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Recent Advances in C-H Trifluoromethylthiolation and Trifluoromethoxylation Reactions

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Abstract: As both trifluoromethylthio (CF_3S) and trifluoromethoxy (CF_3O) moieties have proved to be valuable functionalities in pharmaceutical chemistry, trifluoromethylthiolation and trifluoromethoxylation have received a great deal of attention. For the trifluoromethylthiolation reaction, a variety of efficient methods have been developed. Among these methods, C-H trifluoromethylthiolation avoids the need to prefunctionalize substrates, meaning that this straightforward protocol is quite attractive and promising. The first section of this review summarizes recent advances in this field, including Csp^3-H, Csp^2-H and Csp-H trifluoromethylthiolation and the asymmetric Csp^3-H trifluoromethylthiolation reactions. Trifluoromethoxylation with safe trifluoromethoxylation reagents remains a significant challenge. The second section of this review summarizes the recent progress in trifluoromethoxylation reaction.

Keywords: C-H bond, trifluoromethylthiolation, asymmetric trifluoromethylthiolation, trifluoromethoxylation, trifluoromethoxylation reagent, fluorine.

1. INTRODUCTION

Although elemental fluorine was isolated by Moissan in 1886, organofluorine chemistry was very slow in growing to become a significant field of chemistry [1]. Since the invention of Freons in 1928, followed by the discovery of Teflon in 1938 and the initial pioneering work in medicinal fluorine chemistry in 1954, organofluorine chemistry has played as a distinctive role in the development of various significant industrial and academic areas, such as fluoropolymers, material science, and pharmaceutical and agriculture chemistry [2]. The statistic data that over 150 fluorinated drugs in the market make up about 20% of pharmaceuticals and 30% of agrochemicals clearly demonstrate the exceptional importance of fluorine [3].

The widespread application of fluorine in organic chemistry is due to the unique structure/reactivity relationships observed for fluorine-containing compounds. As the highest electronegative element, fluorine possesses a small atomic radius and exhibits extremely low polarizability. A number of studies have showed that the introduction of fluorine atom(s) or fluorine-containing group(s) into drug candidates can result in many beneficial effects, such as the enhancement of metabolic stability, lipophilicity, membrane permeability, and binding affinity [2d, 4]. Among the various fluorine-containing groups, both trifluoromethylthio (CF_3S) and trifluoromethoxy (CF_3O) moieties has strong electron-withdrawing power [$\sigma_m(CF_3S) = 0.40$, $\sigma_p(CF_3S) = 0.50$; $\sigma_m(CF_3O) = 0.38$, $\sigma_p(CF_3O) = 0.35$], and are highly lipophilic substituents [$\pi(CF_3S) = 1.44$; $\pi(CF_3O) = 1.04$] [5] meaning that the presence of CF_3S- or CF_3O- in drug candidates may provide profound physicochemical modifications [6]. Consequently, determined efforts have been directed towards the development of efficient methods for the incorporation of CF_3S- or CF_3O- groups into organic molecules.

The traditional methods for the incorporation of CF_3S- group include halogen–fluorine exchange reactions [7], trifluoromethylthiolation by CF_3SCl [8] or CF_3SH [9] and trifluoromethylation of sulfur compounds [10]. These methods suffer from the harsh reaction conditions, the use of hazardous or volatile reagent, or the tedious procedure to prepare sulfur compounds. In the past years, a number of general approaches for direct trifluoromethylthiolation have been developed and have proved to be highly efficient due to the mild reaction conditions and high level of functional group tolerance, but many methods require to prefunctionalize substrates [11]. Alternatively, C-H trifluoromethylthiolation represents an attractive protocol owing to atom and step economy. The first section of this review focuses on the recent advances in C-H trifluoromethylthiolation reactions and the asymmetric version. Trifluoromethylthiolation reactions reported in the literature by the end of 2013 have been reviewed by other groups [12], but most of the studies on C-H trifluoromethylthiolation have been reported since 2014. The material in this field appearing in the previous reviews is covered and introduced as background.

The incorporation of CF_3O- group into organic molecules remains a significant challenge [13] The traditional methods including chlorine-fluorine exchange reaction [14] deoxyfluorination of aryl fluoroformates [15] oxidative desulfurization-fluorination [16] and trifluoromethoxylation by CF_3OF [17], suffer from narrow substrate scope or harsh reaction conditions. Trifluoromethylation of alcohols has been found to be a promising method [18]. Clearly, the more straightforward protocol is the direct trifluoromethoxylation avoiding the use of toxic or thermally unstable reagent. The second section of this review summarizes the recent progress in the field of direct trifluoromethoxylation reactions by this protocol.

2. C-H TRIFLUOROMETHYLTHIOLATION

2.1. Csp^3-H trifluoromethylthiolation

Inspired by Togni's recent studies on electrophilic trifluoromethylated hypervalent iodine reagents [10c, 19], the group of Lu

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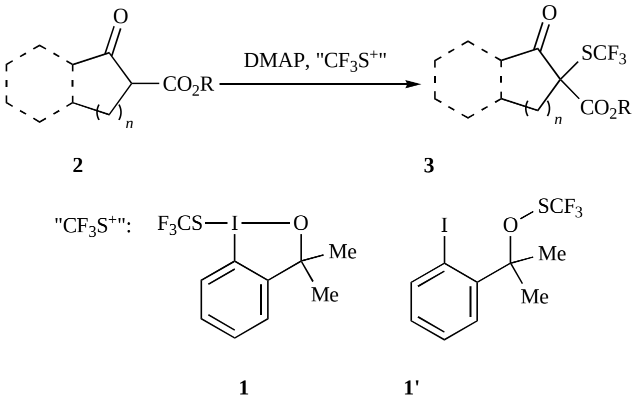
and Shen designed and synthesized a new electrophilic trifluoromethylthiolation reagent **1** to realize trifluoromethylthiolation of cyclic β-ketoesters (Scheme **1**) [20]. The reactions proceeded very well to give the desired products in excellent yields. But the reactions of acyclic β-ketoesters turned out to be quite complex. Although reagent **1** was isolated and characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy, as well as elemental analysis, its structure was found to be problematic by the group of Buchwald [21]. On the basis of a combination of spectroscopic techniques, derivatization experiments, and the crystalline sponge method, Buchwald and coworkers confirmed that **1'** is the correct structure. Before Buchwald's results were published, this reagent was also applied to other reactions (see below). In those reports, they still used the drawing **1** as the structure. But in this manuscript, the correct structure **1'** is used.



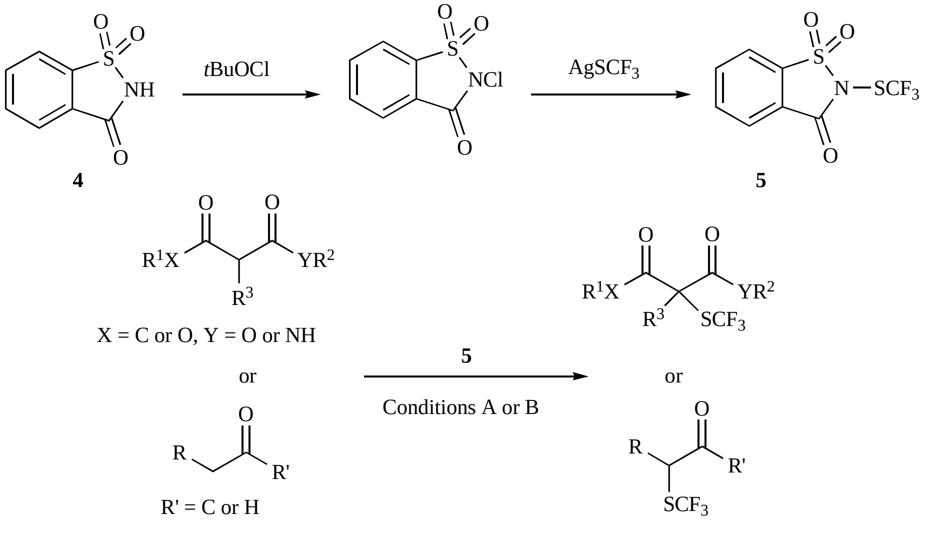
Scheme 1. Trifluoromethylthiolation of cyclic β-ketoesters.

The group of Shen devoted much efforts to explore new trifluoromethylthiolation reagents. Recently, they further developed an electrophilic reagent **5**, which can be easily synthesized from saccharin **4** via chlorination followed by metathesis with $AgSCF_3$ (Scheme **2**) [22]. Reagent **5** can be used for the trifluoromethylthiolation of acyclic β-keto esters and β-ketoamide with the use of NaH as base. Interestingly, NaH is not effective for the reactions aldehydes or ketones. Instead, when morpholine hydrochloride was used as the catalyst, trifluoromethylthiolation of aldehydes or ketones occurred smoothly.

The group of Qing disclosed a copper-catalyzed trifluoromethylthiolation of benzylic C−H bond with readily prepared $AgSCF_3$ via C−H activation (Scheme **3**) [23]. This is the first example of transition-metal-catalyzed direct construction of $Csp^3{-}SCF_3$ bond. Oxidative protocol was employed to activate the $Csp^3{-}H$ bond without the presence of any directing group, which is one of the main challenges of this work. The reaction mechanism is proposed as follows. The redox reaction of Cu(I) with oxidant **7** generates intermediate **In1** and radical **In2**, which can abstract hydride from substrate to produce radical **In3**. The coordination of **In3** to **In1** gives Cu(III) **In4**. The combination of KCl and $AgSCF_3$ produces a new source of $[SCF_3]^-$, ligand exchange of which with **In4** generates **In5**. The reductive elimination of **In5** affords the final product **8** and regenerates the catalyst Cu(I).

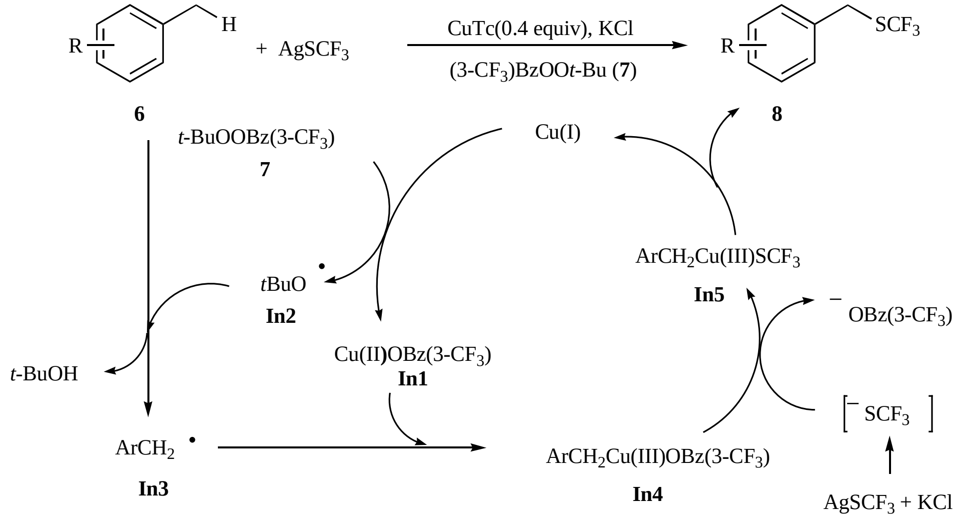
Compared with the above studies on the trifluoromethylthiolation of activated Csp^3-H bond, the trifluoromethylation of unactivated Csp^3-H bond remains challenging. Prompted by the recent work on the construction of Csp^3-F bond through a radical pathway involving the generation of alkyl radicals [24], the group of Chen and Liu investigated the formation of Csp^3-SCF_3 bond through radical Csp^3-H bond activation. They found that the reaction can proceed smoothly with the use of $AgSCF_3$ as the trifluoromethylthio source and $K_2S_2O_8$ as the oxidant (Scheme **4**) [25]. On the basis of the measured kinetic isotope effect (KIE) of 3.3, the radical trapping experiments and the observed reactivity of primary < secondary < tertiary alkanes, they propose that a radical reaction mechanism as shown in Scheme **4** is plausible. $K_2S_2O_8$ is reduced by $AgSCF_3$ to generate sulfate radical anion, which abstracts the hydrogen atom from the substrate to produce the alkyl radical. The oxidation of $AgSCF_3$ by $K_2S_2O_8$ affords $Ag^{II}SCF_3$ species, CF_3S radical, and CF_3SSCF_3, all of which might be readily trapped by the alkyl radical to give the corresponding trifluoromethylthiolated product.

Almost at the same time, Tang and coworkers also reported the trifluoromethylthiolation of unactivated Csp^3-H bond by the same protocol (Scheme **5**) [26]. Interestingly, $Na_2S_2O_8$ was found to be the suitable oxidant, but $K_2S_2O_8$ was not effective at all. Biphasic

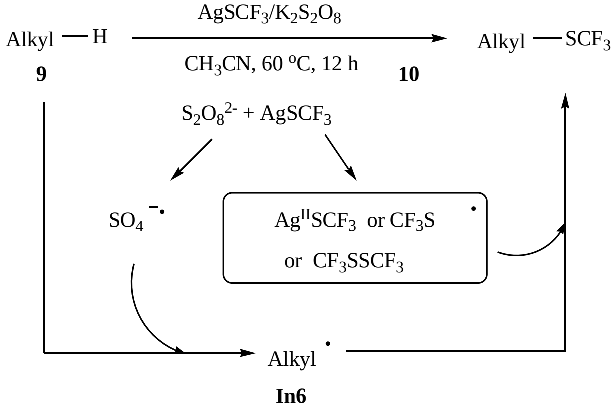


Condition A: NaH as base; Conditions B: morpholine hydrochloride as catalyst

Scheme 2. Trifluoromethylthiolation of acyclic β-ketoesters, aldehydes and ketones.



Scheme 3. Cu-catalyzed benzylic C−H trifluoromethylthiolation.



Scheme 4. Unactivated Csp^3−H trifluoromethylthiolation.

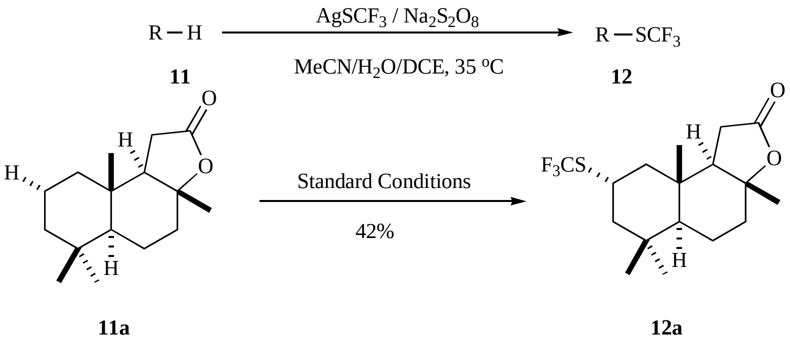
system was used to prevent the oxidation of the starting materials or products by $Na_2S_2O_8$. The reaction shows wide substrate scope and can even be applied to the trifluoromethylthiolation of complex nature product sclareolide **11a**. They propose a similar reaction mechanism as that proposed by Chen and coworkers (Scheme **5**) [25], based on radical trapping experiments and the measured kinetic isotope effect of 3.8.

Very recently, Besset and coworkers describe the Pd-catalyzed trifluoromethylthiolation of unactivated Csp^3-H bond with electrophilic SCF_3 reagent by employing aminoquinoline (8-AQ) as the directing group (Scheme **6**) [27]. At the outset of this study, they anticipated that the reductive elimination pathway for the formation of C-SCF_3 bond formation would be one of the main synthetic issues. Taking into account that the electrophilic SCF_3 reagent might act as both an oxidant and SCF_3 source, readily allowing the C-SCF_3 bond formation via a high Pd oxidation state, they screened various electrophilic SCF_3 reagent and found that reagent **14** was effective for this conversion. The presence of BrØnsted acid PivOH as additive was quite favorable. After ruling out the radical path by radical trapping experiments, they propose that the reaction should occur via C-H activation to produce intermediate **In8**. The oxidative addition of this intermediate and the subsequent selective reductive elimination and protonation afford the final product.

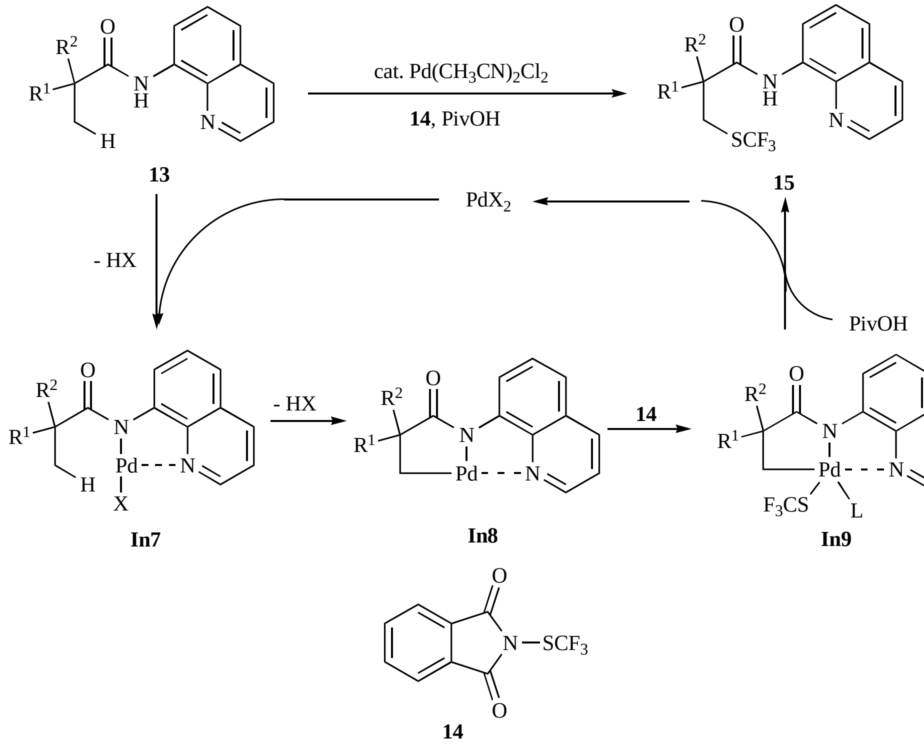
2.2. Csp^2-H trifluoromethylthiolation

In 2012, Daugulis and coworkers reported the first example of a copper-catalyzed ditrifluoromethylthiolation of aromatic Csp^2-H bond with CF_3SSCF_3 (Scheme **7**) [28]. 8-Aminoquinoline (8-AQ) was employed as the directing group in the substrates, and CF_3SSCF_3 was used as the trifluoromethylthiolation reagent. The reaction in DMSO proceeded smoothly to furnish the final products in good yields. They demonstrated that the 8-aminoquinoline group can be efficiently removed in a two-step procedure by amide *N*-methylation followed by base hydrolysis to give trifluoromethylthiolated acid (**19a**) in 85% yield.

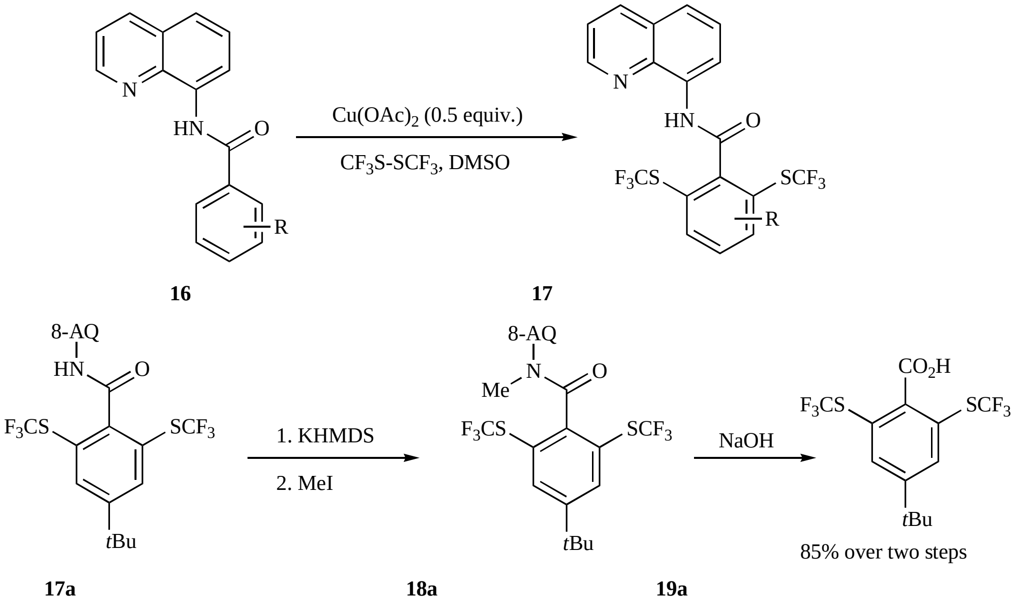
Inspired by Sanford's previous study on Pd-catalyzed selective chlorination of aromatic C−H bond with electrophilic chlorinating reagent NCS [29], the group of Shen investigated the palladium-



Scheme 5. Unactivated Csp^3−H trifluoromethylthiolation.



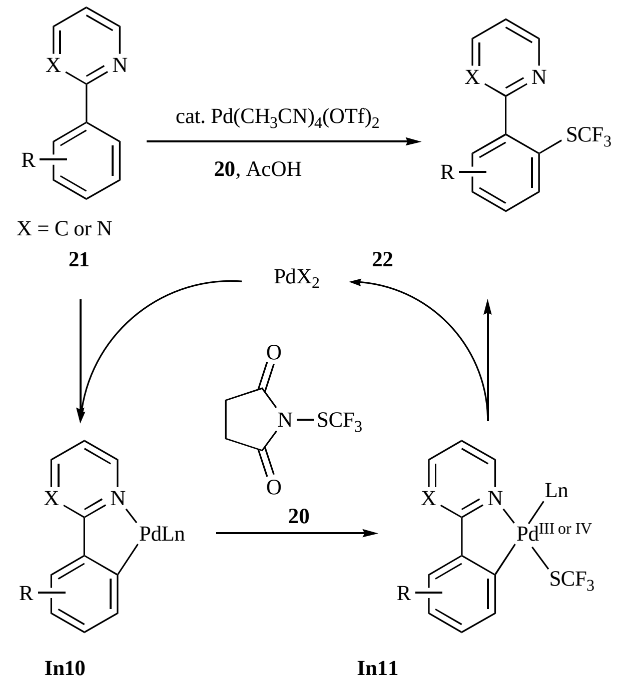
Scheme 6. Pd-catalyzed trifluoromethylthiolation of unactivated Csp^3–H bond.



Scheme 7. Cu-catalyzed trifluoromethylthiolation of aromatic Csp^2-H bond.

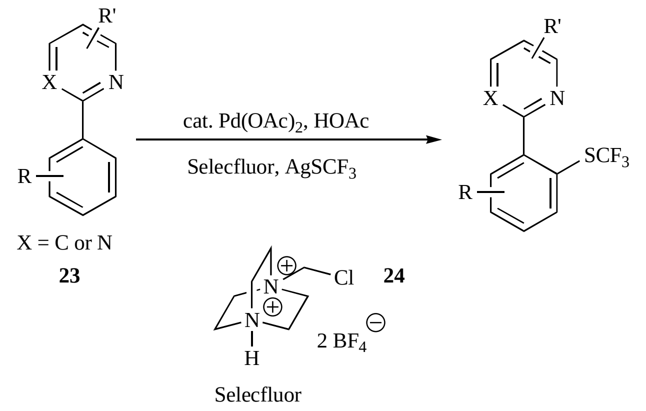
catalyzed monotrifluoromethylthiolation of aromatic Csp^2-H bond reagent with **20**, a structural analog of NCS (Scheme **8**) [30]. The reactions occurred smoothly by employing pyridinyl as the directing group. They carried out some preliminary mechanistic investigations to gain some insights into the reaction. It was found that the final products can be generated from Pd(IV) species, and that C-H bond activation is not the limiting step of this transformation. Based on experimental results, they propose that the reaction is initiated by cyclopalladation of the substrate with catalyst to generate **In10**, followed by oxidative addition to produce Pd(III) or Pd(IV) species **In11**, and reductive elimination to give the desired product. Another pathway that C-SCF3 bond formation proceeds by electrophilic substitution can't be ruled out.

Shortly afterwards, Huang and coworkers developed another protocol for the Pd-catalyzed trifluoromethylthiolation of aromatic Csp^2-H bond (Scheme **9**) [31]. In this work, pyridinyl was also employed as the directing group, but they used the oxidant/"CF_3S^-" system instead of "CF_3S^+" **20** to realize this conversion. After examining various oxidants, they found that Selecfluor was the suitable choice. Interestingly, a positive primary KIE (k_H/k_D=2.7) was observed in both intermolecular and intramolecular KIE experi-



Scheme 8. Pd-catalyzed trifluoromethylthiolation of aromatic Csp^2-H bond.

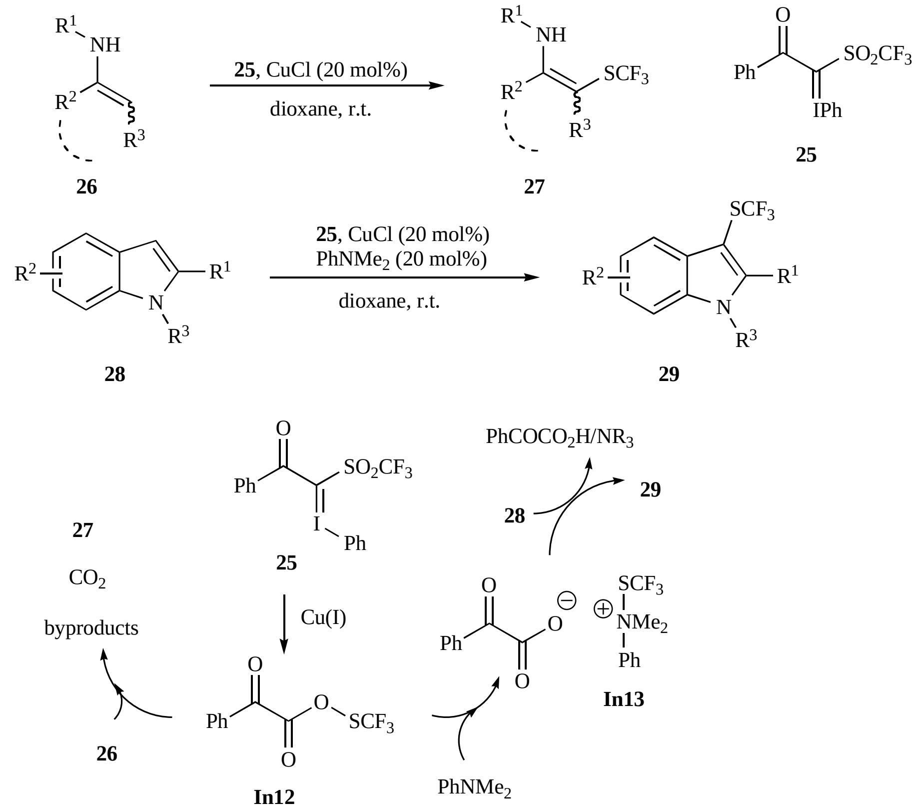
ments, indicating that C-H activation step is the rate-determining step.



Scheme 9. Pd-catalyzed trifluoromethylthiolation of aromatic Csp^2-H bond.

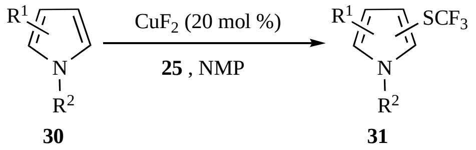
The group of Shibata recently developed a new trifluoromethanesulfonyl hypervalent iodonium ylide (**25**) for copper-catalyzed trifluoromethylthiolation of enamines and indoles (Scheme **10**) [32]. Interestingly, the CF_3S moiety in the products comes from the CF_3SO_2 group in ylide **25**. The CF_3SO_2 group can be in situ reduced to a reactive CF_3S species (**In12**) by intramolecular rearrangement in the presence of Cu(I). The trifluoromethylthiolation of enamines with **In12** may proceed via a single-electron transfer process or an electrophilic path to yield the desired products **27**. But for the trifluoromethylthiolation of indoles, the addition of catalytic amount of $PhNMe_2$ is quite important, which might be because $PhNMe_2$ can convert the intermediate **In12** to another reactive intermediate **In13**. Electrophilic attack of **In13** to indoles affords the final products **29**.

Recently, this group examined the use of reagent **25** in the trifluoromethylthiolation of pyrroles (Scheme **11**) [33]. The reaction conditions are different from that for the trifluoromethylthiolation of indoles. In this work, CuF_2 instead of CuCl was used as the catalyst, and the amine $PhNMe_2$ was not necessary. A broad scope



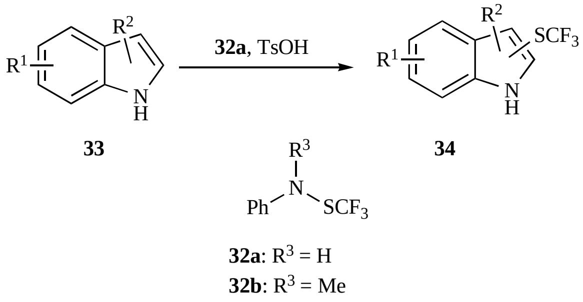
Scheme 10. Hypervalent iodonium ylide for trifluoromethylthiolation of enamines and indoles.

of pyrroles can be converted into the desired products in good to excellent yields. More experimental evidences were collected to prove their hypothesis that **25** can be transformed into **In12** in the presence of copper catalyst.



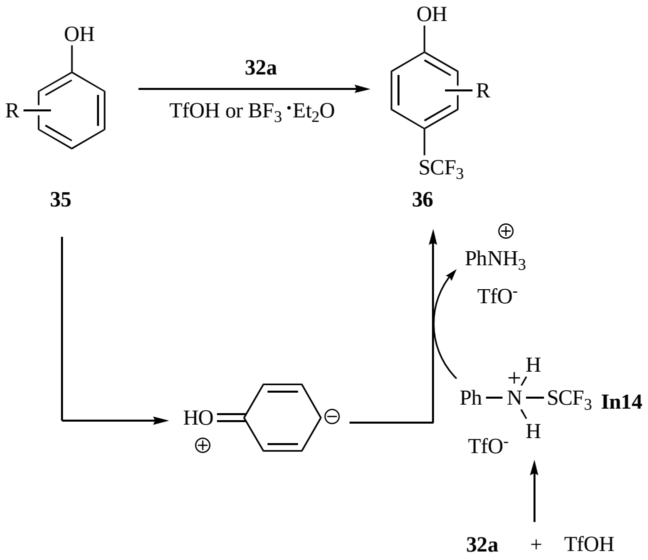
Scheme 11. Hypervalent iodonium ylide for trifluoromethylthiolation of pyrroles.

The group of Billard described an easy synthesis of trifluoromethanesulfanylamides (**32**) and demonstrated that such compounds can act as CF_3S^+ cation equivalent promoted by protic acid or Lewis acid to realize difunctionalization of alkenes [34]. They further tested the trifluoromethylthiolation of various aromatic compounds with **32a** and found that trifluoromethylthiolation of indoles proceeded smoothly in the presence of protic acid (Scheme **12**) [35]. It is proposed that the reacting intermediate is not a real CF_3S^+ cation but a protonated form of **32a** which could be directly attacked by indoles.



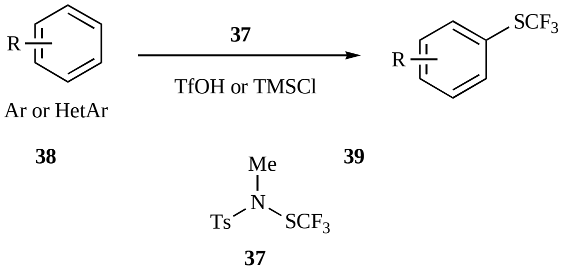
Scheme 12. Electrophilic trifluoromethylthiolation of indoles.

The group of Jereb also examined the reactivity of reagent **32a** and disclosed the electrophilic trifluoromethylthiolation of various electron-rich phenols with this reagent promoted by $BF_3{\cdot}Et_2O$ or triflic acid (Scheme **13**) [36]. They also propose that the protonated form **In14** is the reactive intermediate for this conversion.



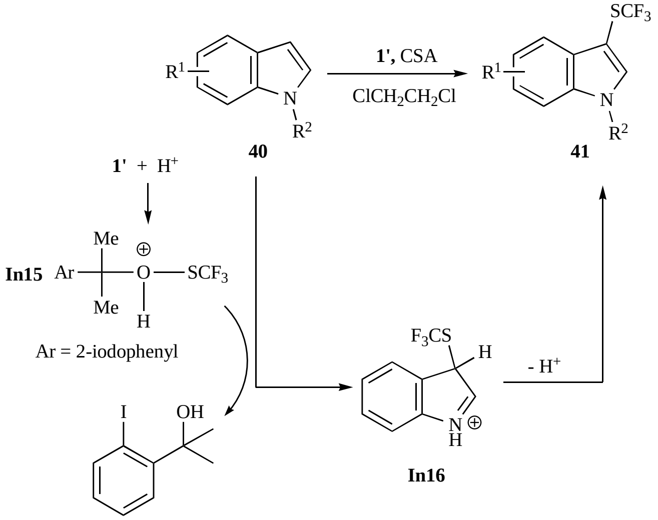
Scheme 13. Electrophilic trifluoromethylthiolation of electron-rich phenols.

Recently, Billard and coworkers developed a 2nd generation of Billard's reagent **37**. which can also act as CF_3S^+ equivalent [37]. Electrophilic trifluoromethylthiolations of various electron-rich aromatic compounds with this new reagent can occur smoothly in the presence of acid (Scheme **14**) [38]. The reaction can also be applied to the aromatic compounds bearing electron-deficient substituents, indicating that this reagent shows higher reactivity compared to its first-generation counterpart **32**.



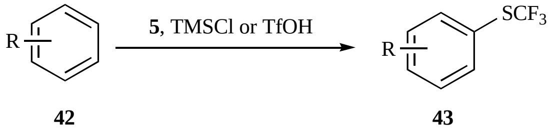
Scheme 14. Electrophilic trifluoromethylthiolation of aromatic compounds.

As described in Scheme **1**, reagent **1'** was developed by Shen and coworkers [20]. They explored an improved method for its synthesis and then further extended the scope of this reagent to trifluoromethylthiolation of indoles (Scheme **15**) [39]. It was found that catalytic amount of CSA (camphorsulfonic acid) can activate reagent **1'** for trifluoromethylthiolation to furnish the desired product in high yields. The protonated form In **15** is proposed to be the active species for this transformation.



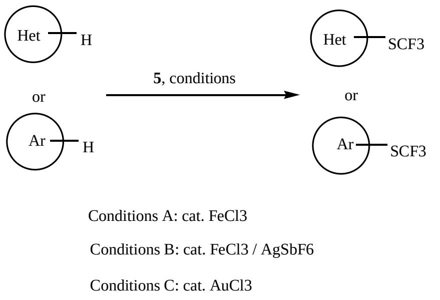
Scheme 15. Electrophilic trifluoromethylthiolation of indoles.

Another reagent **5**, which was also developed by Shen and coworkers, was found to be effective for trifluoromethylthiolation of electron-rich arenes and heteroarenes by the same group (Scheme **16**) [22]. The acid TMSCl or TfOH was quite important for this reaction.



Scheme 16. Electrophilic trifluoromethylthiolation of electron-rich arenas.

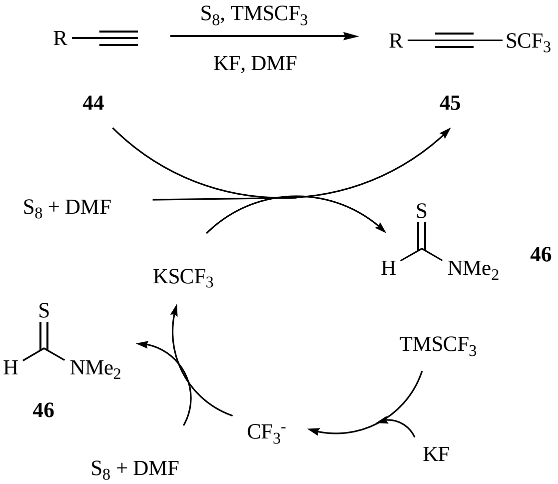
Shortly afterwards, Li and coworkers also reported the synthesis of reagent **5** and the investigation of this reagent in Lewis acid-catalyzed electrophilic trifluoromethylthiolation of (hetero)arenes (Scheme **17**) [40]. For the reaction of electron-rich heteroarenes, the use of $FeCl_3$ as the catalyst can afford the desired products in high yields. But in the cases of activated benzenes, the addition of catalytic amount of $AgSbF_6$ was necessary to activate the catalyst via in situ generation of $Fe(SbF_6)_3$. They also noticed that the sole catalyst $AuCl_3$ instead of $FeCl_3/AgSbF_6$ was also effective for the trifluoromethylthiolation of activated benzenes. The observed KIE of 0.9 suggests that the C-H bond cleavage is probably not involved in the rate-determining step, consistent with the Friedel-Crafts reaction mechanism.



Scheme 17. Lewis acid-catalyzed-electrophilic trifluoromethylthiolation of (hetero)arenas.

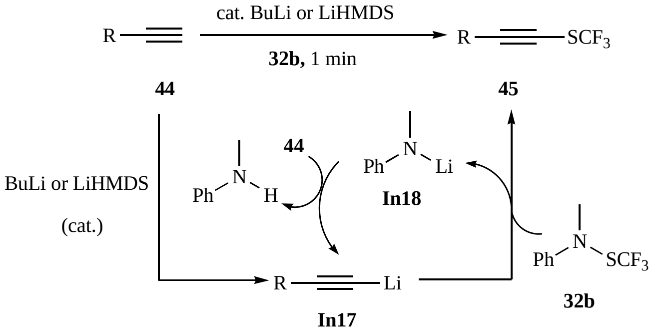
2.3. Csp-H trifluoromethylthiolation

On the basis of their studies on oxidative trifluoromethylation of terminal alkynes [41], Qing and coworkers first reported for the metal-free oxidative trifluoromethylthiolation of terminal alkynes with $TMSCF_3$ and elemental sulfur (Scheme **18**) [42]. The reaction can tolerate various functional groups and afford the expected products in good yields. They propose that the in situ generated CF_3^- anion from $TMSCF_3$ is trapped by elemental sulfur in DMF to produce $KSCF_3$ and compound **46**, followed by the oxidative reaction of CF_3S^- species with terminal alkynes to give the final products. But how the oxidation step occurs remains unknown.



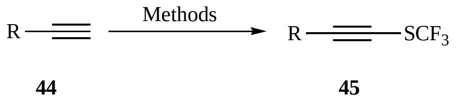
Scheme 18. Metal-free oxidative trifluoromethylthiolation of terminal alkynes.

The group of Billard has previously demonstrated that reagent **32b** can act as CF_3S^+ cation to realize trifluoromethylthiolation of electron-rich substrates [34-35]. They recently further applied this reagent in the base-catalyzed electrophilic trifluoromethylthiolation of terminal alkynes (Scheme **19**) [43]. Interestingly, catalytic amount of base (LiHMDS or BuLi) is enough and the reaction can be completed in 1 min. The reason why the base can catalyze the reaction is that the trifluoromethylthiolation of **In17** with **32b** produces **In18**, which is also a strong base to deprotonate substrates **44** to regenerate **In17**.



Scheme 19. Base-catalyzed electrophilic trifluoromethylthiolation of terminal alkynes.

Both the reagents **1’** and **5** developed by Shen and coworkers were found to be effective for the trifluoromethylthiolation of terminal alkynes (Scheme **20**) [20, 22]. Cu(I) and ligand were necessary in both protocols. The reactions can not only be applicable for aromatic alkynes, but also be applicable for aliphatic alkynes, demonstrating good reactivity of these two reagents.

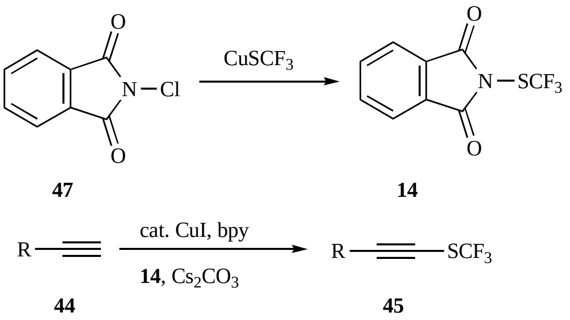


Method A: **1'**, cat. $CuBr(SMe)_2$, bpy, K_2CO_3

Method B: **5**, CuI , pyridine

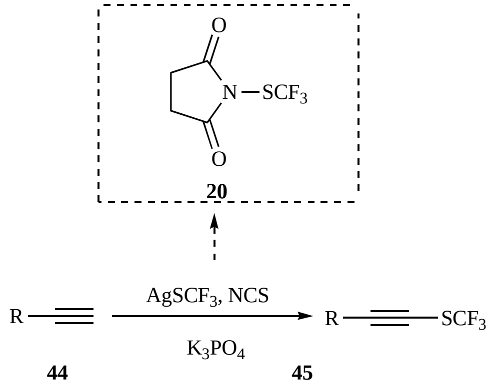
Scheme 20. Cu-mediated trifluoromethylthiolation of terminal alkynes.

The group of Rueping developed a safe method for the synthesis of a convenient and shelf-stable reagent **14** from *N*-chlorophthalimide **47** by employing $CuSCF_3$ as the trifluoromethylthio source (Scheme **21**) [44]. This reagent can also be used to realize Cu-catalyzed trifluoromethylthiolation of terminal alkynes. The transformation can tolerate a wide range of functional groups, including amino, ester, keto, nitro, ethers and heterocyclic groups.



Scheme 21. Cu-catalyzed trifluoromethylthiolation of terminal alkynes.

Inspired by Shen’s work on the synthesis of reagent **1’** from $AgSCF_3$ and hypervalent iodine reagent [20], Qing and coworkers disclosed a Ag-mediated protocol for trifluoromethylthiolation of terminal alkynes by using $AgSCF_3$/oxidant system (Scheme **22**) [45]. They screened various oxidants and found that NCS was quite effective. Intermediate **20** was detected by ^{19}F NMR spectroscopy in the reaction mixture, indicating that it may be the active species in this conversion. However, the reaction of alkynes with reagent **20** instead of $AgSCF_3$/NCS system did not afford the expected product, but 65% yield of the product can be obtained in the presence of $AgNO_3$, suggesting that the reaction is mediated by silver.

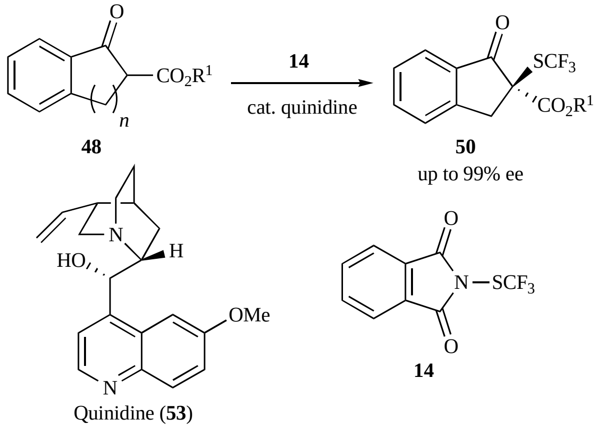


Scheme 22. Ag-mediated trifluoromethylthiolation of terminal alkynes.

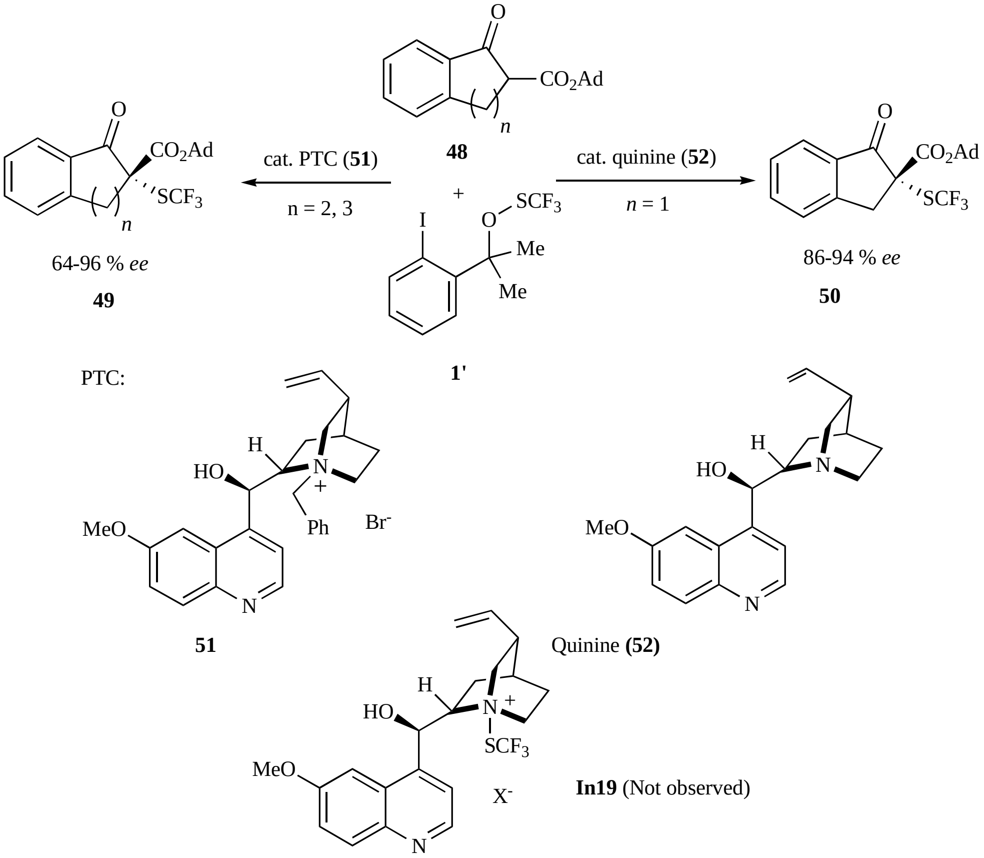
2.4. Asymmetric Csp^3-H trifluoromethylthiolation

Shen and coworkers reported that reagent **1'** can be employed for the asymmetric organocatalytic trifluoromethylthiolation of β-ketoesters (Scheme **23**) [46]. Quinine is an efficient catalyst for the trifluoromethylthiolation of indanone-derived β-ketoesters (five-membered rings) with reagent **1'** to give the expected products **50**. In the cases of tetralone- or 1-benzosuberone-derived β-ketoesters (six- or seven-membered rings), quinine is not effective. Instead, quinine-derived phase-transfer catalyst (PTC) proved to be a good catalyst. The reaction pathway for the quinine-catalyzed trifluoromethylthiolation via **In19** was ruled out based on the experimental evidence that the stoichiometric reaction of reagent **1'** with quinine didn't produce any new species. They propose that the reaction proceeds through the simultaneous activation of the enolate of ketoester and reagent **1'** via the formation of hydrogen bonds with quinine.

Almost at the same time, the group of Rueping disclosed the cinchona alkaloid-catalyzed trifluoromethylthiolation of β-ketoesters with reagent **14** (Scheme **24**) [47]. If quinidine was used as the catalyst, (*S*)-configured products were given with high ee value. Interestingly, if quinine was employed as the catalyst, the products still could be offered with excellent stereoselectivity, but with (*R*)-configuration.

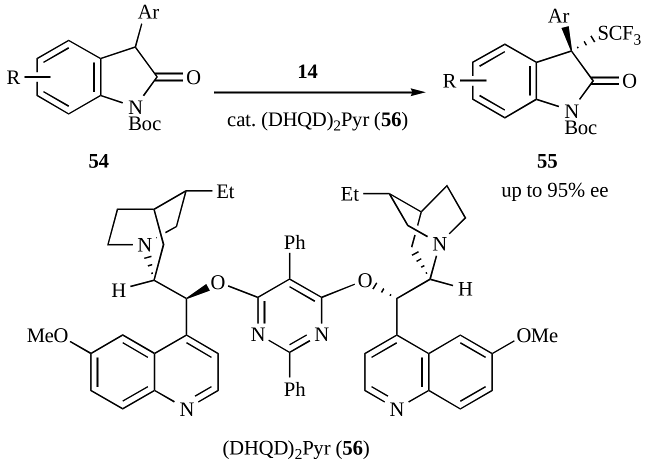


Scheme 24. Asymmetric trifluoromethylthiolation of β-ketoesters.



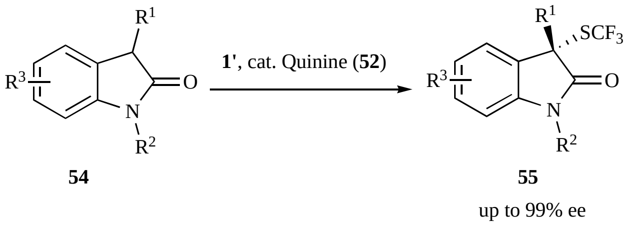
Scheme 23. Asymmetric trifluoromethylthiolation of β-ketoesters.

Shortly afterwards, the same group further applied the cinchona alkaloid-catalyzed strategy to the trifluoromethylthiolation of oxindoles with reagent **14** (Scheme **25**) [48]. Although the use of quinidine as the catalyst can afford the product in high yield, low enantioselectivity was observed. Moderate yield and low ee value were offered when quinine was used as the catalyst. (DHQD)$_2$Pyr was found to be quite effective for this conversion.



Scheme 25. Asymmetric trifluoromethylthiolation of oxindoles.

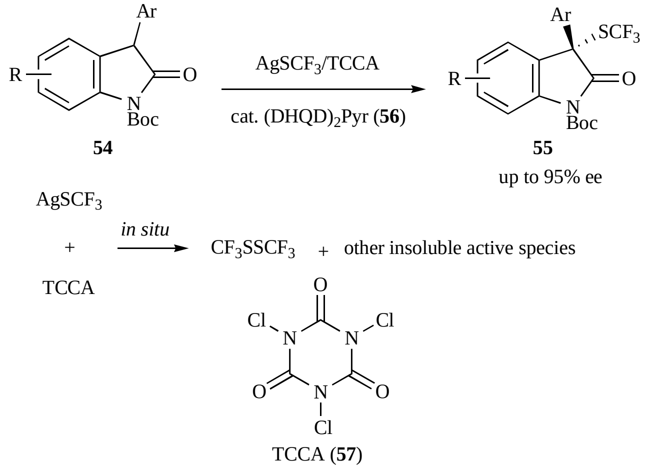
Recently, Shen *et al.* also disclosed the asymmetric trifluoromethylthiolation of oxindoles with the quinine/reagent **1'** system (Scheme **26**) [49] In contrast to the method developed by Rueping [48], this approach seems to show wider substrate scope. Irrespective of whether the R^1 group in 3-position of the substrate is an aryl group or an alkyl group, the substrates can be converted well into the desired products in high yields with high ee value.



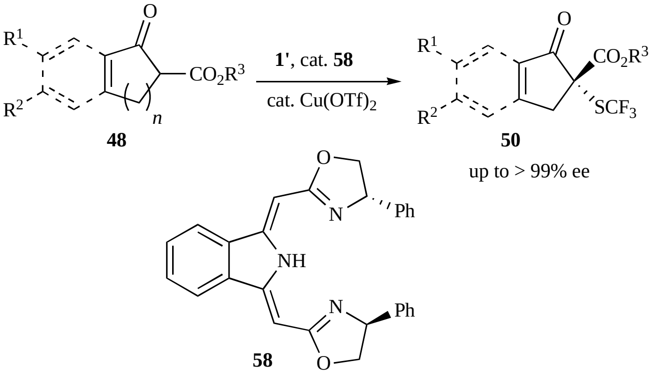
Scheme 26. Asymmetric trifluoromethylthiolation of oxindoles.

The group of Liu and Tan investigated the asymmetric trifluoromethylthiolation of oxindoles with the use of AgSCF$_3$/TCCA system to in situ generate CF$_3$S$^+$ species instead of electrophilic trifluoromethylthiolation reagent (Scheme **27**) [50]. The reaction occurred smoothly to give the expected products in high ee value. They found that the combination of AgSCF$_3$/TCCA can produce CF$_3$S-SCF$_3$, which was confirmed by GC-MS and ^{19}F NMR, and other insoluble species. Interestingly, both CF$_3$S-SCF$_3$ and the insoluble species are active for the asymmetric reaction.

Transition-metal-catalyzed protocol has also recently been utilized for the asymmetric trifluoromethylthiolation. The Cu-Boxmi complexes, which had been shown to be effective for asymmetric trifluoromethylation of β-ketoesters by Gade and coworkers [51], were found to efficiently catalyze for the enantioselective trifluoromethylthiolation of β-ketoesters with reagent **1'** by the same group (Scheme **28**) [52]. EPR and ^{19}F NMR spectroscopy indicates that no reaction occurred between copper complex and reagent **1'**, meaning that copper complex might act as a Lewis acid to stabilize and orientate ester-enolate forms of the substrates.



Scheme 27. Asymmetric trifluoromethylthiolation of oxindoles.



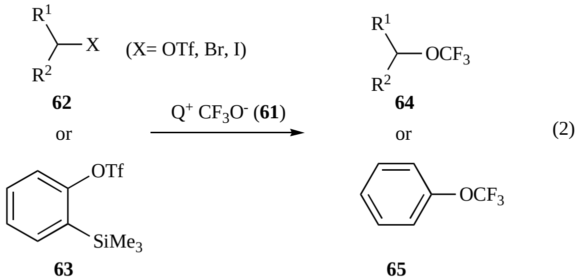
Scheme 28. Cu-catalyzed asymmetric trifluoromethylthiolation of β-ketoesters.

3. TRIFLUOROMETHOXYLATION

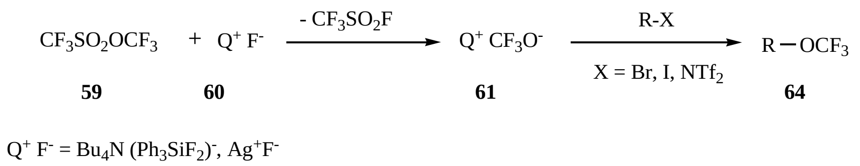
In 2008, Kolomeitsev *et al.* found that anhydrous F$^-$ sources (**60**) can cleave the S-O bond of trifluoromethyl triflate (**59**) to produce trifluoromethoxide salts **61** (eq. 1, Scheme **29**) [53]. Interestingly, some salts are only stable in solvent media, and the others are stable in both solid state and solvent media. These trifluoromethoxide salts can be used to realize trifluoromethoxylation of alkyl triflates, alkyl halides and *o*-trimethylsilylphenyl triflate via nucleophilic substitution or nucleophilic addition (eq. 2).

$$\underset{\mathbf{59}}{CF_3SO_2OCF_3} + \underset{\mathbf{60}}{Q^+ F^-} \xrightarrow{-\ CF_3SO_2F} \underset{\mathbf{61}}{Q^+ CF_3O^-} \qquad (1)$$

Q$^+$ F$^-$ = [(CH$_2$NMe)]$_2$CF$_2$, (M$_2$N)$_3$C$^+$ Me$_3$SiF$_2^-$,
[(CH$_2$NMe)]$_2$CNMe$_2^+$ Me$_3$SiF$_2^-$, Me$_4$NF,
(Me$_2$N)$_3$S$^+$ Me$_3$SiF$_2^-$, Et$_3$N / HF, CsF, KF, AgF



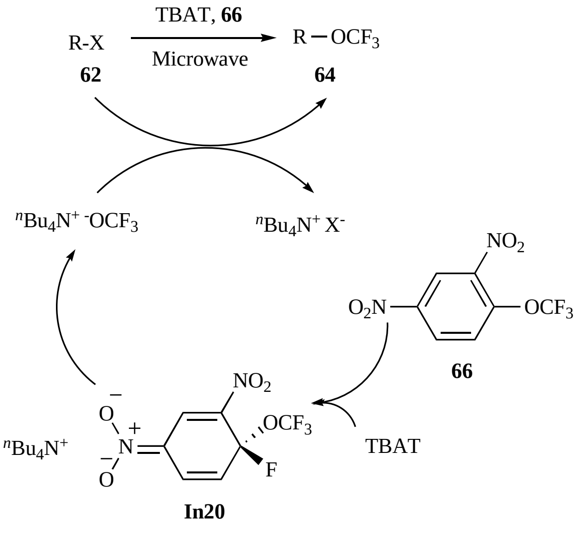
Scheme 29. Nucleophilic trifluoromethoxylation.



Scheme 30. Nucleophilic trifluoromethoxylation.

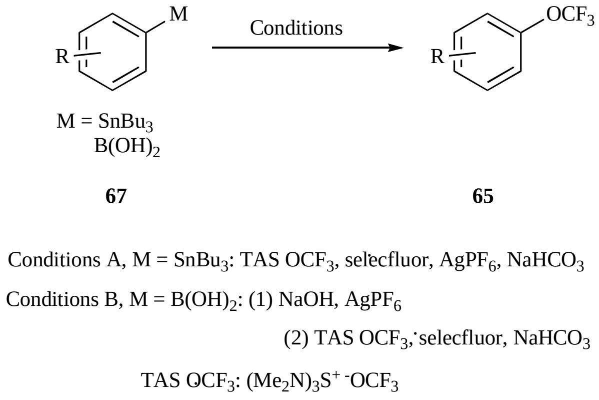
In 2010, the group of Pazenok and Langlois further studied the generation of trifluoromethoxide salts **61** from **59** and their application to trifluoromethoxylation [54]. They concluded that CF_3O^- can be stabilized by bulky counter-cation but the bulkiness of the cation is not the only parameter for stabilization. Both silver fluoride (AgF) and *n*-tetrabutylammonium triphenyldifluorosilicate [($^n Bu_4N^+$)$(Ph_3SiF_2)^-$, TBAT] can react with **59** to in situ produce silver and *n*-tetrabutylammonium trifluoromethoxides, both of which are effective for trifluoromethoxylation of aliphatic bromides and iodides (Scheme **30**). Silver trifluoromethoxide was found to be more efficient for this conversion.

Shortly afterwards, the same group described a new protocol for trifluoromethoxylation (Scheme **31**) [55]. On the basis of the results reported by the group of Amii that C_{Ar}-OCF_3 bond can be cleaved by reduction [56], they reasoned that the CF_3O moiety in an electron-poor (trifluoromethoxy)benzene could be a good leaving-group. Indeed, they found that the moiety in 2,4-dinitro(trifluoromethoxy)benzene **66** can be displaced by fluoride through an S_NAr mechanism. The CF_3O^- generated in situ can substitute reactive bromides such as benzyl and allylic bromides to furnish the trifluoromethoxylation products. Microwave irradiation can broaden the substrate scope of this transformation.



Scheme 31. Nucleophilic trifluoromethoxylation.

In 2011, Ritter *et al.* disclosed the first transition-metal-promoted trifluoromethoxylation. Ag-mediated cross-coupling of functionalized aryl stannanes and arylboronic acids with trifluoromethoxide salt TAS·OCF_3 [57], which had been synthesized by the group of Kolomeitsev [53], afforded the desired product in good yields. Trifluoromethoxylation of arylboronic acids requires a two-step one-pot procedure, but trifluoromethoxylation of the toxic aryl stannanes can be realized in one step (Scheme **32**). Many byproducts may be produced in the reaction of aryl stannanes, such as fluorodestannylation product, hydroxydestannylation product, protodestannylation product, and biaryl product. Although byproduct formation can be minimized in most cases, it remains challenging for some substrates.

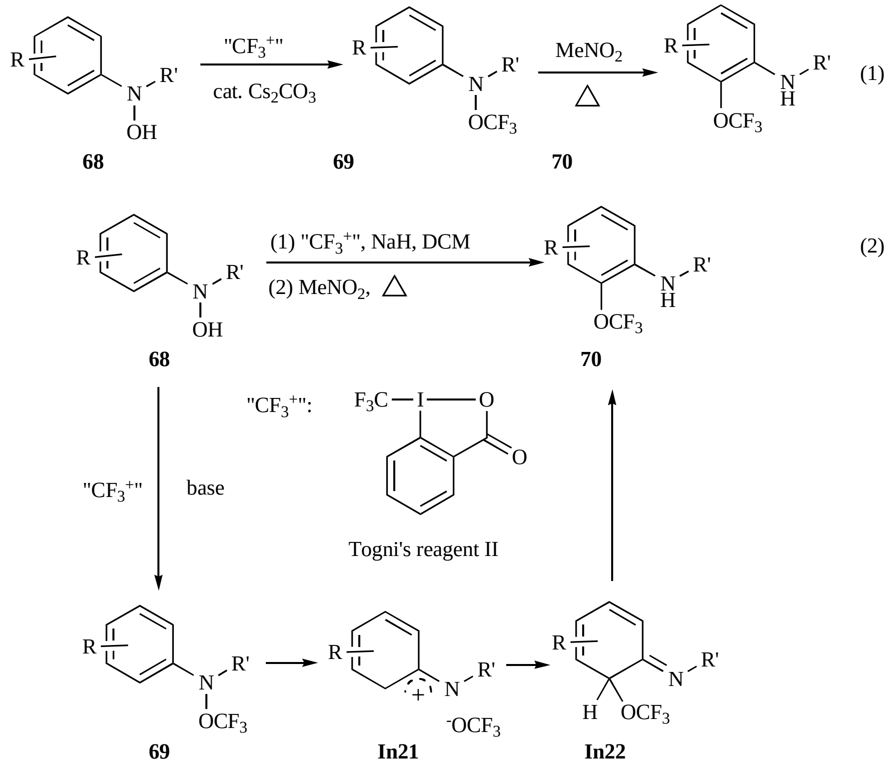


Scheme 32. Ag-mediated trifluoromethoxylation.

Recently, Ngai and coworkers described an interesting protocol for trifluoromethoxylation. They reported that the *N*-aryl-*N*-(trifluoromethoxy)amines (**69**), which can be prepared from protected *N*-aryl-*N*-hydroxylamines (**68**) via trifluoromethylation, can undergo OCF_3 migration to afford the *o*-trifluoromethoxylated aniline derivatives (**70**) (eq. 1, Scheme **33**). Interestingly, the two-step sequence can be integrated into a one-pot transformation without isolating the products **69** (eq. 2). On the basis of experimental evidence and related literature [58], they propose that heterolytic cleavage of N-O bond in compound **69** generates an ion pair of a nitrenium ion and trifluoromethoxide **In21**. Recombination of this ion pair gives intermediate **In22**, facile aromatization of which via tautomerization affords the final product **70**.

4. CONCLUSION

Due to the unique properties of trifluoromethylthio (CF_3S) and trifluoromethoxy (CF_3O) moieties, trifluoromethylthiolation and trifluoromethoxylation reactions have received a great deal of attention. The direct C-H trifluoromethylthiolation avoids the need to prefunctionalize substrates, meaning that this straightforward protocol is quite promising. But for the asymmetric version, the C-H bond has to be highly activated, suggesting that more efforts should be directed towards the development of efficient approaches for the trifluoromethylthiolation of unactivated Csp^3-H bond. Direct trifluoromethoxylation with safe reagents remains a significant challenge. The methods developed so far involves the presence of trifluoromethoxy anion (CF_3O^-), which would be readily decomposed to a highly toxic and corrosive gas difluorophosgene (COF_2). In the field of trifluoromethoxylation, future studies on C-H trifluoromethoxylation and its asymmetric version is highly desirable.



Scheme 33. Trifluoromethoxylation via OCF_3 migration.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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