Review

Strategies for nucleophilic, electrophilic, and radical trifluoromethylations

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Abstract

Recent advances in the development of new strategies in nucleophilic, electrophilic, and radical trifluoromethylations are reviewed. The emphasis is given to the description of the trifluoromethylating agents, their activation mode, their reaction with carbonyl compounds and derivatives, as well as application in asymmetric synthesis.
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Keywords: Trifluoromethylation; Fluorinated compounds; Nucleophilic reagents; Electrophilic reagents; Radical reactions

Contents

1. Introduction

Organofluorine compounds are extremely rare in nature despite the relatively high abundance of fluorine in the earth's crust [1,2]. On the other hand, there is a plethora of synthetic

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fluorinated compounds that contain one or more fluorine atom. Today, the significant expansion in the use of fluorinated molecules in an amazingly wide range of applications is rooted in the outstanding progress made in the field of synthetic organic chemistry [3]. Indeed, the synthesis of fluorinated molecules is a very challenging area of organic chemistry because the rules that govern the synthesis of non-fluorinated analogs cannot be transposed to fluorinated compounds. Nevertheless, due to a better comprehension of the specific fluorine factors on the outcome of organic reactions, remarkable achievements in the field have been reported. A common approach is to exploit readily available fluorinated building blocks in a multi-step process towards more complex fluorinated targets. By contrast, fluorine atom(s) can be introduced in a late stage of a synthetic plan, basically, either by ionic (nucleophilic or electrophilic), or radical reaction. The introduction of a single fluorine atom has received considerable attention due to the development of easy-to-handle fluorinating agents and efficient experimental conditions [4]. Monofluorination is a carbon–fluorine bond forming reaction. Differently, introduction of a CF_3 group in trifluoromethylation reactions is a carbon–carbon bond-forming reaction. Alternatively, trifluoromethyl unit could be constructed from various precursors: (i) from a trichloromethyl unit with the aid of anhydrous hydrogen fluoride, (ii) from a carboxy group by treatment with hydrogen fluoride and sulfur tetrafluoride, (iii) from a dithiocarboxylic acid with xenon difluoride, (iv) by oxidative desulfurisation–fluorination by means of amine-HF complexes and a source of positive halogen, (v) by use of bromine trifluoride and HOF-CH_3CN in the synthesis of α-trifluoromethyl acids, (vi) through a difluorocarbene generated from difluorodiiodomethane or bromodifluoroacetate [5–8]. In the past few years, the field of direct trifluoromethylation has evolved rapidly to become a dynamic field that has attracted the efforts of several research groups [9]. As mentioned earlier in the text, methods that are applicable to non-fluorinated substrates are often not compatible with fluorinated compounds; indeed, trifluoromethylation is far different from methylation. In this review, we present a survey of synthetic methods developed for the direct introduction of a trifluoromethyl group. The emphasis is given to the preparation of trifluoromethylcarbinols, α-trifluoromethylamines, and α-trifluoromethylated carbonyl compounds. Only some aspects of the trifluoromethylation of arenes and heteroarenes are covered in this review [5]. The review is organised by type of trifluoromethylation: nucleophilic, electrophilic, and radical with presentation of the reagents in each section, their applications as well as asymmetric approaches.

2. Nucleophilic trifluoromethylation

Among the strategies for the direct introduction of a trifluoromethyl group into organic molecules, nucleophilic trifluoromethylation has been the most attractive approach during the last few decades. In the early stage, trifluoromethyl metal species (Hg, Cu, Zn, and Cd) have been extensively investigated for synthetic purposes; however, several drawbacks limited their utility [5]. These sluggish trifluoromethyl reagents are usually reserved for the substitution of aromatic iodides or bromides under thermal activation, and many of these reactions suffer from low yields and numerous fluorinated side products. Furthermore, these trifluoromethylation reagents are often not practical for trifluoromethylation of carbonyl groups and related electrophiles. In fact, nucleophilic trifluoromethylation is now tamed thanks to the extensive use of Ruppert–Prakash reagent Me_3SiCF_3. In addition, the utilization of several other nucleophilic trifluoromethylation reagents has made the nucleophilic approach a method of choice for trifluoromethylation of organic substrates.

2.1. Ruppert–Prakash reagent

In the 1980s, several nucleophilic trifluoromethylation reagents containing the silicon element were reported. For example, De Meijere and Hartkopf designed the trialkylsilyl(trifluoromethyl)diazenes **1** (Fig. 1) as tailored reagents for nucleophilic trifluoromethylation of carbonyl compounds to afford tertiary alcohols in moderate yields [10]. Following this pioneering work, trifluoromethylsilicon compounds **2–4** were prepared by Ruppert's group from the not yet banned trifluoromethyl bromide (Halon 1301) [11,12]. However, at that time, these compounds were not synthetically explored as efficient trifluoromethylating reagents. Indeed, after the initial discovery of trifluoromethylation reaction of carbonyl compounds with Me_3SiCF_3 by Prakash's group in 1989 [13], considerable attention has been devoted to the development of different catalytic systems for activation of the so-called Ruppert–Prakash reagent. In efforts to replace Halon 1301, Prakash and co-workers recently disclosed a non-CFC-based process for the preparation of Me_3SiCF_3 [14]. Although some comprehensive reviews have covered almost all the trifluoromethylation reactions of organic molecules with Me_3SiCF_3 [15,16], the aim of this section is to provide an up-to-date overview of the recent applications, the different initiators, and progress in asymmetric synthesis.

2.1.1. Nucleophilic initiators
2.1.1.1. Fluoride anion. Me_3SiCF_3 itself does not react with carbonyl compounds. The trifluoromethide anion must be
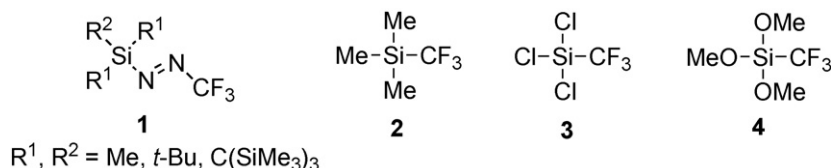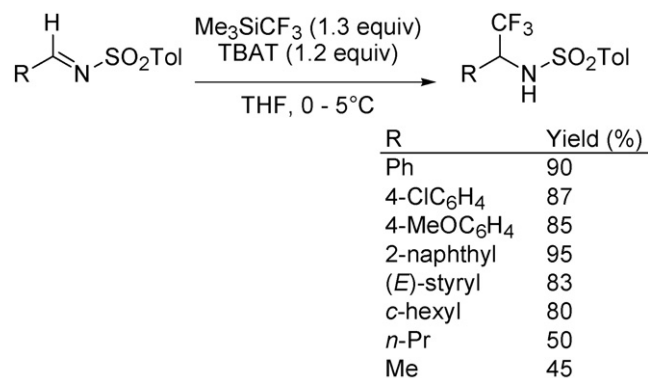

Fig. 1. Trifluoromethylsilicon compounds.

liberated by activation with a nucleophilic initiator (see later in the text for electrophilic initiators). Most commonly, a fluoride anion was employed as initial catalyst. For example, upon addition of a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF) to the reaction mixture of a carbonyl compound and Me_3SiCF_3 in a suitable solvent, the process commences with the initial formation of Me_3SiF and alkoxide adduct **5**, stabilised by the tetrabutylammonium cation (Scheme 1). The reaction between Me_3SiCF_3 and **5** leads to the formation of the pentavalent complex **6** followed by the transfer of the trifluoromethyl group to the electrophilic carbon of the carbonyl function until all of the starting material has reacted [16].

Consequently, a quite impressive number of aldehydes, ketones, esters, and activated imines undergo smooth reaction under the initiation by organic or inorganic fluoride sources such as TBAF, tetramethylammonium fluoride (TMAF), tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT), or CsF [17–19]. In addition, Makosza and co-workers reported another system, $K^+[Ph_3SnF_2]^-$, for activation of Ruppert–Prakash reagent. It was found that in most case the results of trifluoromethylation of aldehydes are comparable with those obtained in the phase-transfer co-catalytic system of KF/*n*-Bu₃MeN⁺HSO₃⁻/Ph₃SnF [20].

Since many synthetic drugs contain nitrogen, the trifluoromethylation of imines has been the subject of intense research. However, imines were reported to be rather unreactive towards Me_3SiCF_3. The addition of trimethylsilylimidazole to the reaction mixture in order to trap the unstable intermediate was beneficial to the reaction [21]. The reaction of *N*-arylimines with Me_3SiCF_3 in the presence of cesium fluoride provided moderate to good yields of trifluoromethylated nitrogen products but conversion of imines was incomplete even with excess of Me_3SiCF_3 and CsF [22]. In addition, CsF is too basic to allow trifluoromethylation of imines with an α-hydrogen atom. Prakash and Olah demonstrated that *N*-tosyl aldimines, which are more electrophilic than *N*-aryl derivatives, could be trifluoromethylated with Me_3SiCF_3 in the presence of TBAT in good to excellent yields. These conditions were applied to aromatic, aliphatic, and α,β-unsaturated aldimines (Scheme 2) [23].

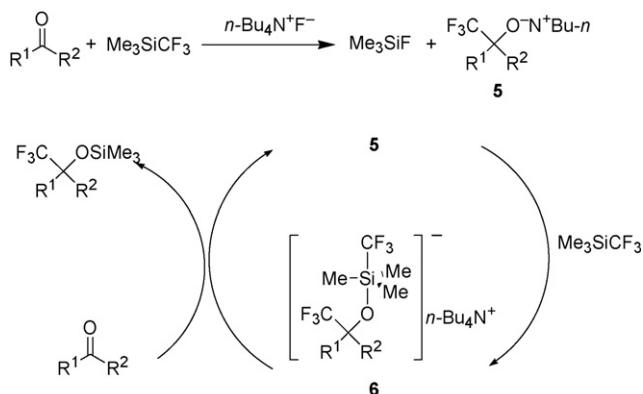| R	Yield (%)
Ph	90
4-ClC₆H₄	87
4-MeOC₆H₄	85
2-naphthyl	95
(*E*)-styryl	83
c-hexyl	80
n-Pr	50
Me	45

Scheme 2.

In 2006, Prakash's group described new reaction conditions for the introduction of CF_3^- to *N*-arylimines. The reactions were carried out with 0.15 equiv. of TBAT in THF at room temperature on *N*-aryl aldimines derived from various aromatic and non-enolisable aldehydes in 38–83% yield [24].

Recently, a variety of poorly electrophilic imides were trifluoromethylated in good to excellent yields using Me_3SiCF_3 under fluoride anion catalysis, CsF or TMAF. Interestingly, while cyclic five-membered imides provided the desired trifluoromethylated lactams, the corresponding six-membered imides failed to undergo the trifluoromethylation reaction (Scheme 3) [25]. This method was successfully applied to the stereoselective synthesis of trifluoromethylated bi- and tricyclic lactams, which could serve as precursors of thrombin inhibitors.

Regioselective trifluoromethylation of enones with Ruppert–Prakash reagent as nucleophilic trifluoromethylating agent is well known. The reaction of acyclic and cyclic enones in the presence of a catalytic amount of fluoride proceeds as a nucleophilic 1,2-addition of the CF_3 group at the carbonyl carbon atom to afford the corresponding trifluoromethylated alcohols after hydrolysis [26]. The reaction of 2-polyfluoroalkyl-4-quinolones and chromones with Ruppert–Prakash reagent represented new examples of a nucleophilic 1,4-trifluoromethylation. However, similar reaction with 2-trifluoromethyl-1-thiochromones resulted in the formation of 1,2-addition products (Scheme 4) [27–29].

Shreeve and Kim developed a new class of ionic liquids as reaction media for nucleophilic trifluoromethylation reactions. CsF or Ph₃P could be used as nucleophilic initiator. The trifluoromethylation reactions of Ruppert–Prakash reagent with carbonyl functionalities, and aryl, benzyl, vinyl, as well as primary halides proceeded smoothly in the morpholinium-based ionic liquids with enhanced nucleophilic reactivity. Despite these good results, the reactivity decreased when the ionic liquid was recycled (Scheme 5) [30].

2.1.1.2. Alkoxide initiators. Metal alkoxides were also found to be efficient initiators for nucleophilic trifluoromethylation reaction. Nelson and co-workers reported the nucleophilic trifluoromethylation of nitrones with Ruppert–Prakash reagent (Scheme 6) [31,32]. Since a nitrone is strongly electrophilic, it
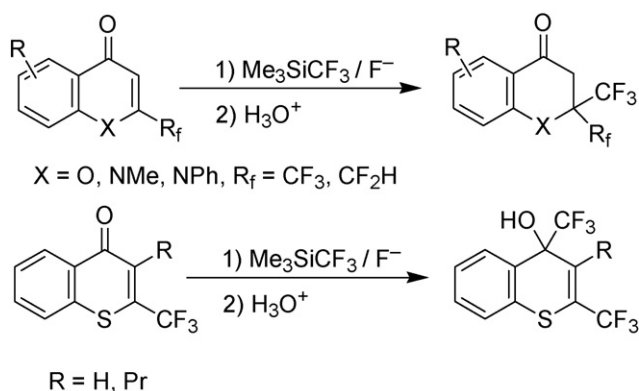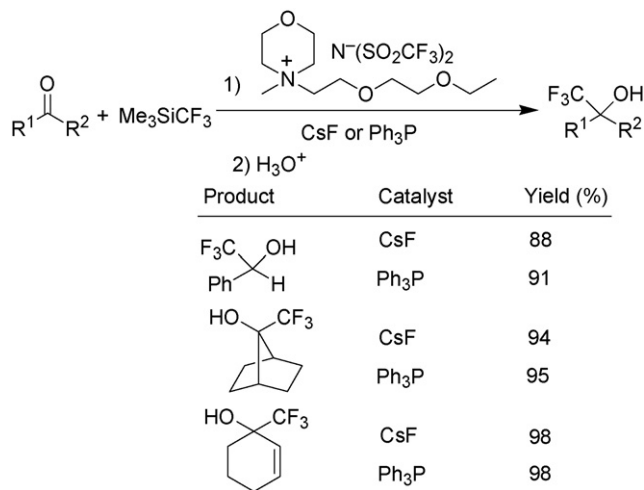

Scheme 1.
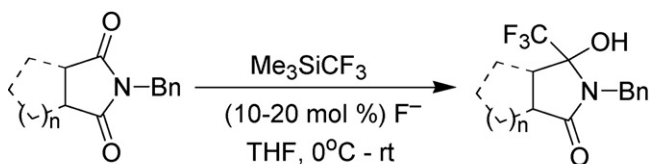
Scheme 3.

readily accepts trifluoromethide ion. Upon addition of the trifluoromethide ion, a negative charge on oxygen develops, resulting in an efficient catalytic initiator. The best results were obtained when potassium *tert*-butoxide was employed as initiator whereas addition–elimination reaction was predominant when other initiators such as CsF and TBAF were used. α,N-diaryl, and α,β-unsaturated nitrones gave good to excellent
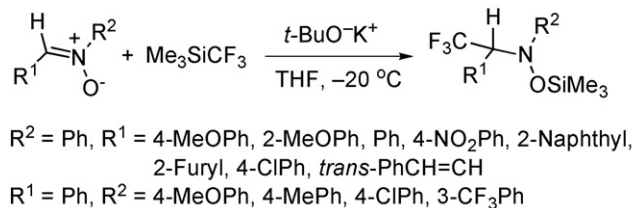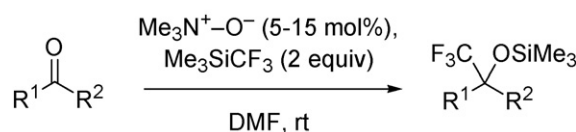

Scheme 4.

Scheme 5.

yields (43–93%) under these conditions, but α-alkyl and N-alkyl nitrones failed to react.

2.1.1.3. Amine N-oxide initiators. Although most of the trifluoromethylation reactions are carried out by using such strong bases as fluoride ion or metal alkoxides for the activation of Ruppert–Prakash reagent, these initiators are unsuitable for the base-labile substrates. Furthermore, these initiators are very sensitive to moisture. In 1997, Fuchikami and co-workers studied the trifluoromethylation reaction of aldehydes by using a variety of Lewis bases [33]. Following this pioneering work, Prakash's group employed trimethylamine N-oxide as a recoverable nucleophilic catalyst for the activation of Me₃SiCF₃ [34]. This methodology is applicable for base sensitive substrates. Various aromatic, aliphatic, and α,β-unsaturated aldehydes provided good to high yields of the corresponding trifluoromethylated products by using substoichiometric amounts of trimethylamine N-oxide (Scheme 7). The loading of the catalyst can be reduced to 2–5 mol% with substantial increase in product yields when DMF was used as a solvent [35]. Other amine oxides such as pyridine N-oxide, p-chloropyridine N-oxide, and N,N-dimethyl-pyridine N-oxide were evaluated; however, triethylamine N-oxide was preferred.
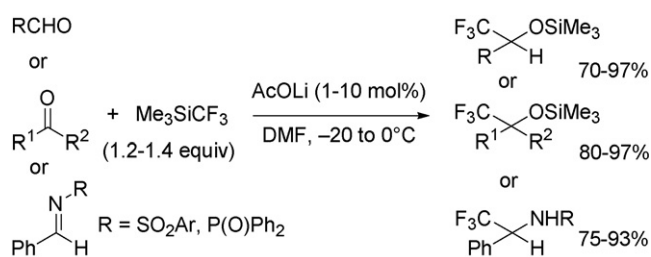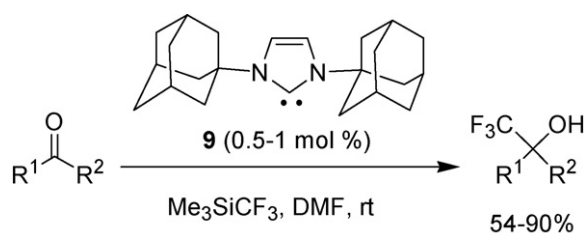

Scheme 6.

Scheme 7.
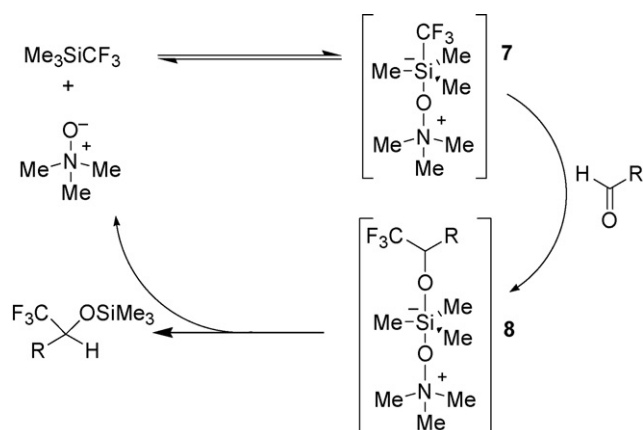
Scheme 8.

Scheme 9.

Mechanistically, trimethylamine oxide-complexed Me$_3$SiCF$_3$ **7** is in equilibrium with the starting material and this complex trifluoromethylates the aldehydes to form the adduct-complex **8** (Scheme 8).

2.1.1.4. Acetate initiators. Lithium acetate was employed as an effective Lewis base catalyst for the activation of trimethylsilyl enolate in aldol, Michael and Mannich-type reactions. It was noted that lithium acetate also catalyses trifluoromethylation reactions via the activation of the carbon–silicon bond of Me$_3$SiCF$_3$ [36,37]. A variety of aldehydes, ketones, and aldimines worked as good acceptors of Me$_3$SiCF$_3$ in the presence of a catalytic amount of lithium acetate (1–10 mol%) to give the corresponding trifluoromethylated products in high yields (Scheme 9). In addition, lithium benzoate, lithium pivalate, and acetates having such counter
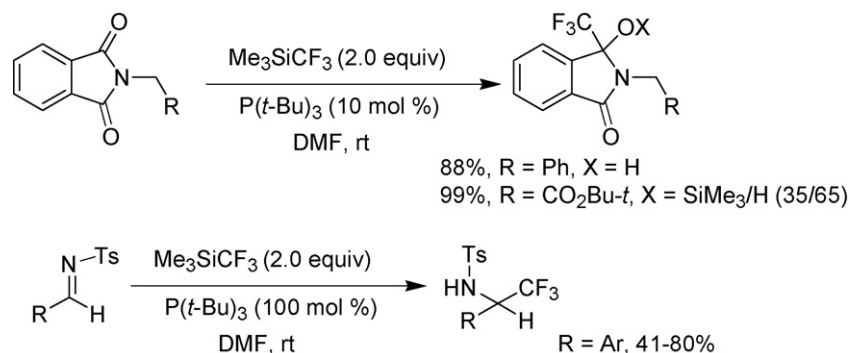

Scheme 10.

cations as sodium, potassium, or ammonium also worked effectively and afforded the desired adducts in excellent yields, but lithium trifluoroacetate did not promote the reaction. This method is truly practical since it only needs such mild, readily available and inexpensive Lewis base catalysts [38].

2.1.1.5. Carbene initiators. N-Heterocyclic carbenes (NHC) have received considerable attention over the past decades. They have been successfully employed as ligands and catalysts for a wide range of organic transformations [39,40]. Song and co-workers described a novel N-heterocyclic carbene-catalysed trifluoromethylation reaction of carbonyl compounds [41]. Both enolisable and non-enolisable aldehydes, as well as α-keto esters undergo facile trifluoromethylation under mild conditions in the presence of only 0.5–1 mol% of the commercially available NHC **9**, affording trifluoromethylated alcohols in good yields. However, low reactive ketones failed to undergo trifluoromethylation reaction. Therefore, selective trifluoromethylation of aldehydes over ketones can be achieved under NHC catalysis (Scheme 10).

2.1.1.6. Phosphine initiators. Triphenylphosphine is a widely used catalyst for trifluoromethylation reactions with Me$_3$SiCF$_3$. The yields are relatively low and longer reaction times are required possibly owing to the poor nucleophilicity of PPh$_3$ [30,33]. Recently, Shibata and co-workers developed an efficient Lewis base-catalysed system for nucleophilic trifluoromethylation of a variety of aldehydes and ketones through the use of tri-*tert*-butylphosphine P(*t*-Bu)$_3$ (0.1–10 mol%) in dimethylformamide [42]. Cyclic five-membered imides were also trifluoromethylated with Me$_3$SiCF$_3$ in high yields to furnish trifluoromethylated products. The scope of this reaction was expanded to imines. Moderate to good yields of several
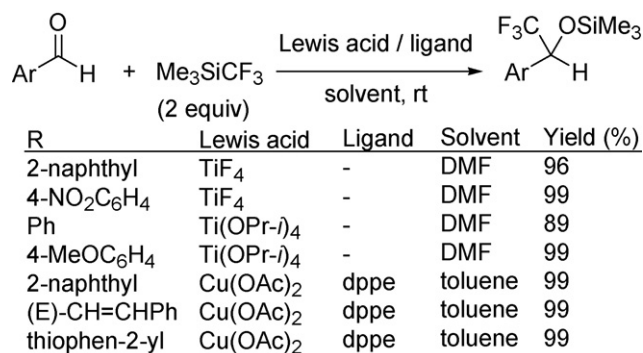

Scheme 11.

trifluoromethyl amines were obtained under the same mild conditions, but a stoichiometric amount of catalyst was required in that case (Scheme 11).

2.1.1.7. Other initiators. Nucleophilic trifluoromethylation of aldehydes and certain activated ketones with Me_3SiCF_3 have also been studied using other nucleophilic catalysts, such as amines, $AsPh_3$ and $SbPh_3$, [33,43] as well as DMF or DMSO in the presence of molecular sieves [44]. It is noteworthy that carbonate and phosphate salts such as K_2CO_3 and $(MeO)_2$-$P(O)O^-NBu_4^+$ also showed efficient catalytic activity in nucleophilic trifluoromethylation reactions [35]. The bidentate nature of CO_3^{2-} anion makes it different and unique from the above-mentioned monodentate catalysts for CF_3 transfer reactions. Prakash and co-workers suggested a possible mechanism via two routes for the potassium carbonate catalysed reaction. In route **A**, a single anionic center is involved in the attack of Me_3SiCF_3 to form the pentavalent **10** or the hexavalent intermediate **11**. Subsequently, **10** or **11** can undergo attack by the carbonyl compounds to form the second set of intermediates **12** and **13**, which can then decompose to give the desired products and regenerate the catalyst. For an alternative route **B**, both the anionic centers in the catalyst can simultaneously attack two molecules of Me_3SiCF_3 to give rise to a double trigonal bipyramidal intermediate **14**, which can further react with two molecules of substrate to give the intermediate **15** from which trifluoromethylated product is formed with regeneration of the catalyst (Scheme 12).

2.1.2. Electrophilic initiators

The first successful activation of Me_3SiCF_3 by Lewis acids was reported in 2006 by Shibata and co-workers [45]. In this case, the Lewis acid truly activates Me_3SiCF_3 whereas in a previous paper by Sevenard et al., a bulky Lewis acid was employed in a trifluoromethylation reaction but as a carbonyl group protector [46]. A wide range of Lewis acids as well as combinations of Lewis acid and ligand were screened in the reaction with non-enolisable aromatic aldehydes. TiF_4/DMF,


R	Lewis acid	Ligand	Solvent	Yield (%)
2-naphthyl	TiF_4	-	DMF	96
$4-NO_2C_6H_4$	TiF_4	-	DMF	99
Ph	$Ti(OPr-i)_4$	-	DMF	89
$4-MeOC_6H_4$	$Ti(OPr-i)_4$	-	DMF	99
2-naphthyl	$Cu(OAc)_2$	dppe	toluene	99
(E)-CH=CHPh	$Cu(OAc)_2$	dppe	toluene	99
thiophen-2-yl	$Cu(OAc)_2$	dppe	toluene	99

Scheme 13.

$Ti(OPr-i)_4$/DMF, and $Cu(OAc)_2$/dppe/toluene were among the best initiators evaluated in the nucleophilic trifluoromethylation of aromatic aldehydes (Scheme 13). Obviously, the next step will be the screening of chiral ligands for enantioselective nucleophilic trifluoromethylation reaction.

2.1.3. Asymmetric trifluoromethylation

Asymmetric trifluoromethylation of amino acids, steroids, carbohydrates, and inositol derivatives as well as sulfinimines and azirines has been reviewed by us in 2004 [47]. Consequently, we are now presenting only the most recent results in the field of asymmetric nucleophilic trifluoromethylation.

Based on their previous work, Mukaiyama and Kawano disclosed the trifluoromethylation of chiral *N*-sulfinylimines with Me_3SiCF_3 under mild conditions by using a Lewis base [48]. The corresponding trifluoromethylated adducts **16** were obtained in good to high yields with good diastereoselectivities when the reactions were carried out by using an equimolar amount of tetrabutylammonium acetate at −40 °C. Aliphatic aldimines having no α-proton adjacent to the imino group reacted smoothly to afford the desired adducts in high yields, whereas those that have α-protons gave the adducts in moderate to good yields in the presence of an equimolar amount of PhONBu$_4$-*n* (Scheme 14).
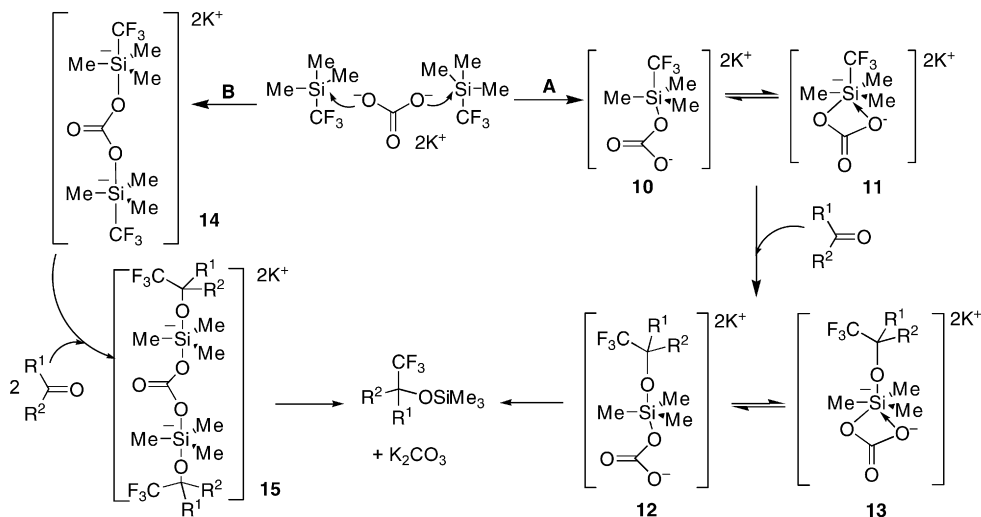
Scheme 12.
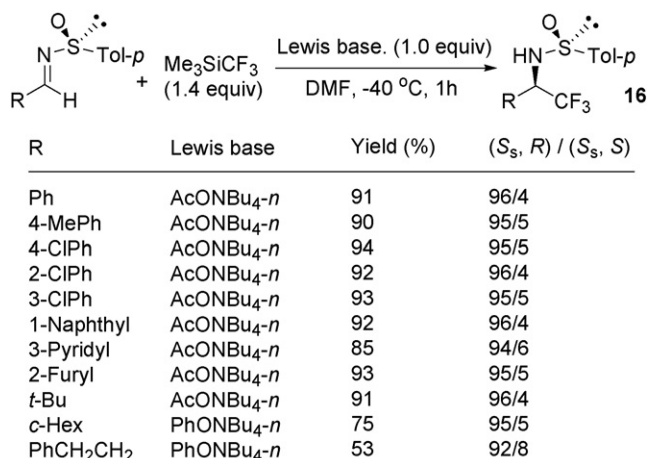
Scheme 14.

Pedrosa and co-workers presented the diastereoselective addition of Me$_3$SiCF$_3$ to chiral 2-acyl-1,3-perhydrobenzoxazine **17** derived from (−)-8-benzylamino menthol [49]. The trifluoromethylated adducts **18** were obtained in very good yields (80–96%) with high to excellent diastereoselectivities (diastereomeric ratio, dr: 11/1 to >50/1). In terms of reactivity and diastereoselectivity, CsF was a better catalyst than TBAF probably as a consequence of the hygroscopic character of the ammonium fluoride. Further transformation of the addition products allowed for the synthesis of enantioenriched 1,2-diols and 1,2-amino alcohols possessing a quaternary stereocenter (Scheme 15).

Mosher's acid is a valuable reagent for the determination of enantiomeric excess of alcohols or amines [50]. A diastereoselective trifluoromethylation of chiral α-keto esters derived

from isosorbide with Me$_3$SiCF$_3$ with the aid of a Lewis base catalyst provided the corresponding trifluoromethylated α-hydroxy esters in good yields with moderate to high diastereomeric excesses [51]. Further hydrolysis with LiOH afforded the (S)-Mosher's acid, while the chiral auxiliary was recovered quantitatively (Scheme 16).

Somewhat later, an alternative methodology has been developed for the synthesis of the precursor of Mosher acid. A highly diastereoselective nucleophilic monotrifluoromethylation of the tartaric acid-derived diketone with Me$_3$SiCF$_3$ provided the corresponding α-keto trifluoromethylcarbinol **19** in 98% diastereomeric excess. Bis(O-methylation) under basic conditions, followed by acidic hydrolysis and oxidative cleavage, gave two different enantiopure products. The functionalised trifluoromethyl derivative **20** is a potential precursor of Mosher acid (Scheme 17) [52].

Recently, Song and his colleagues developed a practical asymmetric process for the synthesis of pharmaceutically active intermediate **21**: α-trifluoromethyl-α-alkyl epoxide [53]. The fluoride-initiated CF$_3$ addition to the starting chiral α-keto ester proceeded with a diastereoselectivity up to 86:14. The major diastereomer was readily obtained with over 99% diastereomeric excess by crystallisation. Further transformations via saponification, reduction, and ring-closure afforded the desired epoxide **21** with excellent purity (99.5:0.5 er) on kilogram-scale (Scheme 18).

Toru and co-workers reported a remote asymmetric trifluoromethylation induced by chiral sulfinyl groups [54]. The reaction was initiated using tetramethylammonium fluoride to give trifluoromethylated products in high yields with high diastereoselectivity (Scheme 19). Further desilylation, recrystallisation, and cleavage of the sulfinyl group
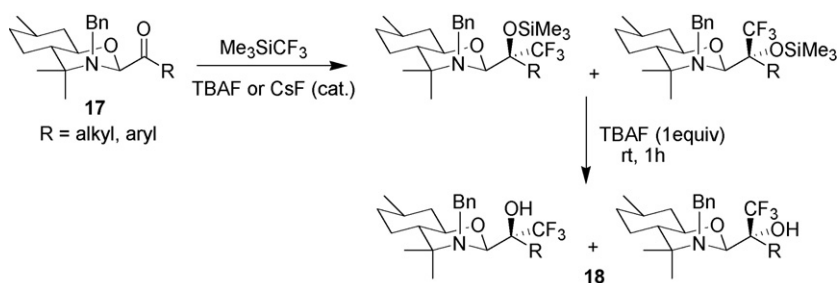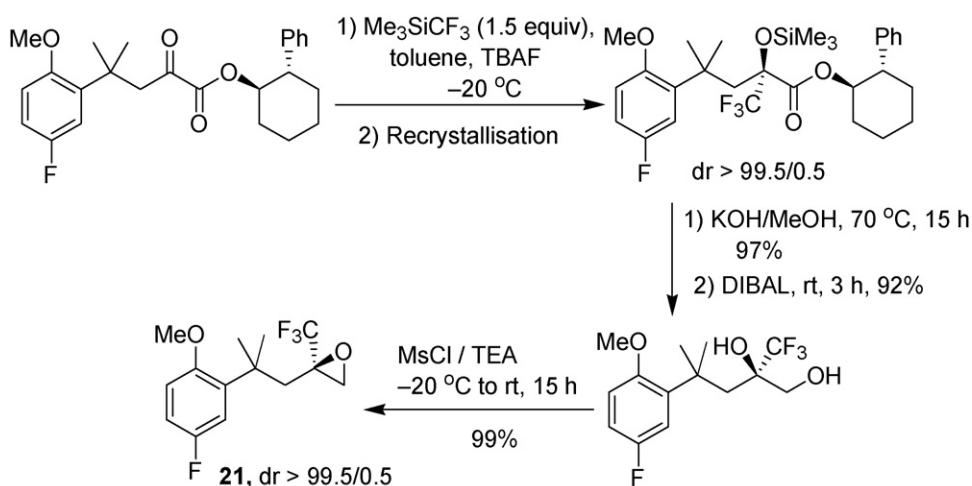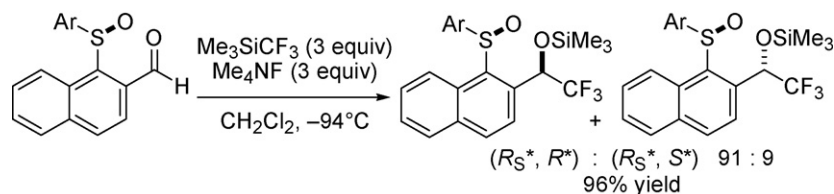

Scheme 15.
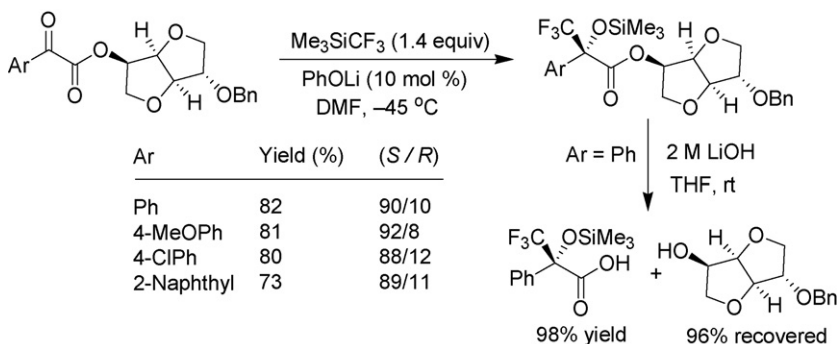
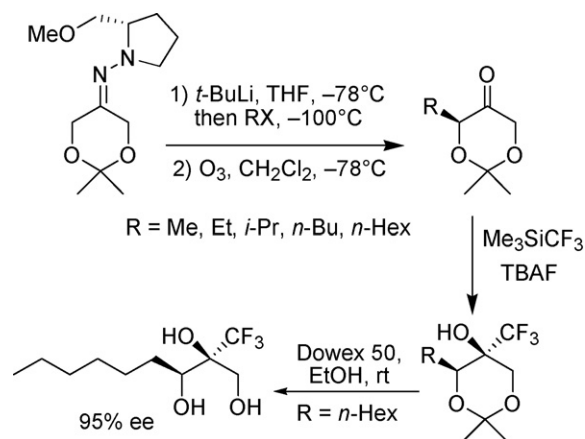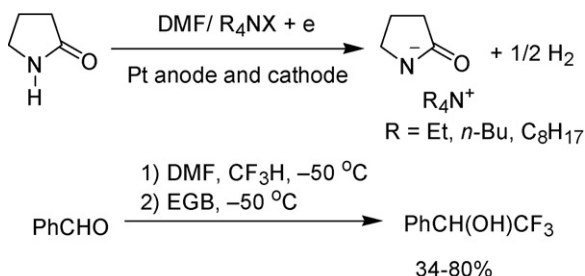Scheme 16.
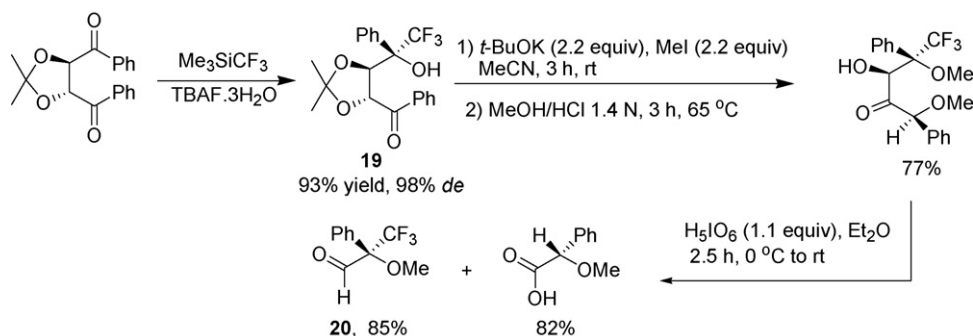
Scheme 17.

Scheme 18.

Scheme 19.

afforded the enantiomerically pure 1-(2-naphthyl)-2,2,2-tri-fluoroethanol.

More recently, Enders and Herriger developed an efficient asymmetric synthesis of 2-trifluoromethylated 1,2,3-triols [55]. The α-alkylated dioxanones were obtained via the SAMP/RAMP hydrazone methodology. The trifluoromethylation was carried out by nucleophilic 1,2-addition of the CF$_3$ group to the α-alkylated dioxanones by means of Ruppert–Prakash reagent and TBAF in high diastereoselectivities (diastereomeric excess ≥96%). Deprotection of dioxanol under acidic conditions gave the corresponding trifluoromethylated triols in essentially enantiomerically pure form (enantiomeric excess, ee 95–96%) (Scheme 20).
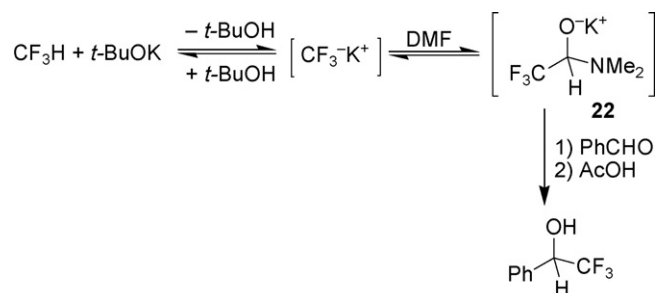
The synthesis of enantioenriched trifluoromethylated compounds by enantioselective nucleophilic trifluoromethylation has been achieved by means of Me$_3$SiCF$_3$ in the presence of a chiral ammonium or sulfonium fluoride in up to 95% ee but

Scheme 20.

Scheme 21.

Scheme 22.

usually in moderate enantiomeric excesses as reviewed by us in 2004 [47]. No new result concerning the use of a combination Me₃SiCF₃/F⁻ in enantioselective nucleophilic trifluoromethylation was published since 2004.

2.2. Fluoroform/base

Fluoroform is a cheap and environmentally benign reagent. In 1991, Shono and co-workers demonstrated that a base generated by electroreduction of 2-pyrrolidone (EGB) deprotonated fluoroform so as to produce a trifluoromethyl anion equivalent, which reacted with a variety of aldehydes and ketones to give trifluoromethylcarbinols in good to high yields (Scheme 21) [56]. Another strong base generated by electroreduction of iodobenzene was also developed to deprotonate fluoroform, inducing its coupling with non-enolisable aldehydes to afford trifluoromethylated alcohols in 12–76% yields [57].

Following these pioneering works, two research groups found that common bases such as alkoxides, dimsylates, or amides are also able to deprotonate fluoroform to generate the trifluoromethyl anion [58–60]. In this reaction DMF has the dual function of solvent and stabilising agent for the anion species. The intermediate formed **22** acted as a "trifluoromethyl reservoir", a masked and quite stable form of the trifluoromethyl anion (Scheme 22). Trifluoromethylated aryl alcohols, ketones, or sulfides can be obtained in good to high yields with the combination CF₃H/base/DMF.

Langlois and co-workers demonstrated that silicon-containing amides $(Me_3Si)_2N^-M^+$ obtained from $N(SiMe_3)_3$ and a

catalytic source of fluoride in the presence of a catalytic amount of DMF behaved similarly to the Me₃SiCF₃/F⁻ reagent. Here again, the true trifluoromethylating agent is the CF₃⁻/DMF adduct. This combination of reagents proved to be more efficient than Me₃SiCF₃ in the case of non-enolisable compounds [61].

2.3. Hemiaminals of fluoral, trifluoroacetate and trifluoromethanesulfinate derivatives, trifluoroacetamide and trifluoromethanesulfinamide derivatives

Based on the above-mentioned concept, Roques at Rhodia Recherche in 1999 exploited hemiaminals of fluoral (trifluoroacetaldehyde) as trifluoromethylating agents [62]. Gaseous fluoral reacted with amines and the adduct was deprotonated with *t*-BuONa to produce the trifluoromethyl anion equivalent $CF_3CH(O^-)NMe_2$. The reaction with benzaldehyde afforded the desired product although in a lower yield than from fluoroform (48% versus 67%). Afterwards, Langlois and co-workers developed stable hemiaminals of fluoral **23** and their silylated derivatives **24** as powerful trifluoromethylating agents towards non-enolisable carbonyl compounds, disulfides, and diselenides under activation by a stoichiometric strong base or catalytic fluoride anion such as CsF, and TBAT (Scheme 23). Fluoroform or more conveniently fluoral methyl hemiketal served as starting material for preparation of **23** and **24** [63–66].

They also found that secondary trifluoroacetamides and trifluoromethanesulfinamides, alkyl trifluoroacetates and trifluoromethanesulfinates, and α,α,α-trifluoroacetophenone behaved, under the action of potassium *tert*-butoxide, as
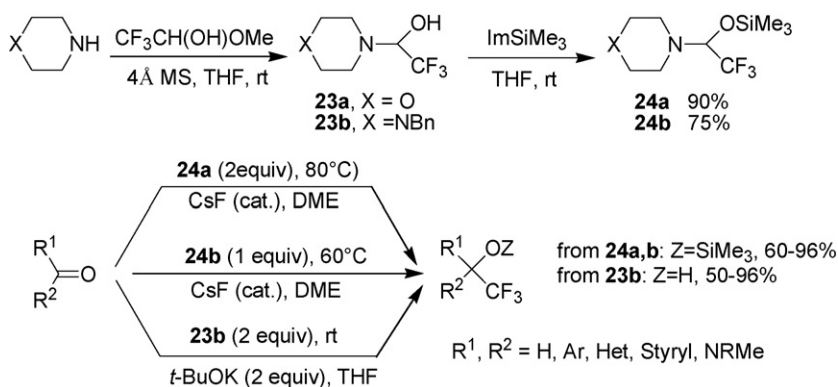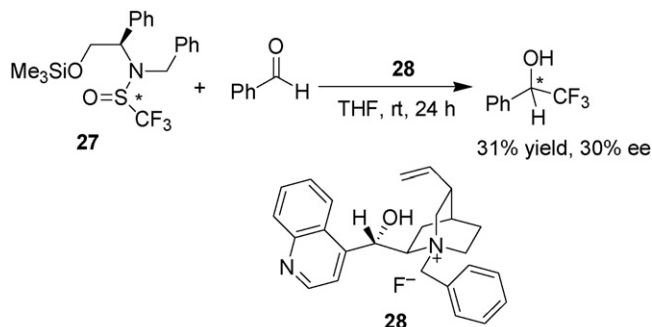

Scheme 23.
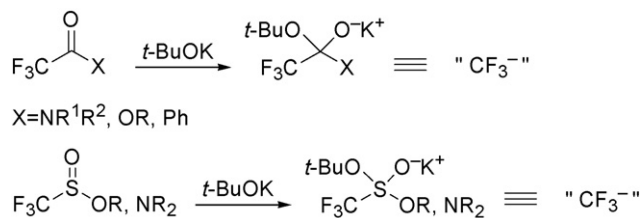
Scheme 24.

efficient trifluoromethylating agents towards non-enolisable carbonyl substrates (Scheme 24). However, the use of a strong base precludes the reaction of enolisable substrates [67–69].

To extend the scope of substrates for trifluoromethylation reaction, Langlois' group designed a variety of novel trifluoroacetamides and trifluoromethanesulfinamides derived from O-silylated vic-aminoalcohols [70,71]. For example, ephedrine derivative **25** was able to trifluoromethylate both enolisable and non-enolisable ketones, as well as reactive aldehydes in good to excellent yields under activation by fluoride anion at room temperature (Fig. 2). Nevertheless, trifluoromethylating agent **25** was not suitable for very acidic carbonyl compounds such as valeraldehyde and dibenzyl ketone. Interestingly, N-trifluoromethanesulfinyl-O-trimethyl-silyl-ephedrine **26** was shown to be successful for trifluoromethylation of both valeraldehyde and dibenzyl ketone (Fig. 2).

In 2005, this group employed trifluoroacetamides and trifluoromethanesulfinamides derived from chiral silylated amino alcohols as chiral trifluoromethylating agents. Low ee values in the range 1–20% were observed with trifluoromethanesulfinamides **27**. In order to improve enantioselectivity, a chiral ammonium fluoride **28** was employed as initiator for the

trifluoromethylation reaction of benzaldehyde with **27**; enantioselectivity was improved to 30% ee in 31% yield (Scheme 25) [72].

Scheme 25.

### 2.4. Trifluoromethylacetophenone-N,N-dimethyltrimethylsilylamine adduct

It is noteworthy that the simple thermal addition of N,N-dimethyltrimethylsilylamine with trifluoromethylacetophenone provided a shelf-stable trifluoromethylating agent **29** in high yield (Scheme 26-a) [73]. A number of trifluoromethylcarbinols, derived from a simple series of non-enolisable aldehydes and ketones, were readily prepared in reactions involving two equivalents of reagent **29** in the presence of cesium fluoride (10 mol%) as the preferred initiator in THF. To improve the reactivity of trifluoromethylating agent **29** with the inherently less electrophilic imine functional group, 2-trimethylsilyloxypyridine was found to be a suitable electrophile, which could trap the unstable intermediate **30** and prevent this intermediate from reverting to starting material. A series of aromatic imines was trifluoromethylated using reagent **29** and 2-trimethylsilyloxypyridine (Scheme 26-b) [74].

2.5. Trifluoromethyl iodide/tetrakis(dimethylamino)ethylene (TDAE)

Trifluoromethyl iodide has been employed for the purpose of nucleophilic trifluoromethylation of carbonyl compounds via
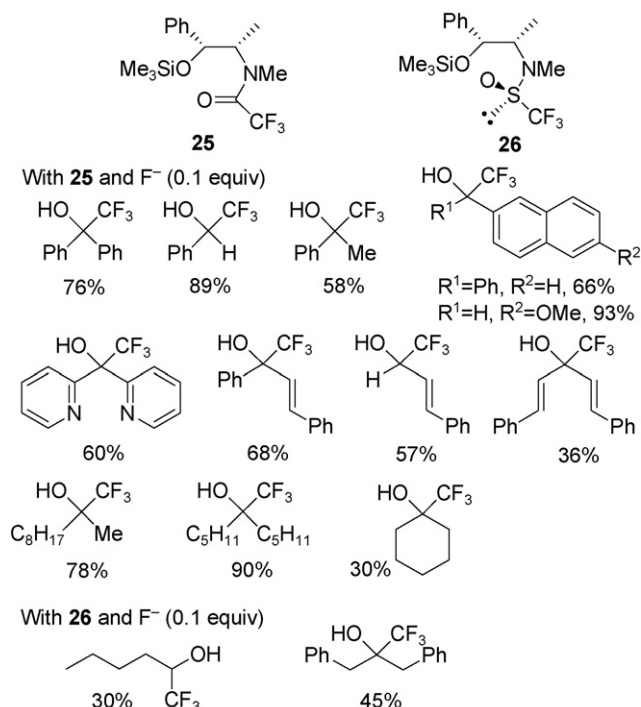
Fig. 2. Trifluoromethylation with ephedrine derivatives **25** and **26**.
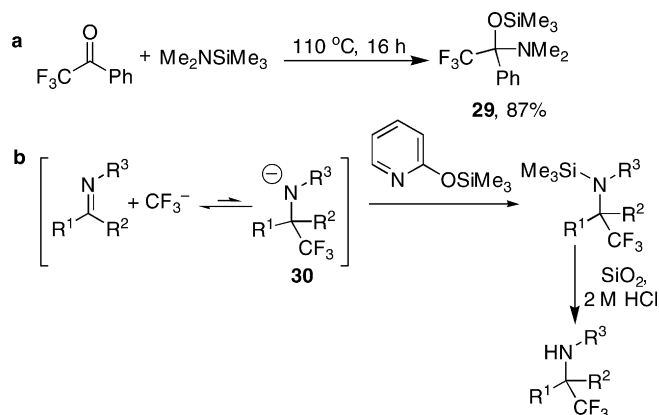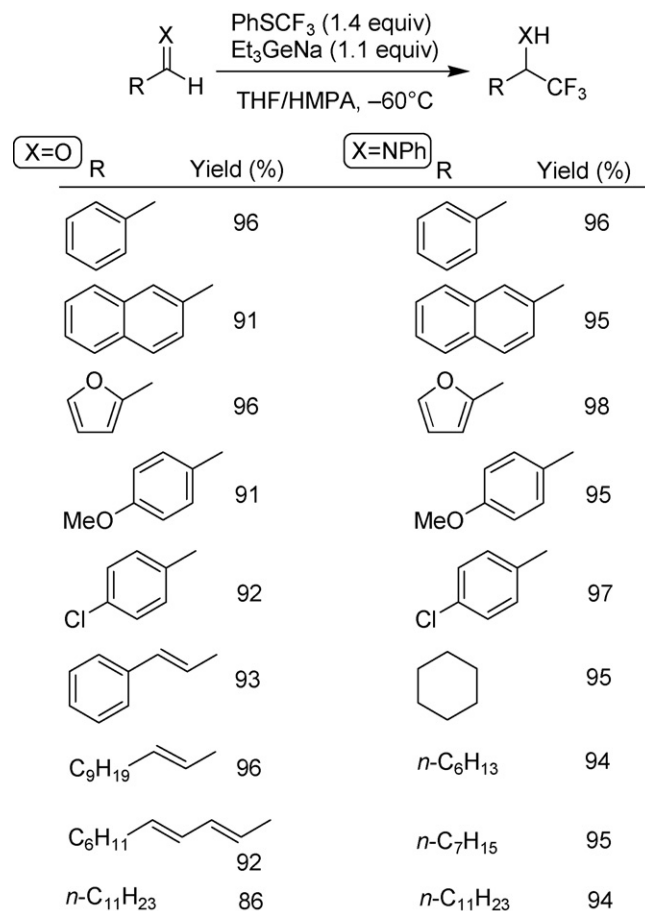

Scheme 26.
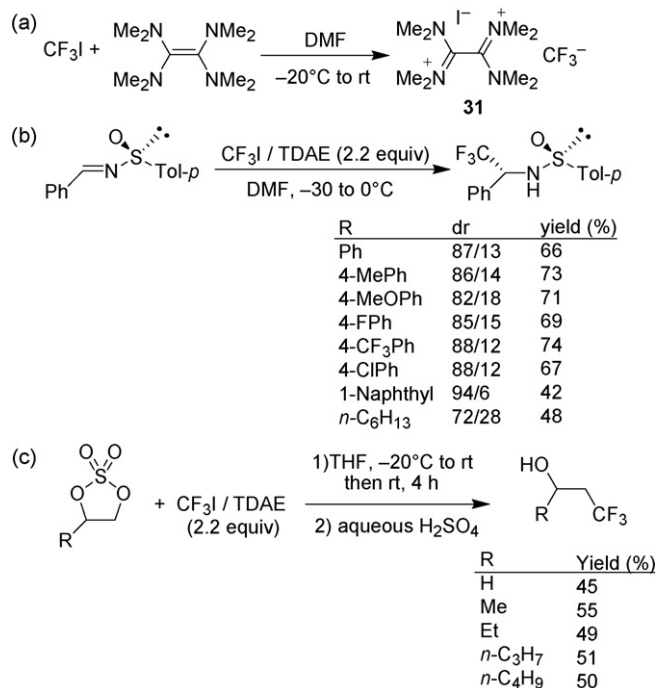
Scheme 27.

Scheme 28.

its derived organometallic reagents. However, as mentioned earlier in the text, some drawbacks have limited their utility in synthesis. Recently, Dolbier and co-workers developed an alternative approach to nucleophilic trifluoromethylation based on earlier work of Pawelke and co-workers [75–78]. The reaction involves an initially formed charge-transfer complex between CF₃I and TDAE, followed by stepwise, photo induced single-electron transfers of two electrons from TDAE to CF₃I to generate a complex **31** between CF₃⁻ anion and TDAE²⁺ dication, which presumably is the active nucleophilic trifluoromethylating agent (Scheme 27-a). A variety of non-enolisable aldehydes, ketones, and aromatic aldimines were trifluoromethylated by using this reagent to give the desired adducts in moderate to high yields. Noteworthy, yields of reactions with aldehydes and ketones were considerably improved in the presence of light. Enolisable aldehydes and methylketones generally gave poor results. Acyl chlorides chemoselectively gave bis-trifluoromethylated products [79] whereas disulfides and diselenides produced two equivalents of thio- and selenoethers, respectively [80]. Furthermore, when nucleophilic trifluoromethylation of *p*-toluenesulfinimides was carried out under these conditions, good diastereoselectivities were observed for a series of substrates (Scheme 27-b). A comparison with Ruppert–Prakash reagent showed that this nucleophilic trifluoromethylating agent also exhibited significant differences such as in its ability to open cyclic sulfates to produce vicinal trifluoromethyl alcohols with high regioselectivity (Scheme 27-c) [81].

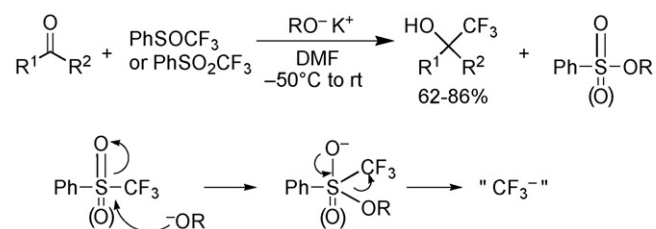## 2.6. Phenyl trifluoromethyl sulfide, sulfoxide, and sulfone

Phenyl trifluoromethyl sulfide, sulfoxide, and sulfone appear to be potential trifluoromethylating reagents by using
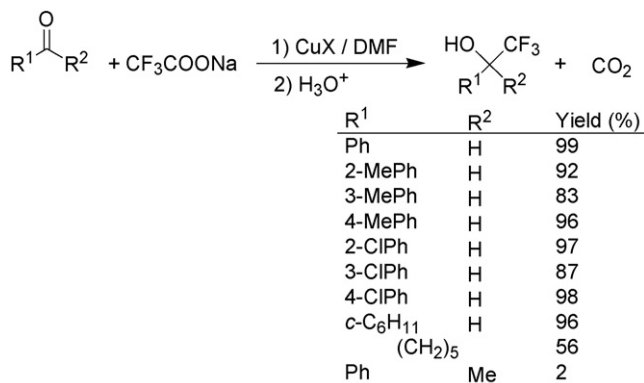
nucleophilic activators. In 1996 and 1997, Yokoyama and Mochida developed the effective formation of trifluoromethyl anion species from the combination of phenyl trifluoromethyl sulfide and Et₃GeNa [82,83]. Temperature is a significant factor for this reaction; at −60 °C, various alkyl, aryl, and unsaturated aldehydes, as well as aldimines could be transformed to the corresponding trifluoromethylated carbinols and amines in good to excellent yields (Scheme 28). However, ketones could not be trifluoromethylated by using this combination system. Interestingly, treatment of various acid methyl esters with the PhSCF₃/Et₃GeNa combination afforded the corresponding trifluoromethyl ketones in excellent yields. This transformation proceeded chemoselectively [84].

Both phenyl trifluoromethyl sulfoxide and sulfone are commercially available materials. Prakash's group presented an efficient potassium *tert*-butoxide induced trifluoromethylation

Scheme 29.

Scheme 30.

R^1	R^2	Yield (%)
Ph	H	99
2-MePh	H	92
3-MePh	H	83
4-MePh	H	96
2-ClPh	H	97
3-ClPh	H	87
4-ClPh	H	98
c-C_6H_{11}	H	96
$(CH_2)_5$		56
Ph	Me	2

by using these two compounds [85]. The trifluoromethyl sulfoxide and sulfone act as CF_3^- donors for transfer to a series of non-enolisable aldehydes and ketones, as well as disulfide into the corresponding trifluoromethylated carbinols and sulfide in good yields (62–86%) (Scheme 29). It is worth noting that DMF is not the only convenient solvent. The reaction also worked well in DMSO. From a mechanistic point of view, the intermediate species, generated from the addition of alkoxide to sulfoxide or sulfone, could act as a real trifluoromethylating agent.

2.7. Miscellaneous

In the 1980s, sodium trifluoroacetate in the presence of copper(I) iodide was employed as a trifluoromethylating agent for aromatic halides [86,87]. Over 20 years later, Chang and Cai developed a novel trifluoromethylation reaction of carbonyl compounds with sodium trifluoroacetate [88,89]. In the procedure, the trifluoromethylated carbinols were obtained in high to excellent yields by using the stoichiometric amount of copper(I) halides or copper(II) bromide as catalysts. Although cyclohexanone could be trifluoromethylated to afford the corresponding product in moderate yield, rather low yield was observed for acetophenone (Scheme 30).

3. Electrophilic trifluoromethylation

It is extremely difficult to generate the trifluoromethyl cation CF_3^+ by chemical reaction. The CF_3^+ ion was suggested in the synthesis of trifluoromethyl triflate from a mixture of triflic acid and fluorosulfuric acid [90]. Otherwise, the CF_3^+ ion has been observed only in the gas phase [91]. The CF_3 group acts as an electrophile when it is polarised in a positive sense by combination with a group containing electronegative elements. With regard to the mechanism of the trifluoromethylation, the controversy remains as for a S_N or a SET mechanism [92–94]. Essentially, two classes of reagents have been developed: the trifluoromethylchalcogen salts (sulfonium, selenonium, telluronium, and oxonium) and the iodonium salts. Umemoto has affirmed that only CF_3 oxonium salts are "real" carriers of CF_3^+ cation [95].

3.1. Trifluoromethylchalcogen salts

In 1984, Yagupol'skii and co-workers described the first electrophilic trifluoromethylating agents 32a,b (Fig. 3), which were prepared by treatment of aryltrifluoromethyl sulfoxides with $SF_3^+BF_4^-$ and subsequent reaction of the fluoro(trifluoromethyl)arylsulfonium salts with arenes. Reagents 32a,b reacted with sodium p-nitrothiophenolate do give the corresponding trifluoromethyl sulfide in 65% yield, but no reaction occurred with N,N-dimethylaniline [96]. Based on this pioneering work, Umemoto and co-workers, in the early 1990s, reported the synthesis of heterocyclic chalcogenium salts, S-, Se-, and Te-trifluoromethyldibenzothio-, seleno, and tellurophenium salts 33 as power-variable electrophilic trifluoromethylating agents (Fig. 3) [97–100].

In the sulfur series, for example, the preparation of reagent 33 started from sulfides 38. After oxidation with m-chloroperbenzoic acid, 39 were cyclised in high yields with the aid of triflic anhydride (Scheme 31). Alternatively, direct fluorination of a mixture of 38 and triflic acid (HBF_4 or BF_3 can also be used) lead to 33 in high yields. Further functional group conversion allowed to get nitro derivatives 40 and sulfonates 34 (Fig. 3, Scheme 31) [101]. Interestingly, the
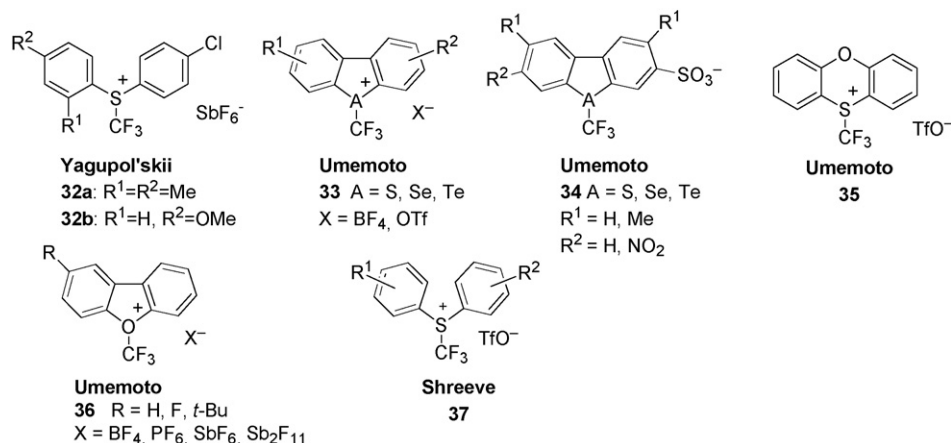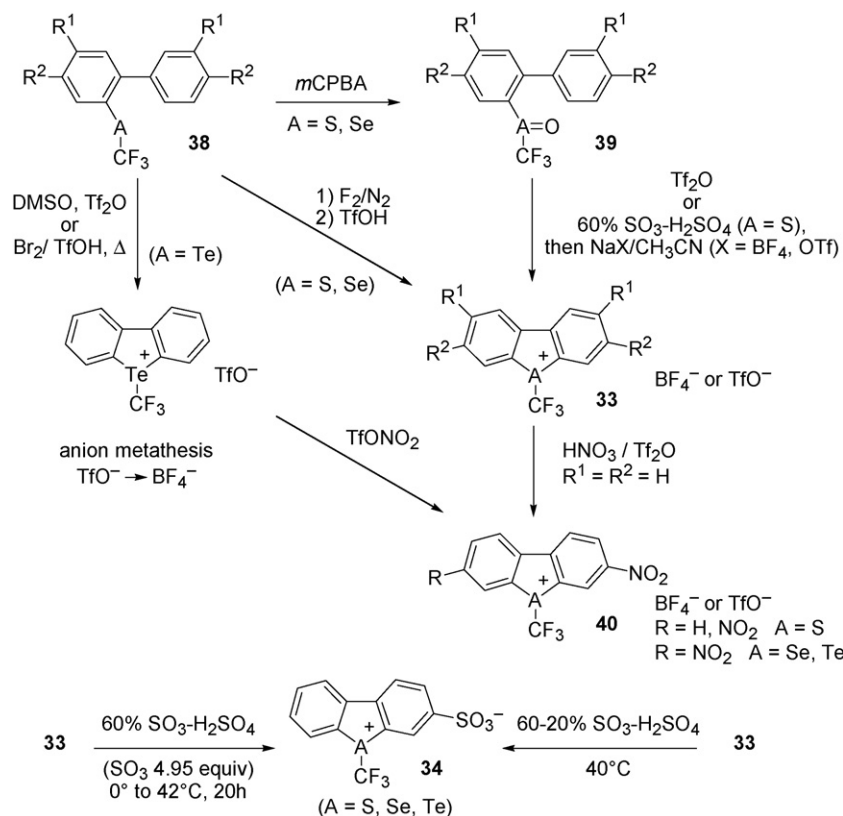

Fig. 3. Electrophilic trifluoromethylating agents.
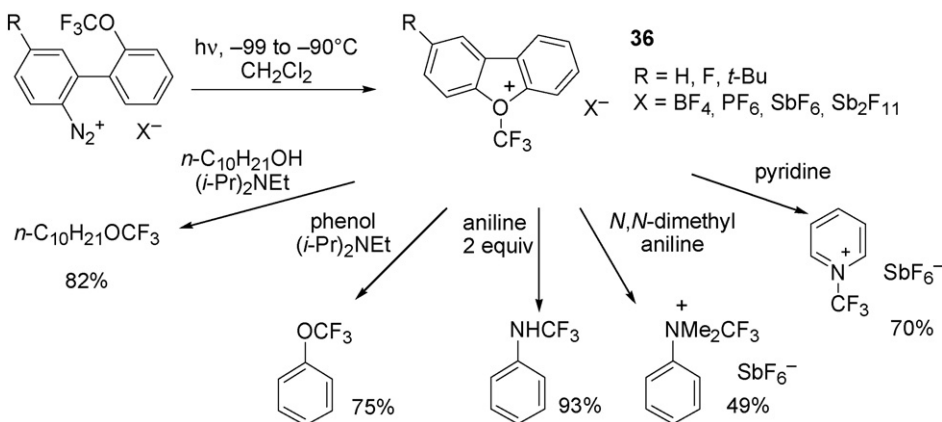
Scheme 31.

counteranion-bound 3-sulfonate derivatives **34** were developed as water-soluble reaction products. The S-trifluoromethylphenoxathiinium triflate **35** was also prepared but in 26% yield.

The reactivity of these reagents increases in the order Te < Se < S and the ring substituents alkyl < H < NO$_2$. Matching the trifluoromethylating agent with the nucleophile (carbanion, silyl enol ether, enamine, phenol, aniline, phosphine, thiolate) made the trifluoromethylation possible as illustrated in Table 1.

In addition to these chalcogenium salts, Umemoto and co-workers described the corresponding *O*-trifluoromethyldibenzofuranium salts **36** (Fig. 3) [95,102]. These thermally unstable
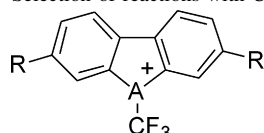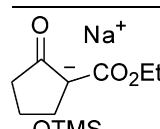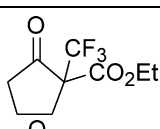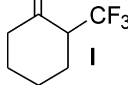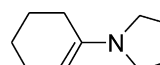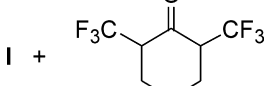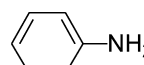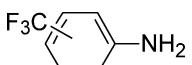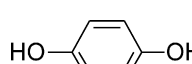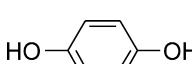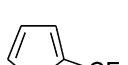
compounds were obtained by chemical decomposition of diazonium salts at very low temperature (Scheme 32). The trifluoromethyloxonium salts decomposed into CF$_4$ and dibenzofuran derivatives from −70 °C and rapidly at −30 °C. However, reaction with *O*- and *N*-centered nucleophiles was possible at low temperature in dichloromethane with in situ generated CF$_3$ oxonium salt; whereas, other chalcogenium salts gave C-trifluoromethylation. This difference in reactivity between O-CF$_3$ and S-, Se, or Te-CF$_3$ reagents allows the author to say that CF$_3$ oxonium salts are real carriers of the electrophilic CF$_3^+$ group.

In 1998, Shreeve and co-workers reported new non-heterocyclic trifluoromethyldiarylsulfonium triflates **37**, which

Scheme 32.

Table 1
Selection of reactions with Umemoto's reagents

33a; A=S, R=H
33b; A=Se, R=H
33c; A=S, R=NO$_2$

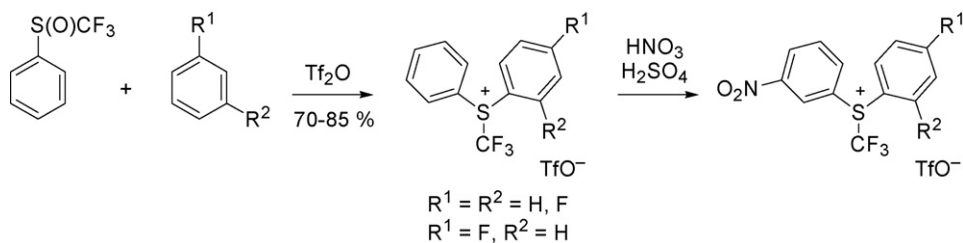| Substrate	Conditions	Product	Yield (%)
	33a 1 equiv., DMF, −65 °C to rt, 2.5 h		67
	33a 1 equiv., Pyr/DMF, 80 °C, 12 h		65
	33a 1 equiv., DM Pyr/DMF, 0 °C, 2 h	I +	57 + 26
Ph≡Li	**33b** 1.1 equiv., THF, −78 °C to rt, 1.25 h	Ph≡CF$_3$	89
	33c 2 equiv., DMF, rt, 0.5 h		*ortho* 54 *para* 20
HO—⬡—OH	**33c** 1 equiv., Pyr/DMF, rt, 2 h		61 + 11 bis(CF$_3$)
	33a 2.5 equiv., DMF, 80 °C, 1.5 h		90
n-C$_{12}$H$_{25}$SNa	**33b** 1 equiv., THF, rt, 0.5 h	*n*-C$_{12}$H$_{25}$SCF$_3$	78
Ph$_3$P	**33c** 1.2 equiv., CH$_3$CN, rt, 5 h	Ph$_3$P$^+$CF$_3^-$, OTf$^-$	78

Scheme 33.

are similar to previous Yagupolskii reagents. Compounds **37** were prepared by treating phenyl trifluoromethylsulfoxide with benzene or its derivatives in triflic anhydride at room temperature (Scheme 33) [103,104].

Reagents with electron-withdrawing substituents on aromatic rings possesses strong electrophilic power. A variety of aromatics that included *p*-hydroquinone, pyrrole, and aniline

reacted under mild conditions with reagents **37** giving modest yields of trifluoromethylated products. The group of Waksel-man recently published a one-pot synthesis of Shreeve's reagents by mixing an aromatic with potassium triflinate in triflic anhydride and dichloromethane at room temperature; interestingly, this procedure allows the in situ formation of the aryl trifluoromethylsulfoxide [105]. Finally, during the 18th
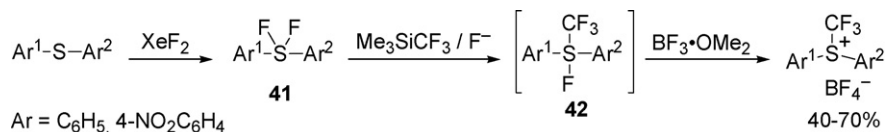
Scheme 34.
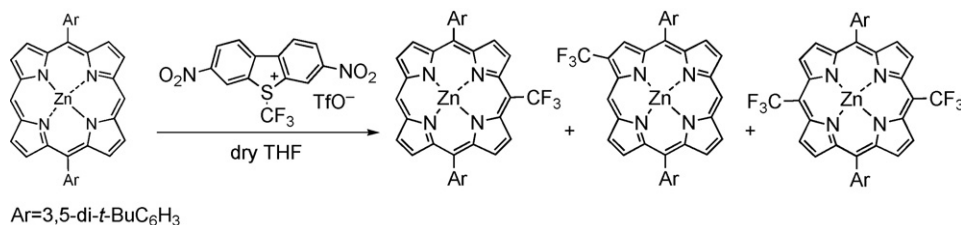
Scheme 35.
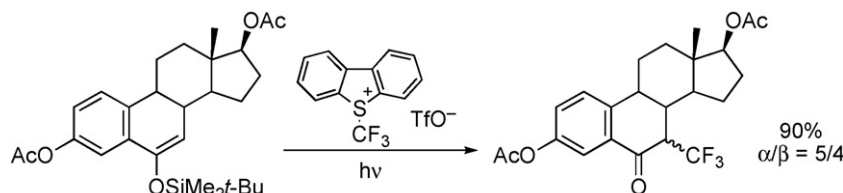
Scheme 36.
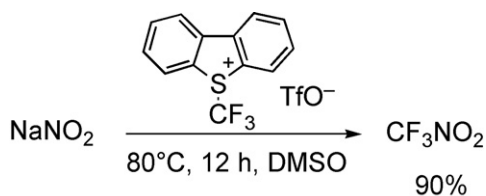
Scheme 37.
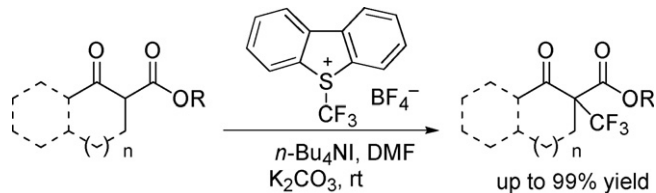
Scheme 38.

ISFC in Bremen, Yagupolskii presented a new synthesis of electrophilic trifluoromethylating agents [106]. The difluorosulfurane **41** obtained from the starting sulfide by treatment with xenon difluoride was reacted with Me₃SiCF₃ in the presence of fluorides to give the intermediate **42** that is further treated with boron trifluoride to end up with the trifluoromethylsulfonium salt (Scheme 34).

In the literature, there are few reports of the use of electrophilic trifluoromethylating agents. Tamiaki and coworkers synthesised trifluoromethylated porphyrins by direct

trifluoromethylation of zinc porphyrins; a mixture of regioisomers was obtained in low yields (Scheme 35) [107].

Estradiol derivatives were trifluoromethylated in 90% yield under UV irradiation by means of 5-(trifluoromethyl)dibenzothiophenium triflate whereas thermal conditions gave only 15% of 7-trifluoromethylated estradiol derivative (Scheme 36) [94].

Shreeve and co-workers demonstrated that trifluoromethylnitromethane can be readily synthesised in 90% yield from the electrophilic trifluoromethylation of sodium nitrite (Scheme 37) [108].

In 2003, we reported the phase-transfer-catalysed electrophilic trifluoromethylation of various ammonium enolates of β-keto esters with the aid of 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (Scheme 38) [109]. The reactions were conducted in the presence of 10 mol% of tetrabutylammonium iodide in DMF at room temperature. Cyclic substrates containing an aromatic ring gave excellent yields whereas acyclic or alicyclic substrates gave moderate yields.

Although the asymmetric electrophilic trifluoromethylation reaction is very important and extremely challenging, chiral reagents are not currently known. Nevertheless, Umemoto reported for the first time in 1994, an enantioselective electrophilic trifluoromethylation mediated by a chiral borepin **43** derived from a binaphthol. The best enantiomeric excess was 45% for 20% yield (Scheme 39) [110].
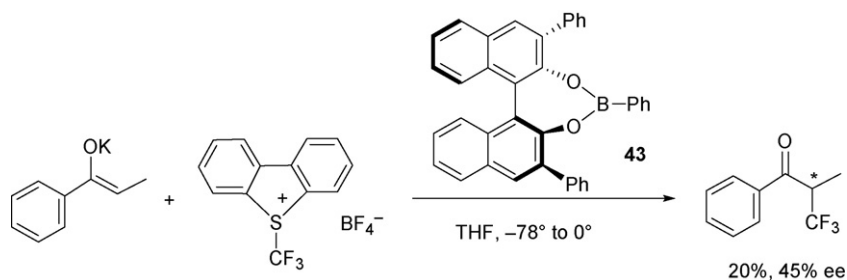
Scheme 39.
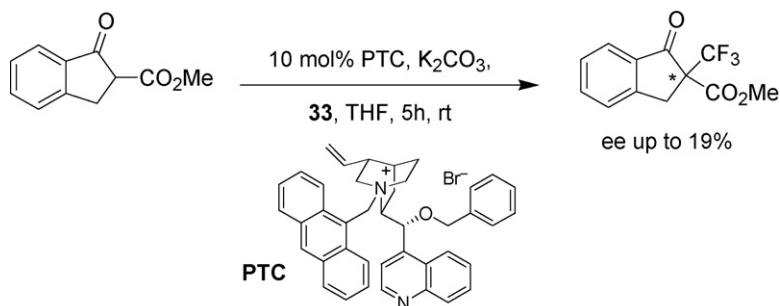
Scheme 40.

As part of our programme for the development of new asymmetric reactions in fluorine chemistry, we examined the use of chiral ammonium salts acting as chiral phase-transfer catalysts (PTCs) in enantioselective electrophilic trifluoromethylation. The glorious history of cinchona alkaloid-derived quaternary ammonium salts led us to consider this family of phase-transfer reagents. We selected the β-keto ester 1-oxo-indan-2-carboxylic acid methyl ester, which gave quantitative yield in the racemic trifluoromethylation, as model substrate for enantioselective electrophilic trifluoromethylation. A screening approach was adopted for the identification of suitable reaction conditions (base, solvent, PTC, temperature). So far, the best enantiomeric excess recorded was 19% (Scheme 40) [111]. This approach looks promising and more experiments will be carried out to get higher ees.

The poor enantioselection observed in this reaction may be attributed to the trifluoromethylation of the potassium enolate rather than the chiral quaternary ammonium enolate. The undesirable process of interfacial trifluoromethylation of the "wrong" ion-pair possessing the potassium cation should be disfavoured and the extraction of the potassium enolate into the bulk organic phase by ion exchange with the chiral quaternary ammonium would be the preferred pathway. To banish the presence of achiral enolates, we decided to use cinchona alkaloids as chiral tertiary bases for promoting enolisation of the β-keto ester and subsequent enantioselective electrophilic trifluoromethylation of the chiral ammonium enolates. Some representative results are reported in Scheme 41.

Chlorinated solvents provided the desired trifluoromethylated product with ee values in the range 10–35%. Hydroquinine gave a higher ee value than hydroquinidine whereas quinine gave a poor yield probably due to its lower solubility in the reaction solvent. Interestingly, a mixture of dichloromethane and hexane (1/2) allowed to obtain the trifluoromethylated product in 53% yield with 71% enantiomeric excess. Such a level of enantioselectivity is attained for the first time for an enantioselective electrophilic trifluoromethylation (previous best ee value was 45% by Umemoto in 1994 [110]) [111].

3.2. Hypervalent iodine(III)-CF$_3$ reagents

It has to be noted that iodonium salts including p-tolylperfluoroalkyliodonium chlorides, perfluoroalkylphenyliodonium triflates (FITS) and perfluoroalkylphenyliodonium hydrogensulfates (FIS), which were described by Umemoto, have been reported as perfluoroalkylating agents but not as trifluoromethylating agents [112–114]. The reason for that is because their synthetic intermediates have low stability compared to the intermediates having R_f groups with more than one carbon atom [92]. It is only recently that Togni and co-workers found an elegant alternative route to trifluoromethylated hypervalent iodine compounds 44 for application in the trifluoromethylation of carbon- and sulfur-centered nucleophiles. The overall protocol depends on a formal umpolung of the CF$_3$ group since a nucleophilic ligand displacement with CF$_3^-$ was carried out at the hypervalent iodine atom during the synthesis of these CF$_3^+$ donor reagents [115,116]. For example, the synthesis of reagent 44a is achieved in a one-pot procedure

Solvent	Base	Temp (°C)	Time (h)	Yield (%)	ee (%)
CH$_2$Cl$_2$	4-ClBzQN	−78	48	0	–
CH$_2$Cl$_2$	QN	−78	12	30	10
CH$_2$Cl$_2$	HQD	−78	12	73	13
CH$_2$Cl$_2$	HQN	−78	3.5	51	29
CHCl$_3$	HQN	20	96	42	25
CHCl$_3$	HQN	−60	96	55	35
CH$_2$Cl$_2$/toluene : 1/1	HQN	−78	72	0	–
CH$_2$Cl$_2$/hexane : 1/1	HQN	−78	72	45	56
CH$_2$Cl$_2$/hexane : 1/2	HQN	−78	96	53	71
CH$_2$Cl$_2$/hexane : 1/3	HQN	−78	96	34	52

Scheme 41.

44a R^1 = Me, R^2 = H
44b R^1 = O, R^2 = H
44c R^1 = CF$_3$, R^2 = H
44d R^1 = CF$_3$, R^2 = Me
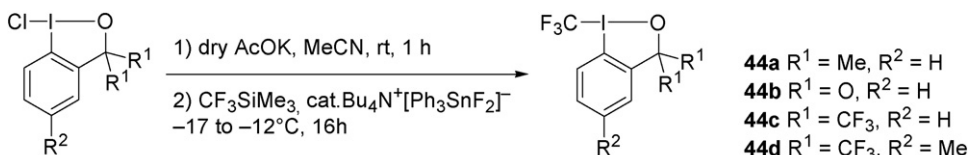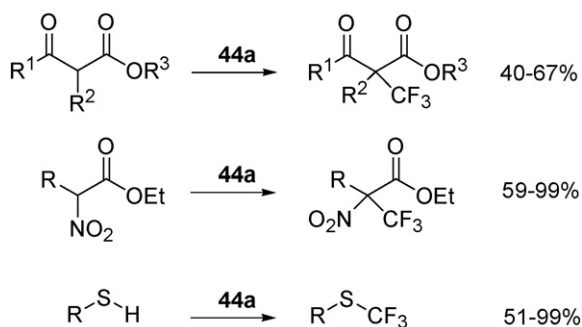
Scheme 42.

Scheme 43.

Fig. 4. Adachi and Ishihara reagents.
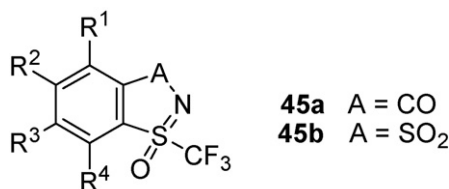
from non-commercial chlorinated substrates in 89% yield (Scheme 42).

Reagent **44a** was found to transfer the electrophilic trifluoromethyl group to cyclic β-keto esters, α-nitro-esters, and to aromatic and aliphatic thiols in moderate to high yields (Scheme 43) [116].

3.3. Neutral S-CF₃ reagents

In 2003, Adachi and Ishihara at Daikin Ind Ltd. patented new reagents, for example **45a** 1-oxo-1-trifluoromethyl-1λ^6-benzo[*d*]isothiazol-3-one (R$^{1-4}$ = H), and **45b** 1-trifluoro-methyl-benzo[1,3,2]dithiazole 1,3,3-trioxide (R$^{1-4}$ = H) as new trifluoromethylating agents (Fig. 4) [93]. With such reagents it was possible to trifluoromethylate carbanions, enamines, and thiolate anions in low to moderate yields.

4. Radical trifluoromethylation

The trifluoromethyl radical can be generated under oxidative, reductive, photochemical, thermal, and electrochemical
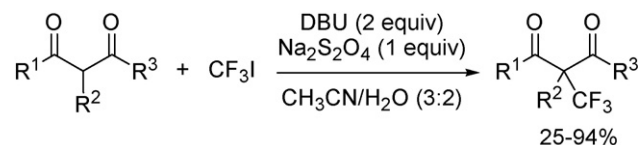
Scheme 44.

conditions. A wide variety of molecules has been used as precursors to trifluoromethyl radicals. Principally, electrophilic trifluoromethyl radicals were reacted with electron rich aromatics and heteroaromatics whereas trifluoromethylation at non-aromatic sites has been somewhat less studied [5]. In this section, only non-aromatic trifluoromethylations will be considered and the most recent publications will be illustrated.

4.1. Trifluoromethyl iodide

Trifluoromethyl radicals have been prepared from trifluoro-methyl bromide, Halon 1301 [117–120], but the Montreal protocol has required its complete phase-out. Replacement of CFCs and halons led to an increased commercial production of trifluoromethyl iodide, in particular for application as a fire extinguishing agent, etching gas, coolant, and trifluoromethy-lating agent. In early works, trifluoromethyl iodide was exploited, for example, in the photochemical trifluoromethyla-tion of steroids [121–123] and in the photochemical reac-tion with enamines to produce α-trifluoromethyl ketones [124,125].

Afterwards, trifluoromethyl iodide has been employed in the sulfinatodehalogenation reaction developed by Huang and co-workers to transfer the CF₃ group to a variety of substrates that include alkenes, alkynes, and arenes. The reaction is promoted by sodium dithionite and related reagent systems [126–128]. Application to this reaction in sugar chemistry was reported by Portella and co-workers [129,130]. More recently, we described the radical trifluoromethylation of ammonium enolates of a series of 1,3-dicarbonyl compounds with CF₃I in the presence of sodium dithionite in CH₃CN-H₂O solution. The ammonium enolates were obtained by action of a nitrogen base such as Et₃N, Et(*i*-Pr)₂N, or DBU (Scheme 44) [131].

The reaction is a free radical process in which sulfinic radical anion generates the highly electrophilic trifluoromethyl radical
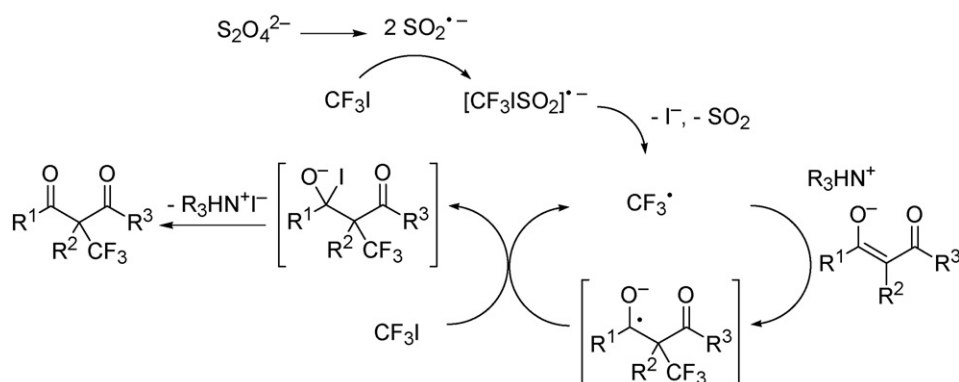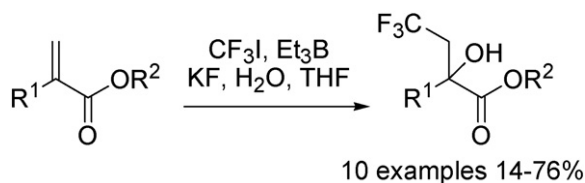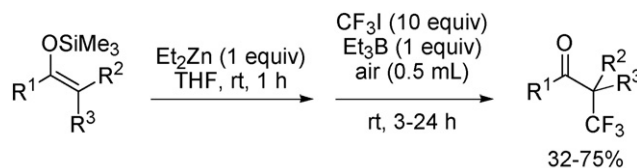

Fig. 5. Proposed mechanism for radical trifluoromethylation of 1,3-dicarbonyl compounds.
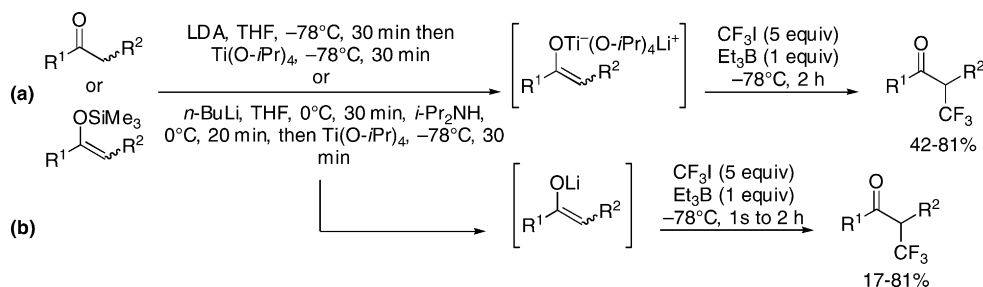
Scheme 45.

Scheme 48.

from CF$_3$I. A mechanism for the radical trifluoromethylation of 1,3-dicarbonyl compounds was proposed (Fig. 5).

The production of trifluoromethyl radical from CF$_3$I could also be mediated by triethylborane. For example, Oshima–Utimoto's group reported the reaction of CF$_3$I with silyl and germyl enol ethers mediated by Et$_3$B in the presence of nitrogen base such as 2,6-dimethylpyridine [132,133]. In 2003, Nagano and co-workers described the radical-mediated hydroxytrifluoromethylation of α,β-unsaturated esters in the presence of Et$_3$B, water, and potassium fluoride in THF (Scheme 45) [134,135].

Recently, Mikami and co-workers have reported radical trifluoromethylations at the α position of a carbonyl group with trifluoromethyl iodide and triethylborane. Noteworthy, the defluorination of the α-CF$_3$ ketone product during the reaction was not observed. Ketone titanium ate enolates were generated from ketone and LDA or from the corresponding silyl enol ether and n-BuLi (Scheme 46-a). The use of excess amounts of LDA and Ti(O-iPr)$_4$ in the generation of titanium ate enolates from cyclic and acyclic aliphatic ketones is crucial to obtain moderate to good yields [136,137]. Highly basic lithium enolates are also applicable to radical trifluoromethylation. The authors demonstrated that the reaction can be extremely fast ca. 1 s (Scheme 46-b) [138–140].

Bidentate ligands were added to the reaction mixture to coordinate lithium enolates and are of particular interest in view of asymmetric radical trifluoromethylation. Although low yields and/or ee values were measured, this approach has great potential and further developments are imminent (Scheme 47) [141].
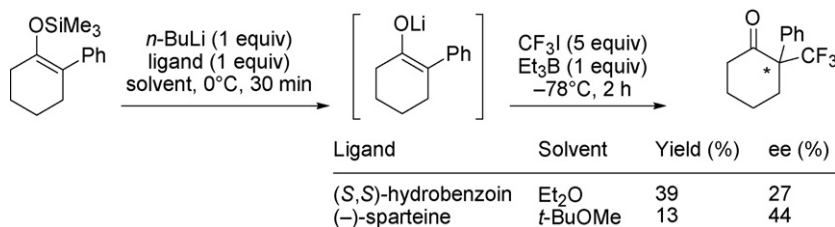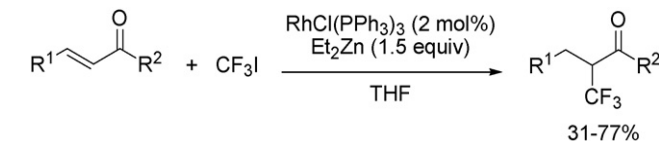
Scheme 49.

Moreover, it complements the diastereoselective trifluoromethylation reported by Iseki and Kobayashi in the 1990s [142–144].

In addition, Mikami and co-workers demonstrated that the formation of enolates from silyl enol ethers could be advantageously replaced by the use of diethylzinc to activate the silyl enol ethers. Indeed, trifluoromethylation of silyl enol ethers in the presence of diethylzinc provided increased yields with wide scope of the ketonic substrates (Scheme 48) [145].

Finally, transition-metal catalysed trifluoromethylation was reported by Ando, Kumadaki and co-workers in a tandem hydrogen transfer—trifluoromethylation on α,β-unsaturated ketones with CF$_3$I in the presence of Et$_2$Zn and RhCl(PPh$_3$)$_3$ (Scheme 49) [146]. A rhodium enolate was proposed as intermediate which reacts with the trifluoromethyl group in a radical or electrophilic manner.

4.2. Trifluoromethylacetyl and trifluoromethylsulfonyl derivatives

In 1979, Zupan reported the reaction of olefins with xenon difluoride in the presence of trifluoroacetic acid in which the

Scheme 46.

Ligand	Solvent	Yield (%)	ee (%)
(S,S)-hydrobenzoin	Et$_2$O	39	27
(−)-sparteine	t-BuOMe	13	44
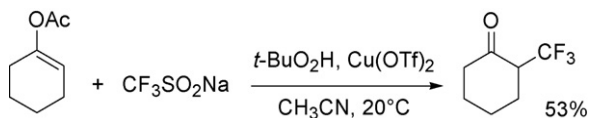
Scheme 47.

Scheme 50.

formation of trifluoromethylated products was explained by the generation of the trifluoromethyl radical [147]. This species can also be electrochemically generated from trifluoroacetic acid and reacted with enolacetates and enols of 1,3-dicarbonyl compounds [148]. Bis(trifluoroacetyl) peroxide was found to trifluoromethylate pyrrole derivatives at low temperature [149]. Trifluoromethylsulfonyl derivatives have been more developed than their trifluoromethylacetyl analogues. Monoelectronic oxidation of sodium trifluoromethanesulfinate with aqueous *t*-butyl hydroperoxide in the presence of copper(II) triflate allowed generation of the electrophilic radical $CF_3^\bullet$ for reaction with enol acetates as described by Langlois and co-workers in 1992 (Scheme 50) [150].

Potassium trifluoromethanesulfinate was used as a source of $CF_3^\bullet$ obtained by electrochemical oxidation; in this way, electron rich alkenes provided mixtures of the corresponding saturated and unsaturated (major) products (Scheme 51-a) [151]. Alkenes were also reacted under photochemical activation with trifluoromethanethiosulfonates CF_3SO_2SR, or trifluorothioacetates CF_3COSR in up to 50% yield (Scheme 51-b) [152].
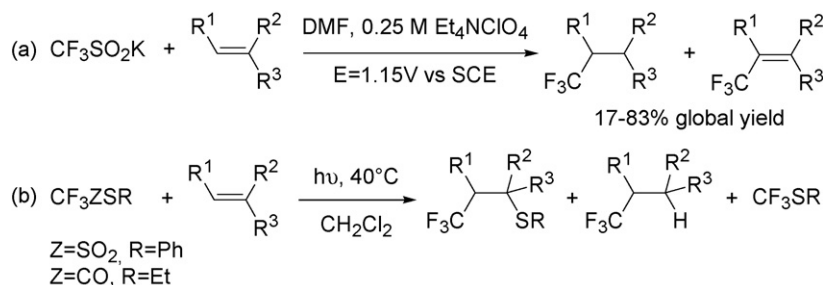
Trifluoromethanesulfonyl chloride has been used in the presence of ruthenium(II) phosphine complex to introduce the

CF_3 group onto alkenes, aromatics, and silyl enol ethers [153–155]. The reaction mechanism involves a redox-transfer reaction between CF_3SO_2Cl and Ru(II) catalyst to afford the corresponding anion radical precursor of CF_3 radical by extrusion of sulfur dioxide. The reaction took place at 120 °C in benzene as illustrated in the case of silyl enol ethers; unfortunately, trifluoromethylation and chlorination occurred depending on the substituent of silyl enol ether (Scheme 52) [153]. Similarly, vinyl ethers and vinyl esters have been reacted with trifluoromethanesulfonyl chloride with the aid of AIBN or benzoyl peroxide [156].

Fuchs and Gong utilised acetylenic triflones in conjugate trifluoromethyl-alkynylation reaction of alkenes. In the presence of AIBN or via photochemical activation, the reaction was instigated by addition of the trifluoromethyl radical to alkene. The yields were dependent on the initiation mode and the reaction time, with the by-products being due to allylic hydrogen abstraction reactions (Scheme 53) [157].

4.3. Other sources of $CF_3^\bullet$ radical

In the early 1980s, Umemoto and co-workers prepared *N*-trifluoromethyl-*N*-nitrosobenzenesulfonamide, TNS-B [158] and *N*-trifluoromethyl-*N*-nitrosotrifluoromethanesulfonamide, TNS-Tf [159] (Fig. 6) in moderate yields by the reaction of trifluoronitrosomethane with hydroxylamine followed by the treatment with sulfonyl chloride in the presence of a base. These stable crystalline solids were good trifluoromethylating agents for aromatic compounds, thiols, and disulfides under

Scheme 51.
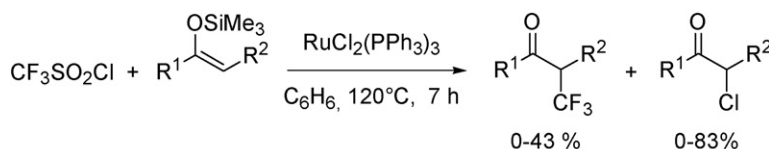
Scheme 52.

Scheme 53.

Scheme 54.

R=(CH$_2$)$_8$CH$_2$OAc, SiMe$_3$, CH$_2$SiMe$_3$,
CH$_2$PO(OEt)$_2$, CH$_2$NHCO(CH$_2$)$_{10}$CH$_3$,
CH$_2$C(CO$_2$Et)$_2$NHAc, CH$_2$OAc, CH$_2$CN
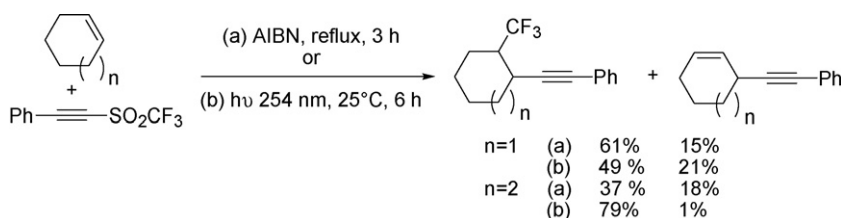
Scheme 55.

Fig. 6. Umemoto's trifluoromethylating agents.

photochemical irradiation or by thermal activation. Compound TNS-Tf generates two CF$_3$ radicals whereas TNS-Nf (Fig. 6) was reported to be a source of both CF$_3$ and n-C$_4$F$_9$ radicals [159]. These reagents were used only in Umemoto's group and not further developed after 1986.

The trifluoromethylation reaction with the aid of Hg(CF$_3$)$_2$, Cd(CF$_3$)$_2$, Te(CF$_3$)$_2$, and Sb(CF$_3$)$_3$ with cyclohexene and aromatics was reported by Naumann and co-workers [160–162]. More recently, the same group described a new system using Bi(CF$_3$)$_3$/Cu(OCOCH$_3$)$_2$, which was applied to the trifluoromethylation of morpholino enamines. Importantly, the reaction occurred only in presence of a copper(II) source (Scheme 54) [163].

Zard and co-workers demonstrated that trifluoromethyl radical obtained by treatment of S-trifluoromethyl xanthates with lauroyl peroxide add at the least hindered side of unactivated alkenes (Scheme 55) [164].
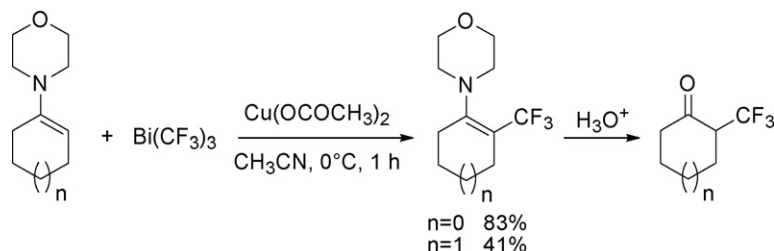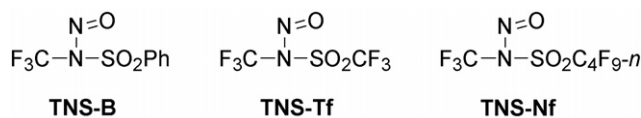
5. Conclusions and perspectives

Creativity in the introduction of the trifluoromethyl group into organic molecules has increased significantly in the past few years. Recent advances in trifluoromethylation reactions are expected to increase the availability of trifluoromethylated compounds and spark off the interest for new building blocks as the basis of valuable active molecules. As highlighted in this review, new reagents have appeared for nucleophilic, electrophilic, and radical trifluoromethylation. Of special interest are the chiral reagents for nucleophilic trifluoromethylation and new methodologies in electrophilic trifluoromethylation.

Indeed, the enantioselective trifluoromethylation is at the forefront of research in fluorine chemistry. Research focused in this area is still under progress and further developments are imminent.

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