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Trifluoromethylation

Recent Advances in Trifluoromethylation Reactions with Electrophilic Trifluoromethylating Reagents

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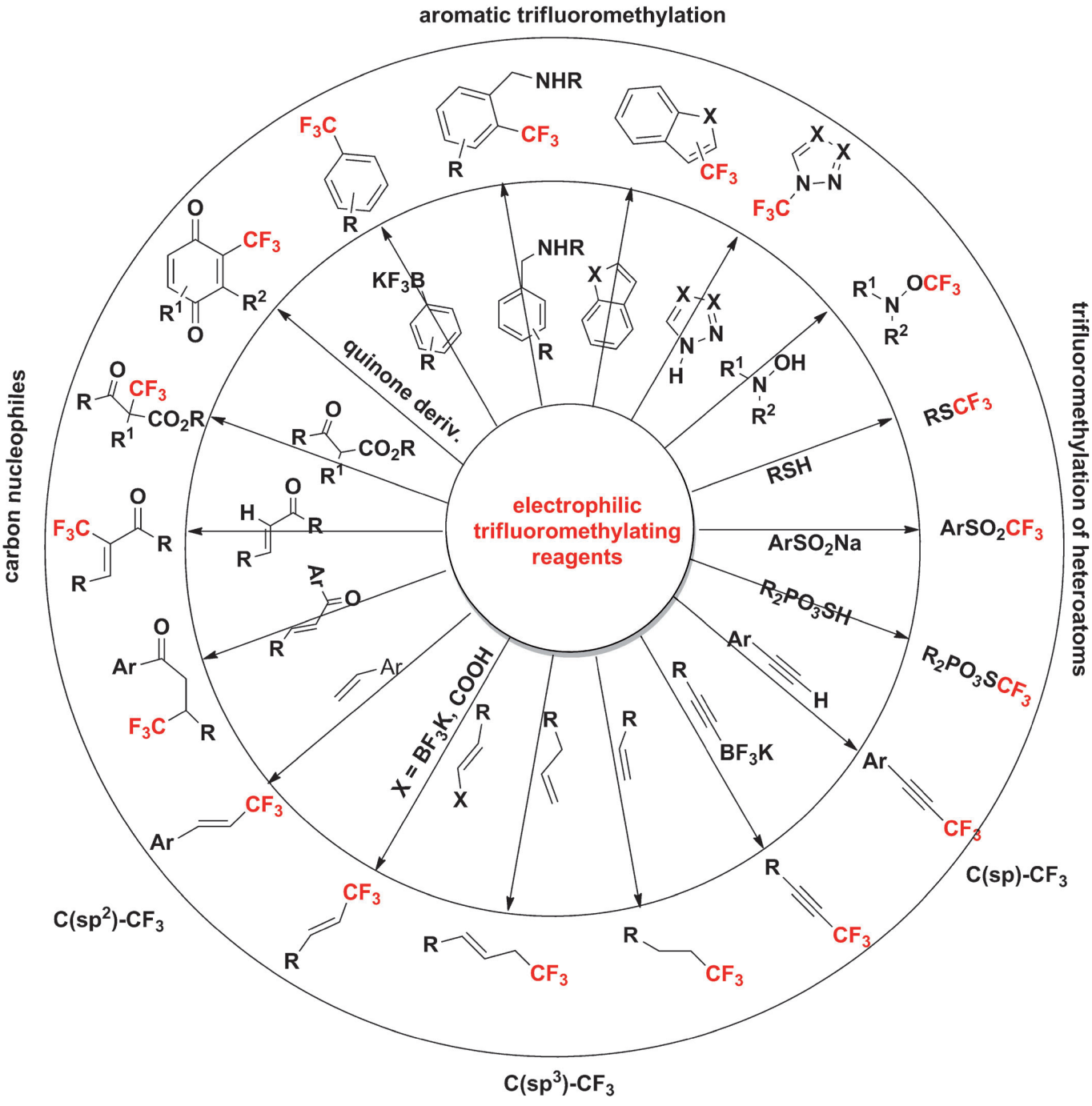

Abstract: Electrophilic trifluoromethylation reactions have been the latest approach to achieve the fluoroalkylation of compounds with newly-discovered reagents, such as the Togni's (1-trifluoromethyl-1,2-benziodoxol-3-(1 H)-one), Umemoto's (S-(trifluoromethyl)dibenzothiophenium tetrafluoroborate), Yagupolskii's (S-(trifluoromethyldiarylsulfonium salts), Shreeve's (S-(trifluoromethyl)dibenzothiophenium triflate), and Shibata's (trifluoromethylsulfoximine salts) reagents. All these reagents produce an electrophilic trifluoromethylating (CF_3^+) species that undergoes reaction with nucleophiles. In addition, these latter reactive species (i.e. CF_3^+) can undergo electron-transfer (ET) processes affording $CF_3^{\cdot}$ radicals that expand the scope to substrates other than conventional nucleophiles that can undergo reaction. In this Review, we shall discuss the trifluoromethylation reactions of diverse families of organic substrates of biological interest as a means to comparing the reagents scope and best reaction conditions. Some, though not all, of these reactions require the assistance of metal or organometallic catalysts. Some require additives and catalysts to promote the fluoroalkylation reaction, but invariably all are initiated and carried out by electrophilic trifluoromethylating species.

1. Introduction

The introduction of a trifluoromethyl group, the most sought-after fluorinated alkyl group, into a selected target in a reliable and efficacious fashion, undoubtedly belongs among the most relevant and desired transformations in fluorine chemistry. Of specific interest are methodologies appropriate for late-stage trifluoromethylation in multistep syntheses which renders them a valuable tool when combined with the classical building block approach. The electrophilic trifluoromethylating reagents have encompassed a new category in fluorine chemistry as demonstrated by the versatility and scope of their reactions.

It is extremely hard to produce the trifluoromethyl cation CF_3^+ by a chemical reaction.[1] Regarding the mechanism of the electrophilic trifluoromethylation reaction, controversy remains as to whether a polar substitution or a single electron transfer (SET) pathway takes place.[1] It is likely that the low stability of the CF_3^+ ion drives, in most instances, the reaction mechanism to an electron-transfer process (ET), assuming the presence of a $CF_3^{\cdot}$ radical as another possible intermediate in the reaction coordinates initiated by the electrophilic trifluoromethylating reagents.

Since the discovery of the trifluoromethylation of thiophenolates by Yagupolskii's reagent (*S*-trifluoromethyl diarylsulfonium salts) in 1984, the design and synthesis of electrophilic trifluoromethylation reagents have been extensively developed due to the significant influence of trifluoromethylated compounds on pharmaceuticals, agricultural chemicals, and functional materials. Thus, a series of prominently developed reagents by Umemoto, Togni, and Shibata, are now commercially available due to their high stability and reactivity and broad substrate scope. All of these reagents produce an initial electrophilic trifluoromethylating (CF_3^+) species that undergoes reaction with soft nucleophiles, such as alkenes, alkynes, (hetero)arenes, phosphines, β-ketoesters, dicyanoalkylidenes, and thiols, and hard ones, such as alcohols, sulfonic acids, and nitriles.

Detailed strategies for electrophilic trifluoromethylation reactions have been introduced in 2007.[1] In 2010, Shibata and Cahard have reviewed electrophilic trifluoromethylation reagents[2] employed from 1984 until 2009. In 2012, Magnier and co-workers have amply described the synthesis and various applications of electrophilic perfluoro- and trifluoroalkylating reagents derived from hypervalent iodine compounds (e.g. Togni's reagent), sulfonium salts (e.g. Yagupolskii's and Shreeve's reagents), sulfoximine derivatives (e.g. Adachi's and Ishihara's reagents), trifluoromethyloxonium compounds, and metal-catalyzed electrophilic trifluoromethylation strategies.[3] Recent review articles[4–6] on asymmetric trifluoromethylation[7] reactions utilizing various electrophilic reagents have been introduced in the literature.

In this Review, we wish to provide a synthetic perspective of the trifluoromethylation reactions of diverse families of organic substrates of biological interest in which the reagents' scope and best reaction conditions are compared and discussed, as have been introduced in the literature since 2010. Methods and reagents utilized for trifluoromethylthiolation processes, for the incorporation of the SCF_3 group into organic substrates, will not be considered in this account.

1.1. Reagents' availability, synthesis, and scope

Among the electrophilic trifluoromethylating reagents currently employed, the Togni's reagents (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one, **1a**, and trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole, **1b**, Scheme 1) have very recently been prepared in an optimized fashion,[8,9] thus rendering these reagents very appropriate for electrophilic trifluoromethylation reactions. The syntheses of various families of electrophilic trifluoromethylating reagents have been reviewed by Cahard and Ma.[1] A very recent metal-free in situ electrophilic reagent has been proposed, utilizing the Ruppert–Prakash reagent, (Me_3SiCF_3), $PhI(AcO)_2$, and KF to effect trifluoromethylation reactions on a vast array of nucleophiles.[10a]

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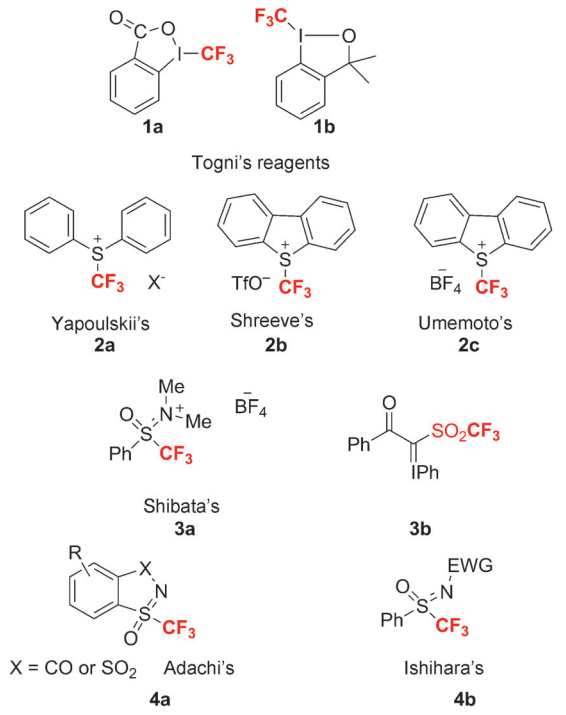

Scheme 1. Different electrophilic trifluoromethylating reagents.

Umemoto,[10b–d] Shreeve,[10e] and Shibata[10f] have come up with sulfur-derived trifluoromethylating reagents that have expanded the scope of organic substrates that can undergo trifluoromethylation reactions (Scheme 1).

1-Trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one **1a** and trifluoromethyl-3,3-dimethyl-1,2-benziodoxol **1b** (Togni's reagents; Scheme 1) are known to trifluoromethylate nucleophiles including keto derivatives, sulfides, arenes, phosphanes, alcohols, amines, sulfonic acids, and enol silyl ethers.[3] Trifluoromethyl dibenzothiophenium triflate and tetrafluoroborate salts[11] (**2b** and **2c**, respectively, Shreeve's and Umemoto's reagents; Scheme 1) have been reported to react with a diverse array of nucleophiles including keto derivatives, sulfides, arenes, enol silyl ethers, dicyanoalkylidenes, and alkynes.[3] Finally, [(Oxido)phenyl(trifluoromethyl)-λ-sulfanylidene]dimethyl ammonium *tetra*fluoroborate **3a** (Shibata's reagent; Scheme 1) is known to trifluoromethylate keto derivatives, dicyanoalkylidenes, and alkynes.[3,12]

2. Trifluoromethylation of alkenes and alkynes

A recent review article on the trifluoromethylation of unsaturated moieties with different reagents, such as trifluoroacetic acid (TFA), CF_3I, trimethylsilyl trifluoromethane ($TMSCF_3$), $NaSO_2CF_3$, and electrophilic ones such as **1a**, or **2b** (Scheme 1), attests to the relevance of these transformations.[13]

2.1. Formation of C(sp^3)–CF_3 bonds

Trifluoromethylation of alkenes to form C(sp^3)–CF_3 bonds (e.g. trifluoromethylation of allylsilanes) employing either reagent **1a** or **2b**, has been studied[14] and was recently summarized by Wu and co-workers.[15]

Transition-metal-catalyzed trifluoromethylation of alkenes to form C(sp^3)–CF_3 bonds with electrophilic fluoroalkylating reagents has been recently revisited by Leroux and co-workers.[16] One such strategy was recently reported that relies on the use of reagent **1a** and terminal alkenes, developed by Wang and co-workers.[17] The scope of the reaction is illustrated in Scheme 2.

More recently,[18] it was established that the electrophilic trifluoromethylation reagents (CF_3^+) undergo SET reduction by a Cu^I catalyst, followed by a radical process and then reverse ET to regenerate the Cu^I catalyst (Scheme 3). Aliphatic alde-

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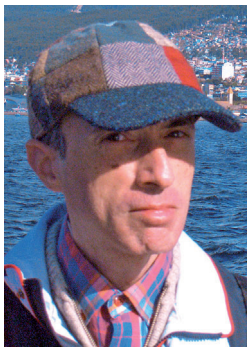
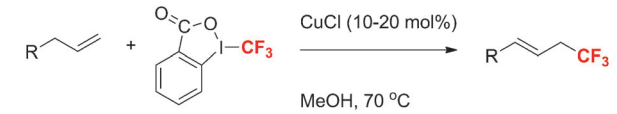
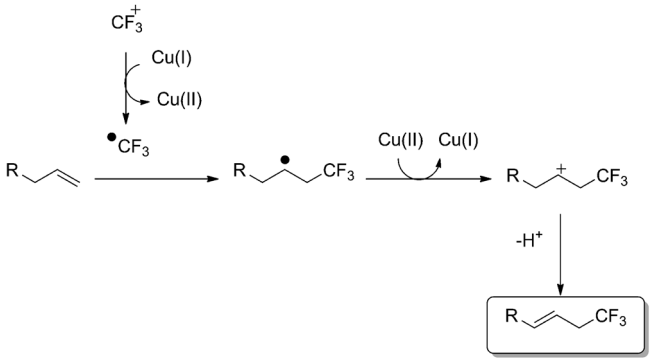


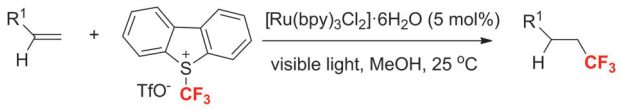


R = C_8H_{17}	89%
= HOC-$(CH_2)_7$	75%
= EtOC(O)-$(CH_2)_7$	87%
= $Et_2NC(O)$-$(CH_2)_7$	93%
= PhC(O)-O-$(CH_2)_2$	66%
= $PhSO_2$-O-$(CH_2)_2$	86%
= 3,4-MeO-C_6H_3	54%
= 4-*t*Bu-C_6H_4	48%
= C_7H_{15}O-C(O)-	63%

Scheme 2. Trifluoromethylation of alkenes with reagent **1a** towards the construction of $C(sp^3)$–CF_3 bonds.

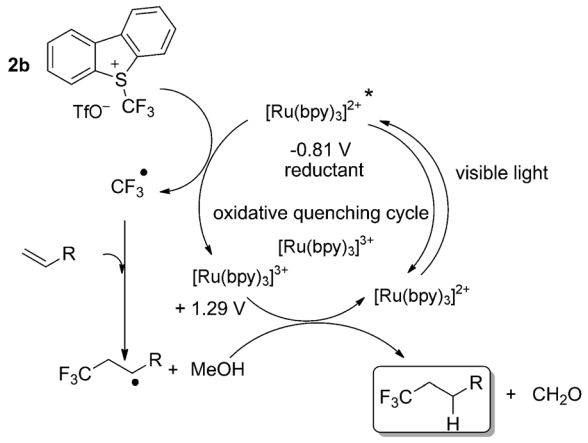


Scheme 3. Electrophilic trifluoromethylating reagents (CF_3^+) undergo SET reduction by a Cu^I catalyst, followed by a radical process and then back ET to regenerate the Cu^I catalyst.



R^1 = $(CH_2)_4$-OC(O)Ph	78%
R^1 = $(CH_2)_4$-OH	47%
R^1 = $(CH_2)_2$-C(O)NHBn	44%
R^1 = $(CH_2)_2$-NHC(O)Ar	50%
R^1 = $(CH_2)_2$-C(O)NH-2Br-C_6H_4	54%

Scheme 4. Hydrotrifluoromethylation of terminal alkenes with reagent **2b**.



Scheme 5. Proposed reaction mechanism for the hydrotrifluoromethylation of terminal alkenes with reagent **2b**.

hydes and the *tert*-butyldimethylsilyl (TBDMS) group are also known to tolerate the reaction conditions.[17]

The postulated reaction mechanism involves intermediate free radicals,[17] as suggested by trapping experiments of reagent **1a** with 2,2,6,6,-tetramethyl-1-piperidinyloxy (TEMPO). The authors claim no evidence on the details of the C–C bond forming step, neither could they trap the allyl radical intermediate using TEMPO.[17]

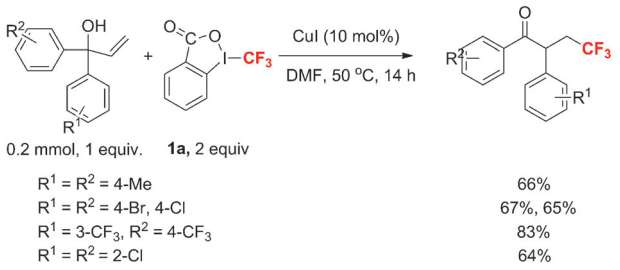
Gouverneur and co-workers recently accomplished the hydrotrifluoromethylation of unactivated alkenes employing reagent **2b** and photocatalyst $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ in methanol as solvent (Scheme 4).[19] Unactivated terminal monosubstituted (Scheme 4) and geminal disubstituted alkenes (not shown) participate in the hydrotrifluoromethylation effectively. A wide range of substrates and functional groups are tolerated,[19] including esters, unprotected and protected alcohols, amines, amides, imides, carbamates, enones, heteroarenes and oxazolidinones.[19] The reaction mechanism is illustrated in Scheme 5.

Irradiation of $[Ru(bpy)_3Cl_2]$ with visible light leads to excited $[Ru(bpy)_3]^{2+}*$ which enters an oxidative quenching cycle (Scheme 5). The reduction potential of reagent **2b** (−0.25 V vs. SCE in MeCN[20]; SCE = saturated calomel electrode) is compatible with the reduction process using excited $[Ru(bpy)_3]^{2+}*$. A SET reduction of **2b** is simultaneous with the oxidation of $[Ru(bpy)_3]^{2+}*$ to $[Ru(bpy)_3]^{3+}$ (−0.81 V vs. SCE in MeCN[19]). The resulting $CF_3^{\cdot}$ radicals would add to the double bond of the alkene substrate. The carbon radical would be converted to the hydrotrifluoromethylation product by using methanol as hydrogen atom donor (Scheme 5).

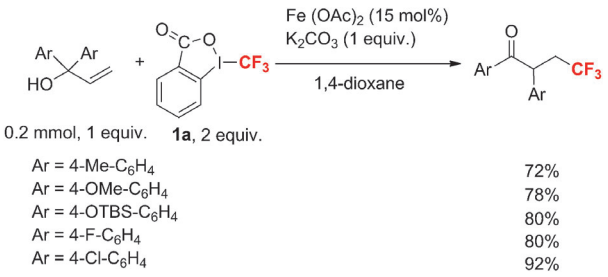
In 2013, Wu and co-workers attempted the copper-catalyzed trifluoromethylation of allylic alcohols in DMF as solvent,[21,15] resulting in a 1,2-migration-driven carbotrifluoromethylation reaction in good yield (Scheme 6).

The reaction mechanism proposed involves the intervention of a cyclohexadienyl-type radical, such as that depicted in Scheme 7. The mechanism (Scheme 7) was postulated on the basis of the chemoselectivity, which suggested a radical (neophyl) rearrangement via intermediate **A** (Scheme 7), rather than a cationic (semipinacol) rearrangement. Reduction of Togni's reagent (**1a**) with Cu^I generates a $CF_3^{\cdot}$ radical, which adds across the double bond of the allyl diaryl alcohol to give radical **A**. Subsequent migration of electron-deficient aryl group via spiro[2,5]octadienyl radical **B** produces intermediate **C** (Scheme 7). Single electron transfer between **C** and Cu^{II} leads to the formation of the desired product.[15,21]

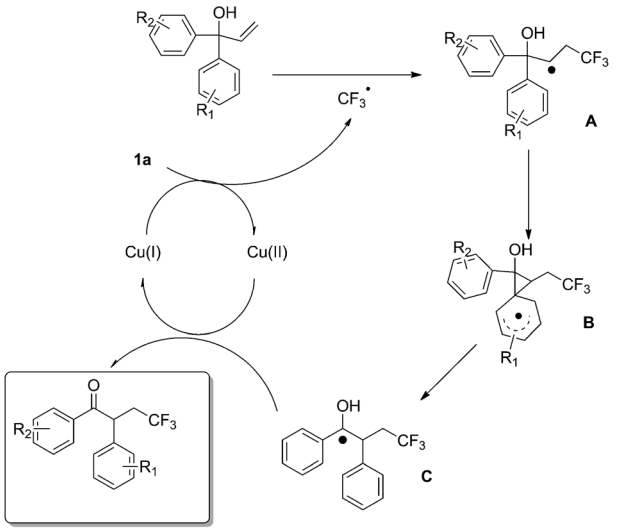
Sodeoka and co-workers reported in 2013 the 1,2-migration-driven carbotrifluoromethylation of alkenes catalyzed by iron acetate (Scheme 8).[22]



Scheme 6. Scope of the copper-mediated trifluoromethylation of diphenyl–allyl alcohols with reagent **1 a**.



Scheme 8. 1,2-Migration-driven carbotrifluoromethylation of symmetrical alkenes catalyzed by iron acetate with electrophilic reagent **1 a**.



Scheme 7. Proposed mechanism for the copper-catalyzed trifluoromethylation of allylic alcohols in DMF as solvent with reagent **1 a**.

Ortho-substituted aryl groups also worked well as migrating groups. The authors attempted other asymmetrical substrates encountering high regioselectivity in several aryl migrating groups, such as those depicted in Scheme 9.[22] For instance, if there is one 4-chloro- and one 2-chloro-substituted aryl ring, both on the allylic carbon, only the 4-chloroaryl group migrates predominantly.

Sodeoka and co-workers noted that the migration of 2-substituted aryl rings was slower than that of the phenyl group,[22] suggesting that the steric hindrance on the aryl ring reduced the migration rate (*cf.* Ph and 2-Cl-C_6H_4, Scheme 9). Also, as observed in Scheme 9, electronic properties of the aryl ring affect the migration rate. Electron-withdrawing groups accelerate the aryl migration ability during the particular trifluoromethylation reaction (*cf.* 4-Cl-C_6H_4 and 4-MeO-C_6H_4, Scheme 9). The authors did not propose a reaction mechanism for the process,[22] but suggested that the intermediate of this reaction is likely to possess a radical nature due to the presence of the hydrotrifluoromethylation product.

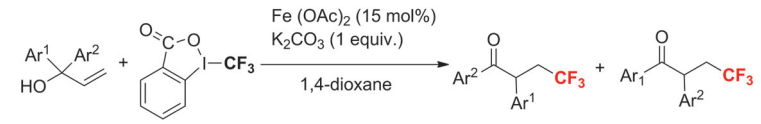
Comparison of the Wu's and Sodeoka's methodologies for achieving the 1,2-migration-driven carbotrifluoromethylation of alkenes revealed similar product yields and synthetic approaches. Whereas Wu's methodology relies on the use of Cu^{I} in DMF as solvent to initiate an ET sequence, Sodeoka's employs an Fe^{II} salt in 1,4-dioxane.[15,21,22]

2.1.2. $C(sp^3)$–CF_3 bond formation with simultaneous cyclization

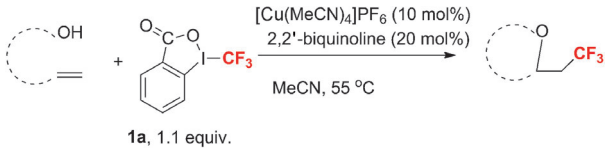
Electrophilic trifluoromethylation reactions of alkenyl moieties to form $C(sp^3)$–CF_3 bonds with a simultaneous cyclization have been studied by several groups. Those involving electrophilic trifluoromethylating reagents are concerned with the oxytrifluoromethylation of unactivated alkenes based on copper-catalyzed oxidative difunctionalization, introduced by Buchwald and co-workers[23] and reviewed by Fu and co-workers[24] (general strategy in Scheme 10).

The trifluoromethylation of alkenoic acids towards the synthesis of CF_3-substituted lactones has recently been accomplished by Akita and co-workers employing the electrophilic reagent **2 c** (Scheme 11).[25]

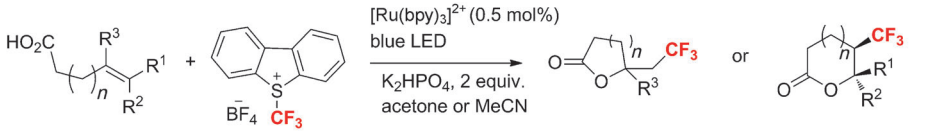
Trifluoromethylation–lactonization of both terminal and internal alkenoic acids by photoredox catalysis is achieved through the use of $[Ru(bpy)_3]^{2+}$ photocatalyst. This is the first



Scheme 9. 1,2-Migration-driven carbotrifluoromethylation of asymmetrical substrates catalyzed by iron acetate with electrophilic reagent **1 a**.



Scheme 10. Oxytrifluoromethylation of unactivated alkenes with Togni's reagent **1 a**.

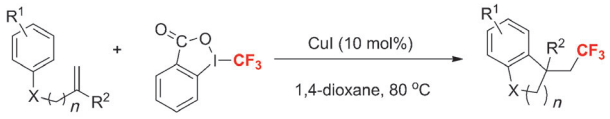


$R^1 = R^2 = H$, $R^3 = Ph$, $n = 1$	90%	
$R^1 = R^2 = H$, $R^3 = 4\text{-MeO-}C_6H_4$, $n = 1$	83%	
$R^1 = R^2 = H$, $R^3 = 4\text{-F-}C_6H_4$, $n = 1$	82%	
$R^1 = R^2 = H$, $R^3 = 4\text{-Cl-}C_6H_4$, $n = 1$	82%	
$R^1 = R^2 = H$, $R^3 = 4\text{-Br-}C_6H_4$, $n = 1$	76%	
$R^1 = H$, $R^2 = Ph$, $n = 0$		82%
$R^1 = H$, $R^2 = 4\text{-MeO-}C_6H_4$, $n = 0$		75%
$R^1 = H$, $R^2 = 4\text{-Me-}C_6H_4$, $n = 0$		72%
$R^1 = H$, $R^2 = 3,4\text{-}F_2\text{-}C_6H_4$, $n = 0$		72%
$R^1 = H$, $R^2 = 3,4\text{-}Cl_2\text{-}C_6H_4$, $n = 0$		81%
$R^1 = H$, $R^2 = 4\text{-Br-}C_6H_4$, $n = 0$		79%
$R^1 = H$, $R^2 = 3\text{-I-}C_6H_4$, $n = 0$		83%

Scheme 11. Trifluoromethylation of alkenoic acids with reagent **2c**.

example of a highly *endo*- and diastereoselective synthesis of CF_3-substituted five-, six-, and seven-membered ring lactones from internal alkenoic acids.[25]

Sodeoka and co-workers recently reported the trifluoromethylation of carbocycles and heterocycles through copper-mediated trifluoromethylation of unactivated alkenes bearing allylic protons coupled with $C(sp^3)$–C_{Ar} bond formation (general strategy in Scheme 12).[26]



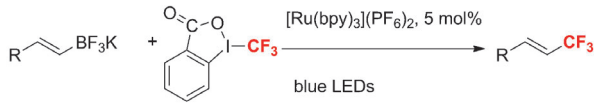
$X = C(CO_2Et)_2$, $n = 1$, $R^1 = R^2 = H$	78%
$X = C(CO_2Et)_2$, $n = 1$, $R^1 = 4\text{-MeO}$, $R^2 = H$	63%
$X = CH_2$, $n = 2$, $R^1 = R^2 = H$	76%
$X = CH_2$, $n = 2$, $R^1 = 7\text{-Me}$, $R^2 = H$	61%
$X = NBoc$, $n = 1$, $R^1 = R^2 = H$	85%
$X = NTBS$, $n = 1$, $R^1 = R^2 = H$	67%
$X = NBoc$, $n = 1$, $R^1 = 5\text{-MeO}$, $R^2 = H$	84%
$X = NBoc$, $n = 1$, $R^1 = 5\text{-I}$, $R^2 = H$	82%
$X = NBoc$, $n = 1$, $R^1 = 5\text{-F}$, $R^2 = H$	86%
$X = NBoc$, $n = 2$, $R^1 = R^2 = H$	93%

Scheme 12. Copper-mediated trifluoromethylation of unactivated alkenes bearing allylic protons coupled with $C(sp^3)$–C_{Ar} bond formation with reagent **1a**.

2.2. Formation of $C(sp^2)$–CF_3 bonds

The strategies developed to trifluoromethylate alkenes in order to form $C(sp^2)$–CF_3 bonds can involve the use of prefunctionalized alkenes, which can be classified as vinylboronic acids, vinyl borates, vinyl halides, vinyl sulfonates, or vinyl carboxylic acids,[27–33] or the use of unfunctionalized alkene substrates (terminal alkenes). The groups of Shen and Liu showed in 2011 the nonstereoselective trifluoromethylation of vinyl boronic acids by Cu^I catalyst.[34] In 2012, Buchwald and co-workers reported the Fe^{II}-catalyzed stereoselective trifluoromethylation of vinylfluoroborates.[29] These methods exhibit limited substrate scope with respect to functional groups and heteroaromatic compounds.

Recently, potassium vinyl trifluoroborates were shown to undergo trifluoromethylation with Togni's reagent in the presence of the photoredox catalyst $[Ru(bpy)_3](PF_6)_2$ (Scheme 13).[31] In particular, this method is effective in the selective and large-scale synthesis of (*E*)-trifluoromethylated alkenes bearing a π-deficient aromatic moiety (and heteroaromatic compounds), which are difficult to access by previous catalytic methods.



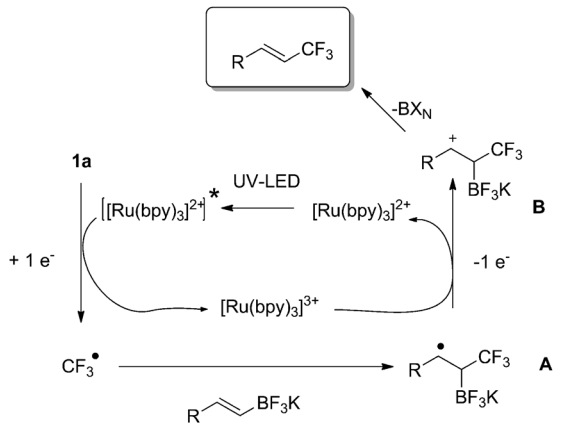
$R = 4\text{-Me-}C_6H_4$	81%
$= 4\text{-MeO-}C_6H_4$	88%
$= 4\text{-Cl-}C_6H_4$	72%
$= 4\text{-}CF_3\text{-}C_6H_4$	79%
$= 4\text{-CN-}C_6H_4$	78%
$= 2\text{-Me-}C_6H_4$	70%
= 3-pyridyl	68%
= 3-quinoline	71%

Scheme 13. Trifluoromethylation of vinylborates in the presence of photoredox catalyst $[Ru(bpy)_3](PF_6)_2$ with electrophilic reagent **1a**.

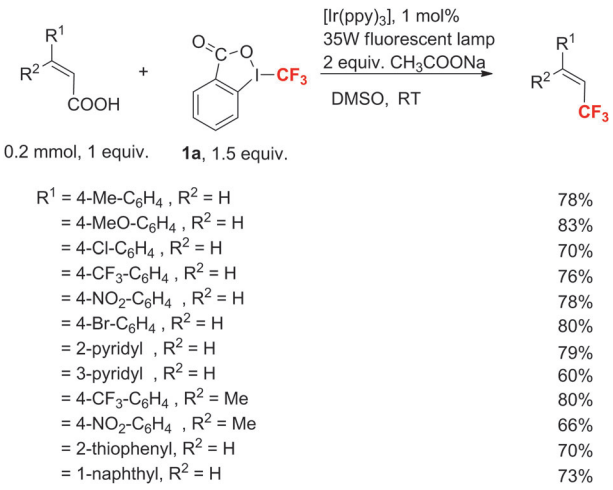
Also vinyl borates containing heteroaryl groups such as thiophene, pyridine, quinoline, and benzothiazole rendered trifluoromethyl-substituted alkenes.[31] A plausible reaction mechanism takes into account a SET photoredox process (Scheme 14).

$CF_3^{\cdot}$ radicals can be generated by one-electron reduction of the electrophilic Togni's reagent **1a**. These $CF_3^{\cdot}$ radicals react with the carbon–carbon double bonds of vinyl trifluoroborates to afford β-borato-stabilized radical intermediates **A** (Scheme 14)[31] in a regioselective manner. Subsequent one-electron oxidation by $[Ru(bpy)_3]^{3+}$ produces β-borato cation intermediates **B** (Scheme 14). Then, *trans*-selective Petersen elimination of the boron-based group provides (*E*)-trifluoromethylated alkenes.[31] Although this strategy cannot be regarded as a direct electrophilic process, the participation of radical species was confirmed. However, the authors were unable to rule out radical cation intermediates.[31] The involvement of the photocatalyst enables a radical pathway to intervene.

In 2014, Zhu and co-workers developed a photocatalytic method to achieve the room-temperature decarboxylative tri-



Scheme 14. Reaction mechanism for conversion of vinyl trifluoroborates in vinyl trifluoromethanes using reagent **1a**.



Scheme 15. Decarboxylative trifluoromethylation of α,β-unsaturated carboxylic acids by photoredox catalyst with reagent **1a**. *E* selectivities > 96%.

fluoromethylation of α,β-unsaturated carboxylic acids with electrophilic reagent **1a**.[35] The photocatalyst employed was *fac*-[Ir(ppy)$_3$], in conjunction with sodium acetate as additive in DMSO as solvent, with a 35W fluorescent lamp (Scheme 15).

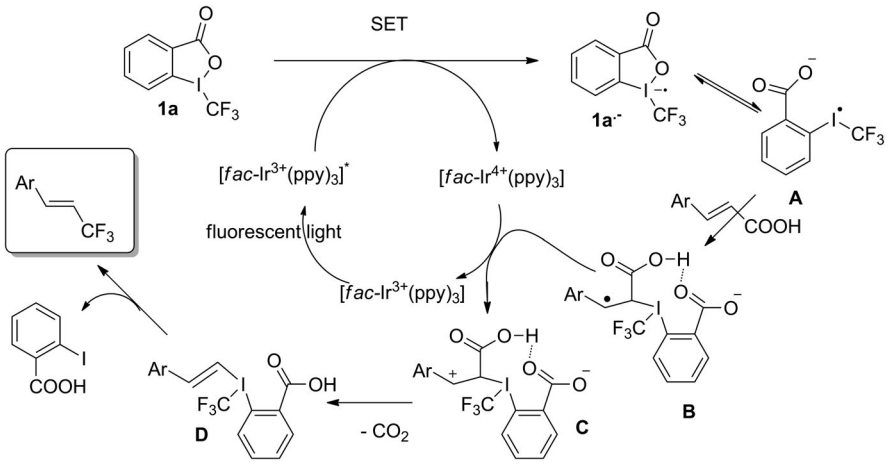
The *E*-stereoselectivity in all cases ranged from 96% to 99% for the trifluoromethylated olefins obtained.[35] The authors postulate a radical mechanism (radical addition–decarboxylative reaction; Scheme 16).

In the mechanism (Scheme 16), the photocatalyst *fac*-Ir^{3+}(ppy)$_3$ undergoes photoexcitation to form the excited *fac*-[Ir^{3+}(ppy)$_3$]*.[35] The electrophilic Togni's reagent **1a** is reduced by *fac*-[Ir^{3+}(ppy)$_3$]* to afford the corresponding radical anion **1a**$^{\bullet-}$ (Scheme 16). Collapse of **1a**$^{\bullet-}$ generates intermediate **A** (Scheme 16), which in turn undergoes radical addition to α,β-unsaturated carboxylic acids affording the radical intermediate **B**, which is further oxidized by [Ir^{4+}(ppy)$_3$] to give the carbocation **C** (Scheme 16) through a single-electron oxidation. Intermediate **C** undergoes decarboxylation to afford the thermodynamically stable *E*-alkene **D** (Scheme 16), which renders the desired trifluoromethylated alkene. The favorable half wave reduction potential of [Ir^{4+}(ppy)$_3$] ($E_{1/2red} = +0.77$ V vs. SCE) gives support to the postulated mechanism.[35]

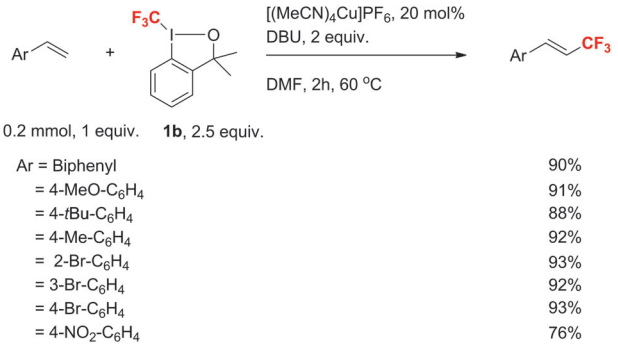
Remarkably, the product yields of the trifluoromethylated olefins obtained by Zhu and co-workers starting from α,β-unsaturated carboxylic acids[35] match well with those reported by Akita and co-workers starting from vinyl trifluoroborates[31] (Schemes 13 and 15). Both methods make use of Togni's reagent **1a** as trifluoromethylating source. The Akita group's methodology employs [Ru(bpy)$_3$](PF$_6$)$_2$ as catalyst, whereas the Zhu group's methodology requires the use of *fac*-[Ir(ppy)$_3$]. The novelty of the Zhu's methodology is the room-temperature photocatalyzed radical addition–decarboxylative reaction of acrylic acid derivatives to afford trifluoromethylated olefins.

Methods to achieve trifluoromethylation of alkenes (or alkynes) without prefunctionalization of substrates represent undoubtedly a more promising synthetic strategy. A trifluoromethylation methodology involving nonfunctionalized alkenes was reported by Xiao and co-workers.[36] The copper-catalyzed trifluoromethylation of terminal aromatic alkenes with reagent **1b** utilizing [(MeCN)$_4$Cu]PF$_6$ as catalyst, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as base in DMF as solvent is achieved in very good yields (Scheme 17).[36] The reaction could tolerate various functional groups. Notably, all products were obtained with excellent stereoselectivity (*E*/*Z* > 97:3).[36]

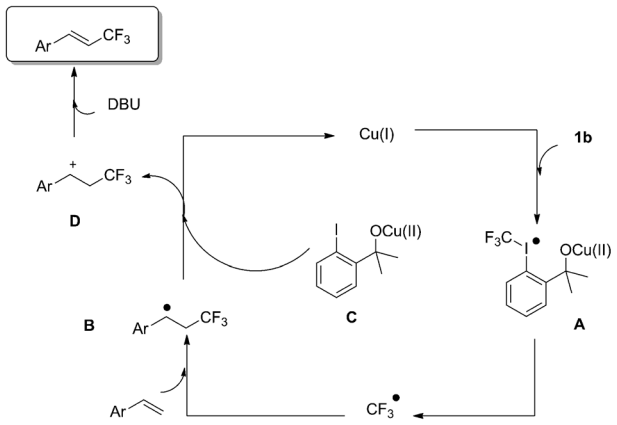
Regarding the reaction mechanism,[36] the authors postulated a pathway involving radical intermediates as evidenced by trapping experiments with TEMPO, a well-known radical scavenger. In this case, the desired trifluoromethylation reaction



Scheme 16. Proposed reaction mechanism for the photocatalyzed decarboxylation of α,β-unsaturated carboxylic acids with electrophilic reagent **1a**.



Scheme 17. Scope of the trifluoromethylation reaction of styrene derivatives with reagent **1 b** with unfunctionalized substrates.

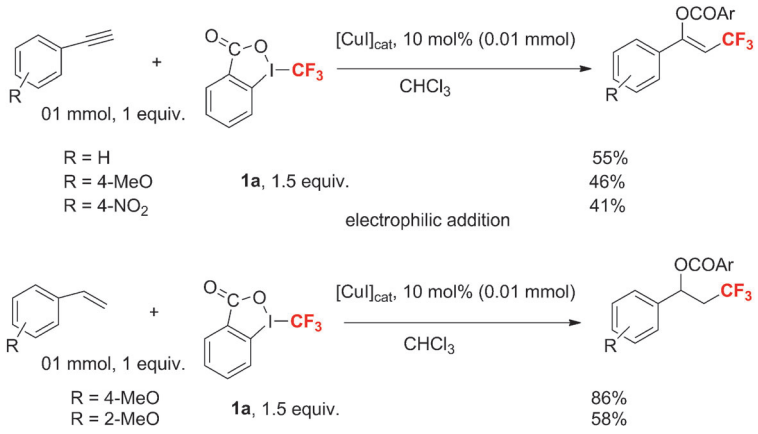


Scheme 18. Postulated mechanism for the trifluoromethylation of styrene derivatives with reagent **1 b**.

was completely suppressed. Based on these results, the authors proposed the mechanism depicted in Scheme 18.

In the postulated mechanism (Scheme 18),[36] the activation of **1 b** by Cu^{I} leads to the formation of radical intermediate **A**. Decomposition of **A** produces [{2-(2-iodophenyl)propan-2-yl}oxy]copper(II) **C** and $CF_3^{\cdot}$ radicals, which are trapped by alkenes to form the trifluoromethylated radical intermediate **B**. Subsequently, the radical intermediate **B** is oxidized by Cu^{II} (**C**) to cationic intermediate **D**, with simultaneous release of catalyst Cu^{I}. In the presence of base, intermediate **D** undergoes proton elimination to afford the final product.[36]

Togni's reagent **1 a** (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one) has recently been reported by Szabó and co-workers to undergo addition reactions with both alkynes and alkenes in the presence of CuI catalyst,[37] affording vinyl–CF_3 and alkyl–CF_3 substituted products, respectively (Scheme 19). These results and others were recently summarized by Liu and co-workers.[38,39]



Scheme 19. Electrophilic trifluoromethylation by copper-catalyzed addition of CF_3-transfer reagent. Ar represents electron-rich and electron-poor aryl rings with reagent **1 a**.

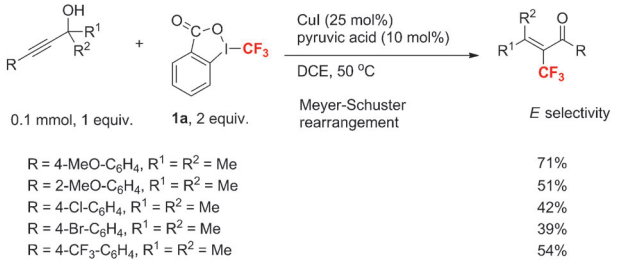
Thus, a series of alkenes, such as 1,1-diphenylethylene, 1-phenylthioethylene, and 2-methoxystyrene, and alkynes, such as phenyldimethylsilyl acetylene, 4-nitrophenyl acetylene, 4-methoxyphenyl acetylene, and phenylacetylene, was trifluoromethylated in yields ranging from 46% to 86%.[37] Szabó and co-workers suggested that the allylic C–H trifluoromethylation with hypervalent iodine reagents takes place by a mechanism that can involve some electron-transfer character. The reaction was partially inhibited by TEMPO, suggesting a radical mechanism involving a single electron transfer (SET) process. The trifluoromethylation–benzoyloxylation is a one-pot procedure with total atom economy.

Togni's reagent **1 a** was very recently used to effect cyanotrifluoromethylation of alkenes in the presence of TMSCN and $Cu(OTf)_2$ as catalyst in DMSO as solvent, in very high yields, in the absence of additives and ligands.[40]

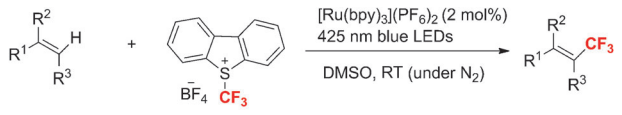
Liu and co-workers reported a novel domino copper-catalyzed trifluoromethylated Meyer–Schuster rearrangement reaction with Togni's reagent leading to α-trifluoromethyl enone products with moderate to good yields.[41a] Furthermore, α-CF_3 enones can be transformed into important trifluoromethyl-substituted heterocyclic motifs in a one-pot version (Scheme 20).

Koike and Akita very recently reported the trifluoromethylation of di- and trisubstituted alkenes by photoredox catalysis employing electrophilic reagent **2 c**, $[Ru(bpy)_3](PF_6)_2$ as photocatalyst in DMSO as solvent in the absence of additives or base in good yields.[41b] The scope of the transformation is depicted in Scheme 21.

Diphenylethenes with electron-donating substituents and halogens produce the trisubstituted CF_3-alkenes in good yields



Scheme 20. Trifluoromethylation of propargyl alcohols with reagent **1 a**.

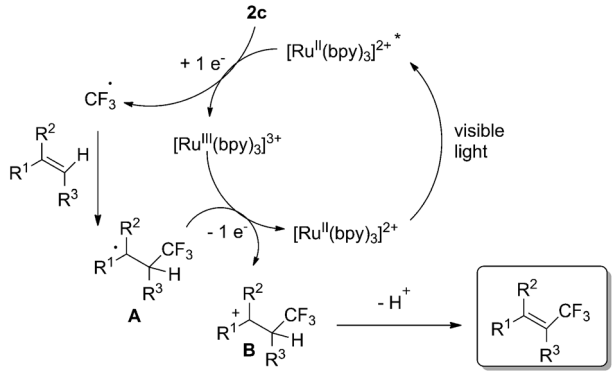


$R^1 = R^2 = Ph, R^3 = H$	82%
$R^1 = R^2 = 4\text{-MeO-}C_6H_4, R^3 = H$	81%
$R^1 = R^2 = 4\text{-Cl-}C_6H_4, R^3 = H$	53%
$R^1 = R^2 = 4\text{-Br-}C_6H_4, R^3 = H$	70%
$R^1 = 4\text{-MeO-}C_6H_4, R^2 = Ph, R^3 = H$	70%
$R^1 = Ph, R^2 = 4\text{-}NO_2\text{-}C_6H_4, R^3 = H$	51%
$R^1 = Ph, R^2 = 3\text{-pyridyl}, R^3 = H$	78%
$R^1 = R^2 = Ph, R^3 = Me$	82%
$R^1 = 4\text{-MeO-}C_6H_4, R^2 = Ph, R^3 = Me$	59%
$R^1 = R^2 = R^3 = Ph$	65%
$R^1 = 4\text{-MeO-}C_6H_4, R^2 = R^3 = Ph$	53%

Scheme 21. Scope of the trifluoromethylation of di- and trisubstituted alkenes by reagent **2c**.

(Scheme 21[41b]). Unsymmetrically substituted substrates were also obtained in moderate yields, but consisted of mixtures of *E*- and *Z*-isomers. Based on the experimental results, the *E/Z* ratios are influenced by the electronic structure of the aryl substituent.[41b] Reactions of trisubstituted alkenes afforded the corresponding trisubstituted CF_3-alkenes in good yields. Koike and Akita postulated the mechanism depicted in Scheme 22.[41b]

One-electron reduction of reagent **2c** by photoactivated Ru catalyst $*[Ru(bpy)_3]^{2+}$ generates $CF_3^{\cdot}$ radicals that add to the alkene, to afford benzyl-type radical intermediate **A** (Scheme 22) in a regioselective manner. Subsequent one-electron oxidation by $[Ru^{III}(bpy)_3]^{3+}$ produces β-CF_3 carbocation intermediate **B** (Scheme 22). Deprotonation of **B** provides the CF_3-substituted alkene.[41b]



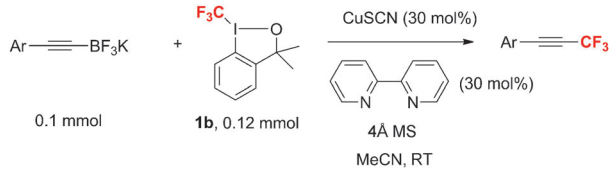
Scheme 22. Proposed mechanism for the trifluoromethylation of substituted alkenes with reagent **2c**.

Koike and Akita also very recently reported that styrene derivatives, in the presence of photocatalyst *fac*-[Ir(ppy)$_3$] and reagent **1a** in DMSO as solvent, produce α-trifluoromethylated ketones.[41c] Apparently, a key intermediate in these reactions is an α-trifluoromethyl-substituted alkoxysulfonium salt produced from reaction of DMSO with an intermediate of the type **B** (as in Scheme 22), which is transformed into α-trifluoromethylated ketones as is the case in the Kornblum oxidation. Thus, by changing photocatalyst and electrophilic reagent, different types of trifluoromethylated products can be obtained from terminal alkenes (e.g. trifluoromethylated substituted alkenes with photocatalyst [Ru(bpy)$_3$] and **2c**, and α-trifluoromethylated ketones with photocatalyst *fac*-[Ir(ppy)$_3$] and reagent **1a**, in DMSO, respectively).[41c]

2.3. Formation of C(sp)–CF_3 bonds and synthesis of trifluoromethyl-substituted allenes

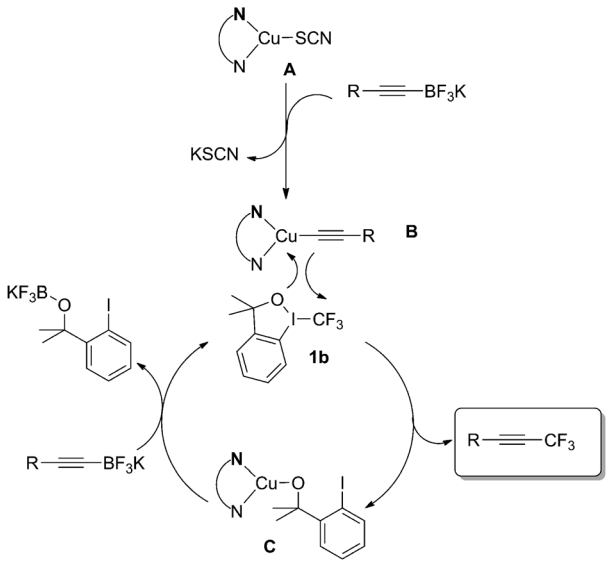
Alkynyltrifluoroborates were recently trifluoromethylated in good yields by Huang. Weng, and co-workers (Scheme 23).[42]

The authors postulated a plausible reaction mechanism for the alkynyltrifluoroborate trifluoromethylation (Scheme 24).[42] Initial complexation of CuSCN with 2,2′-bipyridine forms the copper thiocyanate **A** (Scheme 24) species. Subsequent transmetallation of **A** with the alkynyltrifluoroborate generates copper(I) acetylide species **B** as an intermediate (Scheme 24). Nucleophilic attack of the alkynyl group of **B** at the CF_3 moiety



$Ar = 4\text{-Me-}C_6H_4$	75%
$Ar = Ph$	75%
$Ar = 4\text{-Et-}C_6H_4$	78%
$Ar = n\text{Bu}$	85%
$Ar = 4\text{-F-}C_6H_4$	47%
$Ar = 4\text{-MeO-}C_4H_4$	70%
$Ar = 3,4\text{-}Cl_2\text{-}C_6H_4$	68%

Scheme 23. Scope of the trifluoromethylation of alkynyltrifluoroborates with reagent **1b**.



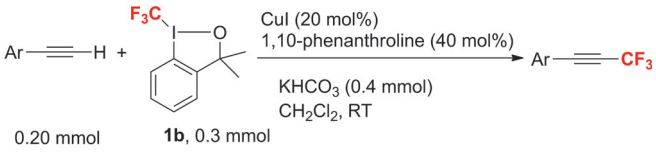
Scheme 24. Proposed reaction mechanism for the copper-catalyzed trifluoromethylation of alkynyltrifluoroborates with electrophilic reagent **1b**.

occurs next, to generate the desired trifluoromethylated acetylene product, along with Cu alkoxide complex **C**. This latter species undergoes reaction with the alkynyltrifluoroborate to regenerate **B** and complete the catalytic cycle.[42] This mechanism does not seem to involve radical intermediates (Scheme 24).

The method depicted in Scheme 23 is remarkable from the point of view of construction of an C(sp)–CF_3 bond. It is interesting to note from comparison of Scheme 23 with Scheme 13 (section **2.2.**) that trifluoromethylation of both vinyl trifluoroborates and alkynyl trifluoroborates can be accomplished by employing electrophilic trifluoromethylating reagents **1a** and **1b**, respectively, albeit under very different reaction conditions.[31,42–44]

Terminal aryl acetylene derivatives have also been reported by Weng, Huang and co-workers to be trifluoromethylated with reagent **1b** in the presence of 1,10-phenanthroline as ligand, CuI as catalyst, $KHCO_3$ as base, in CH_2Cl_2 as solvent in yields ranging from 70–98%,[45] according to Scheme 25.

A plausible mechanism for the trifluoromethylation of terminal alkynes with reagent **1b** is depicted in Scheme 26. A bis-N-ligated [(*N,N*)CuX] complex (**A**) would be initially generated in situ by the reaction of CuI with 1,10-phenanthroline in

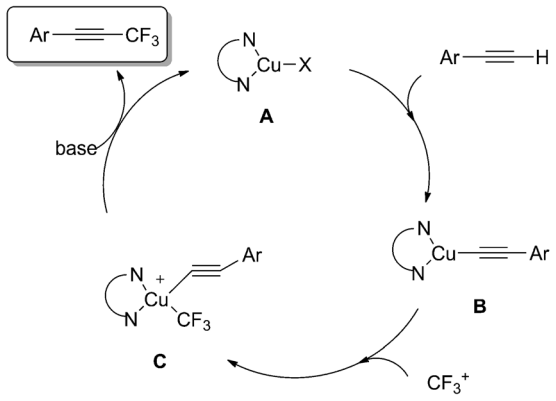


Ar = 4-Me-C_6H_4	91%
Ar = 3-Me-C_6H_4	94%
Ar = *n*Pr-C_6H_4	70%
Ar = 4-H_3CO-C_6H_4	83%
Ar = PhO-C_6H_4	70%
Ar = 2-Br-C_6H_4	71%
Ar = 3-NH_2-C_6H_4	94%
Ar = 4-Br-C_6H_4	81%
Ar = 9-Phenanthroline	91%

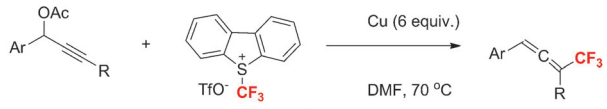
Scheme 25. Scope of the copper-catalyzed trifluoromethylation of aryl acetylenes (unfunctionalized substrates) with reagent **1b**.

CH_2Cl_2 as solvent. The coordination/deprotonation of the alkyne could then follow to form a copper(I) acetylide species **B** in the presence of a base. Subsequent oxidative addition of CF_3 to species **B** leads to the formation of a [Cu(alkynyl)(trifluoromethyl)] complex **C** (Scheme 26). Finally, reductive elimination would then furnish the trifluoromethylated alkyne and regenerate the starting copper complex **A** to complete the catalytic cycle (Scheme 26). Weng, Huang and co-workers postulated Cu^{I} and Cu^{III} intermediates,[45] instead of radicals as suggested for photocatalytic reactions (for example, see Scheme 14).

Xiao and co-workers very recently introduced the copper-mediated trifluoromethylation of propargyl acetates with *S*-(trifluoromethyl)diphenylsulfonium triflate **2b**, leading to trifluoromethyl-allenes (Scheme 27).[46]



Scheme 26. Proposed mechanism for the CuI-catalyzed trifluoromethylation of aryl-acetylenes with reagent **1b**.



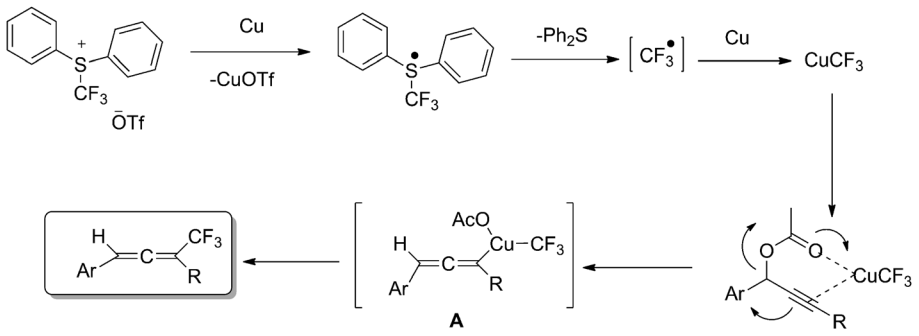
Ar = Ph, R = *n*Bu	94%
Ar = Ph, R = *n*Pr	90%
Ar = Ph, R = C_8H_{17}	85%
Ar = Ph, R = cyclohexyl	76%
Ar = 4-Me-C_6H_4, R = *n*Bu	96%
Ar = 4-MeO-C_6H_4, R = *n*Bu	96%
Ar = 2-MeO-C_6H_4, R = *n*Bu	97%
Ar = 4-Br-C_6H_4, R = *n*Bu	79%
Ar = 4-NO_2-C_6H_4, R = *n*Bu	16%
Ar = β-naphthyl, R = *n*Bu	76%

Scheme 27. Scope of the trifluoromethylation reaction of propargyl acetates with **2b** in DMF as solvent.

This methodology converts a variety of propargyl acetates into trisubstituted trifluoromethyl allenes.[46] The reaction conditions can tolerate various functional groups and afford the trifluoromethylation products with moderate to excellent yields (Scheme 27). Electron-rich substituents are favorable for the reaction. Aryl rings substituted with weak electron-withdrawing groups could still be converted to the expected products in good yield. However, strong electron-withdrawing groups greatly suppressed the desired conversion.[46]

Xiao and co-workers proposed that the reaction proceeded via the oxidative addition of propargyl acetate to the $CuCF_3$ intermediate, which is generated from the reaction of **2a** with copper powder (Scheme 28).[46] Propargyl acetate acts as a bidentate ligand and the coordination to $CuCF_3$ favors oxidative addition to afford intermediate **A**. The reductive elimination of intermediate **A** gives the final product (Scheme 28).

In summary, the electrophilic C(sp^3–CF_3) bond formation reactions can be accomplished by electrophilic reagent **1a** or **2c** and a copper(I) catalyst or by reagent **2b** and a photocatalyst. C(sp^2)–CF_3 bond formation reactions can be carried out with electrophilic reagent **1a** or **1b** and a copper(I) catalyst, or with reagent **2c** and a Ru photocatalyst, whereas C(sp)–CF_3 bond formation reactions are achieved through the employment of electrophilic reagent **1b** and a copper(I) catalyst.



Scheme 28. Proposed reaction mechanism for the trifluoromethylation of propargyl acetates with electrophilic reagent **2a**.

3.1.2. Trifluoromethylation of quinone derivatives

Zhang, Wang, and co-workers reported the direct C–H trifluoromethylation of quinones using Togni's reagent **1a** in the presence of CuI in a *t*BuOH/CH_2Cl_2 mixture as solvent,[18] affording 84% yield of the trifluoromethylated quinone product (Scheme 30).

The authors suggested that the CF_3 radical is involved in the transformation.[18] At first, Togni's reagent **1a** is activated by CuI, generating radical intermediate **A** (Scheme 31). Further decomposition of **A** affords Cu^{II} species **B** with simultaneous release of the CF_3 radical (Scheme 31). It is possible that the Cu^{II} species **B** undergoes a second SET oxidation to produce radical intermediate **A′**. The collapse of **A′** then produces the CF_3 radical and Cu^{III} complex **B′** (Scheme 31).

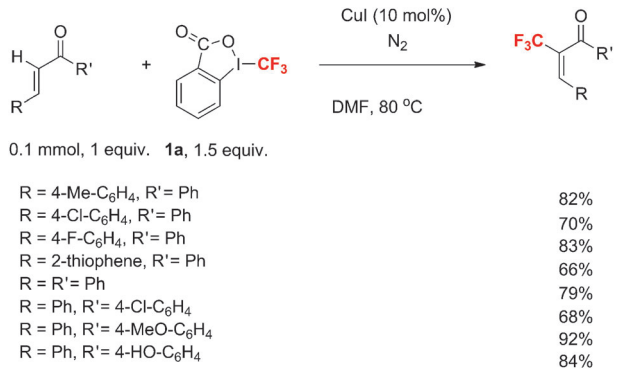
A simultaneous study by Szabó and co-workers on the trifluoromethylation of quinone derivatives using **1a** as a trifluoromethylating reagent, CuCN, and *bis*(pinacolato)diboron (B_2pin_2) affording good yields of trifluoromethylated quinones was also recently reported.[49] The scope of the reaction is illustrated in Scheme 32. The authors postulated a radical mechanism as evidenced by the inhibition of the reaction by TEMPO and isolation of the TEMPO–CF_3 adduct.

Comparison of the Zhang group's[18] and the Szabó group's[49] studies reveals that the two methodologies are simi-

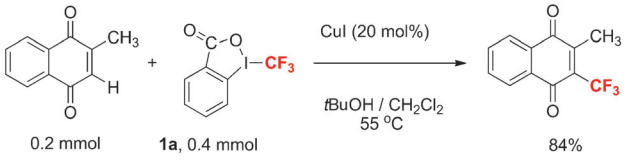
3. Trifluoromethylation of enones, enolates, β-ketoesters, acrylamides, carbamates and hydrazones

Environmentally friendly hypervalent iodine reagents are unusually effective promoters of asymmetric α-functionalization of carbonyl compounds. By using hypervalent iodine reagents, various substituents can be introduced into the α-position of carbonyl compounds. A recent review article by Chen and co-workers surveyed the asymmetric α-functionalization of carbonyl compounds reactions catalyzed by these hypervalent iodine reagents.[47] More recent examples are illustrated in section **3.1.**.

β-Trifluoromethylation of α,β-unsaturated carbonyl compounds can also be achieved through the use of reagents **1a**, **2a**, or **2b** and different copper salts. New instances are depicted in section **3.2.**, whereas enolates and enol ethers in section **3.3.**, acrylamides in section **3.4.**, carbamates in section **3.5.**, and hydrazones in section **3.6.** are shown to be trifluoromethylated efficiently with the aid of electrophilic trifluoromethylating reagents. **1a, 1b, 2c**, or **3a**.



Scheme 29. Scope of the trifluoromethylation of α,β-unsaturated ketones with reagent **1a**.



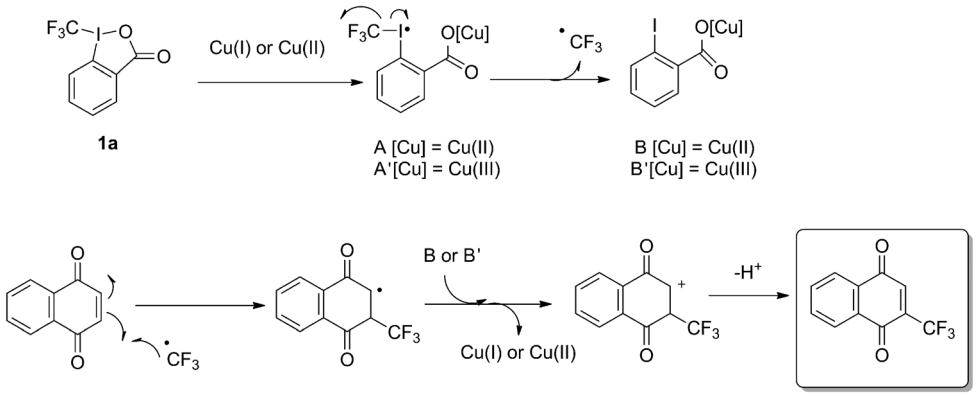
Scheme 30. Trifluoromethylation of quinones with reagent **1a**.

3.1. α-Trifluoromethylation of α,β-unsaturated ketone derivatives with electrophilic reagents

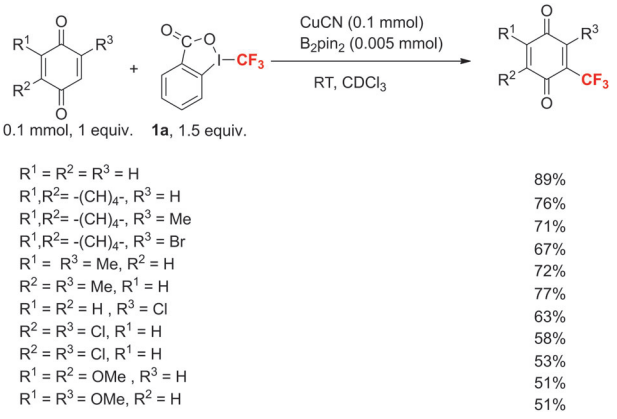
3.1.1. Synthesis of α-CF_3-substituted-α,β-unsaturated ketones

Nucleophilic trifluoromethylation to conjugated alkenes essentially occurs solely via 1,2-addition. However, Bi and co-workers very recently accomplished the trifluoromethylation of α,β-unsaturated ketones with high stereoselectivity and yields, (Scheme 29),[48] employing electrophilic reagent **1a**, and a copper(I) source.

These electrophilic trifluoromethylation reactions proceed in good-to-excellent yields since the α-position of α,β-unsaturated ketones acts as a soft nucleophilic center. However, in the reaction mechanisms, in the presence of metals, radicals cannot be excluded as intermediates. The reactions need to be conducted under N_2 atmosphere, as poor product yields are obtained in the presence of air.[48]



Scheme 31. Proposed reaction mechanism for the SET from Cu^{I} and Togni's reagent **1a** in the trifluoromethylation of quinones.



Scheme 32. Scope of the trifluoromethylation reaction of quinone derivatives with **1a** in the presence of CuCN and $B_2(pin)_2$.

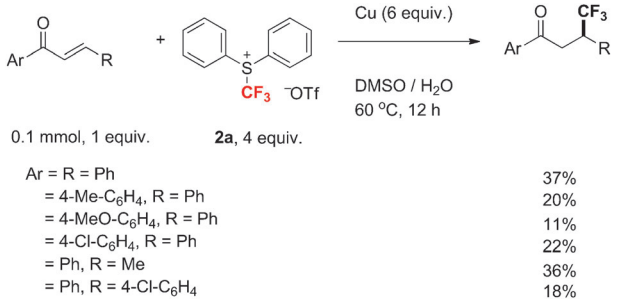
lar but that Szabó's employs $B_2(pin)_2$, which is claimed to accelerate the trifluoromethylation reaction. The optimization of the reaction conditions in the protocol developed by Szabó, however, fails to attempt the employment of CuI in the mixture of *t*BuOH/CH_2Cl_2, as claimed by Zhang and co-workers to improve the reaction yields.

3.2. β-Trifluoromethylation of α,β-unsaturated ketone derivatives with electrophilic reagents

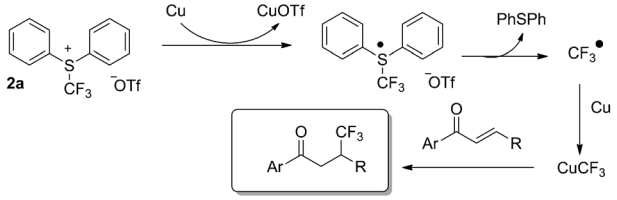
The copper-mediated trifluoromethylation at the benzylic position by using shelf-stable electrophilic trifluoromethylating reagent **2a** was recently reported by Shibata and co-workers.[50] More recently, the same authors disclosed the regioselective 1,4-addition of the CF_3 group into simple conjugated acyclic enones,[51] including chalcones,[52] using reagent **2a** and a copper system (Scheme 33). However, it is apparent that the yields are moderate to low.

The authors postulated a reaction mechanism involving radical species arising from one-electron reduction of **2a** in the presence of copper, affording CF_3 radicals (Scheme 34).[51]

The CF_3 radicals are reduced by Cu, affording the nucleophilic $CuCF_3$ species which provides the 1,4-CF_3 adduct (Scheme 33) in low to moderate yield. Although the true reactive species including CF_3 radical and/or $CuCF_3$ are not clear, the naked CF_3 radical should be ruled out since high regioselectivity was observed.[51] This mechanism involves an initial electrophilic trifluoromethylating species (**2a**), which, in the presence of Cu, affords CF_3 radicals, which are ultimately reduced to a nucleophilic CF_3 species ($CuCF_3$) that acts as a soft nucleophile in a 1,4-addition manner with α,β-unsaturated carbonyl systems.



Scheme 33. Scope of the trifluoromethylation of enones with reagent **2a**.



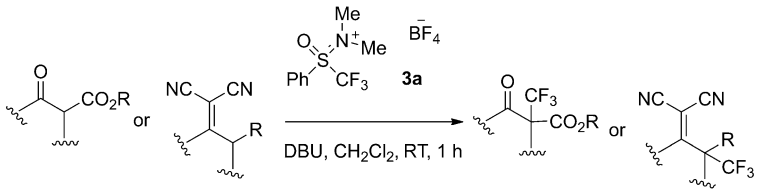
Scheme 34. Mechanism for the 1,4-trifluoromethylation of enones.

3.3. Trifluoromethylation of enolates and enols with electrophilic reagents

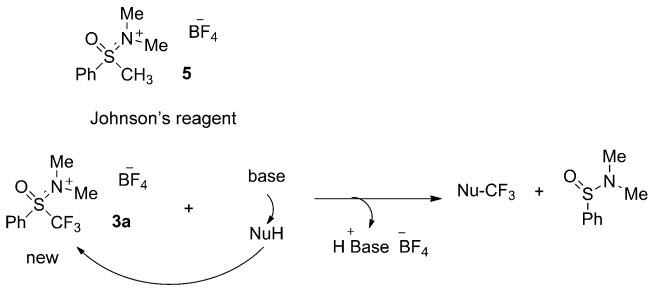
3.3.1. Synthesis of α-CF_3-substituted-β-keto-esters

A recent review article on another type of electrophilic trifluoromethylating species—fluorinated sulfoximines (**3a** and **3b**; Scheme 1)—attests to the diverse applications of these reagents.[12] These reagents are especially useful for the trifluoromethylation of α,β-unsaturated carbon nucleophile systems. Shibata and co-workers accomplished the electrophilic α-trifluoromethylation of β-ketoesters with [(oxido)phenyl(trifluoromethyl)-λ-sulfanylidene]dimethyl ammonium tetrafluoroborate **3a** (Scheme 35) in dichloromethane as solvent in the presence of base.[53]

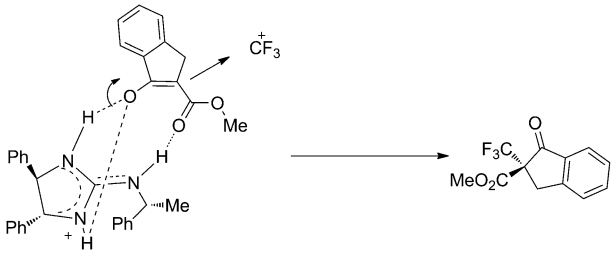
This electrophilic reagent **3a** was designed to resemble Johnson's reagent **5** (Scheme 36) for the transfer of a CF_3



Scheme 35. Trifluoromethylation of carbon nucleophiles with reagent **3a**.



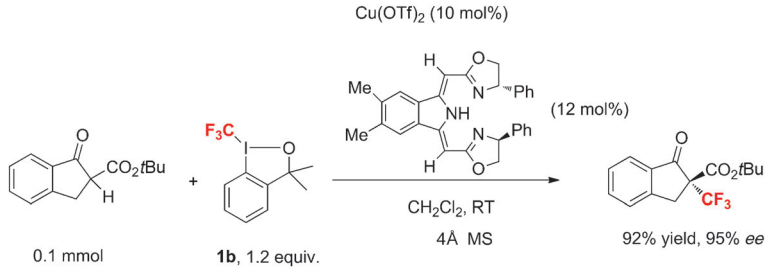
Scheme 36. Johnson's reagent **5**, and newly-designed reagent **3a**.



Scheme 38. Proposed transition-state structure for the enantioselective trifluoromethylation of β-ketoesters with reagent **2c**.

group. The transfer of the CF_3 group from **3a** (Scheme 36) proceeds via the reaction with the nucleophiles to afford the trifluoromethylated adducts, and displacement of the reagent.

Shibata and co-workers argued that the transfer of CF_3 group is not hampered by the strong basic medium.[53] Other substrates such as dicyanoalkylidenes could also be trifluoromethylated in good yields.

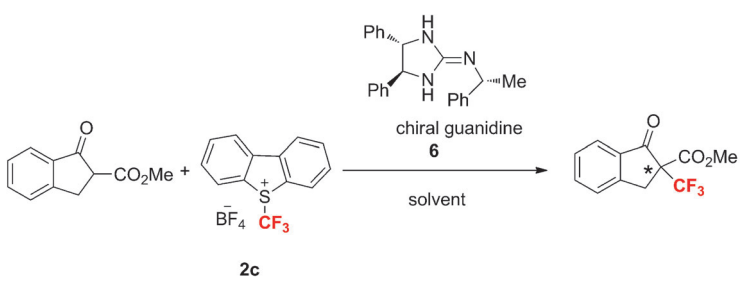


Scheme 39. Trifluoromethylation with Togni's reagent **1b**.

The enantioselective trifluoromethylation of β-ketoesters was achieved with reagent **2c** in the presence of chiral guanidine **6** (Scheme 37).[54] However, the enantiomeric excesses obtained were very limited and did not surpass 60%.

The proposed transition-state structure for enantioselective induction in the above reaction is shown in Scheme 38.

Gade and co-workers recently reported on the highly enantioselective catalytic trifluoromethylation of β-ketoesters under mild conditions by using Togni's reagent **1b** (1-trifluoromethyl-1,2-benziodoxol-3,3-(1*H*)-dimethyl; Scheme 39).[55]

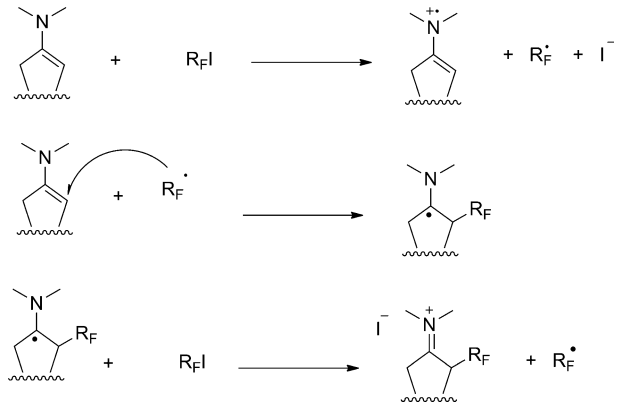


Scheme 37. Enantioselective trifluoromethylation of β-ketoesters with reagent **2c**.

Indanone-derived *tert*-butyl β-ketoesters generated the corresponding products in high yields with excellent enantioselectivities (92–99%) regardless of the nature and the position of the substituents of the β-ketoester derivatives.[55] In the presence of electron-withdrawing or donating groups, or even methylthio units on the aromatic ring, very good yields and enantioselectivities were obtained. Methyl and benzyl β-ketoesters also yielded the corresponding products showing that the size of the ester group has a slight influence on the enantiocontrol.

3.3.2. Trifluoromethylation of silyl enol ethers

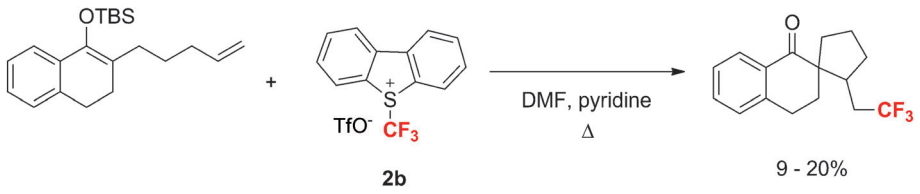
Magnier and co-workers recently attempted to disclose the mechanism for the electrophilic trifluoromethylation reaction of carbon nucleophiles with *S*-(trifluoromethyl)dibenzothiophenium trifluoroacetate.[56] Thermodynamic and electronic considerations suggest a nucleophilic attack side-on to the carbon trifluoromethyl sulfur bond, accompanied by one- or two-electron exchange.[53,57] The ratio of *ortho*/*para* (8:2) compounds obtained during the trifluoromethylation of aniline cannot be used to discriminate between CF_3^+ or $CF_3^{\cdot}$ as intermediate species. Nevertheless, in previous works employing soft nucleophiles, such as enamines, the authors proved that a SET process was involved in the reaction between enamines and perfluoroalkyl iodides (Scheme 40).[56]



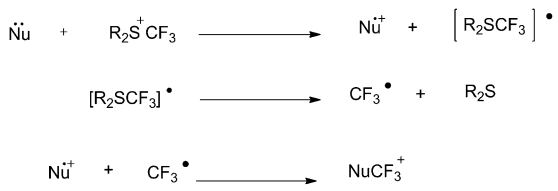
Scheme 40. Involvement of radical species in the reaction of enamines with perfluoroalkyl iodides (R_FI).

To cast some light on the mechanism of the reaction with soft nucleophiles and trifluoromethyl dibenzothiophenium salts, Magnier and co-workers developed the reaction depicted in Scheme 41, utilizing a silyl enol ether.[56]

The presence of the spiro compound reveals the intermediacy of a radical species, and the mechanism postulated is shown in Scheme 42. The solvent of choice was DMF or acetonitrile, and the trifluoromethylating reagent was *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate **2c**.

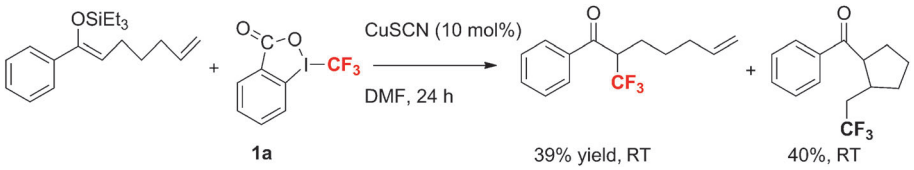


Scheme 41. Trifluoromethylation of soft nucleophiles with trifluoromethyl dibenzothiophenium salts **2b**.



Scheme 42. SET mechanism postulated in the presence of trifluoromethyl dibenzothiophenium salts.

More recently, Li, Chen, and Guo attempted to disclose the mechanism of the reaction of silyl enol ethers with reagent **1a** through trapping experiments and mechanistic probes, with a radical-clock reaction (Scheme 43).[58]



Scheme 43. Use of a radical clock substrate.

The radical-clock experiment confirmed the existence of a CF_3 radical in the reaction mixture, which was captured by both of the double bonds (Scheme 43). Based on the above and other experimental evidence,[58] the postulated mechanism is depicted in Scheme 44.

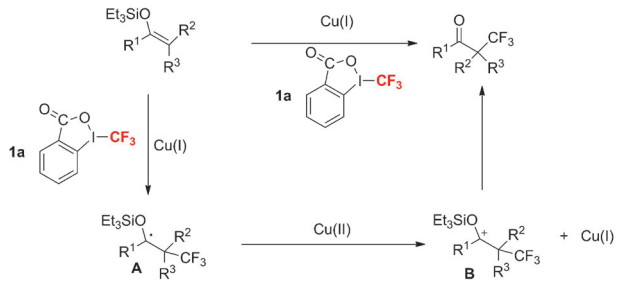
The reaction of Cu^I with **1a** produces CF_3 radicals which add to silyl enol ethers to afford a radical intermediate **A** (Scheme 44), which would be oxidized by copper(II) to afford a cationic intermediate **B** and to regenerate Cu^I. The loss of the silyl group would produce the α-CF_3-substituted ketone.[58]

Electrophilic trifluoromethylation of β-ketoesters selectively occurs on the carbon centers of enolates, rather than on the corresponding oxygen atoms. The same applies for the enantioselective trifluoromethylthiolation of β-ketoesters in the presence of reagent **1b** and copper–Boxmi complexes (Boxmi = (1*Z*,3*Z*)-1,3-bis[{(*S*)-4-phenyl-4,5-dihydrooxazol-2-yl}methylene]isoindoline).[59] However, control of C and O regioselectivity in enolate alkylation is one of the oldest subjects in organic chemistry. The C/O regioisomer ratio is sensitive to the extent of enolization of substrates that are highly dependent on the structure of carbonyl compounds and also on the nature of the alkylating reagents and reaction conditions, in particular, the solvent and base. It has been shown that *C*-alkylation tends to be occur more frequently with softer electrophiles, whereas *O*-alkylation is preferred with harder electrophiles.[60,61]

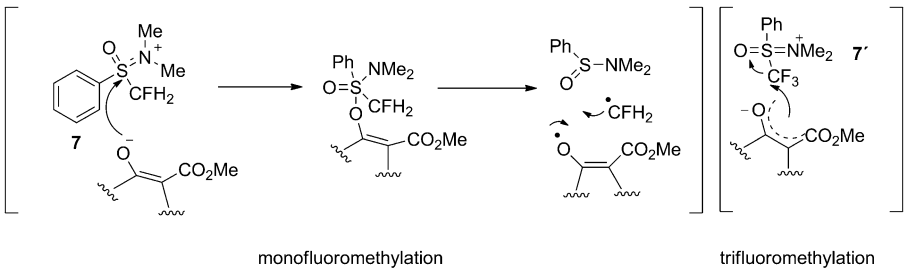
Umemoto and co-workers reported that the reaction pathway can change from involving a $CF_3^{\cdot}$ radical to a CF_3^+ cation, depending on the nature of the nucleophile.[62] A SET mechanism has then been suggested in the trifluoromethylation reaction through trapping experiments with radical scavengers.

Shibata and co-workers proposed that *O*-fluoroalkylation of β-ketoesters takes place with monofluoromethyl phenyl sulfoximine triflate **7** (Scheme 45) and *C*-fluoroalkylation of β-ketoesters is effected by the use of trifluoromethyl phenyl sulfoximine triflate **7′** (Scheme 45).[60] Thus, a nucleophilic attack of the β-carbon atom of the β-ketoesters towards **7′** gives rise to the *C*-fluoroalkylation product, whereas the *O*-fluoroalkylation is observed with reagent **7** instead, through a radical pathway.

Even so, Togni and co-workers very recently accomplished the trifluoromethylation of oxygen nucleophiles derived from



Scheme 44. Proposed mechanism for the trifluoromethylation of silyl enol ethers with reagent **1 a**.



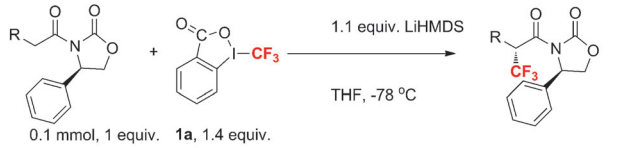
Scheme 45. Reaction mechanism for the monofluoromethylation and trifluoromethylation of O/C nucleophiles.

N-hydroxyl amines (see section **5.2.**) with reagent **1 b** in excellent yields.[63]

3.3.3. Trifluoromethylation of oxazolidinones

Togni and Cahard[64] recently reported a highly diastereoselective trifluoromethylation of chiral imide enolates with reagent **1 a**. The scope of the transformation is illustrated in Scheme 46.

The enolates are generated with lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C.[64] The high reactivity and selectivity of lithium enolates is explained by the strong Lewis acidity of the counterion, which is considered to lead to a tighter chelation and possibly to partial CF_3-reagent activation.[64] Among the chiral auxiliaries, those containing aromatic groups, preferably with a rigidified skeleton, offered the best diastereoselectivity (d.r.) and the reaction scope thereof was studied by using (*R*)-4-phenyl-1,3-oxazolidin-2-one (Scheme 46). With increasing steric bulk of the acyl group, the yield of isolated product increased. The highest d.r. values were obtained with the most bulky *tert*-butylacetyl-substituted oxazolidinone.

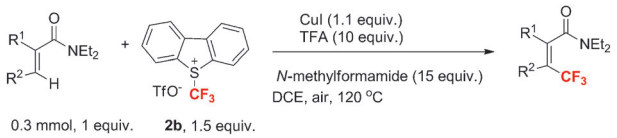


R = Bn	86%, d.r. = 90:10
= Ph	83%, d.r. = 88:12
= 2-naphthyl	40%, d.r. = 77:23
= Me	46%, d.r. = 81:19
= *i*Pr	75%, d.r. = 96:4
= *c*-hex	91%, d.r. = 94:6
= *t*Bu	83%, d.r. = 97:3
= OBn	74%, d.r. = 86:14

Scheme 46. Substrate scope for the trifluoromethylation of oxazolidinone enolates with reagent **1 a**.

3.4. Trifluoromethylation of acrylamide derivatives with electrophilic reagents

In 2014, Cahard and Besset reported the regio- and diastereoselective Cu-mediated trifluoromethylation of functionalized alkenes (acrylamide derivatives) utilizing electrophilic reagent **2 b** and a copper catalyst in TFA-*N*-methylformamide, affording *Z*-alkenes in moderate to good yields.[52] In this manner, α- and β-substituted *N*,*N*-diethylacrylamides undergo a copper-mediated direct β-trifluoromethylation reaction. The amide moiety acts as a directing group for the regio- and the stereocontrolled introduction of the trifluoromethyl group. The reaction is carried out under acidic conditions in the presence of reagent **2 b**. This method does not require prefunctionalized substrates and delivers excellent stereoselectivity, albeit the product yields are moderate to low. The scope of the reaction is illustrated in Scheme 47.[52]



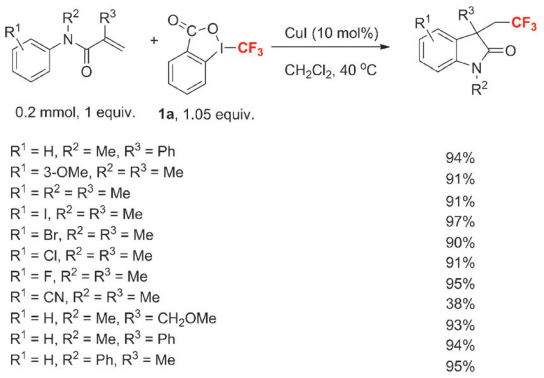
R^1 = Ph, R^2 = H	62%
R^1 = 4-MeO-C_6H_4, R^2 = H	69%
R^1 = 4-*t*Bu-C_6H_4 , R^2 = H	66%
R^1 = 4-Cl-C_6H_4, R^2 = H	54%
R^1 = 2-Et-C_6H_4, R^2 = H	34%
R^1 = *n*-C_4H_9, R^2 = H	19%
R^1 = R^2 = Ph	11%
R^1 = H, R^2 = Ph	35%

Scheme 47. Copper-mediated trifluoromethylation α- and β-substituted *N*,*N*-diethylacrylamides with reagent **2 b**.

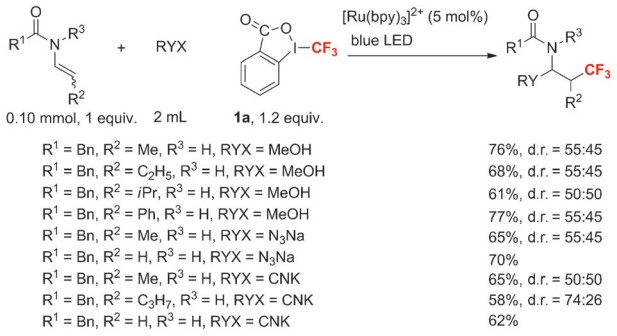
Functionalized acrylamides have recently been reported to undergo trifluoromethylation reactions with Togni's reagent **1 a** in very good yields in DMSO as solvent,[65] with remarkable stereospecificity. The reaction provides the *cis* trifluoromethylated stereoisomer.

Sodeoka and co-workers reported the synthesis of oxindole derivatives with a trifluoroethyl group through acryloanilide derivatives and Togni's reagent **1 a** (Scheme 48).[66]

The reactions of acryloanilide derivatives incorporating an electron-donating group (OMe) on the phenyl ring proceeded smoothly, and the corresponding oxindole derivatives were ob-



Scheme 48. Carbotrifluoromethylation of acryloanilides derivatives with reagent **1 a**.



Scheme 49. Scope of the trifluoromethylation of carbamates with reagent **1 a**.

tained in good yields (Scheme 48). Notably, carbon–halogen bonds (X = I, Br, Cl, F) withstood the present reaction conditions. Strong electron-withdrawing groups, such as CN, on the aryl ring retarded the reactions and lowered the oxindole derivative yields.[66] The authors postulated that the unidentified active species generated from Togni's reagent **1 a** interacts with the C=C double bond of acryloanilide, followed by electron transfer from the aryl ring through the C=C bond coupled with simultaneous C–C bond formation to construct the oxindole scaffold.[66]

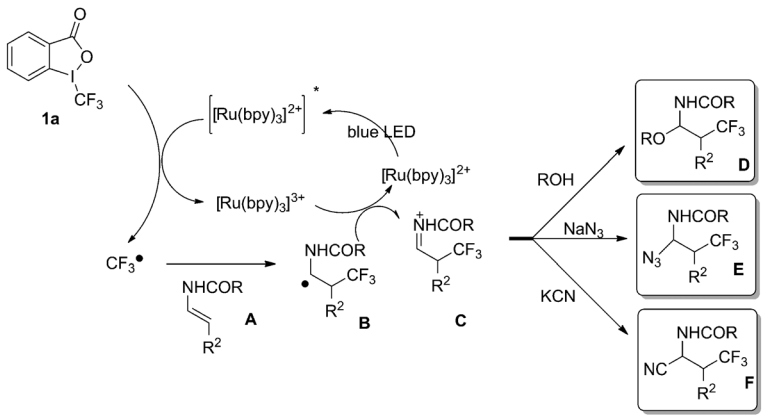
Trifluoromethylation of *N*-acryloanilides leading to trifluoromethyl-substituted oxindoles has also been achieved utilizing other non-electrophilic trifluoromethylating reagents such as $TMSCF_3$[67] with $Pd(AcO)_2$ as catalyst. On the other hand, the difluoromethylation[68] of *N*-acrylanilides towards the construction of difluoromethyl-substituted oxindoles, has been attained through the use of $PhSO_2CF_2I$ reagent and $Pd_2(dba)_3$ as catalyst.[69]

3.5. Trifluoromethylation of carbamates with electrophilic trifluoromethylating reagents

Magnier and co-workers recently accomplished the oxytrifluoromethylation, aminotrifluoromethylation, and cyanotrifluoromethylation of ene-carbamates employing electrophilic reagent **1 a** under photocatalytic conditions with $[Ru(bpy)_3]^{2+}$ (Scheme 49).[70]

A wide range of β-substituted ene-carbamates bearing either a linear or branched alkyl group reacted efficiently to afford the expected trifluoromethylated adducts in good to excellent yields (60–92%). However, in some cases, the authors found that the trifluoromethylated products were contaminated with impurities (<10%) that were identified as the iodinated products.[70] These side products resulted from the iodination of ene-carbamates with iodine generated during the reaction, which had not previously been reported. The authors could suppress these side-products by the addition of a catalytic amount of Ph_3P as an iodine trap, and the desired β-trifluoromethyl amines were produced with similar yields.[70]

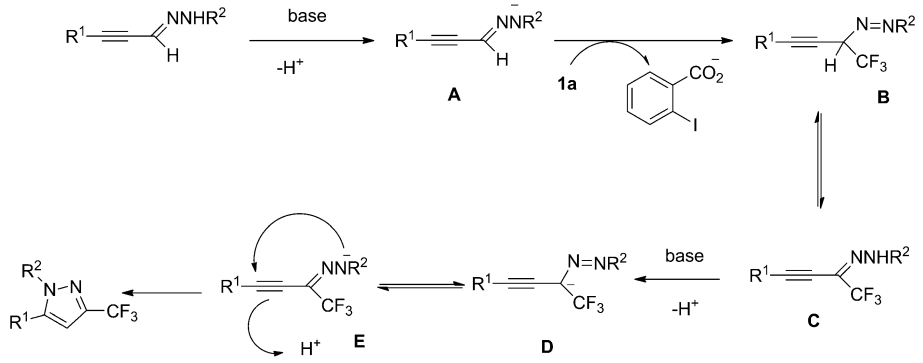
The mechanism proposed by the authors is depicted in Scheme 50.[70] First, irradiation with visible light excites $[Ru(bpy)_3]^{2+}$ into a strong reductant species $*[Ru(bpy)_3]^{2+}$, which performs a single electron transfer (SET) to generate $CF_3^{\cdot}$ radicals from Togni's reagent **1 a**. Subsequent regioselective addition of electrophilic $CF_3^{\cdot}$ radicals to ene-carbamate **A** leads to the α-amido radical **B**, which can be rapidly oxidized into *N*-acyliminium cation **C** by SET from $[Ru(bpy)_3]^{3+}$. Final nucleophilic trapping by alcohol, NaN_3, or KCN, affords the corresponding trifluoromethylated adducts **D, E**, or **F**, respectively. It is also worth noting that in the case of amino- and carbotrifluoromethylation, the desired products **E** or **F** were not observed on sequential addition of NaN_3 or KCN, respectively, thus suggesting that the equilibrium between hemiaminal **D** (R = H) and *N*-acyliminium cation **C** does not take place during the reaction and that **C** is directly trapped by NaN_3 or KCN.[70]



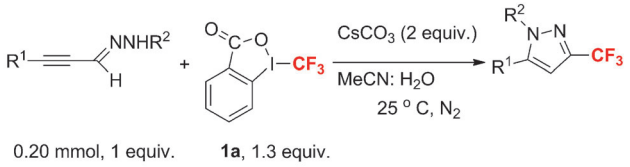
Scheme 50. Proposed reaction mechanism of ene carbamates with reagent **1 a** photocatalyzed by $[Ru(bpy)_3]^{2+}$.

3.6. Trifluoromethylation of hydrazones

Wang and co-workers recently reported the trifluoromethylation of α,β-alkynyl hydrazones with reagent **1a** and $CsCO_3$ as base, in MeCN/H_2O as a solvent mixture towards the synthesis of 3-trifluoromethylpyrazoles in moderate to good yields.[71] The scope of the transformation is illustrated in Scheme 51.



Scheme 52. Proposed mechanism for the trifluoromethylation of alkynyl hydrazones with reagent **1a**.



$R^1 = R^2 = Ph$	70%
R^1 = 4-Me-C_6H_4, R^2 = Ph	59%
R^1 = 2-Me-C_6H_4, R^2 = Ph	62%
R^1 = biphenyl, R^2 = Ph	58%
R^1 = 4-MeO-C_6H_4, R^2 = Ph	63%
R^1 = 4-Cl-C_6H_4, R^2 = Ph	65%
R^1 = 4-I-C_6H4, R^2 = Ph	64%
R^1 = 4-CF_3-C_6H_4, R^2 = Ph	55%
R^1 = 4-NO_2-C_6H_4, R^2 = Ph	72%
R^1 = 2-thiophenyl, R^2 = Ph	57%
R^1 = 3-pyridyl, R^2 = Ph	52%
R^1 = Ph, R^2 = Boc	30%
R^1 = 4-Me-C_6H_4, R^2 = H_2NO_2S-C_6H_4	52%, celocoxib

Scheme 51. Scope of the trifluoromethylation of α,β-alkynyl hydrazones towards the synthesis of 3-trifluoormethylpyrazoles with reagent **1a**.

The reaction exhibits good functional group tolerance in general. The reaction of electron-neutral α,β-alkynic hydrazones and α,β-alkynic hydrazones with electron-withdrawing groups on the aromatic ring, provides the corresponding 3-trifluoromethylpyrazoles in moderate to good yields (Scheme 51). Chloro- and iodo-substituted aryl alkynic hydrazones, undergo smooth conversion. The strong electron-withdrawing groups CF_3 and NO_2 (Scheme 51) are also compatible with the reaction conditions. Substrates bearing thiophene and pyridine moieties afford good yields of substituted pyrazoles.[71] With this protocol, the drug celocoxib (Scheme 51, R^1 = 4-Me-C_6H_4, R^2 = H_2N-O_2S-C_6H_4) was obtained in 52% yield.

Use of TEMPO in the standard reaction conditions reduced the yields of substituted-products, but it did not suppress the reaction entirely. These observations, according to the authors,[71] do not support a pure trifluoromethyl radical pathway. Condensation of phenyl alkynyl trifluoromethyl ketone (Ph-C≡C-C(O)–CF_3) with phenyl hydrazine ($PhNHNH_2$), affords 1,5-diphenyl-3-(trifluoromethyl)-1*H*-pyrazole in good yields.[71] Based on the evidence, Wang and co-workers proposed the reaction mechanism depicted in Scheme 52.

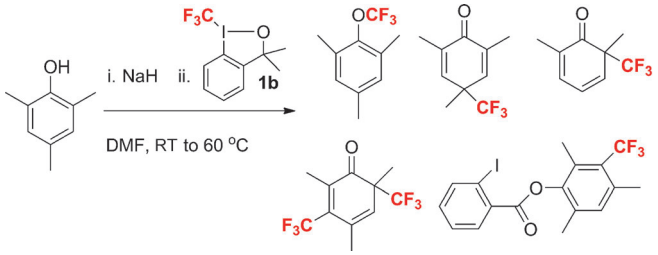
The reaction is initialized with deprotonation of α,β-alkynic hydrazones with a base to form the anionic intermediate **A** (Scheme 52), which reacts with a highly electrophilic Togni's reagent **1a** to form the C–CF_3 bond, affording azo intermediate **B** or α,β-alkynic hydrazone **C**.[71] Species **B** or **C** undergoes a deprotonation/cyclization/protonation sequence to give 1,5-diaryl-3-(trifluoromethyl)-1*H*-pyrazole.[71] However, since the trifluoromethyl radical has been trapped by TEMPO in this reaction, a radical mechanism cannot be strictly ruled out, according to the authors.[71] Further studies are needed to firmly establish the reaction mechanism.

In summary, the electrophilic trifluoromethylation of enones can be performed through the use of electrophilic reagent **1a** and a copper(I) catalyst, or reagent **2a** and copper. β-Ketoesters are trifluoromethylated with electrophilic reagent **1b**, **2c**, or **3a** in good yields, employing a base. Imide enolates are trifluoromethylated with reagent **1a** in the presence of base, whereas ene-carbamates can undergo a trifluoromethylation reaction with reagent **1a** and a photocatalyst.

4. Electrophilic trifluoromethylation of aromatic and heteroaromatic rings

In 2012, Beller and co-workers published a review article on trifluoromethylation reactions of arenes and heteroarenes, where some of the processes employ electrophilic trifluoromethylating reagents.[72]

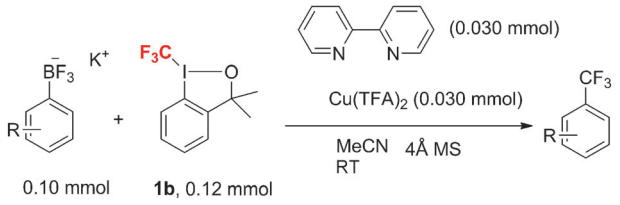
The trifluoromethylation of 2,4,6-trimethylphenol with 1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole **1b** afforded a mixture of compounds (Scheme 53).[73]



Scheme 53. Electrophilic trifluoromethylation of phenol derivative with electrophilic reagent **1b** in dimethylformamide.

In contrast, the nucleophilic difluoromethylation of phenols with fluoroform leads to difluoromethyl aryl ethers in excellent yields.[74] For this class of substrates, the nucleophilic methodology surpasses the electrophilic approach in terms of reaction yields.

In 2012, Weng and co-workers reported an efficient room-temperature copper-catalyzed trifluoromethylation of organotrifluoroborates using the electrophilic trifluoromethylating reagent **1 b** in good yields (Scheme 54).[75]



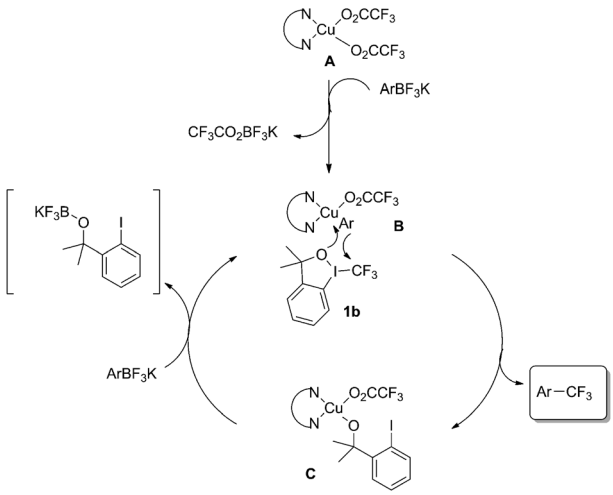
R = 4-*t*Bu	91%
R = 4-BnO	92%
R = 4-Ph	95%
R = 3-Ph	82%
R = 4-Me	69%
R = 4-MeO	60%
R = 2,3-Me_2	65%
R = 4-MeC(O)	42%
R = 4-CHO	39%
R = 4-Cl	50%

Scheme 54. Scope of the trifluoromethylation reaction of aryl trifluoroborates with reagent **1 b**.

A plausible mechanism for the trifluoromethylation of potassium arylborates with Togni's reagent **1 b** is proposed in Scheme 55.

The bipyridine-ligated [(*N*,*N*)Cu(CF_3CO_2)$_2$] complex (**A**; Scheme 55) could be initially generated in situ. **A** then undergoes the transmetallation reaction with potassium arylborate to give a copper(II) intermediate **B**. Subsequent nucleophilic attack of the aryl group of **B** on the CF_3^+ moiety in Togni's reagent **1 b** might proceed to form the product and a Cu–alkoxide complex (**C**), which can further react with potassium arylborate to regenerate **B** to complete the catalytic cycle. This mechanism bears some resemblance to that depicted in Scheme 24 (section **2.3.**).

The Pd^{II}-catalyzed *ortho*-C–H trifluoromethylation of benzylamines was achieved by Yu and co-workers utilizing the electrophilic CF_3 reagent **2 c**. Additives, such as H_2O and Ag_2O, were found to be crucial for obtaining good yields.[76] The general reaction scope is depicted in Scheme 56. This protocol is useful for the preparation of *ortho*-trifluoromethyl-substituted benzylamines.



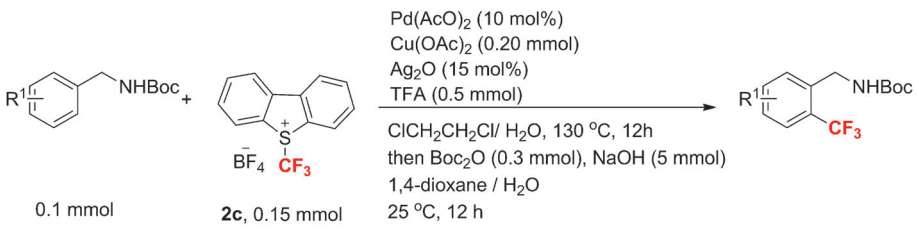
Scheme 55. Proposed reaction mechanism for the trifluoromethylation of aryl trifluoroborates with reagent **1 b**.

Recently, Ma and co-workers accomplished the visible-light-promoted radical trifluoromethylation of free anilines with electrophilic reagent **1 a** in reasonable to good yields. The photocatalyst employed was tris[2-phenylpyridinato-C^2,*N*]iridium(III), [Ir(ppy)$_3$].[77]

Trifluoromethylation of heterocycles was recently reviewed by Shermolovich and co-workers.[78] Electrophilic trifluoromethylation of heterocycles, such as pyrrole, indole, 3-methylindole, imidazoles, benzimidazoles, and pyridines with Togni's reagent has also been carried out in good yields.[79]

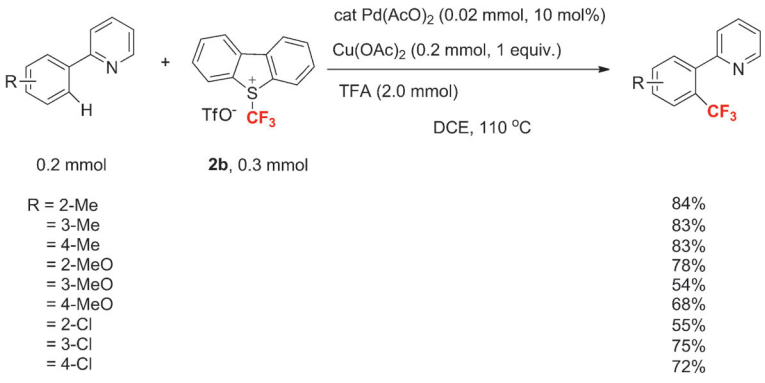
Yu and co-workers reported on the $ArPd^{II}$ species generated from C–H activation of aromatic rings and secondary reaction with reagent *S*-(trifluoromethyl)dibenzothiophenium triflate **2 b**,[80] and obtained the CF_3-substituted aryl ring in excellent yields (Scheme 57).[76,81]

Yu and co-workers examined the substrate scope and showed that electron-donating groups on the aryl ring are well tolerated.[80] Moderate electron-withdrawing groups such as Cl are also compatible with this protocol. The use of substrates containing strong electron-withdrawing groups such as



R^1 = 2-Me	79%
= 3-Me	60%
= 4-Me	30%
= H	24%
= 3-MeO	42%
= 3-Cl	28%

Scheme 56. *Ortho*-C–H trifluoromethylation of benzylamines with electrophilic reagent **2 c**.



Scheme 57. Electrophilic trifluoromethylation of 2-phenylpyridine with $Pd(OAc)_2$, $Cu(OAc)_2$ as co-oxidant with TFA as additive in dichloroethane as solvent with reagent **2b**.

keto, ester, and nitro functionalities was found to afford the desired products in yields lower than 20%.

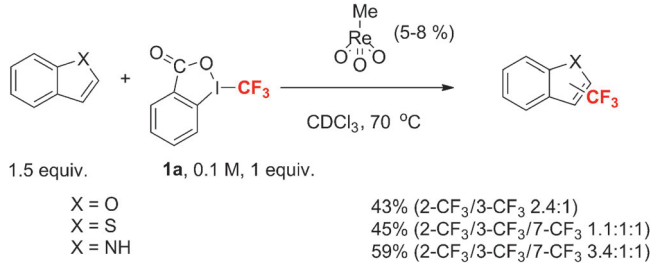
Magnier and co-workers carried out the trifluoromethylation of aromatic nuclei with reagent **2b** in ionic liquids, obtaining good substitution yields.[82]

Togni and co-workers accomplished the trifluoromethylation of a series of heteroaromatic compounds using the hypervalent iodine reagent 1-(trifluoromethyl)-1,2-benziodoxol-3-(1*H*)-one **1a** (Scheme 58) and methyltrioxorhenium (MTO) as catalyst. Very recently, reagent **1a** was also used in the perfluoroalkylation of phenanthridines through a radical mechanism in dioxane as solvent, in the absence of MTO catalyst.[83]

The authors argue that the C–H bond breaking process is the rate limiting step, and proposed the mechanism shown in Scheme 59.[83]

The first stage of the reaction starts with the activation of **1a** by coordinating the Lewis acid (MTO) **A**, making the hypervalent iodine reagent more electrophilic (hence a better oxidant) promoting the SET from the benzene moiety in the encounter complex **B**. This forms an aromatic radical cation species **C**, which is coupled with singlet diradical. The cage pair collapses transferring CF_3^- to afford the radical intermediate **D** (Scheme 59), which, upon H atom loss, affords the CF_3-substituted aryl ring.

In summary, electrophilic trifluoromethylation of aryl trifluorobotates can be accomplished with reagent **1b** and a Cu^{II} catalyst. C–H trifluoromethylation of aryl rings has been performed by electrophilic reagent **2c** and Pd^{II} and Cu^{II} catalysts. C–H trifluoromethylation of heteroaryl rings has been achieved with reagent **1a** and a Re complex.

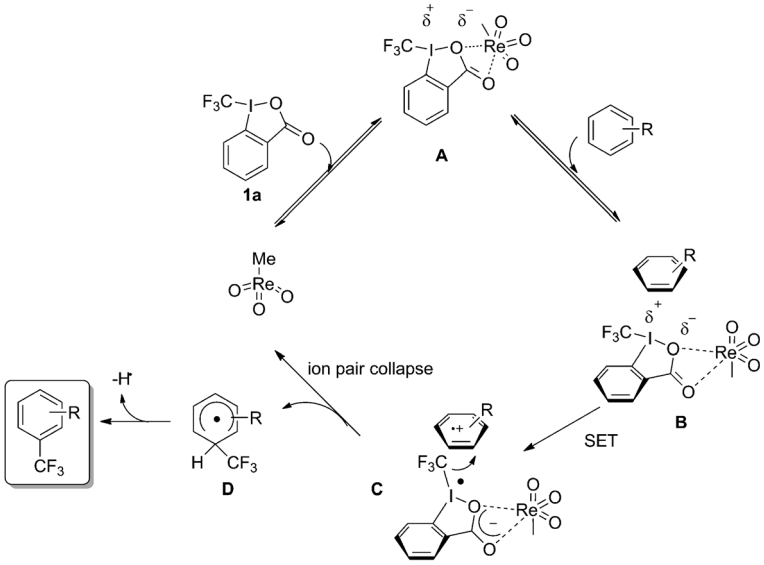


Scheme 58. Use of Togni's reagent **1a** and methyltrioxorhenium as catalyst for the trifluoromethylation of heteroaromatic compounds.

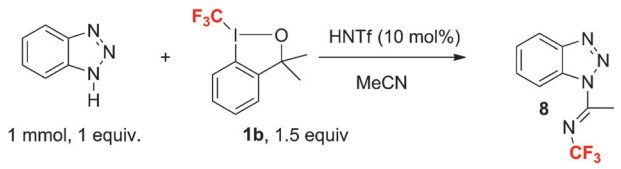
5. Electrophilic trifluoromethylation of heteroatoms and isonitriles

5.1. Trifluoromethylation of *N*-centers

Direct electrophilic trifluoromethylation at nitrogen atoms of benzotriazole and a series of imidazole derivatives has been attempted by Togni and co-workers in acetonitrile as solvent (Scheme 60).[84]



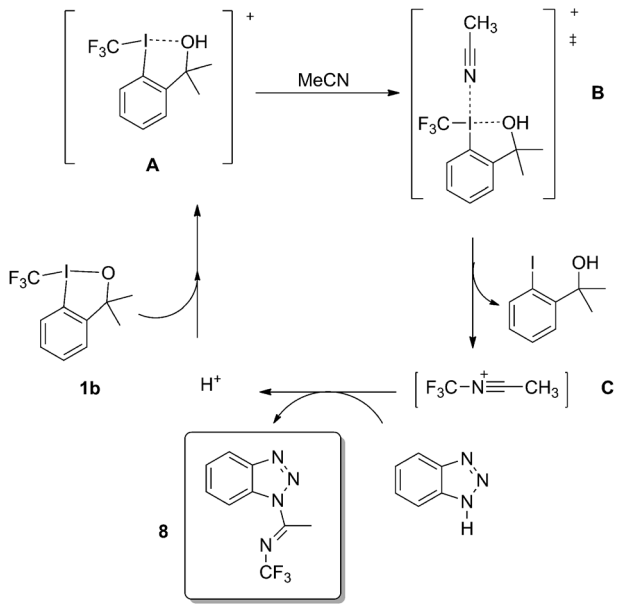
Scheme 59. Mechanism for the trifluoromethylation of aromatic compounds with Togni's reagent **1a** and methyltrioxorhenium as catalyst.



Scheme 60. Reaction of benzotriazole with reagent **1b**: The catalyst is bis(trifluoromethanesulfonyl)imide ($HNTf_2$).

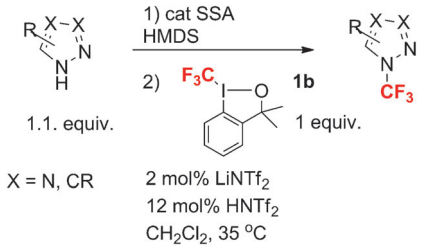
The postulated mechanism where acetonitrile intervenes in the reaction sequence is depicted in Scheme 61.

The protonated form of reagent **1b** (**A**, Scheme 61) is the reactive species. A coordinated acetonitrile (**B**, Scheme 61) subsequently undergoes the formation of *N*-trifluoromethyl nitrilium ion **C** by a reductive -elimination process, as the rate-determining step. The nitrilium ion is then rapidly trapped by benzotriazole to form product **8**, thus releasing a proton and completing the catalytic cycle (Scheme 61).[84]



Scheme 61. Proposed mechanism for the acid-catalyzed Ritter-type reaction of reagent **1b** with benzotriazole.

In a more recent work, Togni and co-workers accomplished the trifluoromethylation of azoles, with a series of additives and base.[85] Thus the use of 1,1,1,3,3,3-hexamethyldisilazane (HMDS), in the presence of catalytic silica sulfuric acid (SSA), followed by trifluoromethylation in highly concentrated CH_2Cl_2 at 35 °C, in the presence of catalytic amounts of *bis*(trifluoromethanesulfonyl)imide ($HNTf_2$), afforded the *N*-trifluoromethylated products (Scheme 62).

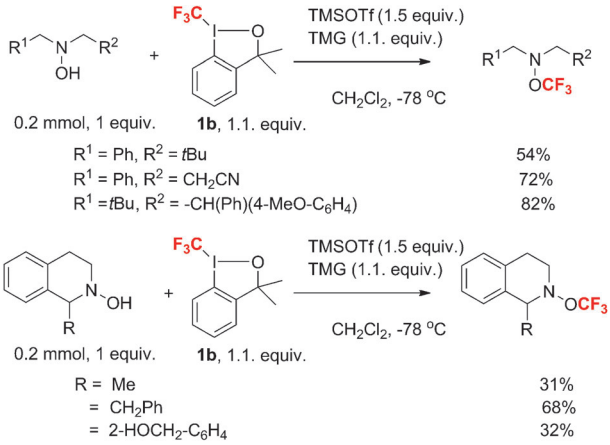


Scheme 62. Trifluoromethylation of heterocycles with Togni's reagent **1b**.

Heterocycles with electron-donating groups afford higher yields of *N*-trifluoromethylated products.[85] This can be explained by the fact that electron-poor groups lead to slower reactions allowing formation of side products. Indazoles are preferentially trifluoromethylated at the *N*-2 position.

5.2. Trifluoromethylation of *O*-centers

A recent review article by Leroux and co-workers on the synthesis of trifluoromethyl ethers (and thioethers) revealed the peculiar properties that OCF_3 (and SCF_3) groups impart to molecules.[86] Very recently, Togni and co-workers reported the trifluoromethylation of *N,N*-disubstituted hydroxylamines towards the synthesis of N–O–CF_3 compounds in moderate to good yields, employing the electrophilic reagent **1a** or **1b**.[63] The authors found that for simple aliphatic hydroxylamines (*N,N*-disubstituted), the best reaction conditions involved the use of electrophilic reagent **1b**, Hünig's base (*N,N*-diisopropyl ethyl amine) in CH_2Cl_2 as solvent, at room temperature (Scheme 63). However, for cyclic hydroxylamines, the reaction



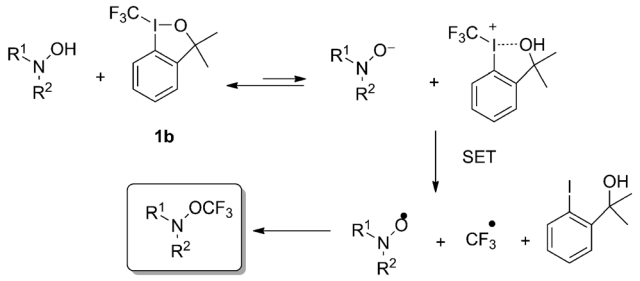
Scheme 63. Scope for the trifluoromethylation of *N*-hydroxylamines with reagent **1b**.

conditions had to be varied employing a powerful silylating agent such as trimethylsilyl trifluoromethanesulfonate (TMSOTf) in combination with a strong amine base, such as tetramethyl guanidine (TMG).[63] However, for both classes of substrates, the combination of TMSOTf and TMG afforded better product yields. Reaction scopes for both acyclic and cyclic *N*-hydroxylamines are presented in Scheme 63.

Esters as well as nitrile functionalities are tolerated in the trifluoromethylation reaction. Primary and tertiary amide substrates can be trifluoromethylated, as well as primary and secondary alcohol groups. The method is not sensitive to the steric bulk of the R substituents (Scheme 63).[63]

To provide evidence for the radical nature of the process, Togni and co-workers employed the radical scavenger TEMPO, which was added to the reaction mixture in a stoichiometric amount.[63] Under these reaction conditions, competitive trifluoromethylation of the excess amount of TEMPO completely suppressed the formation of product derived from dibenzyl-*N*-hydroxyl amine substrate. They considered this result a strong indication for a radical pathway with a CF_3 radical as the key intermediate. However, trifluoromethylation of the potential radical clock 1-allyl-3,4-dihydroisoquinolin-2(1*H*)-ol failed to provide a single product.[63]

The proposed reaction mechanism (Scheme 64) involves a proton transfer pre-equilibrium followed by SET affording radical pairs leading to the recombination products.[63] This transformation is quite surprising since, as shown in Scheme 45 (section **3.3.2.**), only monofluoromethylation rather than trifluoromethylation of oxygen nucleophiles is observed.



Scheme 64. Proposed reaction mechanism for the trifluoromethylation of *N*-hydroxylamines with **1 b**.

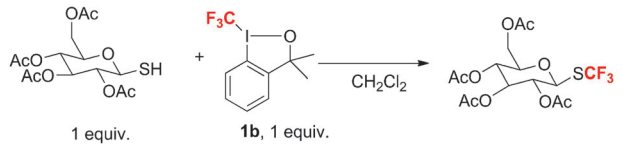
5.3. Trifluoromethylation of *S*-centers

Sulfur centers can easily be trifluoromethylated by the employment of hypervalent iodine(III)–CF_3 reagents.[87] An interesting example is presented in Scheme 65.

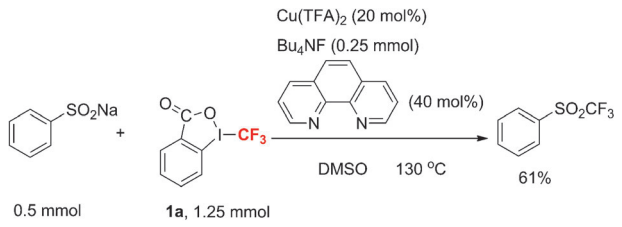
Aryl sulfinate salts have recently been shown to be trifluoromethylated in good yields by the use of electrophilic Togni's reagent **1 a**, in the presence of catalysts.[88] The optimum reaction conditions are depicted in Scheme 66.

The electrophilic trifluoromethylation of *S*-hydrogen phosphorothioates was also accomplished by the same group in good yields (Scheme 67).[89]

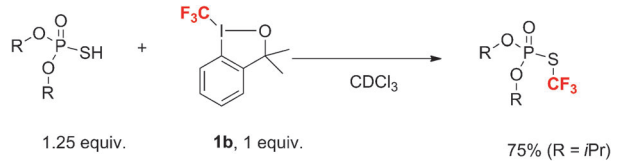
The mechanism of the reaction is depicted in Scheme 68.[90] It is proposed that, after the protonation of the reagent and coordination to the iodonium core, the remote methoxy group further stabilizes the intermediate, thereby slowing down the



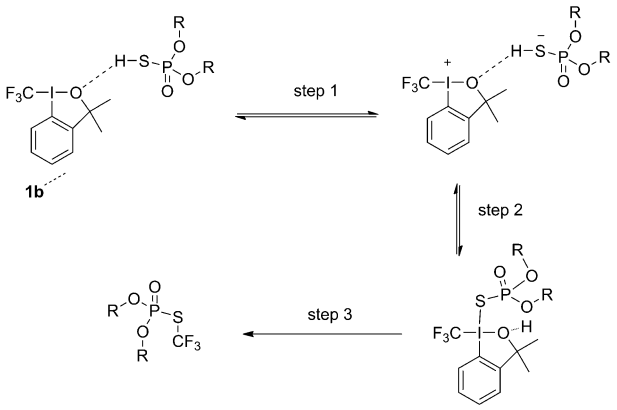
Scheme 65. Trifluoromethylation of *S*-centers with reagent **1 b**.



Scheme 66. Optimum reaction conditions for the trifluoromethylation of sulfinate salts with reagent **1 a**.



Scheme 67. Electrophilic trifluoromethylation of *S*-hydrogen phosphorothioates with reagent **1 b**.



Scheme 68. Mechanism of the electrophilic trifluoromethylation of *S*-hydrogen phosphorothioates with reagent **1 b**.

reductive elimination step (Scheme 68, step 3), resulting in a lower overall relative rate. This kind of stabilization has already been noted before for different hypervalent iodine(III) reagents.[89]

5.4. Trifluoromethylation of *P*-centers

Aryl and alkylphophines can be trifluoromethylated with the use of Togni's reagent **1 a** or **1 b** in excellent yields.[90] Hydrogen phosphates have also been reported to be trifluoromethylated with reagent **1 b**.[91] Togni and co-workers reported an acceleration of the reaction due to increased steric bulk of the substrates' substituents.[91] The yields of trifluoromethylated phosphates are rather low. Later, the trifluoromethylation of primary phosphines was achieved, towards the synthesis of useful *p*-bis(trifluoromethyl) binaphthyl (BINAP) derivatives.[92]

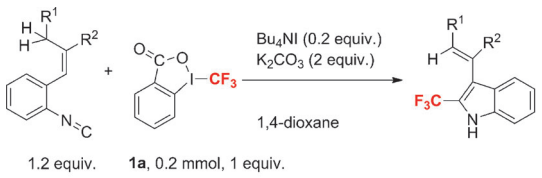
5.5. Trifluoromethylation of isonitriles

Very recently, Studer and co-workers reported the trifluoromethylation of isonitriles, towards the synthesis of 2-substituted trifluoromethyl indole derivatives in fairly good yields, employing electrophilic reagent **1 a** (one equivalent), and substrate (1.2 equivalents; Scheme 69).[93]

If the reaction conditions are varied so that reagent **1 a** is used in excess (3 equivalents) with regards to the substrate (1.2 equivalents), bis-trifluoromethylation is observed (Scheme 70).[93]

Either two or three C–C bonds are formed in the synthesis of 2-trifluoromethylindoles starting with readily prepared isonitriles and Togni's reagent **1 a** as CF_3 radical precursor. These transformations occur in the absence of transition metals, and products are obtained in moderate to good yields with excellent diastereoselectivity.[93]

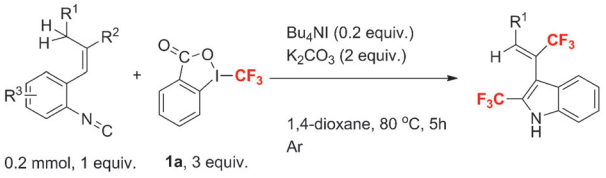
Yu and co-workers have attempted the trifluoromethylation of biphenyl isocyanides towards the synthesis of phenanthridine derivatives with electrophilic Umemoto's reagent **2 c**.[94] In this manner, the preparation of 6-(trifluoromethyl)phenanthridine derivatives was carried out using ionic isocyanide insertion from biphenyl isocyanide derivatives and reagent **2 c**



1.2 equiv. **1a**, 0.2 mmol, 1 equiv.

$R^1 = CH_3$, $R^2 = Ph$	67%, *E*/*Z* = 17:1
$R^1 = CH_3$, $R^2 = 4\text{-Me-}C_6H_4$	65%, *E*/*Z* = 12:1
$R^1 = CH_3$, $R^2 = 4\text{-MeO-}C_6H_4$	70%, *E*/*Z* = 12:1
$R^1 = CH_3$, $R^2 = 4\text{-Br-}C_6H_4$	70%, *E*/*Z* = 22:1
$R^1 = CH_3$, $R^2 = 4\text{-Cl-}C_6H_4$	71%, *E*/*Z* = 14:1
$R^1 = C_2H_5$, $R^2 = Ph$	73%, *E*/*Z* = 29:1
$R^1 = CH_3$, R^2 = thiophenyl	56%, *E*/*Z* = 6:1
$R^1 = H$, $R^2 = CO_2Et$	52%

Scheme 69. Trifluoromethylation of isonitriles employing reagent **1a**.



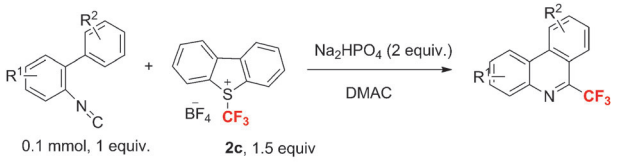
0.2 mmol, 1 equiv. **1a**, 3 equiv.

$R^1 = R^3 = H$, $R^2 = CO_2Me$	72%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = 4\text{-F}$	66%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = 3\text{-F}$	62%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = 4\text{-Cl}$	66%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = 3\text{-Cl}$	66%
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = 2,4\text{-Cl}_2$	65%, *Z*/*E* = 21:1
$R^1 = H$, $R^2 = CO_2Me$, $R^3 = 4\text{-Cl}$	63%
$R^1 = H$, $R^2 = R^3 = CO_2Et$	45%
$R^1 = H$, $R^2 = CO_2Et$, $R^3 = 4\text{-Me}$	65%, *Z*/*E* = 36:1

Scheme 70. Scope of the bis-trifluoromethylation of isonitriles with reagent **1a**.

in dimethylacetamide (DMAC) as solvent (Scheme 71). These reactions were promoted only by inorganic base, resulting in good-to-excellent chemical yields without any external stoichiometric oxidants or radical initiators.[94] The scope of the reaction is depicted in Scheme 71.

The mechanism of the reaction is depicted in Scheme 72. Umemoto's reagent **2c** generates trifluoromethyl radicals, which add onto isocyanide **A** (Scheme 72) to give imidoyl radical **B**. The imidoyl radical **B** undergoes intramolecular homolytic aromatic substitution to provide radical **C**, which is oxidized by **2c** to give cation **D**. After deprotonation, the desired product **E** is obtained (Scheme 72).[94]



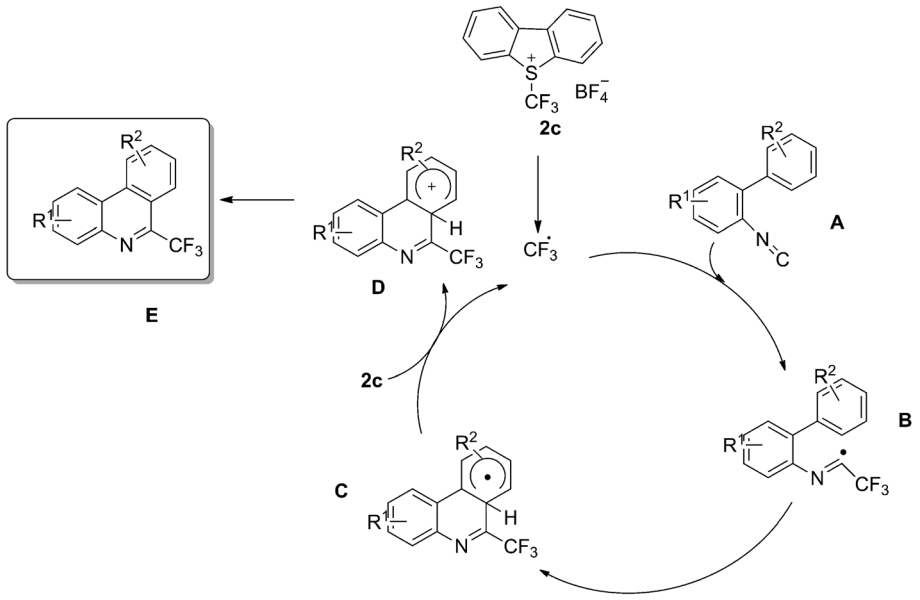
0.1 mmol, 1 equiv. **2c**, 1.5 equiv

$R^1 = 4\text{-Me}$, $R^2 = H$	89%
$R^1 = R^2 = H$	73%
$R^1 = 4,6\text{-Me}_2$, $R^2 = H$	73%
$R^1 = 5\text{-MeO}$, $R^2 = H$	78%
$R^1 = 4\text{-F}$, $R^2 = H$	67%
$R^1 = 4,6\text{-F}_2$, $R^2 = H$	83%
$R^1 = 5\text{-NO}_2$, $R^2 = H$	67%
$R^1 = 5\text{-CF}_3$, $R^2 = H$	76%
$R^1 = H$, $R^2 = 4\text{-Ph}$,	71%
$R^1 = H$, $R^2 = 4\text{-Cl}$	71%
$R^1 = H$, $R^2 = 4\text{-MeO}$	79%
$R^1 = H$, $R^2 = 2\text{-MeO}$	22%

Scheme 71. Scope of the trifluoromethylation of isocyanides towards the synthesis of 6-CF_3-substituted phenanthridine derivatives with electrophilic reagent **2c**.

6. Summary and Outlook

Outstanding progress has recently been made in the development of methodologies and shelf-stable electrophilic trifluoromethylation reagents; however, there are still important challenges due to the current limitations of these reagents. Within the examples described in this account, a wide variety of soft and hard nucleophiles has been successfully used as substrates affording the trifluoromethylated products in good to excellent yields which renders them important synthetic targets and intermediates in the pharmaceutical and agrochemical industries. Mechanistic studies with appropriate analytical tools should be conducted in order to obtain a thorough insight into the transfer of the electrophilic CF_3 group. A bimolecular nucleophilic substitution, S_N2 type mechanism, is often suggested, although



Scheme 72. Proposed reaction mechanism for the production of 6-CF_3-substituted phenanthridines with electrophilic reagent **2c**.

a single electron transfer mechanism cannot be ruled out depending on the reagent and reaction conditions. The intervention of metals and metal-organic catalyst promote the ET character in the reactions. Despite remarkable advancements in asymmetric introduction of trifluoromethyl groups, further developments are necessary for chiral non-racemic trifluoromethylated molecules. We hope that this review will stimulate the design of new reagents and optimization of the present ones for selective electrophilic trifluoromethylation reactions of a wider range of substrates.

Note added in proof: At the time this article was under review, a review article on electrophilic trifluoromethylation reactions using Togni's reagents appeared: J. Charpentier, N. Fru, A Togni, *Chem. Rev.* **2014**. DOI: 10.1021/cr500223h.

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Keywords: electrophilic addition · fluorinated compounds · radical reactions · synthetic methods · trifluoromethylation

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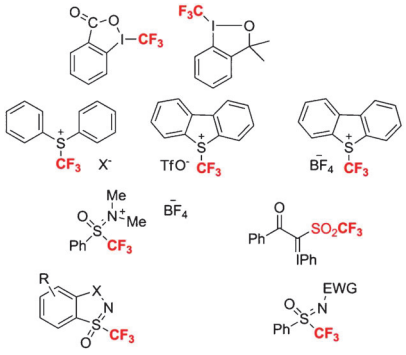
REVIEW

Trifluoromethylation of alkenes, alkynes, α,β-unsaturated carbonyl compounds, hard nucleophiles such as alcohols, thiols, and also aromatic compounds can be achieved through the use of electrophilic trifluoromethylating reagents, such as Togni's, Umemoto's, and Shibata's reagents. These reagents produce an electrophilic trifluoromethylating (CF_3^+) species that undergoes reaction with nucleophiles.

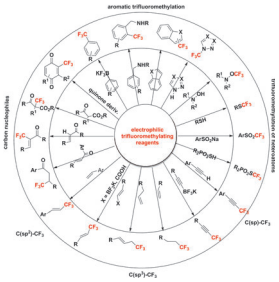


Trifluoromethylation

*S. Barata-Vallejo, B. Lantaño, A. Postigo**

■■ – ■■

Recent Advances in Trifluoromethylation Reactions with Electrophilic Trifluoromethylating Reagents



Trifluoromethylation

Electrophilic trifluoromethylation reactions with recently discovered reagents, such as Togni's, Umemoto's, Yagupolskii's, Shreeve's, and Shibata's reagents, is a highly prominent approach to achieving the fluoroalkylation of a diverse array of compounds, as discussed by Postigo et al. in their Review on page ■■ ff. Trifluoromethylation of alkenes, alkynes, α,β-unsaturated carbonyl compounds, hard nucleophiles such as alcohols, thiols, and also aromatic compounds can be achieved through the use of these electrophilic trifluoromethylating reagents. These reagents produce an electrophilic trifluoromethylating (CF_3^+) species that undergoes reaction with nucleophiles.