alkene to form the radical **29**, which was trapped by the aryldiazonium salt to give the radical cation **30**. Finally, **30** was reduced by $[Ru(bpy)_3]^{2+*}$ to end up with the product **31** (Scheme 13).

Scheme 13: Photocatalytic azotrifluoromethylation of alkenes with aryldiazonium salts and CF_3SO_2Na.

The aminotrifluoromethylation of alkenes in an intramolecular version was reported by Zhang and co-workers in 2017 (Scheme 14) [33]. Langlois' conditions with *tert*-butyl hydroperoxide and a catalytic amount of copper(II) triflate were used to prepare a series of CF_3-containing indoline, pyrrolidine, lactam and lactone.

Scheme 14: Copper-promoted intramolecular aminotrifluoromethylation of alkenes with CF_3SO_2Na.
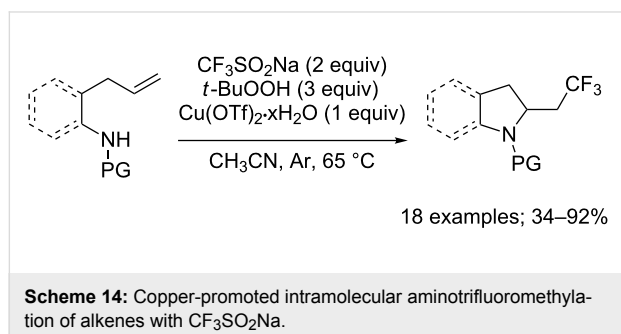
Oxytrifluoromethylation of alkenes: The difunctionalisation of alkenes including a trifluoromethylation step was extended to carbon–oxygen bond formation via oxytrifluoromethylation. We have already described some examples of such a reaction leading to α-trifluoromethyl ketones (vide supra) [26]. Now synthetic routes are presented leading to vicinal trifluoromethyl alcohols. In 2013 Qing and Jiang described the oxytrifluoromethylation of alkenes with hydroxamic acids **32** and CF_3SO_2Na under Langlois' conditions with the couple *t*-BuOOH/copper salt (Scheme 15) [34]. A competitive formation of two radicals, $CF_3^{\bullet}$ and the amidoxyl radical $[ArN(CO_2Me)O^{\bullet}]$ **33**, would lead to two regioisomeric oxytrifluoromethylated products. Fortunately, this issue was solved by the primary formation of the CF_3 radical and thus a regioselective addition. After optimization of the reaction conditions with styrene as model alkene, the method was applied to a wide range of alkenes featuring various functional groups. Further reduction of the N–O bond by $Mo(CO)_6$ gave the corresponding alcohols.

Scheme 15: Oxytrifluoromethylation of alkenes with CF_3SO_2Na and hydroxamic acid.
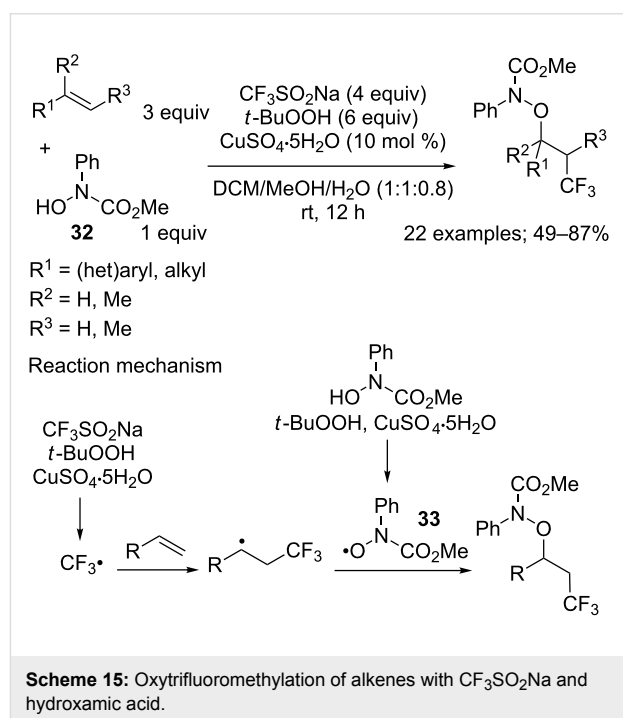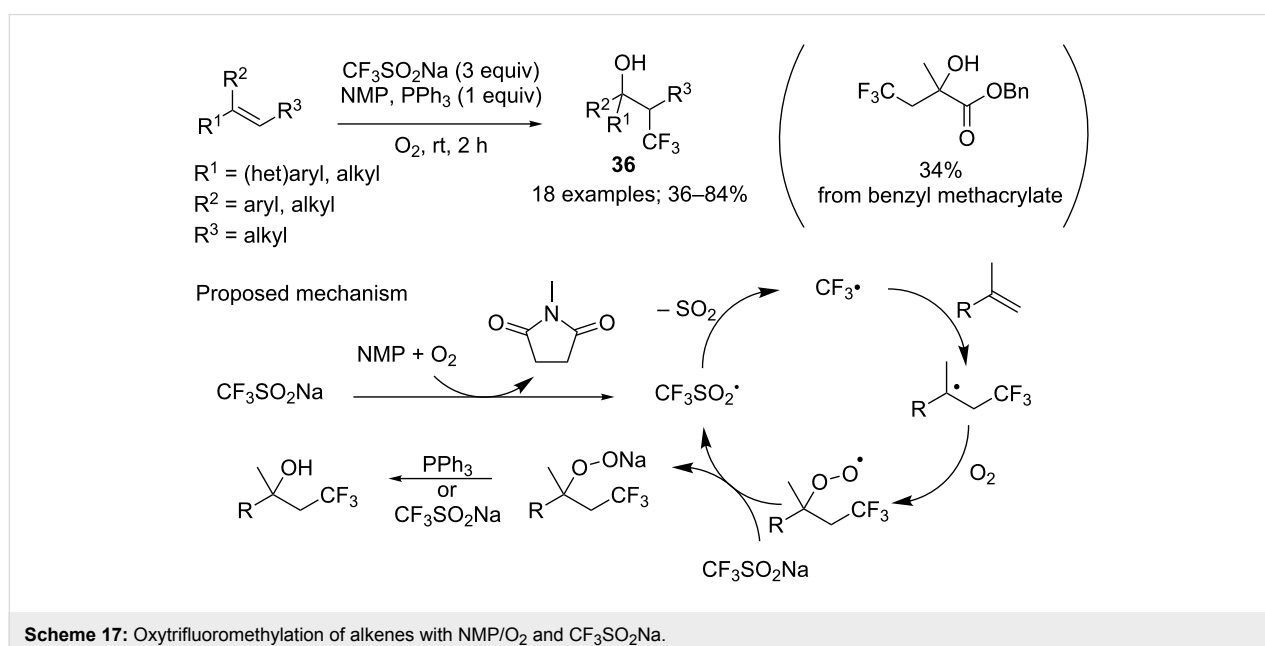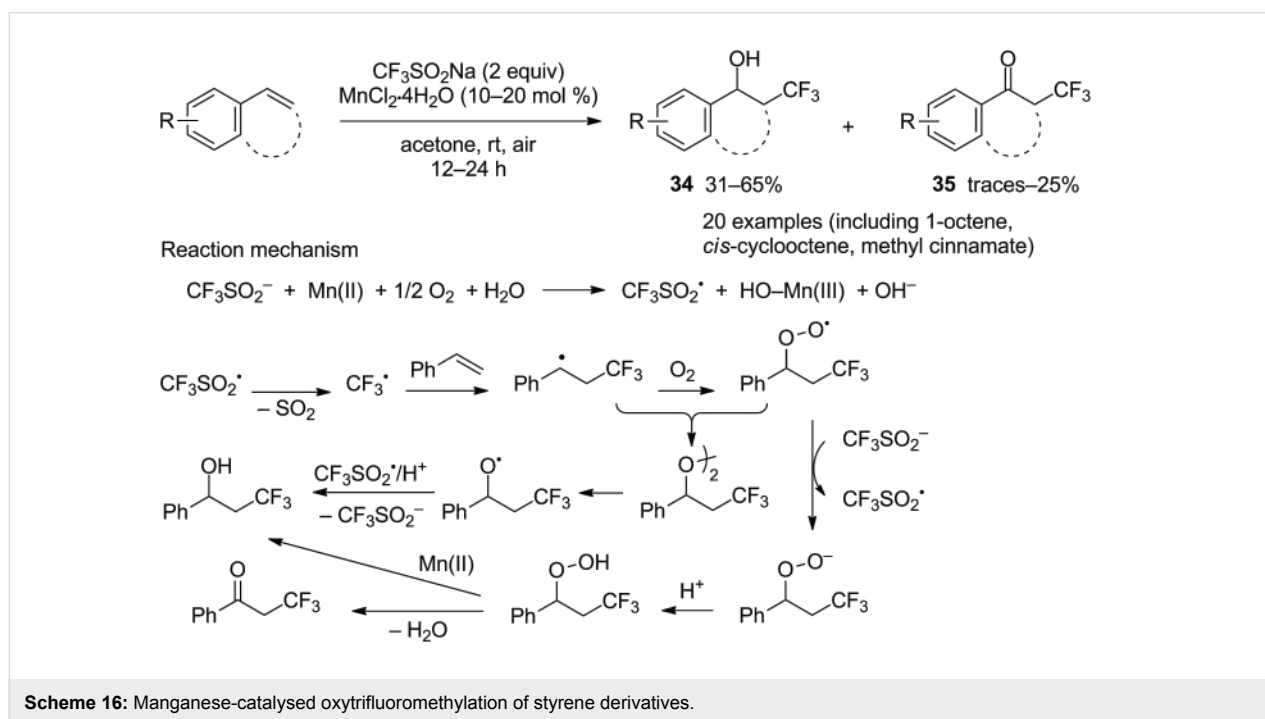
A protocol free of peroxide initiator was developed by Yang, Vicic and co-workers using a manganese salt and O_2 from air [35]. Styrene derivatives were transformed preferentially into hydroxytrifluoromethylated compounds **34** versus the corresponding ketones **35** in moderate to good selectivities (Scheme 16). In the case of 1,2-disubstituted alkenes, mixtures of *syn*- and *anti*-isomers were obtained. A radical pathway was supported by several observations: (i) addition of TEMPO suppressed the reaction; (ii) an induction period was observed

followed by acceleration with consumption of styrene; (iii) vinyl triflone was detected indicating the formation of $CF_3SO_2^{\bullet}$; (iv) formation of $CF_3SO_3^-$ via oxidation of $CF_3SO_2^{\bullet}$ (Scheme 16).

A metal-free approach with in situ generation of the peroxide from the combination of NMP and O_2 as the radical initiator was proposed by Lei and co-workers [36]. This method was based on a previous work by Maiti (see Scheme 5) [24] but did

not require a metal to generate the CF_3 radical. Tertiary β-trifluoromethyl alcohols **36** were obtained in good yields from a variety of di- and trisubstituted alkenes (Scheme 17). Labelling and IR experiments were conducted to investigate the reaction mechanism as well as kinetic studies that revealed the reaction rate dependence on O_2 diffusion.

A case of intramolecular oxytrifluoromethylation of alkenes leading to oxazolines **37** was described by Fu and co-workers in
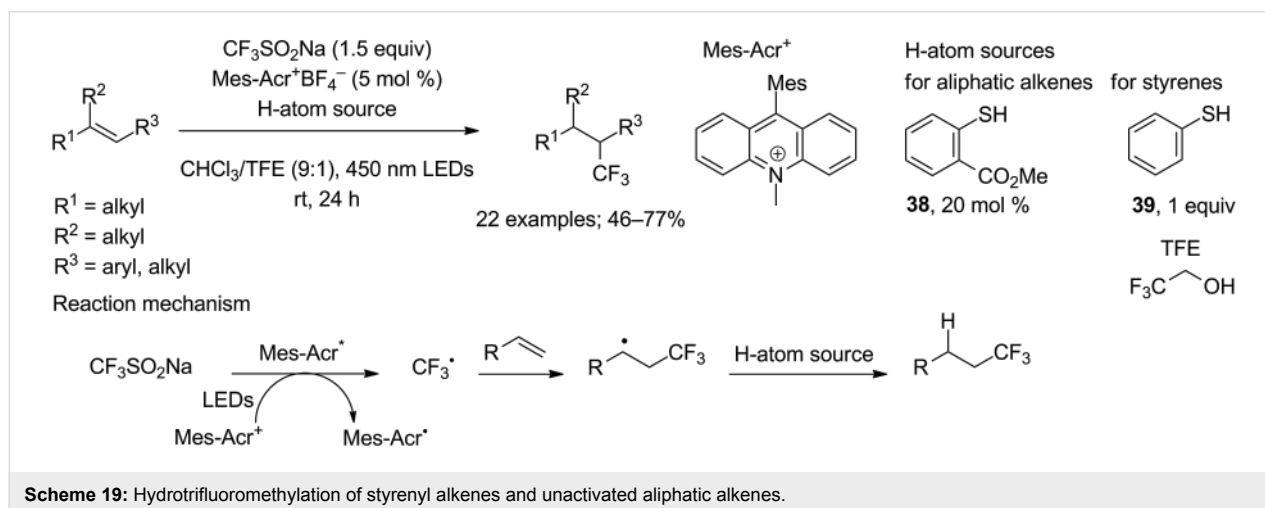

Scheme 16: Manganese-catalysed oxytrifluoromethylation of styrene derivatives.

Scheme 17: Oxytrifluoromethylation of alkenes with NMP/O_2 and CF_3SO_2Na.

2014 [37]. In this work iodobenzene diacetate (PIDA) was used as the oxidant to generate the CF$_3$ radical from CF$_3$SO$_2$Na (Scheme 18).
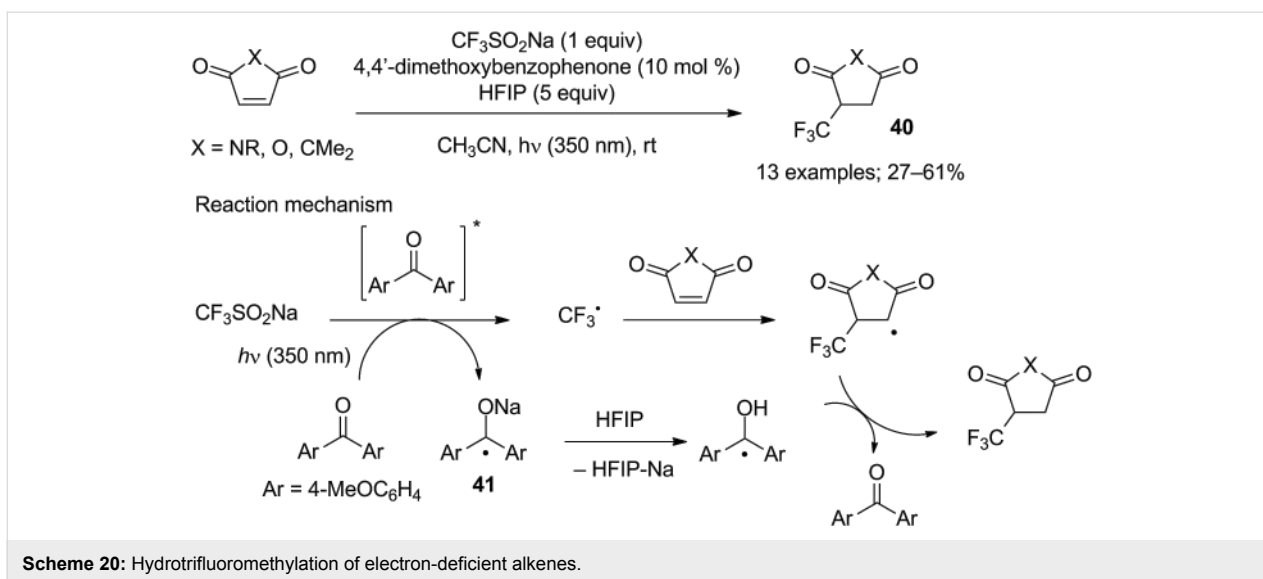

Scheme 18: Intramolecular oxytrifluoromethylation of alkenes.
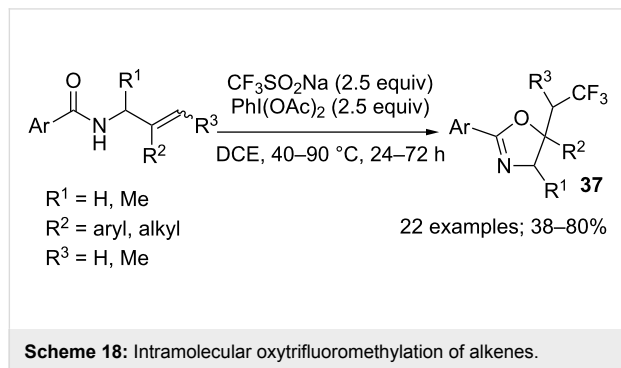
Hydrotrifluoromethylation of alkenes: Direct alkene hydrotrifluoromethylation by means of CF$_3$SO$_2$K under electrochemical oxidation was first reported by Tommasino and co-workers in 2002 on three alkenes but yields were below 20% due to the formation of oxidised byproducts [38]. Nicewicz and co-workers in 2013 found suitable reaction conditions for the alkene hydrotrifluoromethylation using CF$_3$SO$_2$Na [39]. The single electron oxidation of CF$_3$SO$_2$Na was performed by visible-light activated *N*-methyl-9-mesitylacridinium as a photoredox catalyst. Two hydrogen atom donors, 20 mol % of methyl thiosalicylate **38** for aliphatic alkenes (or 1 equiv of thiophenol **39** for styrenyl alkenes) and 2,2,2-trifluoroethanol (TFE), worked in concert for the hydrogen atom transfer with complete suppression of the oxidised trifluoromethylated byproducts. The method was regioselective for mono-, di-, and trisubstituted aliphatic alkenes and styrenyl alkenes with a broad substrate scope (Scheme 19). As an exception, 1,2-disubstituted alkenes and chalcone gave low regioselectivities with mixed Markovnikov and anti-Markovnikov products.

The CF$_3$ radical is electrophilic in nature and, as such, not prone to readily react with electron-deficient alkenes. Nevertheless, Lefebvre, Hoffmann and Rueping reported that *N*-substituted maleimides, maleic anhydride and dimethyl maleate were hydrotrifluoromethylated with CF$_3$SO$_2$Na in the presence of 4,4'-dimethoxybenzophenone as photosensitiser under near-UV irradiation (350 nm) and hexafluoroisopropanol (HFIP) as a proton donor (Scheme 20) [40]. The reactions were performed in batch and under continuous flow conditions with rate enhancement for the latter setup. It was proposed that the CF$_3$ radical added onto the substrate while the ketyl radical **41** was protonated by HFIP. Then, hydrogen transfer gave the hydrotrifluoromethylated product **40** and the sensitiser was regenerated (Scheme 20). In the same paper, the authors also realised the same chemical transformation under visible light irradiation at 450 nm by means of the iridium photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ ([4,4'-bis(*tert*-butyl)-2,2'-bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]iridium(III) hexafluorophosphate), which delivered comparable and even higher yields of the products in longer reaction times but with lower catalyst loading (1 mol %).

Both unactivated terminal alkenes and electron-deficient alkenes (Michael acceptors) were successfully hydrotrifluoromethylated under irradiation with 36 W blue LEDs in the presence of an iridium photoredox catalyst as reported by Zhu, Zhang and co-workers [41]. Of the photocatalysts tested, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ had appropriate redox potentials and gave the best results. A wide range of terminal alkenes featuring several functional groups reacted with exclusive anti-Markovnikov selectivity. Notably, styrene failed to react under these conditions. A selection of α,β-unsaturated electron-withdrawing motifs that included a sulfone, esters, an amide, and a ketone were investigated for the first time and the β-addition products were obtained regioselectively in moderate to good
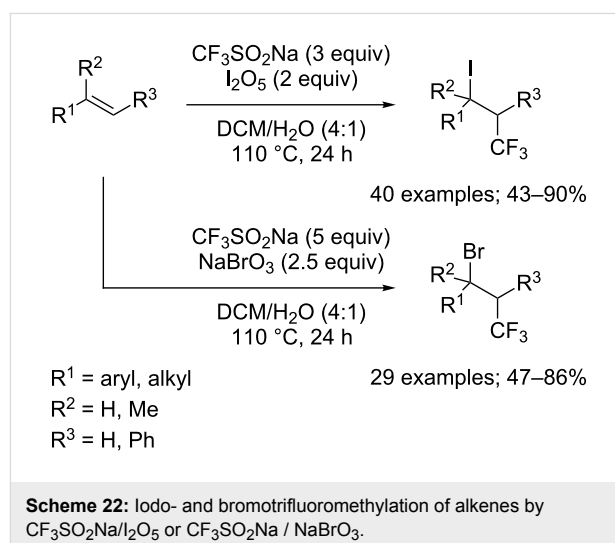

Scheme 19: Hydrotrifluoromethylation of styrenyl alkenes and unactivated aliphatic alkenes.

Scheme 20: Hydrotrifluoromethylation of electron-deficient alkenes.

yields (Scheme 21). It was suggested that the methylene radical formed by addition of the CF$_3$ radical onto the alkene was reduced by the sulfinate anion and the corresponding carbanion was protonated by methanol.

Scheme 21: Hydrotrifluoromethylation of alkenes by iridium photoredox catalysis.
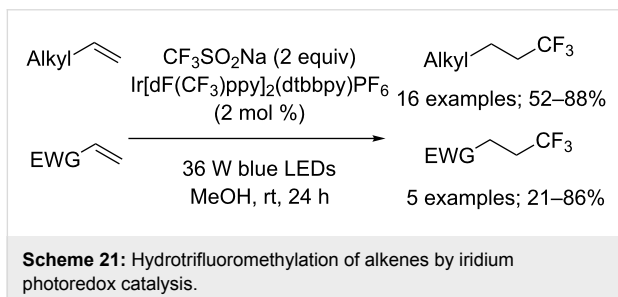
Halo- and pseudohalotrifluoromethylation of alkenes: The direct iodotrifluoromethylation was previously achieved by means of gaseous CF$_3$I until Liu and co-workers reported the convenient use of CF$_3$SO$_2$Na and iodide pentoxide, I$_2$O$_5$, in combination for the iodotrifluoromethylation of alkenes and alkynes (see later in the text) [42]. After an optimisation with 4-chlorostyrene, the reaction was developed with a wide range of terminal and internal alkenes bearing diverse functional groups such as halogens, nitro, sulfonate, sulfamide, carboxylate, amide, ether, carbonyl, and hydroxy that were all well-tolerated (Scheme 22). A mixed solvent system of dichloromethane and water was used in a sealed tube at 110 °C. Mechanistic studies by electron spin resonance were carried out in which both the CF$_3$• and the β-CF$_3$ alkyl radical intermediate were observed by using 2-methyl-2-nitrosopropane as a radical spin trap. A single-electron oxidative free-radical process was clearly ascertained. For the iodination step, the authors proposed that the β-CF$_3$ alkyl radical was intercepted by I$_2$, which

was formed by a multistep redox process from I$_2$O$_5$. In continuation of this work, the same research group described the bromotrifluoromethylation of alkenes under similar reaction conditions but using sodium bromate, NaBrO$_3$, as a bromine source (Scheme 22) [43].

Scheme 22: Iodo- and bromotrifluoromethylation of alkenes by CF$_3$SO$_2$Na/I$_2$O$_5$ or CF$_3$SO$_2$Na / NaBrO$_3$.

The photoredox-catalysed chloro-, bromo- and also (trifluoromethylthio)trifluoromethylation of unactivated alkenes was studied by Liu and co-workers in 2017 (Scheme 23) [44]. The Langlois reagent was combined with *N*-halophthalimides **42a**,**b** or *N*-trifluoromethylthiosaccharin **43** in the presence of *N*-methyl-9-mesitylacridinium under visible light irradiation at room temperature. Terminal, internal, and *gem*-substituted alkenes bearing imide, ester, amide, ketone, aldehyde and electron-rich aryl functional groups were suitable substrates. Notably, diethyl 2,2-diallylmalonate as a diene gave the
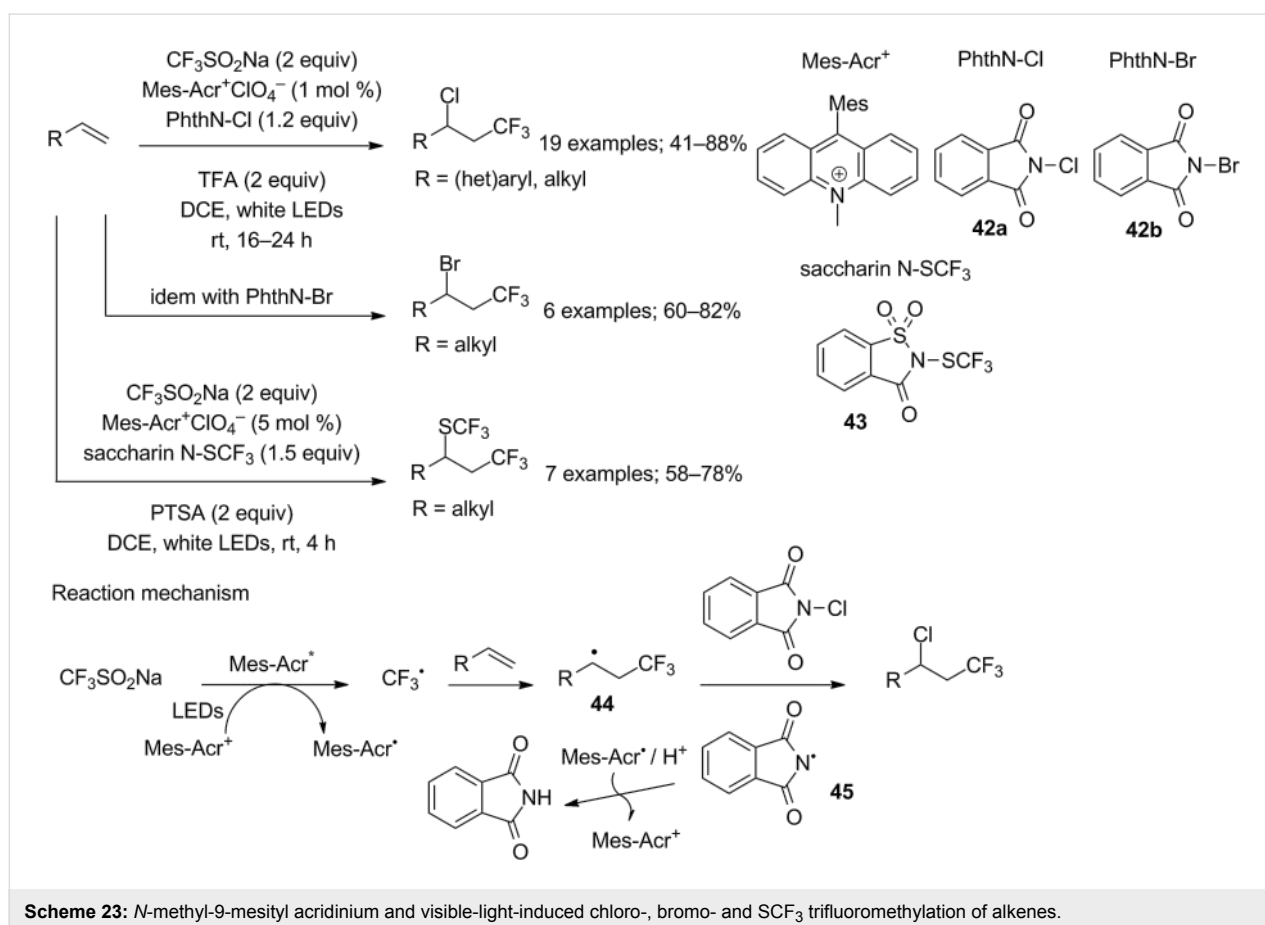
cyclised product resulting of a radical cascade. It has to be noticed that the reactions were conducted in the presence of 2 equivalents of trifluoroacetic or *p*-toluenesulfonic acid; yet, there was no mention of hydrotrifluoromethylated side-products. The mechanism was similar to previous examples to generate the β-CF$_3$ alkyl radical intermediate **44**, which was trapped by halogen atom transfer from the halogenating agent. The nitrogen-centered radical **45** oxidised Mes-Acr* by a single-electron-transfer process to restart the catalytic cycle (Scheme 23).
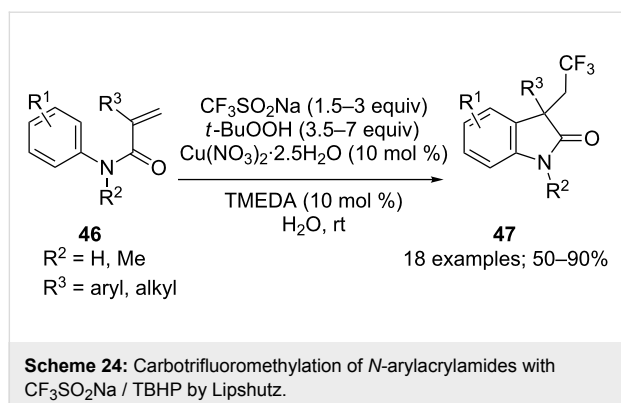
Carbotrifluoromethylation of alkenes: The strategies for carbotrifluoromethylation of alkenes with CF$_3$SO$_2$Na are very much based on methods described earlier in the text: (i) reactions mediated by *tert*-butyl hydroperoxide and a catalytic amount of copper; (ii) metal-catalysed or metal-free reactions with K$_2$S$_2$O$_8$, I$_2$O$_5$ or a hypervalent iodine reagent, and (iii) photochemical activation. Most of the works concerned cascade intramolecular reactions in which a C–C bond is formed after the initial trifluoromethylation.

Therefore, Lipshutz and co-workers reported a copper-catalysed intramolecular carbotrifluoromethylation of *N*-arylacryl-

amides **46** with CF$_3$SO$_2$Na to produce oxindoles **47** [45]. Addition of the CF$_3$ radical to such an electron-deficient alkene should be unfavourable. However, the subsequent annulation step drove the cascade process toward oxindole synthesis. The reaction utilised Langlois' conditions with *tert*-butyl hydroperoxide and a catalytic amount of Cu(II), but with 10 mol % of tetramethylethylenediamine (TMEDA). Organic solvents were replaced by pure water and the aqueous medium can be recycled up to five times. The substrate scope was large when tertiary amides were used. A secondary arylamide failed to give the expected product. With a substituent at the *meta*-position of the aniline ring, a mixture of regioisomers was obtained. Various alkenes with substituents (R^3) were investigated and the oxindoles were obtained in moderate to high yields (Scheme 24).

Simultaneously, Lei and co-workers published the same reaction under slightly different conditions [46]. They used a combination CF$_3$SO$_2$Na/TBHP in the presence of catalytic amounts of copper chloride and triphenylphosphine. Trisubstituted alkenes (R^3 and R$^4 \neq$ H) were employed as substrates and diastereoisomers were obtained. The *tert*-butoxyl radical was generated from TBHP and Cu(*n*) via a SET process, which then, it reacted
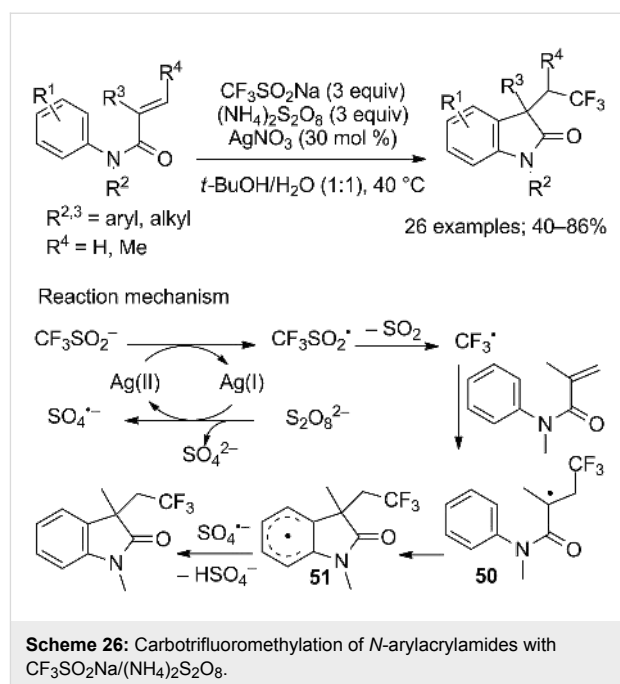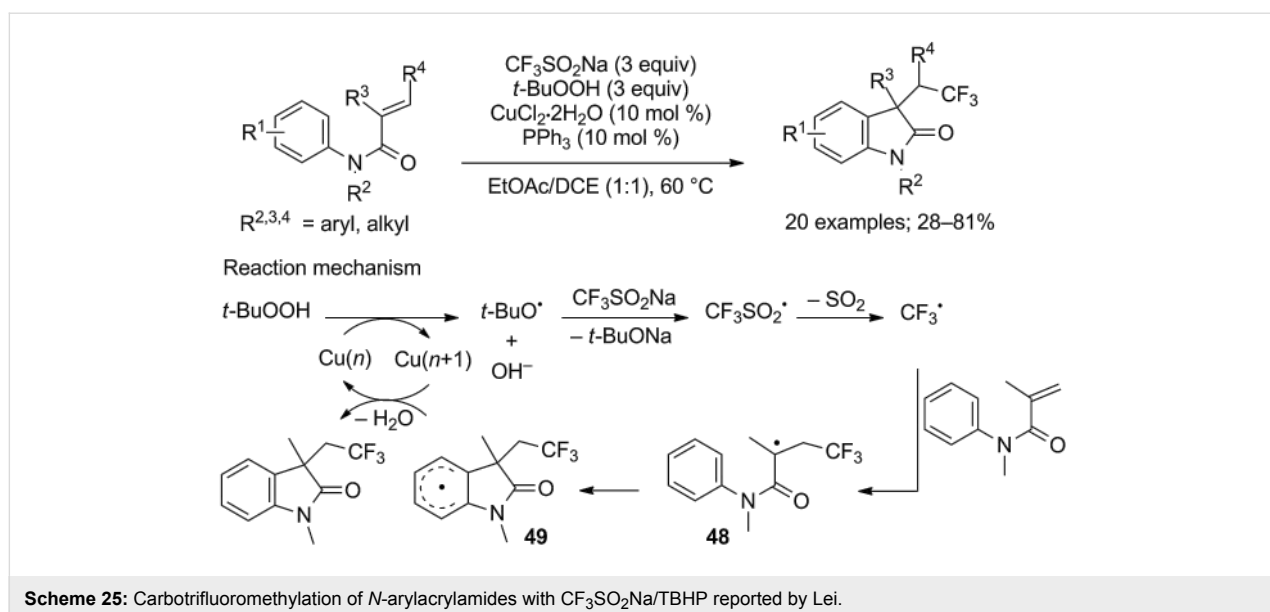

Scheme 23: *N*-methyl-9-mesityl acridinium and visible-light-induced chloro-, bromo- and SCF$_3$ trifluoromethylation of alkenes.

Scheme 24: Carbotrifluoromethylation of *N*-arylacrylamides with CF$_3$SO$_2$Na / TBHP by Lipshutz.

with CF$_3$SO$_2$Na to liberate CF$_3$•. The subsequent addition of CF$_3$• to the β-position of the C=C bond of the acrylamide gave the intermediate **48**, which underwent an intramolecular radical annulation to produce the aryl radical **49**. Finally, oxidation of **49** by Cu(n + 1) and aromatisation afforded the oxindole and regenerated the copper catalyst (Scheme 25).
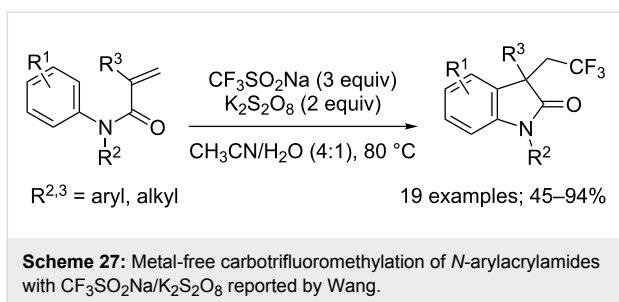
The same indoles bearing a 2,2,2-trifluoroethyl side-chain were also obtained in reactions performed with CF$_3$SO$_2$Na and (NH$_4$)$_2$S$_2$O$_8$ as the oxidant in the presence of a catalytic amount of AgNO$_3$ as reported by Tan and co-workers (Scheme 26) [47]. In the absence of AgNO$_3$ the reaction did not work. Notably, *N*-alkyl and *N*-aryl protected substrates worked well, whereas *N*-acyl and *N*–H derivatives failed to deliver the desired products. Mechanistically, Ag(I) was initially oxidised to Ag(II) by the persulfate anion; then, CF$_3$SO$_2$⁻ was oxidised to CF$_3$SO$_2$• that generated CF$_3$• by release of SO$_2$. Addition of the CF$_3$ radical to the alkene led to the radical intermediate **50**, which underwent intramolecular cyclisation into **51**. The sulfate

radical anion then oxidised intermediate **51** into the final oxindole (Scheme 26).

Scheme 26: Carbotrifluoromethylation of *N*-arylacrylamides with CF$_3$SO$_2$Na/(NH$_4$)$_2$S$_2$O$_8$.
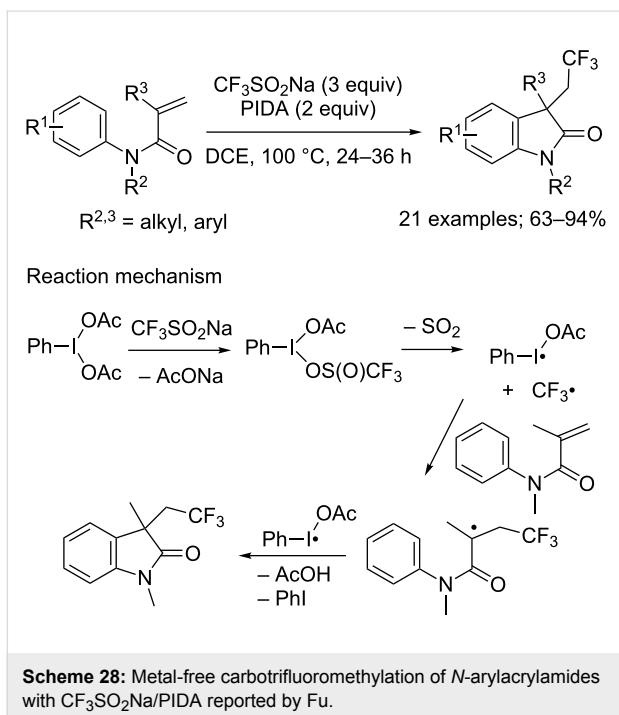
In an independent work Wang and co-workers demonstrated that silver nitrate was not necessary for the reaction to proceed in acetonitrile and water at 80 °C (Scheme 27) [48]. Again, *N*-acyl and *N*–H derivatives failed to deliver the desired products and *meta*-substituted phenyl rings produced mixtures of regioisomers. Under these metal-free conditions, it was proposed that the CF$_3$ radical was formed uniquely by reaction of CF$_3$SO$_2$Na with K$_2$S$_2$O$_8$.

Scheme 25: Carbotrifluoromethylation of *N*-arylacrylamides with CF$_3$SO$_2$Na/TBHP reported by Lei.

**Scheme 27:** Metal-free carbotrifluoromethylation of *N*-arylacrylamides with $CF_3SO_2Na/K_2S_2O_8$ reported by Wang.

N-Arylacrylamides could also react with CF_3SO_2Na under metal-free conditions by replacing *tert*-butyl hydroperoxide or the persulfate by hypervalent iodine oxidants such as iodobenzene diacetate (PIDA, Scheme 28) [49], or iodobenzene bis(trifluoroacetate) (PIFA) [50]. Fu and co-workers proposed the reaction mechanism depicted in Scheme 28. PIDA reacted with CF_3SO_2Na under heating conditions to produce two radicals: $CF_3^•$ along with $PhI^•OAc$. Addition of the CF_3 radical to the alkene followed by intramolecular cyclisation mediated by $PhI^•OAc$ gave the desired oxindole with release of PhI and AcOH (Scheme 28) [49].

Scheme 28: Metal-free carbotrifluoromethylation of *N*-arylacrylamides with $CF_3SO_2Na/PIDA$ reported by Fu.
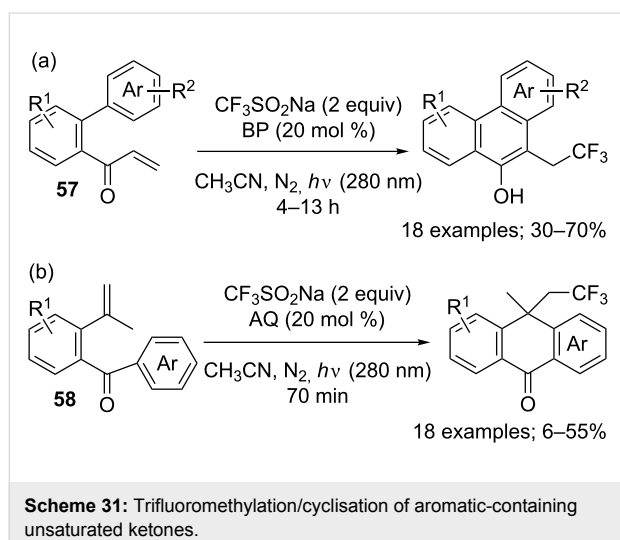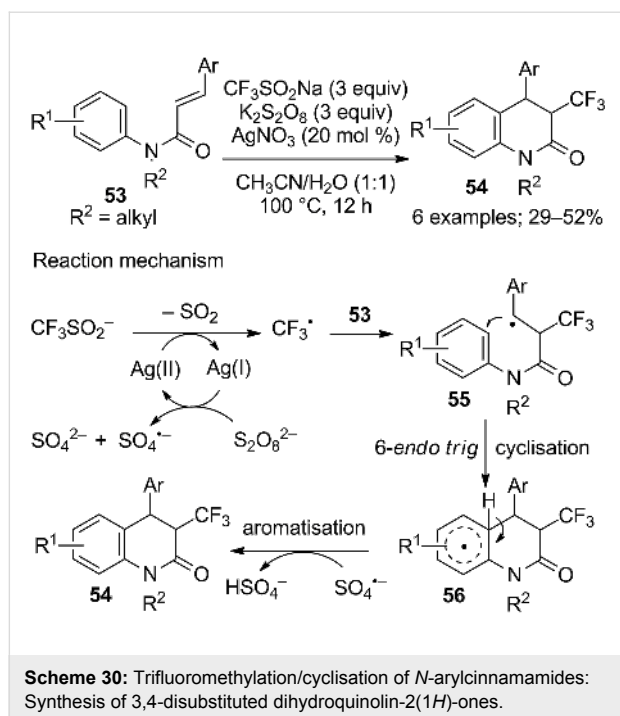
For another metal-free trifluoromethylation/cyclisation of *N*-arylacrylamides by means of a different oxidant, Liu and co-workers reported the use of CF_3SO_2Na in combination with iodide pentoxide in a similar way to their iodotrifluoromethylation of alkenes (see earlier in the text) [42] (Scheme 29a) [51]. Interestingly, this cascade reaction was also applied to enynes for the synthesis of pyrrolidines **52** (Scheme 29b) [51]. A

single-electron oxidative free-radical process was ascertained for the generation of $CF_3^•$. From enynes, the iodination step was realised by I_2, which was formed by a multistep redox process from I_2O_5.

Scheme 29: Metal-free cascade trifluoromethylation/cyclisation of *N*-arylmethacrylamides (a) and enynes (b) with CF_3SO_2Na/I_2O_5.
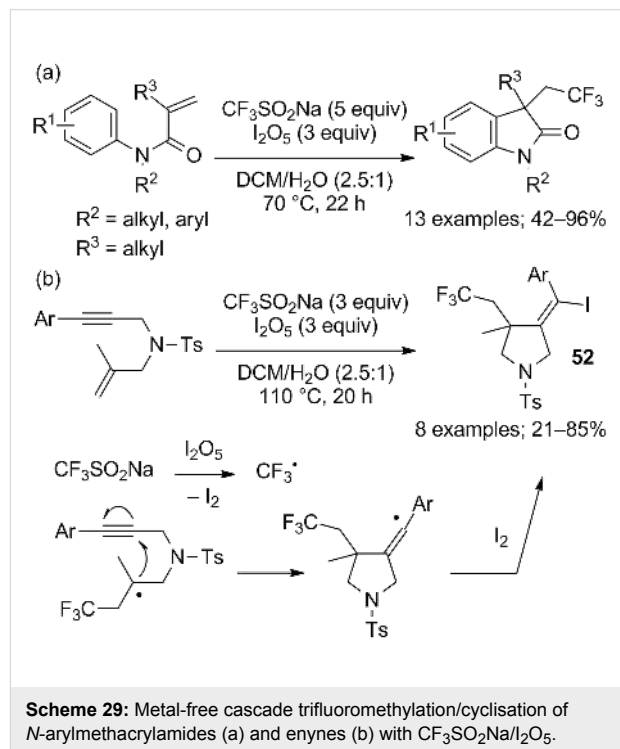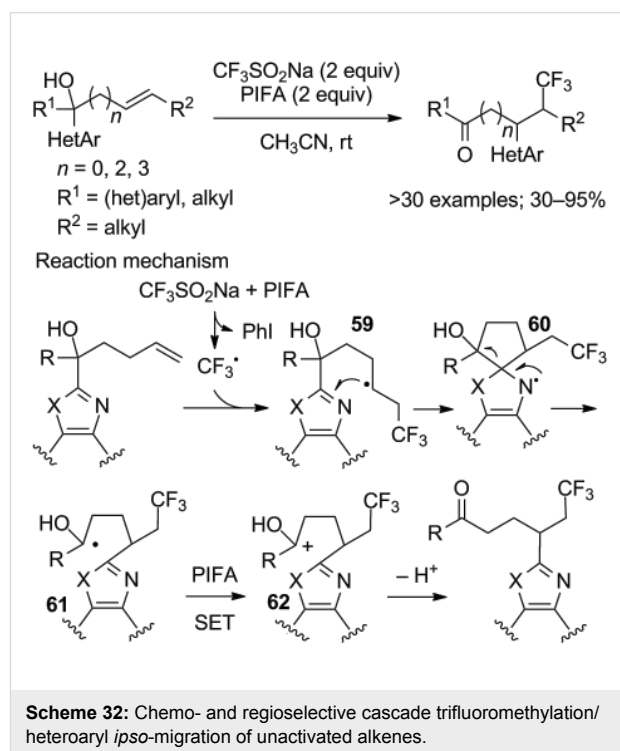
The intramolecular carbotrifluoromethylations of alkenes from acrylamides and methacrylamides, so far described, provided oxindoles via a 5-*exo trig* cyclization. Starting from cinnamamides **53**, Mai, Xiao and co-workers reported a 6-*endo trig* cyclisation leading to 3,4-disubstituted dihydroquinolin-2(1*H*)-ones **54** (Scheme 30) [52]. Ag(I) was oxidised by the persulfate anion ($S_2O_8^{2−}$) to generate the Ag(II) cation and the sulfate radical anion; then, the Ag(II) oxidised CF_3SO_2Na into $CF_3^•$ with extrusion of SO_2. The CF_3 radical reacted with the C=C double bond of the cinnamamide leading to the intermediate **55** that underwent 6-*endo trig* cyclisation to **56** that finally aromatised to the desired product **54** *trans*-selectively (Scheme 30).

In 2016, Xia and co-workers described a metal-free, UV-light-mediated difunctionalisation of alkenes with CF_3SO_2Na for the synthesis of phenanthrene and anthrone derivatives [53]. The substrates were either α,β-unsaturated ketones **57** (Scheme 31a) or γ,δ-unsaturated ketones **58** (Scheme 31b). Benzophenone (BP) or anthracene-9,10-dione (AQ) were used as sensitizers under irradiation using a UV lamp at 280 nm. A radical pathway that involves $CF_3^•$ was established after a negative reaction in the presence of TEMPO (TEMPO–CF_3 was detected by GC–MS).

Scheme 30: Trifluoromethylation/cyclisation of *N*-arylcinnamamides: Synthesis of 3,4-disubstituted dihydroquinolin-2(1*H*)-ones.

Scheme 31: Trifluoromethylation/cyclisation of aromatic-containing unsaturated ketones.

An example of difunctionalisation of unactivated alkenes with CF_3SO_2Na and an heteroaryl group in which the heteroarylation was realised by a distal heteroaryl *ipso*-migration was provided in 2017 by Zhu and co-workers (Scheme 32) [54]. A variety of nitrogen containing heteroaryl groups showcased the migratory aptitude selectively in the presence of an aryl or an alkyl group. The number of methylene units between the alkene and the tertiary alcohol function was studied: $n = 0$, 2, and 3 were suitable for generating thermodynamically favoured 3, 5, and 6-membered cyclic transition states; the reaction failed with $n = 1$, 4. Experimental and computational studies allowed the authors to propose the mechanism depicted in Scheme 32. First,

the CF_3 radical was generated from CF_3SO_2Na and PIFA. Then, addition of $CF_3{}^{\bullet}$ to the alkene gave the alkyl radical **59** that added to the *ipso* position of the heteroaryl group to form radical **60**. Next, homolysis of the C–C σ-bond in **60** provided the more stable hydroxyalkyl radical **61**. This radical was oxidised by PIFA to yield the cationic intermediate **62**, which finally lost a proton to furnish the reaction product.
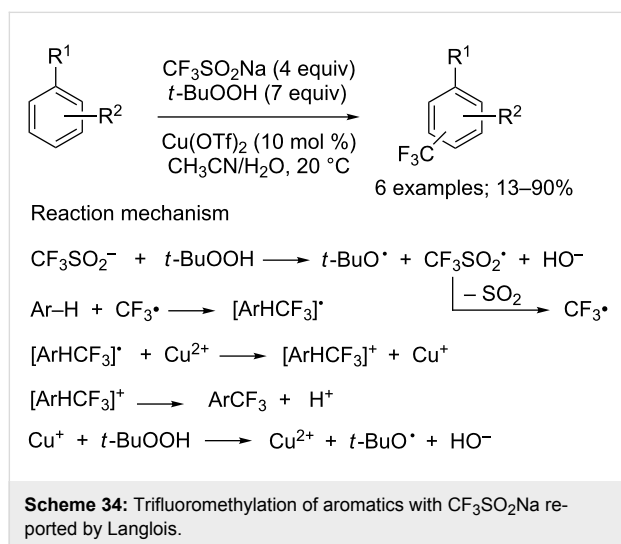

Scheme 32: Chemo- and regioselective cascade trifluoromethylation/heteroaryl *ipso*-migration of unactivated alkenes.

1,2-Bis-trifluoromethylation of alkenes: Alkenes were efficiently and chemoselectively bis-trifluoromethylated under Langlois' conditions with CF_3SO_2Na. Indeed, Qing and co-workers prepared 1,2-bis(trifluoromethylated) compounds **63** with in situ generated CF_3 radicals (Scheme 33). In order to avoid the formation of dimerised side products, it was demonstrated that an increase of the CF_3 radical concentration, obtained by increasing the amount of copper catalyst, was beneficial to the chemoselectivity. Both styrene derivatives and terminal unactivated alkenes were suitable substrates in this transformation but not internal alkenes [55].

Scheme 33: Copper-mediated 1,2-bis(trifluoromethylation) of alkenes.
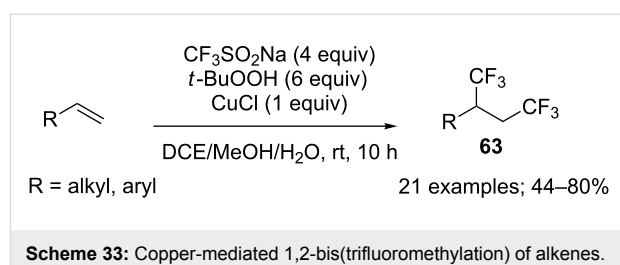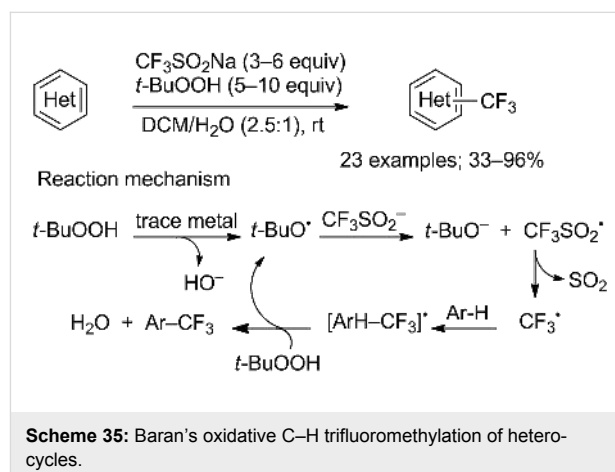
C$_{sp2}$–CF$_3$ bond-forming reactions

Direct trifluoromethylation of arenes and heteroarenes: In 1991, Langlois and co-workers reported the first trifluoromethylation of aromatic compounds with sodium trifluoromethanesulfinate under oxidative conditions (Scheme 34) [16]. The scope was quite narrow with electron-rich aromatics and mixtures of regioisomers were often obtained. For instance, from aniline, two isomers were obtained in 13% overall yield, and from 1,3-dimethoxybenzene, four products (regioisomers + bis-CF$_3$ compounds) were obtained in 90% overall yield. For this transformation, a radical process was proposed: the trifluoromethyl radical CF$_3^{\bullet}$ was generated by reaction of *tert*-butyl hydroperoxide with CF$_3$SO$_2$Na in the presence of a copper(II) catalyst (Scheme 34).

innate reactive positions of the heterocycles; however, it was noticed that the regioselectivity can be tuned simply by solvent choice. Langlois and others employed catalytic metal salts for reaction initiation but Baran's group demonstrated that metal additives were not required for a productive reaction, only trace metals found in Langlois' reagent could be responsible for reaction initiation. The scope was evaluated on pyridines, pyrroles, indoles, pyrimidines, pyrazines, phthalazines, quinoxalines, deazapurine, thiadiazoles, uracils, xanthenes and pyrazolinopyrimidines (Scheme 35). The combination of previous studies with new observations allowed to propose a putative mechanism (Scheme 35) as well as unproductive pathways (formation of CF$_3$H from CF$_3^{\bullet}$ by abstraction of a hydrogen atom or reaction of CF$_3^{\bullet}$ with isobutene generated from *t*-BuOOH).

Scheme 34: Trifluoromethylation of aromatics with CF$_3$SO$_2$Na reported by Langlois.

Scheme 35: Baran's oxidative C–H trifluoromethylation of heterocycles.

Substrates with sensitive functional groups may not be tolerated under such reaction conditions and a large excess amount of peroxide was necessary to reach high yields. That is how, in 1998, Smertenko and co-workers described a milder electrochemical trifluoromethylation of a series of aromatic compounds using CF$_3$SO$_2$Na in acetonitrile [56]. Furthermore, the electrochemical oxidation of the trifluoromethylsulfinate anion (from CF$_3$SO$_2$K) generated the trifluoromethyl radical for the reaction of electron-rich aromatics and alkenes [38].

It is twenty years after Langlois' pioneering work that the direct trifluoromethylation of heteroaromatic compounds was re-investigated by Baran and co-workers in 2011 [57]. This group reported a C–H trifluoromethylation protocol that was operationally simple, scalable, achieved at room temperature, working with a variety of electron-deficient and -rich heteroaromatic systems tolerating various functional groups such as unprotected alcohols, amines, ketones, esters, halides and nitriles. Importantly, the trifluoromethylation proceeded at the

This oxidative trifluoromethylation method was exploited for the synthesis of modified nucleosides, in particular 8-CF$_3$-2'-deoxyguanosine and 8-CF$_3$-inosine in 39 and 73% yields, respectively [58].

The same copper-free method was applied for the trifluoromethylation of a variety of electron-deficient 4-substituted acetanilides or anilines (Scheme 36). In these reaction conditions, Cao's group reported that acetanilides or anilines featuring electron-donating substituents at the *para*-position of the acetamino group afforded mixtures of isomeric C–H trifluoromethylation products in moderate yields. However, with substrates bearing electron-withdrawing groups, *ortho*-CF$_3$ acetanilides or anilines were obtained as sole products [59].

To meet high expectations of environmentally low impact chemical reactions, Lipshutz and co-workers carried out the trifluoromethylation of heterocycles using aqueous micellar conditions based on the surfactant TPGS–750–M in water at room temperature. The trifluoromethyl radical was generated from CF$_3$SO$_2$Na and *t*-BuOOH. In comparaison to Baran's
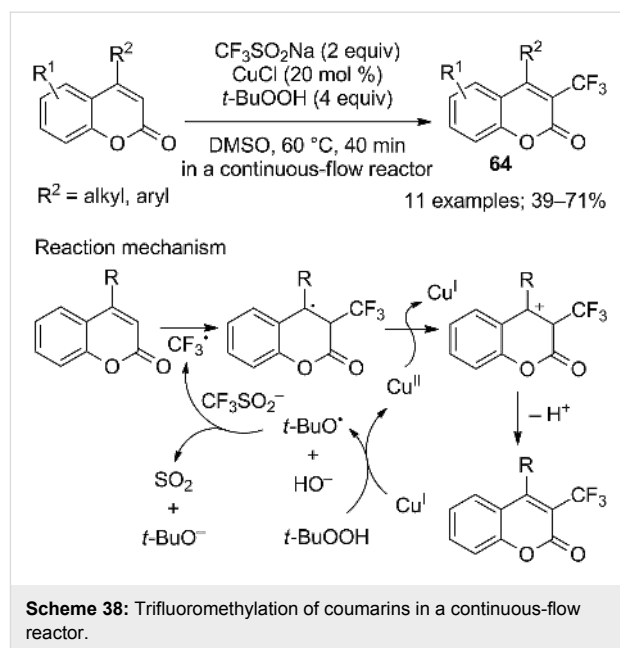
Scheme 36: Trifluoromethylation of acetanilides and anilines.
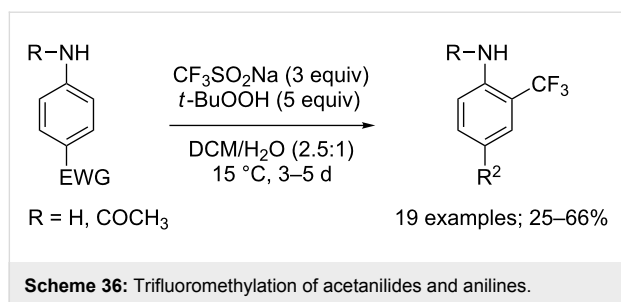
results, in all cases, the yields were improved. Advantageously, the aqueous medium can be recycled (Scheme 37) [60].

Scheme 37: Trifluoromethylation of heterocycles in water.
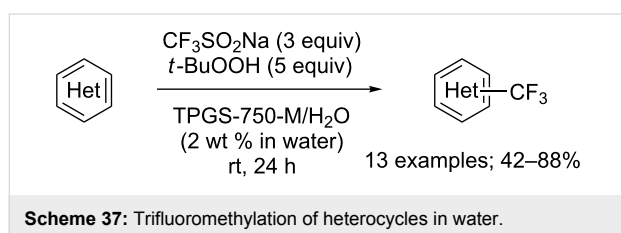
Even though it is a proven fact after 2011 and Baran's work that no-added metal trifluoromethylation with CF_3SO_2Na are highly efficient, the original Langlois' conditions were nevertheless applied to a series of heteroarenes. Li and co-workers reported the synthesis of 3-trifluoromethylcoumarins **64** by Cu(I)-catalysed trifluoromethylation with CF_3SO_2Na and *t*-BuOOH in a continuous-flow reactor [61]. After optimisation of the reaction conditions in batch, the optimal reaction conditions were established in a continuous-flow reactor at a flow rate of 100 µL min^{-1} at 60 °C for 40 min. The substrate scope was evaluated on 11 coumarins and showed that both electron-rich and electron-deficient functional groups were tolerated (Scheme 38).

Zou and co-workers applied the conditions described by Langlois or Baran (CF_3SO_2Na/*t*-BuOOH/cat. Cu(II) or CF_3SO_2Na/*t*-BuOOH, respectively) for the trifluoromethylation of coumarins but no reaction was observed. By testing other oxidants, they found that Mn(OAc)$_3$ was a good oxidant for this reaction and allowed to carry out the trifluoromethylation exclusively at the α-position of the carbonyl group in the pyranone ring. The substrate scope was large and included 17 coumarins, 2 quinolines and 3 pyrimidinones. With coumarins bearing electron-donating groups on the phenyl ring, the 3-trifluoromethylated compounds were obtained in 50–56% yields. However, coumarins bearing electron-withdrawing groups gave yields up to 70%. As for the mechanism, the trifluoromethyl radical was generated from CF_3SO_2Na and Mn(OAc)$_3$, then CF$_3^•$ added regioselectively onto the coumarin to give intermediate radical **65**, which was oxidised by

Scheme 38: Trifluoromethylation of coumarins in a continuous-flow reactor.
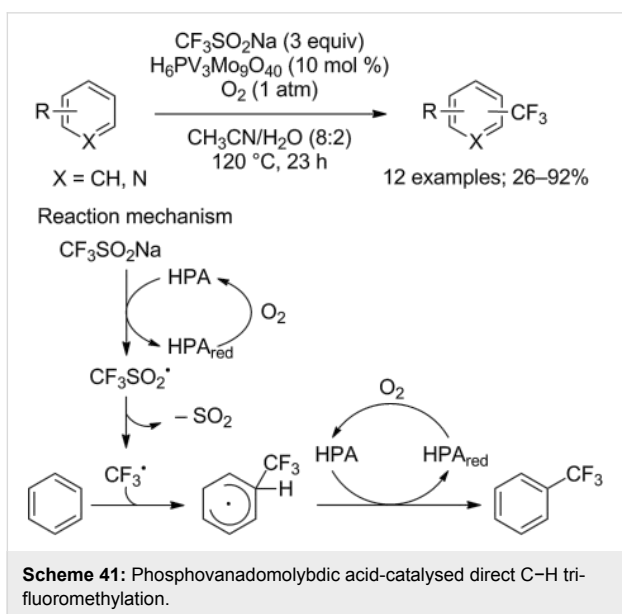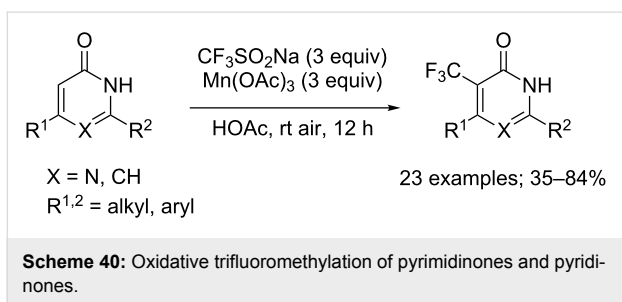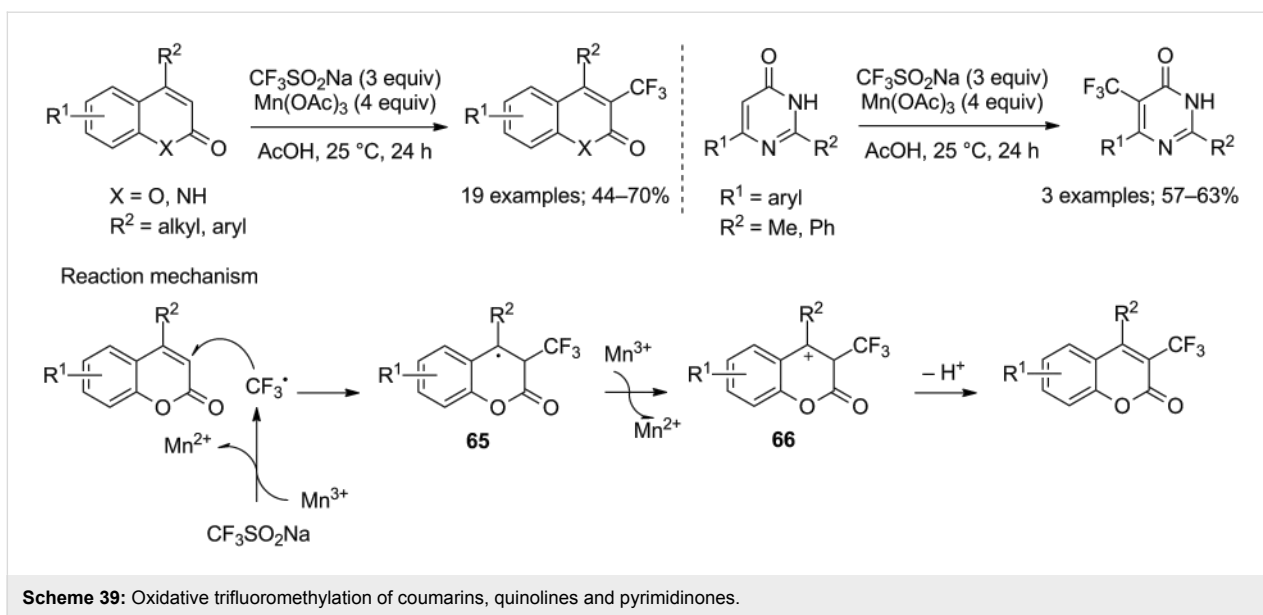
Mn(OAc)$_3$ to form the carbocation **66** and, after deprotonation, the trifluoromethyl compounds (Scheme 39) [62].

The same group also reported a straightforward method for the trifluoromethylation of pyrimidinones and pyridinones under the same reaction conditions. 5-Trifluoromethylpyrimidinones and 3-trifluoromethylpyridinones were selectively obtained in moderate to good yields (Scheme 40). It was observed that the substituent R^1 provided no stabilisation for the radical intermediate, so the less bulky substituents at 6-position of pyrimidinones or 4-position of pyridinones facilitated the trifluoromethyl radical attack [63].

Catalytic amounts of phosphovanadomolybdic acid, a heteropolyacid catalyst (HPA), was used by Mizuno, Yamaguchi and co-workers for the oxidative C−H trifluoromethylation of arenes and heteroarenes in the presence of CF_3SO_2Na and O$_2$ as the terminal oxidant. This method allowed the trifluoromethylation of arenes bearing electron-donating as well as electron-withdrawing groups in moderate to good yields (Scheme 41) [64]. It has to be noted that bis-CF$_3$ products as well as regioisomers were also characterised or detected in small amounts in most cases. A radical mechanism was proposed as described in Scheme 41.

Imidazopyridines have demonstrated many interesting features toward biological activities and the incorporation of a trifluoromethyl group into such architectures was expected to alter their properties. Therefore, Hajra and co-workers reported a direct and regioselective method for the trifluoromethylation of imidazopyridines **67** and other imidazoheterocycles **68** [65]. The
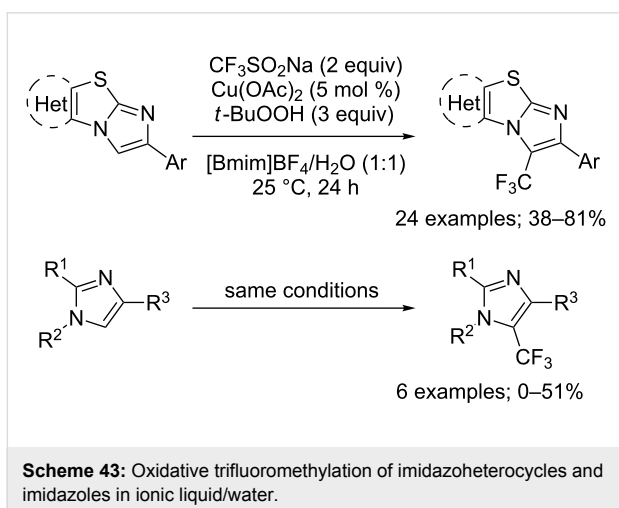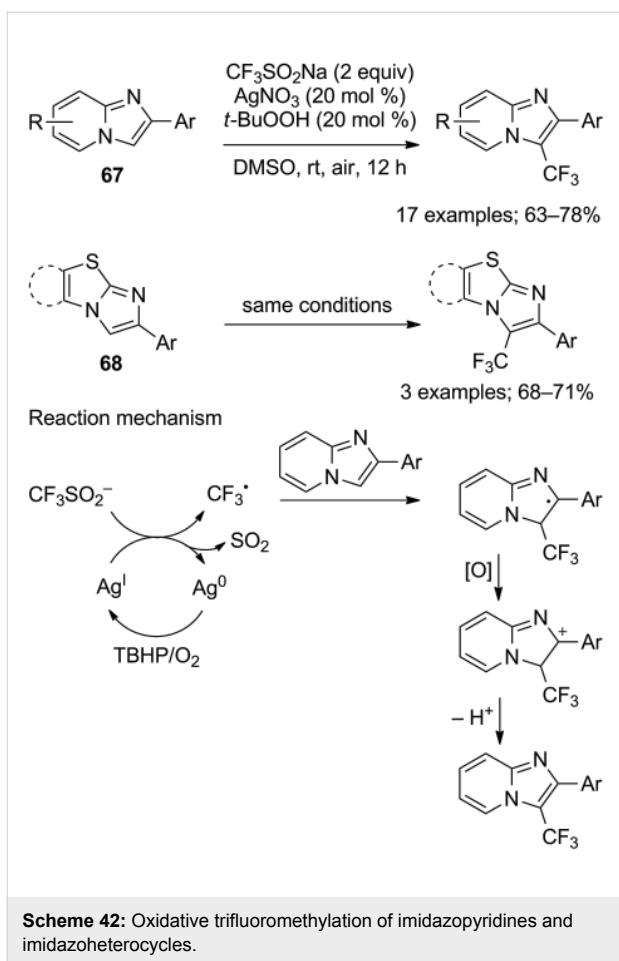
Scheme 39: Oxidative trifluoromethylation of coumarins, quinolines and pyrimidinones.

Scheme 40: Oxidative trifluoromethylation of pyrimidinones and pyridinones.

Scheme 41: Phosphovanadomolybdic acid-catalysed direct C−H trifluoromethylation.

combination CF_3SO_2Na/t-BuOOH/cat. $AgNO_3$ at room temperature under air was applied to 17 imidazopyridines and 3 imidazoheterocycles (Scheme 42). Good yields were obtained when

the phenyl moiety was substituted by electron-donating groups. As a result of absence of reactivity in presence of the radical scavenger TEMPO, a radical pathway was proposed. Under argon atmosphere, only trace amounts of the CF_3 product were obtained clearly indicating the crucial role of aerial oxygen in the catalytic cycle (see mechanism in Scheme 42).

Simultaneously, Tang and co-workers reported a greener strategy for the trifluoromethylation of imidazoheterocycles with CF_3SO_2Na in a recyclable mixed medium of 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) and water [66]. The substrate scope was investigated on 11 imidazothiazoles, 13 imidazo[1,2-*a*]pyridines and 6 imidazoles (Scheme 43). The reaction was simple, achieved at room temperature and had a good tolerance for various functional groups. However, for the trifluoromethylation of imidazoles, it was essential to have a phenyl as a substituent in order to get good yields. A radical mechanism was proposed but the role of oxygen was not discussed.

Aminoquinoline derivatives are found in naturally occurring and synthetic bioactive compounds, most notable for their antimalarial activity. So, it was not surprising that trifluoromethyl analogues were prepared in particular by means of CF_3SO_2Na. Indeed, 5-trifluoromethyl-8-aminoquinoline derivatives **69** were regioselectively synthesised under various reaction conditions. Cai and co-workers reported the trifluoromethylation of 8-aminoquinolines selectively at position 5 by using CF_3SO_2Na, $CuBr_2$ in a catalytic amount and azobisisobutyronitrile (AIBN) as an oxidant (Scheme 44) [67]. This process had a broad tolerance toward a wide range of functional groups. Aliphatic amides, aromatic amides and carboxamides with hetero-

Scheme 42: Oxidative trifluoromethylation of imidazopyridines and imidazoheterocycles.

Scheme 43: Oxidative trifluoromethylation of imidazoheterocycles and imidazoles in ionic liquid/water.
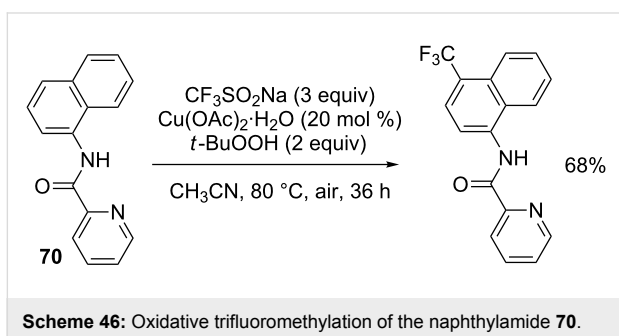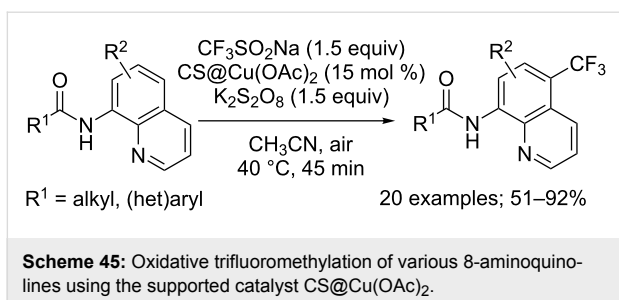
cyclic substituents were compatible with the reaction conditions. A series of control experiments that included the inhibition of the reaction in the presence of TEMPO, deuteration and isotope effect experiments were carried out and led the authors to propose the single-electron transfer mechanism presented in Scheme 44.

Scheme 44: Oxidative trifluoromethylation of 8-aminoquinolines.
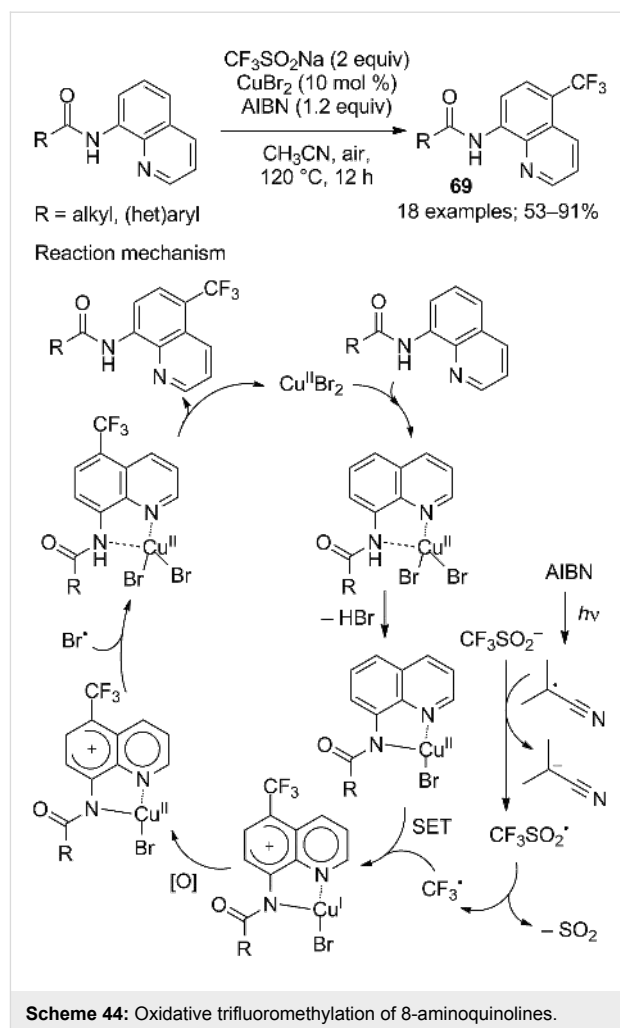
Simultaneously, Shen, Zhang and co-workers reported a milder regioselective trifluoromethylation of 8-aminoquinolines using the supported catalyst CS@Cu(OAc)$_2$ (CS = chitosan), potassium persulfate as the oxidant and CF$_3$SO$_2$Na as the CF$_3$• source (Scheme 45) [68]. After optimisation of the reaction conditions, the authors studied the effect of structural variations in the substrate (R^1 = aryl, heteroaryl, alkyl; R^2 = H, 6-OMe, 2-Me). Aniline amides gave no conversion nor did quinoline having an ester group at the 8 position instead of the 8-amino group. The chitosan-based copper catalyst was efficiently reused in five cycles of this heterogeneous trifluoromethylation.

In 2017, Lu, Weng and co-workers reported a protocol for the *para*-selective trifluoromethylation of naphthylamide **70**, instead of the previously studied quinolines, with CF$_3$SO$_2$Na, *tert*-butyl hydroperoxide and Cu(OAc)$_2$·H$_2$O as oxidant (Scheme 46) [69].

tert-Butyl hydroperoxide could be replaced by sodium persulfate as demonstrated in 2016 by Gong and co-workers who re-

Scheme 45: Oxidative trifluoromethylation of various 8-aminoquino-lines using the supported catalyst CS@Cu(OAc)$_2$.

Scheme 46: Oxidative trifluoromethylation of the naphthylamide **70**.

Scheme 47: Oxidative trifluoromethylation of various arenes in the presence of CF$_3$SO$_2$Na and sodium persulfate.

ported a direct C−H trifluoromethylation of arenes with CF$_3$SO$_2$Na in a mixture of water and acetonitrile (Scheme 47) [70]. Various trifluoromethylated arenes were obtained in moderate to excellent yields. However, to achieve high yields in this trifluoromethylation, one (or more) alkoxy group(s) must be present on the arenes in order to stabilise the free-radical intermediate (see mechanism in Scheme 47). Control experiments such as the trapping of the trifluoromethyl radical with the scavenger TEMPO or with benzoquinone were performed and a radical process was proposed. This mild and safe transformation had a good tolerance for various functional groups.

In 2013, Shibata and co-workers reported a transition-metal-free oxidative trifluoromethylation of arenes with CF$_3$SO$_2$Na and phenyliodine bis(trifluoroacetate) (PIFA) instead of *tert*-butyl hydroperoxide as the oxidant in hexafluoroisopropanol (HFIP) at room temperature [71]. In order to obtain good results for this transformation, it should be noted that the electron-donating nature of the aromatic substituents was a crucial point. In the case of unsymmetrical biaryl substrates, mixtures of regio-isomers at C4 and C5 were obtained (Scheme 48). In the reaction mechanism, PIFA played a dual role in the activation of the arene via a π-complex and in the generation of the CF$_3$ radical from CF$_3$SO$_2$Na.

More recently, Maruoka and co-workers reported the synthesis of trifluoromethylated coumarin **71** and flavone **72** with CF$_3$SO$_2$Na (2 equiv), the hypervalent iodine F$_5$-PIFA (pentaflu-orophenyliodine bis(trifluoroacetate)) (2 equiv) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.6 equiv). The

Scheme 48: Trifluoromethylation of electron-rich arenes and unsymmetrical biaryls with CF$_3$SO$_2$Na in the presence of PIFA.
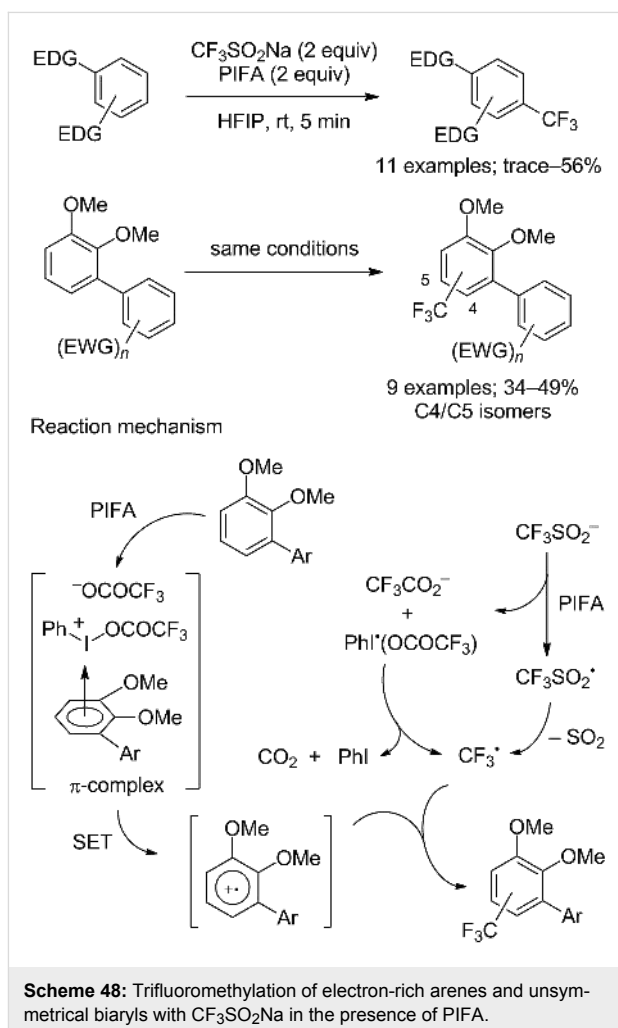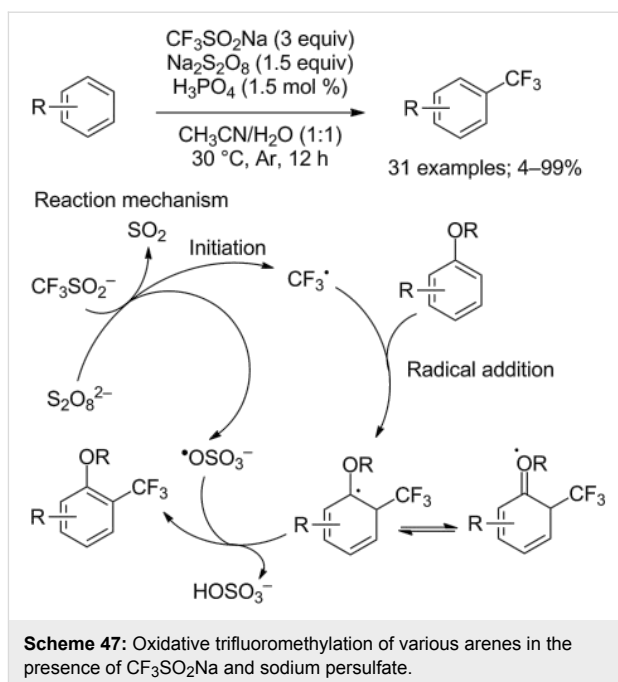
trifluoromethylated compounds were obtained in moderate yields (Figure 1) [50].

Figure 1: Trifluoromethylated coumarin and flavone.

coumarin **71**; 58%

flavone **72**; 29%
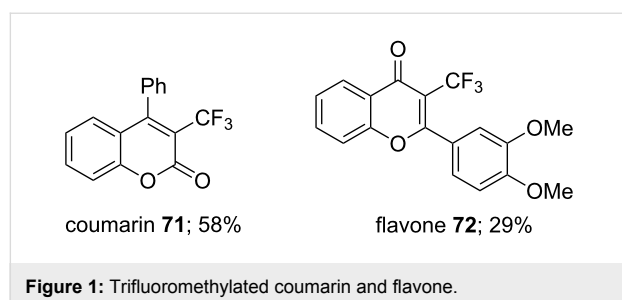
To avoid the use of transition-metal catalysts and/or an excess amount of oxidants, the Itoh group reported a simple metal-free, direct trifluoromethylation of arenes and heteroarenes using a photoredox-based process under visible-light irradiation. This method used CF_3SO_2Na as source of the trifluoromethyl group and a catalytic amount of anthraquinone-2-carboxylic acid (AQN-2-CO_2H). The scope was achieved on arenes and heteroarenes (10 examples). Once more, electron-rich aromatic compounds were converted into the corresponding trifluoromethylated products in good yields (Scheme 49). The oxidation–reduction potentials were determined by cyclic voltammetry and a catalytic cycle was proposed in which the CF_3 radical was generated from CF_3SO_2Na via the organocatalyst AQN-2-CO_2H and visible light (Scheme 49) [72].

**Scheme 49:** Metal-free trifluoromethylation catalysed by a photoredox organocatalyst.
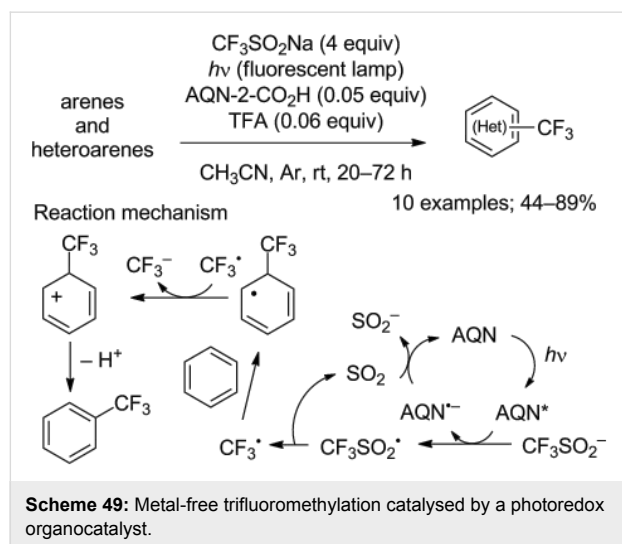
Rueping's group described three examples of prototypical (hetero)aromatic substrates that were trifluoromethylated with CF_3SO_2Na in the presence of 4,4'-dimethoxybenzophenone as photosensitiser under near-UV irradiation (350 nm) and HFIP as a proton donor [40]. More recently, Yuan and co-workers reported an efficient and operationally simple method for the

direct trifluoromethylation of a wide variety of arenes and heteroarenes under visible-light irradiation [73]. The substrate scope was evaluated on 30 arenes and heteroarenes using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as photocatalyst and CF_3SO_2Na as the CF_3 radical source. The reaction conditions tolerated a broad range of functional groups and the yields ranged from 31 to 68% (Scheme 50). During the process, the quinone was converted into hydroquinone and a regeneration process was established by passing through a cartridge of MnO_2. A mechanism for this transformation was proposed as a result of electron paramagnetic resonance spectroscopy experiments (Scheme 50).

Scheme 50: Quinone-mediated trifluoromethylation of arenes and heteroarenes.
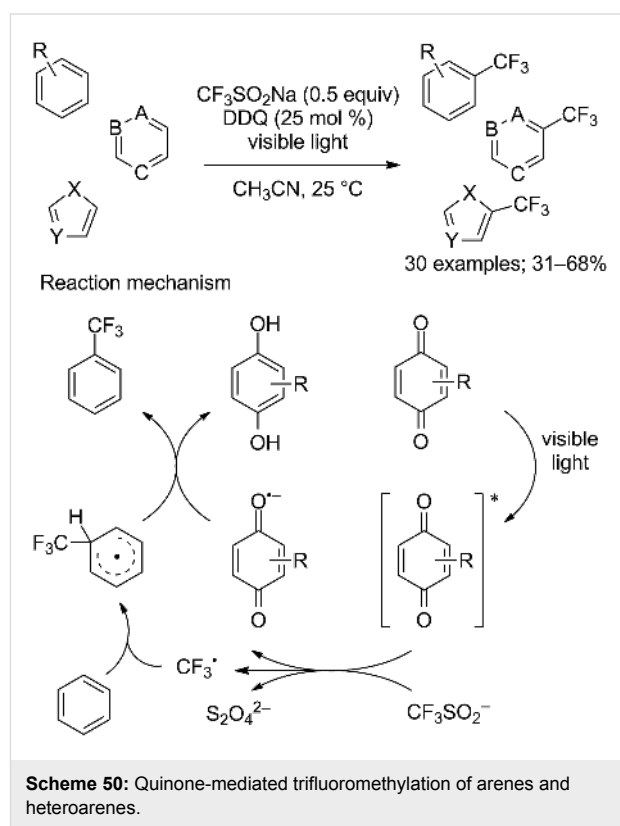
In 2016, Li, Mi and co-workers reported a simple and clean approach for the direct trifluoromethylation of unactivated arenes and heteroarenes through a photoreduction without any metal catalyst nor oxidant. The radical initiators were as simple as acetone or diacetyl for the generation of CF_3 radicals. Indeed, the authors demonstrated that photoexcited acetone was capable to trigger the trifluoromethylation reaction efficiently. So, acetone in this process was used as solvent and photosensitiser. The reactions were carried out under UV irradiation with either a 300 W xenon lamp (emission wavelengths between 200 and 1000 nm) or the photoreactor (λ = 254 nm). This photochemical process allowed the synthesis of trifluoromethylated arenes (Scheme 51), but also heteroarenes and nucleosides in good

yields [74]. Further to this work, it should be noted that Davies, MacMillan and co-workers have designed an integrated small-scale photoreactor that enabled acceleration of this photocatalytic reaction [75].


Scheme 51: Metal- and oxidant-free photochemical trifluoromethylation of arenes.
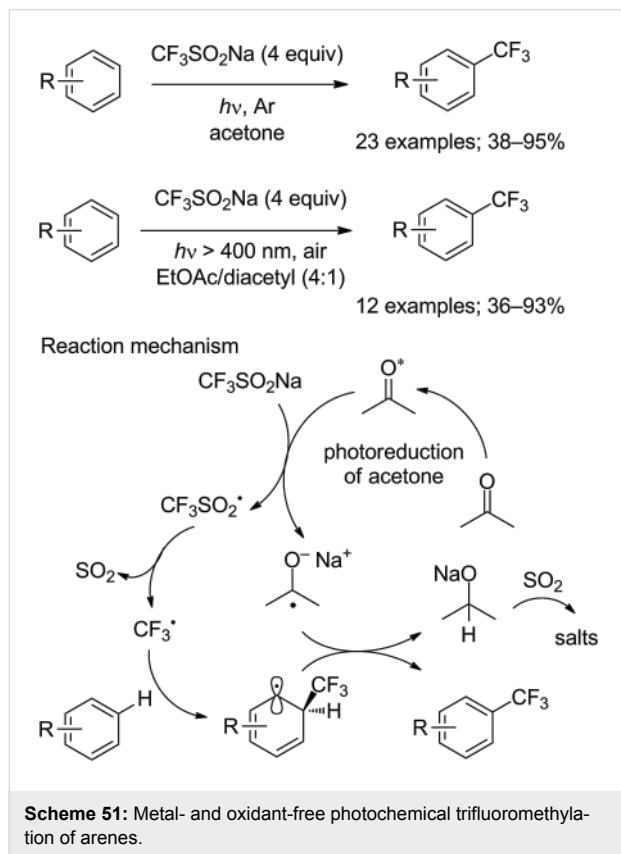
**Trifluoromethylation of arenediazonium compounds:** Langlois' conditions were applied in the copper-mediated Sandmeyer-type trifluoromethylation of aryldiazonium compounds. The scope of this reaction was investigated on 12 aryldiazonium compounds. The mild reaction conditions allowed the tolerance of various groups such as ester, aryl, nitrile, amine, ketone, nitro, sulfonate and bromo (Scheme 52). In this process, the CF_3 radical was stabilised by the presence of an excess amount of $CuBF_4(MeCN)_4$ and the tridentate ligand 2,2';6',2"-terpyridine (tpy) [76]. Notably, a change in the copper source caused the predominant trifluoromethanesulfonylation of the substrate (introduction of the SO_2CF_3 group, vide infra). A one-pot version starting from anilines was recently developed [77].

Trifluoromethylation of aryl-, vinyl-, alkynylboronic acids: In 2012, Sanford and co-workers reported, for the first time, the copper-mediated radical trifluoromethylation of aryl- and heteroarylboronic acids using CF_3SO_2Na and TBHP as an oxidant. The substrate scope was evaluated on 24 aryl and heteroaryl boronic acids. The process was compatible with

**Scheme 52:** Copper-mediated trifluoromethylation of arenediazonium tetrafluoroborates.
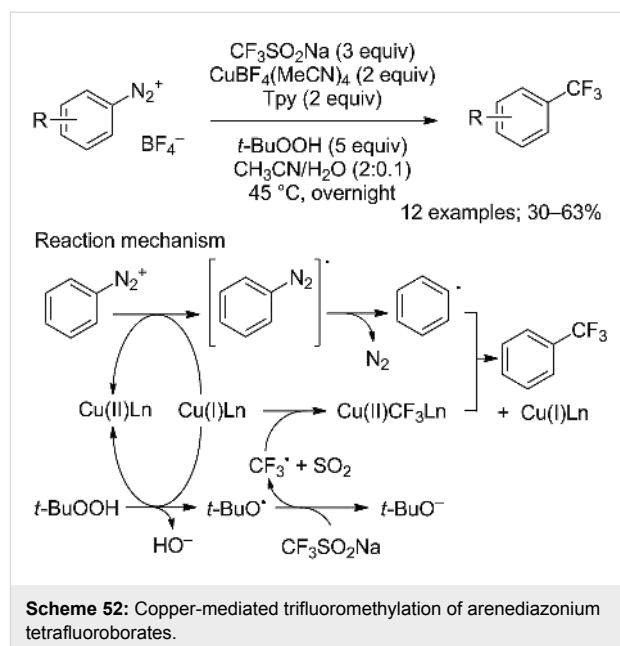
various functional groups. Arenes bearing electron-donating groups reacted in excellent yields under the CuCl-mediated conditions. However, arenes with electron-withdrawing substituents necessitated $(MeCN)_4CuPF_6$ and a base, $NaHCO_3$, to allow the trifluoromethylation to proceed in good yields (Scheme 53) [78].

Scheme 53: Oxidative trifluoromethylation of aryl- and heteroaryl-boronic acids.
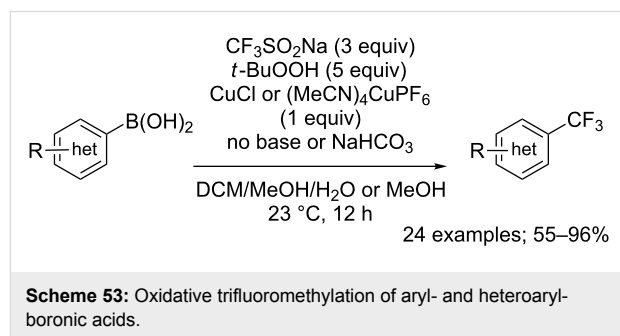
In the continuity of Sanford's work, Beller's group reported the synthesis of trifluoromethylated arenes from arylboronic acids as well as trifluoromethylated vinylarenes [79]. The substrate scope was realised on 17 arylboronic acids and 8 vinylboronic acids (Scheme 54). The protocol was robust and tolerated various functional groups. However, large excesses of both CF_3SO_2Na and TBHP were required. In this process, a ligand, 2,4,6-collidine, was used in order to increase the yield of the transformation. For the styrenylboronic acids, electron-withdrawing and electron-donating substituents on the aryl ring were compatible with the reaction conditions. Based on experimental observations, the authors proposed two possible mechanisms for this trifluoromethylation (Scheme 54). In path A,

transmetallation of the boronic acid with the active Cu(II) species **73** gave the arylcopper(II) complex **74**, which reacted with CF$_3^•$ to afford the arylcopper(III) complex **75**. Next, a reductive elimination gave the trifluoromethylated product with release of the Cu(I) complex **76** that was re-oxidised to the active copper(II) catalyst **73** to close the cycle. In path B, the copper(II) complex **73** reacted with CF$_3^•$ to form the copper(III) complex **77**, which after transmetallation with the boronicacid gave the same intermediate **75**.

Scheme 54: Oxidative trifluoromethylation of aryl- and vinylboronic acids.
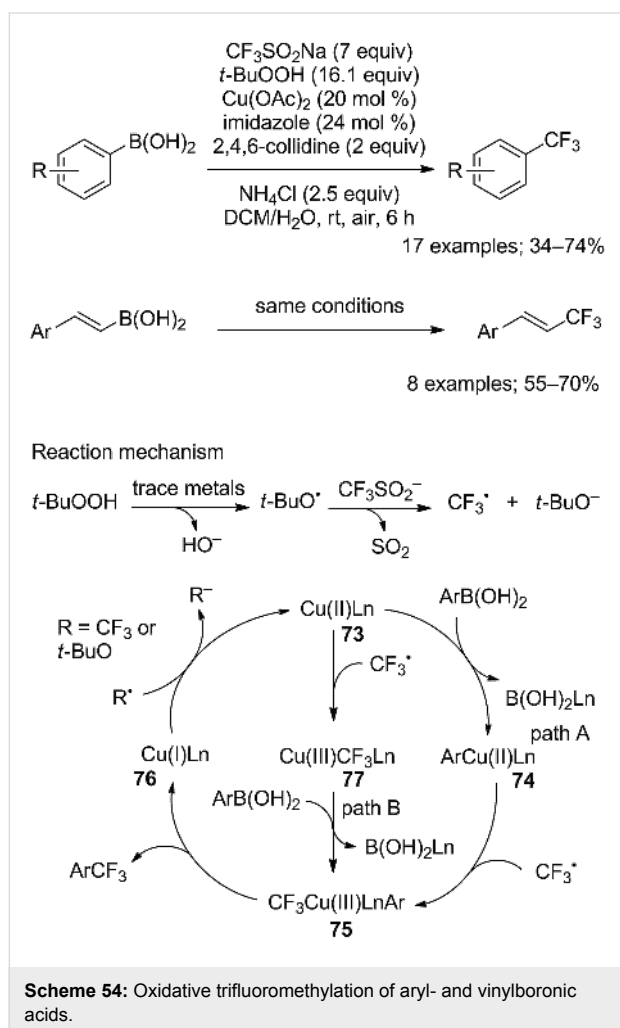
Trifluoromethylation of potassium organotrifluoroborates: In 2013, Molander, Rombouts and co-workers simply applied the reaction conditions described by Sanford for boronic acids to a series of unsaturated potassium organotrifluoroborates (Scheme 55) [80]. In the case of aryl- and heteroaryltrifluoroborates, electron-rich substrates were efficiently trifluoromethylated although the increase of the steric hindrance caused a decrease in yields. On the other hand, the yields obtained with electron-poor potassium organotrifluoroborates were lower. In the same paper, the preparation of trifluoromethyl-substituted

alkynes and alkenes from alkynyl- and alkenyltrifluoroborates was demonstrated albeit in moderate yields. The yields of the trifluoromethylation of alkenyltrifluoroborates strongly depended on the substitution of the olefin (Scheme 55).


Scheme 55: Oxidative trifluoromethylation of unsaturated potassium organotrifluoroborates.
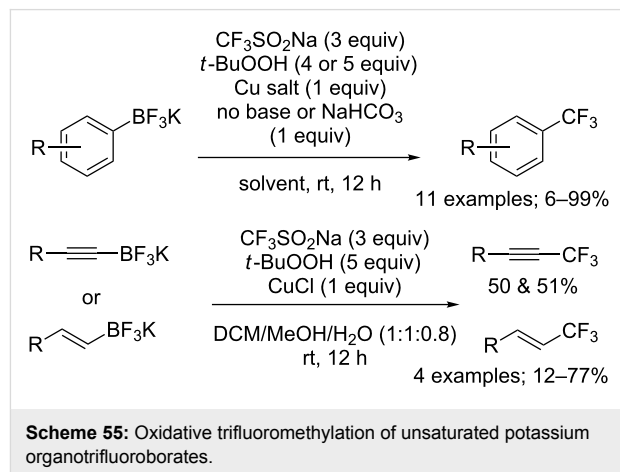
Simultaneously, Dubbaka and co-workers reported the trifluoromethylation of aryl-, heteroaryl-, and vinyltrifluoroborates with CF$_3$SO$_2$Na (Scheme 56) [81]. The authors used basically the same protocol as Sanford and Molander but observed that a more diluted reaction medium gave improved reaction yields.

Scheme 56: Oxidative trifluoromethylation of (hetero)aryl- and vinyltrifluoroborates.
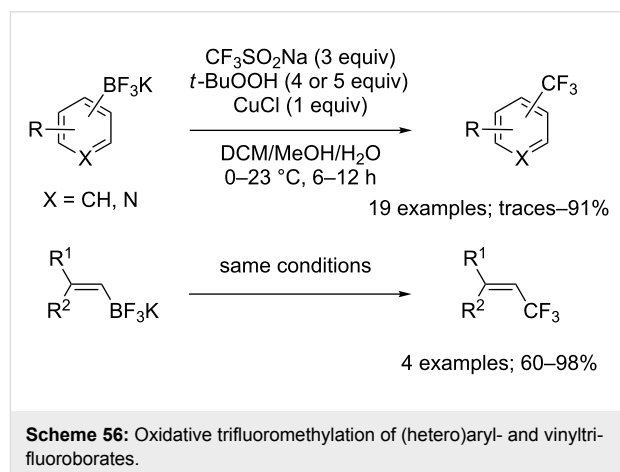
Trifluoromethylation of alkenes by decarboxylation: Liu and co-workers were the first to describe the copper-catalysed decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids in the presence of CF$_3$SO$_2$Na and TBHP [82]. Various (hetero)arenes were compatible with these reaction conditions (Scheme 57); nevertheless, cinnamic acids bearing electron-donating groups afforded the corresponding products in better yields. The stereoselectivity was moderate to high from 76:24 to 99:1. Interestingly, aryls bearing a nitro or a chloro substituent gave the corresponding α-trifluoromethyl ketones.

This process was interesting for the construction of C_{vinyl}–CF_3 bonds via a radical addition–elimination (Scheme 57).

Scheme 57: Copper–catalysed decarboxylative trifluoromethylation of cinnamic acids.
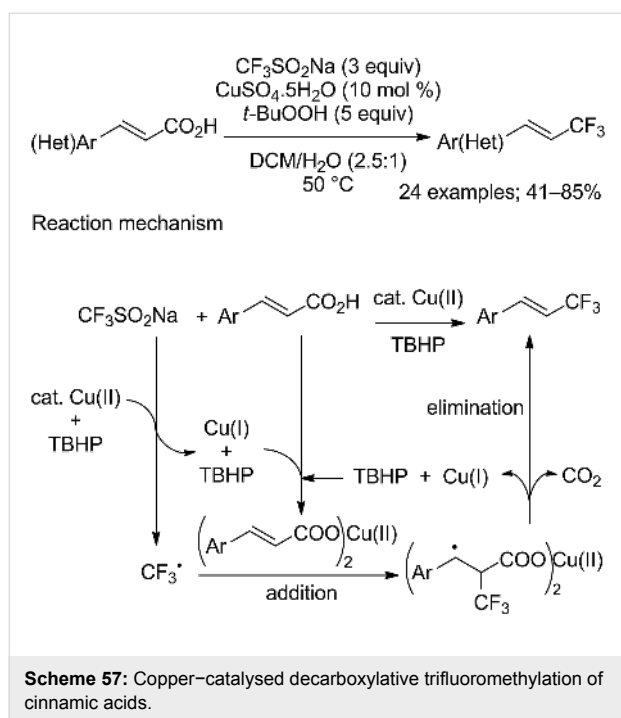
Soon after, Maiti and co-workers reported an iron-mediated trifluoromethylation of α,β-unsaturated carboxylic acids with CF_3SO_2Na, iron(III) chloride and potassium persulfate as oxidant [83]. The substrate scope was evaluated on 10 cinnamic acids (Scheme 58). Under these conditions, both electron-rich or electron-poor arenes gave the vinylic CF_3 products in good yields and with excellent stereoselectivities. A mechanism was proposed starting from the generation of iron carboxylate and the reaction with the CF_3 radical followed by extrusion of CO_2 and radical coupling (Scheme 58).

Two major drawbacks appeared in the above-mentioned works: halo-substituted aryl derivatives failed to give the expected products and α,β-unsaturated carboxylic acids substituted at the β-position were not studied. Accordingly, Li, Duan and co-workers reported a copper/silver-catalysed decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids with CF_3SO_2Na that tolerated various substrates bearing halogens as well as α,β-unsaturated carboxylic acids substituted at the β-position (Scheme 59) [84]. It was even noticed that β-methyl or β-phenyl-substituted cinnamic acids gave better yields compared to unsubstituted cinnamic acid. All products were obtained with excellent stereoselectivity. To gain insight about the mechanism, the authors used TEMPO as a radical scavenger and concluded that CF_3 radical was involved in this reaction (Scheme 59).

Scheme 58: Iron-mediated decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids.

Scheme 59: Cu/Ag-catalysed decarboxylative trifluoromethylation of cinnamic acids.
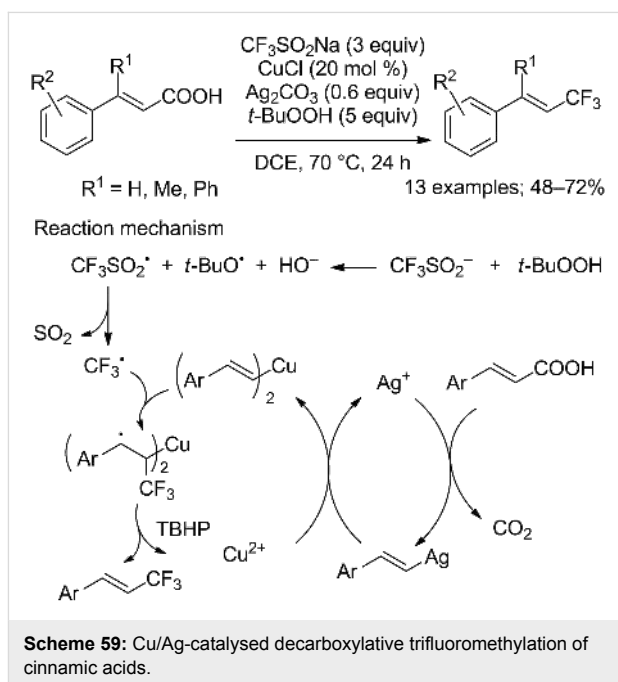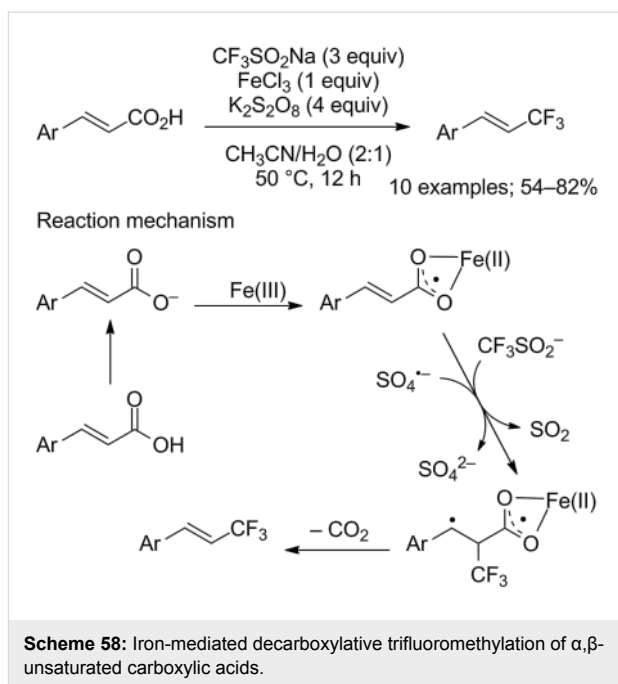
A metal-free protocol for the decarboxylative trifluoromethylation of cinnamic acids with CF_3SO_2Na was reported by Shang, Liu and co-workers using iodine pentoxide (I_2O_5) as oxidant. The substrate scope was evaluated on 9 α,β-unsaturated carboxylic acids substituted by electron-rich aryls (Scheme 60) [85]. The mild conditions gave the trifluoromethylated products in excellent yields with high stereoselectivities. Nevertheless, the reaction conditions did not allow the formation of products with electron-withdrawing substituents on the aromat-

ic ring, such as the nitro group. The case of halogen-substituted cinnamic acids was not studied. Finally, mechanistic studies conducted by electron-spin resonance and by spin trapping technology suggested a free-radical addition– elimination process (Scheme 60).


Scheme 60: I$_2$O$_5$-Promoted decarboxylative trifluoromethylation of cinnamic acids.
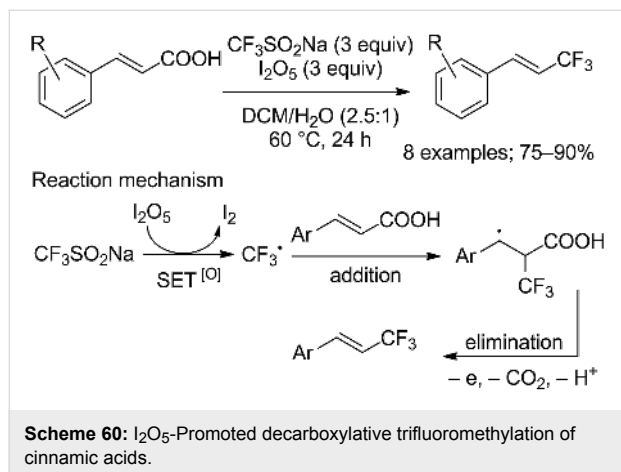
Trifluoromethylation of alkenes by denitration: Another route to the C$_{vinyl}$–CF$_3$ bond is the denitrative trifluoromethylation of β-nitrostyrenes. More generally, this transformation has attracted much attention as a useful method for the construction of C$_{vinyl}$–R moieties. In 2016, Li, Duan and co-workers reported this trifluoromethylation by means of CF$_3$SO$_2$Na catalysed by silver nitrate in the presence of a large excess of di-*tert*-butyl peroxide (DTBP) as the oxidant and tetrabutylammonium iodide (TBAI) as a phase-transfer catalyst (Scheme 61) [86]. The substrate scope was evaluated on 16 β-nitrostyrenes and substrates bearing electron-donating groups as well as halides afforded the corresponding trifluoromethylstyrenes in moderate to good yields. However, the substrates with electron-withdrawing groups (CN, NO$_2$) led to trifluoromethylated products in poor yields. This transformation was highly stereoselective, only (*E*)-isomers of the products were obtained. Experiments in the presence of 1,1-diphenylethylene as a radical scavenger led the authors to propose a radical process for the trifluoromethylation as described in Scheme 61.

Trifluoromethylation of styrene derivatives: An obviously simple route for the synthesis of trifluoromethylated styrene derivatives is the direct C–H trifluoromethylation of alkenes. Very recently, Shen, Loh and co-workers reported a copper-catalysed direct trifluoromethylation of the vinylic C$_{sp2}$–H bond of styrene derivatives with CF$_3$SO$_2$Na, di-*tert*-butyl peroxide, 10 mol % of copper(I) iodide, 1-methylimidazole (NMI) as ligand to copper and tetrabutylammonium iodide (TBAI) as additive (Scheme 62) [87]. The mild reaction conditions allowed a wide variety of functional groups to be tolerated and afforded a

Scheme 61: Silver(I)-catalysed denitrative trifluoromethylation of β-nitrostyrenes.
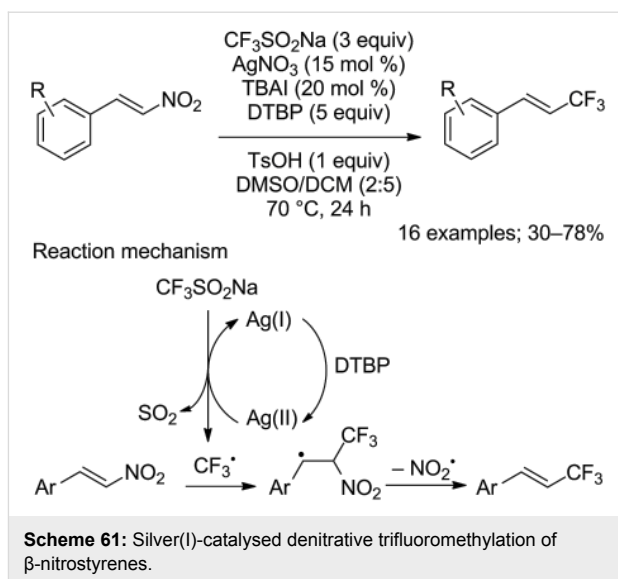
series of trifluoromethylated styrenes in moderate to good yields and with excellent stereoselectivity. However, aliphatic alkenes or styrenes bearing electron-withdrawing groups were not suitable for this reaction. Based on control experiments, the authors proposed a radical pathway for this reaction (Scheme 62).


Scheme 62: Copper-catalysed direct trifluoromethylation of styrene derivatives.
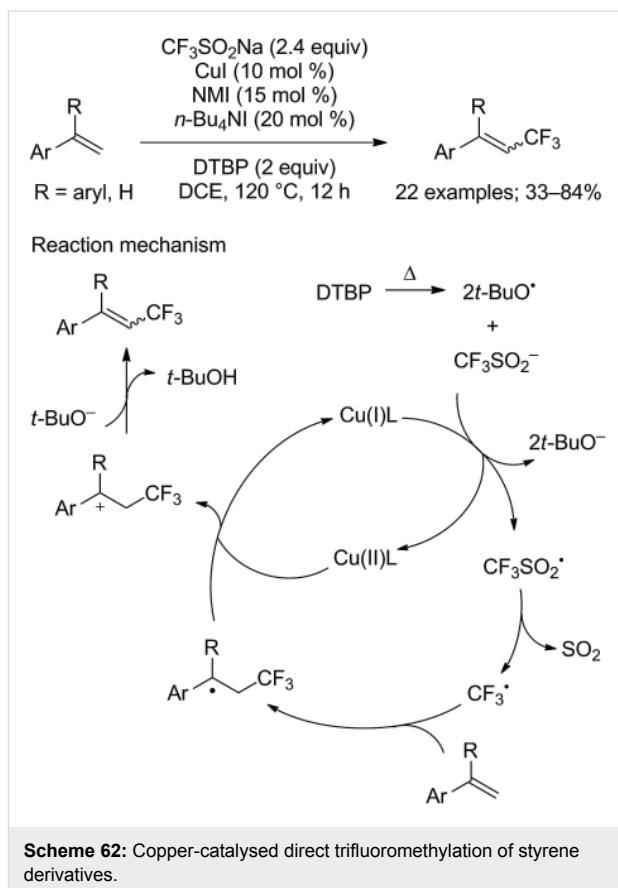
Trifluoromethylation of enamines: Highly functionalised alkenes represented by (*Z*)-methyl-3-(phenylamino)acrylates **78** were subjected to Baran's conditions for the synthesis of β-trifluoromethylated enamines. Indeed, Jiang, Wu and co-workers reported mild, transition-metal-free conditions, insensitive to air and water, for the synthesis of a wide range of CF$_3$-enamines using CF$_3$SO$_2$Na and TBHP as initiator and oxidant (Scheme 63) [88]. Moderate to good yields were obtained and only (*E*)-isomers were observed. The authors carried out several experiments such as the use of TEMPO or 2,6-di-*tert*-butyl-4-methylphenol (BHT) as scavengers in order to investigate the mechanism of this reaction (Scheme 63).
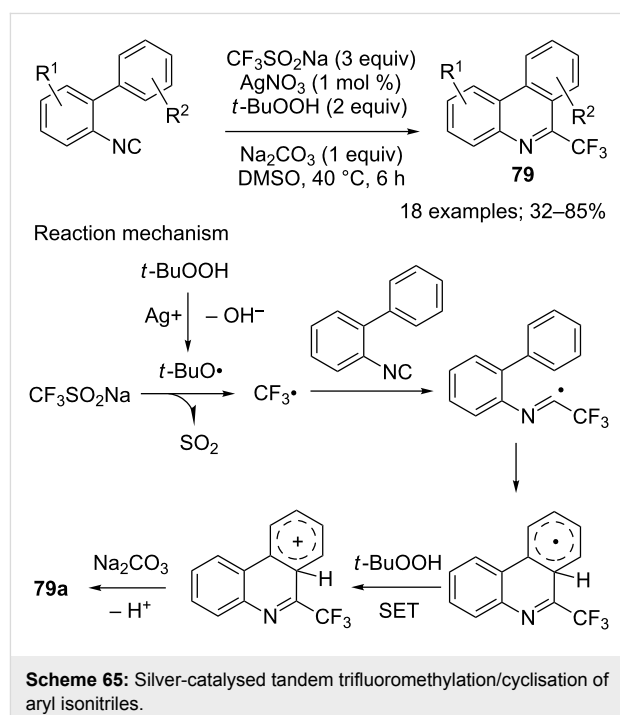

Scheme 63: Transition-metal-free synthesis of β-trifluoromethylated enamines.
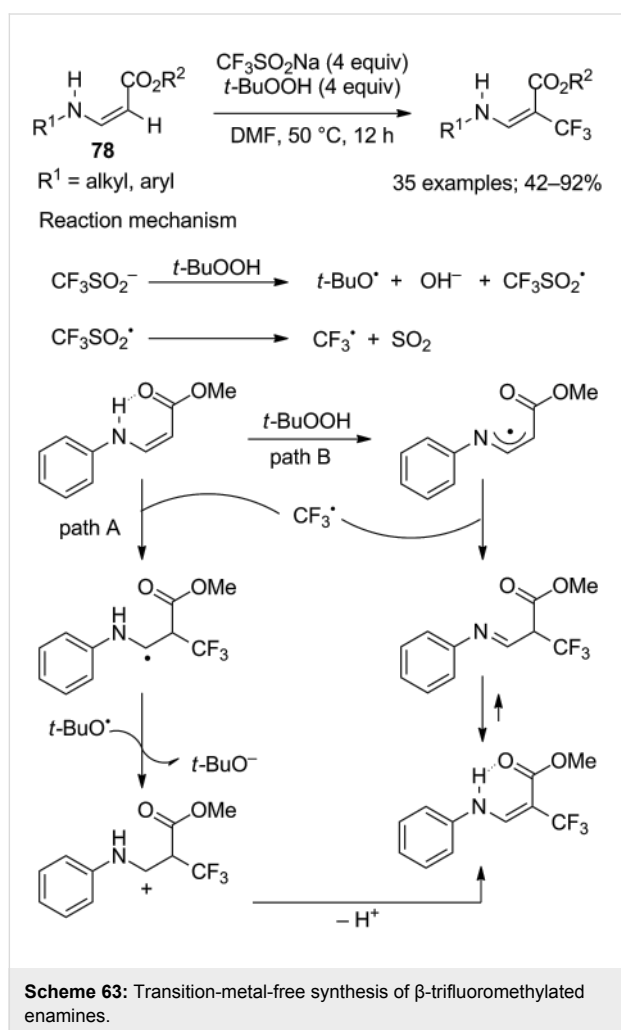
Trifluoromethylation of alkynes: Together with the iodotrifluoromethylation of alkenes leading to C$_{sp3}$–CF$_3$ products (see Scheme 22), the Liu group extended the free-radical iodotrifluoromethylation to alkynes with the combination of CF$_3$SO$_2$Na/ I$_2$O$_5$ and assistance of NaHCO$_3$ (Scheme 64) [42]. The substrate scope was carried out on various aryl-substituted alkynes and one propargylic ester; (*E*)-CF$_3$ alkenyl iodides were ob-

tained stereoselectively in moderate to high yields via a free-radical process.
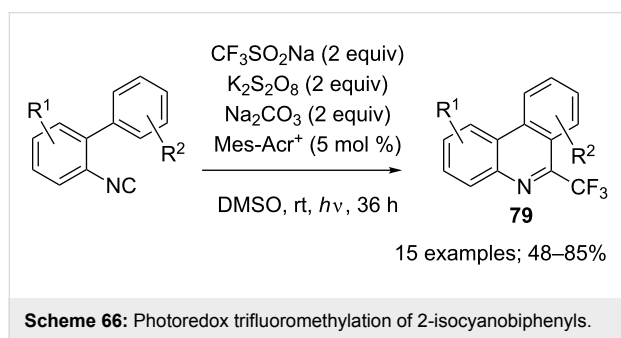

Scheme 64: I$_2$O$_5$-mediated iodotrifluoromethylation of alkynes.
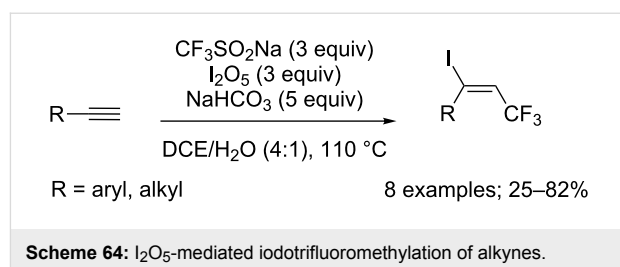
Trifluoromethylation of isonitriles: The synthesis of trifluoromethylated phenanthridines **79** from aryl isonitriles has been the recent subject of several investigations as potential structural unit in pharmaceuticals. In this context, CF$_3$SO$_2$Na was used by Zhang and co-workers in a silver-catalysed tandem trifluoromethylation and cyclisation of aryl isonitriles (Scheme 65) [89]. A wide variety of aryl isocyanides were transformed into the corresponding phenanthridines in moderate to good yields; some regioisomers were obtained depending on the biphenyl substituents. Here again, a radical pathway was established for this transformation (Scheme 65).

Scheme 65: Silver-catalysed tandem trifluoromethylation/cyclisation of aryl isonitriles.

Simultaneously, Lu and co-workers reported a transition-metal-free synthesis of the trifluoromethylphenanthridine **79a** in 58% yield using the system CF$_3$SO$_2$Na/K$_2$S$_2$O$_8$/K$_2$CO$_3$ in H$_2$O/ CH$_3$CN at 80 °C [90]. In addition, Maruoka and co-workers used the system CF$_3$SO$_2$Na/PIFA/AcONa in AcOEt at room

temperature for 1.5 h to get **79a** in 74% yield [50]. Mid 2017, Ao, Liu and co-workers exploited the reaction conditions developed previously for the photoredox trifluoromethylation of vinyl azides (see Scheme 8) in the synthesis of fluorinated phenanthridines **79**. The yields were moderate to good and regioselectivity issues appeared depending on the biphenyl substituents (Scheme 66) [91].

with a wide variety of functionalised nitrosoarenes and the corresponding trifluoromethylated hydroxylamines **83** were obtained in moderate to good yields (Scheme 68). The authors proposed a radical mechanism with two pathways for the generation of the CF_3 radical, either by copper species or by *tert*-BuO• (Scheme 68). Interestingly, N–CF_3 anilines were easily obtained after reduction of the N–O bond.

Scheme 66: Photoredox trifluoromethylation of 2-isocyanobiphenyls.

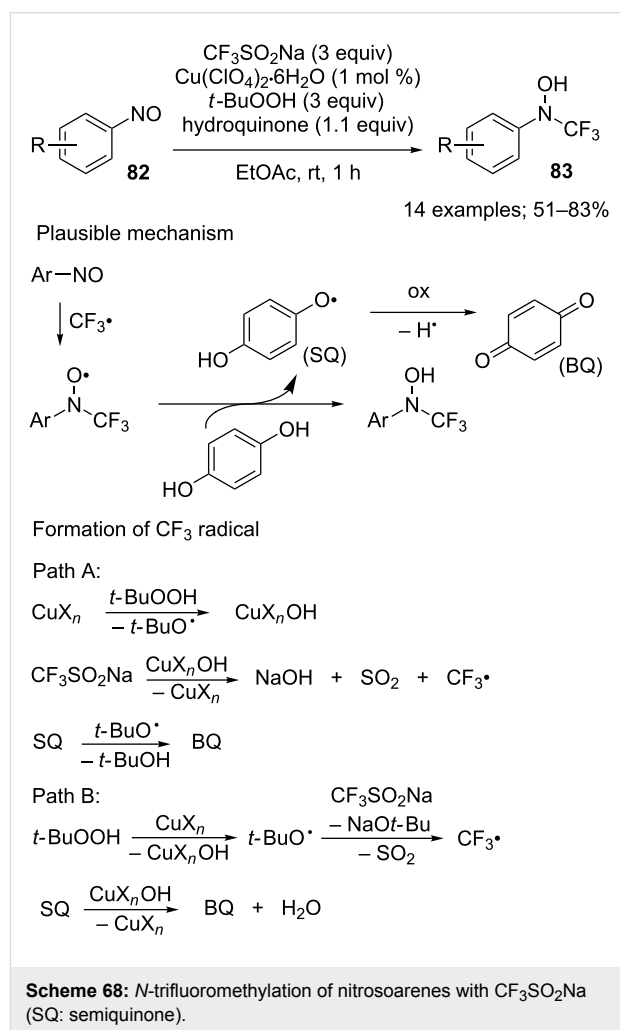## C_{sp}–CF_3 bond-forming reactions

For the synthesis of trifluoromethylacetylenes **81**, a copper-mediated trifluoromethylation of potassium alkynyltrifluoroborates **80** with CF_3SO_2Na was developed by Dubbaka and co-workers (Scheme 67) [92]. The scope was large including aryl, heteroaryl, alkenyl, and aliphatic alkynyltrifluoroborates and the yields were moderate. Mechanistically, the CF_3 radical was generated under Langlois' conditions by means of *tert*-butyl hydroperoxide and CuCl.

Scheme 67: Trifluoromethylation of potassium alkynyltrifluoroborates with CF_3SO_2Na.
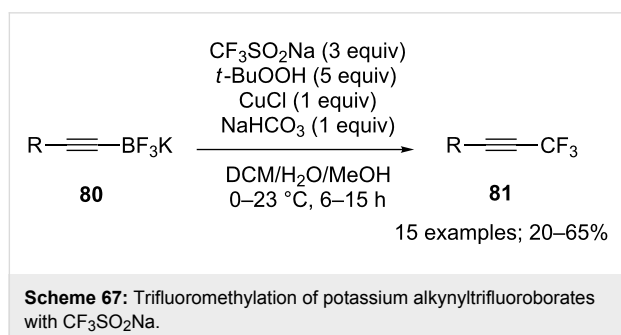
N–CF_3 bond-forming reactions

C-, O-, and S-trifluoromethylated compounds are common in the field of biologically active molecules unlike the N–CF_3 motif despite the huge number of nitrogen-containing pharmaceuticals. In 2017, Selander and co-workers reported a chemoselective *N*-trifluoromethylation of nitrosoarenes **82** in the presence of CF_3SO_2Na, a catalytic amount of copper(II), *tert*-butyl hydroperoxide as oxidant and hydroquinone as additive [93]. No reaction was observed in the absence of the copper salt. The scope was evaluated on 14 nitrosoarenes featuring electron-poor and electron-rich groups. The reaction conditions were suitable

Scheme 68: *N*-trifluoromethylation of nitrosoarenes with CF_3SO_2Na (SQ: semiquinone).

S–CF_3 bond-forming reactions

Synthetic routes to trifluoromethylthiolated compounds are diverse, one is the S–CF_3 bond formation (see next section for C–SCF_3 bond formation). For this purpose, Langlois and co-workers used aliphatic and aromatic disulfides, RS–SR, which reacted with CF_3SO_2Na in the presence of an oxidant, *t*-BuOOH providing the best yields, to afford the trifluoromethyl thioethers (Scheme 69a) [20]. Other oxidants such as $K_2S_2O_8$ and $(NH_4)_2Ce(NO_3)_6$ displayed lower reactivity and selectivity. Only one sulfenyl moiety of the disulfide was trifluoromethylated in this approach, the second being oxidised without trifluoromethylation. Aryl disulfides exhibited a lower

reactivity and selectivity because side radical aryl C–H tri-fluoromethylation occurred competitively. This approach was applied to the synthesis of *S*-trifluoromethyl-containing amino acids **85** from dithio-amino acids **84** (Scheme 69b) [94].

Scheme 69: Trifluoromethylation of disulfides with CF_3SO_2Na.
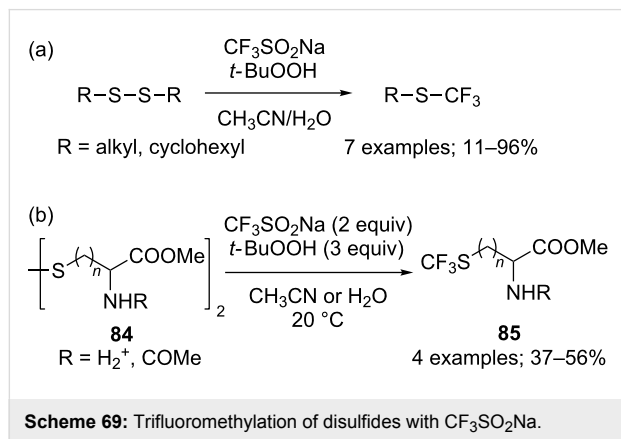
Apart from disulfides, thiols were also used as substrates by Yi and co-workers to produce several trifluoromethyl thioethers and aliphatic trifluoromethylthiols. Their contribution was inspired by the previous work of Liu, using iodine pentoxide as an inexpensive inorganic oxidant [42] to generate the CF_3 radical and release of iodine, which then reacted with the thiol to first form the corresponding disulfide **86** (detected as reaction intermediate) and further the sulfenyl iodide **87**. The final SCF_3 product was the result of the reaction of $CF_3^\bullet$ with either **86** or/and **87** (Scheme 70) [95]. The reaction performed well only at high reaction temperature (110 °C) for both thiophenols, benzylthiols and mercapto derivatives. The same research group recently reported different reaction conditions to obtain the same SCF_3 products by means of CF_3SO_2Na in the presence of potassium persulfate and a catalytic amount of silver nitrate at 80 °C in acetonitrile and water [96].
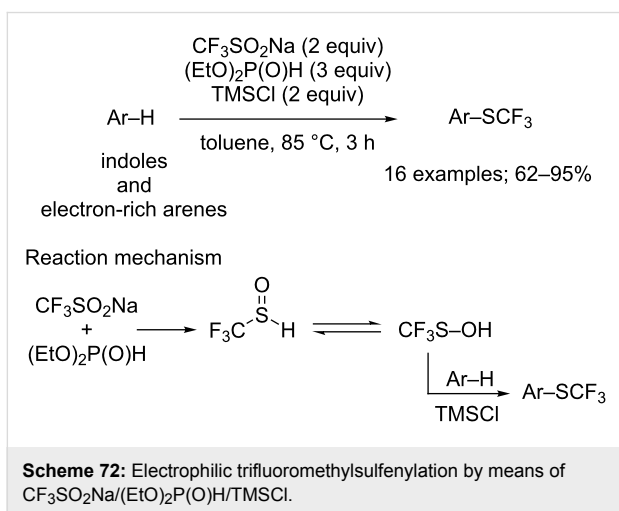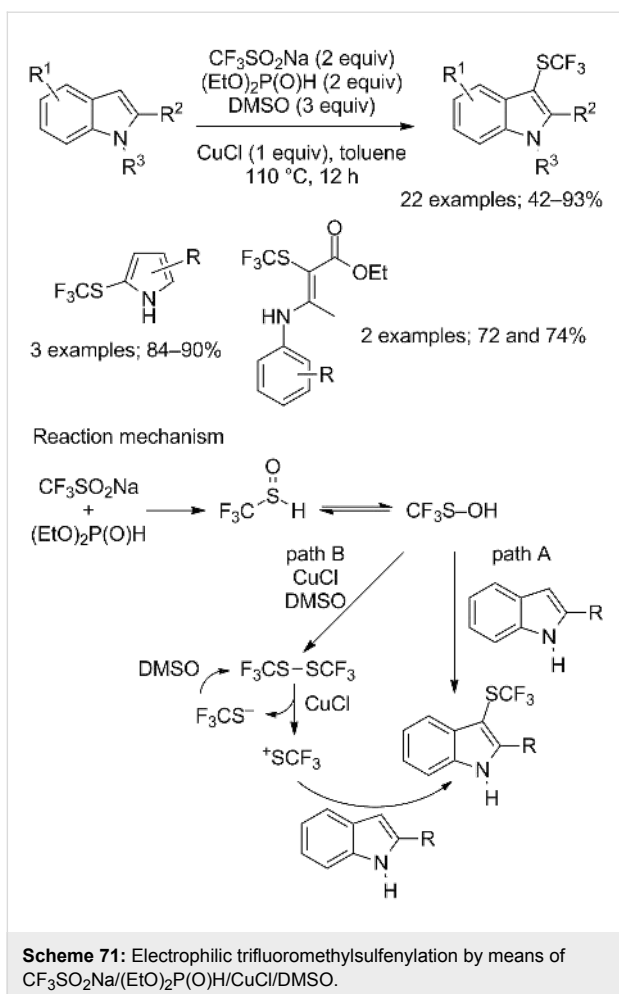
2 Trifluoromethylsulfenylation

In the early development of the direct electrophilic trifluoromethylthiolation, trifluoromethanethiol (CF_3SH), trifluoromethanesulfenyl chloride (CF_3SCl), and bis(trifluoromethyl) disulfide (CF_3SSCF_3) were the only reagents available, but their gaseous and toxic nature precluded a wider use. Fortunately, in the recent years, a collection of stable and easy-to-handle reagents was designed to perform efficient trifluoromethylthiolations [97]. Less sophisticated and suitable for large scale industrial use, CF_3SO_2Na was first used in trifluoromethylthiolation reactions in 2015 by Yi, Zhang and co-workers who reported the direct copper-catalysed trifluoromethylthiolation of indoles, pyrroles as well as enamines in the presence of $(EtO)_2P(O)H$ as reductant, CuCl and DMSO in toluene at 110 °C (Scheme 71) [98]. Unlike its use in trifluoromethylation
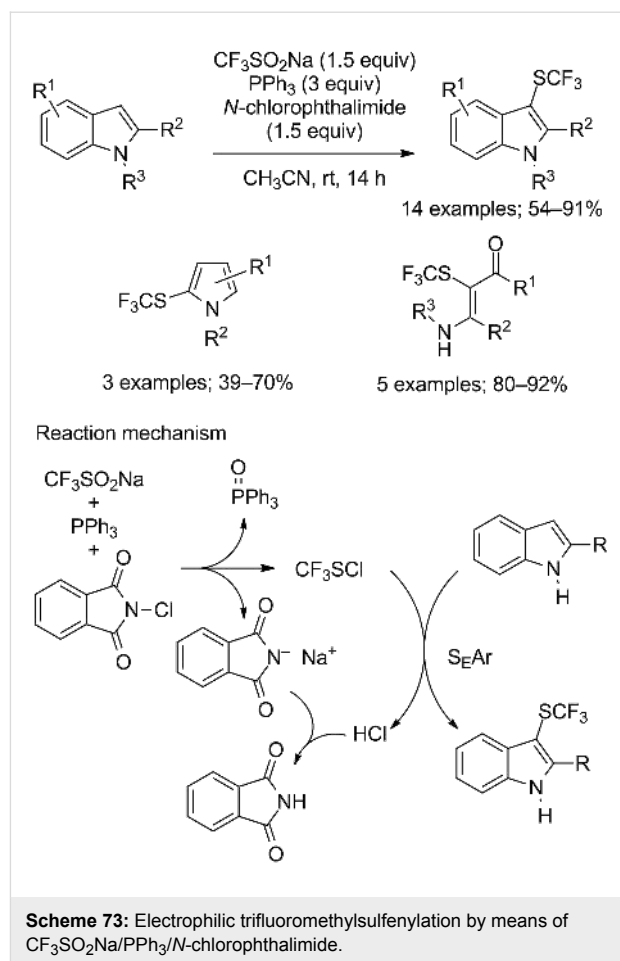

Scheme 70: Trifluoromethylation of thiols with CF_3SO_2Na/I_2O_5.
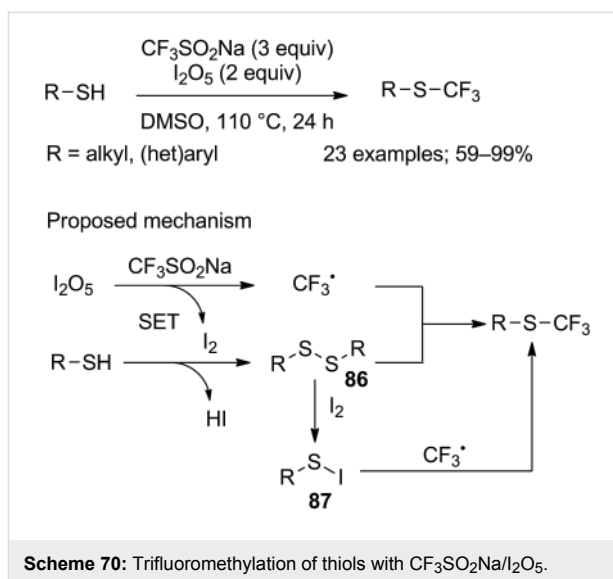
reactions, here, no extrusion of SO_2 ocurred from CF_3SO_2Na thus allowing the transfer of the SCF_3 motif. Under these reaction conditions, indoles bearing an electron-donating group gave better yields compared to those with electron-rich groups. Using the same protocol, the trifluoromethylsulfenylated pyrroles and enamines were obtained in good to excellent yields. After mechanistic studies by ^{19}F NMR spectroscopy, the authors proposed that bis(trifluoromethyl) disulfide, CF_3SSCF_3, was generated in situ (Scheme 71, path B). The route through path A and CF_3SOH was also envisaged but should lead only to the formation of small amount of product.

The same authors further demonstrated that the trifluoromethyl-sulfenylation can be conducted under metal-free conditions by replacing CuCl with trimethylsilyl chloride (TMSCl) to generate the cation CF_3S^+ in the presence of $(EtO)_2P(O)H$ [99]. Again, the electrophilic trifluoromethylsulfenylation of indoles was studied but also the trifluoromethylthiolation of electron-rich arenes (Scheme 72). Using this protocol, trifluoromethyl-sulfenylated compounds were obtained in moderate to excellent yields. Compared to the CuCl-mediated approach, this method directly converted CF_3SOH into CF_3S^+ by reaction with TMSCl (Scheme 72).

Based on this above-mentioned work and simultaneously to the metal-free approach, Cai and co-workers reported the direct trifluoromethylsulfenylation of indoles, pyrroles and enamines, with CF_3SO_2Na, triphenylphosphine and *N*-chlorophthalimide without added metal and at room temperature (Scheme 73) [100]. In general, the substrates were successfully trifluoromethylsulfenylated in moderate to excellent yields by in situ generated CF_3SCl as suggested by ^{19}F NMR studies and previous literature reports.

Scheme 71: Electrophilic trifluoromethylsulfenylation by means of $CF_3SO_2Na/(EtO)_2P(O)H/CuCl/DMSO$.

Scheme 72: Electrophilic trifluoromethylsulfenylation by means of $CF_3SO_2Na/(EtO)_2P(O)H/TMSCl$.

Scheme 73: Electrophilic trifluoromethylsulfenylation by means of $CF_3SO_2Na/PPh_3/N$-chlorophthalimide.

Cai using PPh_3 and N-chlorophthalimide, here, PCl_3 was used both as a reducing and chlorinating reagent. ^{19}F NMR investigation of reaction intermediates showed the signal of CF_3SCl, species which was interpreted as the key intermediate in the reaction system. Noteworthy, switching from PCl_3 to $P(O)Cl_3$ allowed the synthesis of the trifluoromethylsulfinyl derivatives instead of the trifluoromethylsulfenyl ones (see next section).

Scheme 74: Electrophilic trifluoromethylsulfenylation by means of CF_3SO_2Na/PCl_3.

Different phosphorus reductive reagents were evaluated by Liu, Lin and co-workers. It was found that phosphorus trichloride (PCl_3) allowed to react with CF_3SO_2Na and a series of indoles afforded the corresponding 3-CF_3S derivatives selectively in good to excellent yields (Scheme 74) [101]. Unlike the work of
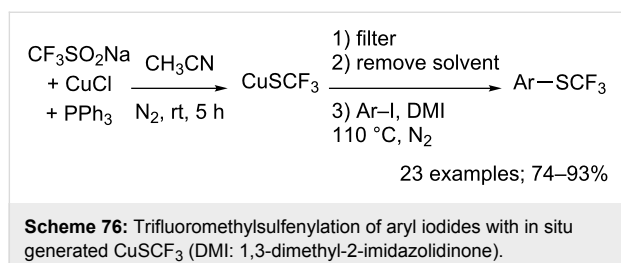
At the same time, Zhao, Lu and co-workers described similar observations. The trifluoromethylsulfenylation of indoles and electron-rich aromatics was realised with CF_3SO_2Na in the presence of PCl_3 (1.2 instead of 3 equivalents) in acetonitrile at

60 °C (Scheme 75) [102]. The authors proposed a reaction mechanism that involved the 3-trifluoromethylsulfinyl intermediate **88** (Scheme 75). Consequently, a decrease of the amount of PCl$_3$ and the temperature was proposed to interrupt the reaction and to obtain **88** selectively (see next section).


Scheme 75: Electrophilic trifluoromethylsulfenylation by means of CF$_3$SO$_2$Na/PCl$_3$.
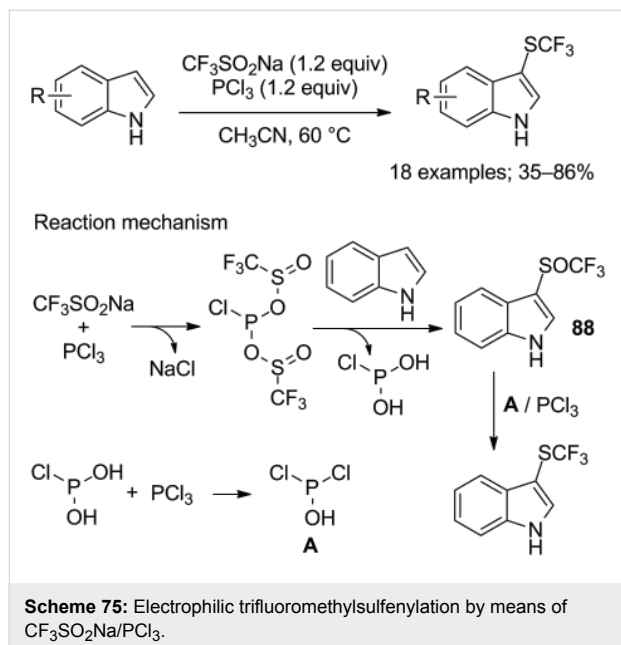
Aryl iodides served as substrates in a programmable regioselective trifluoromethylsulfenylation by direct coupling with CuSCF$_3$ generated form CF$_3$SO$_2$Na in the presence of copper(I) chloride and triphenylphosphine. Indeed, Yang, Vicic and co-workers described the deoxygenative reduction of CF$_3$SO$_2$Na to form the ligand-free CuSCF$_3$ intermediate that reacted with a diverse array of aryl iodides in high yields (Scheme 76) [103]. In addition, CuSCF$_3$ was reacted with various ligands to furnish air-stable [LCu(SCF$_3$)] complexes as trifluoromethylsulfenylating agents.

**Scheme 76:** Trifluoromethylsulfenylation of aryl iodides with in situ generated CuSCF$_3$ (DMI: 1,3-dimethyl-2-imidazolidinone).

3 Trifluoromethylsulfinylation

In 1999, Langlois and co-workers used the system CF$_3$SO$_2$Na/POCl$_3$ as an efficient and inexpensive equivalent of the CF$_3$S(O)$^+$ cation for the trifluoromethylsulfinylation of various amines, alcohols as well as carbon nucleophiles (Scheme 77)

[104]. In the case of primary amines, the addition of one equivalent of diisopropylethylamine to the reaction medium was necessary to trap acidic phosphoric species coming from the reaction and to reach higher product yields. *N*-Methylpyrrole was used as an example of C-nucleophile affording the corresponding S(O)CF$_3$ product in 60% yield.

**Scheme 77:** Pioneering trifluoromethylsulfinylation of N, O, and C-nucleophiles.
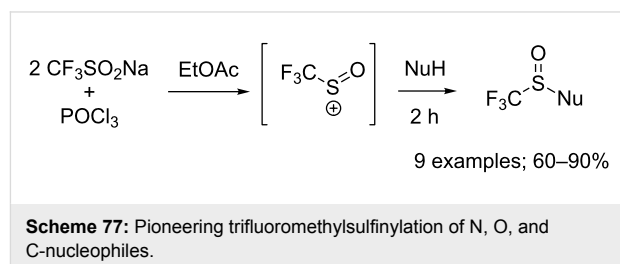
A few years later, the same group reported the synthesis of the trifluoromethanesulfinamide **89** derived from (1*R*,2*S*)-ephedrine using the process described above (Scheme 78). Compound **89** was used as an efficient trifluoromethylating agent for a wide range of non-enolisable and enolisable carbonyl compounds [105].

Scheme 78: Trifluoromethylsulfinylation of (1*R*,2*S*)-ephedrine (Im: imidazole; DIEA: *N*,*N*-diisopropylethylamine).
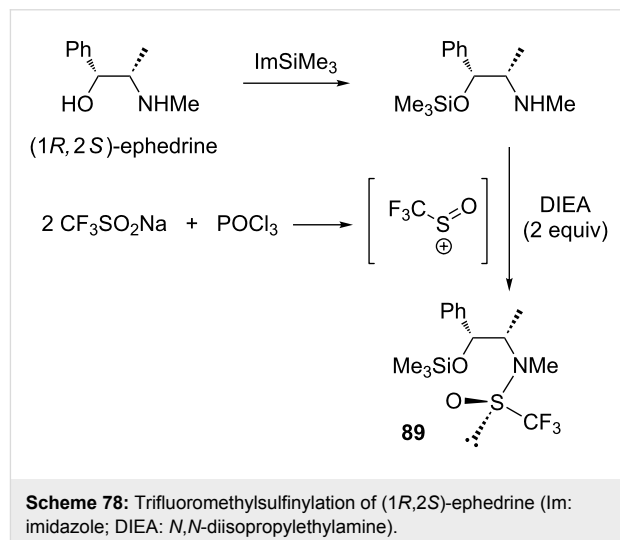
Other *N*-aryl- and *N*-alkyltrifluoromethanesulfinamides have been prepared from the corresponding anilines or aliphatic amines with CF$_3$SO$_2$Na and phosphoryl chloride for further reactions with arynes [106] or in the synthesis of trifluoromethylsulfonimidates [107].

Another direct trifluoromethylsulfinylation method was described by Wakselman's group in 2001 with CF$_3$SO$_2$Na in the presence of triflic acid (Scheme 79) [108]. This method was applied to simple aryls featuring a halogen atom, a OCF$_3$ group or an acetanilide function. In this reaction, *ortho*/*para* regio-

isomers were formed in ratios from 25:75 to 3:97. With regard to the mechanism, the sulfinate was protonated to generate the highly electrophilic $CF_3S(OH)_2^+$ species that underwent an S_EAr with arenes. A further development of the method consisted in the replacement of triflic acid with triflic anhydride in dichloromethane, and this strategy has been applied to the synthesis of trifluoromethylsulfonium salts, known as Umemoto's reagents [109-111].


Scheme 79: Trifluoromethylsulfinylation of substituted benzenes with CF_3SO_2Na/CF_3SO_3H.
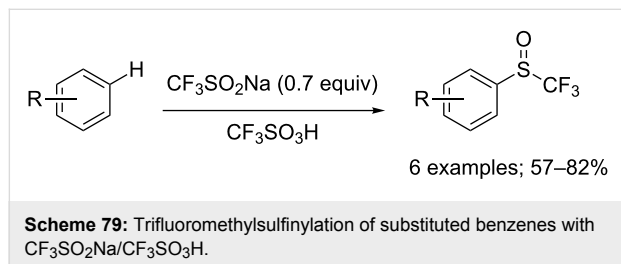
After these initial works, it is only in 2017 that new results using CF_3SO_2Na appeared in the field. As briefly mentioned in the preceding section, Liu, Lin and co-workers evaluated different phosphorus reductive reagents and found that PCl_3 (3 equiv) afforded the corresponding 3-CF_3S derivatives whereas $P(O)Cl_3$ (1 equiv) allowed to get selectively the trifluoromethylsulfinyl derivatives **90** (Scheme 80) [101].

Scheme 80: Trifluoromethylsulfinylation of indoles with $CF_3SO_2Na/P(O)Cl_3$.
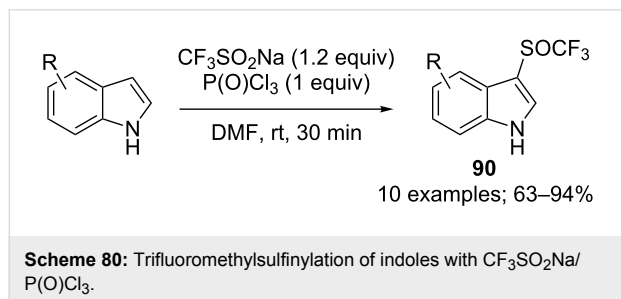
With the same objective of partial reduction of CF_3SO_2Na with phosphorus reagents for the selective trifluoromethylsulfinylation, Zhao, Lu and co-workers noticed that a decrease of the amount of PCl_3 and a slight lowering of the temperature were beneficial to the desired trifluoromethylsulfinylation (Scheme 81) [102].
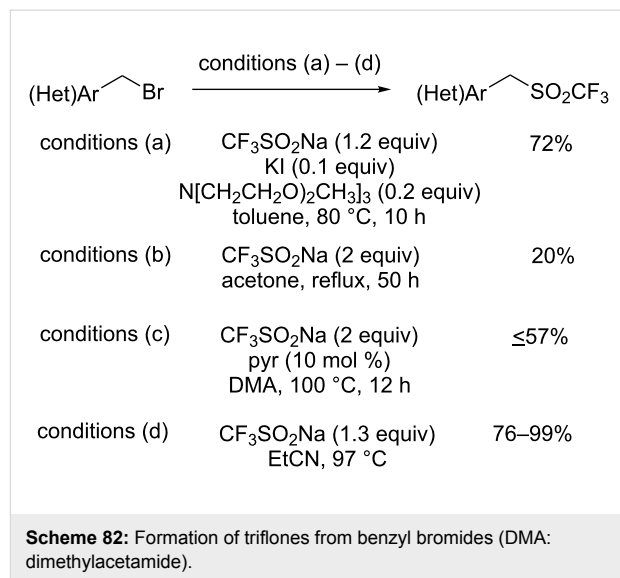
4 Trifluoromethylsulfonylation

The trifluoromethylsulfonyl motif (SO_2CF_3, Tf, triflyl) is highly electron-withdrawing (SO_2CF_3, $\sigma_m = 0.79$, $\sigma_p = 0.93$) and trifluoromethylsulfones (or triflones), in which the trifluoromethylsulfonyl group is attached to a carbon atom, are moderatly lipophilic (SO_2CF_3, $\pi = 0.55$ versus CF_3, $\pi = 0.88$). Therefore, the SO_2CF_3 group has been frequently employed in catalysts and ligands, as subunit of bioactive compounds, or as

**Scheme 81:** Trifluoromethylsulfinylation of indoles with CF_3SO_2Na/PCl_3.
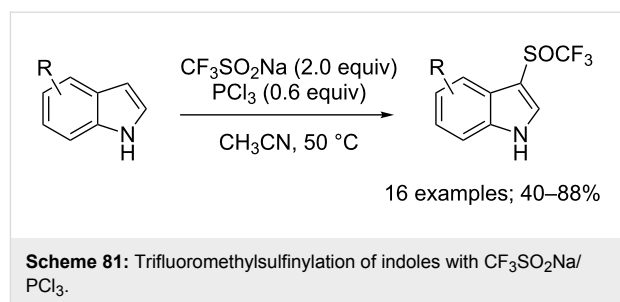
building block for advanced functional materials. Trifluoromethylsulfones have been prepared by several approaches [5], in particular by means of CF_3SO_2Na as compiled hereafter.

C_{sp3}–SO_2CF_3 bond-forming reactions

The trifluoromethanesulfinate, triflinate anion, possesses a low nucleophilicity thus affecting its potential in substitution reactions. Mainly primary bromides and some secondary ones (α-bromo ketones and esters) could be converted into trifluoromethylsulfones. From benzyl bromides, phase-transfer conditions [112] and/or high temperatures [113-115] were required to obtain the triflones in low to high yields (Scheme 82). Using benzyl chloride in propionitrile at reflux led to 90% yield of the corresponding triflone [115]. Methyl iodide was also used as substrate for the formation of methyl trifluoromethylsulfone [116]. The displacement of a tosyl group by CF_3SO_2Na in the presence of *n*-Bu$_4$NI in THF worked with 60 % yield [117].

Scheme 82: Formation of triflones from benzyl bromides (DMA: dimethylacetamide).

α-Trifluoromethylsulfonyl ketones, esters, and amides were prepared by displacement of the corresponding bromide (Scheme 83a) [112,118] or chloride (Scheme 83b,c) [118,119] under various conditions. Long reaction times and high temperatures were often required.

**Scheme 83:** Formation of α-trifluoromethylsulfonyl ketones, esters, and amides.
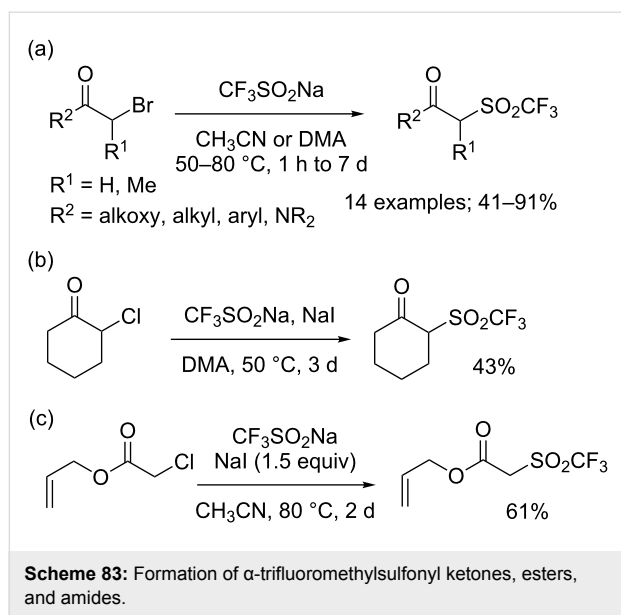
Allylic trifluoromethylsulfones could be prepared from aromatic allylic alcohols or esters and CF_3SO_2Na in the presence of *p*-toluenesulfonic acid at 100 °C in dioxane. The reaction was highly regioselective, worked well with primary, secondary and tertiary allylic alcohols, and tolerated a wide range of functions (Scheme 84) [120]. The reaction proceeded through an S_N1-type mechanism by the formation of a cationic Π-allyl intermediate by means of *p*-toluenesulfonic acid.

Scheme 84: Allylic trifluoromethanesulfonylation of aromatic allylic alcohols.
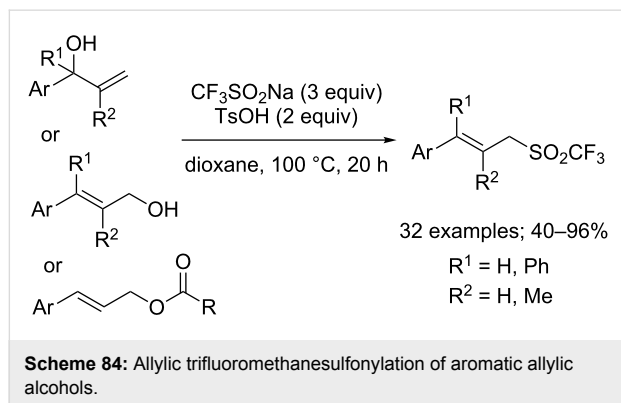
C_{sp2}–SO_2CF_3 bond-forming reactions

Aryl triflones: The synthesis of aryl trifluoromethylsulfones was investigated by Shekhar and co-workers in 2013. First, Pd- and Cu-catalysed coupling reactions with iodobenzene or aryl-boronic acids failed because of the poor nucleophilicity of CF_3SO_2Na [121]. It was next found that aryl iodonium salts reacted with CF_3SO_2Na in the presence of copper catalysts. In particular cuprous oxide in DMF gave the triflones in moderate to high yields from a variety of symmetrical and unsymmetrical (het)aryl iodonium salts **91** bearing various functional groups

and counteranions (Scheme 85) [121]. The reaction was sulfonyl-retentive and was likely to proceed via a nonradical pathway, probably involving Cu(I)/Cu(III) intermediates.

**Scheme 85:** Copper-catalysed couplings of aryl iodonium salts with CF_3SO_2Na.
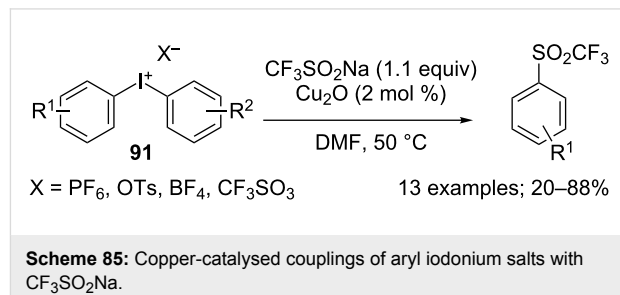
Another example of trifluoromethanesulfonylation of a diaryl iodonium salt was reported by Li and co-workers as a single case, among several other nucleophiles, using 10 mol % of copper(II) triflate in dichloroethane at 80 °C [122]. The hypervalent iodine species could also be generated in situ [123].

In 2016, Shekhar's group finally succeeded in the trifluoromethanesulfonylation of the more readily available (het)aryl triflates and some aryl chlorides using a combination of $Pd_2(dba)_3$ and the bulky RockPhos phosphine ligand in toluene and tris(3,6-dioxaheptyl)amine (TDA) as phase-transfer catalyst to facilitate the reaction with the sparingly soluble CF_3SO_2Na (Scheme 86) [124].

Scheme 86: Palladium-catalysed trifluoromethanesulfonylation of aryl triflates and chlorides with CF_3SO_2Na.
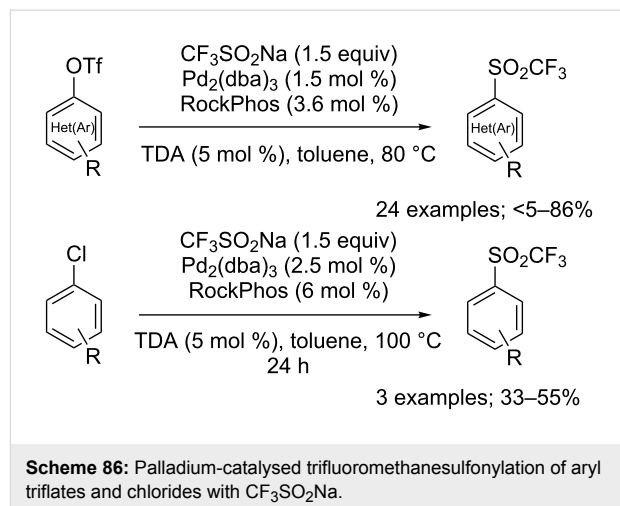
Arenediazonium tetrafluoroborates **92** were also suitable substrates for the formation of triflones. Xu, Qing and a co-worker demonstrated that CF_3SO_2Na produced triflones when engaged in a Cu-catalysed reaction in DMSO (Scheme 87) [76]. The reaction was sulfonyl-retentive whereas in the presence of the oxidant *tert*-butyl hydroperoxide the chemoselective trifluoromethylation was obtained (see Scheme 52).

Scheme 87: Copper-catalysed coupling of arenediazonium tetrafluoroborates with CF$_3$SO$_2$Na.
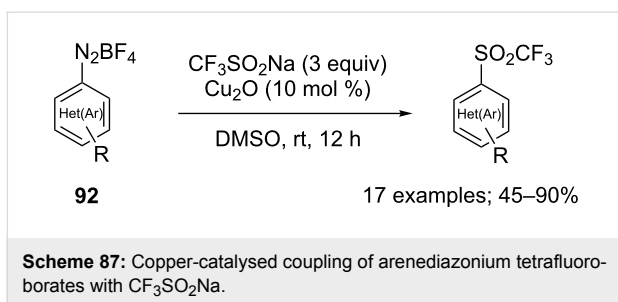
Finally, a metal-free protocol was reported by Singh and co-workers, in which in situ generated benzyne was reacted with CF$_3$SO$_2$Na (Scheme 88) [125].

Scheme 88: Synthesis of phenyltriflone via coupling of benzyne with CF$_3$SO$_2$Na.
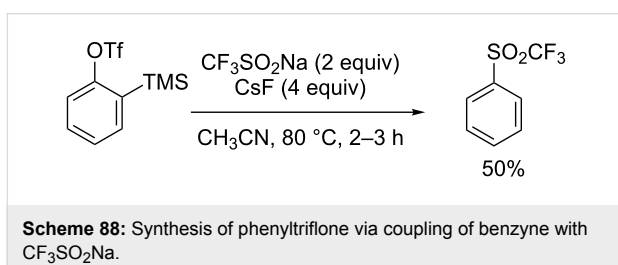
**Vinyl triflones:** The synthesis of two vinyl trifluoromethylsulfones was reported in 2004 by Ochiai and co-workers by treatment of λ^3-bromane **93** with CF$_3$SO$_2$Na in DCM at 0 °C (Scheme 89) [126]. The reaction also produced 1-alkynyltriflones as minor products. The 1-alkynyl-λ^3-bromanes acted as Michael acceptors for the sulfinate anion and underwent tandem Michael addition–carbene insertion reactions to yield the 1-trifluoromethanesulfonylcyclopentenes.

Scheme 89: Synthesis of 1-trifluoromethanesulfonylcyclopentenes from 1-alkynyl-λ^3-bromanes and CF$_3$SO$_2$Na.
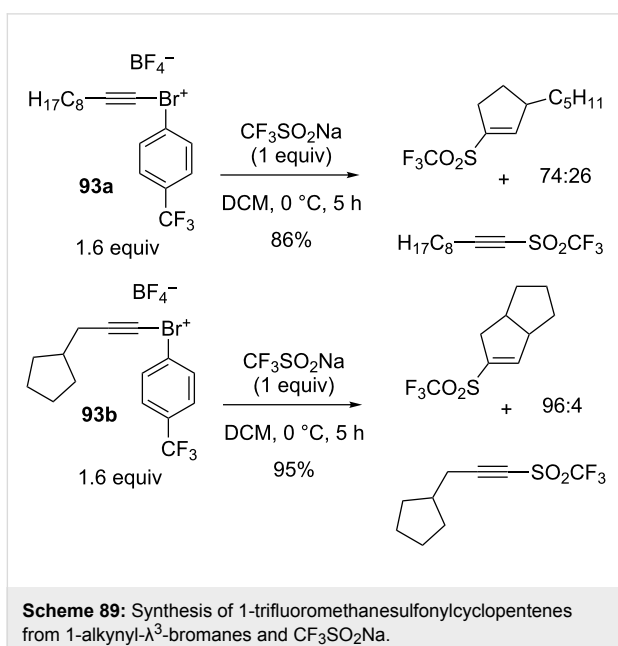
Vinyl triflones with exclusive *E*-selectivity could also be prepared from allylic alcohols and CF$_3$SO$_2$Na under metal-free conditions as reported by Xu, Ji and co-workers (Scheme 90) [127]. Under acidic conditions, the π-allylic carbocation reacted with the sulfinyl anion leading to allylsulfone **95**, which underwent an electrophilic addition of PIDA and capture of the benzylic carbocation by water. Then, a concerted proton elimination and C–I bond cleavage occurred to give the triflylated allylic alcohol **94**.

Scheme 90: One-pot synthesis of functionalised vinyl triflones.
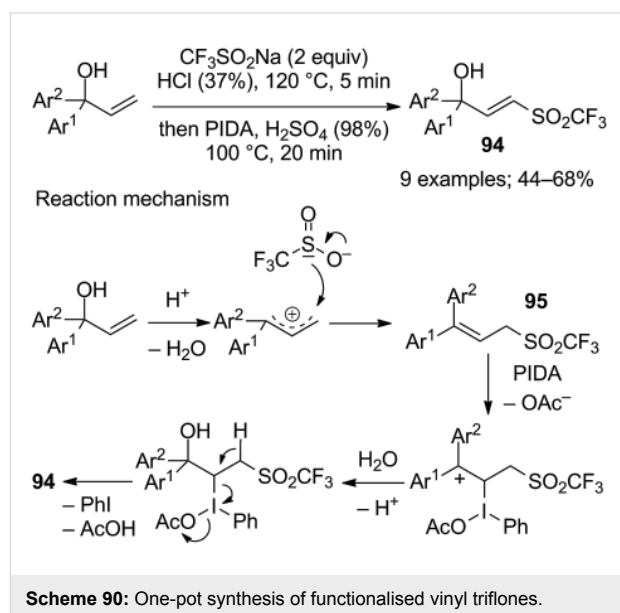
Huang, Xu and co-workers demonstrated that styrenes, but also vinylbenzofuran and vinylthiophene, reacted with CF$_3$SO$_2$Na in the presence of iodine and CuCN to afford regioselectively the internal vinyl triflones **96** (Scheme 91) [128]. A cationic reaction mechanism was proposed by electrophilic addition of I$_2$ (or the in situ generated CF$_3$SO$_2$I) to the olefin. The highly strained iodonium bridge subsequently reacted with the sulfinyl anion to afford the iodotriflylated product, which eliminated HI to give the vinyl triflone. The role of CuCN was not precised at this stage.

Scheme 91: Regioselective synthesis of vinyltriflones from styrenes.
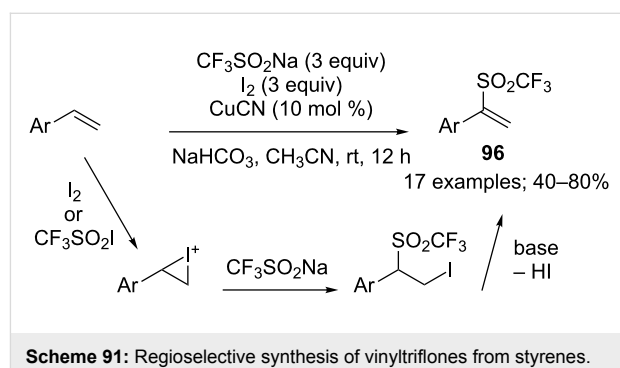
C$_{sp}$–SO$_2$CF$_3$ bond-forming reactions

Apart from the side products described in Scheme 89, a variety of acetylenic triflones **98** was proposed by Zhang and co-workers. Alkynyl(phenyl) iodonium tosylates **97** reacted with CF$_3$SO$_2$Na in a transition metal-free protocol to furnish the acetylenic triflones under mild conditions (Scheme 92) [129]. The authors suggested that alkylidene carbene intermediates might be formed followed by a 1,2-rearrangement to yield the triflones. The reaction from ethynylbenzene and CF$_3$SO$_2$Na in the presence of Koser's reagent allowed to obtain the corresponding triflone albeit in a 33% yield.

**Scheme 92:** Trifluoromethanesulfonylation of alkynyl(phenyl) iodonium tosylates by CF$_3$SO$_2$Na.
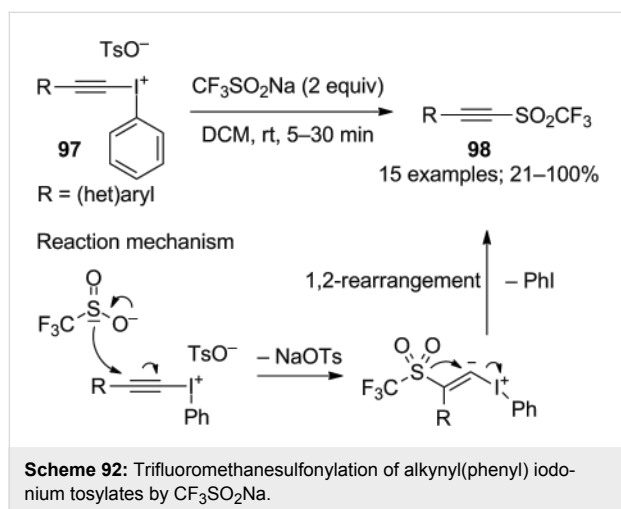
S–SO$_2$CF$_3$ and Se–SO$_2$CF$_3$ bond-forming reactions

Langlois' group prepared thiotrifluoromethanesulfonates **100** from sulfenyl chlorides **99** or disulfides **101** by two methods: first, sulfenyl chlorides were reacted with CF$_3$SO$_2$Na in DCM at room temperature [130]; second, a wider scope was obtained by reaction of disulfides with CF$_3$SO$_2$Na under oxidative conditions with either bromine [130] or PIFA [131] (Scheme 93a). These methodologies were extended to phenylselenyl chloride and diphenyl diselenide (Scheme 93b).

Conclusion

Sodium trifluoromethanesulfinate was used for the first time in direct radical trifluoromethylation under oxidative conditions by the Langlois group in 1991. Since that time its chemistry has evolved sporadically till 2011 and then immensely thanks to Baran's contribution. It enjoyed a rapid growth not only as donor of the trifluoromethyl group but also as a trifluoromethyl-sulfenylating agent, for the transfer of the whole SCF$_3$ motif, and as trifluoromethanesulfinylating agent for S(O)CF$_3$ transfer. CF$_3$SO$_2$Na is an easy-to-handle, inexpensive reagent that has became versatile for the construction of sophisticated fluorinated products in the pharmaceutical chemistry. It is the authors' hope that this review will contribute to stimulate

Scheme 93: Synthesis of thio- and selenotrifluoromethanesulfonates.
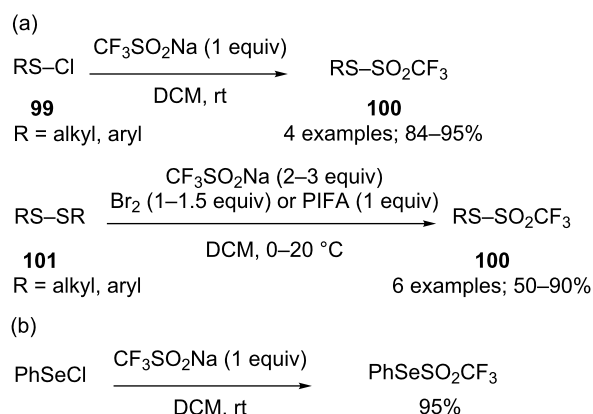
further research toward new reactions and applications for this reagent that could include the formation of new bonds with other heteroatoms, novel tandem reactions, and the exploration of asymmetric reactions, so far absent with CF$_3$SO$_2$Na, to cite but a few examples.

ORCID® iDs

Hélène Chachignon - https://orcid.org/0000-0001-6657-1728
Dominique Cahard - https://orcid.org/0000-0002-8510-1315

References

1. Kirsch, P. *Modern Fluoroorganic Chemistry;* Wiley-VCH: Weinheim, 2004.
2. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015,** *58,* 8315–8359. doi:10.1021/acs.jmedchem.5b00258
3. Harsanyi, A.; Sandford, G. *Green Chem.* **2015,** *17,* 2081–2086. doi:10.1039/c4gc02166e
4. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016,** *116,* 422–518. doi:10.1021/acs.chemrev.5b00392
5. Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015,** *115,* 731–764. doi:10.1021/cr500193b
6. Matheis, C.; Wagner, V.; Goossen, L. J. *Chem. – Eur. J.* **2016,** *22,* 79–82. doi:10.1002/chem.201503524
7. Glenadel, Q.; Ismalaj, E.; Billard, T. *Eur. J. Org. Chem.* **2017,** 530–533. doi:10.1002/ejoc.201601526

8. Besset, T.; Jubault, P.; Pannecoucke, X.; Poisson, T.
    Org. Chem. Front. **2016,** *3,* 1004–1010. doi:10.1039/c6qo00164e
9. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990,** *29,* 1320–1367.
    doi:10.1002/anie.199013201
10. McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992,** *48,* 6555–6666.
    doi:10.1016/S0040-4020(01)80011-9
11. Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007,** *128,* 975–996.
    doi:10.1016/j.jfluchem.2007.04.026
12. Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010,** *6,*
    No. 65. doi:10.3762/bjoc.6.65
13. Ye, Y. e-EROS Encyclopedia of Reagents for Organic **2014,** 1–4.
    doi:10.1002/047084289X.rn01689
14. Haszeldine, R. N.; Kidd, J. M. *J. Chem. Soc.* **1955,** 2901–2910.
    doi:10.1039/JR9550002901
15. Roesky, H. W.; Holtschneider, G. *J. Fluorine Chem.* **1976,** *7,* 77–84.
    doi:10.1016/s0022-1139(00)83984-6
16. Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991,** *32,*
    7525–7528. doi:10.1016/0040-4039(91)80524-a
17. Zhang, C. *Adv. Synth. Catal.* **2014,** *356,* 2895–2906.
    doi:10.1002/adsc.201400370
18. Langlois, B. R. Once Upon a Time Was the Langlois' Reagent: A
    "Sleeping Beauty". In *Modern Synthesis Processes and Reactivity of
    Fluorinated Compounds;* Groult, H.; Leroux, F.; Tressaud, A., Eds.;
    Elsevier, 2017; pp 125–140.
19. Lefebvre, Q. *Synlett* **2017,** *28,* 19–23. doi:10.1055/s-0036-1588643
20. Clavel, J.-L.; Langlois, B.; Laurent, E.; Roidot, N.
    Phosphorus, Sulfur Silicon Relat. Elem. **1991,** *59,* 169–172.
    doi:10.1080/10426509108045716
21. Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992,** *33,*
    1291–1294. doi:10.1016/s0040-4039(00)91604-6
22. Lu, Y.; Li, Y.; Zhang, R.; Jin, K.; Duan, C. *J. Fluorine Chem.* **2014,**
    161, 128–133. doi:10.1016/j.jfluchem.2014.01.020
23. Deb, A.; Manna, S.; Modak, A.; Patra, T.; Maity, S.; Maiti, D.
    Angew. Chem., Int. Ed. **2013,** *52,* 9747–9750.
    doi:10.1002/anie.201303576
24. Maji, A.; Hazra, A.; Maiti, D. *Org. Lett.* **2014,** *16,* 4524–4527.
    doi:10.1021/ol502071g
25. Luo, H.-Q.; Zhang, Z.-P.; Dong, W.; Luo, X.-Z. *Synlett* **2014,** *25,*
    1307–1311. doi:10.1055/s-0033-1341057
26. Lu, Q.; Liu, C.; Huang, Z.; Ma, Y.; Zhang, J.; Lei, A. *Chem. Commun.*
    2014, *50,* 14101–14104. doi:10.1039/c4cc06328g
27. Qin, H.-T.; Wu, S.-W.; Liu, J.-L.; Liu, F. *Chem. Commun.* **2017,** *53,*
    1696–1699. doi:10.1039/c6cc10035j
28. Lv, W.-X.; Zeng, Y.-F.; Li, Q.; Chen, Y.; Tan, D.-H.; Yang, L.;
    Wang, H. *Angew. Chem., Int. Ed.* **2016,** *55,* 10069–10073.
    doi:10.1002/anie.201604898
29. Konik, Y. A.; Kudrjashova, M.; Konrad, N.; Kaabel, S.; Jarving, I.;
    Lopp, M.; Kananovich, D. G. *Org. Biomol. Chem.* **2017,** *15,*
    4635–4643. doi:10.1039/C7OB00680B
30. Huang, H.-L.; Yan, H.; Gao, G.-L.; Yang, C.; Xia, W.
    Asian J. Org. Chem. **2015,** *4,* 674–677. doi:10.1002/ajoc.201500096
31. Matcha, K.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2014,** *53,*
    11960–11964. doi:10.1002/anie.201406464
32. Yu, X.-L.; Chen, J.-R.; Chen, D.-Z.; Xiao, W.-J. *Chem. Commun.*
    2016, *52,* 8275–8278. doi:10.1039/c6cc03335k
33. Zhang, H.-Y.; Huo, W.; Ge, C.; Zhao, J.; Zhang, Y. *Synlett* **2017,** *28,*
    962–965. doi:10.1055/s-0036-1588400
34. Jiang, X.-Y.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013,** *52,*
    14177–14180. doi:10.1002/anie.201307595
35. Yang, Y.; Liu, Y.; Jiang, Y.; Zhang, Y.; Vicic, D. A. *J. Org. Chem.*
    2015, *80,* 6639–6648. doi:10.1021/acs.joc.5b00781
36. Liu, C.; Lu, Q.; Huang, Z.; Zhang, J.; Liao, F.; Peng, P.; Lei, A.
    Org. Lett. **2015,** *17,* 6034–6037. doi:10.1021/acs.orglett.5b03035
37. Yu, J.; Yang, H.; Fu, H. *Adv. Synth. Catal.* **2014,** *356,* 3669–3675.
    doi:10.1002/adsc.201400144
38. Tommasino, J.-B.; Brondex, A.; Medebielle, M.; Thomalla, M.;
    Langlois, B. R.; Billard, T. *Synlett* **2002,** 1697–1699.
    doi:10.1055/s-2002-34210
39. Wilger, D. J.; Gesmundo, N. J.; Nicewicz, D. A. *Chem. Sci.* **2013,** *4,*
    3160–3165. doi:10.1039/c3sc51209f
40. Lefebvre, Q.; Hoffmann, N.; Rueping, M. *Chem. Commun.* **2016,** *52,*
    2493–2496. doi:10.1039/c5cc09881e
41. Zhu, L.; Wang, L.-S.; Li, B.; Fu, B.; Zhang, C.-P.; Li, W.
    Chem. Commun. **2016,** *52,* 6371–6374. doi:10.1039/c6cc01944g
42. Hang, Z.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2014,** *16,* 3648–3651.
    doi:10.1021/ol501380e
43. Liu, Z.-Q.; Liu, D. *J. Org. Chem.* **2017,** *82,* 1649–1656.
    doi:10.1021/acs.joc.6b02812
44. Fang, J.; Wang, Z.-K.; Wu, S.-W.; Shen, W.-G.; Ao, G.-Z.; Liu, F.
    Chem. Commun. **2017,** *53,* 7638–7641. doi:10.1039/c7cc01903c
45. Yang, F.; Klumphu, P.; Liang, Y.-M.; Lipshutz, B. H. *Chem. Commun.*
    2014, *50,* 936–938. doi:10.1039/c3cc48131j
46. Lu, Q.; Liu, C.; Peng, P.; Liu, Z.; Fu, L.; Huang, J.; Lei, A.
    Asian J. Org. Chem. **2014,** *3,* 273–276. doi:10.1002/ajoc.201300236
47. Liu, J.; Zhuang, S.; Gui, Q.; Chen, X.; Yang, Z.; Tan, Z.
    Eur. J. Org. Chem. **2014,** 3196–3202. doi:10.1002/ejoc.201400087
48. Wei, W.; Wen, J.; Yang, D.; Liu, X.; Guo, M.; Dong, R.; Wang, H.
    J. Org. Chem. **2014,** *79,* 4225–4230. doi:10.1021/jo500515x
49. Shi, L.; Yang, X.; Wang, Y.; Yang, H.; Fu, H. *Adv. Synth. Catal.* **2014,**
    356, 1021–1028. doi:10.1002/adsc.201300995
50. Sakamoto, R.; Kashiwagi, H.; Selvakumar, S.; Moteki, S. A.;
    Maruoka, K. *Org. Biomol. Chem.* **2016,** *14,* 6417–6421.
    doi:10.1039/c6ob01245k
51. Zhang, L.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2014,** *16,* 3688–3691.
    doi:10.1021/ol5014747
52. Mai, W.-P.; Wang, J.-T.; Yang, L.-R.; Yuan, J.-W.; Xiao, Y.-M.;
    Mao, P.; Qu, L.-B. *Org. Lett.* **2014,** *16,* 204–207.
    doi:10.1021/ol403196h
53. Li, B.; Fan, D.; Yang, C.; Xia, W. *Org. Biomol. Chem.* **2016,** *14,*
    5293–5297. doi:10.1039/c6ob00912c
54. Wu, Z.; Wang, D.; Liu, Y.; Huan, L.; Zhu, C. *J. Am. Chem. Soc.* **2017,**
    139, 1388–1391. doi:10.1021/jacs.6b11234
55. Yang, B.; Xu, X.-H.; Qing, F.-L. *Org. Lett.* **2015,** *17,* 1906–1909.
    doi:10.1021/acs.orglett.5b00601
56. Smertenko, E. A.; Datsenko, S. D.; Ignat'ev, N. V.
    Russ. J. Electrochem. **1998,** *34,* 46–51.
57. Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.;
    Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2011,**
    108, 14411–14415. doi:10.1073/pnas.1109059108
58. Musumeci, D.; Irace, C.; Santamaria, R.; Montesarchio, D.
    Med. Chem. Commun. **2013,** *4,* 1405–1410. doi:10.1039/c3md00159h
59. Wu, M.; Ji, X.; Dai, W.; Cao, S. *J. Org. Chem.* **2014,** *79,* 8984–8989.
    doi:10.1021/jo501221h
60. Fennewald, J. C.; Lipshutz, B. H. *Green Chem.* **2014,** *16,* 1097–1100.
    doi:10.1039/c3gc42119h
61. Zhang, X.; Huang, P.; Li, Y.; Duan, C. *Org. Biomol. Chem.* **2015,** *13,*
    10917–10922. doi:10.1039/c5ob01516b
62. Cao, X.-H.; Pan, X.; Zhou, P.-J.; Zou, J.-P.; Asekun, O. T.
    Chem. Commun. **2014,** *50,* 3359–3362. doi:10.1039/c3cc49689a

63. Zhang, P.-Z.; Li, C.-K.; Zhang, G.-Y.; Zhang, L.; Jiang, Y.-J.; Zou, J.-P. *Tetrahedron* **2016,** *72,* 3250–3255. doi:10.1016/j.tet.2016.04.048

64. Li, C.; Suzuki, K.; Yamaguchi, K.; Mizuno, N. *New J. Chem.* **2017,** *41,* 1417–1420. doi:10.1039/c6nj03654f

65. Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. *J. Org. Chem.* **2015,** *80,* 1332–1337. doi:10.1021/jo502928e

66. Ji, X.-M.; Wei, L.; Chen, F.; Tang, R.-Y. *RSC Adv.* **2015,** *5,* 29766–29773. doi:10.1039/C5RA02888D

67. Jin, L.-K.; Lu, G.-P.; Cai, C. *Org. Chem. Front.* **2016,** *3,* 1309–1313. doi:10.1039/c6qo00369a

68. Shen, C.; Xu, J.; Ying, B.; Zhang, P. *ChemCatChem* **2016,** *8,* 3560–3564. doi:10.1002/cctc.201601068

69. Li, J.-M.; Wang, Y.-H.; Yu, Y.; Wu, R.-B.; Weng, J.; Lu, G. *ACS Catal.* **2017,** *7,* 2661–2667. doi:10.1021/acscatal.6b03671

70. Wang, D.; Deng, G.-J.; Chen, S.; Gong, H. *Green Chem.* **2016,** *18,* 5967–5970. doi:10.1039/c6gc02000c

71. Yang, Y.-D.; Iwamoto, K.; Tokunaga, E.; Shibata, N. *Chem. Commun.* **2013,** *49,* 5510–5512. doi:10.1039/c3cc41667d

72. Cui, L.; Matsaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. *Adv. Synth. Catal.* **2013,** *355,* 2203–2207. doi:10.1002/adsc.201300199

73. Chang, B.; Shao, H.; Yan, P.; Qiu, W.; Weng, Z.; Yuan, R. *ACS Sustainable Chem. Eng.* **2017,** *5,* 334–341. doi:10.1021/acssuschemeng.6b01682

74. Li, L.; Mu, X.; Liu, W.; Wang, Y.; Mi, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2016,** *138,* 5809–5812. doi:10.1021/jacs.6b02782

75. Le, C. C.; Wismer, M. K.; Shi, Z.-C.; Zhang, R.; Conway, D. V.; Li, G.; Vachal, P.; Davies, I. W.; MacMillan, D. W. C. *ACS Cent. Sci.* **2017,** *3,* 647–653. doi:10.1021/acscentsci.7b00159

76. Zhang, K.; Xu, X.-H.; Qing, F.-L. *J. Org. Chem.* **2015,** *80,* 7658–7665. doi:10.1021/acs.joc.5b01295

77. Hong, J.; Wang, G.; Huo, L.; Zheng, C. *Chin. J. Chem.* **2017,** *35,* 1761–1767. doi:10.1002/cjoc.201700311

78. Ye, Y.; Künzi, S. A.; Sanford, M. S. *Org. Lett.* **2012,** *14,* 4979–4981. doi:10.1021/ol3022726

79. Li, Y.; Wu, L.; Neumann, H.; Beller, M. *Chem. Commun.* **2013,** *49,* 2628–2630. doi:10.1039/c2cc36554e

80. Presset, M.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2013,** *78,* 12837–12843. doi:10.1021/jo4023233

81. Dubbaka, S. R.; Salla, M.; Bolisetti, R.; Nizalapur, S. *RSC Adv.* **2014,** *4,* 6496–6499. doi:10.1039/C3RA46837B

82. Li, Z.; Cui, Z.; Liu, Z.-Q. *Org. Lett.* **2013,** *15,* 406–409. doi:10.1021/ol3034059

83. Patra, T.; Deb, A.; Manna, S.; Sharma, U.; Maiti, D. *Eur. J. Org. Chem.* **2013,** 5247–5250. doi:10.1002/ejoc.201300473

84. Yin, J.; Li, Y.; Zhang, R.; Jin, K.; Duan, C. *Synthesis* **2014,** *46,* 607–612. doi:10.1055/s-0033-1338578

85. Shang, X.-J.; Li, Z.; Liu, Z.-Q. *Tetrahedron Lett.* **2015,** *56,* 233–235. doi:10.1016/j.tetlet.2014.11.076

86. Huang, P.; Li, Y.; Fu, X.; Zhang, R.; Jin, K.; Wang, W.; Duan, C. *Tetrahedron Lett.* **2016,** *57,* 4705–4708. doi:10.1016/j.tetlet.2016.09.016

87. Wu, L.-H.; Zhao, K.; Shen, Z.-L.; Loh, T.-P. *Org. Chem. Front.* **2017,** *4,* 1872–1875. doi:10.1039/c7qo00416h

88. Jiang, H.; Huang, W.; Yu, Y.; Yi, S.; Li, J.; Wu, W. *Chem. Commun.* **2017,** *53,* 7473–7476. doi:10.1039/c7cc03125d

89. Liu, Y.-R.; Tu, H.-Y.; Zhang, X.-G. *Synthesis* **2015,** *47,* 3460–3466. doi:10.1055/s-0034-1378810

90. Lu, S.; Gong, Y.; Zhou, D. *J. Org. Chem.* **2015,** *80,* 9336–9341. doi:10.1021/acs.joc.5b01518

91. Fang, J.; Shen, W.-G.; G.-Z., Ao; Liu, F. *Org. Chem. Front.* **2017,** *4,* 2049–2053. doi:10.1039/C7QO00473G

92. Dubbaka, S. R.; Nizalapur, S.; Atthunuri, A. R.; Salla, M.; Mathew, T. *Tetrahedron* **2014,** *70,* 2118–2121. doi:10.1016/j.tet.2014.02.005

93. van der Werf, A.; Hribersek, M.; Selander, N. *Org. Lett.* **2017,** *19,* 2374–2377. doi:10.1021/acs.orglett.7b00908

94. Langlois, B.; Montègre, D.; Roidot, N. *J. Fluorine Chem.* **1994,** *68,* 63–66. doi:10.1016/0022-1139(93)02982-k

95. Ma, J.-J.; Yi, W.-B.; Lu, G.-P.; Cai, C. *Catal. Sci. Technol.* **2016,** *6,* 417–421. doi:10.1039/c5cy01561h

96. Ma, J.-j.; Liu, Q.-r.; Lu, G.-p.; Yi, W.-b. *J. Fluorine Chem.* **2017,** *193,* 113–117. doi:10.1016/j.jfluchem.2016.11.010

97. Chachignon, H.; Cahard, D. *Chin. J. Chem.* **2016,** *34,* 445–454. doi:10.1002/cjoc.201500890

98. Jiang, L.; Qian, J.; Yi, W.; Lu, G.; Cai, C.; Zhang, W. *Angew. Chem., Int. Ed.* **2015,** *54,* 14965–14969. doi:10.1002/anie.201508495

99. Yan, Q.; Jiang, L.; Yi, W.; Liu, Q.; Zhang, W. *Adv. Synth. Catal.* **2017,** *359,* 2471–2480. doi:10.1002/adsc.201700270

100. Bu, M.-j.; Lu, G.-p.; Cai, C. *Org. Chem. Front.* **2017,** *4,* 266–270. doi:10.1039/c6qo00622a

101. Sun, D.-W.; Jiang, X.; Jiang, M.; Lin, Y.; Liu, J.-T. *Eur. J. Org. Chem.* **2017,** 3505–3511. doi:10.1002/ejoc.201700661

102. Zhao, X.; Wei, A.; Yang, B.; Li, T.; Li, Q.; Qiu, D.; Lu, K. *J. Org. Chem.* **2017,** *82,* 9175–9181. doi:10.1021/acs.joc.7b01226

103. Yang, Y.; Xu, L.; Yu, S.; Liu, X.; Zhang, Y.; Vicic, D. A. *Chem. – Eur. J.* **2016,** *22,* 858–863. doi:10.1002/chem.201504790

104. Billard, T.; Greiner, A.; Langlois, B. R. *Tetrahedron* **1999,** *55,* 7243–7250. doi:10.1016/s0040-4020(99)00364-6

105. Roussel, S.; Billard, T.; Langlois, B. R.; Saint-Jalmes, L. *Synlett* **2004,** 2119–2122. doi:10.1055/s-2004-831322

106. Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005,** *127,* 13112–13113. doi:10.1021/ja054079p

107. Richards-Taylor, C. S.; Martinez-Lamenca, C.; Leenaerts, J. E.; Trabanco, A. A.; Oehlrich, D. *J. Org. Chem.* **2017,** *82,* 9898–9904. doi:10.1021/acs.joc.7b01628

108. Wakselman, C.; Tordeux, M.; Freslon, C.; Saint-Jalmes, L. *Synlett* **2001,** 550–552. doi:10.1055/s-2001-12316

109. Magnier, E.; Blazejewski, J.-C.; Tordeux, M.; Wakselman, C. *Angew. Chem., Int. Ed.* **2006,** *45,* 1279–1282. doi:10.1002/anie.200503776

110. Okazaki, T.; Laali, K. K.; Reddy, A. S. *J. Fluorine Chem.* **2014,** *165,* 91–95. doi:10.1016/j.jfluchem.2014.06.021

111. Umemoto, T.; Zhang, B.; Zhu, T.; Zhou, X.; Zhang, P.; Hu, S.; Li, Y. *J. Org. Chem.* **2017,** *82,* 7708–7719. doi:10.1021/acs.joc.7b00669

112. Eugene, F.; Langlois, B.; Laurent, E. *J. Fluorine Chem.* **1994,** *66,* 301–309. doi:10.1016/0022-1139(93)02909-x

113. Meshcheryakov, V. I.; Shainyan, B. A. *Russ. J. Org. Chem.* **2004,** *40,* 390–396. doi:10.1023/B:RUJO.0000034977.74026.b3

114. Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006,** *8,* 3175–3178. doi:10.1021/ol060939a

115. Hasegawa, A.; Ishikawa, T.; Ishihara, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2005,** *78,* 1401–1410. doi:10.1246/bcsj.78.1401

116. Zhu, S.; Chu, Q.; Xu, G.; Qin, C.; Xu, Y. *J. Fluorine Chem.* **1998,** *91,* 195–198. doi:10.1016/s0022-1139(98)00240-1

117. Wu, W.-L.; Asberom, T.; Bara, T.; Bennett, C.; Burnett, D. A.;
Clader, J.; Domalski, M.; Greenlee, W. J.; Josien, H.; McBriar, M.;
Rajagopalan, M.; Vicarel, M.; Xu, R.; Hyde, L. A.; Del Vecchio, R. A.;
Cohen-Williams, M. E.; Song, L.; Lee, J.; Terracina, G.; Zhang, Q.;
Nomeir, A.; Parker, E. M.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2013,**
23, 844–849. doi:10.1016/j.bmcl.2012.11.047

118. Kong, H. I.; Crichton, J. E.; Manthorpe, J. M. *Tetrahedron Lett.* **2011,**
52, 3714–3717. doi:10.1016/j.tetlet.2011.05.015

119. Kong, H. I.; Gill, M. A.; Hrdina, A. H.; Crichton, J. E.; Manthorpe, J. M.
J. Fluorine Chem. **2013,** *153,* 151–161.
doi:10.1016/j.jfluchem.2013.03.020

120. Liao, J.; Guo, W.; Zhang, Z.; Tang, X.; Wu, W.; Jiang, H.
J. Org. Chem. **2016,** *81,* 1304–1309. doi:10.1021/acs.joc.5b02674

121. Cullen, S. C.; Shekhar, S.; Nere, N. K. *J. Org. Chem.* **2013,** *78,*
12194–12201. doi:10.1021/jo401868x

122. Xie, F.; Zhang, Z.; Yu, X.; Tang, G.; Li, X. *Angew. Chem., Int. Ed.*
2015, *54,* 7405–7409. doi:10.1002/anie.201502278

123. Wang, F.; Yu, X.; Qi, Z.; Li, X. *Chem. – Eur. J.* **2016,** *22,* 511–516.
doi:10.1002/chem.201504179

124. Smyth, L. A.; Phillips, E. M.; Chan, V. S.; Napolitano, J. G.; Henry, R.;
Shekhar, S. *J. Org. Chem.* **2016,** *81,* 1285–1294.
doi:10.1021/acs.joc.5b02523

125. Aithagani, S. K.; Yempalla, K. R.; Munagala, G.; Vishwakarma, R. A.;
Singh, P. P. *RSC Adv.* **2014,** *4,* 50208–50211.
doi:10.1039/c4ra07370c

126. Ochiai, M.; Tada, N.; Nishi, Y.; Murai, K. *Chem. Commun.* **2004,**
2894–2895. doi:10.1039/B410830B

127. Chu, X.-Q.; Meng, H.; Xu, X.-P.; Ji, S.-J. *Chem. – Eur. J.* **2015,** *21,*
11359–11368. doi:10.1002/chem.201500469

128. Hua, L.-N.; Li, H.; Qing, F.-L.; Huang, Y.; Xu, X.-H.
Org. Biomol. Chem. **2016,** *14,* 8443–8447. doi:10.1039/C6OB01567K

129. Han, J.-B.; Yang, L.; Chen, X.; Zha, G.-F.; Zhang, C.-P.
Adv. Synth. Catal. **2016,** *358,* 4119–4124.
doi:10.1002/adsc.201600717

130. Billard, T.; Langlois, B. R.; Large, S.; Anker, D.; Roidot, N.; Roure, P.
J. Org. Chem. **1996,** *61,* 7545–7550. doi:10.1021/jo960619c

131. Billard, T.; Langlois, B. R. *J. Fluorine Chem.* **1997,** *84,* 63–64.
doi:10.1016/s0022-1139(97)00009-2