REVIEW

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Recent advances in direct trifluoromethylation of olefinic C–H bonds

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The aim of this review is to provide a comprehensive overview of the direct trifluoromethylation of olefinic C–H bonds with special attention on the mechanistic aspects of the reactions. The review is divided into two major sections. The first focuses exclusively on trifluoromethylation of terminal alkenes, while the second will cover trifluoromethylation of internal alkenes. Literature has been surveyed until the end of April 2019.

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1. Introduction

Today, fluorine-containing organic compounds are prominent in the various branches of the chemical sciences, particularly in medicinal, agricultural, and materials chemistry.[1] Approximately 25% of modern pharmaceuticals and 40% of agrochemicals[2] contain fluorine atoms in their structure, because fluorinated compounds exhibit a high chemical stability, bioavailability and lipophilicity over their non-fluorinated analogues.[3] Particularly, molecules bearing a trifluoromethyl ($-CF_3$) group show a wide range of pharmacological and biological properties.[4] Although a variety of efficient and practical methodologies for the construction of $C_{alkyl}-CF_3$ and $C_{aryl}-CF_3$ bonds have been developed over the last few years,[5] much less reports are available for the fabrication of $C_{alkenyl}-CF_3$ bonds. Moreover, alkenes are key intermediates in many organic cyclocondensation reactions.[6–10] As evidenced in the literature, $C-CF_3$ bond formation in alkenes usually relied on the use of prefunctionalized substrates, such as vinyl halides,[11] vinylboronic acids,[12] vinyl borates,[13] vinyl sulfonates,[14] vinyl carboxylic acids,[15] and nitro olefins.[16] Unfortunately, most of these strategies suffer from limited substrate scope, multistep synthesis, and/or toxic waste stream.

An alternative protocol for the preparation of CF_3-substituted alkenes involves the direct trifluoromethylation of corresponding olefins via C–H activation. As this synthetic

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strategy avoid wasteful pre-functionalization of starting materials, it is undoubtedly more cost effective, atom-economical, practical, and eco-friendly alternative compared to the traditional procedures. To the best of our awareness, a comprehensive review has not appeared on the direct trifluoromethylation of olefinic C–H bonds in the literature as yet. In continuation of our recent reviews on the direct C(X)–H bonds functionalization,[17] cross-coupling reactions and heterocyclic synthesis,[18] herein, we will highlight recent discoveries and developments on the direct C–H trifluoromethylation of alkenes (Scheme 1), with special attention on the mechanistic aspects of the reactions.

2. Terminal alkenes

2.1. Transition-metal-catalyzed reactions

In 2012, Sodeoka and colleagues reported that a combination of cationic copper catalyst ([(MeCN)$_4$Cu]PF$_6$), Brønsted acid (para-toluenesulfonic acid), and Togni's reagent 2 (1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one) enables direct trifluoromethylation of olefinic C–H bonds of styrene derivatives 1 giving β-trifluoromethyl styrenes 3 in high yields and outstanding (E)-selectivity (Scheme 2).[19] Although only two examples were disclosed, this paper represents the first example of direct trifluoromethylation of alkenyl C–H bonds. It should be noted that the presence of a Brønsted acid was crucial for the success of this transformation. In the absence of p-TsOH, the reaction failed to give the desired trifluoromethylated styrenes 3, providing instead oxy-trifluoromethylated products. The authors suggested that the reaction proceeded through the formation of oxy-trifluoromethylated intermediate A via an oxy-trifluoromethylation process followed by E1 reaction.

At the same time, with the objective of designing a general procedure to the direct olefinic C–H bonds trifluoromethylation, Feng and Loh were able to revealed that

a diverse set of enamides 4 can undergo Cu-catalyzed (E)-selective trifluoromethylation using Togni's reagent 2 as the source of CF$_3$.[20] The reaction were carried out in the presence of 10 mol% of [(MeCN)$_4$Cu]PF$_6$ as the catalyst in THF under an inert atmosphere and provided the target trifluoromethyl-substituted olefins 5 in moderate to excellent yields, ranging from 40% to 92% (Scheme 3). It should be mentioned that the amido moiety introduced onto the olefin moiety had a dual role: (i) stabilizing the putatively formed α-carbonium; and (ii) inducing the subsequent proton elimination or a migration process during the reaction. The outcomes of the radical trapping experiments by addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-tert-butyl-pcresol (BHT) to the reaction mixture and electron paramagnetic resonance (EPR) spectroscopy studies suggested that the mechanism of this reaction cannot be involved a radical pathway. A plausible mechanism is shown in Scheme 4. This transformation starts with the reaction between Togni's regent 2 and Cu(I), leading to the formation of the reactive intermediate A, which after the reaction with enamide 4 affords the iodo(III) cyclopropane intermediate B. Subsequently, reductive elimination of intermediate B produces the α-trifluoromethyl imine intermediate C that, after coordination with Lewis acidic Cu(I) generates complex D. Finally, elimination (or transfer) of α-proton affords the final olefinic trifluoromethylation product 5 and concomitantly regenerates the Cu(I) catalyst for the next catalytic cycle.

Shortly afterwards, the same authors extended the substrate scope of their methodology and reported the direct olefinic C–H bond trifluoromethylation of acrylamide derivatives 6 with Togni's regent 2.[21] Thus, a library of β-CF$_3$-functionalized acrylamides 7 were obtained in up to 90% yields employing 10 mol% of commercially available and inexpensive CuCl as a catalyst and DMSO as the solvent in the absence of any additive (Scheme 5). In this system, the reaction shows a remarkable degree of stereospecificity and occurs selectively

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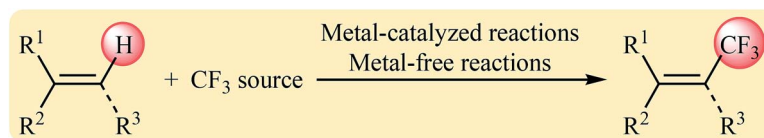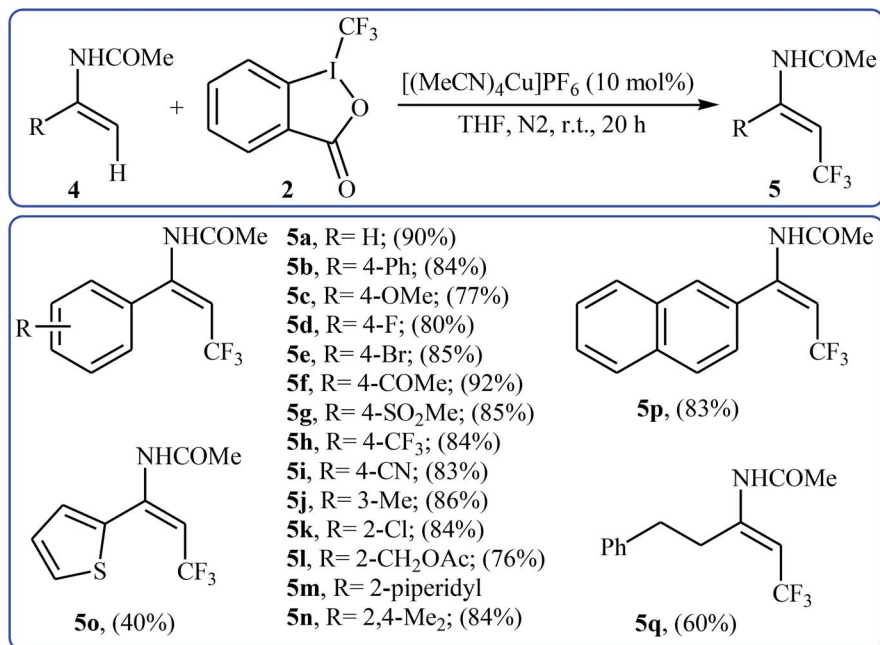
**Scheme 1** Direct trifluoromethylation of olefinic C–H bonds.
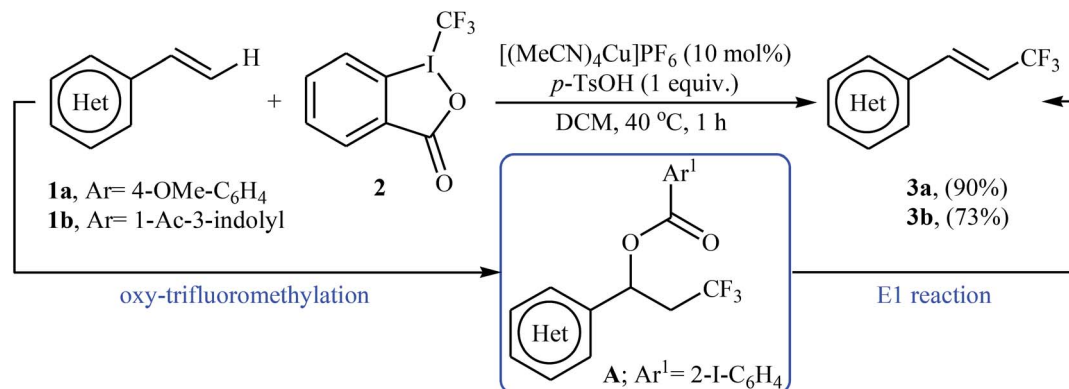
Scheme 2 Cu-catalyzed trifluoromethylation of styrenes **1** using Togni's reagent.

in the *cis* position with respect to the Ts-protected amide directing group. Of note, other Cu-catalysts such as CuBr, CuI, CuOAc, Cu(OAc)$_2$, Cu$_2$O, and [(MeCN)$_4$Cu]PF$_6$ were also found to promote this trifluoromethylation reaction, albeit with reduced efficiencies.

In related work, Xiao and co-workers have reported the synthesis of β-trifluoromethylated styrenes **10** through the direct trifluoromethylation of corresponding styrene derivatives **8** with Togni's reagent **9** utilizing [(MeCN)$_4$Cu]PF$_6$ as catalyst

and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as base in DMF (Scheme 6a).[22] The scope of this reaction was broad, and various important functional groups (*e.g.*, OMe, CHO, F, Cl, Br, NO$_2$) were well tolerated. The reaction was also shown to be compatible with terminal heteroaromatic alkenes. Noteworthy, all products were obtained with excellent stereoselectivity (*E/Z* > 97 : 3). Recently, Shen and Loh along with their co-workers reported the fabrication of 1,1-diaryl-2-trifluoromethylethenes **12** shown in Scheme 6b.[23] These compounds were formed by

Scheme 3 Direct trifluoromethylation of enamides **4** with Togni's regent.
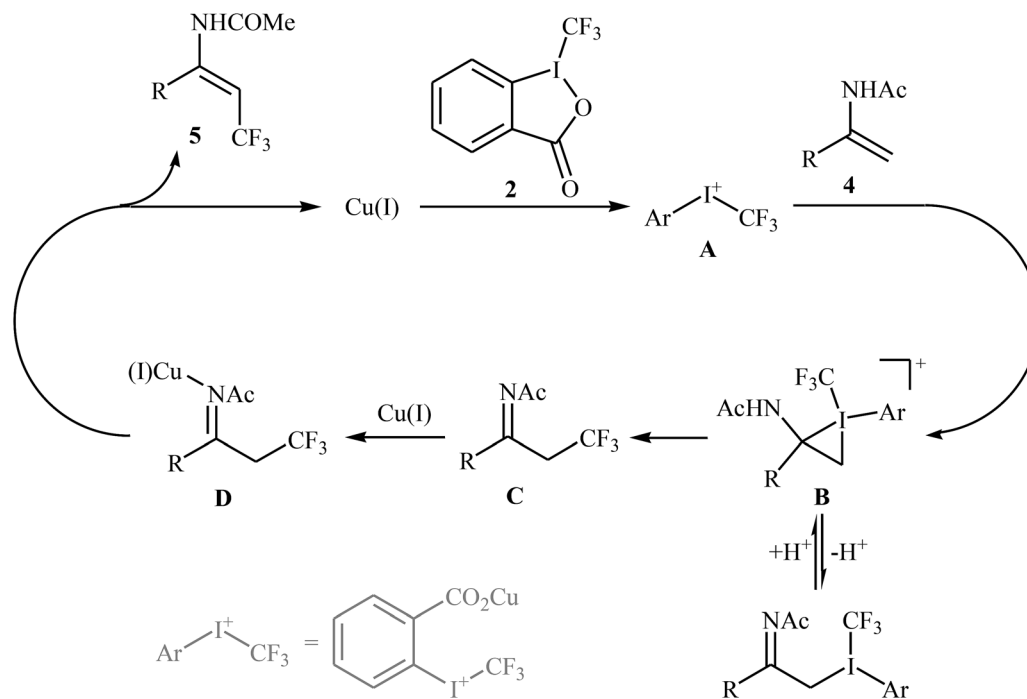
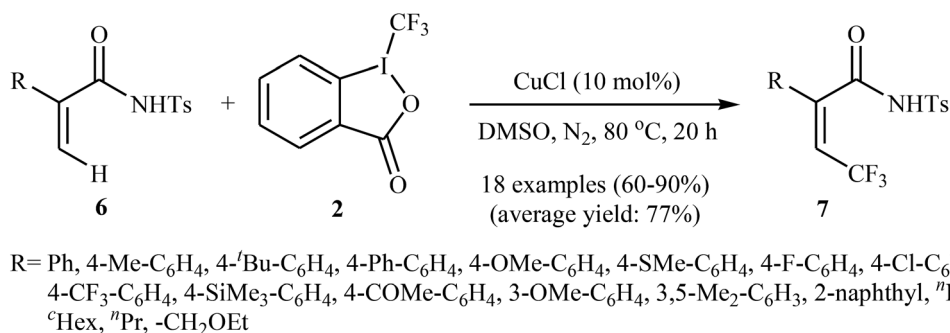**Scheme 4** Mechanism for the trifluoromethylation of enamides **4**.

reaction of corresponding diarylethenes **11** with the Langlois reagent (CF$_3$SO$_2$Na) as an easy-to-handle and inexpensive trifluoromethylating agent through a radical process. The reaction carried out in the presence of CuI/1-methylimidazole/^{n}Bu$_4$NI/DTBP combination as a catalytic system in DCE at 120 °C resulted in relatively slow trifluoromethylthiolation to give good to high isolated yields of trifluoromethylated products **12** with a strong preference for (E)-isomers. The results demonstrated that substrates bearing an electron-donating group afforded better yields than those with an electron-withdrawing group. The mechanism proposed by the authors to explain the title reaction is depicted in Scheme 7.

2.2. Visible-light-mediated photoredox-catalyzed reactions

In 2012, the group of Cho developed a mild and general approach for visible light-mediated direct trifluoromethylation of terminal alkenes **13** with CF$_3$I using commercially available Ru(Phen)$_3$Cl$_2$ as a photocatalyst and DBU as an additive.[24] The
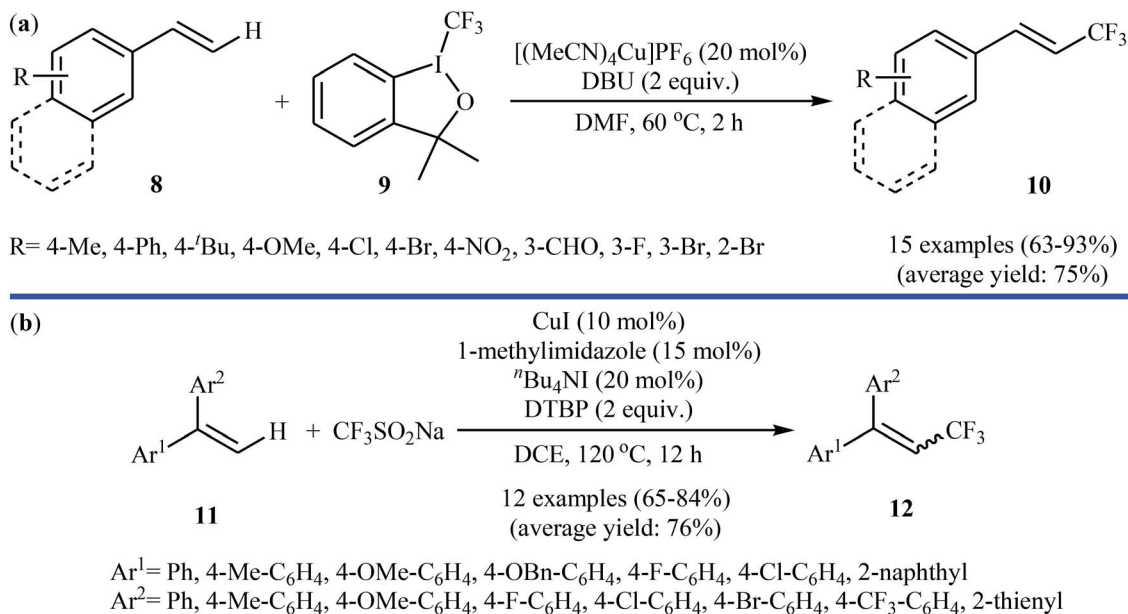
reaction proceeded smoothly in MeCN under a 14 W household light bulb at room temperature, giving generally high to excellent yields of trifluoromethyl-substituted olefins **14** with only (E)-stereochemistry (Scheme 8). Although the reactions of terminal alkenes are regio- and stereoselective, those of internal alkenes generated a mixture of isomers. Of note, aromatic systems were unreactive under the reaction conditions. Interestingly, in this reaction DBU played a dual role; the base and the reductant.

Not long after this report, Akita and co-workers disclosed that 1,1-disubstituted-2-trifluoromethylethenes **17** could be successfully synthesized from the reaction of corresponding 1,1-disubstituted alkenes **15** with Umemoto's reagent **16**, as a CF$_3$ source in the presence of [Ru(bpy)$_3$](PF$_6$)$_2$ (bpy = 2,2′-bipyridine) as the photocatalyst under visible light irradiation.[25] As shown in Scheme 9, a series of sensitive substituents (e.g., NO$_2$, NHBoc, Cl, Br) and heterocycles were all compatible under the conditions. In addition, this system also worked for direct

R= Ph, 4-Me-C$_6$H$_4$, 4-^{t}Bu-C$_6$H$_4$, 4-Ph-C$_6$H$_4$, 4-OMe-C$_6$H$_4$, 4-SMe-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, 4-SiMe$_3$-C$_6$H$_4$, 4-COMe-C$_6$H$_4$, 3-OMe-C$_6$H$_4$, 3,5-Me$_2$-C$_6$H$_3$, 2-naphthyl, ^{n}Hex, ^{c}Hex, ^{n}Pr, -CH$_2$OEt

Scheme 5 Cu(I)-catalyzed trifluoromethylation of acrylamide derivatives **6** with Togni's regent **2**.

(a)

R= 4-Me, 4-Ph, 4-^{t}Bu, 4-OMe, 4-Cl, 4-Br, 4-NO$_2$, 3-CHO, 3-F, 3-Br, 2-Br

15 examples (63–93%)
(average yield: 75%)

(b)

CuI (10 mol%)
1-methylimidazole (15 mol%)
^{n}Bu$_4$NI (20 mol%)
DTBP (2 equiv.)

DCE, 120 °C, 12 h

12 examples (65–84%)
(average yield: 76%)

Ar^1= Ph, 4-Me-C$_6$H$_4$, 4-OMe-C$_6$H$_4$, 4-OBn-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 2-naphthyl
Ar^2= Ph, 4-Me-C$_6$H$_4$, 4-OMe-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-CF$_3$-C$_6$H$_4$, 2-thienyl

Scheme 6 (a) Xiao's synthesis of β-trifluoromethylated styrenes **10**; (b) direct trifluoromethylation of diarylethenes **11** with the Langlois reagent.
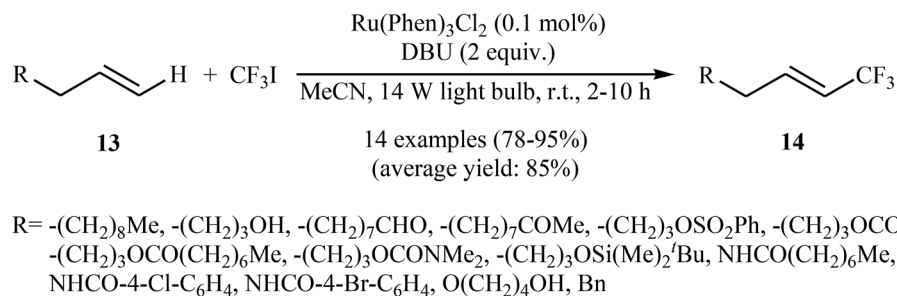
trifluoromethylation of trisubstituted aryl alkenes, and the target products were isolated in moderate to high yields. Additionally, use of an excess amount of trifluoromethylating agent (4 equiv.) induced double C–H trifluoromethylation to afford geminal bis(trifluoromethyl)alkenes. A plausible mechanistic pathway was proposed by the authors for this reaction (Scheme 10) that involves the initial formation of the trifluoromethyl radical ($^•$CF$_3$) via an one-electron-reduction of electrophilic Umemoto's reagent **16** by the photoactivated Ru catalyst, [Ru(bpy)$_3$]$^{2+*}$, which after reaction with alkene **15** leads to the benzyl radical-type intermediate **A**. Subsequently, one-electron-oxidation of this intermediate by highly oxidizing Ru species, [Ru(bpy)$_3$]$^{3+}$ gives β-CF$_3$ carbocation intermediate **B**. Finally, elimination of the olefinic proton from this intermediate affords the observed trifluoromethylated alkene **17**.

In 2014, Lin, Xu, and Qing developed an interesting stereo-controlled direct trifluoromethylation of olefinic C–H bonds through an appropriate combination of the photoredox catalyst and of the CF$_3$-containing substrate.[26] They showed that trifluoromethylation of styrene derivatives **18** with Togni's reagent **9** in the presence of Ru(bpy)$_3$Cl$_2$·6H$_2$O as the photocatalyst under visible light irradiation gave exclusively more thermodynamically stable (E)-trifluoromethylated styrenes **19**, whereas reaction with Umemoto's reagent **16** in the presence of Ir(ppy)$_3$ lead to less thermodynamically stable (Z)-trifluoromethylated alkenes **20** with high to excellent stereoselectivity (Scheme 11). According to the authors, the mechanism of (E)-selective reaction is analogous to the one depicted in Scheme 10. The putative mechanism for the (Z)-selective trifluoromethylation is based on the initial formation of a thermodynamically stable (E)-
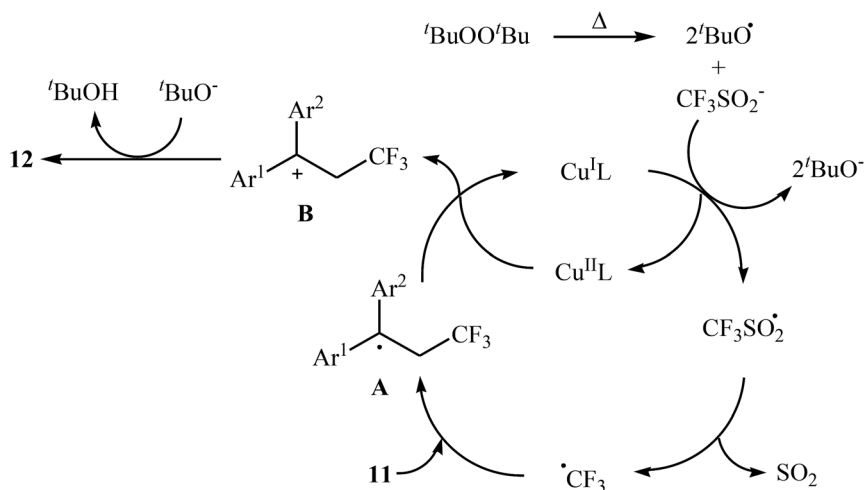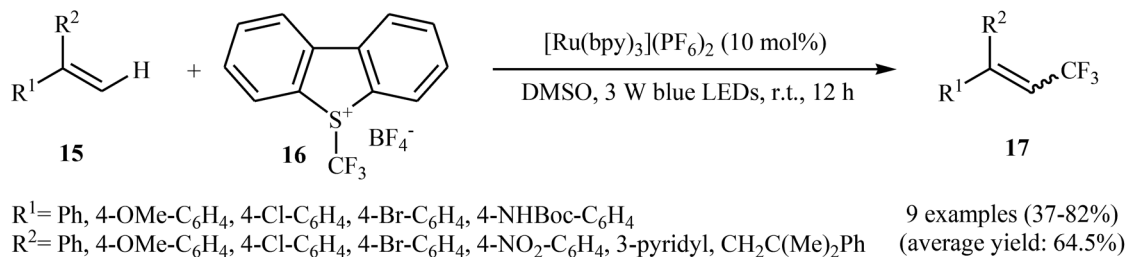

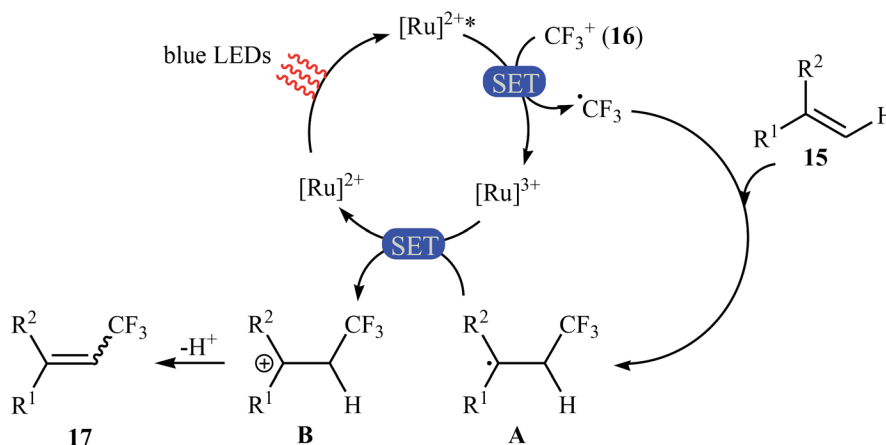**Scheme 7** Mechanistic proposal for the reaction in Scheme 6a.

Scheme 8   Visible light–mediated direct trifluoromethylation of terminal alkenes **13** developed by Cho.

R= -(CH$_2$)$_8$Me, -(CH$_2$)$_3$OH, -(CH$_2$)$_7$CHO, -(CH$_2$)$_7$COMe, -(CH$_2$)$_3$OSO$_2$Ph, -(CH$_2$)$_3$OCOPh, -(CH$_2$)$_3$OCO(CH$_2$)$_6$Me, -(CH$_2$)$_3$OCONMe$_2$, -(CH$_2$)$_3$OSi(Me)$_2^t$Bu, NHCO(CH$_2$)$_6$Me, NHCO-4-Cl-C$_6$H$_4$, NHCO-4-Br-C$_6$H$_4$, O(CH$_2$)$_4$OH, Bn

14 examples (78-95%)
(average yield: 85%)

Scheme 9   Akita's synthesis of trifluoromethylated alkenes **17**.

R^1= Ph, 4-OMe-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-NHBoc-C$_6$H$_4$
R^2= Ph, 4-OMe-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$, 3-pyridyl, CH$_2$C(Me)$_2$Ph

9 examples (37-82%)
(average yield: 64.5%)

Scheme 10   Mechanism that accounts for the formation of trifluoromethylated alkenes **17**.

isomer, which after the triplet–triplet energy transfer (TTET) process converts into (*Z*)-isomer.

Another innovative example on direct C–H trifluoromethylation of alkenes is shown in Scheme 12, where *fac*-Ir(ppy)$_3$ was used as heterogeneous photocatalyst.[27] Mono-trifluoromethylated vinylarenes **22** were easily formed in moderate to excellent yields and high *E/Z* selectivity under continuous-flow conditions and visible light irradiation *via* the treatment of the corresponding alkenes **21** with CF$_3$I in the presence of CsOAc as a base in DMF. The authors found that transferring continuous-flow conditions to batch reactions also provided high yield for the desired compounds, albeit with considerably reduced *E/Z* ratio. This fact can be explained by the shorter reaction times in flow.

Recently, an elegant and efficient protocol for photoredox-catalyzed (*Z*)-diastereoselective trifluoromethylation of methylene *exo*-glycals at room temperature using the Umemoto's reagent **16** was explored by Vincent *et al.*[28] By this procedure, a diverse array of unsubstituted *exo*-glycals **23** were successfully converted to the corresponding mono-trifluoromethyl analogues **24** with yield ranging from 47% to 83% and excellent (*Z*)-stereoselectivity (Scheme 13). The authors also showed that the synthesis of the same products were possible by performing the reaction in the presence of a catalytic amount of CuI in chloroform at 120 °C under microwave irradiation. The results demonstrated that the photoredox-catalyzed reaction is in general more efficient compared to the latter reaction.
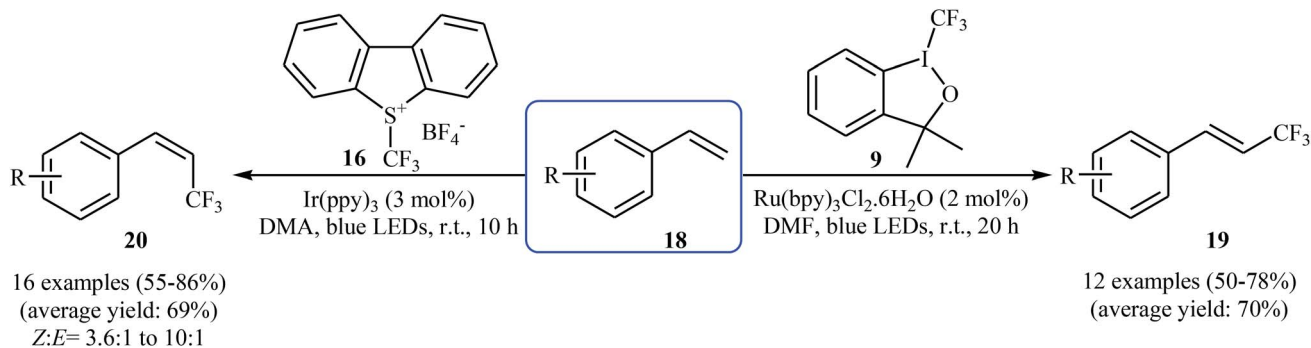
Scheme 11 Chemo-, regio-, and stereoselective trifluoromethylation of styrenes 18 developed by Qing.
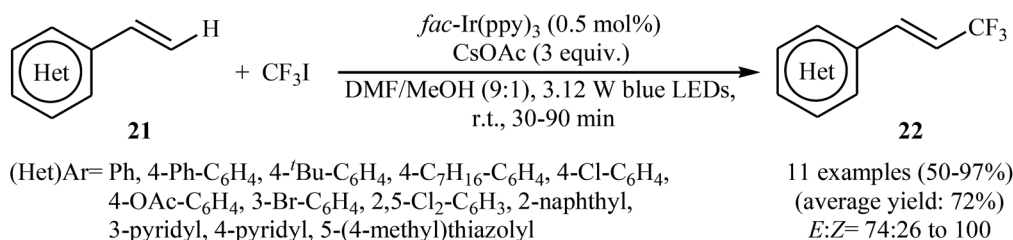
Scheme 12 Photocatalytic trifluoromethylation of terminal alkenes 21 with CF$_3$I.

2.3. Transition-metal-free reactions

In 2014, Tan and Liu along with their co-workers reported an interesting iodide-induced metal-free direct C–H trifluoromethylation of α,β-unsaturated carbonyl compounds 25 with Togni's reagent 2 using over-stoichiometric amounts of

^{n}Bu$_4$NI as an initiator and NaOAc as an additive in MeCN at 80 °C (Scheme 14).[29] The reaction proceeds with outstanding regioselectivity for β-site and stereoselectivity to the E-isomers and afforded the corresponding (E)-β-trifluoromethyl α,β-unsaturated hydroxamic acid derivatives 26 in moderate to good
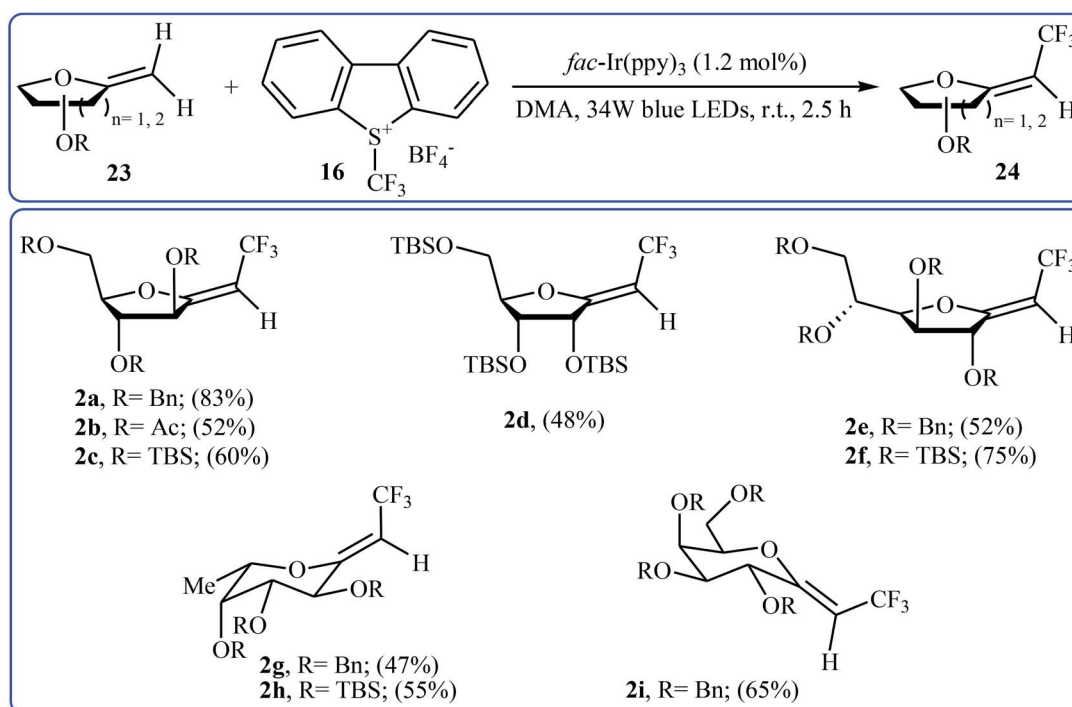
Scheme 13 Photoredox-catalyzed (Z)-diastereoselective trifluoromethylation of methylene exo-glycals 23 using the Umemoto's reagent.

yields. The reaction could also be extended for β-tri-fluoromethylation of acrylamide derivatives. The mechanism of this trifluoromethylation reaction probably involves the generation of the highly reactive iodine(III) intermediate **A** from the reaction of ^{n}Bu$_4$NI with Togni's reagent, followed by reaction with activated alkene **25** to form intermediate **B**, which after an elimination and deprotonation sequential process furnishes the desired product **26** (Scheme 15).

Later, an interesting protocol for the stereoselective tri-fluoromethylation of enamides **27** with the Umemoto's reagent **16** was reported by Yu et al.[30] This photochemical, metal-free reaction was proceeded under visible light irradiation without any photocatalyst at room temperature and only inexpensive K$_2$HPO$_4$ is needed to promote this transformation. Both cyclic and acyclic substituents are well-tolerated and all the trifluoromethylated enamides were isolated in (E)-configuration exclusively. Some of the reported examples are shown in Scheme 16.

2.4. Miscellaneous reactions

Very recently, Yang and Tsui presented a very elegant method for the synthesis of trifluoromethylated alkenes using easy-to-handle and commercial Me$_3$SiCF$_3$ as the CF$_3$ source.[31] They showed that the trifluoromethylation of unactivated aliphatic alkenes **29** under a combination of N-iodosuccinimide (NIS) and visible light in the absence of any photocatalyst afforded the corresponding trifluoromethylated (E)-alkenes **30** in moderate to high yields, ranging from 42% to 86% (Scheme 17). The reaction was shown to be remarkably tolerant toward a large number of functional groups such as fluoro, chloro,

bromo, iodo, cyano, hydroxyl, acid, ester, ether, ketone, and aldehyde functionalities. However, 2-vinylnaphthalene did not take part in this trifluoromethylation and therefore no other aromatic terminal alkenes were examined in the protocol. The procedures could also be adapted to gram-scale tri-fluoromethylation of a series of natural product derivatives (e.g., estrone, umbelliferone, flavone, and quinine cores). The putative mechanism for this NIS-promoted reaction is depicted in Scheme 18.

3. Internal alkenes

3.1. Cyclic internal alkenes

3.1.1. Transition-metal-catalyzed reactions. In 2013, Szabó and co-workers showed that functionalized (benzo)quinone derivatives **31** can undergo direct C–H mono-trifluoromethylation with Togni's reagent **2** in the presence of Cu-salts, according to Scheme 19a.[32] After the optimization of the reaction conditions, the use of a stoichiometric amount of CuCN and 5 mol% of bis(pinacolato)diboron (B$_2$pin$_2$) as the mediator and as radical activator, respectively, in CHCl$_3$ at room temperature were required for high product yields. Unfortunately, almost all of the tested substrates for this reaction were exclusively electron-rich derivatives. At the same time, a closely related study was published by Wang et al.[33] Here, (benzo)quinones **33** were trifluoromethylated, using 20 mol% of CuI as the catalyst in a 1 : 1 mixture of ^{t}BuOH/DCM at 55 °C. The desired CF$_3$-substituted quinones **34** were obtained with yield
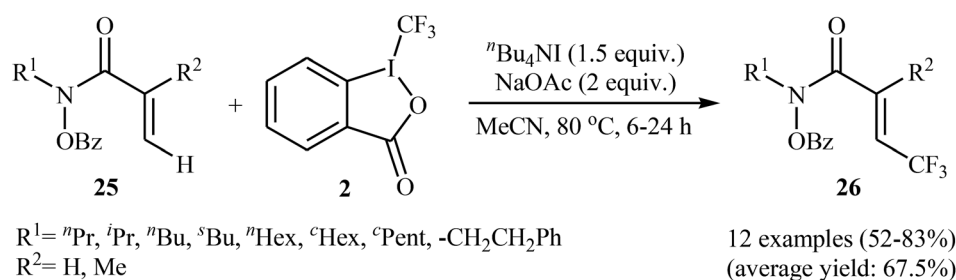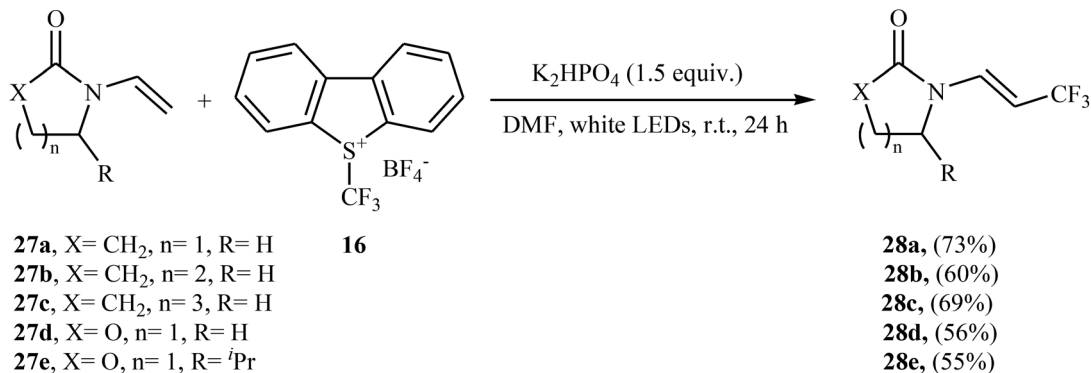

Scheme 14 Iodide-induced direct C–H trifluoromethylation of α,β-unsaturated carbonyl compounds **25** with Togni's reagent.
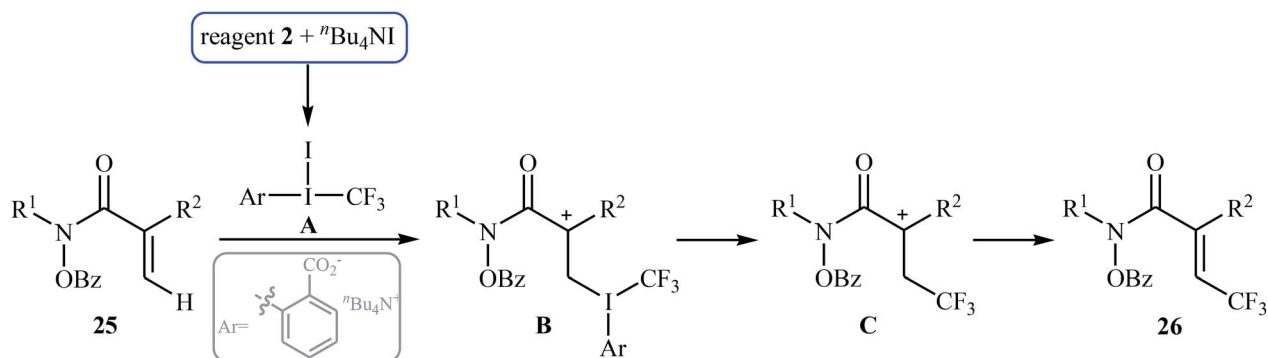
Scheme 15 Mechanism proposed to explain the formation of (E)-β-trifluoromethyl α,β-unsaturated hydroxamic acids **26**.
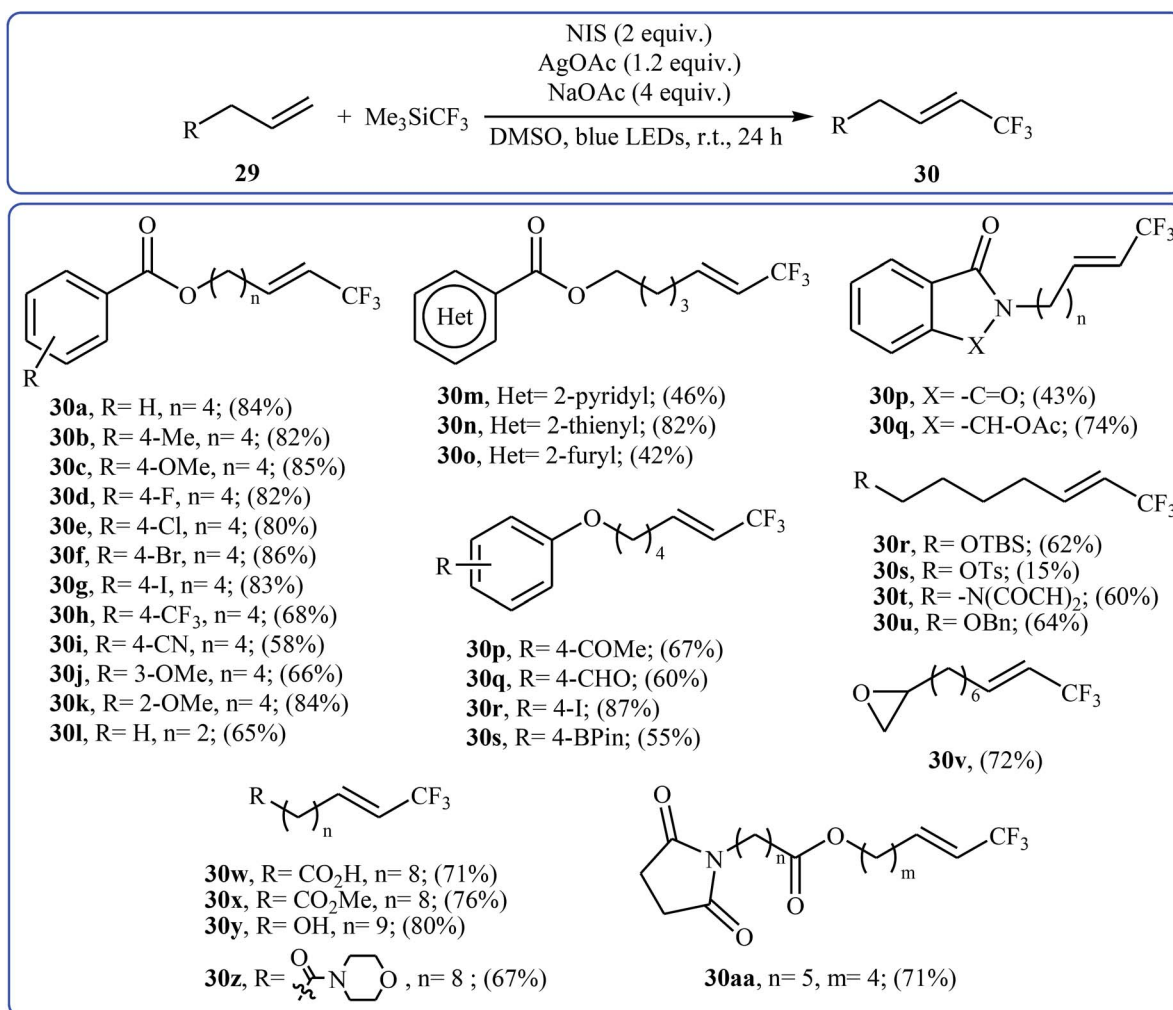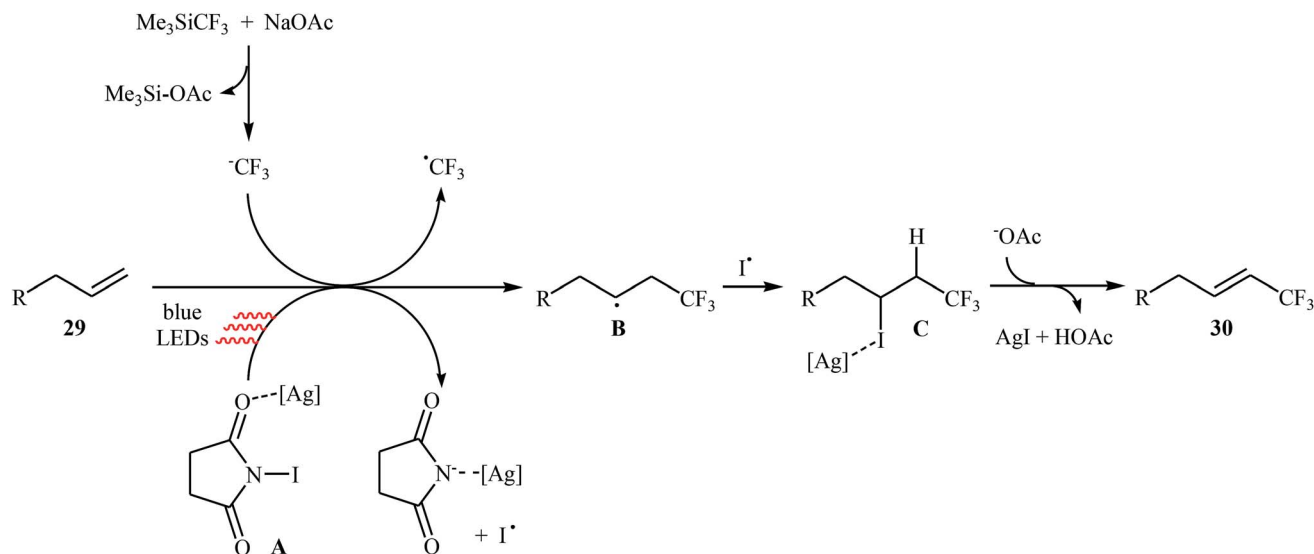
Scheme 16 Yu's trifluoromethylation of enamides **27**.

ranging from 33% to 83% (Scheme 19b). Both groups suggested that the CF$_3$ radical is involved in the transformation.

Two years later, Gillaizeau and colleagues have demonstrated that, in the presence of a catalytic amount of FeCl$_2$ in DCM, various cyclic enamides **35** undergo a mild and regioselective trifluoromethylation at the C3 position with the Togni's reagent **2** to afford the corresponding β-CF$_3$-enamides **36** in modestly to excellent yields.[34] Some reported examples are shown in Scheme 20. Other metal catalysts such as SnCl$_2$, AlCl$_3$, CuCl, and Cu(OAc)$_2$ displayed lower reactivity compared to FeCl$_2$ in this transformation and Sc(OTf)$_3$ and Cu$_2$O proved to be completely ineffective. It should be mentioned that the

Scheme 17 NIS-promoted trifluoromethylation of unactivated alkenes **29** with Me$_3$SiCF$_3$.

Scheme 18 Mechanism that accounts for the formation of trifluoromethylated (*E*)-alkenes **30**.

reaction was also applied to acyclic enamides and indole derivatives.

Another direct C–H trifluoromethylation method for cyclic alkenes was described by Wang, Xiong, and Ye in 2015 with Umemoto's reagent under visible light irradiation.[35] They showed that the reaction of glycals **37** with Umemoto's reagent **16** in the presence of *fac*-Ir(ppy)$_3$ as catalyst under the household blue LED irradiation smoothly afforded the corresponding trifluoromethylated glycals **38** in moderate to good yields (Scheme 21). Glycals bearing both electron-withdrawing and electron-donating protective groups were compatible with the reaction conditions. More significantly, the reaction can be

applied to the trifluoromethylation of the biologically important 2,3-unsaturated *N*-acetylneuraminic acid (Neu2en) derivatives.

3.1.2. Transition-metal-free reactions. The first and only study on metal-free direct trifluoromethylation of cyclic alkenes was reported by Georg and co-workers in 2014.[36] It described the regioselective introduction of a CF$_3$ group at the C-5 position of 2,3-dihydropyridin-4(1*H*)-ones (cyclic enaminones) using PhI(OAc)$_2$ as an oxidant and the Ruppert's reagent. A screening of reaction conditions proved that KF and MeCN were the most effective base and solvent, respectively. With these optimized reaction conditions, a series of electron-rich and electron-deficient 2,3-dihydropyridin-4(1*H*)-ones **39** was successfully trifluoromethylated (Scheme 22). This strategy was also
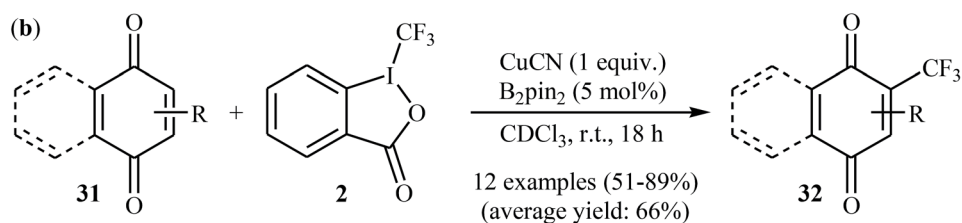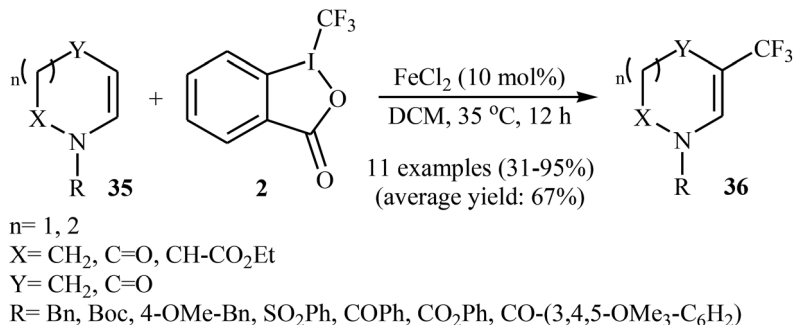

R= H, 2-Me, 2-Cl, 2-Br, 2,3-(OMe)$_2$, 2,5-Cl$_2$, 2,6-Me$_2$, 2,6-(OMe)$_2$, 2,6-Cl$_2$, 2-Me-5,6-(OMe)$_2$
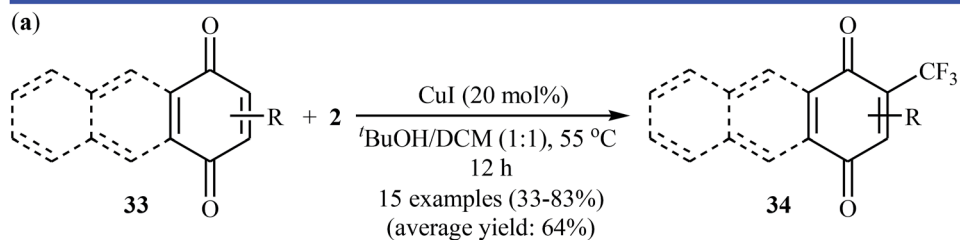
R= H, 2-Me, 2,5,6-Me$_3$, 2-Cl, 2-N(Me)Ph, 2-(4-Me-C$_6$H$_4$), 2-(4-OMe-C$_6$H$_4$), 2-(4-Br-C$_6$H$_4$), 2-(4-CO$_2$Me-C$_6$H$_4$), 2-Me-4,5-(OMe)$_2$, 2,5-Me$_2$-6-(4-^{t}Bu-C$_6$H$_4$), 5,6-bicyclo[2.2.1]heptyl

Scheme 19 (a) Cu-catalyzed trifluoromethylation of (benzo)quinones **31** with Togni's reagent; (b) Wang's synthesis of CF$_3$-substituted quinones **34**.

Scheme 20 Fe-catalyzed regioselective trifluoromethylation of cyclic enamides **35**.

n= 1, 2
X= CH₂, C=O, CH-CO₂Et
Y= CH₂, C=O
R= Bn, Boc, 4-OMe-Bn, SO₂Ph, COPh, CO₂Ph, CO-(3,4,5-OMe₃-C₆H₂)
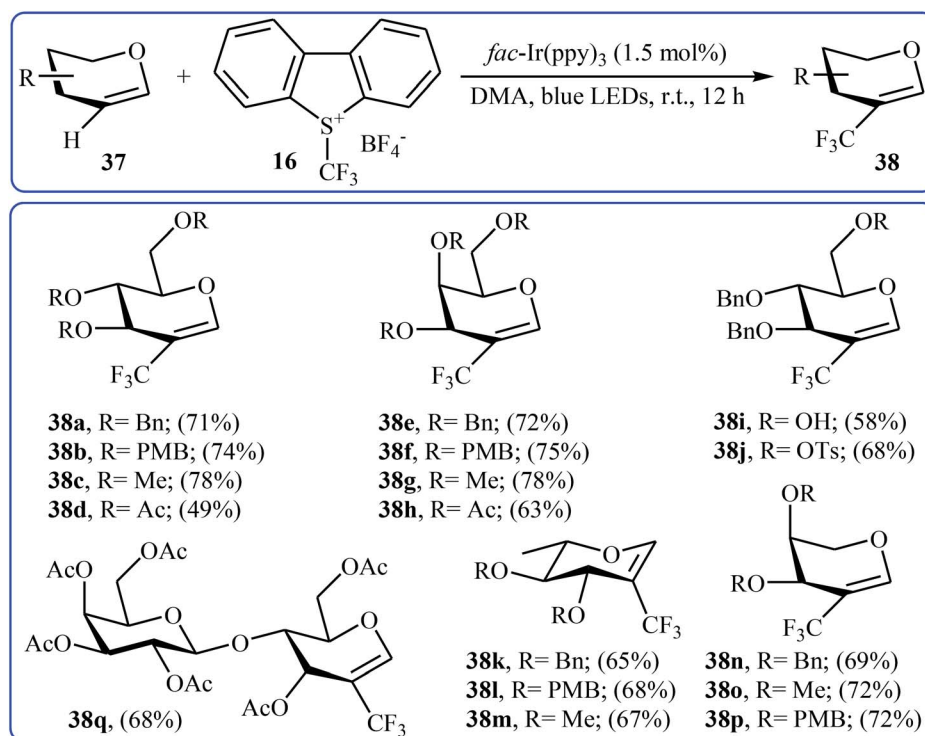
Scheme 21 Photoredox-catalyzed direct trifluoromethylation of glycals **37** with Umemoto's reagent.

successfully used for the trifluoromethylation of pyridin-4(1*H*)-one, quinolin-4(1*H*)-one, and 3-aminocyclohex-2-enone derivatives. To the best of our awareness, this is only example dealing with the metal-free direct trifluoromethylation of cyclic alkenes thus far.
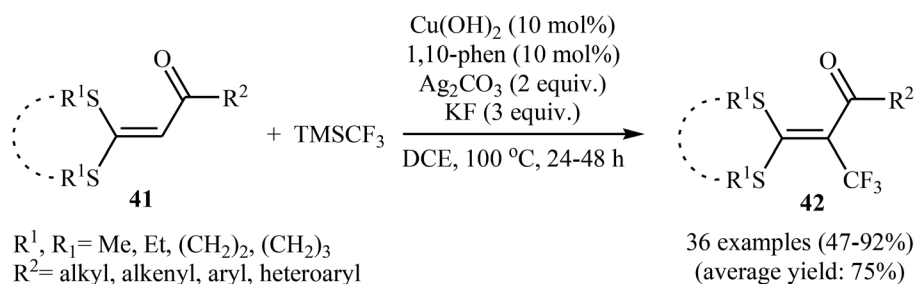
3.2. Acyclic internal alkenes

3.2.1. Transition-metal-catalyzed reactions. In 2014, Yu and colleagues developed an efficient copper-catalyzed direct trifluoromethylation of internal olefinic C–H bonds by using TMSCF₃, which provides a practical method to obtain trifluoromethylated tetrasubstituted olefins.[37] The optimization of the reaction conditions employing α-oxoketene dithioacetal as the model reactant, indicated that Cu(OH)₂ was more effective than other Cu catalysts (*e.g.*, CuI, CuOAc, Cu(OAc)₂) and compared to other oxidants Ag₂CO₃ was the best choice for the

transformation. The results also showed that KF was the best base over CsF, K₂CO₃, NaOAc, and KO*t*Bu. Under the optimized conditions, various cyclic and acyclic dithioalkyl α-oxoketene acetals **41** were tolerated well and provided the expected trifluoromethylated products **42** in moderate to excellent yields (Scheme 23). Interestingly, no kinetic isotope effect ($K_H/K_D = 1$) was observed with deuterium-labelled compounds under the standard conditions, signifying that the cleavage of the internal olefinic C–H bond was not involved in the rate-determining step of this reaction. The radical-trapping experiments clearly indicated that these reactions proceed *via* a radical mechanism.

Concurrently, the group of Bi accomplished regioselective C–H α-trifluoromethylation of α,β-unsaturated carbonyl compounds **43** through the employment of Togni's reagent **2** in DMF as the solvent, with the intervention of CuI as catalyst in the absence of any oxidant and base (Scheme 24).[38]
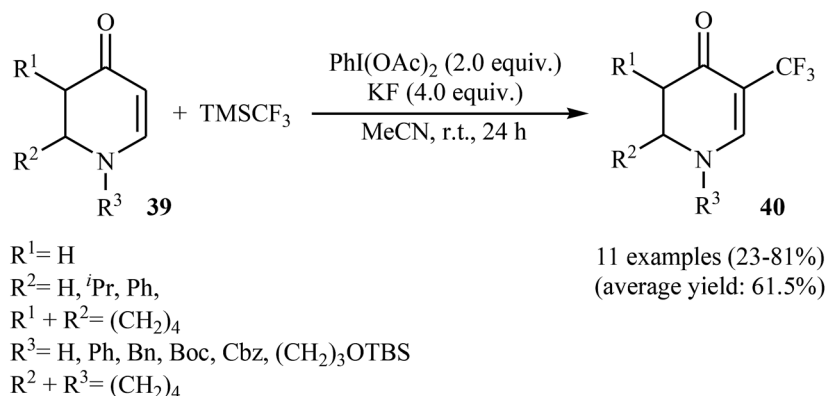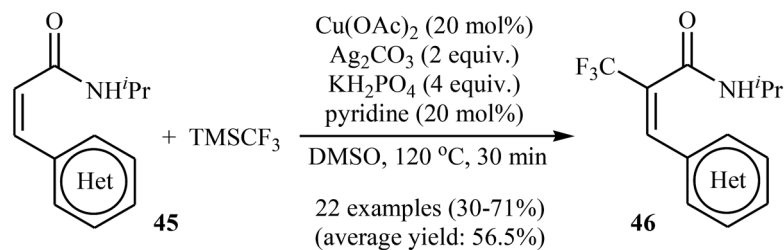
Scheme 22 Metal-free direct trifluoromethylation of cyclic alkenes **39** developed by Georg.

$R^1 = H$
$R^2 = H, ^iPr, Ph,$
$R^1 + R^2 = (CH_2)_4$
$R^3 = H, Ph, Bn, Boc, Cbz, (CH_2)_3OTBS$
$R^2 + R^3 = (CH_2)_4$

11 examples (23-81%)
(average yield: 61.5%)

Scheme 23 Cu-catalyzed trifluoromethylation of internal olefinic C–H bonds by using TMSCF$_3$.

$R^1, R_1 = Me, Et, (CH_2)_2, (CH_2)_3$
$R^2 = alkyl, alkenyl, aryl, heteroaryl$

36 examples (47-92%)
(average yield: 75%)

Interestingly, a diverse array of α,β-unsaturated carbonyl compounds including enones as well as α,β-unsaturated esters, thioesters, and amides were applicable to this reaction. It is noteworthy to mention that this procedure was applied to the high yielding C–H trifluoromethylation of commercialized drugs such as tranilast, hymecromone, flavone, and 2′-deoxy-uridine. In a related investigation, Monteiro–Bouyssi and collaborators have reported the direct β-trifluoromethylation of α,β-unsaturated aldehyde *N,N*-dibenzylhydrazones with Togni's reagent employing CuCl as catalysts and chloroform as solvent at room temperature.[39] Moderate to good yields were obtained and excellent (*E*)-stereoselectivity were observed.

Very recently, Sun, Xu, and Dai have reported the copper-catalyzed α-selective C–H trifluoromethylation of acrylamides **45** with TMSCF$_3$.[40] Employment of the Cu(OAc)$_2$/Ag$_2$CO$_3$/KH$_2$PO$_4$/pyridine combination as the catalytic system in DMSO at 120 °C produce satisfactory results providing the corresponding (*E*)-trifluoromethylated products **46** in moderate yields (Scheme 25). Interestingly, the reaction proceeded very fast (30 min) and was compatible with the presence of a wide range of arenes and heteroarenes at the β-position of acrylamides. The authors proposed mechanism for this reaction is outlined in Scheme 26.

3.2.2. Transition-metal-free reactions. In 2013, Wang, Liu and co-workers described the direct sp^2 C–H
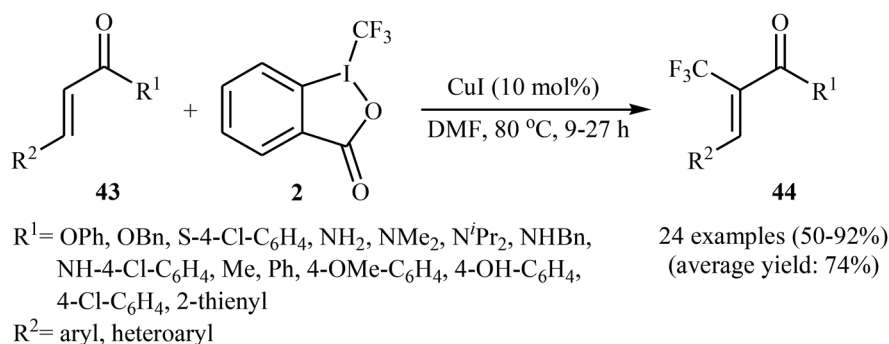
Scheme 24 Regioselective C–H α-trifluoromethylation of α,β-unsaturated carbonyl compounds **43** using CuI as catalyst.

$R^1 = OPh, OBn, S-4-Cl-C_6H_4, NH_2, NMe_2, N^iPr_2, NHBn,$
$NH-4-Cl-C_6H_4, Me, Ph, 4-OMe-C_6H_4, 4-OH-C_6H_4,$
$4-Cl-C_6H_4, 2-thienyl$
$R^2 = aryl, heteroaryl$

24 examples (50-92%)
(average yield: 74%)

Scheme 25 Copper-catalyzed α-selective C−H trifluoromethylation of acrylamides **45** with TMSCF₃.

(Het)Ar= Ph, 4-Me-C₆H₄, 4-Ph-C₆H₄, 4-OMe-C₆H₄, 4-OCF₃-C₆H₄, 4-F-C₆H₄, 4-Br-C₆H₄, 4-NO₂-C₆H₄, 3-OCF₃-C₆H₄, 3-CF₃-C₆H₄, 3-Br-C₆H₄, 3-CN-C₆H₄, 2-Me-C₆H₄, 2-F-C₆H₄, 2,6-F₂-C₆H₃, 3,4,5⁻(OMe)₃-C₆H₂, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl, 4-thiazolyl
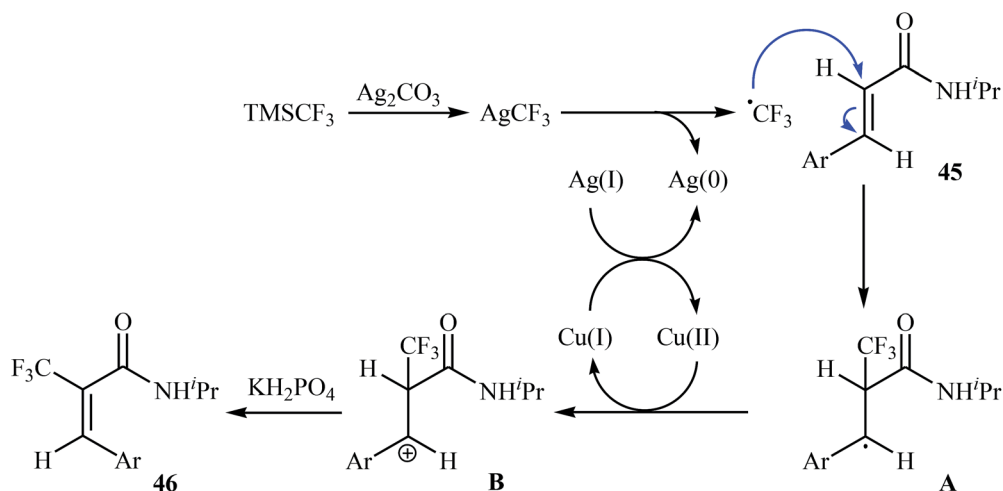
Scheme 26 Plausible mechanism for reaction in Scheme 25.

trifluoromethylation of ketene dithioacetals by *in situ* generated hypervalent iodide trifluoromethylating species [PhICF₃]⁺ under mild transition metal-free conditions.[41] Various substituted cyclic as well as acyclic ketene dithioacetals **47** are readily α-trifluoromethylated by adding TMSCF₃ to a premixed mixture of PhI(OAc)₂ and KF in MeCN, affording the corresponding 3,3,3-trifluoro-1,1-bis(alkylthio)prop-1-ene derivatives **48** in good to high yields (Scheme 27). Likewise, 2-substituted indoles were trifluoromethylated selectively at the 3-position by [PhICF₃]⁺ species. In accord to the presumed reaction mechanism,
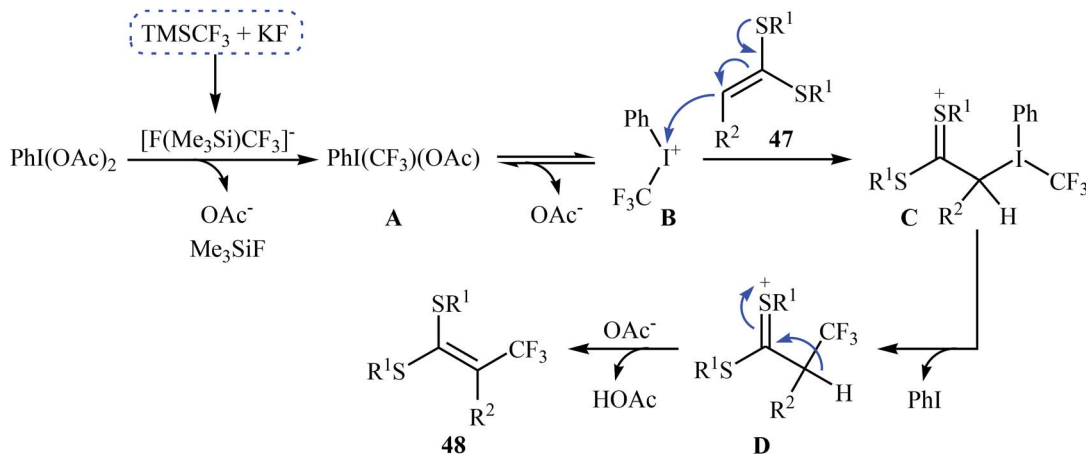
trifluoromethylation of ketenes proceeds through the following key steps (Scheme 28): (i) initial formation of PhI(CF₃)(OAc) (**A**) *via* the reaction of PhI(OAc)₂ with TMSCF₃ in the presence of KF; (ii) cleavage of the I–O bond of the intermediate **A** to give phenyl(trifluoromethyl)iodonium **B**; (iii) nucleophilic attack of the α-carbon of ketene dithioacetal **47** at cation **B** to afford the thionium intermediate **C**; (iv) reductive elimination of PhI from intermediate **C** to produce intermediate **D**; and (v) abstraction of the acidic proton of **D** to form the final products **48**.
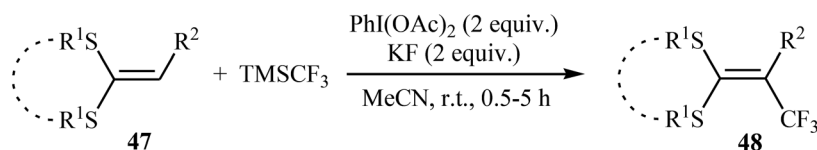
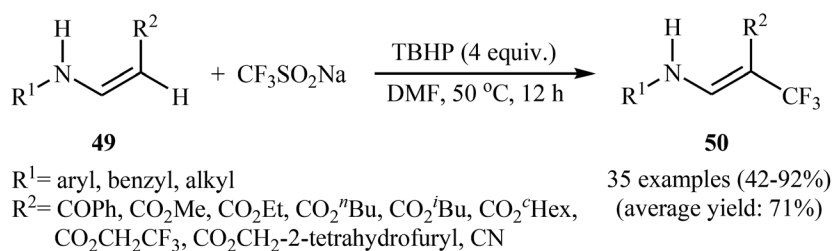R¹, R₁= Me, Et, (CH₂)₂, (CH₂)₃
R²= COMe, COEt, COPh, CO-4-Me-C₆H₄, CO-4-Cl-C₆H₄, CN, 4-Me-C₆H₄, 4-F-C₆H₄, 4-Cl-C₆H₄

12 examples (64-85%)
(average yield: 74%)

Scheme 27 Metal-free direct C−H trifluoromethylation of ketene dithioacetals **47** with TMSCF₃.

Scheme 28 The possible radical reaction mechanism for trifluoromethylation of ketene dithioacetals **47**.

49
R^1= aryl, benzyl, alkyl
R^2= COPh, CO_2Me, CO_2Et, $CO_2{}^nBu$, $CO_2{}^iBu$, $CO_2{}^cHex$,
$CO_2CH_2CF_3$, CO_2CH_2-2-tetrahydrofuryl, CN

50
35 examples (42–92%)
(average yield: 71%)

Scheme 29 Synthesis of β-trifluoromethyl substituted enamines **50** by trifluoromethylation of corresponding enamines **49** with Langlois reagent.

Afterwards, the group of Jiang–Wu reported a mild transition-metal-free synthesis of a wide range of β-trifluoromethyl substituted enamines **50** by treatment of activated enamines **49** with Langlois reagent in the presence of *tert*-butyl hydroperoxide (TBHP) as an oxidant and initiator in DMF (Scheme 29).[42] Moderate to excellent yields were obtained and only (*E*)-isomers were observed. Noteworthy, the reaction is insensitive to air and water.

review showed a remarkable degree of regio- and stereospecificity. We hope that this review will contribute to stimulate further thinking and research in this important and interesting research field.

Conflicts of interest

There are no conflicts to declare.

4. Conclusion

Needless to say that the introduction of the trifluoromethyl group (–CF_3) into organic molecules usually enhances their chemical stability, bioavailability and lipophilicity. Consequently, considerable effort has been directed towards the development of practical and efficient methods for the synthesis of CF_3-substituted compounds. Recently, direct trifluoromethylation of organic compounds *via* C–H bond activation has drawn significant attention from synthetic chemists because of its high atom, step, and pot economy. Along this line, a variety of catalytic system has been developed to promote the direct trifluoromethylation of olefinic C–H bonds using various trifluoromethylthiolating reagents. As illustrated, trifluoromethylation of both terminal and internal alkynes were successfully achieved through this new page of CF_3-substituted organic compounds synthesis. Interestingly, almost all of the trifluoromethylation reactions covered in this

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