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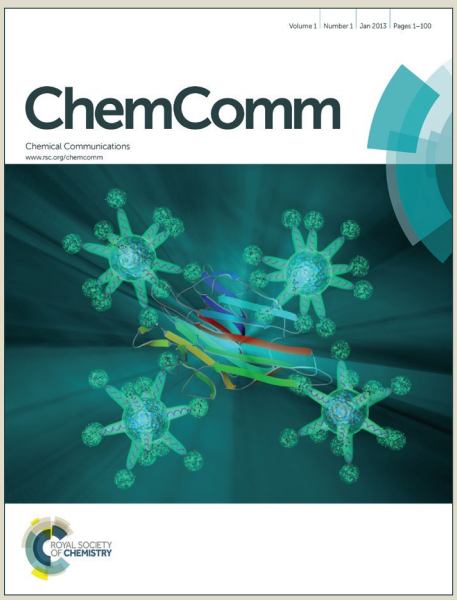

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Electrophilic Trifluoromethylation of Carbonyl Compounds and their Nitrogen Derivatives under Copper Catalysis

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Recent advances in electrophilic trifluoromethylation reactions of carbonyl compounds and their usual surrogates are highlighted with a particular focus on copper-catalysed (or mediated) C-CF_3 bond forming reactions. Ketones and aldehydes (notably via their enol ether and enamine derivatives) enable electrophilic trifluoromethylation at the α-carbon of the carbonyl compound whereas aldehyde *N,N*-disubstituted hydrazones undergo electrophilic attack of the cationic or radical CF_3 species at the azomethine carbon, thus providing an umpolung alternative to nucleophilic trifluoromethylation of carbonyl compounds. A reversal in reactivity is also observed for conjugated systems. While α,β-unsaturated ketones regioselectively incorporate the CF_3 moiety at the α-position of the enones, trifluoromethylation occurs preferentially at the olefinic β-carbon of the corresponding hydrazones.

Introduction

Today, organofluorine compounds, and notably molecules incorporating a trifluoromethyl (CF_3) moiety are at the leading edge of many new developments in the pharmaceutical, agrochemical and material sciences.[1] Thus, tremendous research efforts from both industry and academia are currently focusing on the development of efficient, modular methods that will allow site-selective incorporation of the CF_3 group into a wide range of important scaffolds,[2] an important part of these efforts being concerned with the discovery of new, practical CF_3-transfer reagents such as the Togni (**1**, **2**) and Umemoto (**3**, **4**) reagents (Fig. 1).[3] In this context, transition metal-catalyzed (or -mediated) processes have attracted special attention, notably for the formation of C-CF_3 bonds. For instance, copper salts have been found to be highly efficient CF_3 transfer catalysts,[4] among others.[5-8] Importantly, the low cost and toxicity of copper-based catalytic systems make them particularly attractive when considering to upscale reactions.

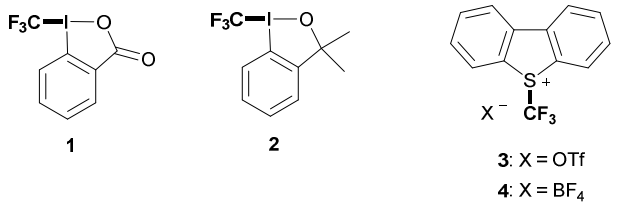

Fig. 1 Commonly used electrophilic CF_3-transfer reagents

As a very timely topic, trifluoromethylation has necessarily been reviewed extensively in recent years.[2-14] The purpose of this review is to highlight recent advances made in the specific field of electrophilic and radical trifluoromethylation of carbonyl compounds and their derivatives, which include enol ethers, enamines, as well as azomethine compounds.

Nucleophilic trifluoromethylation of carbonyl compounds and their nitrogenous derivatives, has led to the development of many synthetically useful processes notably based on the use of Ruppert-Prakash reagent (Me_3SiCF_3) for the synthesis of valuable fluorinated compounds.[9,10] Carbonyl compounds, e.g. aldehydes and esters, undergo nucleophilic 1,2-addition of the trifluoromethyl anion at the carbonyl carbon atom, which provides an attractive synthetic route to trifluoromethylketones (TFMKs, $RCOCF_3$). These are important components of many biologically active compounds and widely used building blocks in the synthesis of fluorinated molecules.[11] Alternatively, azomethine derivatives, e.g. imines and to a much lesser extent hydrazones, readily available from carbonyl compounds and amino derivatives, although less reactive, also react with the CF_3 anion and provide access to α-trifluoromethylated amines and hydrazines, respectively.[12]

Recently, various electrophilic and radical C(sp^2)-CF_3 and C(sp^3)-CF_3 bond formation protocols have been developed for the trifluoromethylation of carbonyl derivatives.[8,13-14] In this area, particular efforts have been made towards introduction of a CF_3 group at the α-position of carbonyl compounds. In some instances, enol ethers as well as enamines have been used as stabilized, metal-free surrogates of carbonyl enolates.[8] Nitrogen-containing derivatives like the azomethines may also be used to modify the reactivity of the carbonyl moiety towards trifluoromethylation and open further opportunities for new

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synthetic strategies or chemical transformations. For instance, trifluoromethylation of aldehydes via their hydrazones is of special interest. *N,N*-Dialkylhydrazones have been extensively used as stable, readily available surrogates for carbonyl-containing compounds and imines.[15] However, they are also especially attractive as umpolung carbonyl reagents due to the presence of the electron-releasing amino component[16] that should activate the azomethine carbon atom position towards electrophilic fluoroalkylation. Interestingly, this could offer an alternative approach to TFMKs upon acidic hydrolysis of the hydrazone moiety. Recent attention has also been payed to C(sp^2)-H trifluoromethylation of conjugated systems as a means of accessing α- or β-trifluoromethylated α,β-unsaturated carbonyl derivatives.[13] Indeed, α,β-unsaturated carbonyl compounds are expected to regioselectively incorporate the CF_3 moiety at the α-position of the enones while hydrazones should undergo preferential trifluoromethylation at the olefinic β-carbon. Conjugated carbonyl compounds - that should also include alkynyl as well as allenyl derivatives - are also expected to be highly attractive substrates for trifluoromethylation-initiated cascade reactions, and notably aryltrifluoromethylation processes. Such complexity-inducing processes enable the efficient synthesis of important fluorine-containing molecules from readily available, properly designed starting materials via a single operation (Fig. 2).

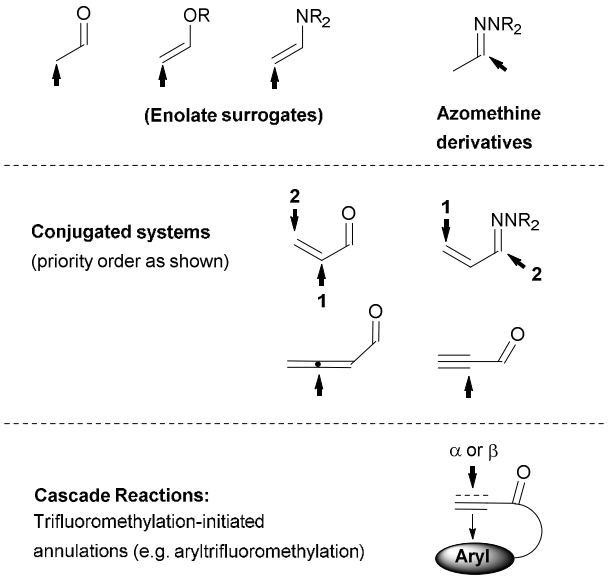
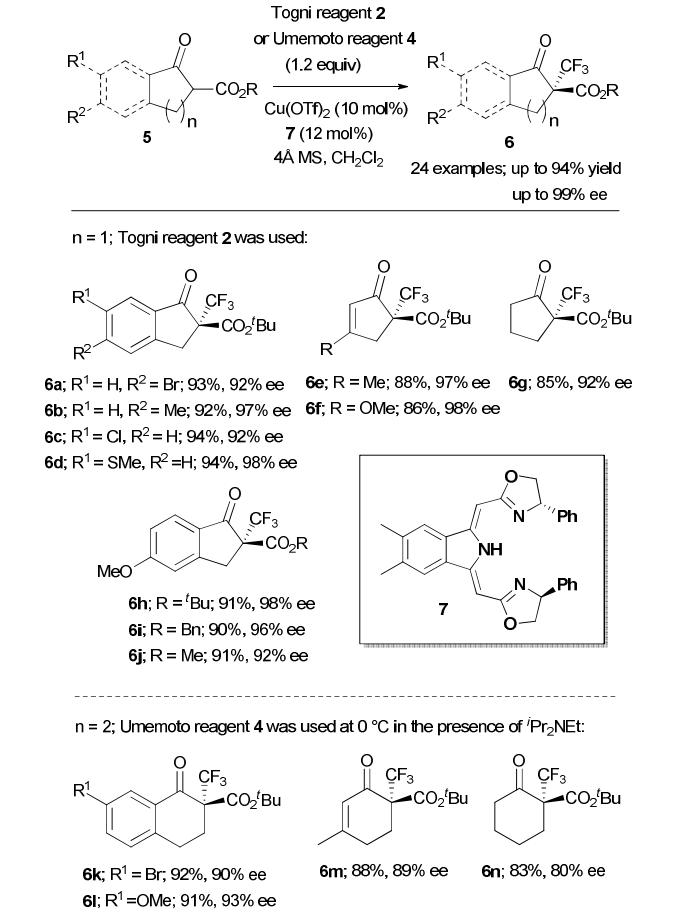


Fig. 2 Carbonyl compounds and some of their surrogates: experimentally observed site selectivity in electrophilic and radical trifluoromethylation

The present article will discuss observed reactivities in electrophilic and radical trifluoromethylation reactions of carbonyl compounds and their usual surrogates, and on this basis will outline site-selectivity issues along with some mechanistic considerations. This review is not meant to be a complete discussion of this area. It has a particular focus on copper-catalysed C-CF_3 bond forming reactions targeting trifluoromethyl-substituted carbonyl derivatives.

1. Trifluoromethylation of carbonyl compounds and surrogates.

As previously mentioned, increasing attention has been devoted in recent years to developing new protocols for direct C(sp^3)-H introduction of a CF_3 group at the α-position of carbonyl compounds, including ketones, aldehydes, esters and amides.[8,17] Notably, Togni and co-workers[18] reported in 2007 that trifluoromethylating reagent **2** was particularly effective for the formal transfer of a CF_3^+ to β-ketoesters and α-nitroesters with no additional base being required since an alkoxide is generated from **2** in the transfer process. Interestingly, they noticed a better reactivity for the otherwise poorly reactive α-nitroesters in the presence of catalytic amounts of a copper salt. Latest significant achievements in this area have been made in the design of asymmetric versions of reactions based on copper catalysis. For instance, Gade and co-workers[19] described in 2012 the highly enantioselective trifluoromethylation of β-ketoesters **5** (Scheme 1). The reaction proceeded best under $Cu(OTf)_2$ catalysis in the presence of the bisoxazoline boxmi (**7**) as stereodirecting ligand. A broad range of cyclic α-CF_3 β-ketoesters **6** were produced with high ee's. While the Togni reagent **2** was found effective for five-membered ring substrates, higher enantioselectivities were obtained with Umemoto reagent **4** in the presence of a base, $^iPr_2NEt$, in the case of the more easily enolizable six-membered ring derivatives. Notably, acyclic ketoesters were found to be unreactive under these reaction conditions.



Scheme 1. Enantioselective trifluoromethylation of β-ketoesters

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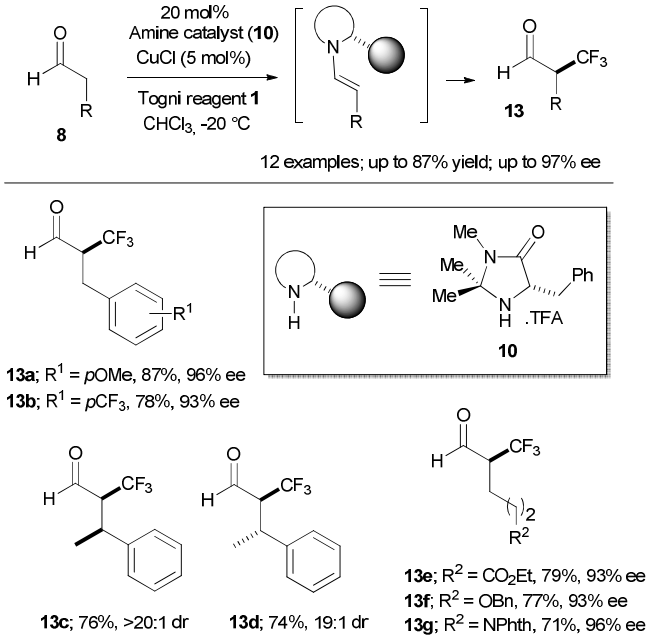
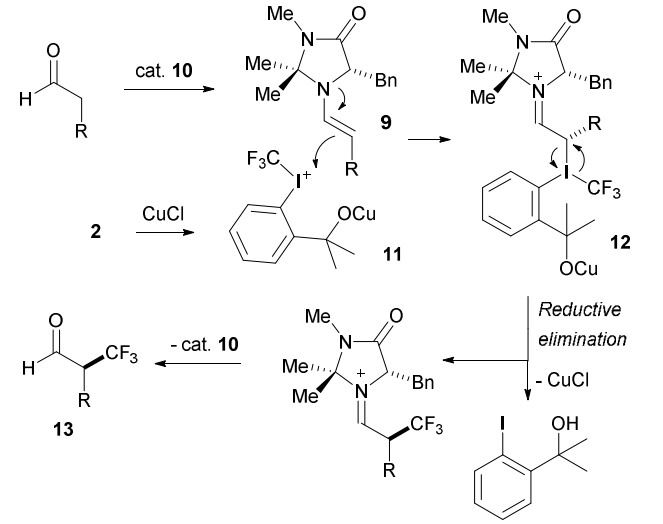
Earlier, in 2010, the group of McMillan[20] had proposed a catalytic enantioselective protocol using Togni reagent **1** for the α-trifluoromethylation of aldehydes that proceeds through enamine activation (Scheme 2). The reaction combines chiral organocatalysis (enamine-activation of aldehydes) and Lewis acid catalysis (activation of Togni reagent) as depicted in Scheme 3. The chiral enamine **9**, generated from imidazolidinone catalyst **10**, is suggested to react with iodonium ion **11** resulting from Togni reagent activation by copper chloride. The resulting iodine species **12** would undergo reductive elimination with stereoretentive alkyl transfer. Hydrolysis would then liberate the α-formyl CF_3 product **13** and recycle catalyst **10**.



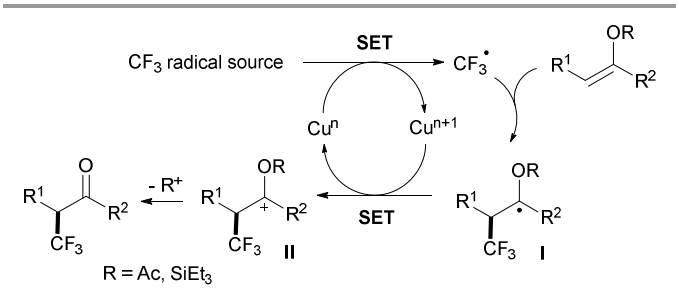
Scheme 2. Enantioselective trifluoromethylation of aldehydes via enamine activation



Scheme 3. Mechanistic rationale for the direct α-trifluoromethylation of aldehydes

It should be noted that copper-catalyzed $C(sp^2)$-H trifluoromethylation of enamides using the Togni reagents has since been described by Loh and co-workers giving the corresponding (*E*)-β-trifluoromethylated enamides.[21]

Copper-catalyzed trifluoromethylation of carbonyl compounds via their enol ethers has also been investigated. Reactions are suggested to proceed via a radical/single-electron transfer (SET) mechanism involving copper-promoted generation of a CF_3 radical. The radical would then add to the enol to form radical intermediate **I**. The latter would subsequently be oxidized via another SET mechanism to the cationic species **II** thereby regenerating the catalyst, and finally providing the α-CF_3-substituted ketone (Scheme 4).



Scheme 4. A general mechanism proposed for Cu-catalyzed trifluoromethylation of enol ethers

As early as in 1992, Langlois and co-workers[22] studied the reaction of aliphatic enol acetates **14** with sodium trifluoromethane sulfinate (CF_3SO_2Na (**15**), the Langlois reagent[23]) in the presence of *tert*-butyl hydroperoxide (TBHP), and observed that addition of a catalytic amount of copper(II), known to be effective in the oxidation of carbon-centered radicals, had the beneficial effect in promoting cleaner reactions (Scheme 5, part 1). Recently, Li and Duan[24] expanded the scope of the reaction to include (hetero)aryl enol acetates, using this time copper iodide as a catalyst (Scheme 5, part 2). Mechanistically, the authors assumed that Cu(I) could catalyse generation of a CF_3 radical from the combination of CF_3SO_2Na and TBHP. The last step in the reaction pathway involves deacetylation of intermediate cationic species **18** that produces the expected α-trifluoromethylated ketone **16**. However, competing abstraction of a hydrogen atom α to the cationic centre could also be observed when aliphatic substrates were used, furnishing the corresponding trifluoromethylated enol acetates **19** as side products (Scheme 6).

Silyl enol ethers **20** have also been investigated as alternative carbonyl surrogates (Scheme 7).[25] The Togni reagent **1** proved very effective as CF_3-transfer reagent, compared to others such as the Umemoto reagent **3**. Interaction of the Cu(I) catalyst with the Togni reagent was also suggested to generate a CF_3 radical (vide infra).[4]

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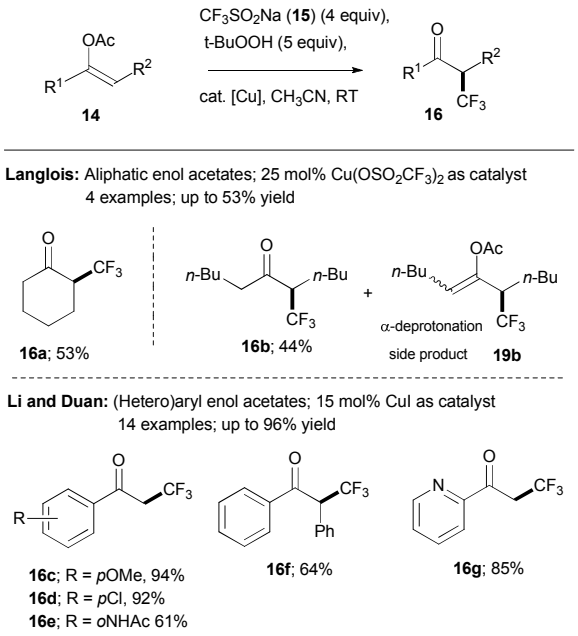
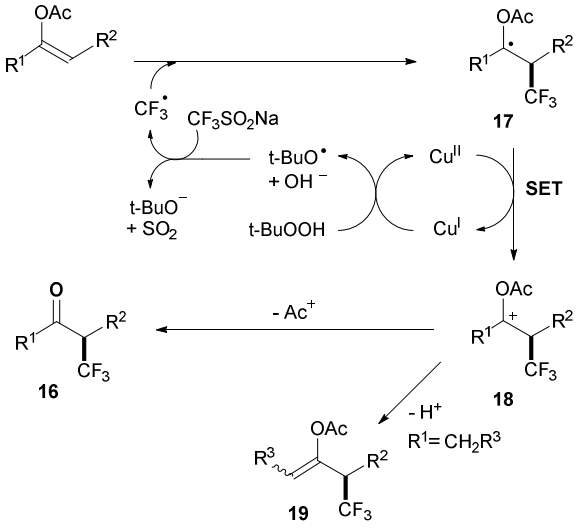


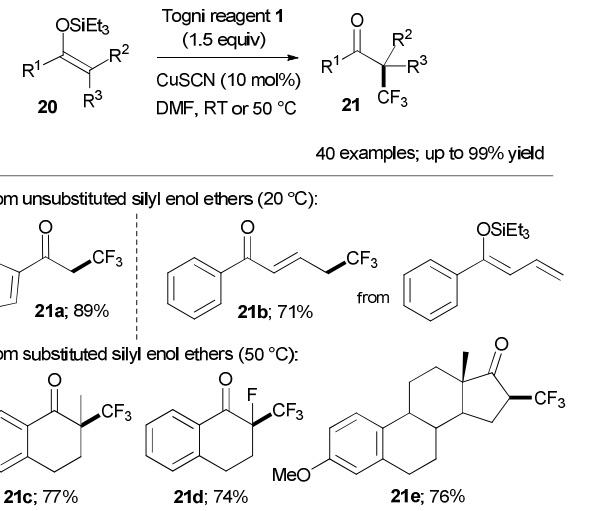
Scheme 5. Trifluoromethylation of enol acetates using the Langlois reagent



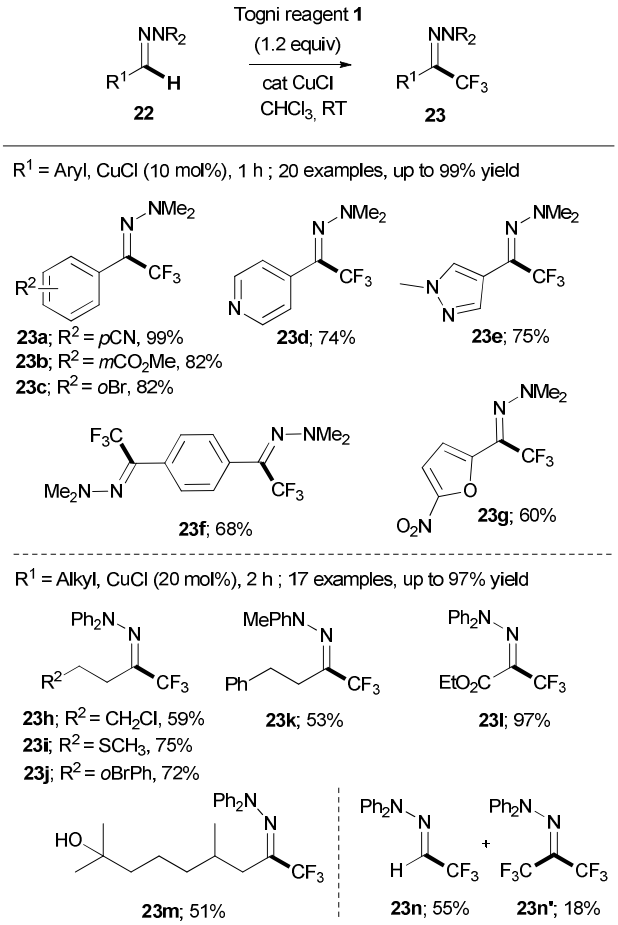
Scheme 6. Possible mechanism for trifluoromethylation of enol acetates using Langlois reagent under copper(I) catalysis

2. Trifluoromethylation of hydrazones.

As mentioned previously, trifluoromethylation of aldehydes via their hydrazones is of special interest. Hydrazones **22** are attractive as umpolung carbonyl reagents that are expected to activate the azomethine carbon atom position towards electrophilic trifluoromethylation. The carbonyl function may then be restored by simple acidic treatment and offer a novel and effective synthetic method to access TFMKs. In 2013, we reported an efficient, mild procedure for the trifluoromethylation of aldehyde *N,N*-dialkylhydrazones based on the use of Togni reagent **1** under copper chloride catalysis, and affording *Z*-isomers of the CF_3-hydrazones **23** exclusively.



Scheme 7. Trifluoromethylation of silyl enol ethers using Togni reagent **1**



Scheme 8. Trifluoromethylation of hydrazones

The method showed low efficiencies for trifluoromethylation of aliphatic aldehyde hydrazones (R^1 = alkyl), the substrate scope being primarily limited to (hetero)aromatic derivatives (R^1 = aryl or heteroaryl) (Scheme 8, part 1).[26] However, the choice of the *N,N*-diphenylamino as the terminal hydrazone amino group

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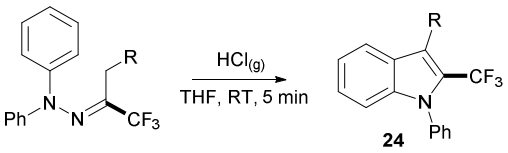
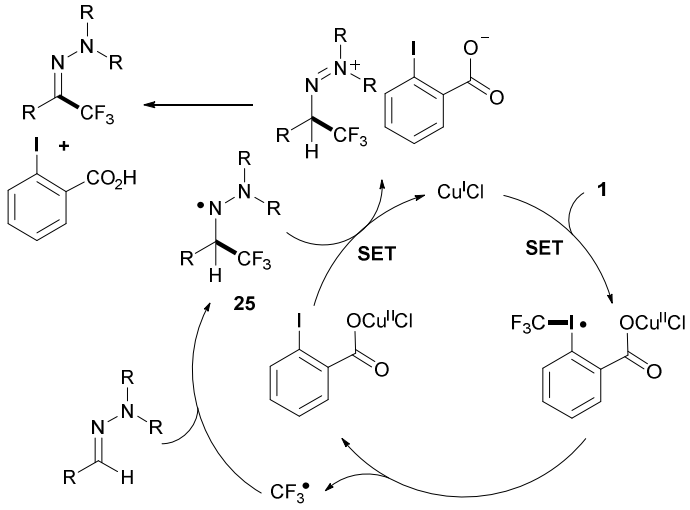
appeared to be the key to efficient trifluoromethylation of aliphatic substrates (Scheme 8, part 2).[27] Trifluoromethylated aliphatic aldehyde *N,N*-diphenylhydrazones were obtained as *E*-isomers, and their synthetic utility was then illustrated as a means of accessing 2-trifluoromethylindole derivatives **24** through Fischer indole-type heteroannulations (Scheme 9).



Scheme 9. Trifluoromethylation of hydrazones applied to 2-CF_3-indole synthesis

A plausible mechanism as depicted in Scheme 10 was proposed. The reaction pathway begins with formation of CF_3 radical, by interaction of the Togni reagent with Cu(I), which would be trapped by the hydrazone to generate the trifluoromethylated aminyl radical intermediate **25**, stabilized by the lone pair of the adjacent nitrogen atom. Finally, oxidation of this intermediate with Cu(II) followed by proton abstraction would restore the hydrazone functional group and recycle Cu(I). The process produced 2-iodobenzoic acid as side-product.



Scheme 10. Tentative mechanism for trifluoromethylation of hydrazones.

3. Trifluoromethylation of conjugated systems.

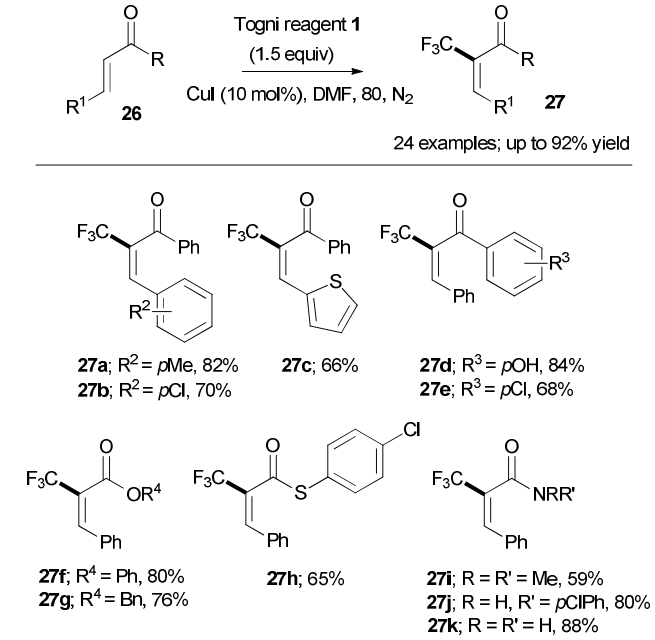
3.1. α-Trifluoromethylation of α,β-unsaturated carbonyl derivatives

Protocols for the direct introduction of a CF_3 group to the double bond of α,β-unsaturated carbonyl derivatives remain rare,[28] electrophilic species being expected to react at the more electron rich α-position of the deactivated double bond.

Bi and co-workers[29] have developed a relatively general method employing a combination of Togni reagent **1** and copper iodide (10 mol%) in DMF that allows an entry into α-(*E*)-trifluoromethylated conjugated enones, esters, thioesters, and amides **27** with a total (*E*)-selectivity (Scheme 11). Again, it is believed that this reaction proceeds via a radical mechanism involving CF_3 radical addition to the conjugated ketone. The carbocation intermediate **29** would evolve to the corresponding alkene with (*E*)-configuration predominantly by deprotonation (Scheme 12).

The groups of Zhang and Wang,[30] as well as Szabo[31] have demonstrated that electron-deficient quinones **30** could also undergo trifluoromethylation with Togni reagent **1** (Scheme 13). Zhang and Wang proposed a CuI-catalysed trifluoromethylation whereas Szabó established a procedure using a catalytic amount of bis(pinacolato)diboron (B_2pin_2) and a stoichiometric amount of CuCN. Both groups also suggested that a radical trifluoromethylation process might be involved in these transformations. B_2pin_2 is believed to act as a radical activator. Zhang and Wang attributed the success of these reactions to the special structure of quinones, since other electron-deficient double bonds (e.g. maleimide, maleic anhydride, and pyrone derivatives) were found unreactive.

Apart from methodologies involving Togni reagent **1**, Yu and co-workers[32] have shown that cyclic and acyclic α-oxoketene dithioacetals **32** could easily undergo α-trifluoromethylation using the Ruppert-Prakash reagent, copper hydroxide as catalyst in the presence of silver carbonate and potassium fluoride (Scheme 14). This high-yielding reaction allowed to obtain a wide range of substrates and showed a good tolerance for functional groups.



Scheme 11. α-Trifluoromethylation of conjugated carbonyl compounds

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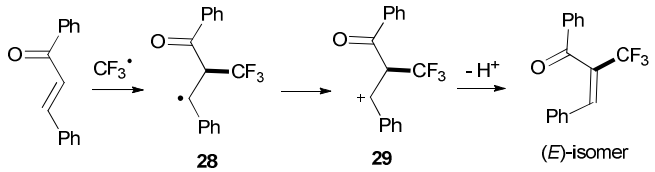
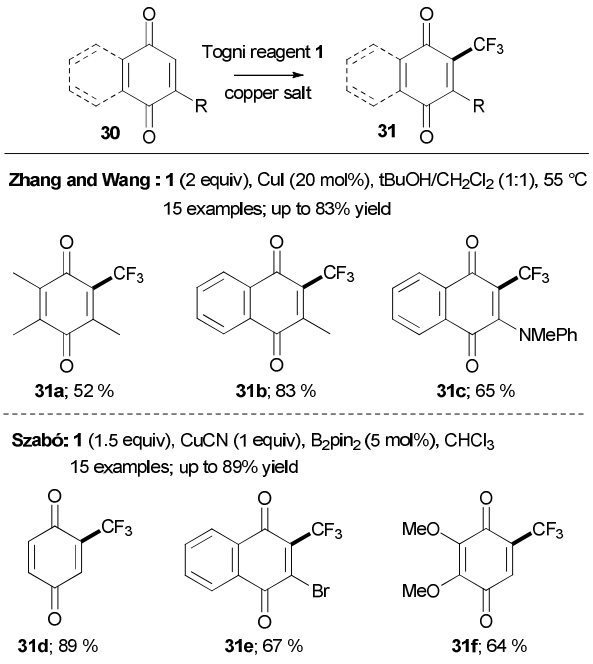
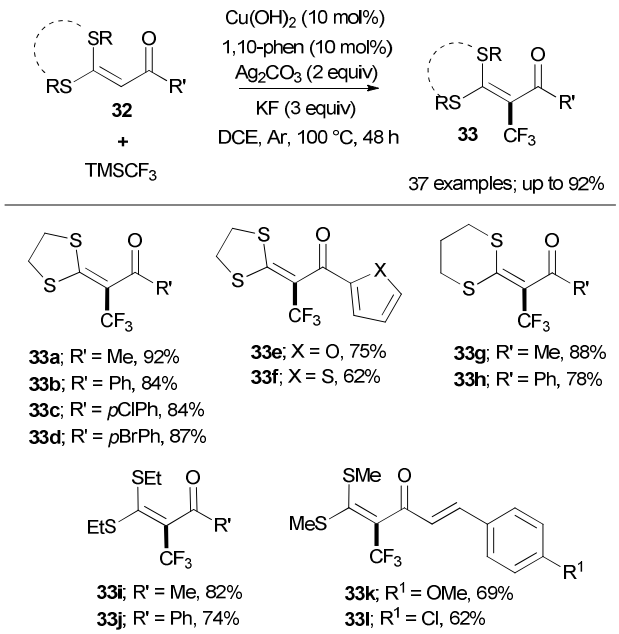


Scheme 12. Regioselective CF_3 radical addition mechanism

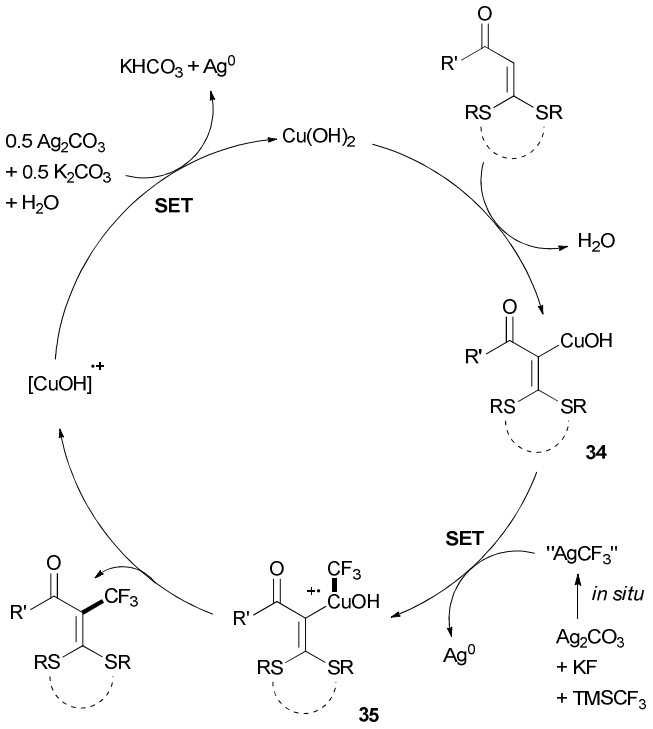


Scheme 13. Trifluoromethylation of quinone derivatives

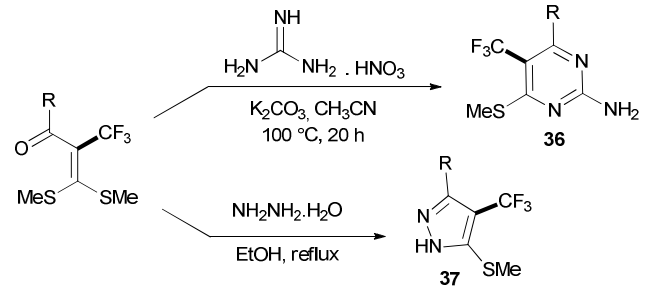


Scheme 14. α-Trifluoromethylation of α-oxoketene dithioacetals with $TMSCF_3$

The postulated mechanism involves insertion of copper in the α-position of the keto group **34** followed by transfer of a CF_3 radical to copper from $AgCF_3$. The latter species is generated *in situ* from $TMSCF_3$, KF and silver carbonate via a SET pathway. Reductive elimination of copper hydroxide delivers the trifluoromethylated alkene, the copper catalyst being regenerated by another SET process (Scheme 15). The methodology provided an easy access to useful building blocks, which serve as precursors of five- and six-membered *N*-heterocycles. This was illustrated by further condensations of the trifluoromethyl dithioacetals, either with guanidine or hydrazine, to afford attractive functionalized pyridimines **36** or 1*H*-pyrazoles **37**, respectively, in good yields (Scheme 16).



Scheme 15. A mechanism involving Ag-associated CF_3 radical



Scheme 16. Application of α-trifluoromethyl α-oxoketene dithioacetals to *N*-heterocycle synthesis

3.2. β-Trifluoromethylation of α,β-unsaturated carbonyl derivatives

Complementary strategies have been recently developed to achieve regioselective, direct β-trifluoromethylation of

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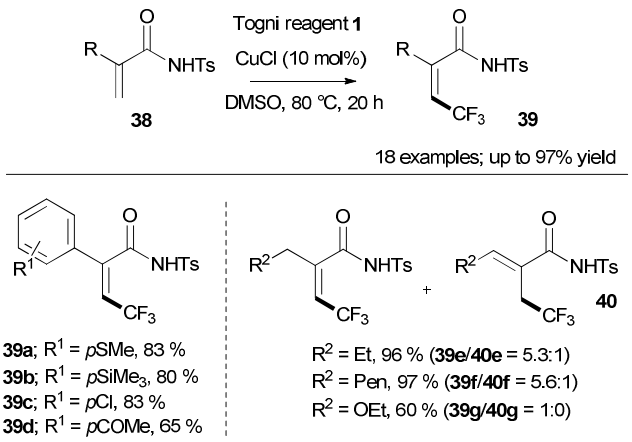
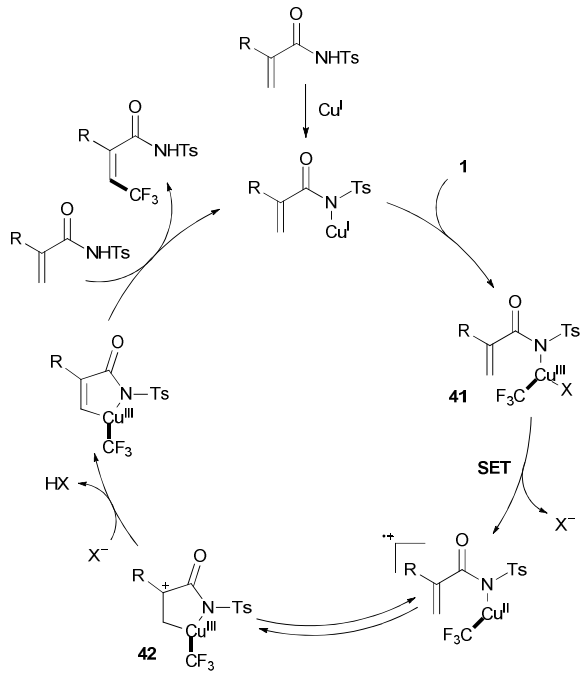
conjugated carbonyl compounds. In 2013, two groups simultaneously reported the β-trifluoromethylation of acrylamides. The first strategy, developed by Loh,[33] involved CuCl as catalyst, the Togni reagent **1** as a source of CF_3 and α-aryl- or alkylacryl *N*-tosylamides as substrates. Owing that all substrates are α-substituted, only the β-regioisomers are selectively formed in good yields. Trifluoromethylation of α-aryl-substituted acrylamides led to the formation of (*Z*)-trifluoromethylated products (**39**) as sole products, whereas α-alkyl-substituted substrates were sometimes accompanied by the allylic trifluoromethyled regioisomer **40** as a side-product (Scheme 17). The *Z* stereochemistry of the double bond seems to be a consequence of attack of the double bond onto a copper species chelated to the nitrogen of the amide moiety **41**, the latter acting as a directing group (Scheme 18). The resulting carbocation intermediate **42** undergoes proton abstraction followed by a reductive elimination of copper to release the final product and regenerate the catalyst. Side products **40** would result from competitive H-elimination at the alkyl group rather than at the α-position of the CF_3 group. Main limitations of the above methods were the necessity of the presence of a substituent in the α-position and the poorer yields obtained when amides were substituted in the β-position.

Shortly after, Cahard and Besset[34] have published a similar reaction starting from α-substituted *N*,*N*-diethylacrylamides. The Umemoto reagent **3** was used as CF_3-transfer reagent in the presence of a stoichiometric amount of copper iodide. This reaction is also highly stereoselective in favor of the (*Z*)-isomers **44** even when the terminal double bond is substituted (Scheme 19).[35]

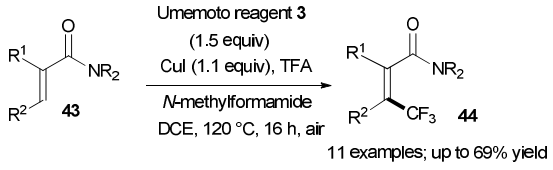


Scheme 17. β-Trifluoromethylation of acryl *N*-tosylamides

In 2014, our group[36] investigated a complementary strategy that takes advantage of the known propensity of α,β-unsaturated *N*,*N*–dialkylhydrazones to undergo 1,4 conjugate addition of electrophiles preferentially by the virtue of the umpolung caused by the electron-releasing terminal amino component. Thus, conjugated aldehyde *N*,*N*-dibenzylhydrazones **45** underwent regioselective β-trifluoromethylation using the Togni reagent **1** in the presence of copper chloride as catalyst, giving access to stereodefined CF_3-alkenyl derivatives **46** with a free α-position. The choice for the sterically hindered *N*,*N*-dibenzylamino group in the hydrazone moiety proved crucial to limit competitive 1,2 addition of the trifluoromethyl group to the azomethine carbon that affords regioisomeric CF_3-hydrazones **47** (Scheme 20). Notably, the reaction furnished the reverse stereoselectivity compared to Cahard or Loh methodologies. When the α-position is unoccupied (R^2= H), trifluoromethylated hydrazones are obtained with a high *E*-selectivity in moderate to good yields, whereas the presence of an alkyl group at the β-position leads to a mixture of *Z*/*E* stereoisomers. The reaction is proposed to be initiated by conjugate CF_3 radical addition to the hydrazone to furnish aminyl radical intermediate **49**. Oxidation of the latter generates the stabilized carbocation species **50** that undergoes reversible trapping by the 2-iodocarboxylate released from Togni reagent to form relatively long-lived oxytrifluoromethylated by-products **51**. Finally, proton abstraction restores the conjugated hydrazone. Again, alkyl-substitution at the α-position of the double bond offers another possible position for the terminating proton abstraction step, and hence the formation of isomers which differ in the position of the double bond (e.g. **48**) may be observed (Scheme 21).



Scheme 18. Tentative mechanism involving a [CF_3Cu(III)] intermediate species



Scheme 19. β-Trifluoromethylation of acrylamides using Umemoto reagent

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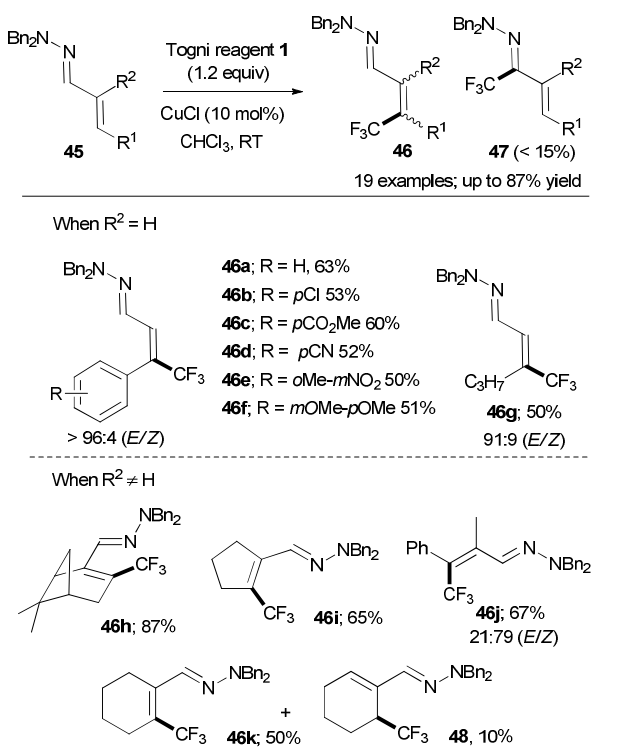
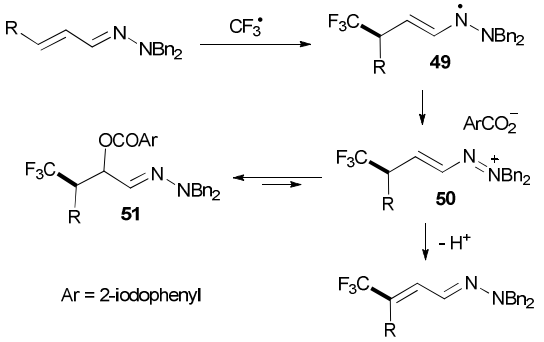


Scheme 20. β-Trifluoromethylation of conjugated hydrazones

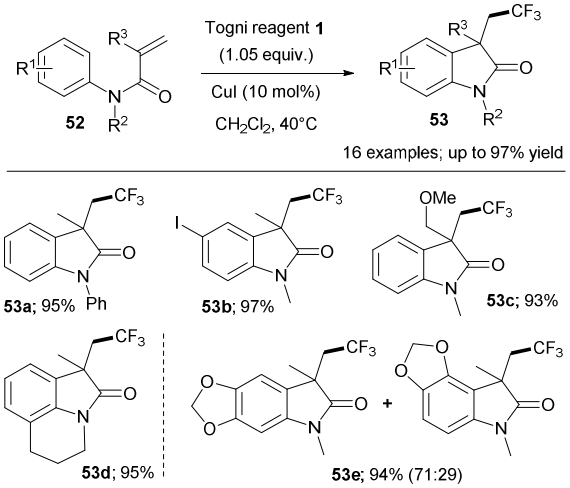


Scheme 21. Conjugate CF_3 radical addition mechanism leading for α-unsubstituted alkenylhydrazones.

3.3. Trifluoromethylation of α,β-unsaturated carbonyl compounds with trapping of the resulting intermediate

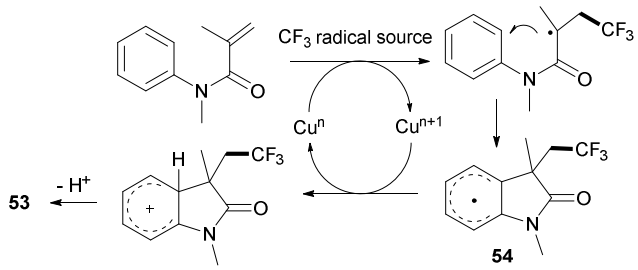
In recent years, copper-catalyzed direct difunctionalization-type trifluoromethylation of alkenes has aroused as a highly attractive strategy for the construction of polyfunctionalized, complex molecules.[13] Notably, aryltrifluoromethylation of acrylamides bearing a pendant aryl moiety have been reported independently by several research groups as a means of accessing nitrogen heterocycles through trifluoromethylation/cyclisation cascade reactions.

First examples based on copper catalysis have been reported by Sodeoka in 2013 starting from *N*-phenyl acrylamides **52** in the presence of the Togni reagent **1** and catalytic copper iodide.[37] Reactions give efficiently trifluoromethyl oxindole derivatives **53** on unsubstituted substrates or substrates having para-substituents on aryl group. However, if reactions are performed on products with meta-substituents and no ortho-substituents, a mixture of two regioisomers is obtained. In this reaction, the CF_3 group is incorporated at the unoccupied β-position of the conjugated system (Scheme 22).



Scheme 22. Aryltrifluoromethylation of acryloanilides with Togni reagent **1**

In the following year, the groups of Liang and Lipshutz,[38] as well as Lei[39] independently reported the same transformation using the combination of Langlois reagent (**15**) and TBHP in the presence of a catalytic amount of Cu(II) salt ($Cu(NO_3)_2$ and $CuCl_2$, respectively). Notably, Lipshutz and co-workers have established reaction conditions that rely on water and ambient temperatures in air. A plausible mechanism for this transformation would involve conjugate CF_3 radical addition to the acrylamide, followed by trapping of the resulting radical intermediate by the aryl moiety to give cyclohexadienyl radical **54**. Subsequent oxidation of **54** and aromatization would then afford the desired oxindole (Scheme 23).



Scheme 23. Tentative mechanism for aryltrifluoromethylation of acryloanilides

In the same year, Wang[40] and co-workers reported the synthesis of CF_3-containing 2-azaspiro[4.5]decanes **56** using the Togni reagent by Cu-catalysed β-trifluoromethylation/dearomative 5-*exo*-cyclisation of *N*-benzylacrylamides **55** bearing a hydroxyl or methoxy group at the para position of the aromatic ring (Scheme 24). Here, the initially formed carbon radical **57** undergoes electrophilic 5-*ipso* cyclisation onto the phenol ring

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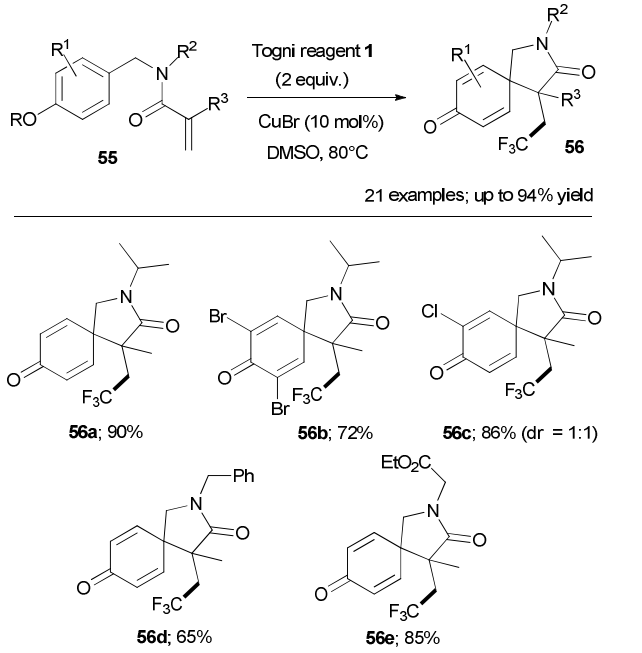
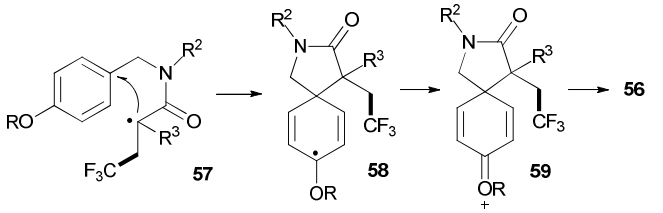
leading to a spiro radical intermediate **58** that is further oxidized to oxonium ion **59**, and finally gives the corresponding azaspirohexadienone (Scheme 25).



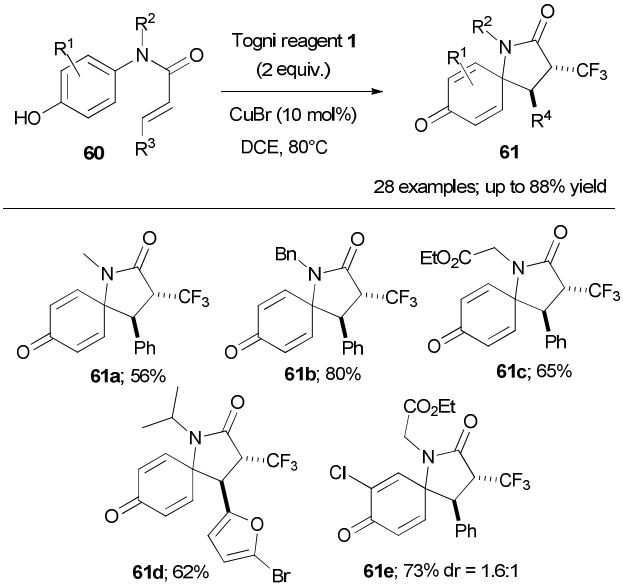
Scheme 24. Aryltrifluoromethylation of *N*-benzyl acrylamides induced by CF_3 β-addition.



Scheme 25. Mechanism involving cascade β-trifluoromethylation/dearomative 5-*exo*-cyclisation.

In a following paper, Wang and co-workers[41] have extended this CF_3-addition-trapping-dearomatization process to include *N*-(4-hydroxy)phenyl cinnamamides **60**. Here, CF_3-radical addition would occur at the α-position of the double bond, and the resulting benzyl carbon radical would then undergo 5-*endo*-cyclisation to finally afford 1-azaspiro[4.5]decanes **61**. This reaction exhibits an excellent regio- and stereoselectivity (Scheme 26).

The Nevado group[42] reported in 2013 a singular reactivity of conjugated tosylamides **62** when treated with the Togni reagent **1** in the presence of a copper salt as catalyst and 2,2'-bipyridine as ligand. The reactivity of these substrates proved highly dependent on the nature of the *N*-substituents of amides. When *N*-aryl substrates **62a** are used, the trifluoromethylation reaction evolved via a desulfonation and a regioselective 1,4-migration of the aryl group to give access to α-aryl-β-trifluoromethyl amides **63** (Scheme 27). The reaction follows another pathway from *N*-alkylamides **62b** furnishing trifluoromethylated oxindoles **64** similar to those previously obtained by Sodeoka (Scheme 28).[37] The proposed mechanism again involves CF_3 radical addition to the activated alkene and subsequent 5-*ipso* cyclisation to form radical species **65**. However, in this case extrusion of SO_2 would then occur to generate an amidyl radical **66**. From this key radical intermediate, evolution of the reaction depends of the nature of the *N*-substituent. With an *N*-aryl group, hydrogen abstraction from the reaction medium would lead to α-aryl-β-trifluoromethyl amides, whereas the presence of a more electron donating alkyl group on the *N*-atom would cause oxidation of the radical by Cu(II) leading to a copper amide anion **67**, which would be trapped by the aromatic ring thus delivering access to trifluoromethylated oxindoles **64** (Scheme 29). This difference in reactivities observed for *N*-substituted tosylamides is indeed remarkable, and adds to the classical reactivity of *N*-H tosylamides as reported by Loh (see Scheme 16).



Scheme 26. Dearomative 5-*endo*-cyclisation of *N*-(4-hydroxy)phenylcinnamides induced by CF_3 α-addition.

Possible extensions of these methodologies to the trifluoromethylation of alkynyl derivatives have also been investigated recently. In 2014, Ding and Lu[43] established $Cu(OAc)_2$-catalysed aryltrifluoromethylation reactions on aryl propiolate derivatives **68** in the presence of Togni reagent **1** to afford trifluoromethylated coumarins **69** (Scheme 30). An interesting feature of this transformation is that it allows installation of a carbonyl function on the aromatic ring without the need for pre-functionalisation. A mechanism similar to that suggested previously for the aryltrifluoromethylation of acrylamides was proposed, though relying on a Cu(II)/Cu(III) catalytic cycle. Here, the process would be initiated by CF_3 radical trapping by the phenyl propiolate at the α-position of the C=O bond leading to vinyl radical species **70** that would then follow the classical pathway (Scheme 31).

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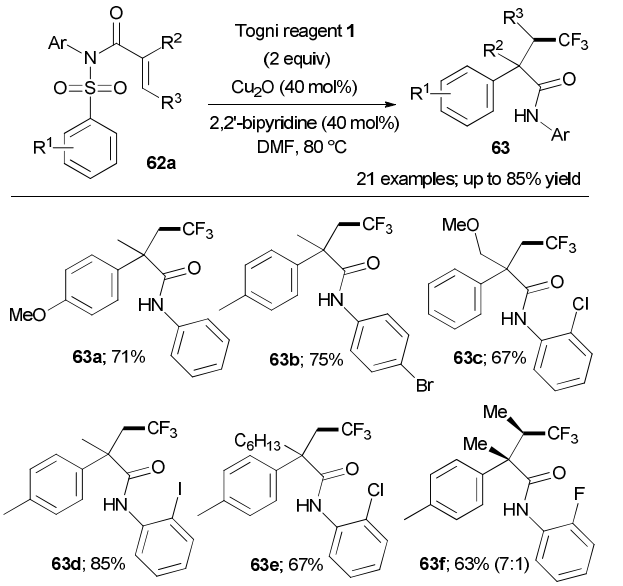
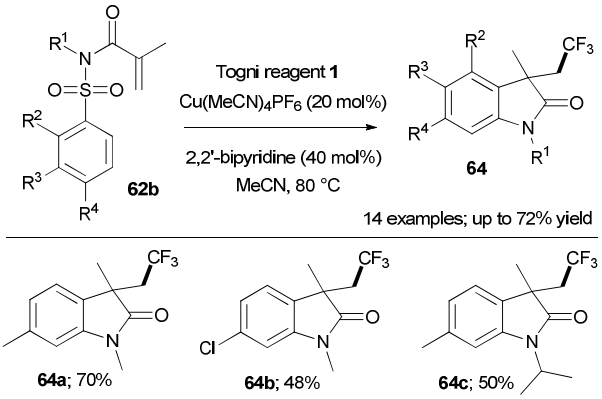
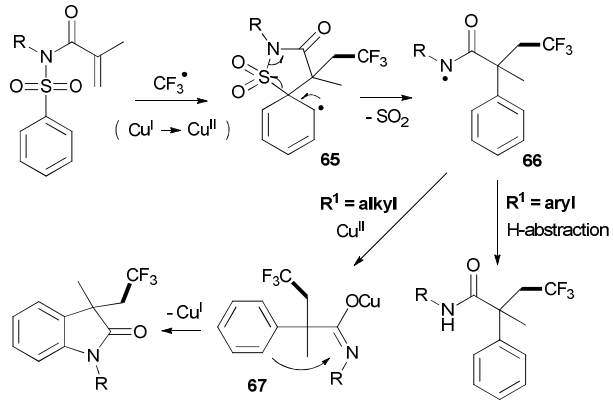


Scheme 27. Desulfonative aryltrifluoromethylation of conjugated *N*-aryl tosylamides

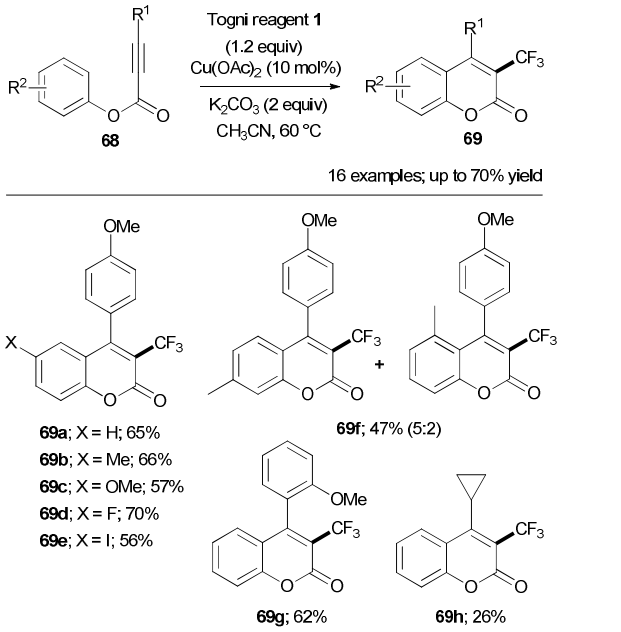


Scheme 28. Desulfonative aryltrifluoromethylation of conjugated *N*-alkyl tosylamides

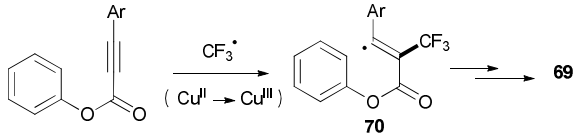


Scheme 29. Mechanism involving cascade β-trifluoromethylation/ desulfonylation/aryl migration/cyclisation

The group of Liang[44] reported a difunctionalizing trifluoromethylation of *N*-arylpropiolamides with the combination of Langlois reagent and TBHP to afford 3-(trifluoromethyl)-spiro[4.5]trienones **72**. The reaction performed best in the presence of $CuSO_4$ (10 mol%) as catalyst and MnO_2 (3 equiv) as additive in a 2:1 CH_3CN/H_2O solvent mixture under air atmosphere (Scheme 32). The reaction also accommodated phenyl propiolates and was suggested to follow an α-trifluoromethylation/5-*endo*-cyclisation pathway to afford cyclohexadienyl radical **73**. In this case, the process is seemingly terminated by trapping of this intermediate by a tert-butylperoxy radical generated in the process to afford peroxide derivative **74**. Finally, **74** undergoes elimination of *t*BuOH to afford the final carbonyl derivative (Scheme 33).



Scheme 30. Aryltrifluoromethylation of aryl propiolates



Scheme 31. Aryltrifluoromethylation induced by CF_3 α-addition to aryl propiolates

Functionalized allenes are also promising substrates for the synthesis of trifluoromethylated heterocyclic compounds. This has been recently illustrated by Ma and co-workers[45] in a cyclic oxytrifluoromethylation of 2,3-allenoic acids **75** to provide β-trifluoromethylated butenolides **76**. The process employed Togni reagent **1** as CF_3 source and CuBr as catalyst. It was found that addition of bidentate ligand 1,10-phenanthroline-5,6-dione (**77**) increased the yields significantly (Scheme 34). Two possible mechanisms are proposed for this reaction. As a first pathway, the capture of a CF_3 radical by the allene moiety would produce the corresponding allyl radical species **78**. This would undergo oxidation to allyl cation **79** that would deliver the desired cyclization product. Alternatively, the 2,3-allenoic acid would interact with the (2-iodobenzoyloxy)copper(II)

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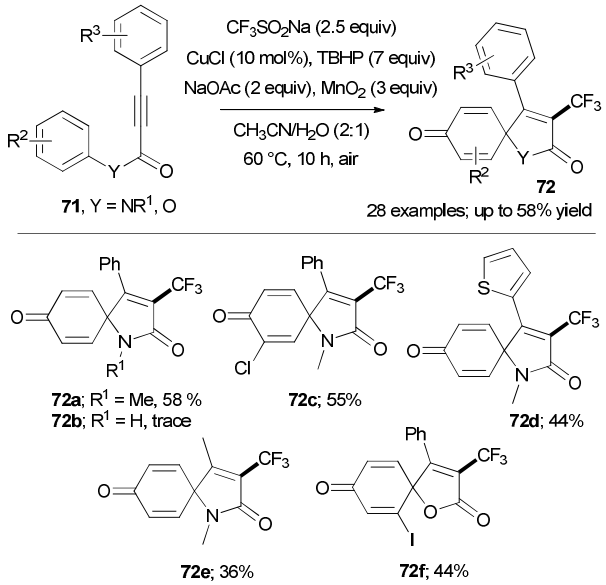
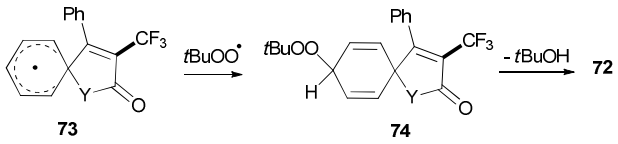
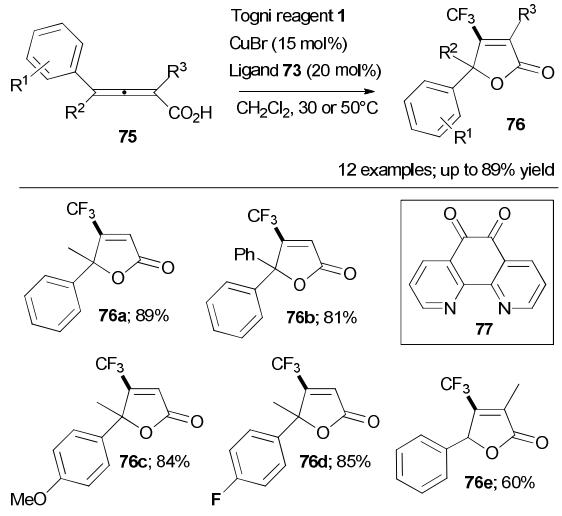
bromide, released from the initial SET process, and generate the corresponding coordination complex **80.** The coordinated allenyl moiety of intermediate **80** would be attacked by the CF_3 radical to form the π-allylic Cu(III) intermediate **81** followed by reductive elimination to release the desired product (Scheme 35).



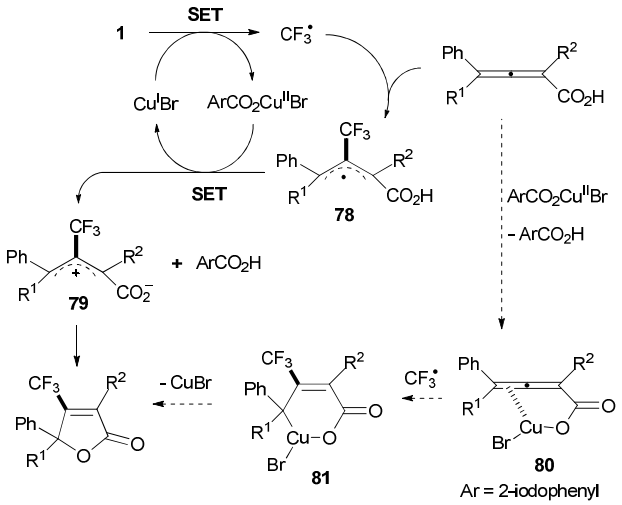
Scheme 32. Trifluoromethylation of *N*-aryl propionyl amides



Scheme 33. Mechanism involving cascade α-trifluoromethylation/dearomative cyclisation



Scheme 34. Cyclic oxytrifluoromethylation of 2,3-allenoic acids



Scheme 35. Two possible pathways toward β-trifluoromethylated butenolides

Conclusions

This review demonstrates that copper-catalyzed electrophilic trifluoromethylation of carbonyl compounds and their derivatives have attracted tremendous attention over the past recent years and have evolved into broadly applicable methodologies that give convenient access to trifluoromethyl-substituted carbonyl derivatives of considerable synthetic value. The starting materials are readily available in great structural diversity and reactions are conducted at low temperatures, and under mild conditions. Powerful methods have been developed for the C(sp^3)-H α-trifluoromethylation of carbonyl compound that also offer new possibilities for asymmetric syntheses. Strategies have been implemented that enable incorporation of a CF_3 group either at the α- or β-position of conjugated systems –essentially acrylamides- with high levels of regioselectivity. However, still other conjugated systems such as ketone and carboxylic acid derivatives have not been fully accommodated in these reactions. Importantly, aldehyde hydrazones provide interesting umpolung reactivity of carbonyl compounds.

The hypervalent iodine-based trifluoromethylating agents developed by Togni remain the most popular reagents in this area. Reactions are often suggested to proceed via a radical/SET mechanism involving copper-promoted generation of a CF_3 radical, though there is still a lack of definitive evidence as for the real active species and reaction pathways. Looking to the future, we expect to see a rapid expansion in the scope of applications and progress in understanding mechanisms.

Note added in proof. Since this article was written, another paper by Wang and co-workers was published concerning aryltrifluoromethylation of *N*-phenylcinnamamides (Q. Wang, G. Han, Y. Liu, Q. Wang, *Adv. Synth. Catal.*, 2015, **357**, 2464).

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Notes and references

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Photographs and biographies

Alexis Prieto was born in 1990 in Cannes. He started studying chemistry at the Institut Universitaire Technologique of Poitiers, and then graduated from ENSICAEN, the national graduate school of chemical engineering of Caen, in 2013. He is currently carrying out doctoral studies at Université Claude Bernard Lyon 1 under the co-direction of Nuno Monteiro and Didier Bouyssi, focusing on the development of new catalytic methods for the fluoroalkylation of aldimines.

Olivier Baudoin completed his PhD in 1998 in the group of Jean-Marie Lehn in Paris. After a post-doc with K. C. Nicolaou in the Scripps Research Institute, he joined ICSN, Gif-sur-Yvette, in 1999 as a CNRS researcher and started his independent career. In 2006, he became a Professor at Université Claude Bernard Lyon 1. In 2015, he moved to the University of Basel where he is currently Full Professor of Chemistry. He received the CNRS Bronze Medal in 2005, the Scholar Award of the French Chemical Society, Organic Division, in 2010, and was a junior member of IUF in 2009-14.

Didier Bouyssi graduated from Université Claude Bernard Lyon 1 where he completed his PhD in 1992 under the guidance of Pr. Jacques Goré and Dr. Geneviève Balme. He was appointed as Maître de Conférences in 1993 in the team of Dr. Geneviève Balme working on the development of new palladium and copper-catalyzed reactions. In 2011, he joined the group of Pr. Olivier Baudoin. His current research activity is focused on transition metal-catalyzed fluoroalkylation of hydrazones.

Nuno Monteiro studied chemistry at Université Claude Bernard Lyon 1 where he obtained his PhD in 1992 under the guidance of Jacques Goré and Geneviève Balme. Following a one-year period as a full-time contractual lecturer at the same university, he joined the team of Varinder K. Aggarwal (University of Sheffield, U.K.) as a Marie Curie post-doctoral fellow. In 1996 he returned to the University of Lyon to work as a CNRS researcher. His research interests have mainly concerned the development of Cu- and Pd-catalyzed synthetic methods toward the construction and functionalization of heterocyclic compounds.

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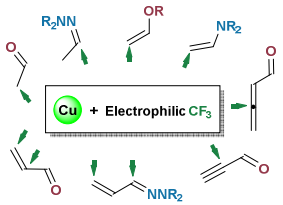
Graphical abstract

Recent advances in copper-catalyzed electrophilic trifluoromethylation of carbonyl compounds and their nitrogen derivatives are highlighted with a particular focus on C-CF_3 bond forming reactions



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