Review Article

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Direct trifluoromethyl-oximation and -peroxidation of alkenes: An overview

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ABSTRACT

This review provides a comprehensive overview of recent advancements in the direct vicinal trifluoromethyl-oximation and -peroxidation of alkenes, highlighting key catalytic systems, mechanistic insights, substrate scope, and current limitations. The review includes literature published through the end of 2024.

1. Introduction

Organofluorine compounds play a considerable role in diverse fields such as pharmaceuticals, agrochemicals, and materials science owing to their unique physicochemical properties, such as strong electronegativity, high thermal and metabolic stability, and increased lipophilicity [1, 3]. These characteristics can improve the bioavailability, binding affinity, and membrane permeability, making this class of compounds highly valuable in the design of drugs, crop protection agents, and advanced functional materials [4].

The trifluoromethyl group (CF_3) is one of the most important and widely used fluorinated moieties in medicinal chemistry, appearing in numerous FDA-approved new drugs across diverse therapeutic areas (Scheme 1), highlighting its critical role in modern drug design and development [5].

In recent years, significant efforts have been devoted to developing efficient methodologies for the synthesis of trifluoromethylated organic compounds, reflecting the growing importance of the CF_3 group in medicinal and materials chemistry [6-8].

Numerous trifluoromethylation strategies have been developed, greatly expanding synthetic access to CF_3-containing molecules with enhanced selectivity and versatility.

In a similar way, ketoximes and peroxides have both drawn considerable attention in recent years

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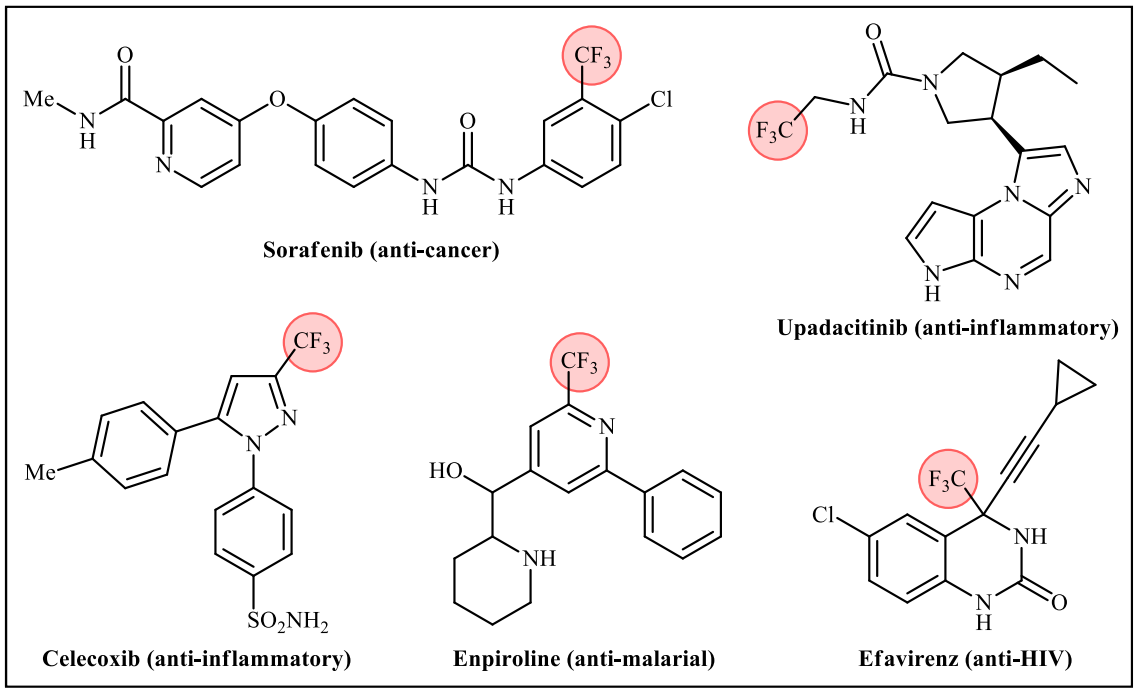
due to their unique chemical and biological properties [9].

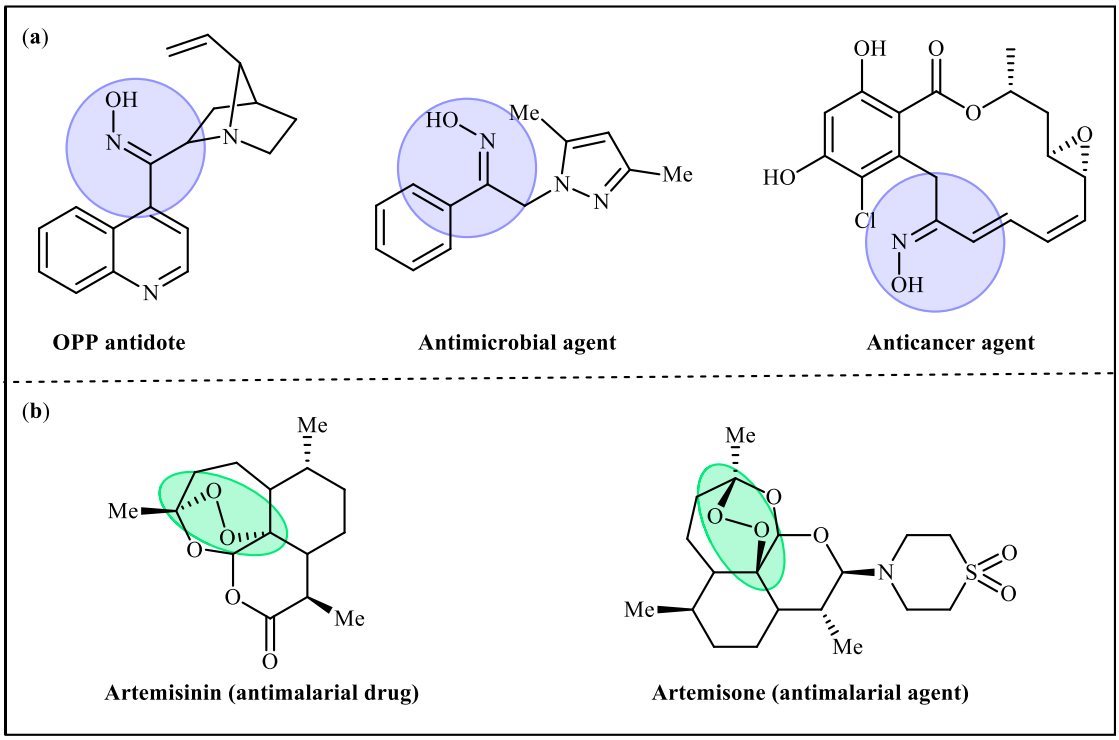
The most significant biological application of ketoximes lies in their ability to treat organophosphate (OP) poisoning through the reactivation of acetylcholinesterase [10].

Additionally, ketoximes have demonstrated promising anti-cancer and antimicrobial activities, making them versatile compounds of interest in pharmaceutical research (Scheme 2a) [11].

On the other hand, peroxide bonds (C-O-O-C) are not only widely found in natural products [12] but also present in various commercial drugs, such as artemisinin and artemisone (Scheme 2b) [13].



Scheme 1. Selected examples of drug molecules containing a trifluoromethyl group in their structures.



Scheme 2. Selected examples of bioactive compounds featuring (a) a ketoxime functional group and (b) a peroxide linkage within their molecular structures.

As mentioned above, the incorporation of trifluoromethyl group into organic molecules has become a powerful strategy in drug discovery and development, owing to its unique physicochemical and biological properties [14]. In recent years, the direct vicinal trifluoromethylative difunctionalization of alkenes has attracted significant attention as an efficient, atom-economical, and versatile approach to access structurally diverse β-functionalized trifluoromethylated compounds [15-19]. In this context, the synthesis of biologically and synthetically valuable β-trifluoromethyl ketoximes and β-trifluoromethyl peroxides *via* direct 1,2-trifluoromethyl-oximation and -peroxidation of olefinic double bonds, respectively, has witnessed notable growth in recent years (Figure 1). Despite these advances, no review has yet been published to comprehensively cover the progress in this emerging area. In this review, we try to summarize available literature in this area, with special emphasis on the mechanistic aspect of the reactions.

2. Trifluoromethyl-oximation

The possibility of synthesizing α-trifluoromethyl ketoxime derivatives through the direct vicinal trifluoromethyl-oximation of alkenes was first investigated by Tang and co-workers in 2019 [20]. Using 4-methylstyrene as the model substrate, along with the Langlois reagent (CF_3SO_2Na) and *tert*-butyl nitrite (^{t}BuONO) as sources of trifluoromethyl and oxime, respectively, various reaction parameters such as catalysts, additives, and solvents were attentively screened. The results indicated that the optimal outcome was achieved in DMSO at room temperature, without the need for any catalyst or additive. Under the optimized conditions, a diverse array of α-trifluoromethyl ketoximes 2 were selectively synthesized in moderated to good yields with outstanding (*E*)-selectivity by reaction of various (hetero)aromatic alkenes 1 with 1.6 equivalents of CF_3SO_2Na and ^{t}BuONO under an inert atmosphere (Scheme 3). Interestingly, the electronic and steric properties of the substituents on the aromatic rings had no significant impact on the reaction outcome. As a result, a wide range of important functional groups positioned at various sites on the aromatic ring of styrenes were well tolerated under the reaction conditions. However, the presence of a substituent on the β-carbon of styrenes (internal alkenes) resulted in lower yields and diminished stereoselectivity. Besides (hetero)aromatic alkenes, this reaction was also successfully extended to aliphatic and benzylic alkenes, as well as α,β-unsaturated carbonyl compounds such as acrylic esters, acrylic amides, and malonic esters. To showcase the synthetic utility of this methodology, "late-stage direct trifluoromethyl-oximation" of a bioactive estrone-derived alkene was found to be compatible with the reaction system, yielding the corresponding α-trifluoromethyl ketoxime in 53% yield with > 95% (*E*)-selectivity. To further assess the synthetic generality of current protocol, a scale-up experiment with 5 mmol of 4-methylstyrene as the substrate was carried out, which led to the corresponding α-trifluoromethyl ketoxime in 51% yield. A plausible mechanism for the formation of α-trifluoromethyl ketoximes 2 was proposed by the authors based on a series of control experiments, as illustrated in Scheme 4. Initially, ^{t}BuONO undergoes decomposition to produce the radicals ^{t}BuO˙ and ˙NO. The ^{t}BuO˙ subsequently oxidizes CF_3SO_2Na through a single electron transfer (SET) process to give ˙CF_3 along with SO_2 and ^{t}BuONa. Next, the ˙CF_3 adds to styrene 1 to form radical intermediate A, which then captures ˙NO to afford the intermediate B. Finally, intermediate B undergoes an intramolecular hydrogen transfer to deliver the observed α-trifluoromethyl ketoxime 2.

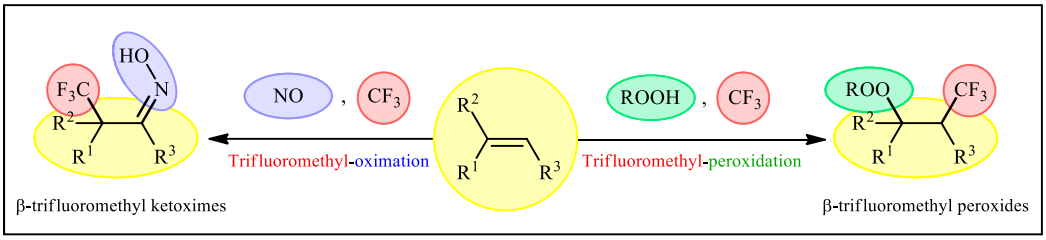
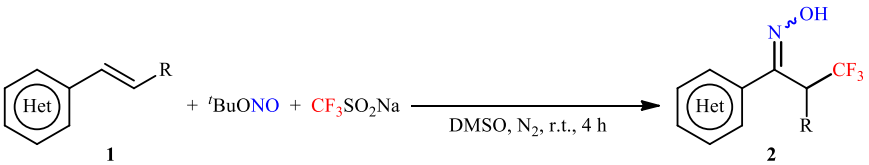


Fig. 1. Direct vicinal trifluoromethyl-oximation/-peroxidation of alkenes.

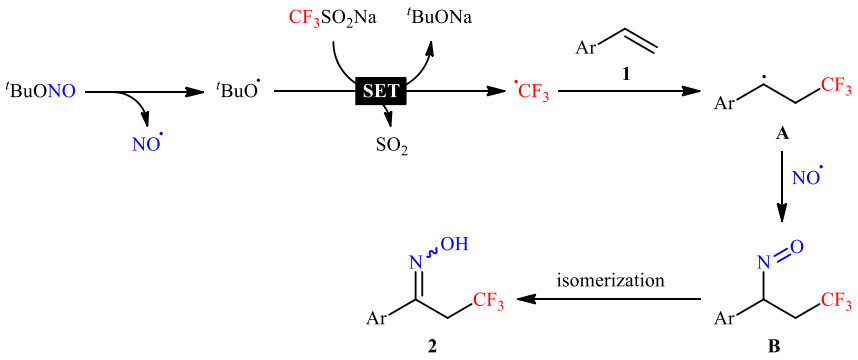


(Het)Ar= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CO_2H-C_6H_4, 4-CH_2Cl-C_6H_4, 4-vinyl-C_6H_4, 3-Cl-C_6H_4, 3-Br-C_6H_4, 2-Cl-C_6H_4, 2-naphthyl, 2-pyridyl

R^2= H, Me

16 examples (48-78%)

Scheme 3. Tang's synthesis of α-trifluoromethyl ketoximes 2.

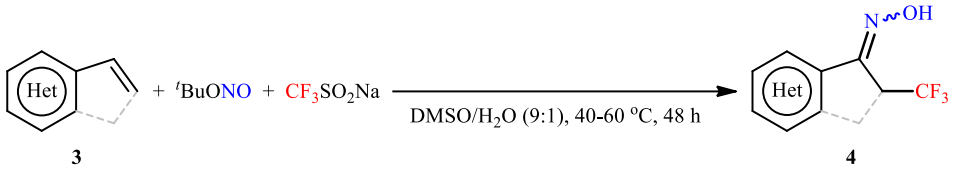


Scheme 4. Mechanistic proposal for the formation of α-trifluoromethyl ketoximes 2.

Concurrently, Lu *et al*. independently reported a closely related strategy for the synthesis of α-trifluoromethyl ketoximes 4 from the corresponding (hetero)aromatic alkenes 3 by simple treatment with CF_3SO_2Na in combination with ^{t}BuONO in a binary solvent DMSO/H_2O with ratio 9:1 at 40-60 °C (Scheme 5) [21]. Here, both electron-donating and electron-withdrawing substituents on the styrenes were compatible with the reaction condition and afforded the target products in modest to good yields. However, internal alkenes exhibited low reactivity under this protocol. Following these works, He, Wang and their colleagues developed an elegant protocol for the direct synthesis of α-oxyimino-β-trifluoromethyl esters **6** from the corresponding acrylates **5** *via* a visible-light-mediated trifluoromethyloximation, employing ^{t}BuONO and CF_3SO_2Na under mild conditions [22]. The reaction took place in the presence of 2 equiv. of K_3PO_4 as a base in ^{t}BuOH, and provided the desired products in modest to good yields (Scheme 6). In addition, a tolerance for styrene was also demonstrated, highlighting versatility of this visible-light-driven, catalyst-free oximation strategy. As an extension of the substrate scope of the methodology, it was demonstrated that a variety of α-sulfonyl ketoximes and α-phosphoryl ketoximes could be successfully synthesized from the corresponding olefinic substrates using S-phenyl arenesulfonothioates and diarylphosphine oxides as the source of sulfonyl and phosphoryl groups, respectively.

Concurrently, Li's research group unraveled that the treatment of styrene 1a with ^{t}BuONO and trifluoroiodomethane (CF_3I) in the presence of an excess amount of tetramethylethylenediamine (TMEDA) under visible light irradiation at room temperature led to the formation of the corresponding α-trifluoromethyl ketoxime 2a in a 48% yield (Scheme 7a) [23]. Although only a single example was demonstrated, this study represents the first reported use of CF_3I as a trifluoromethyl source in the direct trifluoromethyloximation of alkenes. Notably, this photochemical synthetic strategy further extended to the direct vicinal perfluoroalkyloximation of alkenes, employing a range of perfluoroalkyl iodides such as C_3F_7I, ^{i}C_3F_7I, C_4F_9I, $C_6F_{13}I$, $C_8F_{17}I$, and $C_{10}F_{21}I$ as perfluoroalkyl sources. Mechanistically, the reaction is proposed to proceed *via* the formation of an electron donor–acceptor (EDA) complex between the CF_3I and TMEDA. Upon visible-light irradiation, this EDA complex undergoes single-electron reduction, generating trifluoromethyl radical ($^{\bullet}CF_3$), radical cation $TMEDA^{\bullet+}$ and iodide ion I^-. Subsequently, $^{\bullet}CF_3$ radical undergoes chemoselective addition to the styrene 1a to provide carbon-centered radical A, which after trapping by ^{t}BuONO affords nitroso compound B. Finally, Finally, this intermediate B undergoes a quick tautomerization to produce the observed α-trifluoromethyl ketoxime 2a (Scheme 7b).

In 2023, Pattanayak and Chatterjee applied these principles to the direct synthesis of (4-trifluoromethyl)isoxazoles from the corresponding α,β-unsaturated carbonyls through a tandem trifluoromethyloximation/cyclization/elimination sequential process [24]. Thus, by simple treatment of α,β-unsaturated carbonyl compounds 7 with CF_3SO_2Na and ^{t}BuONO under catalyst- and additive-free conditions an array of (4-trifluoromethyl)isoxazoles 8 were obtained in moderate to high yields, ranging from 40% to 85% (Scheme 8). In this study, 30 different α,β-unsaturated ketones and aldehydes were employed to demonstrate the broad applicability of the method. Interestingly, the reaction conditions tolerate a wide range of important functional groups, including OMe, F, Cl, Br, OH, and NO_2, which allows for potential further manipulation of products. In this transformation, the authors hypothesized that ^{t}BuONO plays a dual role, both as the oxidant and as the source of the N–O unit in the isoxazole, thereby eliminating the need for an external oxidant. Based on a series of control experiments, the authors proposed a reaction mechanism that begins with the formation of an α-trifluoromethyl ketoxime B through the nitroso intermediate A. This intermediate undergoes cyclization through an intramolecular nucleophilic attack by the (*E*)-oxime OH group on the carbonyl carbon to form 4-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol C, which subsequently undergoes dehydration to yield the observed product 8 (Scheme 9).

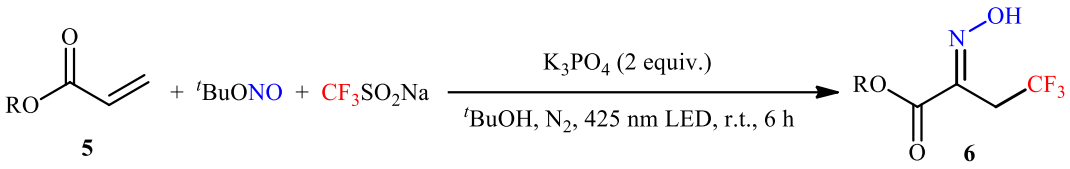


3 **4**

(Het)Ar= Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 4-CN-C_6H_4, 4-CF_3-C_6H_4, 4-CO_2Me-C_6H_4, 4-OAc-C_6H_4,4- (2-pyridyl)-C_6H_4, 3-Cl-C_6H_4, 3-Br-C_6H_4, 2-Cl-C_6H_4, 3,4-$(Cl)_2$-C_6H_3, 2-naphthyl, 2-pyridyl, 2-benzothienyl, 2-quinolinyl

21 examples (36-73%)

Scheme 5. Lu's synthesis of α-trifluoromethyl ketoximes 4.

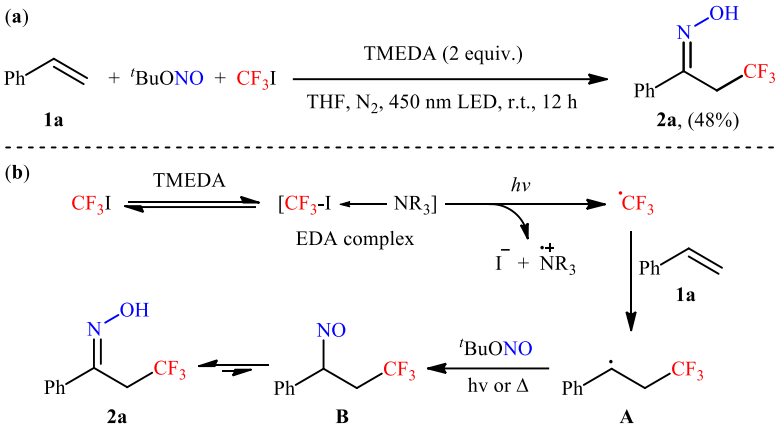


5 **6**

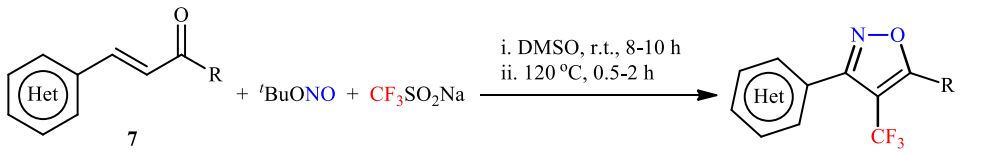
R= Me, ^{t}Bu, Bn, CH_2CH_2OMe, CH_2CH_2Br, CH_2CH_2OH

6 examples (35-72%)

Scheme 6. He-Wang's synthesis of α-oxyimino-β-trifluoromethyl esters 6.



Scheme 7. Li's synthesis of α-trifluoromethyl ketoxime 2.



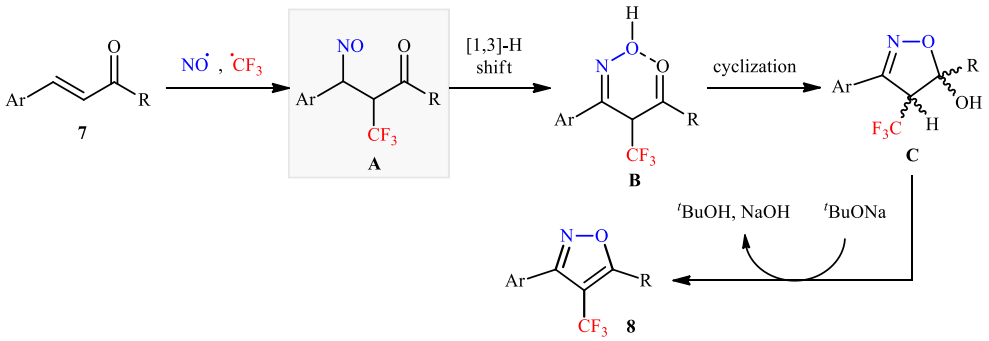
7 **8**

(Het)Ar= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 2-Ph-C_6H_4, 1-naphthyl, 2-thienyl

R= H, Me, Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-OH-C_6H_4, 3-NO_2-C_6H_4, 2-thienyl, 2-furyl

30 examples (40-85%)

Scheme 8. Pattanayak-Chatterjee's synthesis of (4-trifluoromethyl)isoxazoles 8.



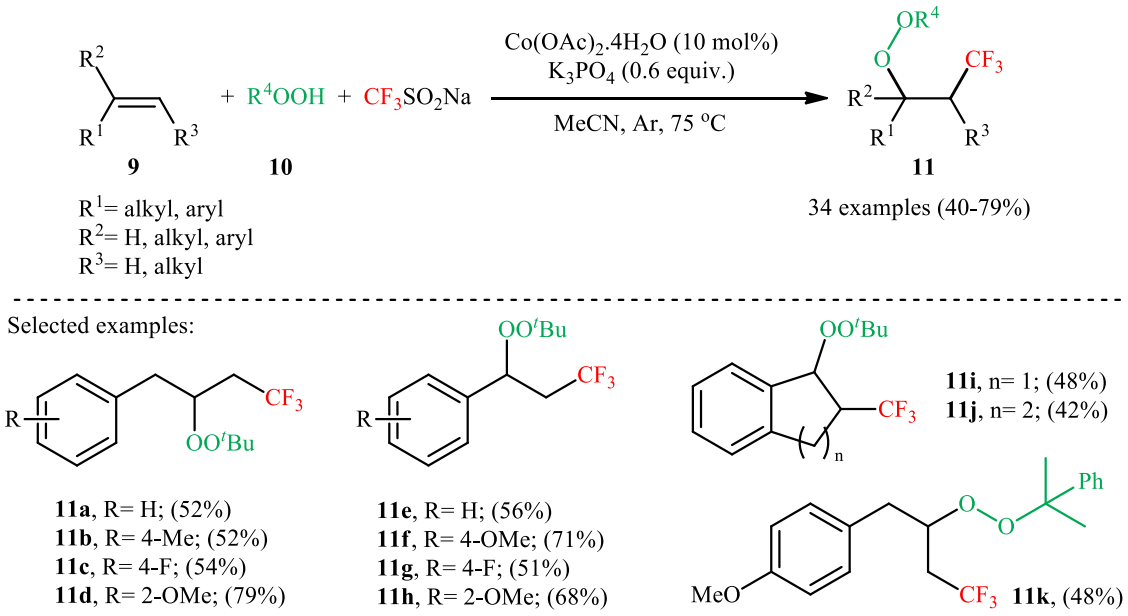
Scheme 9. Proposed mechanistic pathways for the formation of (4-trifluoromethyl)isoxazoles 8.

3. Trifluoromethyl-peroxidation

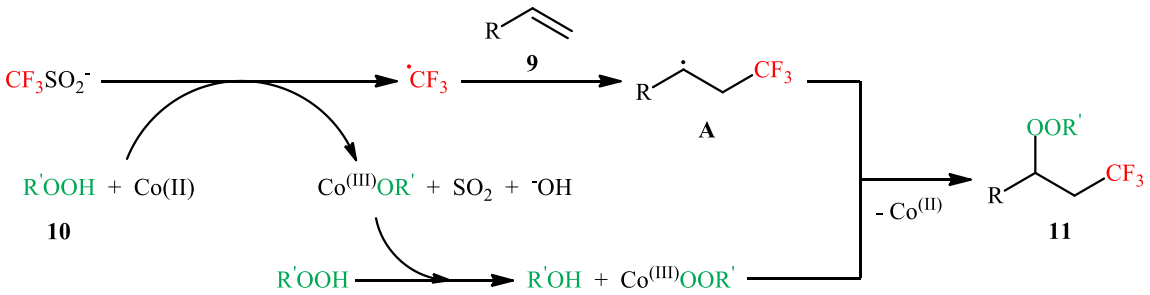
Drawing inspiration from Bao and Wan's work on $Co(acac)_2$-catalyzed direct perfluoroalkyl-peroxidation of styrene derivatives with perfluoroalkyl halides and ^tBuONO [25], in 2017, Zhang and co-workers explored the synthesis of β-peroxyl trifluoroalkyl derivatives *via* direct trifluoromethyl-peroxide difunctionalization of alkene substrates [26].

To determine the optimum conditions, they screened the activities of different metal catalysts (*e.g.*, $Mn(OAc)_2{\cdot}4H_2O$, $Cu(OAc)_2{\cdot}H_2O$, $Mg(OAc)_2{\cdot}3H_2O$, $Co(OAc)_2{\cdot}4H_2O$, $Co(acac)_2$, $CoCl_2{\cdot}6H_2O$), bases (Cs_2CO_3, K_2CO_3, K_3PO_4, KOAc, DABCO), and solvents (*e.g.*, DMF, MeCN, EtOAc) in the trifluoromethylation–peroxidation of 4-allylanisole using CF_3SO_2Na and *tert*-butyl hydroperoxide (TBHP) as the CF_3 and ^tBuOO sources, respectively, as a model reaction. The optimal system was identified using $Co(OAc)_2{\cdot}4H_2O$ in combination with K_3PO_4 in MeCN at 75 °C. Under the optimized conditions, various activated and unactivated alkenes 9 engaged effortlessly with a series of alkyl hydroperoxides 10 and CF_3SO_2Na to give the corresponding vicinal trifluoromethyl-peroxide compounds 11 in moderate to good yields, ranging from 40% to 79% (Scheme 10). In this study, a wide range of alkene substrates was demonstrated, though the scope of hydroperoxide reagents was limited to only *tert*-butyl hydroperoxide and cumyl hydroperoxide.

The protocol was compatible with both aliphatic and aromatic alkenes, including those bearing electron-donating and electron-withdrawing functional groups. However, benzyl acrylate did not work well in this difunctionalization reaction and therefore no other α,β-unsaturated carbonyl compounds were examined in the protocol. The authors proposed the following mechanistic pathway for this trifluoromethyl-peroxide difunctionalization reaction, as illustrated in Scheme 11: Initially, the combination of $Co(OAc)_2$ with CF_3SO_2Na and alkyl hydroperoxide 10 generates the Co^{III}-alkoxy complex ($Co^{III}OR'$) and CF_3 radical. Subsequently, the regioselective addition of $^{\cdot}CF_3$ to the C-C double bond of the alkene 9 affords the alkyl radical A. Meanwhile, Co^{III}-alkoxy complex reacts with another molecule of alkyl hydroperoxide 10 to form cobalt-peroxide complex ($Co^{III}OOR'$). Finally, cross-coupling between alkyl radical A and $Co^{III}OOR'$ provides the observed product 11 along with concomitant regeneration of Co(II)-catalyst.



Scheme 10. Zhang's synthesis of trifluoromethyl-peroxide compounds 11.



Scheme 11. Proposed mechanism for the formation of trifluoromethyl-peroxide compounds 11.

Concurrently, Zhang-Duan's research group explored the potential of metalorganic framework $Cu_3(BTC)_2$ (also well known as HKUST-1) as a heterogeneous catalyst for the direct trifluoromethyl-peroxidation of styrene derivatives using Togni II reagent as CF_3 source and TBHP as the source of peroxide [27].

Using simple styrene as the model substrate, the investigation showed that only 1 mol% of $Cu_3(BTC)_2$ under additive-free conditions yielded the best results, whereas the same loading of other copper catalysts, such as $Cu(OAc)_2$, failed to promote this reaction. To identify the solvent potentially suitable for this trifluoromethyl-peroxidation, the authors first chose $CDCl_3$, THF, MeCN, and toluene.

Among these, MeCN proved to be the most effective, affording the desired trifluoromethyl-peroxide product in high yield. With these optimized reaction conditions, 14 vicinal trifluoromethyl-peroxide products 14 were synthesized in 9–98% yields from the corresponding aromatic alkenes 12, Togni II reagent 13, and TBHP (Scheme 12). Overall, the relative reaction rates of various styrene derivatives followed the order: terminal styrenes > α-substituted styrenes > β-substituted styrenes.

The recycling test established that the catalyst could be easily recovered by simple filtration and re-activated under vacuum heating, and then reused for at least six successive times without significant loss of activity. To gain mechanistic insights, several preliminary experiments were conducted.

A radical pathway was deemed unlikely, as the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT) did not inhibit product formation, and no radical-trapping adducts such as TEMPO–CF_3 were detected. Furthermore, under similar reaction conditions, the use of the nucleophilic cyanation reagent TMSCN in place of TBHP led to the formation of a cyano-trifluoromethylation product in moderate yield, supporting the involvement of an ionic pathway.

Based on these results and previous works, a plausible mechanistic cycle was suggested by the authors for the formation of trifluoromethyl-peroxide compounds 14, as depicted in Scheme 13.

Subsequently, this chemistry was successfully extended to the direct difluoromethyl-peroxidation and trifluoromethylthio-peroxidation of alkenes, enabling the efficient one-step synthesis of β-difluoromethyl peroxides and β-trifluoromethylthio peroxides, respectively [28-30].

Along this line, Li and co-workers reported an effective and practical cobalt-catalyzed peroxy-trifluoromethylation of a variety of alkenes (aliphatic, aromatic, heteroaromatic) using bromotrifluoromethane (CF_3Br) as an electrophilic CF_3 source [31].

The reaction proceeded in the presence of $Co(acac)_2$/DIPEA combination as a catalytic system in MeCN at 65 °C to give the corresponding β-trifluoromethyl peroxide products in high yields (up to 93%).

Very recently, Lv, Li and their co-workers reported their results on the photoinduced iron-catalyzed direct vicinal trifluoromethyl-peroxidation of olefinic double bonds with trifluoromethyl carboxylic acid and TBHP, proceeding through a decarboxylation process [32]. Optimal conditions for this photoinduced decarboxylative functionalization were the use of 390 nm Kessil LEDs as the light source, $FeCl_2$ as the catalyst, and Na_2CO_3 as a base.

The reaction proceeded cleanly at room temperature in MeCN, tolerated a range of alkenes including terminal and internal aliphatic, electron-rich and electron-poor aromatic alkenes as well as α,β-unsaturated carbonyl compounds and enyne substrates 15, and afforded the desired β-trifluoromethyl peroxides 16 in synthetically useful yields within 24 hours (Scheme 14).

Besides CF_3CO_2H, other fluoroalkyl carboxylic acids (*e.g.*, CF_2HCO_2H, $MeCF_2CO_2H$, $PhCF_2CO_2H$, $C_2F_5CO_2H$ and $C_7F_{15}CO_2H$) have also been successfully used as fluoroalkylating reagents in this transformation. To demonstrate the practical utility of their protocol, the authors successfully explored its application in the late-stage functionalization of drug and natural products, including unactivated alkenes derived from sugar, (L)-menthol, sterically hindered (-)-borneol derivatives, non-steroidal anti-inflammatory and analgesic drugs such as celecoxib, sulbactam, and gemfibrozil, as well as steroidal compounds like dehydrocholic acid.

The authors proposed reaction mechanism for this photoinduced iron-catalyzed trifluoromethyl-peroxidation reaction is illustrated in Scheme 15. The reaction starts with the oxidation of Fe(II) by TBHP to give Fe(III) and ^{t}BuO·.

Next, coordination of CF_3CO_2H with Fe(III) furnishes the photoactive Fe(III) carboxylate complex A, which upon photoexcitation leads to the formation of Fe(II) and an acyloxy radical B through a ligand-to-metal charge transfer (LMCT) process.

Subsequently, acyloxy radical B undergoes decarboxylation to release the trifluoromethyl radical C, that after regioselective addition to the alkene 15 affords the nucleophilic radical intermediate D.

Concurrently, ^{t}BuO· abstracts a hydrogen atom from ^{t}BuOOH, producing the ^{t}BuOO· E. Finally, a polaritymatched radical coupling between radicals D and E results in the formation of the observed β-trifluoromethyl peroxide product 16.

Shortly afterwards, this innovative research group reported the usefulness of *N*,*N*-dimethyltrifluoromethanesulfonamide (DMTMSA, 18) as a easily accessible trifluoromethylating reagent in the direct trifluoromethyl-peroxidation of alkene substrates

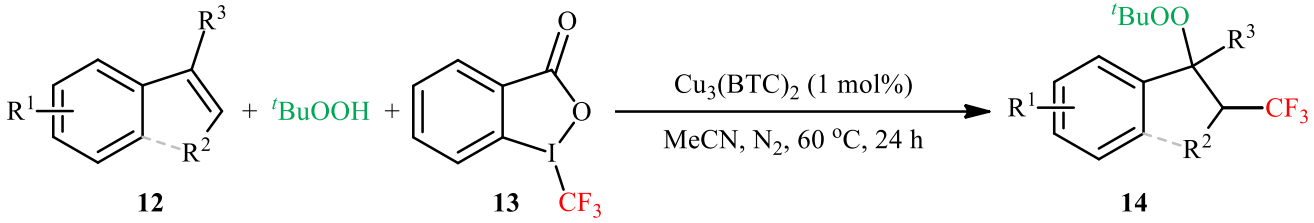
under photocatalytic conditions [33].

Thus, in the presence of 5 mol% of thioxanthylium (TXT) photoredox catalyst under irradiation of UV light, a small library of activated alkenes 17 reacted with DMTMSA and TBHP to give the respective β-trifluoromethyl peroxides 19 in moderate to good yields, ranging from 30% to 80% (Scheme 16).

The results clearly indicated that terminal alkenes gave higher yields compared to 1,1- and 1,2-disubstituted alkenes. Intriguingly, the steric- and electronic-factors of the substituents on the phenyl ring of styrenes had a little impact on the rate of this reaction.

In a notable contribution in this field, this research group developed an elegant four-component strategy for the synthesis of CF_3-functionalized isoxazole derivatives through the Co-catalyzed reaction between alkenes, ICF_3, TBHP, and NaN_3 [34].

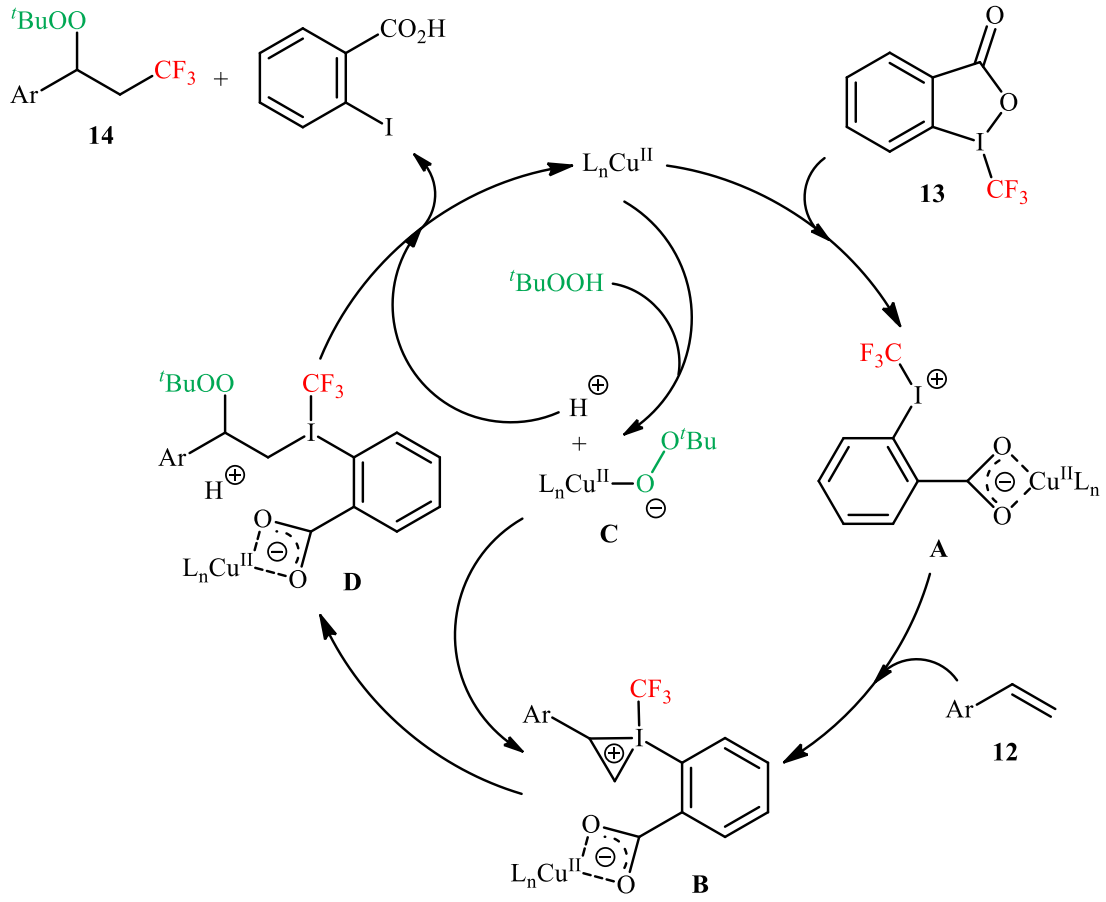
Mechanistic studies suggest that the transformation proceeds through a tandem sequence involving perfluoroalkylation–peroxidation of the alkene, a Kornblum–DeLaMare rearrangement, elimination, substitution, and N–O bond formation.



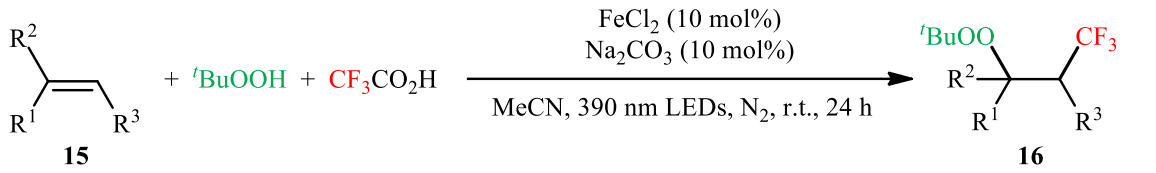
12 **13** **14**

R^1= H, 4-Me, 4-^{t}Bu, 4-Ph, 4-OMe, 4-F, 4-Cl, 2-Me, 2,4,6-$(Me)_3$, 2,3-$(CH{=}CH)_2$- 14 examples (9-98%)
R^2= H, Me, Ph, -CH_2-
R^3= H, Me

Scheme 12. Zhang-Duan's synthesis of trifluoromethyl-peroxide compounds 14.



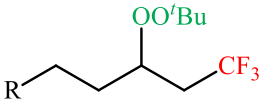
Scheme 13. Possible mechanistic cycle for the formation trifluoromethyl-peroxide compounds 14.



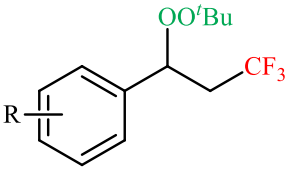
R^1= alkyl, aryl, acetylenyl, CO_2Bn
R^2= H, alkyl, aryl
R^3= H, alkyl, aryl

31 examples (15-91%)

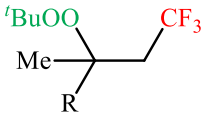
Selected examples:



16a, R= Ph; (77%)
16b, R= OBz; (88%)
16c, R= COPh; (61%)
16d, R= CH_2CH_2OH; (41%)
16e, R= CH_2Br; (55%)

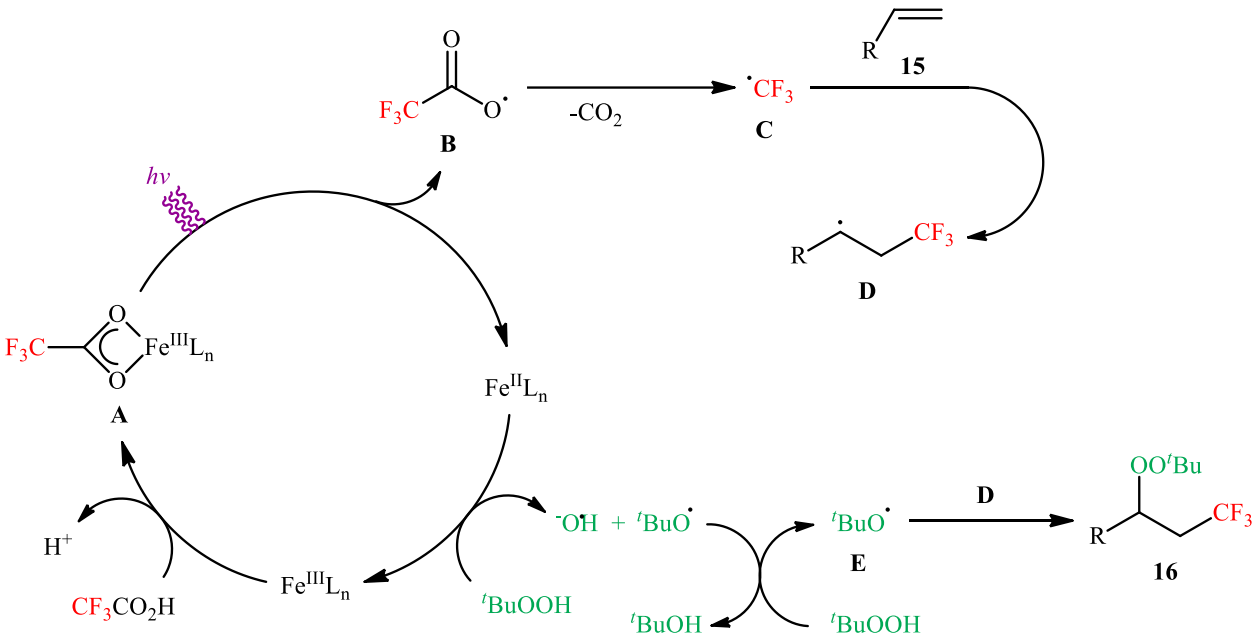


16f, R= H; (74%)
16g, R= 4-^{t}Bu; (68%)
16h, R= 4-NO_2; (47%)

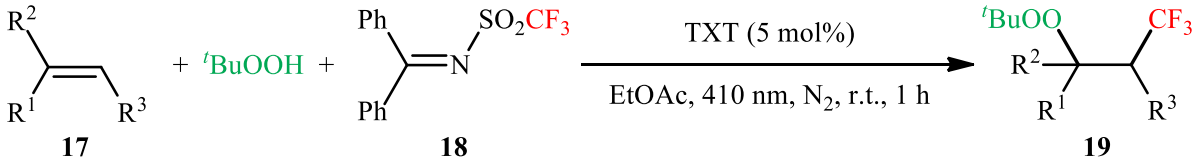


16i, R= CO_2Bn; (35%)
16j, R= CH_2Bn; (53%)
16k, R= CH_2OPh; (34%)
16l, R= $(CH_2)_2OBz$; (77%)

Scheme 14. Lv-Li's synthesis of β-trifluoromethyl peroxides **16**.



Scheme 15. Proposed mechanism for the reaction in Scheme 14.



R^1= CO_2Me, Ph, 4-^{t}Bu-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-OAc-C_6H_4, 3-Me-C_6H_4, 3-Cl-C_6H_4, 2-Cl-C_6H_4
R^2= H, Me, Ph
R^3= H
R^1 + R^3= 

12 examples (30-80%)

Scheme 16. Lv-Li's synthesis of β-trifluoromethyl peroxides 19.

4. Conclusion

During the past decade, significant progress has been made in the development of direct 1,2-difunctionalization reactions, which enable the simultaneous introduction of two distinct functional groups across the C-C double bond of alkenes.

In particular, 1,2-trifluoromethylative difunctionalization strategies have emerged as the most straightforward and practical synthetic strategy for the direct conversion of alkene substrates into value-added β-functionalized trifluoromethylated compounds. In this context, the synthesis of biologically and synthetically valuable β-trifluoromethyl ketoximes and β-trifluoromethyl peroxides *via* direct 1,2-trifluoromethyl-oximation and -peroxidation of alkenes, respectively, has witnessed notable growth in recent years.

The use of readily available starting materials, operational simplicity, high atom- and step-economy, and high environmental compatibility are among the major advantages of these reactions. Despite significant progress in recent years, these research areas remain in their infancy. Therefore, continued investigation is essential to overcome existing limitations, broaden the substrate scope and the variety of trifluoromethylation, oximation, and peroxidation agents, and enhance reaction efficiency by developing novel catalytic system, to fully realize the potential of these transformations.

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