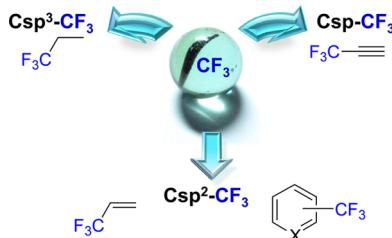


## Carbon Trifluoromethylation Reactions of Hydrocarbon Derivatives and Heteroarenes

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### 1. INTRODUCTION

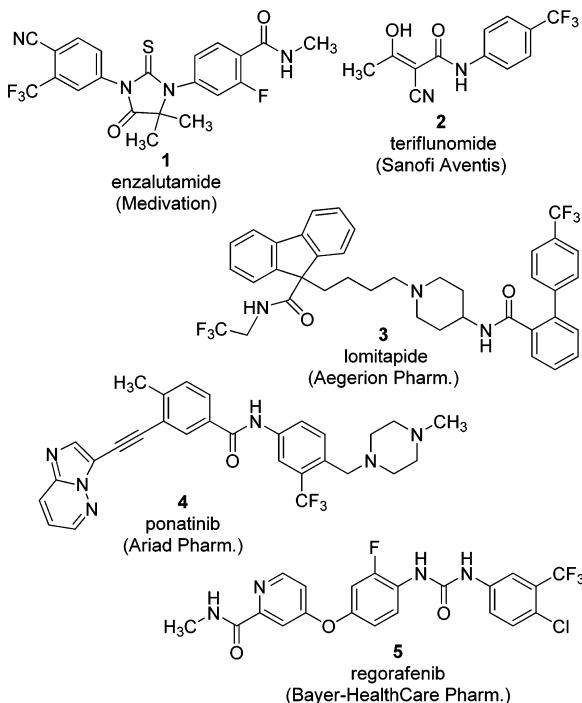
Fluorine has emerged as a “magic element” in medicinal chemistry, crop, and materials science.<sup>1</sup> Although fluorine is the most abundant halogen in the earth’s crust, it is contained in very few molecules with biological origins.<sup>2</sup> However, it is very popular during lead optimization in drug discovery,<sup>3,4</sup> and approximately 20–25% of all drugs contain at least one fluorine atom.<sup>5</sup> In fact, five of the new drugs that were FDA (Food and Drug Administration) approved in 2012<sup>6</sup> contain a trifluoromethyl group, enzalutamide (**1**, Figure 1) for the treatment of metastatic castration-resistant prostate cancer, teriflunomide (**2**, Figure 1) for the treatment of multiple sclerosis, lomitapide (**3**, Figure 1) for the treatment of homozygous familial hypercholesterolemia, ponatinib (**4**, Figure 1) for the treatment of chronic myeloid leukemia, and Philadelphia chromosome positive acute lymphoblastic leukemia and finally regorafenib (**5**, Figure 1) for the treatment of previously treated patients with metastatic colorectal cancer.

The special nature of fluorine inside a therapeutic or diagnostic small molecule candidate for a pharmaceutical compound imparts a variety of features, which can enhance a number of pharmacokinetic and/or pharmacodynamic properties.

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**Figure 1.** New drugs containing a trifluoromethyl group approved by the FDA in 2012.

ties. These include increased membrane permeability, favorable protein–ligand interactions, improved metabolic stability, changes in physical properties, and selective reactivities with a profound effect on its bioactivity, stability, and lipophilicity.<sup>7–9</sup> If the specific metabolic site is known, medicinal chemists may block the site, typically with a fluorine, or replace the metabolically labile group.<sup>10</sup> The use of fluorinated derivatives by means of fragment based drug discovery (FBDD) is a widely used tool for discovering novel therapeutics.<sup>11</sup> The incorporation of the trifluoromethyl group into amino acids<sup>12</sup> may change protein function due to water–protein interactions on solvation dynamics at fluorinated protein surfaces<sup>13</sup> to stabilize proteins for their application in protein-based biotechnologies such as protein therapeutics,<sup>14</sup> biosensors,<sup>15</sup> and for the preparation of fluorinated peptidomimetics.<sup>16</sup>

Moreover, the dramatic effect of fluorine on the biological activity of agrochemicals such as herbicides, insecticides, fungicides, and plant growth regulators has earned fluorine-containing compounds a unique place in the toolbox of the agrochemical chemist, given that they represent about 35% of the active ingredients in crop protection products.<sup>17</sup> Therefore, the introduction of fluorine into agrochemicals is an important strategy in the development of modern crop protection compounds with optimal efficacy, environmental safety, and economical viability. Indeed, the structure–activity optimization process can dramatically modify its biological activity by affecting other parameters, such as binding to a target receptor or enzyme, transporting the bioactive molecule from the point of application to the target site, and blocking metabolic deactivation.<sup>18</sup>

Likewise, fluorine has been recognized as a key element in materials science. Fluorinated materials are gaining importance as chemical tools to pursue improved performance and higher stability under a variety of conditions,<sup>19</sup> in heat-transfer agents,<sup>20</sup> liquid crystals,<sup>21</sup> energy conversion materials,<sup>22</sup>

dyes,<sup>23</sup> surfactants,<sup>24</sup> plastics or elastomers,<sup>25</sup> membranes,<sup>26</sup> and other materials such as lipid bilayers<sup>27</sup> or dendrimers.<sup>28</sup>

Conventional synthetic methods are not always applicable to the preparation of organofluorine derivatives due to the unique characteristics of fluorine. Therefore, the synthetic access to fluorinated compounds was difficult in the past and largely restricted to the use as starting materials of a very limited amount of commercially available fluorinated building blocks<sup>29</sup> or simple synthetic fluorinated templates.<sup>30</sup> However, nowadays the synthetic tools available have increased notably.<sup>31</sup> Taking into account that many biologically active compounds contain the trifluoromethyl group, the introduction of this moiety is a challenging topic, and the development of highly efficient methodologies for trifluoromethylation is of significant importance for many fields of science and technology. Therefore, a great deal of attention has been paid to the development of new synthetic methods for the introduction of trifluoromethyl group into diverse organic derivatives. Historically the trifluoromethyl group has been difficult to install, in part because the reactive intermediates that are generated during trifluoromethylation reactions are unstable under the conditions necessary for the reactions to proceed.<sup>32</sup> The harsh protocols typically required for these reactions can limit the substrates that can be used and/or cause side-product formation.

Several reviews deal with different aspects of the synthetic methodology available to introduce the  $\text{CF}_3$  group into organic molecules. Some of them outline the electronic nature of the reagents employed, which can be radical,<sup>32</sup> electrophilic,<sup>33</sup> or nucleophilic.<sup>34</sup> Other revision works focus on the use of catalysis,<sup>35</sup> on the stereoselectivity of the reactions,<sup>36</sup> or on the type of bond submitted to trifluoromethylation including C–halogen<sup>37</sup> or C–H,<sup>31,38</sup> among others.<sup>39</sup>

In this Review, we aim to focus on the most recent research results, but we also include previous relevant and pioneering contributions to gain a general and systematic view of the evolution of the diverse synthetic methods over the time. This Review is organized according to different strategies for the trifluoromethylation reaction of hydrocarbons and summarizes the methods for the  $\text{Csp}^3\text{--}\text{CF}_3$ ,  $\text{Csp}^2\text{--}\text{CF}_3$ , and  $\text{Csp}\text{--}\text{CF}_3$  bond construction of aliphatic and aromatic hydrocarbons and heterocycles with special emphasis on the literature from 2008 until the end of September of 2014. In every section, we arrange the synthetic methods according to the type of substrate and also to the trifluoromethylating reagent. In this way, our approach will be complementary and of broader scope than that of existing reviews. Trifluoromethylation of carbonyls and  $\alpha$  to carbonyl groups, which is also a valuable tool for the carbon– $\text{CF}_3$  bond construction, is out of the scope of this Review, because it was covered in other reviews.<sup>36,40</sup> Therefore, the focus is on the many different types of trifluoromethylated compounds that can be built with the available chemical tools, in a way that synthetic, medicinal, material, and agrochemical chemists can find very practical.

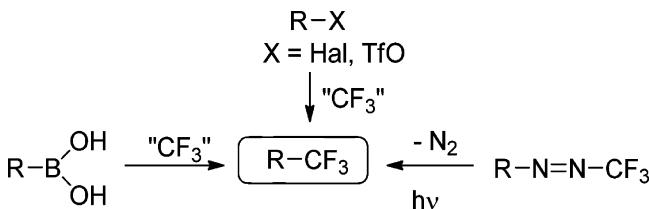
## 2. $\text{Csp}^3\text{--}\text{CF}_3$ BOND FORMATION

The incorporation of a trifluoromethyl group into an organic substrate is an important strategy in preparative organic chemistry. Despite the methods for the formation of  $\text{Csp}^3\text{--}\text{CF}_3$  bonds being limited, these strategies have undergone major developments over the last lustrum.

## 2.1. Alkyl Trifluoromethylation

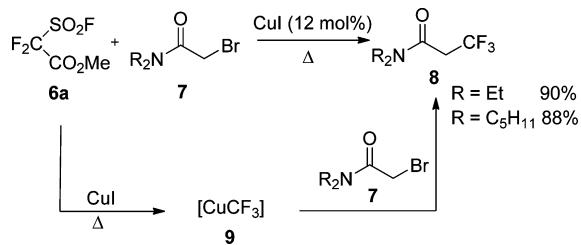
The introduction of a trifluoromethyl group into an aliphatic substrate is not a simple task. Some strategies have been developed on the basis of the use of prefunctionalized alkyl halides or triflates, boronic derivatives, and azo compounds (Scheme 1).

Scheme 1



**2.1.1. From Alkyl Halides or Triflates.** Trifluoromethylation of alkyl halides has been addressed for a long time by using  $[\text{CuCF}_3]$  species, whose spectroscopic evidence was detected by  $^{19}\text{F}$  NMR<sup>41</sup> and prepared in different ways, all having in common the use of  $\text{CF}_3$ -containing reagents and/or precursors and some form of copper. For instance, the first contribution was the trifluoromethylation of some linear alkyl halides ( $\text{C}_{10}\text{H}_{21}\text{X}$ ,  $\text{X} = \text{Br}, \text{I}$ ; 13% and 48%, respectively) with a trifluoromethyl copper complex, prepared from  $\text{CF}_3\text{Cl}$  and Cu powder in hexamethylphosphoric triamide (HMPA).<sup>42</sup> Afterward, methyl fluorosulfonyldifluoroacetate **6a**, in the presence of  $\text{CuI}$  (12 mol %), was used as the source of a trifluoromethyl group, which replaces the halogen in bromomethyl amides **7** giving the corresponding trifluoromethyl derivatives **8** in good yields (Scheme 2).<sup>43</sup> In this process, the formation of a

Scheme 2

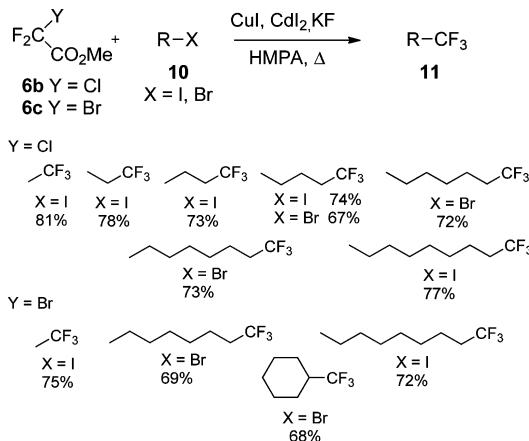


trifluoromethyl copper complex **9** is suggested, and a subsequent nucleophilic substitution to functionalized alkyl halides may give the corresponding alkylamido trifluoromethane derivative **8**.

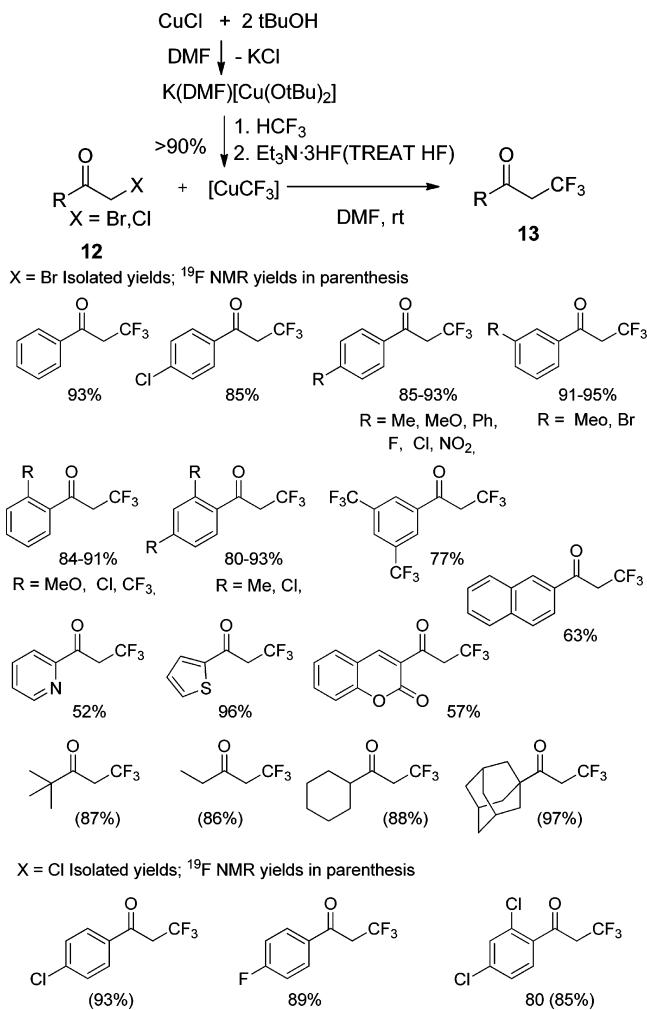
The method was extended to other reagents such as methyl chloro- and bromodifluoroacetate **6b,c** ( $\text{Y} = \text{Cl}, \text{Br}$ , Scheme 3), and in this case the presence of potassium fluoride (KF) became essential to give the corresponding trifluoromethyl compounds **11** with moderate-good yields.<sup>44</sup> Stoichiometric amounts of copper iodide were needed, and yields with either difluoroacetate trifluoromethylating agents **6b** or **6c** were comparable, but iodides **10** ( $\text{X} = \text{I}$ ) were more effective than bromides **10** ( $\text{X} = \text{Br}$ ), while chlorides **10** ( $\text{X} = \text{Cl}$ ) did not react.

Another method for the preparation of  $[\text{CuCF}_3]$  by direct cupration of fluoroform ( $\text{HCF}_3$ ) in very mild conditions (room temperature and atmospheric pressure) has been developed by Grushin et al.<sup>45</sup> (Scheme 4). The copper reagent was stabilized with triethylaminefluoridic acid ( $\text{Et}_3\text{N}\cdot\text{3HF}$ , TREAT HF) and

Scheme 3



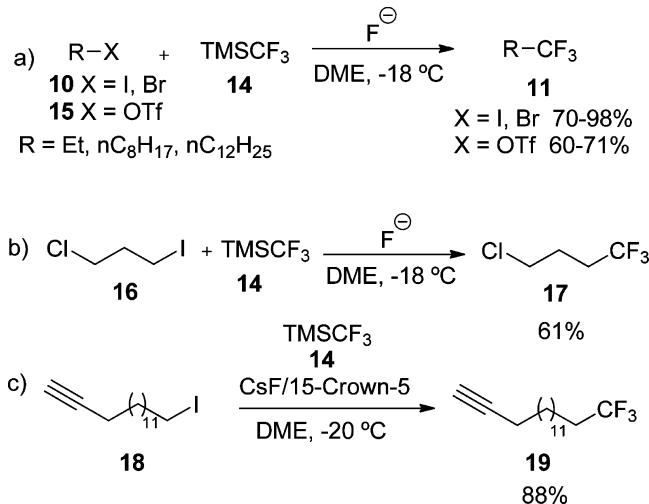
Scheme 4



has been used for an efficient synthesis of  $\alpha$ -trifluoromethylated carbonyl derivatives **13**<sup>36</sup> through nucleophilic trifluoromethylation of  $\alpha$ -haloketones **12** ( $\text{X} = \text{Br}, \text{Cl}$ ).<sup>46</sup> The process has a wide scope with application to aryl, alkyl, and heteroaryl substrates and good functional group tolerance. Moreover, although organocupper reagents usually exhibit low reactivity with electrophilic chloro derivatives, in this case good yields of adducts **13** were obtained.

Fluoride-mediated selective cross-coupling reactions of alkyl halides **10** with trifluoromethyltrimethylsilane **14** (Ruppert–Prakash reagent; RPr)<sup>47</sup> in the absence of any metal catalyst, using CsF/15-crown-5 or Me<sub>4</sub>NF or TASF as fluorine sources, were reported (Scheme 5).<sup>48</sup> Secondary and tertiary alkyl

Scheme 5

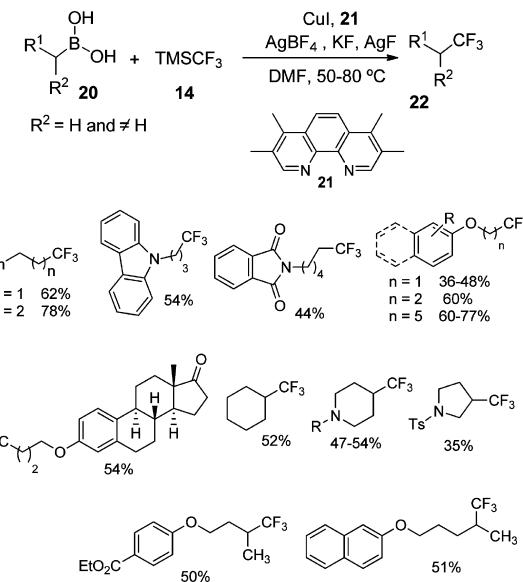


halides underwent  $\beta$ -elimination processes to give the corresponding olefins, while primary alkyl iodides and bromides worked well. However, primary alkyl chlorides seemed to be nonreactive under the reaction conditions, whereas selective desiodination-trifluoromethylation of 1-chloro-3-iodopropane **16** was achieved (Scheme 5b). This synthetic strategy has been also applied for the preparation of 16,16,16-trifluorohexadec-1-yne **19** (Scheme 5c), which has been employed to obtain fluorine-containing organic monolayers.<sup>49</sup> Primary alkyl triflates **15** ( $X = OTf$ ) have also been used with **14** (RPr)<sup>47</sup> in the presence of Me<sub>4</sub>NF for the preparation of 1,1,1-trifluorononane **11** ( $R = C_8H_{17}$ , 60%) and 4-(2,2,2-trifluoroethyl)-4-propylbicyclohexyl (71%).<sup>50</sup>

**2.1.2. From Alkyl Boronic Acids.** Copper-promoted trifluoromethylation of primary alkyl boronic acids **20** ( $R^2 = H$ , Scheme 6) with **14** (RPr)<sup>47</sup> in modest to good yields has been described by using CuI (50 mol %), phenantroline derivative **21**, AgBF<sub>4</sub> as oxidant, and KF as base.<sup>51</sup> The process tolerates functional groups such as amine, amide, ketone, ester, ether, as well as estrone derivative. This strategy can be extended to secondary alkyl boronic acids **20** ( $R^2 \neq H$ , Scheme 6), because a modified procedure has been developed using a copper triflate (CuOTf, 10 mol %) as Cu source and AgOTs as the most effective oxidant. Thus, cyclic and acyclic secondary alkyl boronic acids **20** have been trifluoromethylated in moderated yields, and *N*-protected pyrrolidines and piperidines were well tolerated in the process. Taking into account that alkyl boronic acids are prepared by a Cu-catalyzed borylation process from alkyl halides or tosylates,<sup>52</sup> this strategy can also be considered as a two-step process for the preparation of alkyl trifluoromethylated derivatives **22** from alkyl halides and/or tosylates.

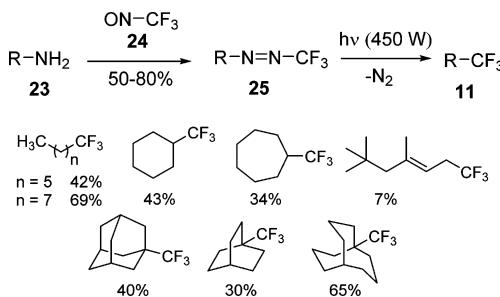
**2.1.3. Photolysis of Azo Derivatives.** A totally different methodology for the preparation of alkyltrifluoromethyl compounds was developed at the end of the 1970s by means of a two-step procedure from alkyl amines.<sup>53</sup> The treatment of alkyl amines **23** with trifluoromethylsulfone **24** gave stable

Scheme 6



trifluoroazo derivatives **25** (Scheme 7), and the photolysis of these compounds with a 450 W medium pressure mercury

Scheme 7



vapor lamp in highly viscous solvents such as *tert*-butyl alcohol or hexadecane afforded trifluoromethyl derivatives **11**. Although high conversions were reported, the isolated yields were low-moderate. The scope of the process is very wide because the introduction of the trifluoromethyl group may be achieved not only in primary and secondary substrates but also in tertiary derivatives.

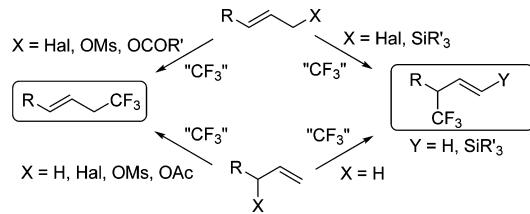
## 2.2. Allylic Trifluoromethylation

The development of allylic trifluoromethylation methods is important because compounds containing allylic trifluoromethyl groups are versatile building blocks for the preparation of CF<sub>3</sub>-containing compounds.<sup>53,54</sup> Protocols for the allylic trifluoromethylation include either reactions from prefunctionalized substrates such as halogen, mesylates, ester, or silyl derivatives, or direct activation of C–H allylic bonds (Scheme 8).

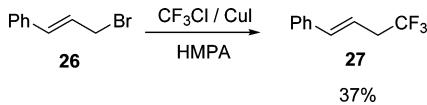
**2.2.1. From Allyl Halides or Mesylates.** The first example of the preparation of allyltrifluoromethyl derivative **27** involved the substitution reaction of bromide by the CF<sub>3</sub> group, generated from the trifluoromethyl copper complex prepared from CF<sub>3</sub>Cl and Cu powder in HMPA<sup>42</sup> (Scheme 9).

Nevertheless, rather than CF<sub>3</sub>Cl, the analogous iodide (CF<sub>3</sub>I) is widely used as trifluoromethylating agent. Thus, palladium-catalyzed (Pd(OAc)<sub>2</sub>) cross-coupling trifluoromethyl-

Scheme 8

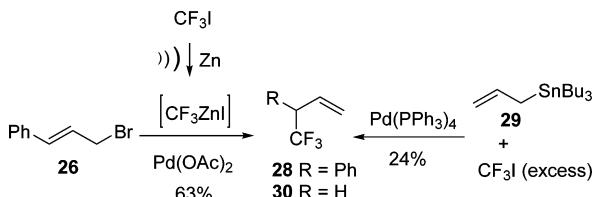


Scheme 9



lation reaction of allyl bromide **26** with trifluoromethyl zinc iodide, which was generated in situ from trifluoromethyl iodide and ultrasonically dispersed zinc power in THF, has been used for the preparation of allylic trifluoromethyl derivative **28** (Scheme 10).<sup>55</sup> Similarly, another palladium-catalyzed (Pd-

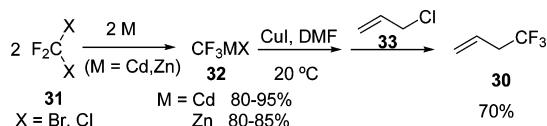
Scheme 10



( $\text{PPh}_3)_4$ ) process between allyl-stannane **29** and trifluoromethyl iodide has also been reported for the synthesis of **30** in low yield (Scheme 10).<sup>56</sup> This process may be considered as a two-step preparation of allyl derivatives from halides, because stannane derivatives can be prepared from allyl halides.<sup>57</sup>

Other halogen derivatives have also been used for the allylic trifluoromethylation by means of the use of the trifluoromethyl copper reagent  $[\text{CuCF}_3]$  described and spectroscopically detected by Burton et al.<sup>41,58</sup> This organometallic compound may be generated by the reaction of dihalogendifluoromethanes **31** (Scheme 11) with either metallic zinc or cadmium in *N,N*-

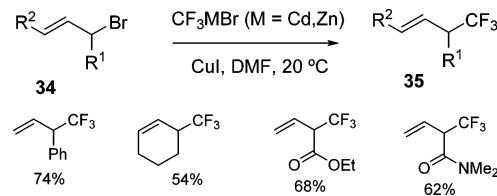
Scheme 11



dimethylformamide (DMF) to give trifluoromethyl metal halide **32** (M = Cd, Zn), followed by transmetalation with CuI. Allyl chloride **33** can be substituted in good yield at room temperature to afford **30**.

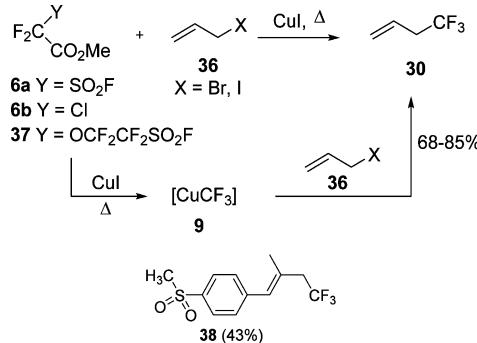
This method was extended to secondary allyl compounds **34** such as acyclic ( $\text{R}^1 = \text{Ph}, \text{R}^2 = \text{H}$ ) and cyclic bromides ( $\text{R}^1\text{R}^2 = (\text{CH}_2)_3$ ), as well as functionalized bromocrotonate ( $\text{R}^1 = \text{CO}_2\text{Et}, \text{R}^2 = \text{H}$ ), or amide ( $\text{R}^1 = \text{CONMe}_2, \text{R}^2 = \text{H}$ ) derivatives (Scheme 12).<sup>59</sup> Allyl compounds **35** can also be prepared in moderate yield by coupling allyl halides with trifluoromethyl copper complexes, obtained by electroreduction of bromotrifluoromethane in the presence of a Cu anode and phosphine or amine ligands.<sup>60</sup>

Scheme 12



Methyl fluorosulfonyldifluoroacetate **6a** (Scheme 13)<sup>43</sup> was used as the source of a trifluoromethyl group, which replaces

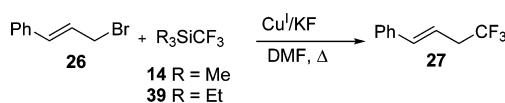
Scheme 13



the halogen in allyl halides **36** in the presence of catalytic amounts of copper iodide (12 mol %) at  $60\text{--}70^\circ\text{C}$ , to give the corresponding trifluoromethyl derivative **30** in good yields (68–70%, Scheme 13). The formation of a trifluoromethyl copper complex is suggested, and a subsequent nucleophilic substitution to allyl halides gave the corresponding allylic trifluoromethyl derivative **30**. The process was extended to new reagents such as methyl chlorodifluoroacetate **6b** in the presence of KF and methyl 3-oxa- $\omega$ -fluorosulfonylperfluoropentanoate **37** (Scheme 13)<sup>62</sup> as trifluoromethylating agents to give trifluoromethyl compound **30** with good yield (81–85%). The strategy based on methyl chlorodifluoroacetate **6b** in the presence of KF has been used for the preparation of the trifluoromethyl derivative **38** (43%), precursor of the COX-2 inhibitor L-784512.<sup>63</sup>

Nucleophilic allylic trifluoromethylation can also be achieved by fluoride ion-induced cross-coupling reaction of allyl halides with trifluoromethyltriethylsilane **39** ( $\text{R} = \text{Et}$ ) in the presence of Cu(I) salts and under mild reaction conditions, to give the corresponding trifluoromethylated product **27** in low yields (23%, Scheme 14).<sup>64</sup> An increased yield up to 42% has been reported by trifluoromethylation reactions of allyl bromide **26** with **14** ( $\text{R} = \text{Me}, \text{RPr}$ )<sup>47</sup> using ionic liquids (IL) as reaction media.<sup>65</sup>

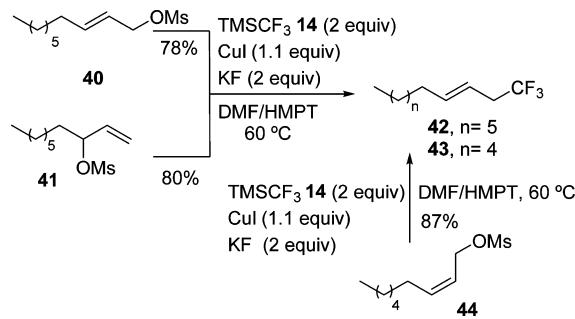
Scheme 14



A simple and efficient copper-mediated trifluoromethylation of allyl methanesulfonates (mesylates) with **14** ( $\text{RPr}$ )<sup>47</sup> as trifluoromethylating source in the presence of CuI and KF has been reported.<sup>66</sup> Linear *E*-allyltrifluoromethylated compound **42** ( $n = 5$ ) with traces of the *Z*-isomer ( $E/Z = 32:1$ ) can be obtained not only from linear *E*-allylic mesylate **40** but also

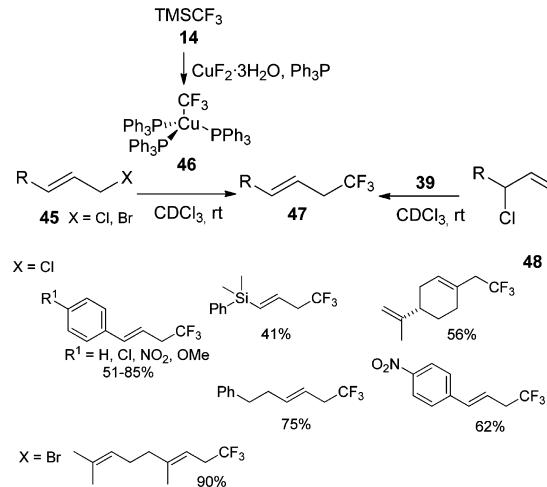
from secondary mesylate **41**. Likewise, *E*-allyl trifluoromethylated **43** (*E/Z* = 23:1) as major component (*E/Z* = 23:1) was prepared when linear Z-allylic mesylate **44** was used (Scheme 15). These results seem to indicate that a  $\pi$ -allyl-Cu(I) complex may be involved in the process.

Scheme 15



Trifluoromethylation of allylic halides **45** with a  $[(\text{Ph}_3\text{P})_3\text{CuCF}_3]$  complex **46** (Grushin reagent),<sup>67</sup> generated from **14** (RPr),<sup>47</sup> CuF<sub>2</sub>·3H<sub>2</sub>O, and Ph<sub>3</sub>P for the preparation of compounds **47**, has been reported (Scheme 16).<sup>68</sup> The reaction

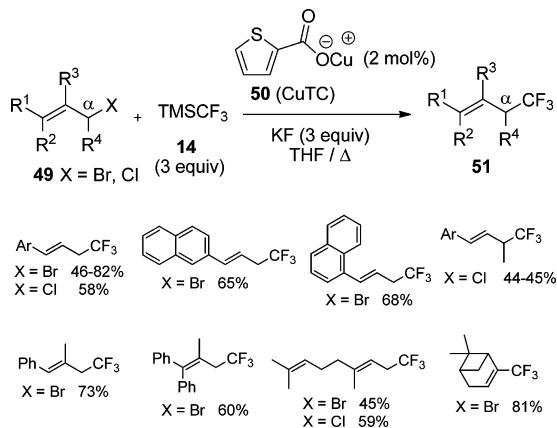
Scheme 16



was performed in CDCl<sub>3</sub> to facilitate the analysis of the conversion by NMR, and under neutral, mild condition without any additives. When cinnamyl-, alkyl-, and silylallyl chlorides **45** were used, moderate-good yields of compounds **47** were obtained. The use of geranyl bromide gave the trifluoromethyl derivative with excellent yield, and the scope of the process was not limited to linear allyl halides **45**, because  $\alpha$ -branched allyl halides **48** also gave the corresponding linear regioisomers **47**, and even terpene derivative was prepared without changing the configuration of the stereogenic carbon.

A more efficient Cu(I)-catalyzed allylic nucleophilic trifluoromethylation of allylic halides **49** in the presence of **14** (RPr)<sup>47</sup> and copper(I)-thiophene-2-carboxylate **50** (CuTC) to give corresponding allylic trifluoromethylated products **51** was reported (Scheme 17).<sup>69</sup> A variety of substituted cinnamyl and naphthyl substrates, as well as  $\beta,\gamma$ - and  $\gamma,\gamma$ -disubstituted allyl halides, are adequate for the process. The approach was also extended to the reaction of secondary allyl halides **49** (R<sup>4</sup> = CH<sub>3</sub>), and moderate yields were obtained, but an increase of

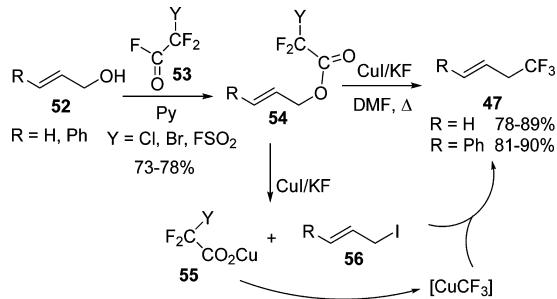
Scheme 17



the catalytic amount of **50** was necessary. Although a detailed reaction mechanism is not clear, a plausible pathway can be proposed on the basis of copper-catalyzed allylic substitution reactions.<sup>70</sup> The initial step may be the formation of [CuCF<sub>3</sub>] complex through a transmetalation reaction of Cu(I) salt **50** and **14** activated by the fluoride anion.<sup>67</sup>

**2.2.2. From Allyl Carboxylic Esters.** Chen and co-workers developed a synthesis of trifluoromethyl compounds from allyl esters by means of a copper(I) iodide-initiated trifluoromethyl-dehydroxylation process.<sup>71</sup> Therefore, allyl esters **54** (Scheme 18) prepared from the allyl alcohols **52** and the acid fluorides

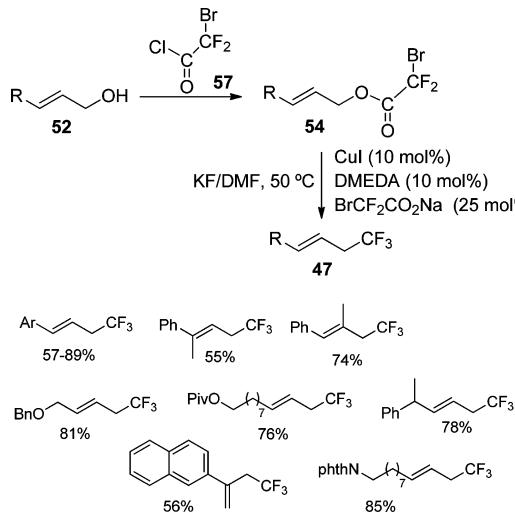
Scheme 18



**55** were heated (50–110 °C) in the presence of CuI and KF in DMF to give the corresponding trifluoromethyl derivatives **47** in good yields. A mechanism similar to that described for reactions in Scheme 13 (vide supra) is proposed. Initially, copper iodide attack on the ester **54** may give allyl iodide **56** and Cu(I) carboxylate **55**, which would generate trifluoromethyl copper. The reaction of the copper reagent with allyl iodides **56** then may afford trifluoromethyl derivatives **47**. This strategy based on the use of substituted difluoroacetates **54** has been also applied to the preparation of the trifluoromethylallyl-laryl derivative **38** precursor of the COX-2 inhibitor L-78451263 with better yield (74%) than when departing from the allyl halide (vide supra, Scheme 13).<sup>63</sup> Allyl trifluoroacetates **54** (Y = F) have also been used as starting materials in the reaction with a  $[(\text{Ph}_3\text{P})_3\text{CuCF}_3]$  complex **46** under mild, neutral conditions and without any additives, to give allyl derivatives with moderate yields (30–61%). In this strategy, trifluoroacetates **54** proved to be less reactive than the halides **45**, and therefore slightly elevated temperature (55 °C) had to be used.<sup>68</sup>

A similar two-step decarboxylative protocol by using acid chloride **57** instead of fluoride **53** for the transformation of allyl alcohols **52** into substituted allyl trifluoromethanes **47** has been reported by Altman et al.<sup>72</sup> making use of catalytic amounts of copper (Scheme 19). The optimized catalyst system included the use of CuI, DMEDA as a ligand, BrCF<sub>2</sub>CO<sub>2</sub>Na, and KF (2 equiv).

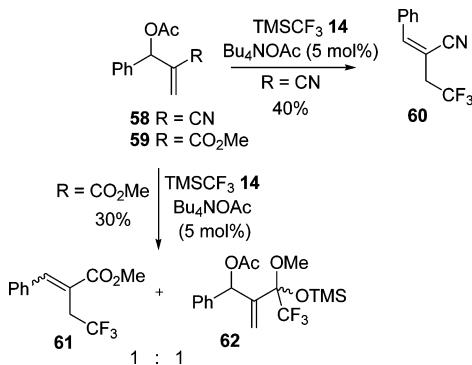
Scheme 19



Bromodifluoroacetic esters **54** were more effective than the corresponding trifluoro, chlorodifluoro, or difluorooiodoacetates. Electron-deficient, electron-neutral cinnamyl derivatives ( $R = Ar$ ) as well as disubstituted and non conjugated aliphatic allyl derivatives, such as benzyl ether, ester, or imide, can be obtained.

Allylic trifluoromethylation of acylated Baylis–Hillman adducts **58** bearing nitrile ( $R = CN$ ) and **59** bearing ester groups ( $R = CO_2Me$ ) with **14** ( $RPr$ )<sup>47</sup> have been described (Scheme 20).<sup>73</sup> The reactions were initiated by Bu<sub>4</sub>NOAc (5

Scheme 20

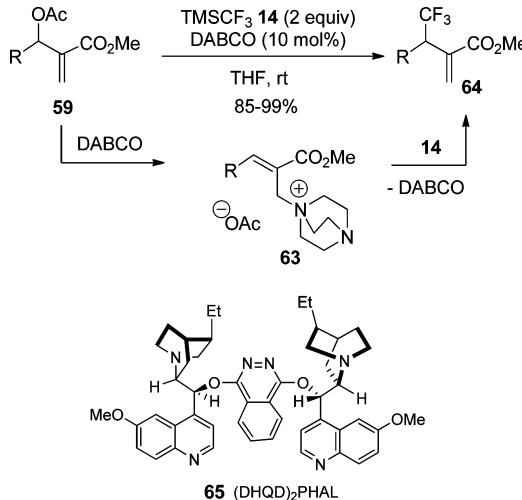


mol %) in MeCN or DMF under mild conditions and, in the case of nitrile derivatives, afforded product of allylic substitution **60** in moderate yield. However, ester substrate **59** ( $R = CO_2Me$ ) gave an inseparable mixture, in a combined yield of 30%, containing trifluoromethylallyl derivative **61** and functionalized olefin **62**, corresponding to the nucleophilic addition of **14** to the carbonyl group of the carboxylic ester.

These adverse results have been overcome by performing the reaction with 1,4-diazabicyclo[2.2.2]octane (DABCO) as

catalyst. Thus, a series of Morita–Baylis–Hillman acetates **59** ( $R = Ar$ ) with a variety of substituents on the aromatic ring, such as chloro, bromo, methyl, methoxy, and nitro group as well as with heteroaryl groups, were regioselectively converted into the corresponding trifluoromethylated products **64** ( $R = Ar$ ) in up to 99% yields<sup>74</sup> with **14** ( $RPr$ ,<sup>47</sup> 2 equiv, Scheme 21).

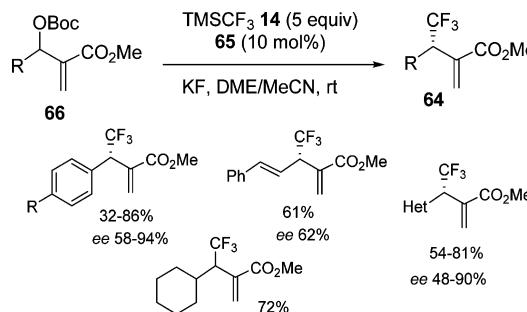
Scheme 21



A formal  $S_N2'$  (1,4-addition–elimination) with the formation of intermediate **63** followed by a successive  $S_N2'$  (1,4-addition–elimination) may explain the formation of allyl derivatives **64**. However, a complex mixture was obtained when a substrate **59** with alkyl substitution ( $R = tBu$ ) was used. Asymmetric allylic alkylation (AAA)<sup>75</sup> is one of the most powerful tools for making enantiomeric compounds. In this sense, enantioselective allylic trifluoromethylation of acetate adducts **59**<sup>74</sup> using, in this case, an excess of commercially available **14** ( $RPr$ ,<sup>47</sup> 5 equiv) and a bis-cinchona alkaloid **65** [((DHQD)<sub>2</sub>PHAL, 10 mol %] as catalyst (Scheme 21) has been achieved with moderate yields (37–60%) and good ee (88–94%).

Jiang et al.<sup>76</sup> proposed that Morita–Baylis–Hillman carbonates **66** may favor this process (Scheme 22). This

Scheme 22

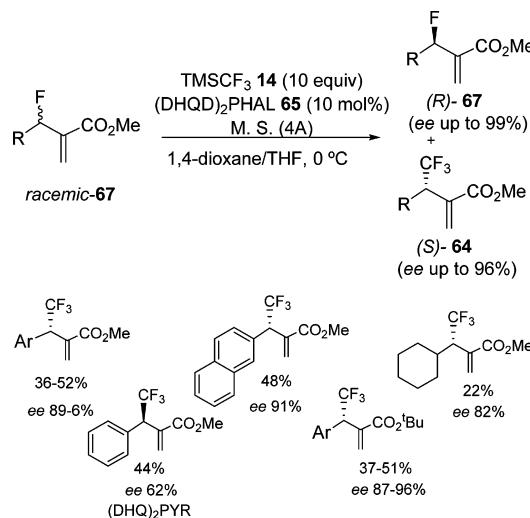


transformation provided the trifluoromethylated products **64** at room temperature with moderate-good yields and enantioselectivities (48–94% ee). Generally, electron-withdrawing groups on the aromatic ring facilitated the reaction, whereas electron-donating substituents retarded the process. It was also found that the reaction could be accelerated using acetonitrile as cosolvent, thus allowing an efficient enantioselective synthesis of this class of compounds at room temperature.

When sterically demanding cyclohexyl substrate **66** ( $R = \text{cyclohexyl}$ ) was employed, the corresponding product **64** ( $R = \text{cyclohexyl}$ ) was successfully isolated (Scheme 22). However, its enantioselective trifluoromethylation could not be achieved even under longer reaction times and at higher temperatures.

The first kinetic resolution of racemic Morita–Baylis–Hillman fluorides **67** and tandem trifluoromethylation of the *S*-enantiomer by means of an organocatalyzed enantioselective allylic trifluoromethylation has been described.<sup>77</sup> An excess of **14** ( $\text{RPr}$ )<sup>47</sup> and a bis-cinchona alkaloid **65** [ $(\text{DHQD})_2\text{PHAL}$ , 10 mol %] as organocatalyst (Scheme 23) was used, and not

Scheme 23

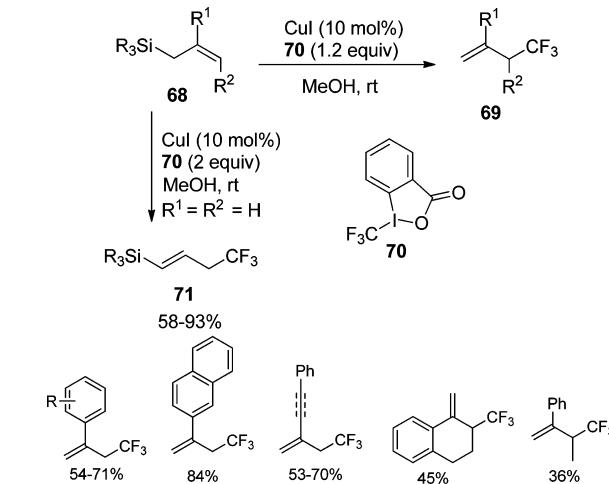


only (*R*)-allyl fluorides **67** ( $R = \text{Ar}$ ; 31–47%; ee 70–99%;  $R = \text{Cy}$ ; 54%; ee 22%), but also (*S*)-allyl trifluoromethylates **64** ( $R = \text{Ar}$ ; 36–51%; ee 87–96%;  $R = \text{Cy}$ ; 22%; ee 82%) with moderate yields and good ee were obtained. Moreover, the reaction of racemic allyl derivative **67** ( $R = \text{Ph}$ ) with alkaloid hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether [ $(\text{DHQD})_2\text{PYR}$ ] as catalyst instead of [ $(\text{DHQD})_2\text{PHAL}$ ] **65** led to the formation of the corresponding enantiomers (*S*)-allyl fluoride **67** ( $R = \text{Ph}$ ; 42%; ee 77%) and (*R*)-allyl trifluoromethylated **64** ( $R = \text{Ph}$ ; 44%; ee 62%). The authors proposed a three-step mechanism involving an initial activation of the carbon–fluorine (C–F) bond by coordination of the fluorine with the silicon atom of **14** ( $\text{RPr}$ ), followed by a kinetic resolution of the allylic fluorides and an organocatalyzed enantioselective trifluoromethylation of (*S*)-isomer in the presence of the alkaloid base [ $(\text{DHQD})_2\text{PHAL}$ ] **65** with formation of the corresponding (*S*)-allyl trifluoromethylated derivatives **64**.

**2.2.3. From Allyl Silanes.** In 2012, two research groups focused on allylsilane trifluoromethylation, hoping that their higher nucleophilicity as compared to nonsubstituted derivatives would increase the reactivity against electrophilic trifluoromethylating reagents. In that way, they envisaged surpassing the limitations of the methods for the direct allylic C–H bond activation, which are sensitive to the steric hindrance of the alkene and therefore mostly limited to monosubstituted terminal olefins (vide infra, section 2.2.4). Thus, the silyl group would work both by increasing the nucleophilicity of the alkene and as a regiodirecting group. In this respect, the first report on allylsilane trifluoromethylation was published by Sodeoka et al.<sup>78</sup> Allylsilanes **68** were

successfully trifluoromethylated using  $\text{CuI}$  (10 mol %) and the trifluoromethylating hypervalent iodine(III) derivative **70** (Togni's reagent,  $\text{TrI}$ )<sup>79,80</sup> at room temperature in methanol, to produce branched terminal olefins **69** and vinylsilanes **71** both containing a trifluoromethyl group in the allylic position (Scheme 24).

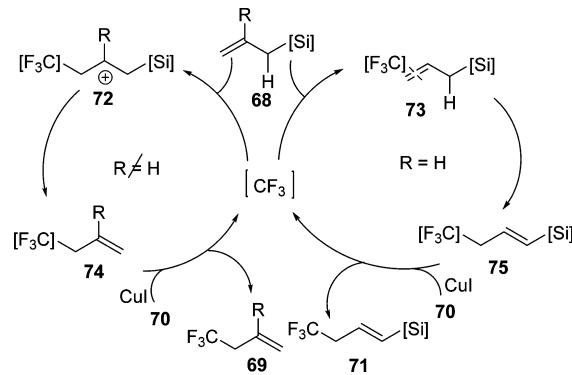
Scheme 24



The reaction worked well for 2-substituted allylsilanes **68** ( $R^1 = \text{H}$ ,  $R^1 = \text{Ar}$ , 2-naphthyl, alkenyl, alkynyl). However, when allylsilanes **68** with substituents in 2 and 3 positions were used,  $\alpha$ -substituted trifluoromethylallyl derivatives **69** ( $R^2 \neq \text{H}$ ) were obtained (Scheme 24), but the yields were poor. When simple allylsilanes **68** ( $R^1 = R^2 = \text{H}$ ) were employed as substrates under the same conditions, trifluoromethylation took place providing vinyl silanes **71** bearing a trifluoromethyl group at the allylic position.

The authors suggested that the active trifluoromethylation agent  $[\text{CF}_3]$  was generated by reaction of the copper catalyst with **70** ( $\text{TrI}$ )<sup>80</sup> and that the reaction of a 2-substituted allylsilane takes place via a cationic intermediate **72** (left cycle, Scheme 25) followed by releasing the silyl cation with the

Scheme 25



construction of the  $\text{C}=\text{C}$  bond. In the case of an allylsilane with no substituent at the 2-position, coordination of the olefin with iodonium cation or copper ion may occur first to produce **73** (right cycle, Scheme 25), and then deprotonation of the allylic hydrogen with formation of a species **75** may happen.

Finally, reductive elimination might give the product **71** via a C–CF<sub>3</sub> bond-construction.

Similar substrates have been studied by Gouverneur et al.<sup>81</sup> In this case, the trifluoromethylating system is a combination of 1.2 equiv of **70** (Tr1)<sup>80</sup> in the presence of CuCl (20 mol %) in methanol at 70 °C (Scheme 24). Allylsilanes **68** (R<sup>1</sup> = Ar, alkyl, alkenyl, R<sup>2</sup> = H, alkyl) with substituents in both 2 and 3 positions were disclosed, and yields up to 84% of trifluoromethylated compounds **69** with a wide range of substituents were reported (Figure 2). Both cationic and a radical mechanism could operate in parallel, progressing at different rates.

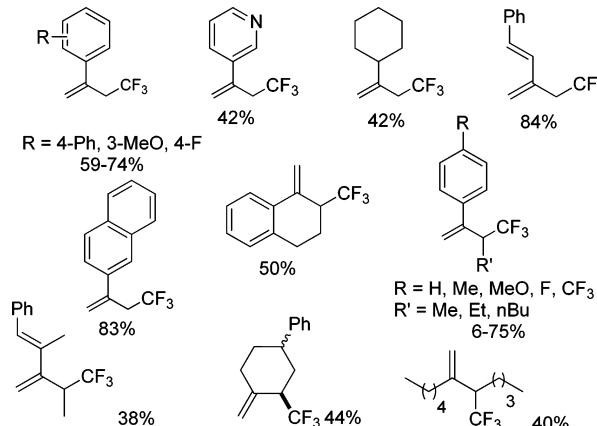


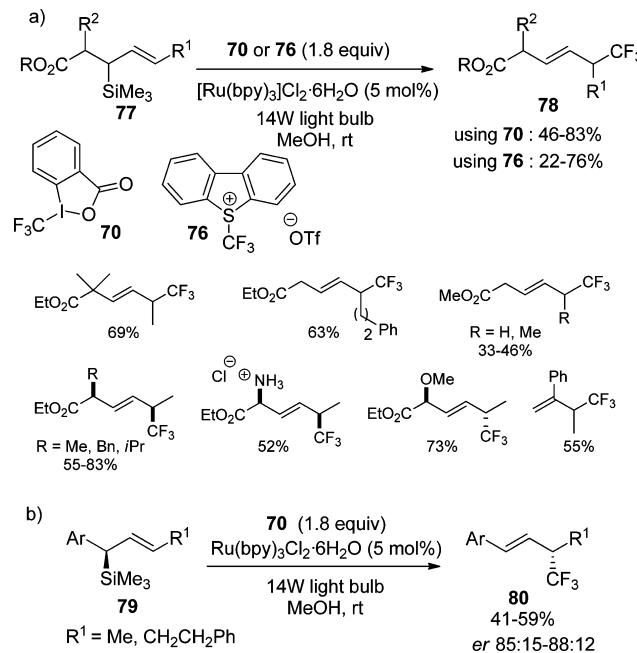
Figure 2. Trifluoromethylated compounds **69** from allylsilanes **68**.

The trifluoromethylation reaction under radical conditions has been studied for a long time, mainly with alkenes, alkynes, and aromatic compounds. Despite the trifluoromethyl radical not being highly specific, it shows a marked preference for sites of high electron density.<sup>82</sup> Principally, trifluoromethyl radical reacts with electron-rich aromatics and heteroaromatics (vide infra, sections 5.1 and 5.2), whereas radical trifluoromethylation at nonaromatic sites has been particularly difficult because the intermediates generated during trifluoromethylation reactions are unstable.<sup>32,40f</sup> The trifluoromethyl radical for atom transfer radical addition (ATRA) can be generated under oxidative, reductive, photochemical, thermal, and electrochemical conditions.

In 2013, a new catalytic method to access secondary allylic CF<sub>3</sub> products based on photoredox catalysis was described by Gouverneur et al.<sup>83</sup> These reactions use the visible light excited [Ru(bpy)<sub>3</sub>]<sup>2+</sup>Cl<sub>2</sub>·6H<sub>2</sub>O catalyst and **70** (Tr1)<sup>80</sup> or the sulphonium salt **76** (Umemoto reagent, Ur),<sup>84</sup> as the CF<sub>3</sub> source (Scheme 26).

Trifluoromethyl-substituted carboxylate **78** (R<sup>1</sup> = R<sup>2</sup> = H, 33%) and functionalized  $\alpha$ -substituted allyl derivatives **78** (R<sup>1</sup> = CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>Ph; R<sup>2</sup> = H, 55–69%) were obtained, when **70** was used, while **76** led to lower yields. The silyl group in the starting material **77** is an important entity to control the regio- and stereoselectivity of the trifluoromethylation, through the stabilization of a plausible  $\beta$ -carbocation intermediate. Furthermore, when departing from *anti*  $\alpha$ -substituted *E*-allylsilanes **77**, this photoredox catalytic system delivered mainly *syn* *E*-allylic trifluoromethylated products **78** containing ester, aminoester, or methoxyester, not accessible under Cu(I) catalysis (Scheme 26a). Enantiomerically enriched allylsilanes **79** were also explored, and the efficiency of chirality transfer

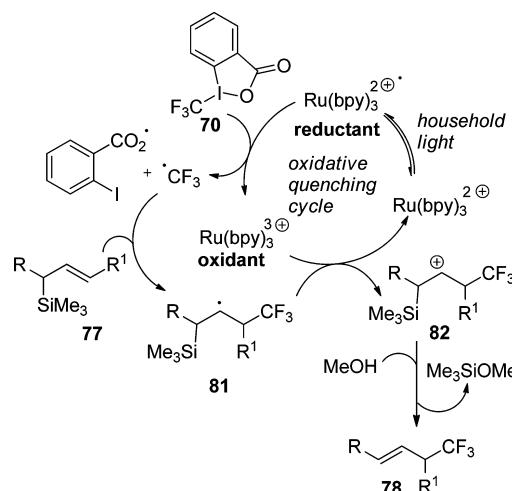
Scheme 26



upon trifluoromethylation was evaluated with enantiomeric ratios (er) ranging from 85:15 to 88:12 for allyl derivatives **80** (Scheme 26b).

The proposed mechanism of the process when **70** (Tr1) is used as CF<sub>3</sub> source may be a catalytic oxidative quenching cycle, as outlined in Scheme 27. The reduction of **70** and the

Scheme 27

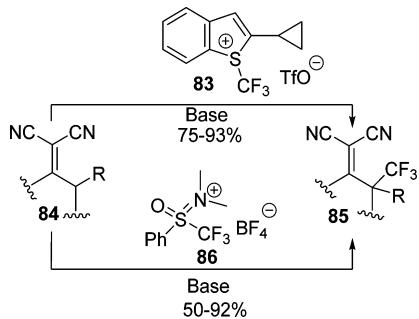


oxidation of Ru(bpy)<sub>3</sub><sup>2+</sup> to Ru(bpy)<sub>3</sub><sup>3+</sup> may occur simultaneously in a single electron transfer (SET) step to produce the electrophilic CF<sub>3</sub> radical, appropriate to give regio- and stereoselective addition to allylsilane **77** and deliver a radical species **81**. This intermediate **81** is then oxidized through a second SET by the strong oxidant Ru(bpy)<sub>3</sub><sup>3+</sup> with formation of the starting photocatalyst Ru(bpy)<sub>3</sub><sup>2+</sup>, giving rise to the stabilized  $\beta$ -silyl cation **82**. Finally, desilylation of **82** with methanol would afford allylsilane **78**. It is not clear what may be the mechanistic base for the different *E/Z* ratio obtained when different sources of CF<sub>3</sub> are used, although the authors could prove that neither the starting allylsilane **77** nor the

trifluoromethylated product **78** undergoes isomerization under the reaction conditions.

**2.2.4. Direct Allylic C–H Trifluoromethylation.** A thiophenium-type derivative **83** developed by Shibata and co-workers has been used to give trifluoromethylallylic compounds **85** (Scheme 28) with good yields, starting from specially

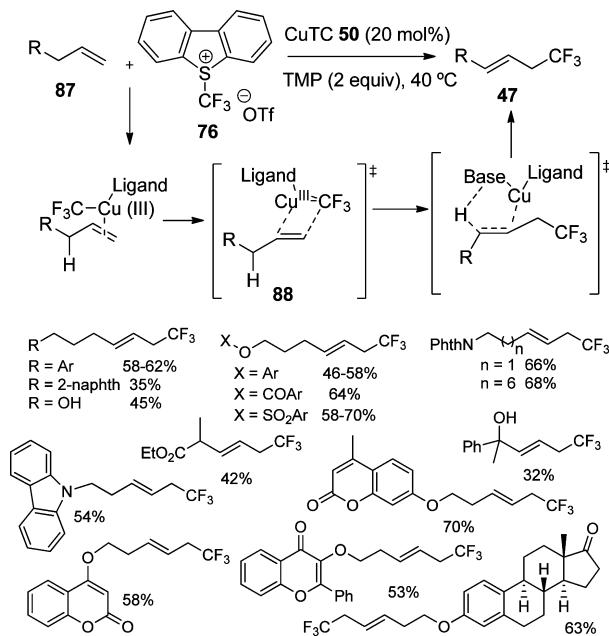
Scheme 28



activated substrates such as dicyano alkylidene substrates.<sup>85</sup> The same group also disclosed the synthesis of a sulfoximinium salt **86** (Scheme 28) as a trifluoromethylated version of the Johnson methyl-transfer reagent.<sup>86</sup> The reagent was also efficient in the trifluoromethylation of dicyanoalkylidenes **84** in the allylic position. In both processes, the metal-mediated contribution is not necessary.

An efficient direct allylic trifluoromethylation can be achieved by the combinations of Cu transition-metal catalysts, oxidants, and trifluoromethyl sources (oxidative trifluoromethylation) providing a general and straightforward way to synthesize allylic trifluoromethylated compounds under mild conditions. Oxidative allylic  $Csp^3$ –H bond activation of terminal alkenes **87** can be carried out with electrophilic reagent **76** (Ur), along with Cu(I) catalysis and 2,4,6-trimethylpyridine (TMP) as additive (Scheme 29).<sup>87</sup> CuI was not efficient for the reaction, and therefore **50** (CuTC) was used instead. The allyl trifluoro-

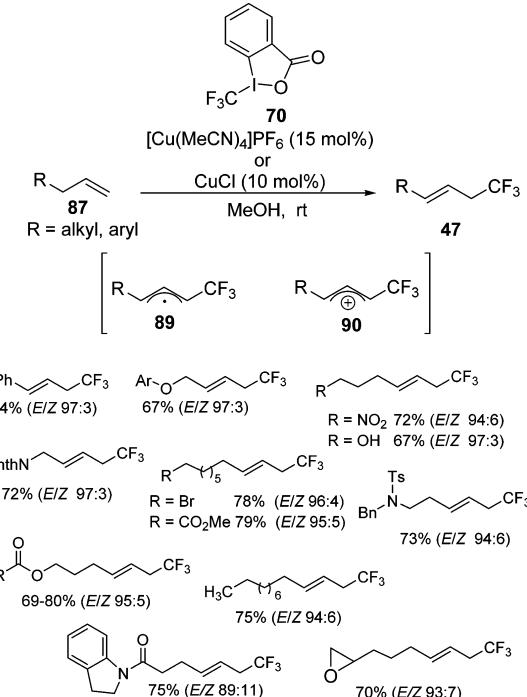
Scheme 29



methanes **47** can be obtained with moderate yields, and many different functional groups are tolerated in the mild conditions needed for the transformation. Both experimental tests and theoretical studies indicate that the Cu-catalyzed trifluoromethylation reaction may proceed through a Heck-like four-membered-ring transition state **88** by a mechanistically uncommon example of Cu-catalyzed allylic C–H activation/functionalization.

Nevertheless, the first successful results in the direct allylic trifluoromethylation with an electrophilic reagent were published by Buchwald et al.<sup>88</sup> by means of Cu-catalyzed reaction using electrophilic trifluoromethylating reagent **70** (Tr1)<sup>80</sup> instead of the aforementioned **76** and providing compounds **47** in good yields and regioselectivity (Scheme 30).

Scheme 30



Thus, addition of **70** (Tr1, 0.8 equiv)<sup>80</sup> to unactivated allyl compounds **87** in the presence of catalytic amounts of Cu(I) (10–15 mol %) afforded linear allylic trifluoromethyl derivatives **47** and good control over *E/Z* geometry (*E/Z* up to 97:3). The initial Cu(I) source was the Lewis acid CuCl, which activates **70** (Tr1) and whose subsequent replacement by [Cu(MeCN)<sub>4</sub>]PF<sub>6</sub> affords higher stereoselectivities. A very large range of functions can tolerate the mild reaction conditions, including ester, ether, nitro derivatives, alcohol, terminal epoxides, protected amines, amides, alkyl bromides, and haloarenes. Nevertheless, branched terminal alkenes and 1,2-disubstituted olefins, as well as cyclic substrates, failed to produce the CF<sub>3</sub> derivatives. For the reaction mechanism of this trifluoromethylation, according to previous reports, it is reasonable to conceive a pathway involving radical species **89**.<sup>89</sup>

Almost simultaneously, another method for direct allylic oxidative trifluoromethylation of **87** was published by Wang.<sup>90</sup> CuCl is a suitable catalyst in this transformation, and the use of the hypervalent iodine reagent **70** (Tr1)<sup>80</sup> provided the product **47** in good yields (Scheme 30). In this case, they used CuCl (10–20 mol %) and methanol (70–90 °C), and the ratio of

olefin **87** and trifluoromethylating reagent **70** (Tr1) ranged from 1:1.6 to 2:1. Many functional groups can survive the smooth reaction conditions including aldehyde, ester, amide, O-acyl- or O-sulfonyl alcohol, protected amine, haloarene, and even trifluoromethylated cycloalkanes were also obtained (Figure 3). A preliminary analysis of the authors suggests that

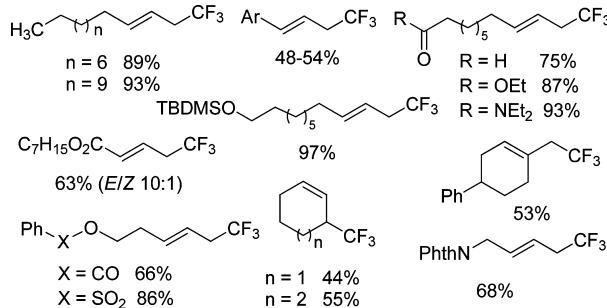
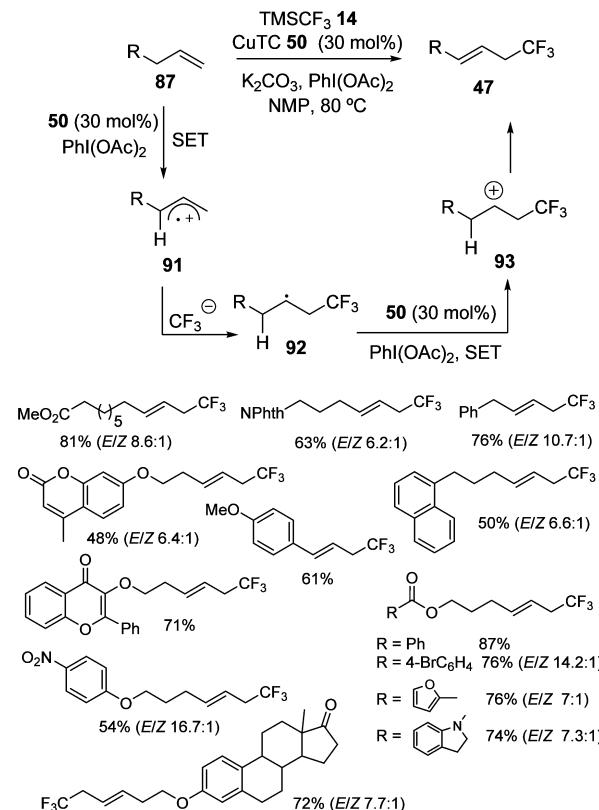


Figure 3. Trifluoromethylated compounds **47** obtained from olefins **87**.

the mechanism of the reaction may be complex and different pathways may be involved. Trapping experiments with the known radical scavenger 2,2,6,6-tetramethylpyridin-1-oxyl (TEMPO) suggested that  $\text{CF}_3$  radical intermediate **89** could be involved in the reaction mechanism, but further investigation showed that a carbocationic intermediate **90** (Scheme 30) is also plausible.

Another efficient  $\text{Csp}^3-\text{CF}_3$  bond-forming reaction via Cu-catalyzed **50** (CuTC) oxidative trifluoromethylation of terminal alkenes **87** (Scheme 31) has also been developed by Qing and co-worker.<sup>91</sup> The reaction proceeds under mild conditions

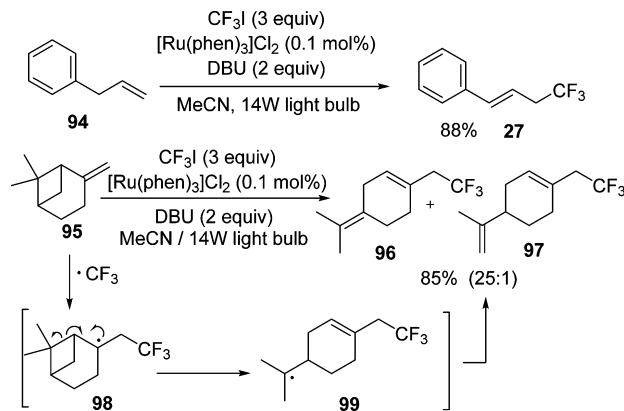
Scheme 31



using NMP as solvent, **14** ( $\text{RPr}$ )<sup>47</sup> as the source of the trifluoromethyl group, and  $\text{PhI}(\text{OAc})_2$  as oxidant, providing the linear allylic trifluoromethylated products **47**, and a wide range of functions are compatible with the process (Scheme 31). No product was observed in the presence of other oxidants such as 1,4-benzoquinone (BQ),  $\text{Ag}(\text{I})$  salts,  $\text{K}_2\text{S}_2\text{O}_8$ , Selectfluor, and even  $\text{PhI}(\text{OCOCF}_3)$ . A SET mechanism may operate in these oxidative trifluoromethylation transformations (Scheme 31), as it was proposed for the hypervalent iodine-induced functionalization of arenes.<sup>92</sup> In the presence of a Cu catalyst and  $\text{PhI}(\text{OAc})_2$ , the allyl derivative **87** might be oxidized to a radical cationic intermediate **91** via SET. Subsequent nucleophilic attack of the  $\text{CF}_3$  anion to the radical cation **91** would give rise to a radical intermediate **92**, which may be then oxidized to form cationic intermediate **93**. Finally, deprotonation of **93** would give the product **47**.

Trifluoromethyl radical addition to allyl benzene **94** was also reported by visible light photoredox catalysis with  $\text{CF}_3\text{I}$ , a base (DBU), and a ruthenium catalyst ( $[\text{Ru}(\text{phen})_3]\text{Cl}_2$ ) with the formation of allyl benzene **27** in excellent yield (Scheme 32).<sup>93</sup>

Scheme 32



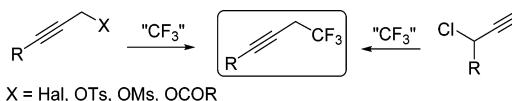
In this case, the formation of a conjugate system may be the driving force for the allyl trifluoromethylation. In similar reaction conditions, when  $\beta$ -pinene **95** was used, the process gave ring-opened dienes **96/97** (25:1). Addition of the  $\text{CF}_3$  radical to the alkene followed by radical rearrangement from intermediate **98** to **99** with final formation of the dienes may explain the process.

### 2.3. Propargylic Trifluoromethylation

The introduction of a trifluoromethyl group into a propargylic substrate is not an easy task, because the competitive formation of the corresponding allene derivatives is often observed.<sup>94</sup> Not only terminal propargyl halides ( $\text{X} = \text{Hal}$ ), tosylates ( $\text{X} = \text{OTs}$ ), mesylates ( $\text{OMs}$ ), or esters ( $\text{X} = \text{OCOR}$ ), but also secondary propargyl chlorides can be used as starting materials for propargylic trifluoromethylation (Scheme 33).

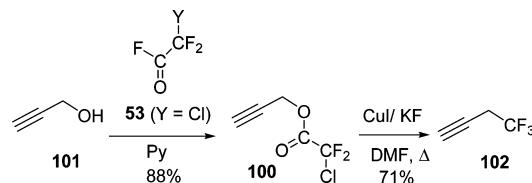
The first synthesis of trifluoromethylpropargyl derivatives involved the use of alcohols and acyl fluorides by means of a  $\text{Cu}(\text{I})$  iodide-initiated trifluoromethyl-dehydroxylation proc-

Scheme 33



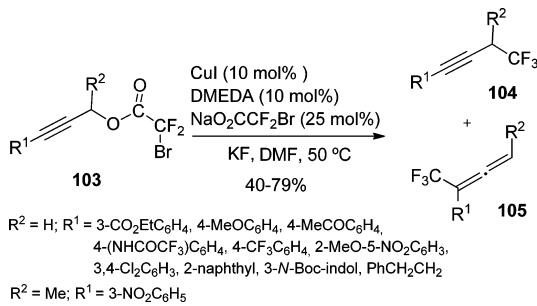
ess.<sup>71</sup> Propargyl ester **100** was prepared from the corresponding chlorodifluoroacetyl fluoride **53** ( $Y = Cl$ ) and propargyl alcohol **101** in the presence of pyridine (88%). Heating (100 °C) the difluoroacetate **100** in the presence of CuI and KF in DMF gave the corresponding trifluoromethyl compound **102** (Scheme 34). A mechanism similar to that shown in Scheme 18 (vide supra) may explain the formation of derivative **102**.

Scheme 34



A copper-catalyzed decarboxylative trifluoromethylation of propargyl bromodifluoroacetates has been used for the generation of a mixture of substituted propargyl trifluoromethanes **104** and allenyl derivatives **105**, making use of catalytic amounts of copper (Scheme 35).<sup>95</sup>

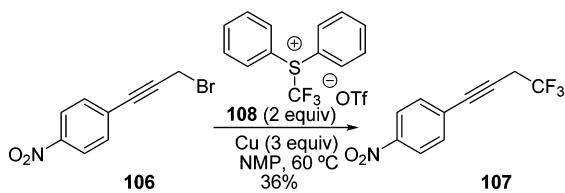
Scheme 35



The optimized catalyst system included the use of CuI, DMEDA as a ligand, BrCF<sub>2</sub>CO<sub>2</sub>Na, and KF (2 equiv). In the case of primary substrates **103** ( $R^2 = H$ ), the proportions of propargyl **104** versus allenyl derivatives **105** ranged from 2.1:1 to 6.3:1, and when the secondary propargyl ester **103** ( $R^2 = Me$ ,  $R^1 = 3\text{-NO}_2\text{C}_6\text{H}_4$ ) was used the conversion was low (41%) with a ratio 1.9:1 of the corresponding propargyl **104** and allenyl derivatives **105**.

Electrophilic trifluoromethylation of propargyl bromide **106** (Scheme 36)<sup>96</sup> was achieved using the sulfur-based electrophilic

Scheme 36

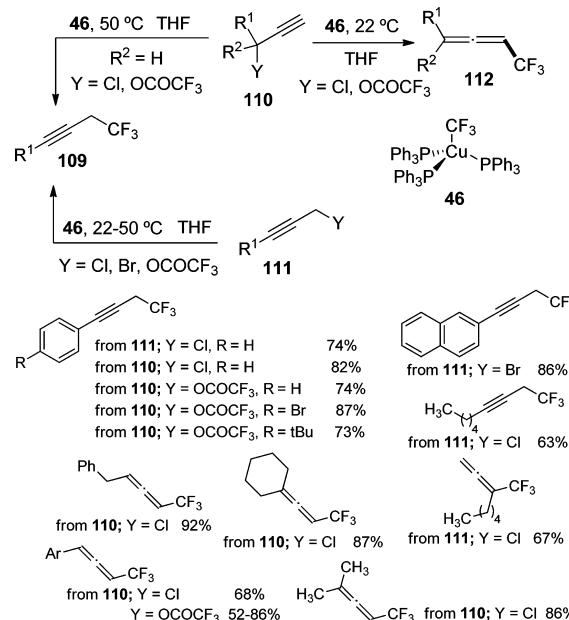


reagent **108**<sup>97</sup> and copper through in situ reductive generation of  $[\text{CuCF}_3]$  species, although low yield was obtained. However, the copper-catalyzed trifluoromethylation of propargyl acetates with the same trifluoromethylating agent **108** led to formation of trifluoromethylated allenes in excellent yields.<sup>98</sup>

Previous attempts to trifluoromethylate propargylic halides and tosylates<sup>94</sup> with  $[\text{CuCF}_3]$  complex generated by trans-

metalation of trifluoromethyl cadmium bromide with CuI produced allenes instead of propargyl trifluoromethylated derivatives.<sup>59</sup> However, trifluoromethylation of propargylic halides **110** and **111** with a  $[(\text{Ph}_3\text{P})_3\text{CuCF}_3]$  complex **46** leading to trifluoromethyl derivatives **109** with high propargyl selectivity has been reported by Szabo et al. (Scheme 37).<sup>99</sup>

Scheme 37

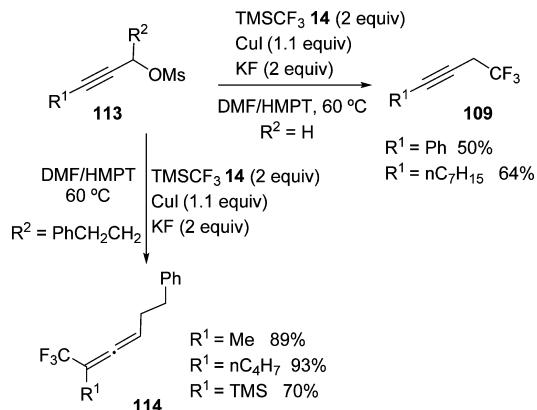


These derivatives can be obtained not only from branched propargylic chlorides **110** ( $Y = Cl$ ,  $R^1 = Ph$ ,  $R^2 = H$ ), but also from linear propargyl halides **111** with aryl ( $Y = Cl$ ,  $R^1 = Ph$ ), naphthyl ( $Y = Br$ ,  $R^1 = 2\text{-naphthyl}$ ), or alkyl ( $Y = Cl$ ,  $R^1 = C_3H_{11}$ ) substituents. Propargyl trifluorooacetates **111** ( $Y = OCOCF_3$ ) reacted under reaction conditions similar to those of their corresponding halides and proceeded smoothly and selectively in the presence of both electron-withdrawing and -donating substituents on the aromatic ring. However, the reaction of branched aryl propargylic derivatives **110** at room temperature instead of 50 °C gave the allenyl product **112**. Furthermore, enantiopure trifluoromethylallene **112** ( $R^1 = Ph$ ,  $R^2 = H$ , 70%, ee 89%) can be obtained from the trifluorooacetate of chiral propargylic alcohol **110** ( $Y = OCOCF_3$ ;  $R^1 = Ph$ ,  $R^2 = H$ , R isomer: 90% ee). Preliminary mechanistic results indicate an ionic mechanism involving nucleophilic transfer of the CF<sub>3</sub> group from the Cu complex to the propargylic substrate. This could be explained by an initial formation of the corresponding allene isomer, which is rearranged to the propargylic one.

An efficient copper-catalyzed trifluoromethylation of propargyl mesylates **113** ( $R^2 = H$ ) with **14** ( $RPr$ )<sup>47</sup> was achieved for the preparation of aromatic and aliphatic linear trifluoromethylpropargyl derivatives **109** (Scheme 38).<sup>66</sup> Aromatic ( $R^1 = Ph$ ) and aliphatic ( $R^1 = n\text{C}_7\text{H}_{15}$ ) linear propargyl derivatives **109** were obtained in moderate yields from the corresponding propargyl mesylates **113**. However, the treatment of branched propargyl mesylates **113** ( $R^2 = CH_2CH_2Ph$ ) with **14** ( $RPr$ )<sup>47</sup> in similar reaction conditions gave exclusively the trifluoromethylated allenes **114** instead of the corresponding substituted propargyl derivatives.

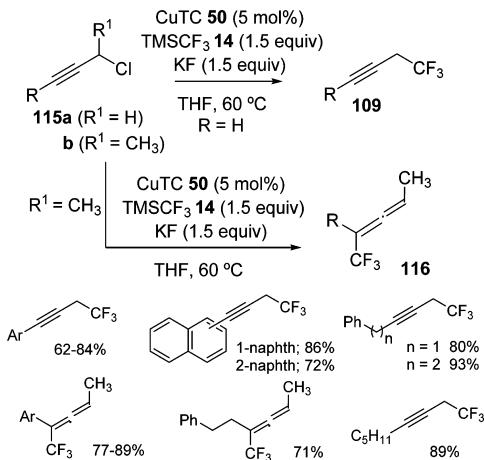
The first catalytic nucleophilic trifluoromethylation of propargylic halides by Shibata et al. has been reported.<sup>100</sup>

Scheme 38



They used reagent **14** (RPr)<sup>47</sup> and KF as CF<sub>3</sub> source and in the presence of catalytic amounts of **50** (CuTC, Scheme 39). When

Scheme 39



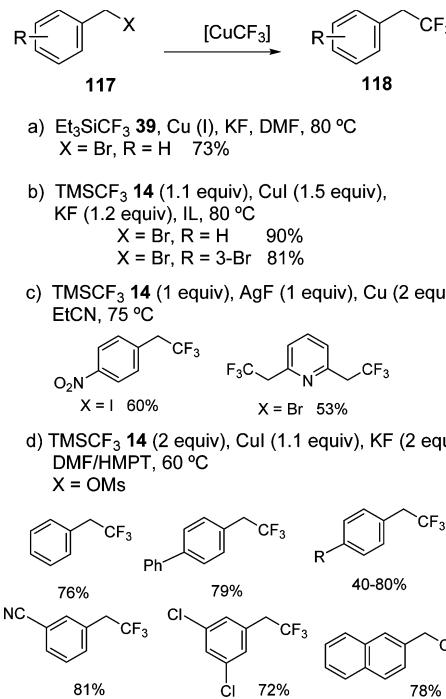
primary propargylic chlorides **115a** (R<sup>1</sup> = H) were used, the corresponding propargylic trifluoromethylated products **109** were obtained in good yields. However, when the process was extended to secondary propargylic halides **115b** (R<sup>1</sup> = CH<sub>3</sub>), in similar reaction conditions, trifluoromethylated allenes **116** were obtained. No chirality transfer was detected when an optically active secondary propargylic chloride **115b** (R isomer, R = Ph) was used, because a complete loss of optical purity was observed. This behavior seems to indicate that this catalytic process involves cationic propargyl/allenyl complexes as reactive intermediates.

#### 2.4. Benzylic Trifluoromethylation

Benzylic trifluoromethylation of benzyl halides has been addressed for a long time by using [CuCF<sub>3</sub>] species prepared in different ways, all having in common the use of CF<sub>3</sub>-containing nucleophilic reagents and some form of copper. Trifluoromethylation of simple benzyl bromide with a trifluoromethyl copper complex prepared either from CF<sub>3</sub>Cl and Cu powder in HMPA (65%)<sup>42</sup> or by electroreduction of CF<sub>3</sub>Br in DMF in the presence of a Cu anode (X = Br, 83%; X = Cl, 50%)<sup>60</sup> or from Hg(CF<sub>3</sub>)<sub>2</sub> and copper metal (R = p-NO<sub>2</sub>, X = Br)<sup>101</sup> has been reported. Methyl 3-oxa- $\omega$ -fluorosulfonylperfluoropentanoate<sup>62</sup> in the presence of CuI and methyl halodifluoroacetate<sup>61</sup> with CuI and KF have also been used as sources of a trifluoromethyl group, which replaces the halogen

in benzyl halides. Furthermore, nucleophilic reagents such as trifluoromethyltriethylsilane **39** with the aid of the fluoride ion as activator showed the ability for the cross-coupling reaction with benzyl bromide, in the presence of Cu(I) salts under mild reaction conditions, to give the corresponding trifluoromethylated product **118** in good yield (Scheme 40a).<sup>64</sup> An increase of the yield up to 90% has been reported by using **14** (RPr)<sup>47</sup> and KF in ionic liquids (IL) as reaction media (Scheme 40b).

Scheme 40

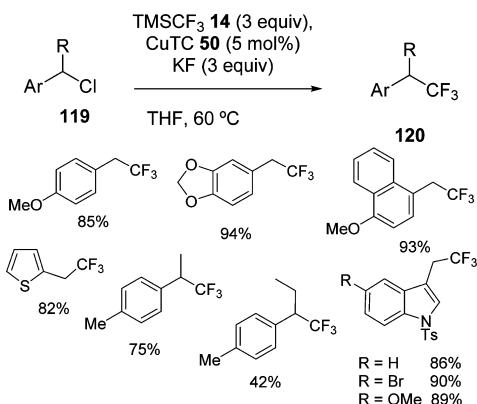


Another method to obtain [CuCF<sub>3</sub>] reagent has been developed via the reaction of silver fluoride and **14** (RPr) followed by a redox transmetalation with elemental copper. This trifluoromethyl copper exhibits excellent selectivity in the substitution of iodine and bromine atoms at sp<sup>3</sup> hybridized carbon atoms (Scheme 40c), and it is also suitable to introduce trifluoromethyl groups into the benzylic position of pyridines.<sup>102</sup>

Mesylates **117** (X = OMs) can also be used for the trifluoromethylation of benzylic substrates by means of [CuCF<sub>3</sub>] reagent. This Cu-mediated (CuI) trifluoromethylation of benzyl methanosulfonates **117** can be performed using **14** (RPr)<sup>47</sup> and KF (Scheme 40d). The scope of this approach is very wide, and not only benzyltrifluoromethane but also products with aryl groups containing electron-withdrawing groups (nitro, cyano, ester, trifluoromethyl) or halogens (Cl, Br) can be obtained.<sup>66</sup>

Copper-catalyzed nucleophilic trifluoromethylation of benzyl chlorides **119** for the preparation of benzyltrifluoromethanes **120** (Scheme 41) has been also described.<sup>103</sup> Reagent **14** (RPr)<sup>47</sup> was used as trifluoromethyl source in the presence of catalytic amounts of **50** (CuTC), and good yields were obtained by the reaction of primary carbocyclic benzylic substrates and 1,1,1-trifluoromethyl heterocycles such as thiophene or indol. However, the transformation of secondary benzyl chlorides **119** (R = Me, Et) into the corresponding trifluoromethylated products is restricted to benzylic substrates

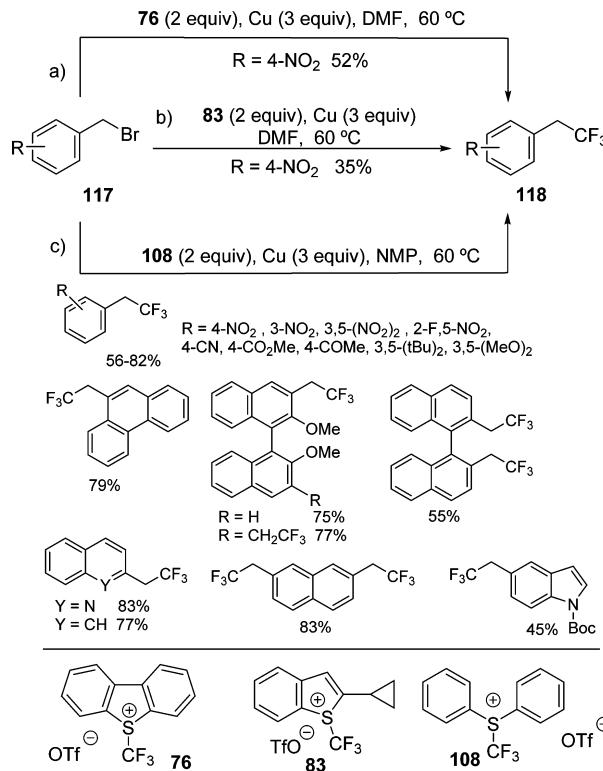
Scheme 41



bearing an electron-donating group. The authors suggested a cationic benzyl-copper intermediate to explain the process.

A similar transformation has also been achieved using sulfur-based electrophilic reagents and copper through in situ reductive generation of  $[\text{CuCF}_3]$  species.<sup>96</sup> Thus, while trifluoromethylsulfoximinium salt **86** did not produce the derivatives **118**, not only reagent **76** ( $\text{Ur}^{84}$ ) but also benzothiophenium salt **83** provided the benzylic trifluoromethylated compounds **118** with low-moderate yields (Scheme 42a,b).

Scheme 42



However, after optimization of the reaction conditions, the best results were obtained with diphenylsulfonium salt **108** (Scheme 42c). Functional groups like ester, ketone, nitrile, nitro, or fluorine tolerate the conditions well, together with indol and quinoline heterocyclic moieties. Nevertheless, the main limitations of the method are that only primary benzyl

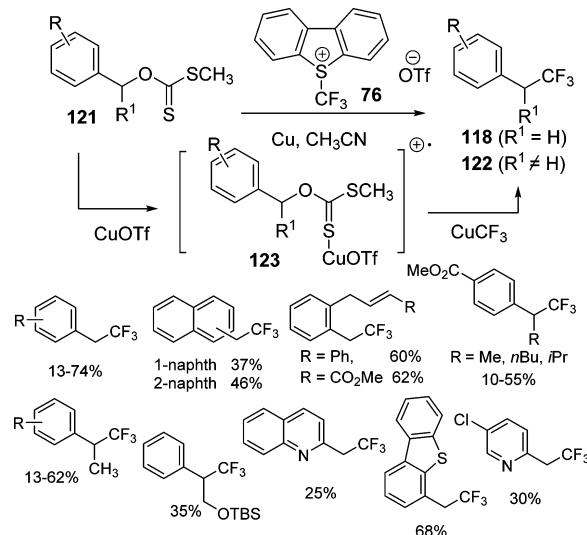
bromides **117** can react, and 3 equiv of Cu and 2 equiv of trifluoromethyl electrophilic reagents are needed.

Finally, in 2012, Prakash et al. reported benzylic trifluoromethylation reaction of benzyl bromide with fluoroform ( $\text{HCF}_3$ ) in  $\text{THF}$  and in the presence of potassium hexamethyldisilazide (KHMDS), although in low yield (10%).<sup>104</sup>

In addition to haloderivatives, dehydroxylation-trifluoromethylation of benzyl alcohols with copper-dibromodifluoromethane has been also reported, but with low yields,<sup>105</sup> while thermal decomposition of substituted difluoroacetates derived from benzyl alcohols in the presence of  $\text{CuI}$  and  $\text{KF}$  in  $\text{DMF}$  gave the corresponding trifluoromethylbenzyl derivatives in good yields.<sup>71</sup>

Copper-mediated deoxygenative trifluoromethylation of benzyl alcohol derivatives such as xanthates **121** was also reported for the preparation of benzyltrifluoromethanes **118** and **122** (Scheme 43).

Scheme 43

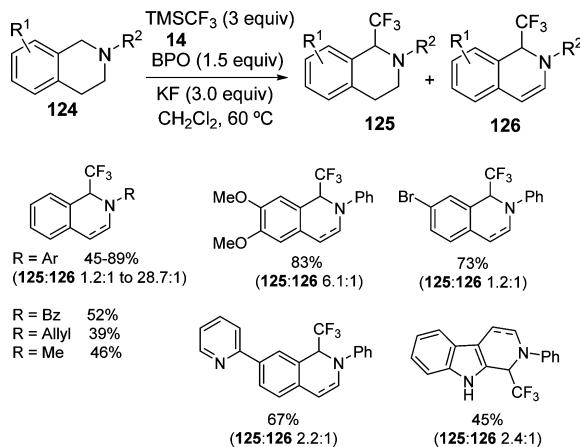


Reagent **76** ( $\text{Ur}^{84}$ ) was used as trifluoromethyl source along with copper powder and a polar aprotic solvent. Moderate-good yields were obtained when benzylic xanthates **121** ( $\text{R}^1 = \text{H}$ ) containing weak and strong electron-withdrawing groups were used, and the process tolerates alkenes in *ortho* position as well as heterocycles.<sup>106</sup> The reaction can be applied to  $\alpha$ -branched benzylic xanthates **121** ( $\text{R}^1 \neq \text{H}$ ), and a cationic radical compound **123** was suggested as an intermediate in the transformation.

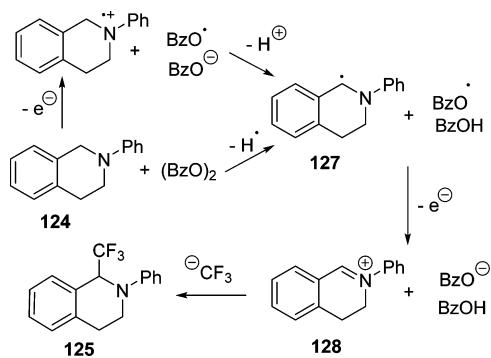
Besides benzyl halide or xanthate substitution, a simple synthetic method, such as the direct trifluoromethylation of the benzylic position in nitrogenated heterocycles via  $\text{Csp}^3-\text{H}$  activation promoted by benzoyl peroxide (BPO) and without transition metal, has been developed by Qing et al.<sup>107</sup> Hence, by treatment of 1,2,3,4-tetrahydroisoquinoline **124** with **14** ( $\text{RPr}^{47}$ )/ $\text{KF}$ , various 1-trifluoromethylated tetrahydroisoquinoline derivatives **125** and **126** were prepared (Scheme 44).

Although the detailed mechanism remains to be elucidated, Qing et al.<sup>107</sup> indicated that a radical intermediate **127** (Scheme 45) was probably formed by hydrogen transfer via either of two different pathways. Electron transfer from radical **127** gave iminium compound **128**, and the subsequent nucleophilic

Scheme 44



Scheme 45



capture of this intermediate 128 by  $\text{CF}_3^-$  anion afforded the isoquinoline derivative 125.

An alternative procedure was developed by Tan's group<sup>108</sup> by means of visible light-induced (using light emitting diodes, LEDs) oxidative C–H functionalization of tertiary amines catalyzed by the combination of graphene oxide (GO) and Rose Bengal (RB). The process was applied to tetrahydroisoquinoline 124 ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{PMP}$ ), and trifluoromethylated *N*-aryltetrahydroisoquinoline product 125 was obtained (75%). In this case, a significant amount (not disclosed) of the byproduct trifluoromethylated *N*-aryldihydroisoquinoline 126 was also obtained.

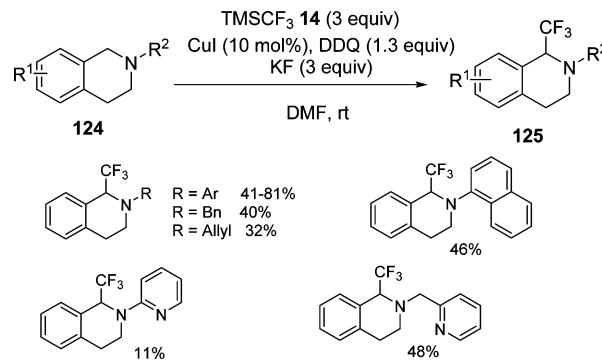
Li and Mitsudera also reported<sup>109</sup> a highly efficient copper-catalyzed trifluoromethylation via oxidative  $\text{Csp}^3$ –H activation of the  $\alpha$ -position to nitrogen in tetrahydroisoquinoline derivatives 124 using DDQ and 14 ( $\text{RPr}$ )<sup>47</sup> under very mild conditions (Scheme 46). The reactions of various tetrahydroisoquinoline derivatives 124 ( $\text{R}^1 = \text{H}$ ) gave the corresponding trifluoromethylated products 125.

### 2.5. Trifluoromethylation of Alkenes

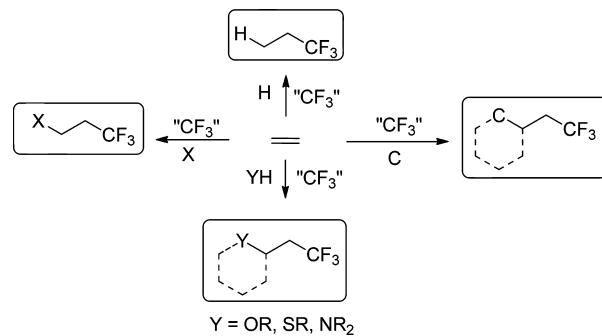
Trifluoromethylated alkanes<sup>110</sup> can also be obtained by hydro- and carbotrifluoromethylation of alkenes, while trifluoromethyl derivatives with a variety of functional groups in  $\beta$  position can be obtained by halo-, oxy-, thio-, and aminotrifluoromethylation (Scheme 47).

This is a frontline research field because in most cases it allows the difunctionalization of vicinal carbons with simultaneous formation of  $\text{C}-\text{CF}_3$  and  $\text{C}-\text{Hal}$ ,  $\text{C}-\text{H}$ ,  $\text{C}-\text{C}$ ,  $\text{C}-\text{O}$ ,  $\text{C}-\text{S}$ , or  $\text{C}-\text{N}$  bonds. Therefore, in a 1-year period, several reviews dealing with the trifluoromethylation of alkenes to

Scheme 46



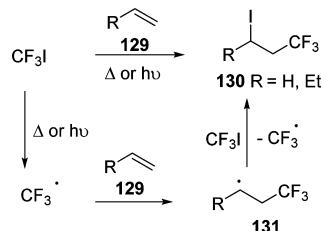
Scheme 47



provide highly and differently functionalized trifluoromethyl derivatives have been published, thus showing the growing interest of this strategy.<sup>111</sup> These reactions seem to take place mainly through a radical pathway. As we stated previously, trifluoromethyl radical may be generated oxidatively, reductively, thermally, photochemically, or electrochemically and the intermolecular ATRA to alkenes yielding trifluoromethyl alkanes as it has been previously reviewed.<sup>32,40f</sup>

**2.5.1. Halotrifluoromethylation of Alkenes.** Pioneering works of Haszeldine<sup>112</sup> reported that  $\text{CF}_3$  radicals are generated from  $\text{CF}_3\text{I}$  through C–I bond homolysis upon irradiation or heating. Formation of 3-iodo-1,1,1-trifluoropropane 130 ( $\text{R} = \text{H}$ ) from 129 ( $\text{R} = \text{H}$ , Scheme 48) through a radical

Scheme 48

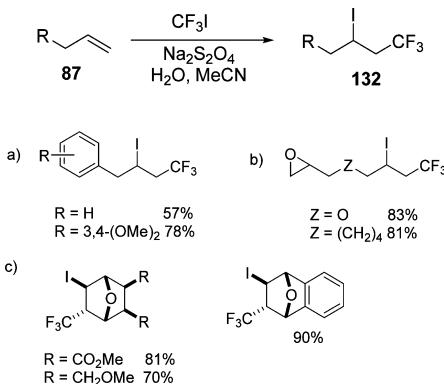


intermediate 131 was reported, while in the case of 129 ( $\text{R} = \text{Et}$ ) terminal trifluoromethyl alkanes 130 ( $\text{R} = \text{Et}$ ) were obtained as the major product resulting from an ATRA reaction. Reaction with internal *Z* and *E* alkenes 129 gave the *erythro*- and *threo*-addition products along with the corresponding dehydroiodination compounds.

Different reagents have been used for radical trifluoromethylation processes. Zupan reported the reaction of styrene with xenon difluoride in the presence of trifluoroacetic acid with the formation of a mixture of trifluoromethylated

products.<sup>113</sup> Furthermore, trifluoromethyl halides in the presence of triethylborane,<sup>114</sup> transition metal catalysts such as iron, cobalt, and ruthenium carbonyl derivatives,<sup>115</sup> or promoters such as sodium dithionite<sup>116</sup> have been used as precursors of trifluoromethyl radicals in addition reactions over alkenes. Dmowski used the latter approach more recently to trifluoromethylate terminal unactivated alkenes in allylbenzenes 87 (R = Ar) in a regioselective fashion (Scheme 49a),<sup>117</sup> to give

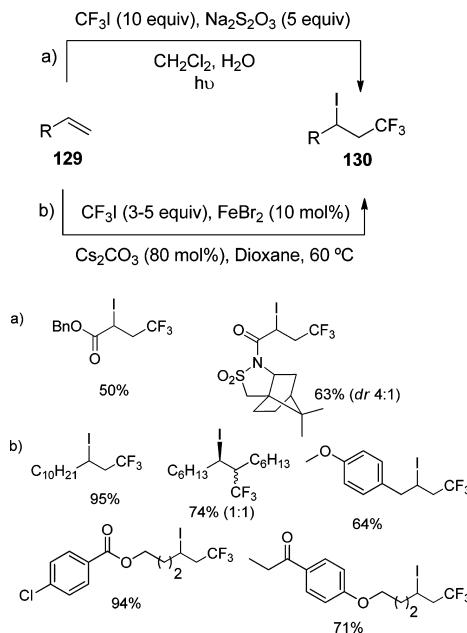
Scheme 49



iodotrifluoromethylated derivatives 132 (R = Ar), which in the presence of DBU can originate allyl- or vinyltrifluoromethyl compounds after  $\beta$ -elimination of HI. Similarly, Bazhin applied the method to the preparation of fluorinated polyethers and oxiranes 132 (Scheme 49b),<sup>118</sup> and Ponomarenko et al. extended it to the iodotrifluoromethylation of internal alkenes in oxanorbornene derivatives, in the course of a synthesis of CF<sub>3</sub>-substituted arenes (Scheme 49c).<sup>119</sup>

Thiosulfate, the reduced product of dithionite, has been also used for the addition of trifluoromethyl iodide to electron-deficient alkenes 129 under UV irradiation, although the yields of trifluoroalkyl derivatives 130 were moderate (Scheme 50a).<sup>120</sup> The use of iron catalyst provided better results over

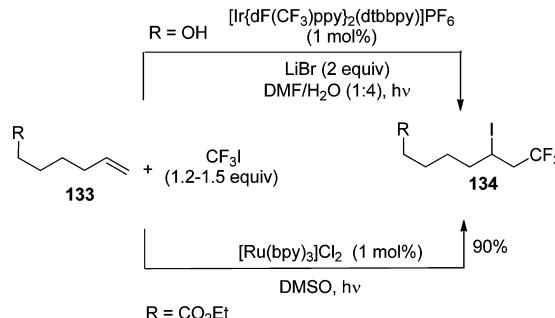
Scheme 50



nonactivated alkenes 129 (Scheme 50b).<sup>121</sup> Internal alkenes also worked well, and the functional groups compatible with the reaction conditions included ester, ether, and ketone. Furthermore, this procedure can be extended to the iodotrifluoromethylation of alkynes (vide infra, section 3.2.1).

Iridium- and ruthenium-containing photoredox catalysts have been employed in the visible light-mediated ATRA of trifluoromethyl iodide onto unactivated alkenes 133 (Scheme 51) such as 5-hexen-1-ol (R = OH) or ethyl 6-heptenoate (R =

Scheme 51



CO<sub>2</sub>Eт) using the oxidative quenching of [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(dtbbpy)]PF<sub>6</sub> or [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> electron donors.<sup>122</sup> However, excess CF<sub>3</sub>I, high boiling solvents (DMF, DMSO), and long irradiation times (48 h) were required for good yields.

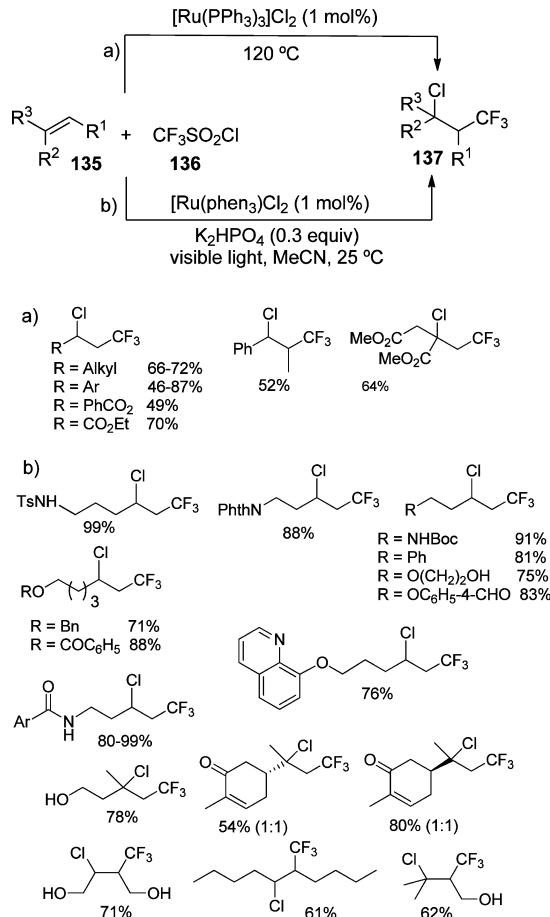
Reagents other than trifluoromethyl iodide have been used for the preparation of halotrifluoromethyl derived from olefins. Thus, trifluoromethanesulfonyl chloride 136 in the presence of ruthenium(II) phosphine complex has been used to introduce the CF<sub>3</sub> group onto alkenes 135 (Scheme 52) to give chlorotrifluoromethyl derivatives 137.<sup>123</sup> This reaction is not restricted to electron-rich alkenes because good results were also achieved with acrylates as radical acceptors, thus documenting the broad scope of this process. The previous method for the chlorotrifluoromethylation has been improved and extended to a big range of unactivated olefins including mono-, di-, and trisubstituted alkenes, by using a different ruthenium(II) complex (Scheme 52b).<sup>124</sup>

In these reactions, the Ru(II) complex first abstracts a chlorine atom from CF<sub>3</sub>SO<sub>2</sub>Cl 136 (Scheme 53) to give a [Ru(III)Cl] complex along with the CF<sub>3</sub>SO<sub>2</sub> radical 139, which undergoes SO<sub>2</sub> elimination to furnish the CF<sub>3</sub> radical. Next, addition to the alkene 129 provides the adduct radical 131, which in turn abstracts a chlorine atom from the [Ru(III)Cl] complex to finally provide product 138 and the starting Ru(II) complex.

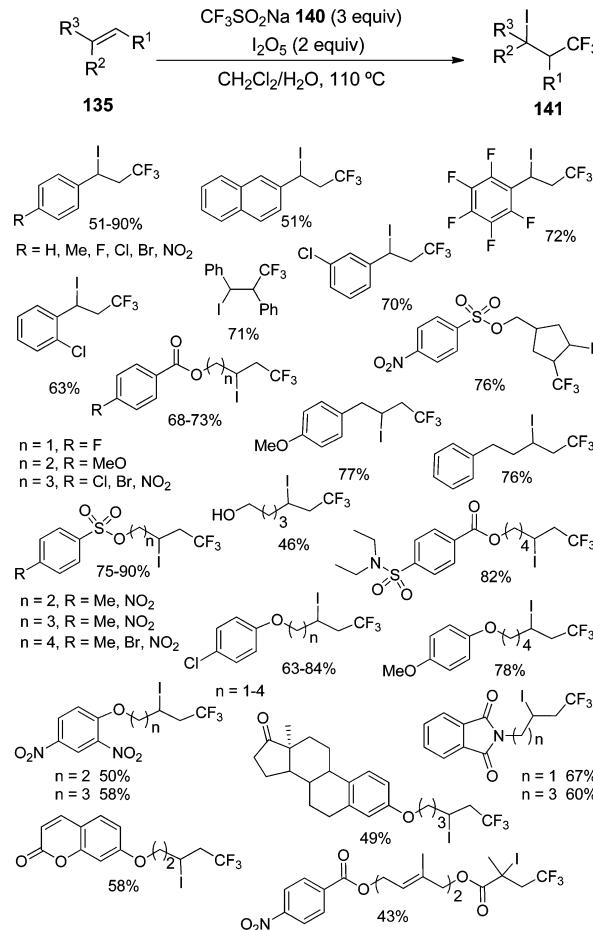
The analogous sulfonyl bromide, obtained by reaction of sodium trifluoromethylsulfonate and bromine, has also been used in the addition to alkenes, through a radical mechanism, to afford bromotrifluoromethyl derivatives.<sup>125</sup>

Finally, a practical method that does not use gaseous CF<sub>3</sub>I neither metal catalysis has been disclosed for the iodotrifluoromethylation of a wide range of alkenes 135 for the preparation of iodotrifluoromethyl-functionalized compounds 141 (Scheme 54).<sup>126</sup> The trifluoromethylating reagent is sodium trifluoromethanesulfinate, Langlois' reagent 140 (Lr),<sup>127</sup> along with iodine pentoxide, both easily managed solid compounds. The reaction takes place in water, through a radical mechanism providing the iodotrifluoromethyl difunctionalized addition products containing many different func-

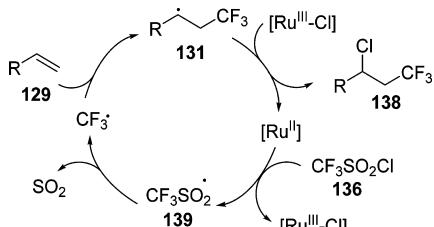
Scheme 52



Scheme 54



Scheme 53

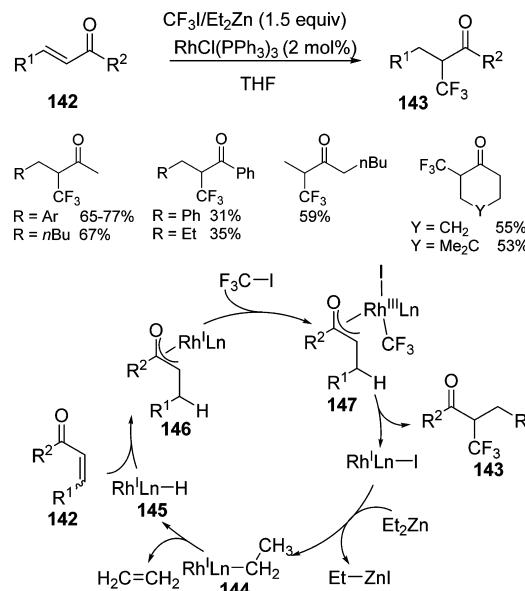


tional groups with good yields. Similar conditions can be applied to the iodotrifluoromethylation of alkynes (vide infra, section 3.2.1).

**2.5.2. Hydrotrifluoromethylation of Alkenes.** **2.5.2.1. Electron-Poor and Electron-Rich Alkenes.** Some examples of hydrotrifluoromethylation of alkenes have been described. For instance, electrochemical hydrotrifluoromethylation of fumaronitrile<sup>128</sup> or dialkyl fumarates<sup>129</sup> gave monotrifluoromethylated compounds.

The treatment of  $\alpha,\beta$ -unsaturated ketones **142** with CF<sub>3</sub>I in the presence of Et<sub>2</sub>Zn and RhCl(PPh<sub>3</sub>)<sub>3</sub> gave  $\alpha$ -trifluoromethylated products **143** with the regioselective introduction of CF<sub>3</sub> group at the  $\alpha$ -position (Scheme 55).<sup>130</sup> The mechanism proposed by the authors starts with the combination of the rhodium catalyst and diethylzinc to give the complex **144**, which decomposes, releasing ethene to give a Rh(I)-H species **145** (Scheme 55). The hydrogen is then transferred to the  $\beta$ -position of the enone (1,4-addition), followed by oxidative

Scheme 55

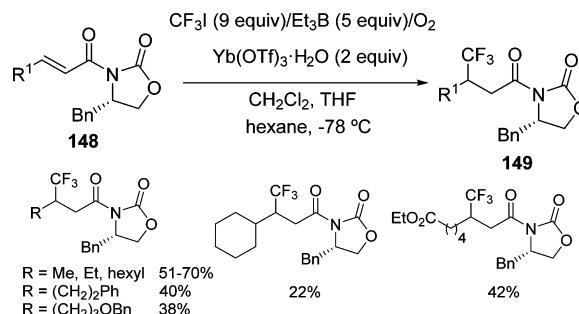


addition of the rhodium complex **146** to the trifluoromethylating agent and reductive elimination of the rhodium complex **147**.<sup>40d,131</sup>

In 2012, a novel conjugate hydrofluoroalkylation of  $\alpha,\beta$ -unsaturated acyl-oxazolidinones **148** to give **149** by means of radical conjugate trifluoromethylation reaction with CF<sub>3</sub>I and

triethylborane as radical initiator was described (dr 1:1, Scheme S6).<sup>132</sup> According to the mechanistic proposal made by the

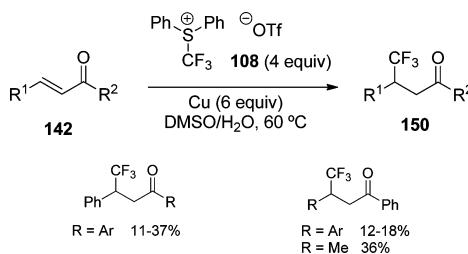
Scheme 56



researchers, after trifluoromethyl radical formation and subsequent conjugate addition to the acyloxazolidinone, a diethylboron enolate would form and rapidly hydrolyze in the presence of water to give the product **149**. The formation of this transient enolate would account for the lack of stereo-selectivity of the reaction. Nevertheless, separation of diastereoisomers, diastereoselective amination, and hydrolysis gave rise to enantiomerically pure  $\beta$ -trifluoromethylated  $\alpha$ -amino acids.

Alternatively, the electrophilic reagent trifluoromethyl diphenylsulfonium salt **108**<sup>97</sup> and Cu can also be used for the conjugate addition, in this case onto  $\alpha,\beta$ -unsaturated ketones **142** under mild conditions, although the yields are low (Scheme S7).<sup>133</sup> According to some experiments carried out

Scheme 57

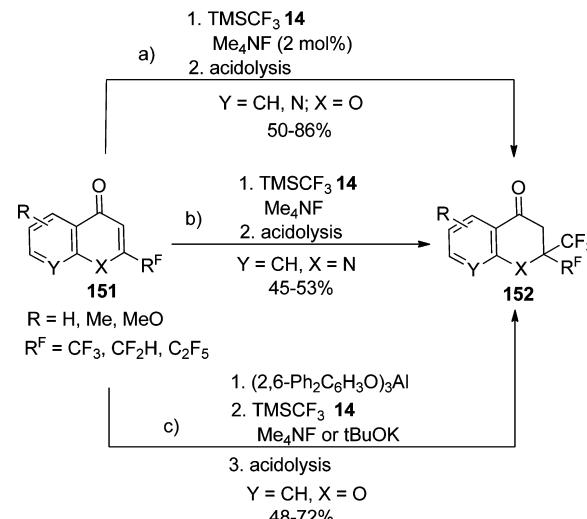


by the authors, a SET process between salt **108** and Cu followed by decomposition of the intermediate would provide a  $\text{CF}_3$  radical. This radical may react directly with the  $\alpha,\beta$ -unsaturated ketone or, more feasibly taking into account the high regioselectivity observed, may form a  $[\text{CuCF}_3]$  species before the conjugate addition.

Hydrotrifluoromethylation of several cyclic  $\alpha,\beta$ -enones has also been achieved using **14** ( $\text{RPr}$ ).<sup>47</sup> Hence, the reaction of fluorine-containing chromones **151** ( $\text{Y} = \text{CH, X} = \text{O}$ ) with **14** ( $\text{RPr}$ ) carried out in the presence of  $\text{Me}_4\text{NF}$  (2 mol %) led to addition products **152** (Scheme 58a), setting up the first regioselective 1,4-trifluoromethylation of an enone, although in some cases 1,2-addition products were also detected.<sup>134</sup> The same procedure was applied to 8-azachromones **151** ( $\text{Y} = \text{N, X} = \text{O}$ ), and a mixture of 1,4-addition **152** and 1,2-addition products in a 55:45 ratio was obtained (Scheme 58a).<sup>135</sup>

However, the regioselectivity completely changed in favor of the 1,2-addition reaction when a phenyl group was present in the  $\beta$  position of the chromone **151** ( $\text{R} = (\text{OH})_2, \text{R}^1 = \text{Ph}, \text{Y} = \text{CH, X} = \text{O}$ ), instead of the fluoroalkyl moiety, probably due to

Scheme 58



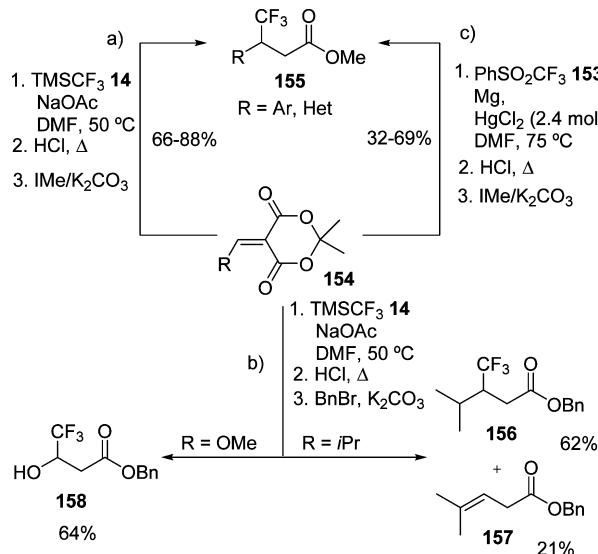
steric hindrance,<sup>136</sup> whereas the conjugate addition was the main reaction when an aryl group is located at the  $\alpha$  carbon of the enone. On the other hand, 4-quinolones **151** ( $\text{Y} = \text{CH, X} = \text{N}$ ) can also react using **14** ( $\text{RPr}$ )<sup>47</sup> in the presence of  $\text{Me}_4\text{NF}$  to yield exclusively the 1,4-adducts **152** ( $\text{Y} = \text{CH, X} = \text{N}$ ) and no traces of 1,2-addition products (Scheme 58b).<sup>135</sup> High 1,4-regioselectivity in the reaction of this type of chromones has been reached by blocking the carbonyl moiety of the electrophile with a bulky aluminum-centered Lewis acid. Indeed, applying the “protect-in-situ” protocol during the trifluoromethylation of chromone derivatives **151** ( $\text{Y} = \text{CH, X} = \text{O}$ ) in the presence of aluminum phenoxide resulted in the formation of the 1,4-adducts **152** as the only products of the reaction (Scheme 58c).<sup>137</sup> The “protect-in-situ” methodology is also amenable to use in the 1,4-trifluoromethylation of cyclohex-2-enone and coumarines.<sup>137</sup>

Nucleophilic trifluoromethylation of olefins with two geminal electron-withdrawing groups such as Meldrum's acids, arylidene malononitriles, and 2-nitrocinnamates has been reported using **14** ( $\text{RPr}$ )<sup>47</sup> or phenyltrifluoromethylsulfone **153**. For instance, Michael nucleophilic trifluoromethylation to arylidene Meldrum's acids **154** using **14** was disclosed (Scheme 59a).<sup>138</sup> The trifluoromethylation reaction proceeded under mild basic conditions, and subsequent transformations of the intermediate carboxylic acid afforded **155** in good overall yields. The scope of the reaction is not limited to aromatic or heteroaromatic substituents, given that aliphatic ( $\text{R} = \text{iPr}$ ) and methoxyalkenyl 1,3-dioxane-4,6-diones **154** ( $\text{R} = \text{OMe}$ ) delivered the corresponding esters **156** and **158**, respectively, in good overall yields (Scheme 59b). The same transformation on aryl and heteroaryl derivatives of Meldrum's acids has also been achieved employing an alternative nucleophilic trifluoromethylating reagent, the phenyltrifluoromethylsulfone **153**, instead of **14** (Scheme 59c).<sup>139</sup> In this case, slightly higher temperature is needed, and lower yields were obtained.

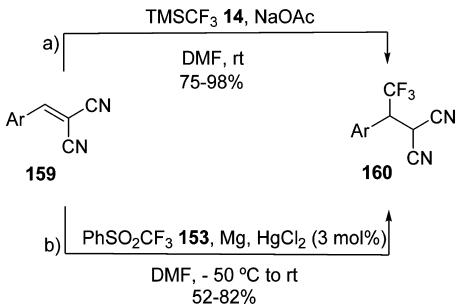
Likewise, arylidene malononitriles **159** have been trifluoromethylated in a conjugated manner with **14** ( $\text{RPr}$ )<sup>47</sup> in the presence of  $\text{NaOAc}$  as a Lewis base, and provided Michael adducts **160** in high yields (Scheme 60a).<sup>140</sup>

The aromatic ring of the substrate can contain electron-withdrawing or -donating substituents, and the same transformation can be performed employing the sulfone **153**

Scheme 59



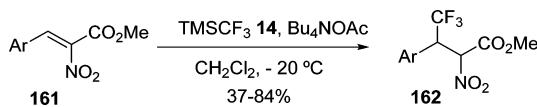
Scheme 60



(Scheme 60b).<sup>139</sup> In this case, although the yields are lower, the scope of the aromatic groups is very broad, including electron-withdrawing and -releasing groups as well as aromatic heterocyclic substituents.

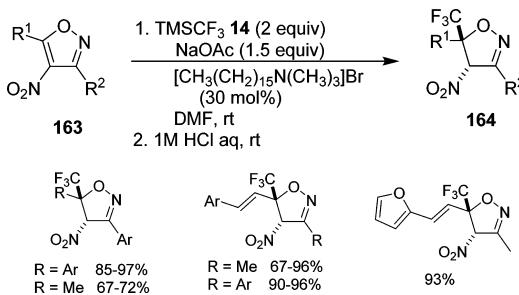
Similarly, the conjugated nucleophilic addition of trifluoromethyl moiety is also successful on 2-nitrocinnamates **161** using **14** ( $\text{RPr}$ ),<sup>47</sup> thus leading to trifluoromethylated esters **162**, which can be converted into the corresponding amino acids by hydrogenation (Scheme 61).<sup>141</sup>

Scheme 61



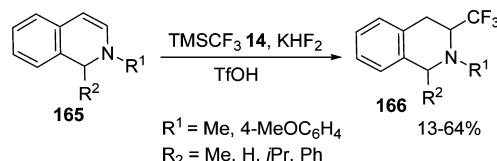
Five-membered heterocycles bearing a nitro functional group such as 4-nitroisoxazoles can be hydrotrifluoromethylated<sup>142</sup> in a regio- and diastereoselective fashion by nucleophilic addition with **14** ( $\text{RPr}$ ).<sup>47</sup> Indeed, the activation of aromatic isoxazoles **163** with a nitro group at the 4-position resulted in the realization of the first diastereoselective trifluoromethylation at the 5-position of isoxazoles (Scheme 62). The process can be applied to a broad range of 3,5-aromatic, heteroaromatic, and aliphatic substrates, which contain diverse functionality. Notably, the nitro group at the 4-position is essential for a successful transformation.

Scheme 62



Regarding electron-rich alkenes, Dilman et al. described a simple method for the hydrotrifluoromethylation of dihydroisoquinolines **165** using **14** ( $\text{RPr}$ )<sup>47</sup> in the presence of  $\text{KHF}_2$  as fluoride source to give 3-CF<sub>3</sub>-substituted 1,2,3,4-tetrahydroisoquinolines **166** (Scheme 63).<sup>143</sup>

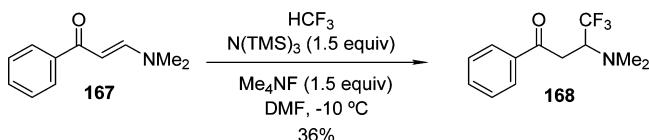
Scheme 63



Other types of activated alkenes such as alkenyl disulfides derived from carbohydrates can be submitted to hydrotrifluoromethylation leading to saturated compounds. Thus, a high degree of diastereoselection was reached starting from a mannose-derived dithioacetal.<sup>144</sup> However, in the case of glucose, poor diastereoselectivity was observed.<sup>145</sup>

An electronically mixed alkene such as *trans*-1-benzoyl-2-(dimethylamino) ethylene **167** can be 1,4-trifluoromethylated with  $\text{HCF}_3/\text{N}(\text{TMS})_3$  (1.5 equiv)/ $\text{Me}_4\text{NF}$  (Scheme 64).<sup>146</sup>

Scheme 64

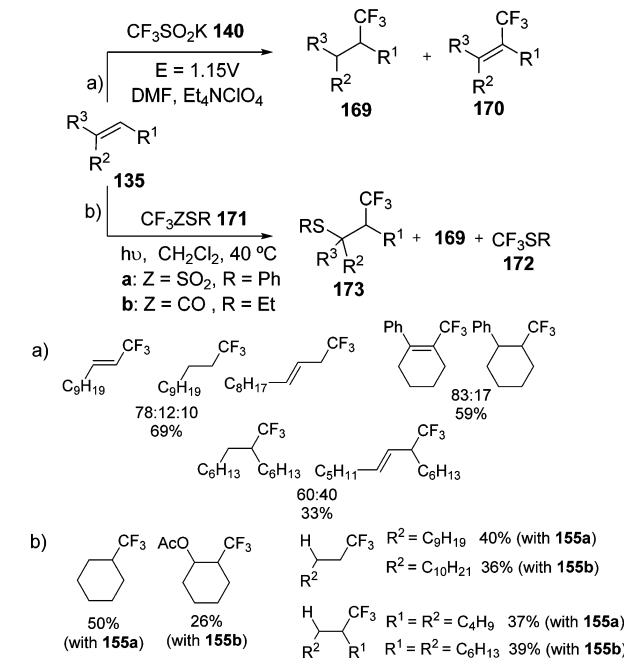


The resulting *N,N*-dimethyl-1-trifluoromethyl-2-benzoylethylamine **168** was transformed into *trans*-1-benzoyl-2-(trifluoromethyl)ethylene by acidic treatment after  $\beta$ -elimination of dimethylamine.

**2.5.2.2. Nonactivated Alkenes.** Metal-mediated hydroalkylation of unactivated alkenes is a very simple strategy for the introduction of alkyl substituents with applications ranging from industrial processes to the synthesis of pharmaceutical agents.<sup>147</sup>

Methallyl cyanide, a nonconjugated alkene, has been used for the preparation of a 5,5,5-trifluoro-3-methyl pentanoic acid (a precursor for the 5,5,5-trifluoro-DL-isoleucine amino acid) by means of trifluoromethyl radicals generated from trifluoroacetic acid, although with low yields (35%).<sup>148</sup> Similar results were achieved when potassium trifluoromethanesulfonate, Langlois' reagent **140** ( $\text{Lr}$ ),<sup>127</sup> was used as a source of  $\text{CF}_3$  radical by electrochemical oxidation. Aliphatic and aromatic alkenes **135** (Scheme 65a) provided mixtures of the corresponding saturated **169** and unsaturated (major) products **170**.<sup>149</sup>

Scheme 65

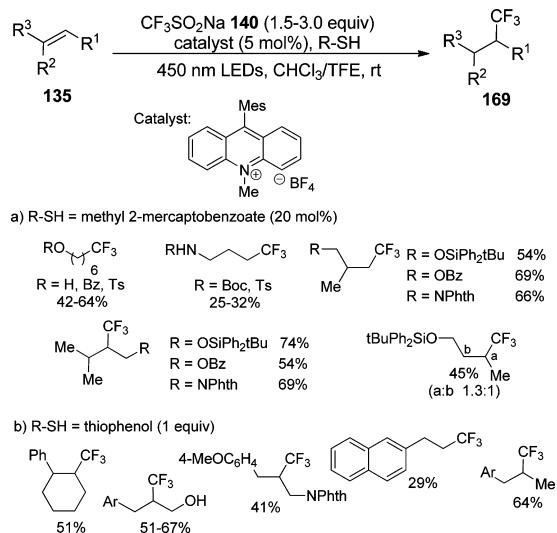


Aliphatic alkenes also reacted under photochemical activation with trifluoromethanethiosulfonates **171a** ( $\text{CF}_3\text{SO}_2\text{SPh}$ ) or trifluorothioacetates **171b** ( $\text{CF}_3\text{COSET}$ ), leading to mixtures of **172**, adducts **173**, and products of hydrotrifluoromethylation **169** always with less than 50% yield (Scheme 65b).<sup>150</sup>

Also with **140** (Lr), but via a photoredox system, a wider range of terminal and internal aliphatic alkenes **135** have been successfully hydrotrifluoromethylated.<sup>151</sup> Thus, employing an acridine catalyst and thiophenol derivative, moderate yields of trifluoromethyl saturated compounds **169** were obtained (Scheme 66a). This methodology can be extended, with very few modifications, to the hydrotrifluoromethylation of styrenes (Scheme 66b) by using stoichiometric thiophenol instead of catalytic amounts of methyl 2-mercaptopbenzoate.

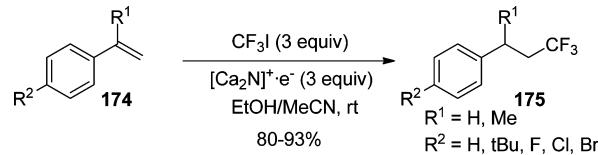
Another way to generate the  $\text{CF}_3$  radical is to employ an inorganic electrode such as calcium nitride ( $[\text{Ca}_2\text{N}]^+ \cdot \text{e}^-$ ). These

Scheme 66



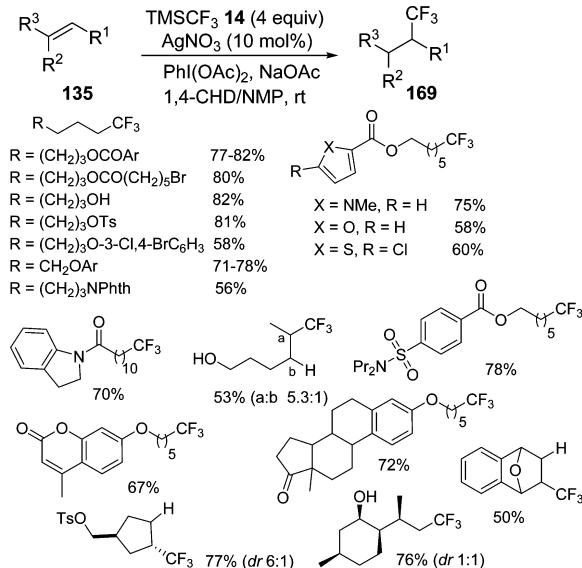
compounds are ionic crystals acting as electron sources and can be used in mild reaction conditions and in alcohol solvents. In this way, hydrotrifluoromethylation of styrenes **174** can be performed with good yields and short reaction times using only 3 equiv of  $\text{CF}_3\text{I}$  as the  $\text{CF}_3$  source (Scheme 67).<sup>152</sup> This procedure can also be extended to hydro- and iodotrifluoromethylation of alkynes (vide infra, section 3.2).

Scheme 67



Another radical-based approach is the hydrotrifluoromethylation of unactivated alkenes **135** using nucleophilic **14** ( $\text{RPr}$ )<sup>47</sup> as the trifluoromethyl source and  $\text{PhI(OAc)}_2$  as oxidant (Scheme 68).<sup>153</sup> The reaction takes place in very mild

Scheme 68



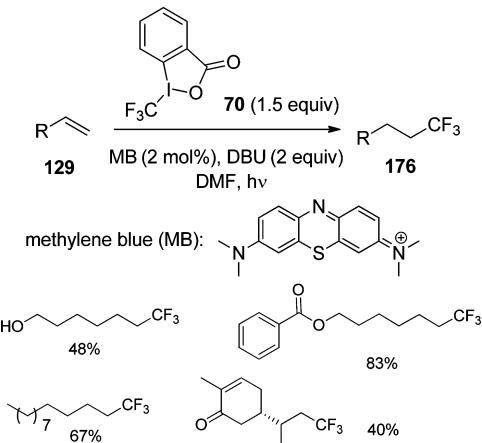
conditions yielding alkanes **169**, which contain many functional groups such as amide, carboxylic ester, sulfonate, ether, and alcohol. According to a preliminary mechanistic investigation,  $\text{CF}_3$  radical species is probably taking part in this efficient transformation.

Allyl trifluoromethyl derivatives can be obtained from conjugated alkenes, because hydrotrifluoromethylation of a conjugated olefin such as isoprene has been reported by means of bis [ $\pi$ -cyclopentadienyl]titanium(II) complexes, although only with moderate yields (41–56%).<sup>154</sup>

Light-mediated trifluoromethylation of unactivated alkenes **129** has been performed by using Methylene Blue (MB) as photosensitizer, **70** (Tr1) as trifluoromethylating source, and without any transition metal assistance (Scheme 69).<sup>155</sup> Similar conditions were used for the hydrotrifluoromethylation of terminal alkynes as well (vide infra, section 3.2.2).

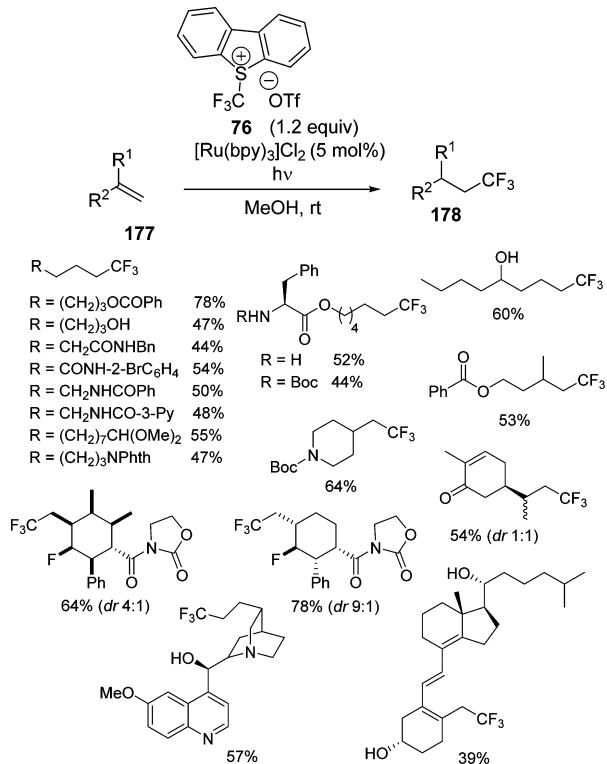
Terminal alkenes **177** can also be converted to the corresponding hydrotrifluoromethyl derivatives **178** employing **76** (Ur)<sup>84</sup> as the  $\text{CF}_3$  source and ruthenium as the metal partner, via a light-mediated reductive intermolecular hydro-

Scheme 69



trifluoromethylation (Scheme 70).<sup>156</sup> This simple protocol can be readily used for the direct introduction of a terminal CF<sub>3</sub>

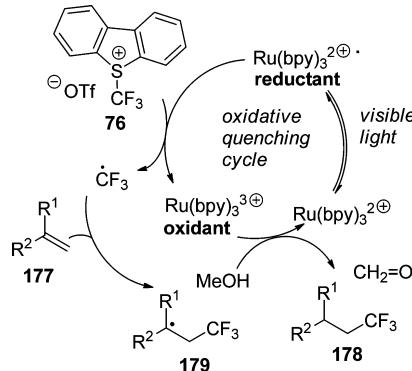
Scheme 70



group on a broad range of simple alkenes with moderate-good yields, at room temperature, in the presence of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> as catalyst and MeOH as reductant. It is remarkable that many functional groups (ester, amine, amide, acetal, carbamate, alcohol, and ketone) tolerate the mild reaction conditions.

A radical-based mechanism may explain the formation of the products. Hydrotrifluoromethylation may occur through an oxidative quenching cycle of Ru(bpy)<sub>3</sub><sup>2+</sup>• (Scheme 71) initiated by irradiation of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> with visible light ( $\lambda_{\text{max}} = 452$  nm). The reagent 76 (Ur)<sup>84</sup> may generate the CF<sub>3</sub> radical, which would add regioselectively to the alkene 177. The resultant carbon radical 179 would subtract a hydrogen atom from the methanol leading to the hydrotrifluoromethylated

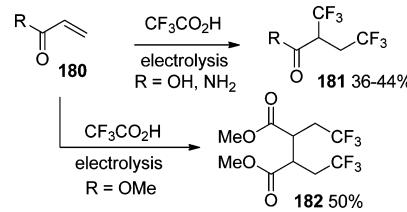
Scheme 71



product 178 (Scheme 71). Simultaneous oxidation of methanol and reduction of Ru(bpy)<sub>3</sub><sup>3+</sup> then would provide the ground-state photocatalyst Ru(bpy)<sub>3</sub><sup>2+</sup>.

**2.5.3. Carbotrifluoromethylation of Alkenes.** **2.5.3.1. Intermolecular Processes.** Trifluoromethylation of functionalized alkenes leading to double olefin addition can be performed with trifluoromethyl radicals generated from trifluoroacetic acid by electrochemical methods,<sup>32</sup> but usually mixtures of compounds are obtained.<sup>157</sup> The yields and relative distribution of the products depend upon the nature of the substituents of the double bond, the current density, and the temperature.<sup>158</sup> For instance, when  $\alpha,\beta$ -unsaturated carboxylic acid<sup>159</sup> **180** (R = OH) or amide<sup>160</sup> **180** (R = NH<sub>2</sub>) were used, bis(trifluoromethyl) derivatives **181** were obtained as major components, while in the case of methyl acrylate **180** (R = OMe) the isolation of the dimeric product **182** was reported<sup>161</sup> (Scheme 72), as a 1:1 mixture of the *meso* and *DL* isomers. This

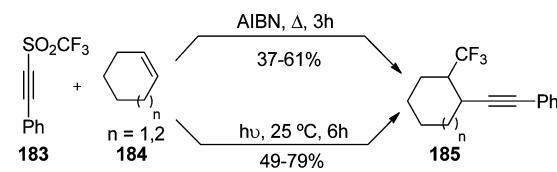
Scheme 72



method has been adapted to be run in an electrochemical microreactor and at continuous flow providing similar or better yields.<sup>162</sup>

Reaction of acetylenic triflones **183** with unactivated alkenes **184** can give double functionalized derivatives in a trifluoromethyl-alkynylation process (Scheme 73). The yields of products **185** were dependent on the initiation mode and the reaction time, and the stereochemistry could only be determined in the case of the cyclohexane derivative (*trans*).<sup>163</sup> Terminal alkenes such as oct-1-ene also produced regioselectively the corresponding trifluoromethylalkynyl de-

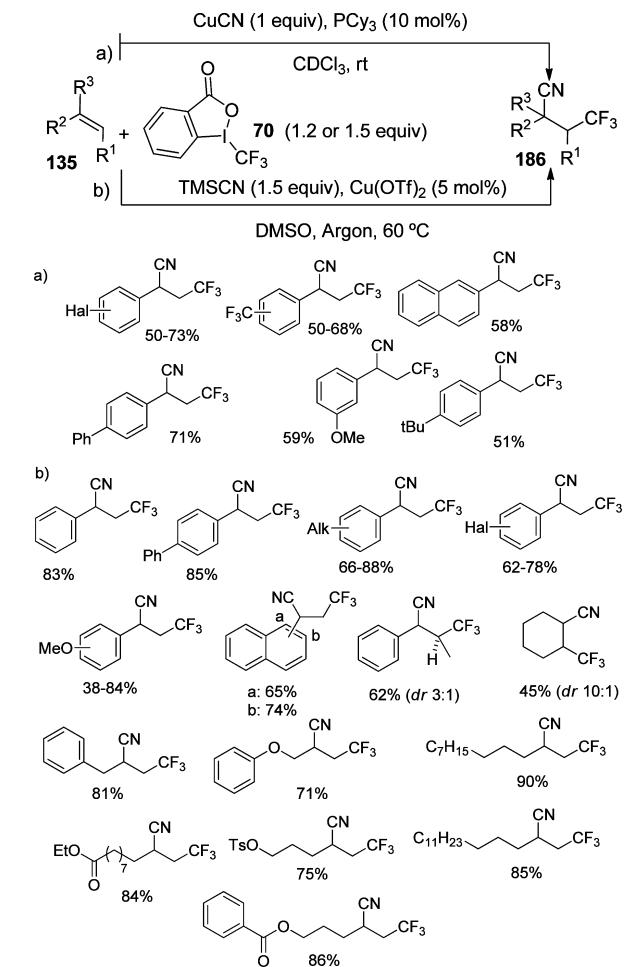
Scheme 73



ivative with the  $\text{CF}_3$  group at the end of the chain (75%). In the presence of azobis(isobutyronitrile) (AIBN) or via photochemical activation, alkyl radical derived from the olefin added to the acetylenic triflone to form a sulfonylvinyl radical intermediate. This species decomposes to furnish a vinylidene carbene that rearranges and combines with a  $\text{CF}_3$  radical to give the product **185**.

An elegant and efficient intermolecular addition of cyano and trifluoromethyl groups to unactivated olefins such as phenyl-substituted styrenes **135** by reaction with **70** (Tr1)<sup>80</sup> in the presence of  $\text{CuCN}$  and a phosphine catalyst has been reported (Scheme 74a).<sup>164</sup> This radical cyanotrifluoromethylation reaction took place in very mild conditions with high regioselectivity and moderate to good yields.

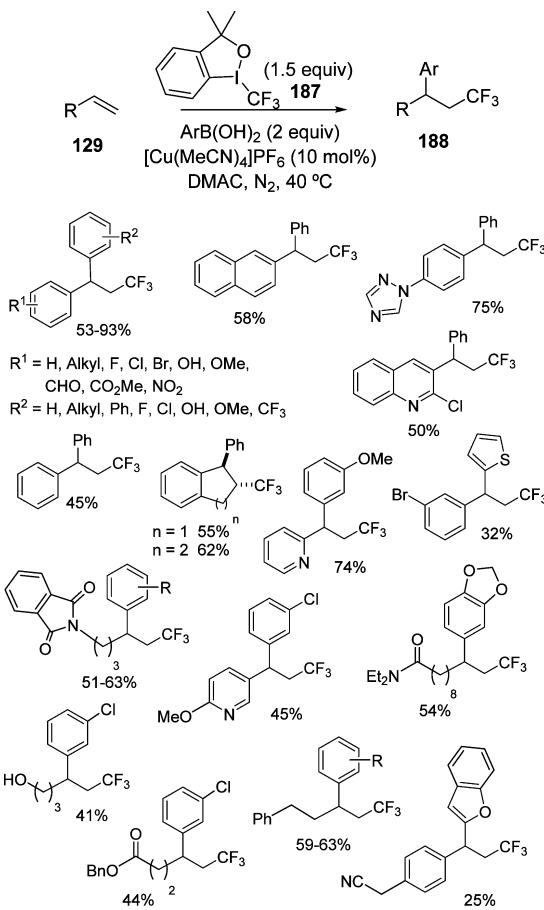
Scheme 74



A much wider scope and better yields can be obtained using a combination of Togni reagent **70** (Tr1), TMSCN, and copper catalysis (Scheme 74b). In this way, different kind of olefins **135** including styrene derivatives as well as aliphatic alkenes have been efficiently cyanotrifluoromethylated.<sup>165</sup>

A general method for the aryltrifluoromethylation of styrenes and unactivated alkenes **129** employing ether-type Togni reagent **187** (Tr2)<sup>80</sup> as trifluoromethyl source, arylboronic acids as arylation reagents, and copper(I) as catalyst has been developed for the synthesis of products **188** and showed compatibility with many functional groups (Scheme 75).<sup>166</sup> It is noteworthy that the other Togni reagent **70** (Tr1) or

Scheme 75



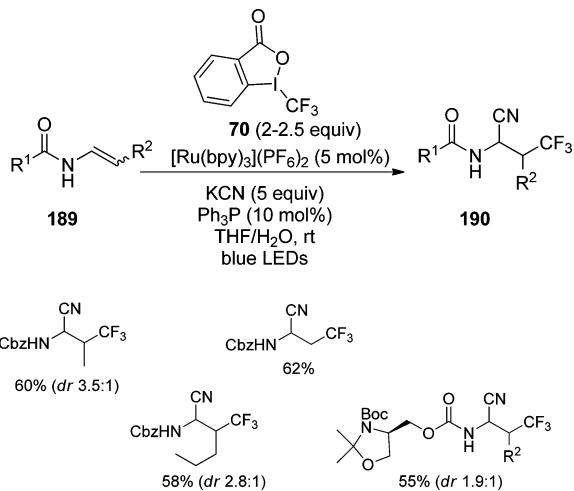
Umemoto reagent **76** (Ur) did not achieve trifluoromethylation reaction. Several kinetic and trapping studies suggested that mutual activation between arylboronic acid and Togni reagent seems to be crucial for the formation of the initial  $\text{CF}_3$  radical, because **187** (Tr2) was inert in the absence of the boronic acids. Other key steps in the mechanism then include transmetalation of  $\text{ArB(OH)}_2$  with  $\text{Cu(II)}$  and the formation of the  $\text{Ar-C}$  bond by means of a  $\text{Cu(III)}$  species.

This tandem cyano-trifluoromethylation has also been developed by using a ruthenium photocatalyst with **70** (Tr1)<sup>80</sup> onto activated substrates such as enecarbamates **189** with average yields (Scheme 76).<sup>167</sup> The same conditions can be employed to accomplish the oxy- and aminotri fluoromethylation of this type of alkenes (vide infra, sections 2.5.4 and 2.5.5).

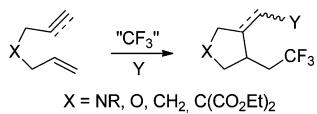
**2.5.3.2. Intramolecular Processes. 2.5.3.2.1. Cyclic Carbotrifluoromethylation.** When departing from substrates containing two isolated unsaturated bonds, such as diallylamines ( $X = \text{NR}$ ), diallyl ethers ( $X = \text{O}$ ), hydrocarbon dienes ( $X = \text{CH}_2$ ), or malonate derivatives ( $X = \text{C}(\text{CO}_2\text{Et})_2$ ) (Scheme 77), the trifluoromethylation reaction would lead to cyclization reactions. In these processes, the second unsaturated bond contributed to the intramolecular C–C bond construction by trapping the initially generated trifluoromethyl radical species.

The first example was the reaction of allylamines **191** with trifluoroacetic acid (TFA) for the preparation of the pyrrolidine **192** as a *cis* isomer (Scheme 78),<sup>168</sup> but more recently this type of cyclization has been performed with different trifluoromethylating reagents and conditions. For instance, a silver-

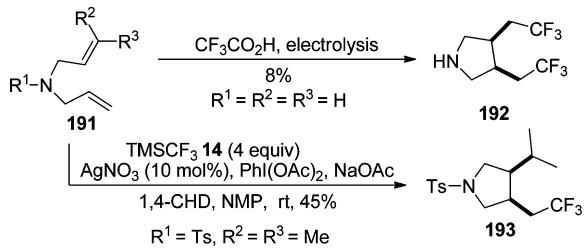
Scheme 76



Scheme 77



Scheme 78



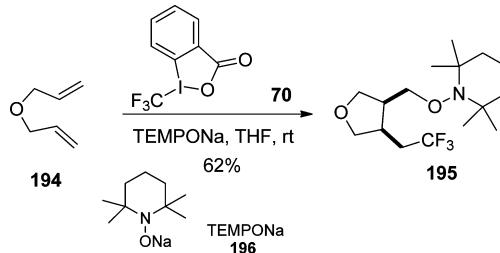
catalyzed trifluoromethylation of a simple alkene using nucleophilic **14** (RPr)<sup>47</sup> as the trifluoromethyl source in the presence of PhI(OAc)<sub>2</sub> as oxidant allowed access to trifluoromethylated pyrrolidine **193** (dr = 1.5:1, Scheme 78).<sup>153</sup> A preliminary mechanistic investigation suggests that a CF<sub>3</sub> radical species may be involved in the transformation.

Analogously, diallyl ether **194** can cyclize in a radical transition-metal-free trifluoromethylaminooxylation reaction by using reagent **70** (Tr1)<sup>80</sup> as source of trifluoromethylating agent and TEMPONa **196**, which is readily generated in situ upon treatment of the commercially available 2,2,6,6-tetramethylpiperidine-N-oxyl radical (TEMPO) with Na in THF.<sup>169</sup> In this case, initial radical CF<sub>3</sub> addition is terminated by the TEMPO-trapping reaction as illustrated by the formation of the tetrahydrofuran derivative **195** (dr = 3.6:1, Scheme 79).

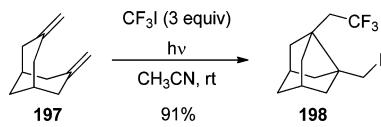
The approach has also been employed to make carbocycles. Thus, treatment of a diene derived from bicyclo[3.3.1]nonane **197** with trifluoromethyl iodide upon irradiation with a Hg lamp gave the corresponding trifluoromethylated noradamantane **198** (Scheme 80).

Similarly, five-membered carbocycles **200** and **201** were formed in low yields (Scheme 81a) when a diene **199** derived from malonate reacted with reagent **70** (Tr1)<sup>80</sup> in the presence of a copper catalyst, the same conditions employed for the trifluoromethylation of allyl derivatives (vide supra, section

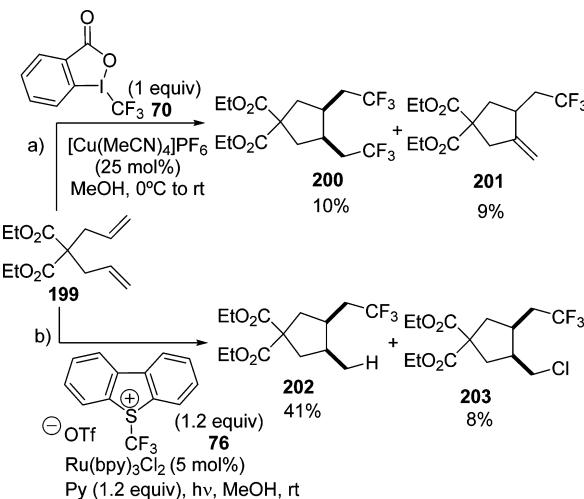
Scheme 79



Scheme 80



Scheme 81

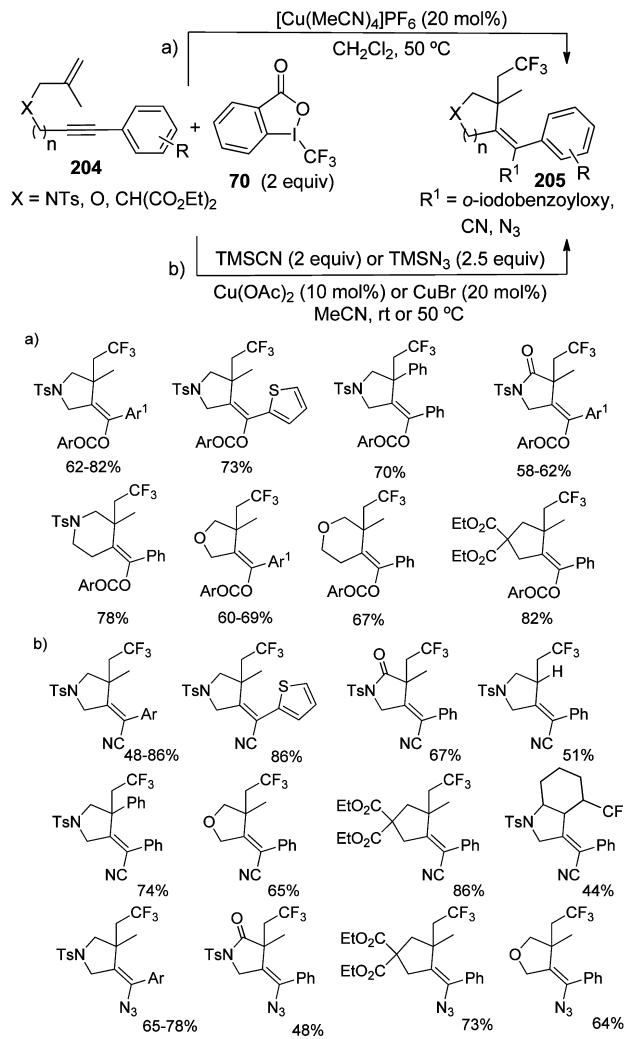


2.2.4).<sup>88</sup> Better but still low yields were obtained when **76** (Ur)<sup>84</sup> in the presence of Ru(bpy)<sub>3</sub>Cl<sub>2</sub> was used (Scheme 81b).<sup>156</sup> This radical-based transformation operates at room temperature, and the process is characterized by its operational simplicity giving rise to the *cis* isomer (dr = 13:1) of compound **202** as the major component, although a small proportion of chlorotrifluoromethylated product **203** was also obtained.

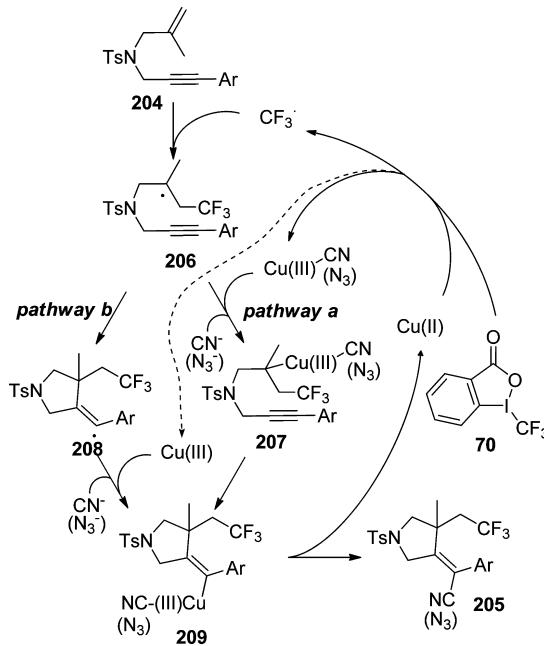
Furthermore, apart from dienes, enynes **204** are also able to react with a trifluoromethylating reagent leading to carbocycles and heterocycles **205** in an intramolecular trifluoromethylation process involving the alkyne moiety. As an example, copper-catalyzed trifluoromethylation of enynes **204** containing mainly unactivated olefin moieties has been achieved using reagent **70** (Tr1)<sup>80</sup> under very mild reaction conditions (Scheme 82a).<sup>171</sup> Five-membered carbocycles **205** (X = CH(CO<sub>2</sub>Et)<sub>2</sub>) and five- and six-membered heterocycles **205** (X = O, NTs) with very different functional groups around their structure can be efficiently prepared.

Furthermore, these authors took advantage of the radical intermediate formed in the course of the reaction and were able to trap it with cyanide for the generation of cyclic derivatives **205** (R<sup>1</sup> = CN) or azides **205** (R<sup>1</sup> = N<sub>3</sub>), thus providing methods for the cyanotrifluoromethylation/azidotrifluoromethylation concomitant with carbocyclization of 1,6-enynes **204** (Scheme 82b).<sup>172</sup>

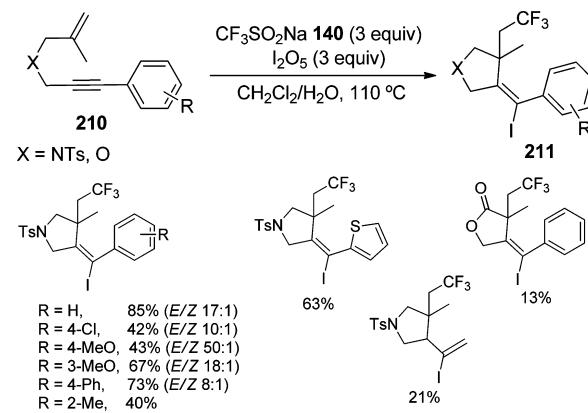
Scheme 82



Scheme 83



Scheme 84

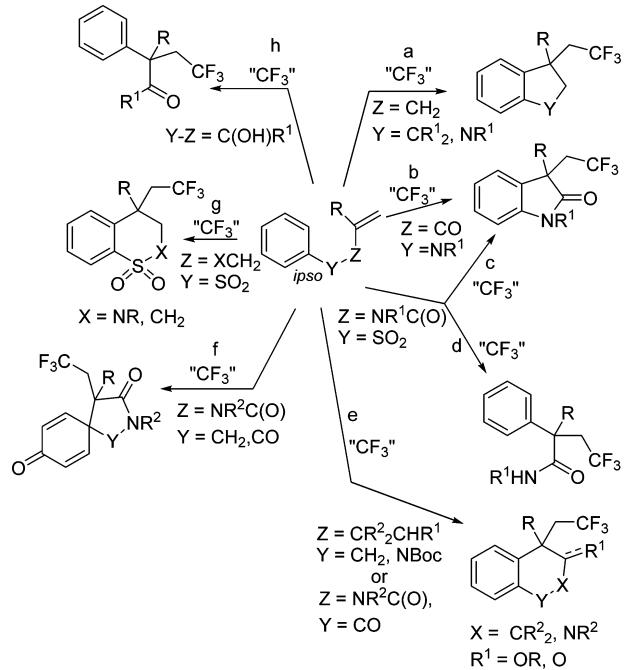


procedure has been also applied to the synthesis of trifluoromethylated oxindoles, as can be seen in the next section.

**2.5.3.2.2. Aryltrifluoromethylation.** Two general processes for the intramolecular aryltrifluoromethylation of aryl alkenes with corresponding formation of bicyclic derivatives and/or functionalized aryl compounds have been reported. In some cases, the *ortho* carbon of the aryl moiety is concerned so *ortho*-cyclization takes place (Scheme 85a, b, e, and g). Alternatively, the *ipso* aromatic carbon can be involved, and trifluoromethylation occurs along with formation of spiro compounds (Scheme 85f) or with migration, thus giving rise to either heterocycles (Scheme 85c) or an open-chain compound (Scheme 85d). Likewise, in some instances, where diaryl allylic derivatives are the starting substrates (Scheme 85h, Y-Z = C(OH)R<sup>1</sup>), trifluoromethylation of the alkene takes place alongside subsequent aryl group migration leading to a formal carbotrifluoromethylation of the olefin function. The latter process takes place via a rearrangement involving also an *ipso* aromatic carbon in the substrate.

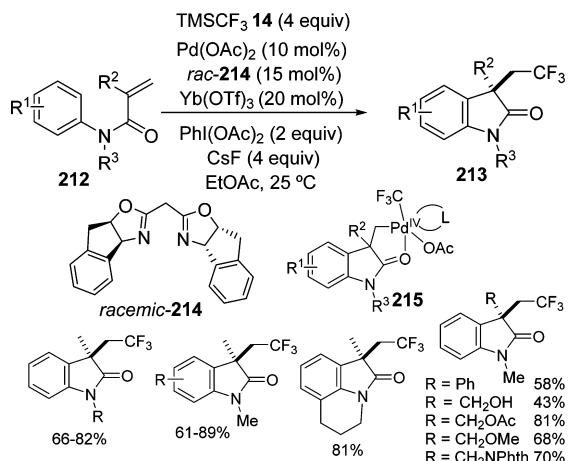
Regarding the first strategy, aryltrifluoromethylation on both electron-poor and unactivated alkenes has been reported as a

Scheme 85



useful tool for the construction of trifluoromethylated carbocycles and heterocycles. For example, olefins such as *N*-aryl acrylamides **212** underwent Pd-catalyzed intramolecular oxidative aryltrifluoromethylation by using **14** (*RPr*)<sup>47</sup>/CsF as trifluoromethyl source, racemic oxazolidine **214** as ligand, and PhI(OAc)<sub>2</sub> as oxidant (Scheme 86).<sup>174</sup> The reaction allowed an

Scheme 86



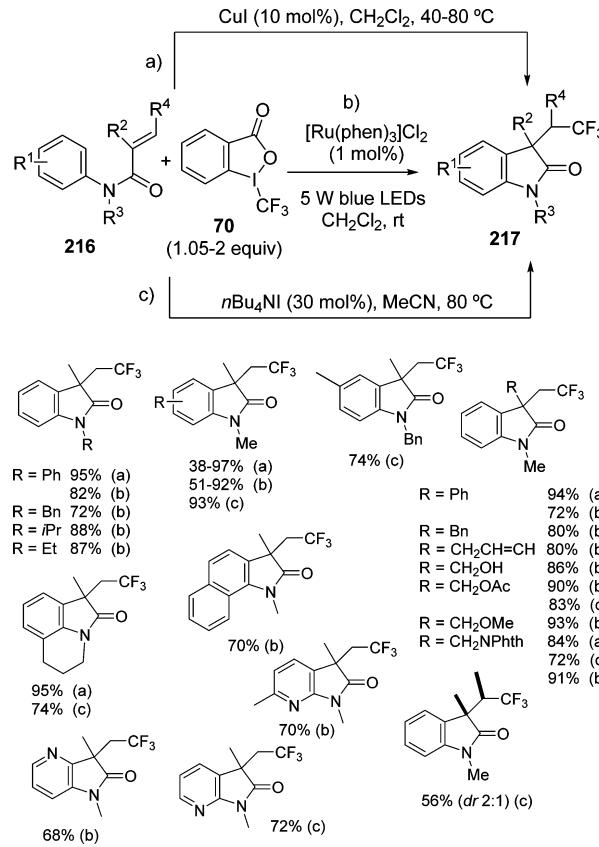
efficient synthesis of a variety of CF<sub>3</sub>-containing oxindoles **213** bearing a quaternary carbon atom, as racemic mixtures and with good yields (Scheme 86). Preliminary mechanistic studies indicate that the reaction may proceed through initial arylpalladation of alkene, followed by oxidation and reductive elimination, and may support a Csp<sup>3</sup>-[Pd(IV)(CF<sub>3</sub>)] intermediate **215**, which would undergo reductive elimination to afford a Csp<sup>3</sup>-CF<sub>3</sub> bond.

Silver fluoride has also been used to promote this reaction, although overstoichiometric amounts (3 equiv) were needed,<sup>175</sup> along with **14** (*RPr*)<sup>47</sup> in DMF and no additives. A wide range of oxindoles are obtained with moderate to good

yields and good regioselectivity when a *meta*-substituted acrylamide was employed. The same tandem trifluoromethylation/cyclization has been performed in metal-free conditions by two different research groups using **14** (*RPr*)<sup>47</sup> and the hypervalent iodine(III) reagent PhI(OAc)<sub>2</sub> to generate an electrophilic CF<sub>3</sub> radical able to initiate a SET process leading to the formation of the oxindoles **213**. In one case, KF as a base in EtOAc was employed,<sup>176</sup> and in the other NaOAc in NMP,<sup>177</sup> the latter providing slightly better yields of oxindoles. The former conditions, however, have been applied to imides and sulphonamides to yield isoquinolinolindones and oxindoles (vide infra, this section).

A similar transformation, providing also oxindole derivatives **217** bearing a trifluoroethyl group at the 3 position, has been achieved using **70** (Tr1)<sup>80</sup> as trifluoromethyl source and either CuI catalyst (Scheme 87a) or visible light in the presence of a

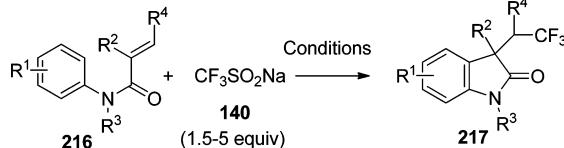
Scheme 87



ruthenium photocatalyst from *N*-arylacrylamides **216** (Scheme 87b). In the first case,<sup>178</sup> the experimental procedure is very simple and the yields of the indoles were notably better than those obtained previously in the reaction with the nucleophilic **14** (*RPr*)<sup>47</sup> (vide supra, Scheme 86). The light-induced approach also works in a very efficient manner to produce oxindoles **217** with a wide range of functional groups, at room temperature and with good yields (Scheme 87b).<sup>179</sup> Some experiments seem to support a radical mechanism involving the formation of a cationic intermediate just after the cyclization step that could be the rate-limiting one. Because light is needed all of the time, there is probably not a radical chain propagation reaction pathway, although the authors do not rule out this hypothesis.

Togni reagent **70** ( $\text{Tr1}^{80}$ ) can also be activated by a soft nucleophile providing a metal-free method for the aryltrifluoromethylation of acrylamides. Indeed, substoichiometric amounts of tetrabutylammonium iodide have been successfully employed for the preparation of oxindoles **217** (Scheme 87c).<sup>180</sup> As in the above reports, several substitution patterns in the aromatic ring and different groups on the nitrogen were compatible with the reaction conditions and provided oxindoles **217** even from  $\beta$ -substituted acrylamides **216** ( $R^4 = \text{Me}$ ). In these conditions, however, the experiments carried out by the authors indicated that the mechanism probably is nonradical and goes through a cationic intermediate.

Besides trifluoromethylating reagents **14** ( $\text{RPr}$ ) and **70** ( $\text{Tr1}$ ), cheaper Langlois' reagent **140** has also been used by several research groups to prepare oxindoles **217** departing from *N*-aryl acrylamides **216**. First reports made use of TBHP and catalytic amounts of  $\text{Cu}(\text{II})$  salts. For instance, Lipshutz et al. described the use of  $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$  and TMEDA in a 1:1 ratio and run the reaction "on water", at room temperature (Scheme 88a).<sup>181</sup> In these remarkable mild, economical, and

Scheme 88<sup>a</sup>

<sup>a</sup>Conditions: (a) TBHP (3.5 equiv),  $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$  (10 mol %), TMEDA (10 mol %), "on water", rt; (b) TBHP (3 equiv),  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (10 mol %),  $\text{PPh}_3$  (10 mol %),  $\text{EtOAc}/\text{DCE}$ , 60 °C; (c)  $\text{AgNO}_3$  (30 mol %),  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (30 mol %),  $t\text{BuOH}/\text{H}_2\text{O}$ , 40 °C; (d)  $\text{K}_2\text{S}_2\text{O}_8$  (2 equiv),  $\text{MeCN}/\text{H}_2\text{O}$ , 80 °C; (e)  $\text{PhI}(\text{OAc})_2$  (2 equiv), DCE, 100 °C; (f)  $\text{I}_2\text{O}_5$  (3 equiv),  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ , 70 °C.

eco-friendly conditions, they obtained good yields of **217** in short reaction times. Analogously, Lei and co-workers used  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (10 mol %) and  $\text{PPh}_3$  (10 mol %) in  $\text{EtOAc}/\text{DCE}$  at 60 °C (Scheme 88b).<sup>182</sup> Radical trapping experiments, IR monitoring, and kinetic isotope experiments provided evidence for a radical mechanism initiated by the formation of a *tert*-butoxy radical by reaction between TBHP and copper. This oxygen radical could then react with **140** to generate the reactive  $\text{CF}_3$  radical, which may add to the terminal carbon in the alkene to start the cyclization reaction.

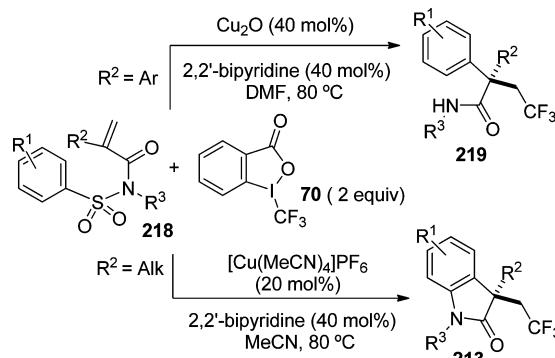
Apart from copper, silver has been employed for the same goal. Thus, trifluoromethylating reagent **140**, catalytic  $\text{AgNO}_3$ , and  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  as oxidant were used in a mixture of *tert*-butanol and water to give the oxindoles **217**, including those derived from acrylamides **216** bearing benzyl, acetoxymethyl, and phthalimidylmethyl at the  $\alpha$ -position ( $R^2 = \text{CH}_2\text{Ph}$ ,  $\text{CH}_2\text{OAc}$ ,  $\text{CH}_2\text{NPhth}$ , Scheme 88c) and also methyl groups at the  $\alpha$ - and  $\beta$ -carbons ( $R^2 = R^4 = \text{Me}$ ).<sup>183</sup> Interestingly, the latter reaction has been achieved without any metal participation and changing the catalytic  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  oxidant with the analogous  $\text{K}_2\text{S}_2\text{O}_8$  salt in overstoichiometric amounts (Scheme 88d).<sup>184</sup> This metal-free approach provided better yields than the silver-catalyzed method, especially when electron-withdrawing groups are present in the aromatic ring.

Therefore, metals are not always necessary to help Langlois' reagent **140** to generate the active  $\text{CF}_3$  radical in these aryltrifluoromethylation reactions. Indeed, not only sulfur-containing oxidants but also hypervalent iodine derivatives have

been used for the preparation of oxindoles **217** in the absence of any metal (Scheme 88e,f). As far as we know, the first contribution on this matter was disclosed by Fu et al., who employed iodobenzene diacetate [ $\text{PhI}(\text{OAc})_2$ ] as the oxidant and dichloroethane as solvent (Scheme 88e) to produce a wide range of oxindoles **217** with good yields.<sup>185</sup> Another metal-free contribution to the trifluoromethylation of *N*-arylacrylamides with reagent **140** makes use of iodine pentoxyde  $\text{I}_2\text{O}_5$ ,<sup>173</sup> the same conditions used for the trifluoromethylation/cyclization of enynes (vide supra, previous section). Mechanistic studies carried out on these metal-free reactions suggest the formation of a free  $\text{CF}_3$  radical by combination of sulfur or iodine(III) oxidants with reagent **140** and loss of  $\text{SO}_2$ .

A trifluoromethylation-aryl migration of acrylic *N*-sulphonamides **218** leading alternatively and in a regioselective way to  $\beta$ -trifluoromethylamides **219** or to oxindoles **213** trifluoroalkylated at the 3 position has been developed (Scheme 89).<sup>186</sup>

Scheme 89

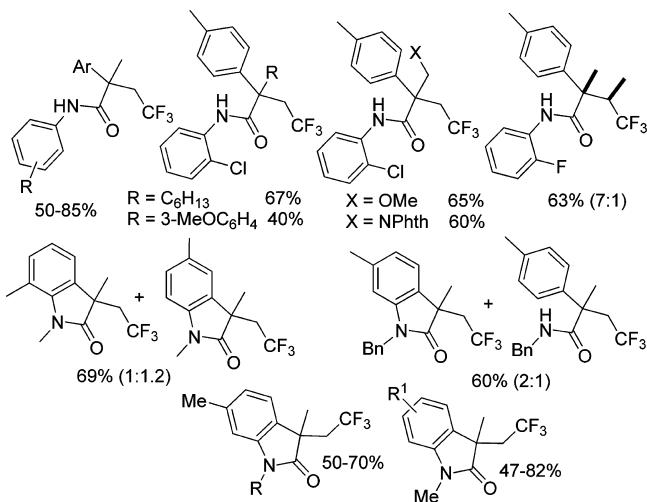


Reagent **70** ( $\text{Tr1}^{80}$ ) is the trifluoromethyl source, and copper(I) or (II) catalysis and 2,2'-bipyridine are needed to aid in these remarkable transformations. Furthermore, new quaternary centers are obtained in both cases. The formation of those two possible compounds depends mainly on the nature of the substituent present ( $R^3$ ) in the nitrogen atom of the acrylamide: aromatic groups lead to open-chain amides **219**, whereas alkyl substituents yield oxindoles **213**.

In the preparation of the novel  $\alpha$ -aryl- $\beta$ -trifluoromethyl amides containing a quaternary stereocenter **219**, electron-releasing and electron-withdrawing groups present in the aromatic ring of the sulfonamide moiety can be used with efficiency, while the presence of some electron-withdrawing functions in the aryl group linked to the nitrogen atom reduced the yield of the reaction (Figure 4). These open-chain compounds **219** can also be obtained through a metal-free approach that employs  $n\text{Bu}_4\text{I}$  (50 mol %) instead of copper catalyst.<sup>180</sup>

The substitution in the alkene can be varied introducing cycloalkyl, methoxymethyl, phthalimidemethyl, and aromatic groups, although in the latter case low yield was obtained. Furthermore, the synthesis of oxindoles **213** occurred with lower overall yields particularly when more electron-poor aryl groups take part (Figure 4). Nevertheless, it is remarkable that the reaction performs well with different alkyl groups, including some sterically demanding ones, in the nitrogen atom.

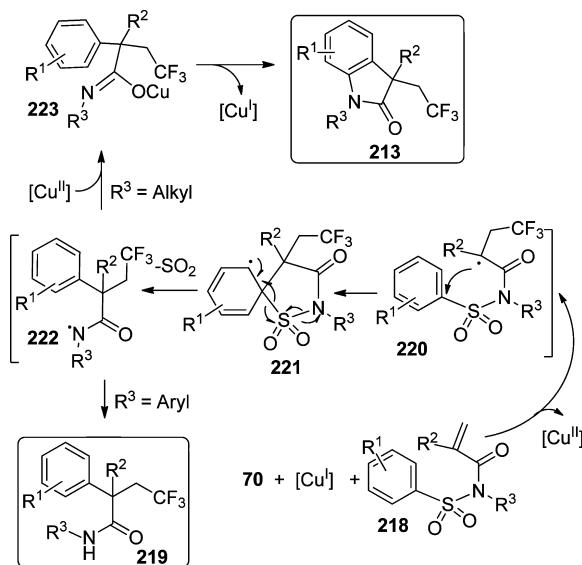
The mechanism proposed for the preparation of amides **219** or oxindoles **213** may start with the reaction between the  $\text{Cu}(\text{I})$ -activated reagent **70** ( $\text{Tr1}^{80}$ ) and the alkene **218** to produce the  $\text{CF}_3-\text{C}_{\text{sp}^3}$  bond and an alkyl radical intermediate



**Figure 4.** Trifluoromethylated compounds **219** from *N*-sulphonamides **218**.

**220** that undergoes a *5-ipso* cyclization on the sulphonyl aromatic ring (Scheme 90). This radical cyclic intermediate **221**

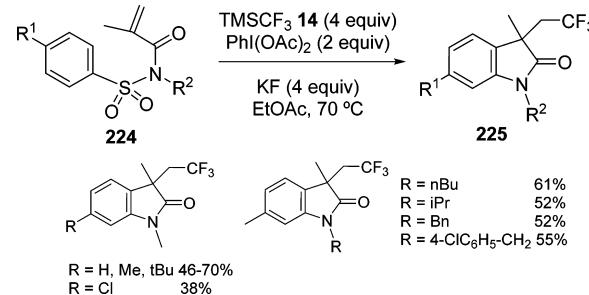
**Scheme 90**



expels  $\text{SO}_2$  to form an amidyl radical **222**, which could then follow two alternative pathways, either hydrogen abstraction to give acyclic amides **219** when the substituent in the nitrogen atom is aryl, or oxidation to an intermediate copper enolate **223** that can be trapped by the aromatic ring with formation of oxindoles **213**, when electron-releasing alkyl groups are present on the amidyl nitrogen.

The trifluoromethylation/aryl migration/desulfonation reaction from sulfonamides **224** to generate oxindoles **225** can also be achieved with reagent **14** ( $\text{RPr}$ )<sup>47</sup> in metal-free conditions (Scheme 91).<sup>176</sup> In this way, several oxindoles **225** with different substituents at the nitrogen atom were obtained, and it is remarkable that, by comparison with the copper-catalyzed reaction, the *N*-benzyl derivatives ( $\text{R}^2 = \text{Bn}, 4\text{-ClC}_6\text{H}_5\text{-CH}_2$ ) yielded oxindoles exclusively with no traces of the open-chain trifluoromethylated products. The mechanism proposed by the authors starts with the generation of  $\text{CF}_3$  radical and addition to

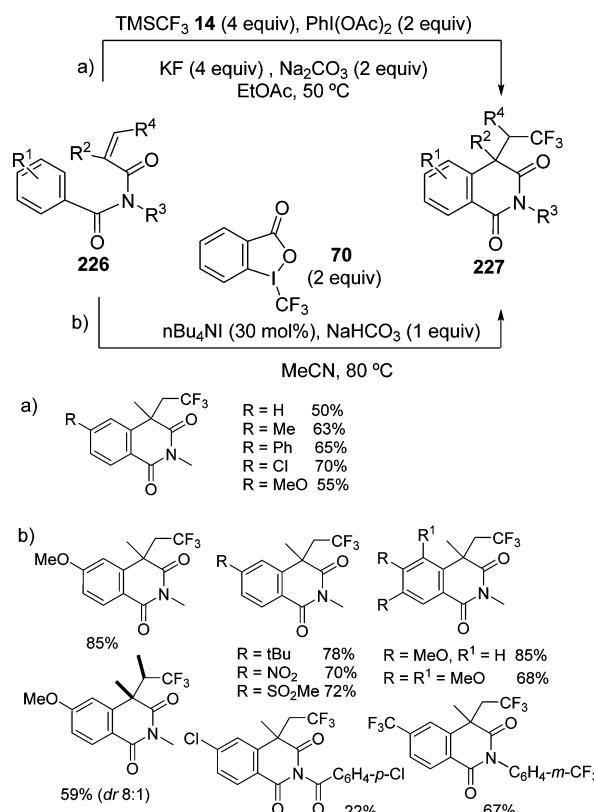
**Scheme 91**



the  $\beta$ -carbon of the acrylamide in a path very similar to that described in Scheme 90.

When the acrylamide nitrogen is linked to an aromatic ring through a carbonyl or methylene moiety instead of a sulphonyl group, isoquinolinediones or spirobicyclic compounds are obtained. For instance, nearly the same conditions reported above for the trifluoromethylation of the sulphonyl **224** were successfully applied to  $\alpha,\beta$ -unsaturated imides **226**, and the corresponding six-membered isoquinoline derivatives **227** were isolated with good yields (Scheme 92a).<sup>176</sup>

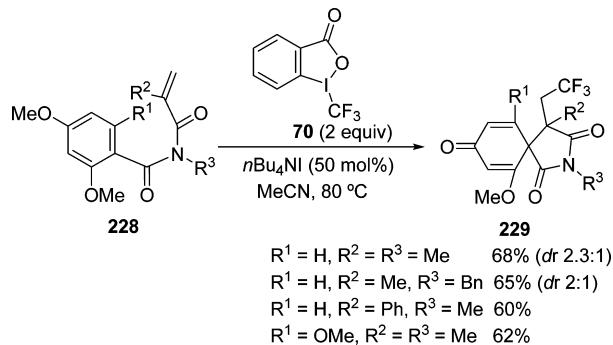
**Scheme 92**



Previously, this type of substrate **226** had been trifluoromethylated with Togni's reagent **70** ( $\text{Tr1}$ )<sup>80</sup> and  $\text{nBu}_4\text{I}$  in another metal-free approach to isoquinolinediones **227** (Scheme 92b).<sup>180</sup> In this case, the yields are better, and it is noteworthy that when the alkyl group in the nitrogen is replaced by an aromatic ring ( $\text{R}^3 = m\text{-CF}_3\text{-C}_6\text{H}_4$ ), only the cyclization leading to isoquinolinedione and not the one forming the oxindole took place with excellent selectivity.

Furthermore, di- and trimethoxy-substituted substrates **228** did not produce neither oxindole nor isoquinoline derivatives but spirobicycles **229** (Scheme 93) with good yields and in

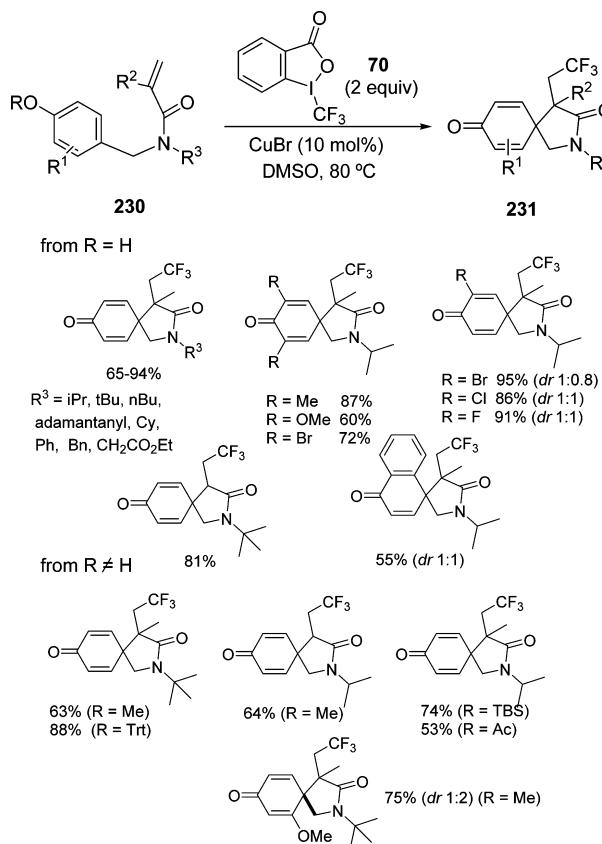
Scheme 93



some cases excellent diastereoselectivity. Regarding the mechanism of this transformation, the authors propose the initial formation of a carbocationic intermediate resulting from the addition of a highly electrophilic iodine(III) species to the  $\beta$ -carbon of the acrylamide. A 5-*ipso* cyclization then takes place on the aromatic ring giving a cationic spirobicyclic intermediate that after losing a methyl cation from one of the methoxy groups would yield the final product **229**.

Trifluoromethylated spirobicyclohexenones **231** have also been obtained starting from *N*-benzyl-substituted acrylamides **230** by using Togni's reagent **70** ( $TrI$ )<sup>80</sup> and copper(I) catalysis (Scheme 94).<sup>187</sup> As in the above case, it was necessary

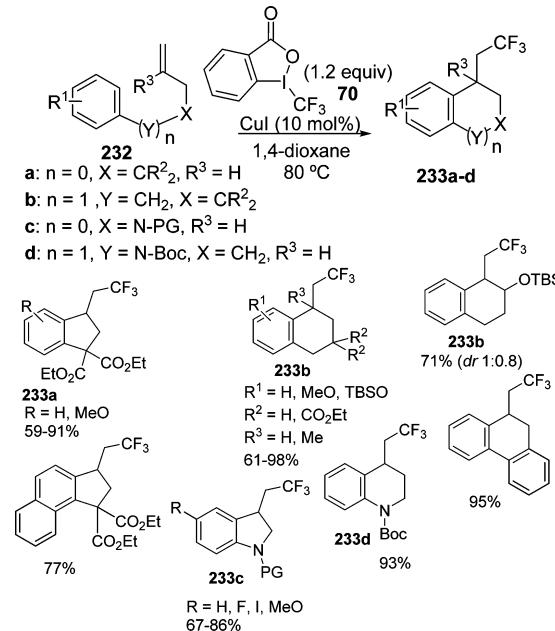
Scheme 94



the presence of a phenol or alkoxy-type group in the *para* position of the benzylic aromatic ring. Although better yields were obtained departing from phenol derivatives, substrates containing phenol groups masked with methyl, triphenylmethyl, *tert*-butyldimethylsilyl, and acetyl protecting groups reacted well to produce the spirobicyclic compounds **231**.

Unactivated alkenes can also be involved in intramolecular carbotrifluoromethylation processes. Thus, a copper-catalyzed  $Csp^3-CF_3$  trifluoromethylation of alkenes **232** by using reagent **70** ( $TrI$ )<sup>80</sup> combined with intramolecular  $Csp^3-C_{Ar}$  bond formation to afford the cyclic compounds **233** in good to high yields has been described (Scheme 95).<sup>188</sup> The process has

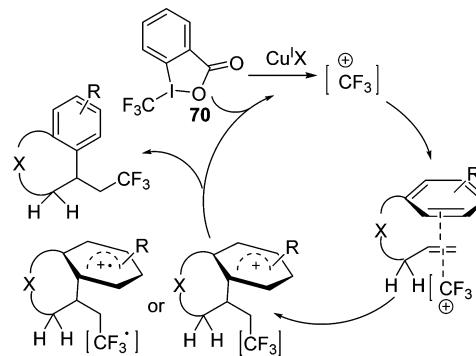
Scheme 95



been applied to the formation of both five- **233a** ( $n = 0$ ) and six-membered rings **233b** ( $n = 1$ ). This reaction was also successfully applied to *N*-protected allylanilines **232c** ( $n = 0$ ) and homoallylaniline **232d** ( $n = 1$ ) derivatives, thus affording trifluoromethylated dihydroindoles **233c** and tetrahydroquinoxline **233d**, respectively (Scheme 95).

The proposed mechanism is illustrated in Scheme 96. Although the true active species is not clear, electrophilic active species may be generated by the reaction of copper iodide with the trifluoromethylating agent **70** ( $TrI$ ).<sup>80</sup> The alkene moiety is

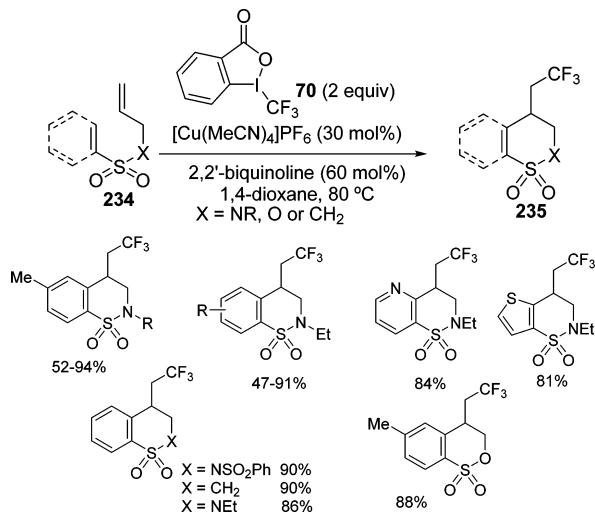
Scheme 96



first activated by this electrophilic species, and then electron transfer from the aryl ring through the C=C bond and C–C bond formation might occur. On the basis of the fact that the reaction of the six-membered ring was faster than that of the five-membered ring, the acceleration by orbital interaction of the aryl ring and the alkene may be crucial for this carbo-trifluoromethylation.

Another example of aryltrifluoromethylation of unactivated olefins using **70** ( $\text{Tr1}$ )<sup>80</sup> and copper catalysis has been reported. This method starting from aryl or heteroaryl sulfone derivatives **234** afforded six-membered sulfur, nitrogen, or oxygen heterocycles **235** with moderate to good yields and great tolerance toward many functional groups present either in the aromatic ring or in the heteroaromatic cycle formed (Scheme 97).<sup>189</sup> After several kinetic experiments and isotopic labeling

Scheme 97

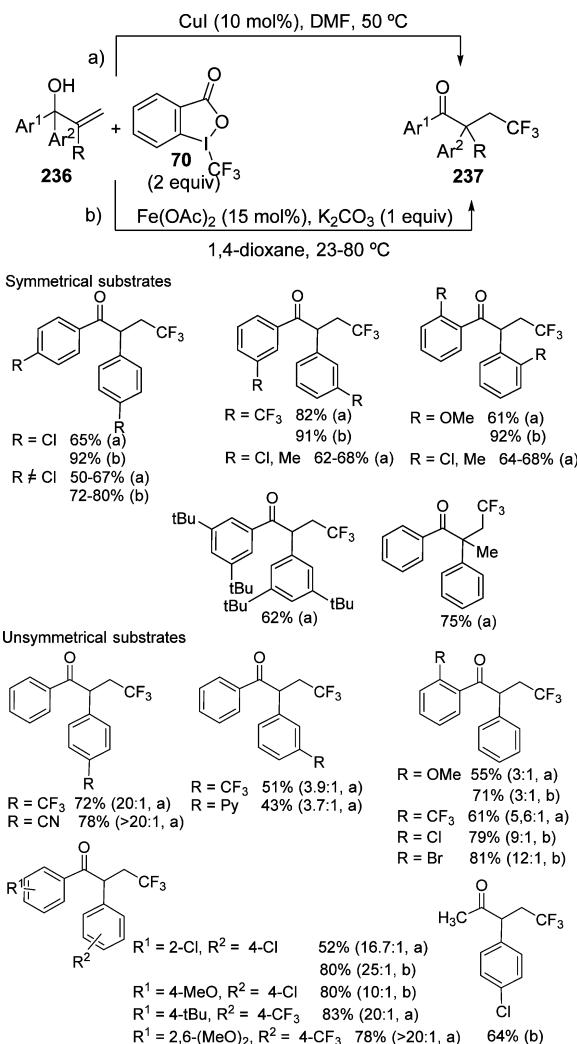


studies, the authors proposed the participation of two related catalytic cycles involving cationic and radical intermediates. Most of the reactions probably go through a radical pathway, and only when a benzyl group is attached to the nitrogen atom does a cationic mechanism predominate.

On the other hand, different substrates such as diarylallyl alcohols can also be involved in intramolecular aryltrifluoromethylation processes because they can be associated with the rearrangement of an aryl group. Thus, diarylallylic derivatives **236** can be used for the preparation of  $\beta$ -trifluoromethyl ketones **237** (Scheme 98).<sup>190</sup> The trifluoromethyl source is **70** ( $\text{Tr1}$ ),<sup>80</sup> and the reactions are catalyzed by metals such as copper and iron. In the case of copper catalysis, a great variety of  $\alpha$ -aryl- $\beta$ -trifluoromethyl ketones were obtained starting from both symmetrical and unsymmetrical diaryl allylic alcohols. Some representative examples are illustrated in Scheme 98. Starting from unsymmetrical substrates, the preferential migrations of electron-poor *meta*- and *para*-substituted aryl groups along with DFT calculations both supported the radical mechanism. Theoretical calculations also proved that non-*ortho*-substituted aryl groups migrate better than *ortho*-substituted ones probably due to steric hindrance.

The mechanism seems to involve an initial addition of  $\text{CF}_3$  radical to the terminal carbon of the olefin **236** followed by a 1,2-aryl migration through a three-membered ring transition state **238** (Scheme 99). The same trifluoromethylation-

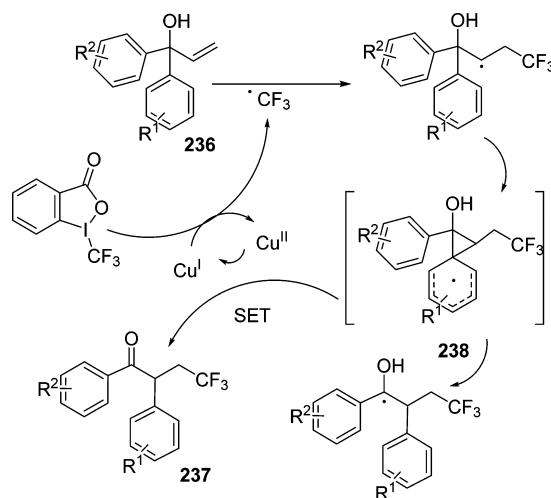
Scheme 98



migration happens with iron as catalyst, providing better yields also in mild reaction conditions (vide supra, Scheme 98b).<sup>191</sup>

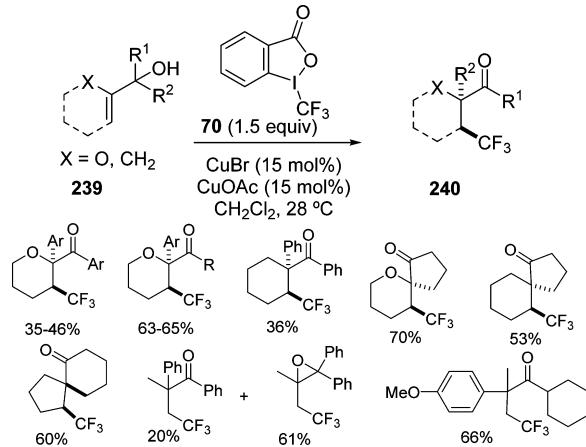
Likewise, the reaction catalyzed with Cu(I) has been extended to internal alkenes **239** containing either one or two aromatic groups. This trifluoromethylation-semipinacol-

Scheme 99



rearrangement takes place with high regioselectivity providing  $\beta$ -trifluoromethyl ketones **240** bearing a quaternary carbon center at the  $\alpha$  position including pyranil or cyclohexyl ketones as well as spiroketones **240** (Scheme 100).<sup>192</sup>

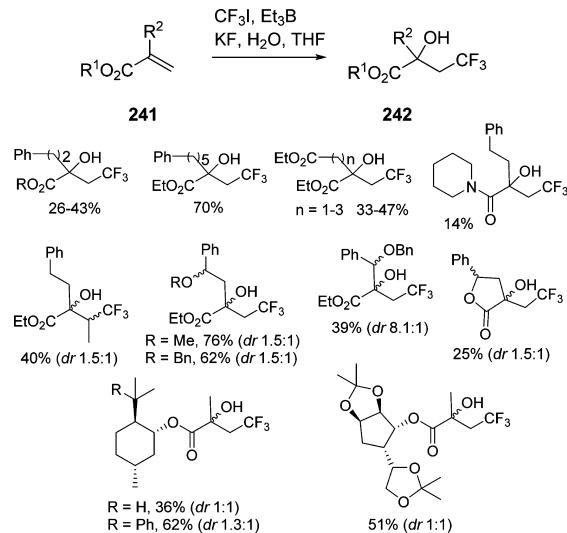
Scheme 100



**2.5.4. Oxytrifluoromethylation of Alkenes.** **2.5.4.1. Intermolecular Processes.** Oxytrifluoromethylation of alkenes was first performed on  $\alpha,\beta$ -unsaturated esters with trifluoroacetic acid under electrochemical conditions, but mixtures of trifluoromethylation/oxidation and dimerization compounds were obtained.<sup>193</sup> Higher yielding methods have been since developed, making use of other trifluoromethylating reagents such as  $\text{CF}_3\text{I}$ , **70** ( $\text{Tr1}$ ),<sup>80</sup> or (trifluoromethyl)-diphenylsulfonium triflate **108**.<sup>97</sup> For instance, radical-mediated hydroxytrifluoromethylation of  $\alpha,\beta$ -unsaturated esters **241** was achieved by means of gaseous  $\text{CF}_3\text{I}$  in the presence of  $\text{Et}_3\text{B}$ , water, and potassium fluoride in THF to give a wide range of functionalized hydroxyfluorinated derivatives **242** (Scheme 101).<sup>194</sup>

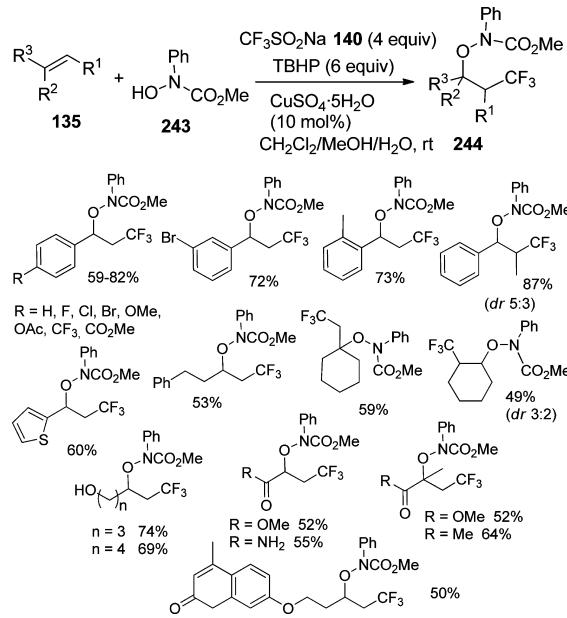
Employing **140** ( $\text{CF}_3\text{SO}_2\text{Na}$ ,  $\text{Lr}^{127}$ ) as the  $\text{CF}_3$  source and  $\text{CuSO}_4 \cdot \text{SH}_2\text{O}$  as the essential catalyst, a copper-catalyzed three-component regioselective oxytrifluoromethylation of alkenes **135** in the presence of *N*-hydroxy-*N*-phenylacetamide **243** has

Scheme 101



been developed (Scheme 102).<sup>195</sup> A wide range of functional groups such as styrenes, unactivated alkenes,  $\alpha,\beta$ -unsaturated

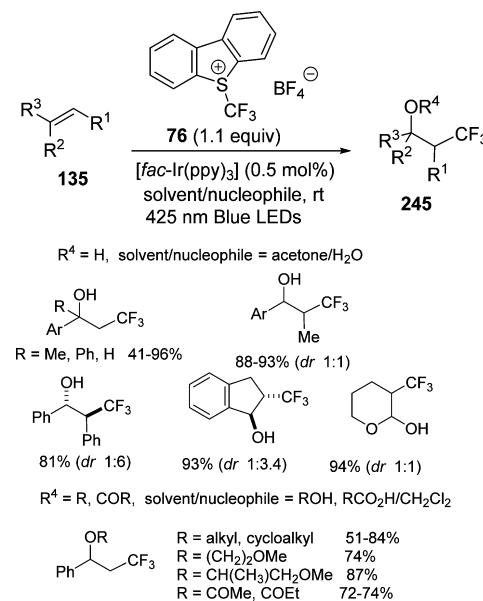
Scheme 102



ketones, esters, and amides were employed giving the corresponding products **244** in moderate to good yield. Pentene-1-ol and 5-hexen-1-ol provided the trifluoromethylated alcohols, and a derivative from 4-methylumbelliferone was also used to give the corresponding trifluoromethylated compound.

Besides electron-poor alkenes, aliphatic and aromatic olefins as well as electron-rich double bonds have also been oxytrifluoromethylated. As an example, a visible-light photocatalytic protocol has been developed to obtain trifluoromethyl alcohols **245** ( $\text{R}^4 = \text{H}$ ) from alkenes **135** and **76** ( $\text{Ur}$ )<sup>84</sup> as trifluoromethyl source in the presence of an iridium complex (Scheme 103).<sup>196</sup> The reaction is highly regioselective for both terminal and internal alkenes and also shows remarkable

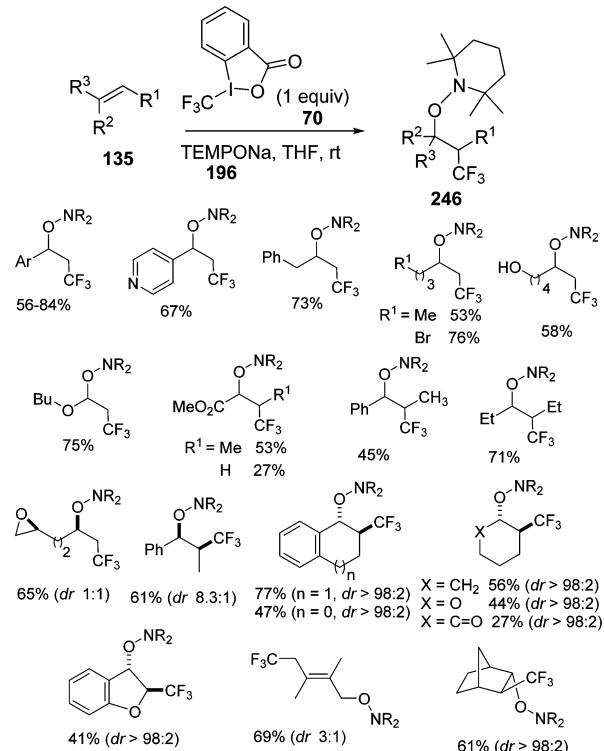
Scheme 103



diestereoselectivity in some cases. Using alcohols or carboxylic acids instead of water as solvent, alkoxy and acyloxy derivatives **245** ( $R^4 = R$ , COR) can also be obtained in the same reaction conditions. The authors suggested a radical mechanism for the process.

In another instance, aliphatic and aromatic alkenes have proved to be good substrates for the preparation of alkoxyamines by radical transition-metal-free trifluoromethylaminoxylation. <sup>169</sup> Hence, **70** (Tr1)<sup>80</sup> was used as a source of trifluoromethylating agent along with TEMPONA **196** as a reducing reagent in a SET process. In the presence of an alkene **135** (Scheme 104), the  $CF_3$  radical thus formed adds to the

Scheme 104

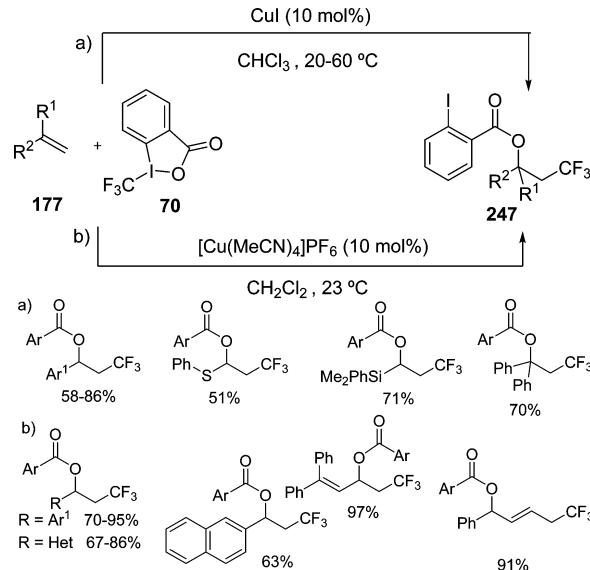


radical acceptor to give the corresponding secondary alkyl radical, which in turn is trapped by TEMPO to eventually provide the trifluoromethylaminoxylation products **246** in moderate to good yields. Alkenes can hold differently substituted aromatic, aliphatic, and electron-withdrawing groups, and even cyclic alkenes reacted with very good stereoselectivity. Furthermore, this methodology allows the additional cyclization step when starting from bisallyl ethers, as it has been mentioned in section 2.5.3.2.1 (vide supra, Scheme 68). The product alkoxyamines **246** obtained through these radical addition/trapping reactions are readily transformed (89–94%) into the corresponding alcohols by N–O bond cleavage with Zn in acetic acid, thus rendering this method as a formal hydroxytrifluoromethylation reaction.

Trifluoromethylating reagent **70** (Tr1)<sup>80</sup> has also been employed by other research groups for the addition of the  $CF_3$  moiety to aromatic and electron-rich alkenes **177** leading to a benzyloxy-trifluoromethylated product **247**. In one instance, the CuI-catalyzed addition to styrenes, vinyl sulfides, and silanes **177** takes place with high regioselectivity placing a  $CF_3$  group in the terminal carbon of the alkene and 2-

iodobenzoate (coming from the Tr1) in the other one, in a formal trifluoromethyl-benzoyloxylation reaction (Scheme 105a).<sup>197</sup> The mechanism seems to be similar to that of the

Scheme 105



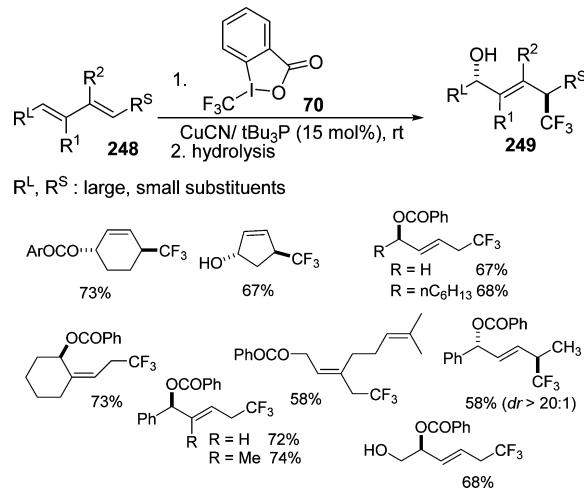
copper-catalyzed allylic C–H trifluoromethylation reactions<sup>87,88,90</sup> and probably involves SET steps through a trifluoromethyl radical intermediate. Alternatively, **70** (Tr1)<sup>80</sup> could oxidize Cu(I) to Cu(III) to form a  $[Cu(III)CF_3]$  complex. Competitive experiments show that electron-donating groups increase the reaction rate and also that alkene reacts faster than alkyne, therefore indicating the electrophilic nature of this addition reaction.

Sodeoka et al. performed the same reaction on terminal aromatic, heteroaromatic, and conjugated alkenes, by using a different copper catalyst and very mild reaction conditions to provide a wide variety of trifluoromethylated derivatives in good yields (Scheme 105b).<sup>198</sup> Rather than a radical pathway, the authors propose the addition of cationic  $CF_3$  with consequent formation of a benzyl cationic intermediate, which can be trapped by oxygen nucleophiles. The reaction products **247** can be transformed either in the corresponding 1,2-hydroxytrifluoromethyl compounds by base hydrolysis ( $K_2CO_3$ , MeOH) in 95% yield or in the trifluoromethylated alkenes (vide infra, section 3) after elimination reaction.

Xu et al. described an elegant synthesis of trifluoromethylated allylic alcohols **249** by a Cu(I)-catalyzed diastereoselective 1,4-hydroxytrifluoromethylation of conjugated dienes **248** accelerated by bulky phosphine ligands such as tri(*tert*-butyl)-phosphine.<sup>199</sup> In the case of monosubstituted dienes, the  $CF_3$  group is transferred to the terminal position. Acyclic as well as cyclic disubstituted dienes can also be used as substrates (Scheme 106). Even when starting from an internal diene bearing a phenyl and a methyl group in terminal positions, an *anti*-addition with excellent diastereoselectivity (58%, dr > 20:1) was observed. A mechanism involving  $CF_3$  radical may explain the results of the process and the origin of ligand (phosphine)-accelerated catalysis.

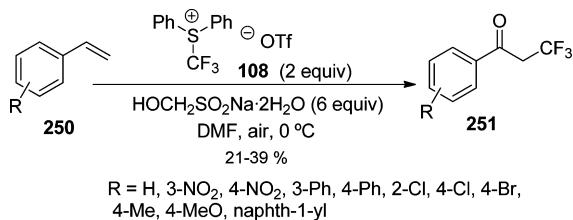
Apart from the preparation of hydroxy, alkoxy, and acyloxy derivatives by oxytrifluoromethylation of alkenes, some methods have resulted in the synthesis of  $\alpha$ -trifluoromethyl ketones by an oxidative trifluoromethylation reaction of olefins.

Scheme 106



Thus, styrenes **250** have been oxidatively trifluoromethylated leading also to  $\alpha$ -trifluoromethyl ketones **251** (Scheme 107).

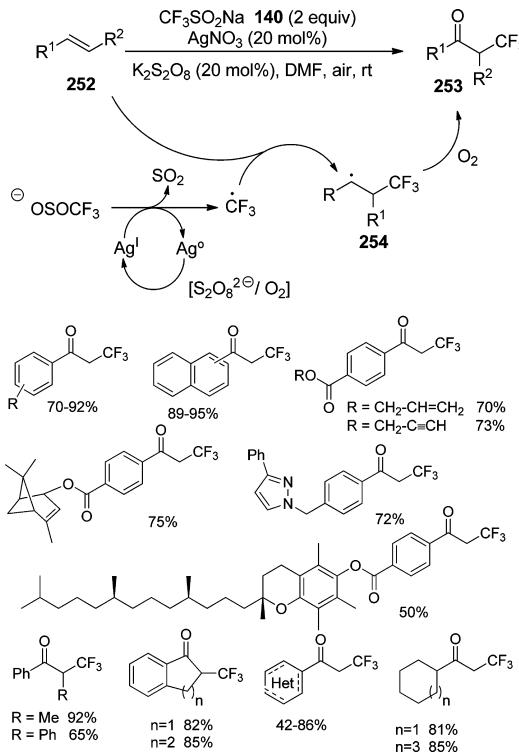
Scheme 107



For instance, one of the first applications of the chalcogenium salt *S*-(trifluoromethyl)diphenylsulfonium triflate **108**<sup>97,200</sup> beyond the typical CF<sub>3</sub> transfer was disclosed by Xiao et al.<sup>201</sup> who combined reagent **108** with the reducing agents Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> or HOCH<sub>2</sub>SO<sub>2</sub>Na. Despite the electrophilic character of the sulfonium triflate **108**, presumably this reagent is reduced by Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> or HOCH<sub>2</sub>SO<sub>2</sub>Na under suitable conditions to generate, via a SET mechanism, the CF<sub>3</sub> radical without further reduction to the anion. This radical is then trapped by the alkene, and the benzylic radical intermediate was oxidized by O<sub>2</sub> to produce the final compound **251**.

A much more efficient method has been developed for the synthesis of these  $\alpha$ -trifluoromethyl-substituted ketones from alkenes. Indeed, **140** (Lr)<sup>127</sup> in the presence of catalytic silver in DMF at room temperature are the mild conditions needed for the preparation of these oxytrifluoromethylated derivatives **253** (Scheme 108) starting from aryl alkenes **252** ( $\text{R}^1 = \text{Ar}$ ), heterocyclic alkenes **252** ( $\text{R}^1 = \text{Het}$ ), and vinyl cycloalkanes **252** ( $\text{R}^1 = \text{C}_6\text{H}_{11}, \text{C}_8\text{H}_{15}$ ).<sup>202</sup> These conditions are mild enough to allow the presence of many functionalities on the benzene ring. These include alkyl, halogen, nitro, cyano, ester, methoxy, and aldehyde, and also different heterocyclic moieties (thiophene, pyrazine, and benzofuran). Furthermore,  $\beta$ -substituted styrenes react efficiently to produce cyclic ketones and also some vinyl cycloalkenes were trifluoromethylated/oxidized successfully, although long-chain aliphatic olefins did not deliver identifiable products. The mechanism probably involves a CF<sub>3</sub> radical, formed by oxidation of **140** and subsequent loss of SO<sub>2</sub>. As usual, this radical adds to the terminal carbon of the alkene **252** giving rise to an alkyl radical

Scheme 108

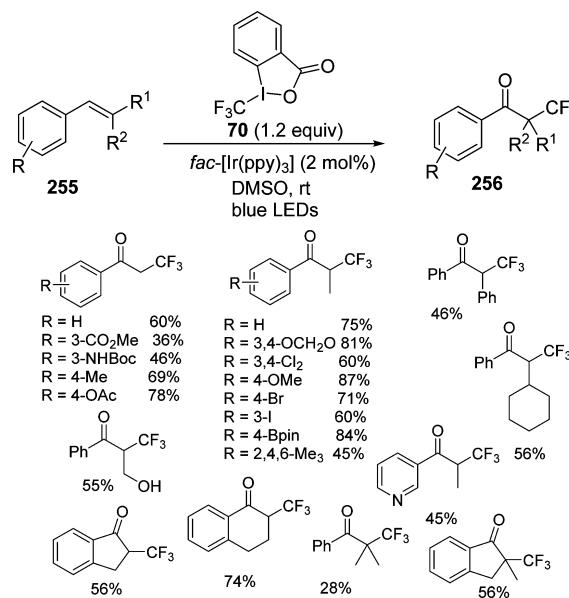


254, which is oxidized either by air or by K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> to form the ketone **253** (Scheme 108).

Likewise, Togni's reagent **70** (Tr1)<sup>80</sup> has also been employed successfully for the oxytrifluoromethylation of aromatic alkenes **255** in a photocatalytic reaction leading to the formation of  $\alpha$ -trifluoromethyl ketones **256** (Scheme 109).<sup>203</sup> The process takes place with the aid of *fac*-[Ir(ppy)<sub>3</sub>] catalyst and DMSO as mild oxidant at room temperature, and even quaternary trifluoromethylated carbons can be obtained.

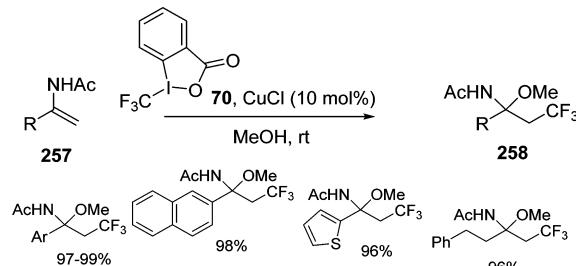
Regarding electron-rich alkene oxytrifluoromethylation, the reagent **70** (Tr1)<sup>80</sup> has proved able to oxytrifluoromethylate

Scheme 109



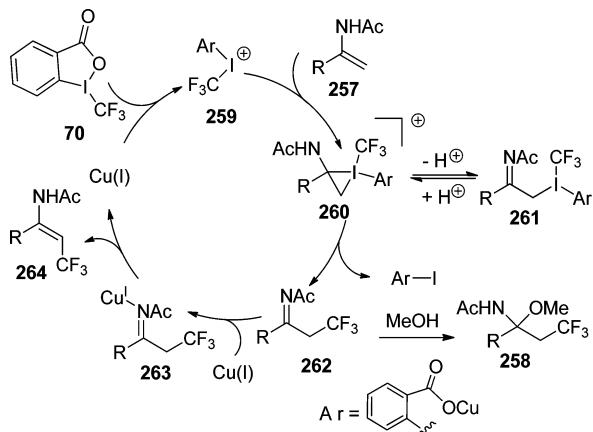
not only vinylsulfides (vide supra, Scheme 105), but also enamides **257**, therefore leading to amines **258** containing aryl, heteroaryl, and aliphatic groups, in nearly quantitative yields (Scheme 110).<sup>204</sup> Catalytic CuCl was needed, and methanol was the source of alkoxy group to be added to the olefin at room temperature.

Scheme 110



After several experiments designed to know the reaction mechanism, the authors do not exclude the radical pathway but they propose a cationic mechanism (Scheme 111) initiated by

Scheme 111

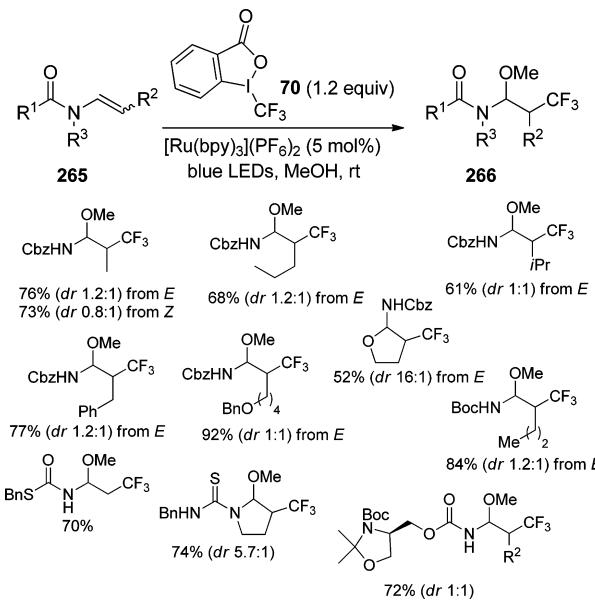


the reaction between **70** ( $\text{Tr1}$ )<sup>80</sup> and Cu(I) salt to give a cationic intermediate **259**, which then reacts with the enamide **257**. The formation of a I(III) cyclopropane intermediate **260** in equilibrium with the corresponding open imine **261**, followed by reductive elimination, generates a trifluoromethyl imine intermediate **262**. This species can be trapped by methanol when CuCl is used, yielding the oxytrifluoromethylated product **258**. However, when a different Cu catalyst and solvent are employed, a complex **263** with the Lewis acidic Cu(I) linked to the nitrogen is formed, and subsequent proton elimination would release the alkene trifluoromethylated product **264** in an alternative pathway (vide infra, section 3.1.4).

As in the case of enamides, enecarbamates **265** can also be alkoxymethylated with reagent **70** ( $\text{Tr1}$ ), in this case through a photocatalytic method with  $[\text{Ru}(\text{bpy})_3(\text{PF}_6)_2]$  and blue LEDs (Scheme 112).<sup>167</sup> Sometimes it was necessary to add some  $\text{Ph}_3\text{P}$  to avoid the iodination of the substrate with iodine generated during the reaction.

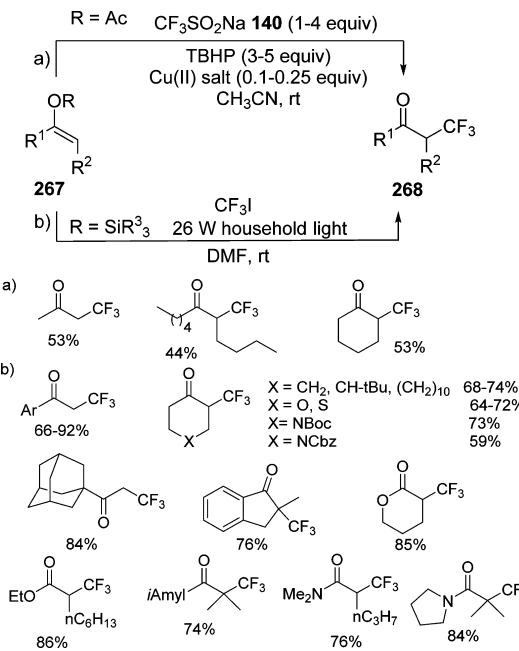
In some cases, electron-rich alkenes, such as enol acetates or silyl enol ethers, have resulted in the synthesis of  $\alpha$ -trifluoromethyl ketones by an oxidative trifluoromethylation

Scheme 112



reaction of olefins. For example, reagent **140** ( $\text{Lr}$ )<sup>127</sup> and *tert*-butyl hydroperoxide (TBHP) in the presence of catalytic amounts of Cu(II) were used to oxidatively trifluoromethylate enol acetates **267** ( $\text{R} = \text{OAc}$ ), thus producing  $\alpha$ -trifluoromethyl ketones **268** in moderate yields (Scheme 113a).<sup>205</sup>

Scheme 113

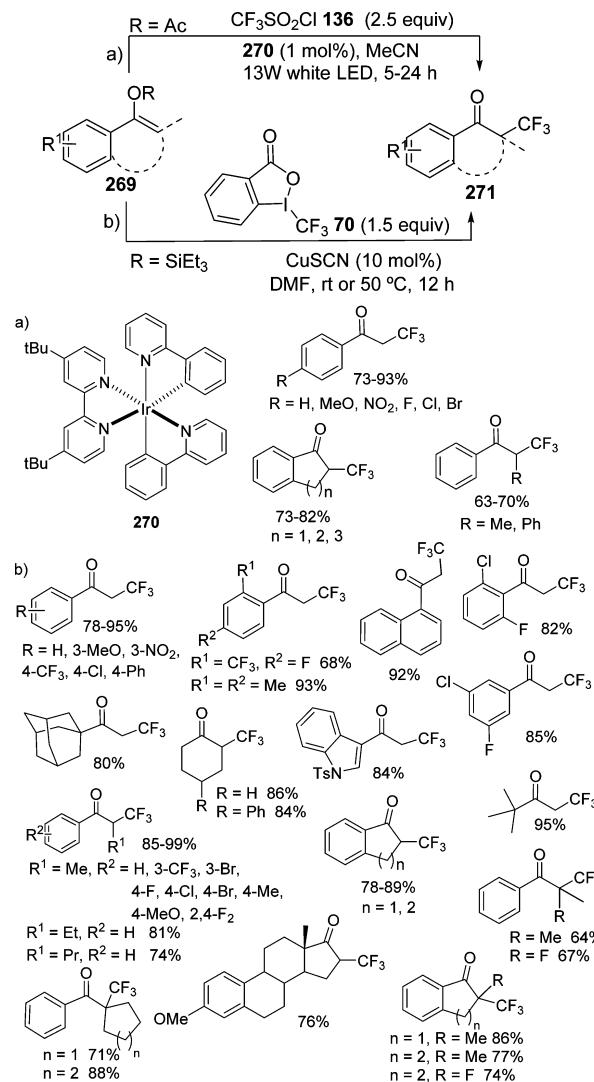


Better results were disclosed by MacMillan when using  $\text{CF}_3\text{I}$  on enol silanes, silylketene acetals, and *N,O*-acetals **267** ( $\text{R} = \text{SiR}^3_3$ ) to yield ketones, esters, and amides **268**, respectively (Scheme 113b).<sup>206</sup> The methodology has been adapted to the preparation of  $\alpha$ -trifluoromethyl ketones using a continuous-flow, two-step procedure.<sup>207</sup> Aliphatic, aromatic, and heteroaromatic ketones were obtained when silyl enol ethers **267** were mixed with  $\text{CF}_3\text{SO}_2\text{Cl}$  as the source of trifluoromethyl radicals and Eosin Y as catalyst and exposed to the light

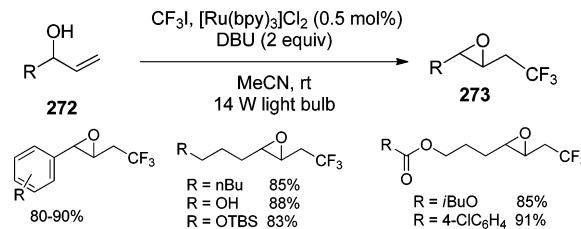
generated by a cool-white 30 W compact fluorescent lamp.  $\alpha$ -Trifluoromethylated ketones **268** were obtained in moderate to good yields.

$\alpha$ -Trifluoromethyl ketones were prepared also, by using visible-light photoredox catalysis method.<sup>208</sup> Enol acetates **269** reacted with  $\text{CF}_3\text{SO}_2\text{Cl}$  **136** as the trifluoromethyl radical source, with  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  **270** as the photocatalyst in  $\text{CH}_3\text{CN}$  as the solvent to give  $\alpha$ -trifluoromethyl ketones **271** in satisfactory yields (Scheme 114a).

Scheme 114



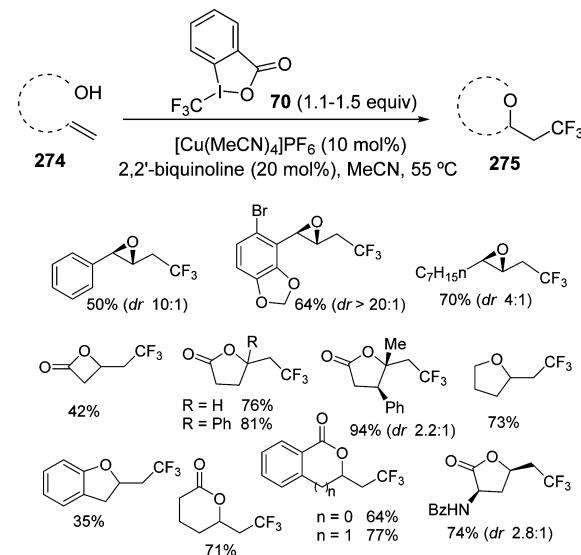
Scheme 115



nucleophilic addition to the cation or substitution of the halogen would produce the epoxide. The role of the DBU might be to act as a reductive quencher for the ruthenium catalyst and to increase the nucleophilicity of the alcohol in the reaction.

This intramolecular cyclization had been previously developed by using **70** ( $\text{Tr1}$ )<sup>80</sup> and proved to be a mild, versatile, and convenient method for the oxytrifluoromethylation of unactivated alkenes **274** containing a carboxylic, phenol, or hydroxyl group (Scheme 116).<sup>211</sup> This methodology, based

Scheme 116



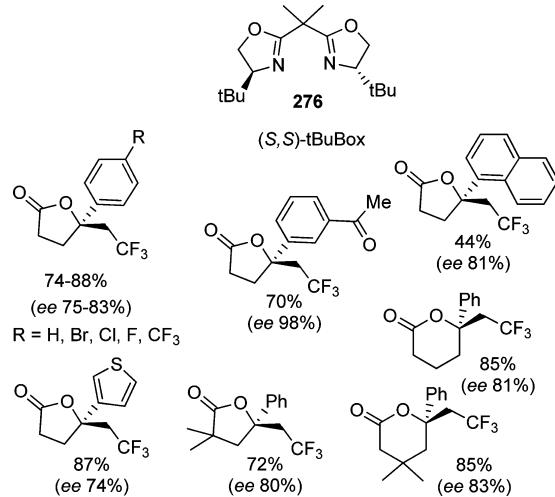
on a copper-catalyzed oxidative difunctionalization strategy, takes advantage of the presence of hydroxy-containing functional groups in the molecule to provide access to a variety of synthetically useful  $\text{CF}_3$ -containing cyclic building blocks **275** such as lactams, furan derivatives, or oxiranes, departing from simple starting materials. Epoxides were obtained with a dr ranging from 4:1 to more than 20:1.

The combination of  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$  and (*S,S*)-tBuBox **276** as ligand in methyl *tert*-butyl ether (MTBE) at room temperature enabled the use of this strategy (Figure 5) in the copper-catalyzed enantioselective oxytrifluoromethylation of alkenes. The corresponding trifluoromethylated lactones have been obtained in good yields and useful enantiomeric excesses (Figure 5).<sup>212</sup> Evidence was found in support of a redox radical addition mechanism, in which a C–O bond is enantioselectively formed via a carbon radical intermediate.

In 2014, the first example of an *endo*-trifluoromethylative carbolactonization of internal alkenoic acids **277** ( $\text{R}^1 = \text{H}, n = 1, 2$ ) by photoredox catalysis using a Ru photocatalyst and **76** as a  $\text{CF}_3$  cation source has been reported (Scheme 117).<sup>213</sup> The

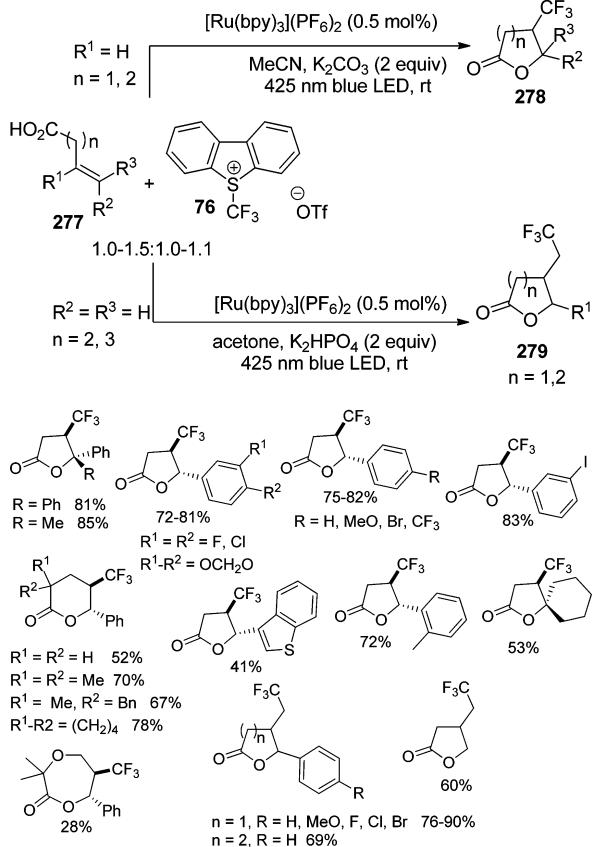
Similarly, the reaction of silyl enol ethers **269** with the electrophilic trifluoromethylating reagent **70** ( $\text{Tr1}$ )<sup>80</sup> in the presence of  $\text{CuSCN}$  gave the corresponding  $\alpha$ -trifluoromethyl ketones **271** in moderate to high yields (Scheme 114b).<sup>209</sup>

**2.5.4.2. Intramolecular Processes.** Trifluoromethyl-containing oxiranes **273** have been synthesized starting from allylic alcohols **272** and using  $\text{CF}_3\text{I}$  as the trifluoromethyl origin in a visible-light-induced reaction with ruthenium photocatalysis (Scheme 115).<sup>210</sup> This protocol also works for the synthesis of aziridines as will be shown in section 2.5.5. The reaction probably takes place by initial addition of  $\text{CF}_3$  radical to the alkene, followed by oxidation with the ruthenium photocatalyst to form an intermediate trifluoromethyl iodide or cation. Next, internal



**Figure 5.** Trifluoromethylated lactones **275** obtained from alkenes **274** and ligand (S,S)-tBuBox **276**.

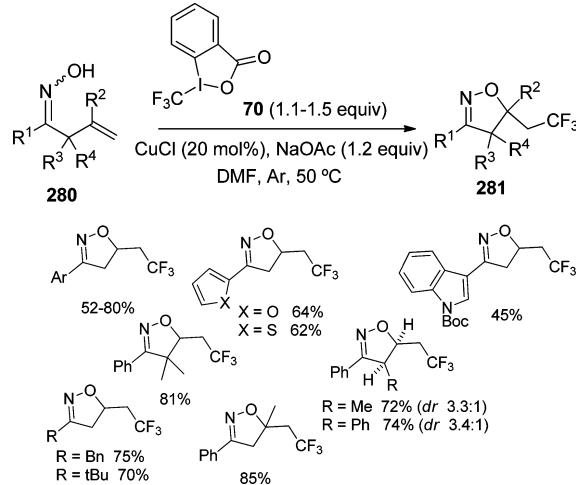
**Scheme 117**



nucleophilic attack of carboxylate group to the carbocation intermediate achieves regioselectively a variety of CF<sub>3</sub>-substituted five-, six-, and seven-membered ring *endo*-lactones **278** bearing many functional groups in a diastereoselective manner (Scheme 117). Terminal alkenoic acids **277** ( $R^2 = R^3 = H$ ,  $n = 2, 3$ ) with electron-donating, electron-withdrawing, and halogen groups on the benzene ring afforded the corresponding five-membered ring lactones **278**.

Similarly, trifluoromethylated isoxazolines **281** have been obtained when oximes were treated with a different copper catalyst like CuCl (Scheme 118).<sup>214</sup> A range of aryl, heteroaryl,

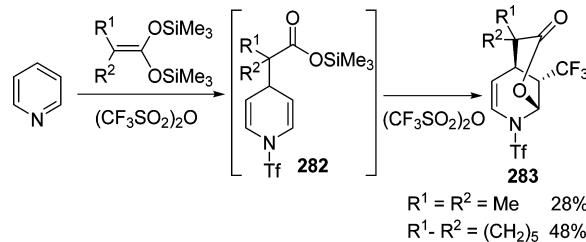
**Scheme 118**



benzyl, and alkyl 5-subsituted isoxazolines **281** can be built with moderate to good yields starting from mono- or 1,1-disubstituted alkenes but not from 1,2-disubstituted olefins. An attempt to make the six-membered heterocycle using a homoallylic oxime only produced trace amounts of the product because this is a nonfavored 6-*exo-trig* cyclization.

Another formal trifluoromethylation of enamines was observed in the reaction of pyridine, triflic anhydride (Tf<sub>2</sub>O), and ketene acetals. This transformation, termed as “exotic”, was unexpectedly found in the course of a research intended to find new activation methods for the functionalization of pyridine nucleous. Initially, the enamine derivative **282** may be generated followed by the trifluoromethylation into  $\beta$ -carbon atom of the enamino moiety of **282** and intramolecular O–C bond formation giving rise to piperidine-fused  $\delta$ -lactone **283** containing the trifluoromethyl group through a formal intramolecular acyloxytrifluoromethylation process (Scheme 119).<sup>215</sup>

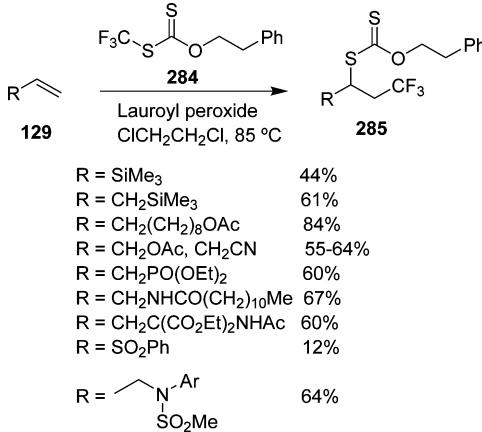
**Scheme 119**



**2.5.5. Thio- and Aminotrifluoromethylation of Alkenes.** Unlike oxytrifluoromethylation, thiotrifluoromethylation reactions of alkenes are very scarce in the chemical literature. One of the first reports dates back in 1992 and utilizes CF<sub>3</sub>I to trifluoromethylate vinyl ether bearing a trialkylstannyl sulfide group in a photochemical reaction, yielding trifluoromethylated oxathiolanes.<sup>216</sup> Although trifluoromethyl iodide has been widely used as source of radical CF<sub>3</sub> (vide supra, sections 2.2.1, 2.2.4, 2.5.1, 2.5.2, and 2.5.4),<sup>32,40</sup> it is not easy to experiment with gaseous CF<sub>3</sub>I when controlling its concentration, in particular if the reactions are conducted at high temperature. As an alternative, Zard et al. demonstrated that trifluoromethyl radical obtained by treatment of *S*-

trifluoromethylxanthate **284** with lauroyl peroxide added at the less substituted side of unactivated terminal alkenes **129** (Scheme 120), with simultaneous incorporation of the xanthate moiety in the adjacent carbon atom and formation of compounds **285** (a formal xanthate-trifluoromethylation).<sup>217</sup>

Scheme 120



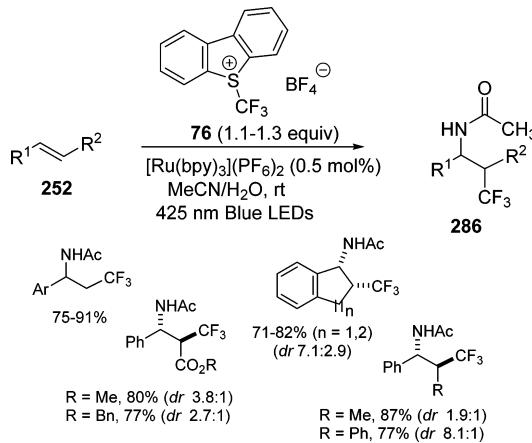
Except for vinyl sulfone **285** ( $R = SO_2Ph$ ), yields from thiotrifluoromethylation are moderate to good, and the conditions are mild enough to keep several functional groups unchanged, including silyl, phosphonate, amide, ester, and nitrile. The *S*-trifluoromethylxanthate **284** is not a commercial compound and needs to be prepared by treatment of the sodium xanthate with trifluoroacetyl anhydride.<sup>217</sup>

Slightly modified experimental conditions were applied to the thiotrifluoromethylation of an electron-rich alkene such as 2,3-dihydrofuran. Thus, instead of 1,2-dichloroethane and lauroyl peroxide, dichloromethane and catalytic amounts of  $BEt_3$  as the free radical initiator were used along with the previously used xanthate **284**. In this conditions, the addition to 2,3-dihydrofuran gave regio- and stereoselectively the *trans*-3-trifluoromethyl-2-xanthate with 52% yield.<sup>218</sup>

Aminotrifluoromethylation of alkenes **252** is an interesting reaction because it can provide  $\beta$ -trifluoromethylamino derivatives **286**, which are useful synthetic intermediates in the preparation of bioactive compounds. Nevertheless, very few methods are available to perform this transformation. The first intermolecular aminotrifluoromethylation of alkenes **252** has been achieved by means of a visible-light-induced trifluoromethylation with **76** ( $Ur$ ),<sup>84</sup> acetonitrile ( $MeCN$ ), and  $[Ru(bpy)_3](PF_6)_2$  as photocatalyst (Scheme 121).<sup>219</sup> In this process, acetonitrile ( $MeCN$ ) was used as nitrogen nucleophile, because this reagent can be used as an aminative carbocation trap agent (Ritter reaction)<sup>220</sup> and many functional groups in the benzene ring including methyl, trifluoromethyl, halogen, aldehyde, ester, *N*-Boc, boronic acid ester, and acetonitrile are tolerated. Furthermore, 1,2-disubstituted alkenes **252** can furnish the aminotrifluoromethylated products **286** including  $\beta$ -aminoesters with high regioselectivity and yields, although only a moderate level of diastereoselectivity. The same authors have used this protocol with an iridium photocatalyst to accomplish the analogous hydroxytrifluoromethylation of alkenes (vide supra, Scheme 103).<sup>196</sup>

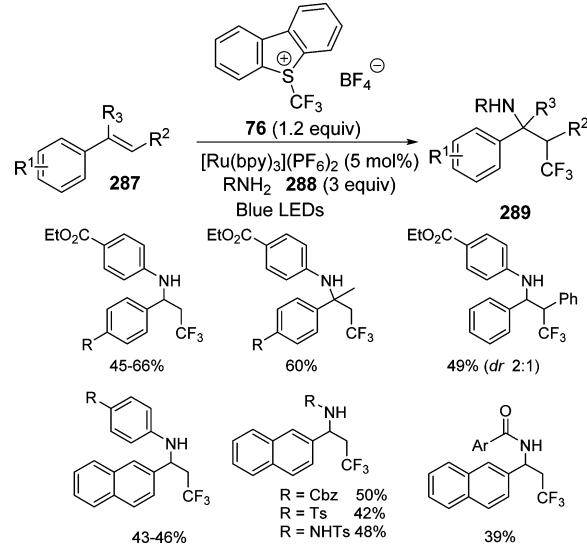
A visible-light-induced regioselective three-component aminotrifluoromethylation of styrenes **287** with aryl amines **288**

Scheme 121



and **76** ( $Ur$ )<sup>84</sup> as  $CF_3$  source has been developed (Scheme 122).<sup>221</sup>

Scheme 122

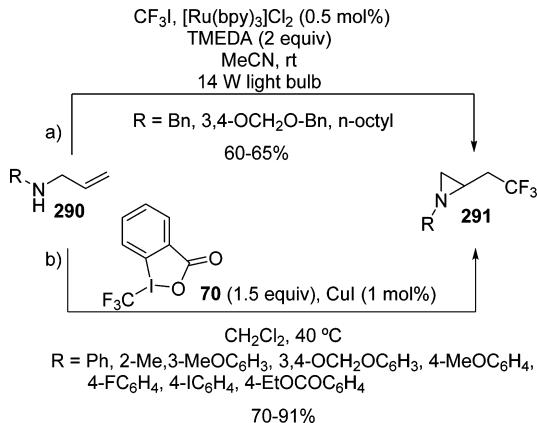


In this photoredox process,  $[Ru(bpy)_3](PF_6)_2$  was used as photocatalyst under mild conditions (rt). The process is limited to aryl amines **288**, although it tolerates less nucleophilic amines derivatives such as carbamates, amides, sulfonamides, as well as hydrazines, and  $\alpha$ - and  $\beta$ -substituted styrenes containing electron-withdrawing or -donating groups can also be used.

Intramolecular aminotrifluoromethylation leading to aziridines **291** has been successfully achieved for the first time starting from allylic amines **290** and using  $CF_3I$  as the trifluoromethyl source in a visible-light-induced reaction with ruthenium catalyst (Scheme 123a).<sup>210</sup> The same conditions were reported for the analogous conversion from allylic alcohols to oxiranes (vide supra, Scheme 115).<sup>210</sup>

Trifluoromethylated aziridines **291** from allylamines **290** have also been prepared in better yields making use of **70** ( $Tr1$ )<sup>80</sup> and  $CuI$  as a catalyst (Scheme 123b).<sup>222</sup> In very mild conditions several aromatic aziridines derived from aniline were obtained although *N*-(tert-butoxycarbonyl)allylamine did not produce the corresponding aziridine. The aziridines prepared have been submitted to opening reactions using sulfur and nitrogen nucleophiles with the aid of Lewis acids to produce a

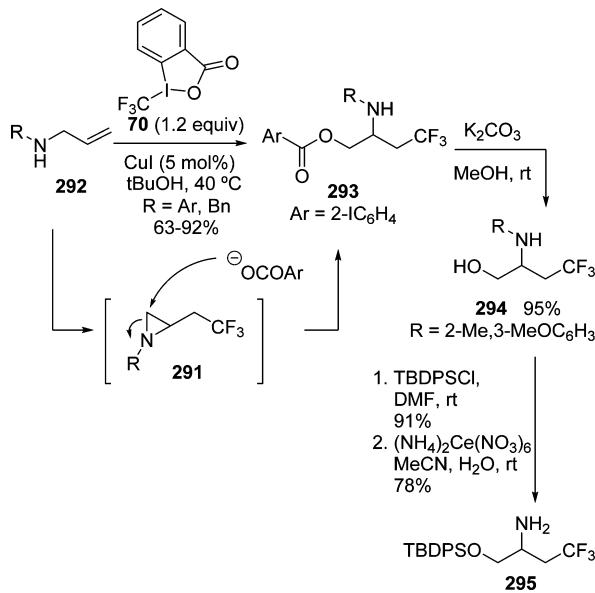
Scheme 123



variety of  $\beta$ -trifluoromethylamine derivatives. Indeed the whole transformation can be performed in one-pot starting from the allylamines and without isolation of the intermediate aziridines.

The aziridines 291 shown above (Scheme 123) are presumably the intermediates in the synthesis of 3-trifluoromethyl-2-aminopropan-1-ol derivatives 293, 294 and 295 in a formal N-migratory oxy/amino/trifluoromethylation reaction (Scheme 124). Thus, when the protocol for the formation of

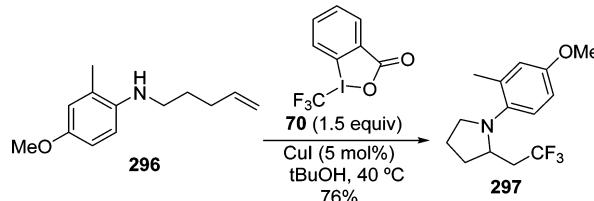
Scheme 124



aziridines 291 (vide supra, Scheme 123b) was modified by using tBuOH instead of CH<sub>2</sub>Cl<sub>2</sub>, a series of trifluoromethylated aminoalcohol derivatives 294 was obtained with good yields from allylamines 292.<sup>222</sup> These trifluoromethylation/amination/migration/acylation products 294 can easily undergo transformation into synthetically useful compounds 295 by hydrolysis of the ester or oxidative removal of the aromatic group on the nitrogen, thus leaving behind the hydroxyl or the primary amine moieties, respectively.

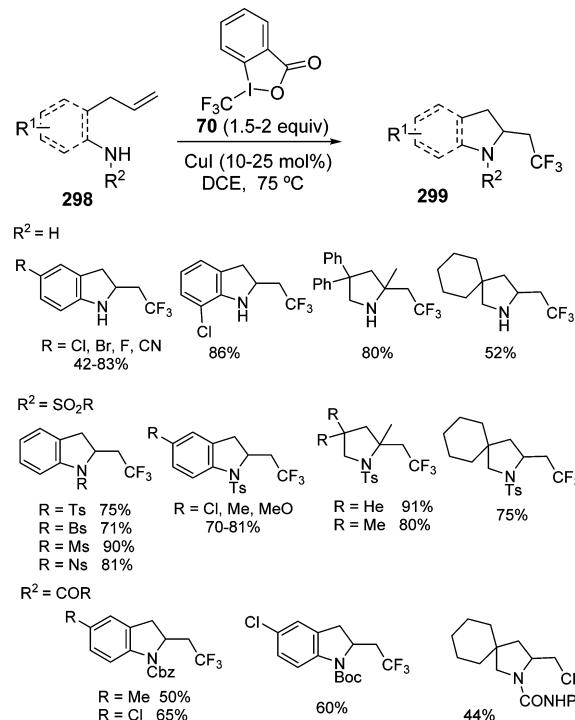
It is noteworthy that not only aziridines and their acyclic derivatives can be obtained by this strategy, because a homologated analogue of allylamines, such as 4-pentenyl aniline derivative 296, reacted efficiently to generate a five-membered heterocycle 297 in good yield (Scheme 125).<sup>222</sup>

Scheme 125



However, a light modification of the latter process, when 2-allyl anilines 298 were used with the same trifluoromethylating agent 70 (Tr1)<sup>80</sup> and CuI as a catalyst, opened a new entry to trifluoromethylated indolines 299 in good to excellent yields through a simple and efficient intramolecular aminotrifluoromethylation (Scheme 126).<sup>223</sup> The strategy can be extended

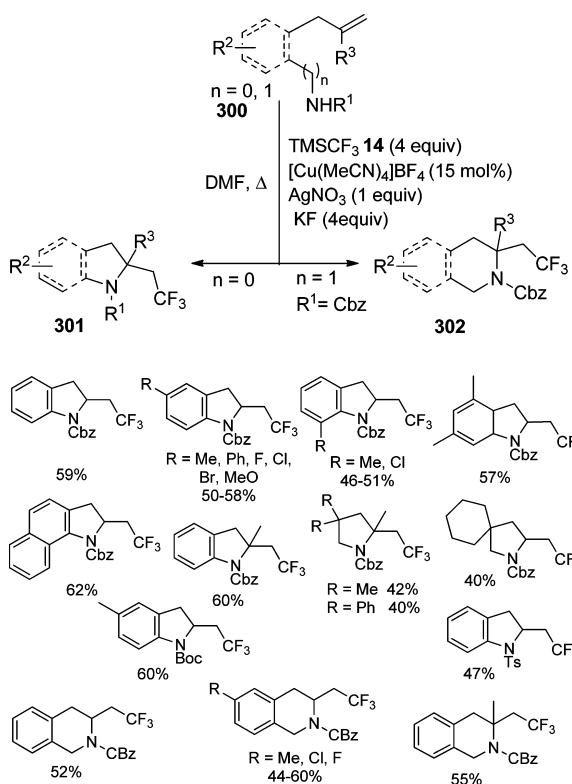
Scheme 126



to the copper-catalyzed aminotrifluoromethylation of acyclic 4-pentenyl aminoderivatives, and the corresponding cyclic trifluoromethylated substituted and spiro pyrrolines were obtained. The process tolerates a wide range of nitrogenated nucleophiles such as primary aliphatic and aromatic amines 298 ( $\text{R}^2 = \text{H}$ ), carbamates 298 ( $\text{R}^2 = \text{Cbz, Boc}$ ), ureas 298 ( $\text{R}^2 = \text{CONHPh}$ ), and sulfonamides 298 ( $\text{R}^2 = \text{SO}_2\text{R}$ ) including tosylates ( $\text{Ts, R} = p\text{-MePh}$ ), besylates ( $\text{Bs, R} = \text{Ph}$ ), mesylates ( $\text{Ms, R} = \text{Me}$ ), and 4-nitrophenylsulfonyl ( $\text{Ns}$ ) derivatives.

The same group reported the first copper(I)-catalyzed intramolecular aminotrifluoromethylation of unactivated olefins with 14 ( $\text{RPr}$ )<sup>47</sup> as trifluoromethyl source and has been applied for the preparation of five- and six-membered azaheterocycles 302 (Scheme 127), when the process was achieved with KF in the presence of catalytic amounts of  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  and  $\text{AgNO}_3$  in DMF.<sup>224</sup> *N*-Protected indolines 301 ( $n = 0$ ;  $\text{R}^1 = \text{Cbz, Boc, Ts}$ ) and pyrrolines 301 ( $n = 0$ ;  $\text{R} = \text{Cbz}$ ) were obtained from *N*-substituted 2-allylanilines 300 ( $n = 0$ ;  $\text{R}^1 = \text{Cbz, Boc, Ts}$ ) and from acyclic pentenyl carbamates 300 ( $n =$

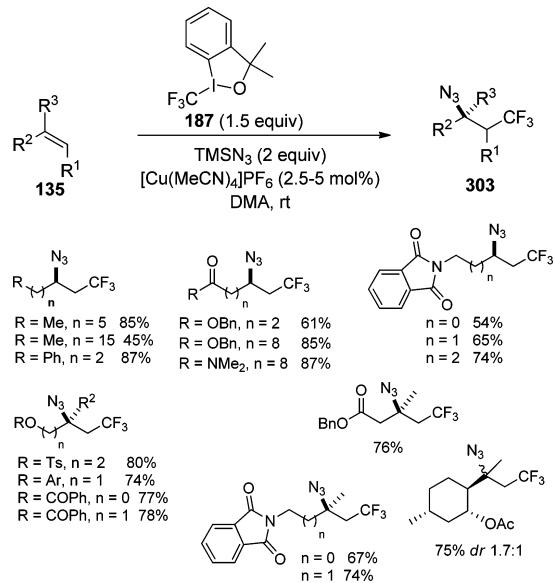
Scheme 127



0; R = Cbz). The process was also extended to 2-allylbenzylamine derivatives 300 ( $n = 1$ ; R<sup>1</sup> = Cbz), and *N*-protected (Cbz) isoquinoline derivatives 302 were prepared in moderate yields.

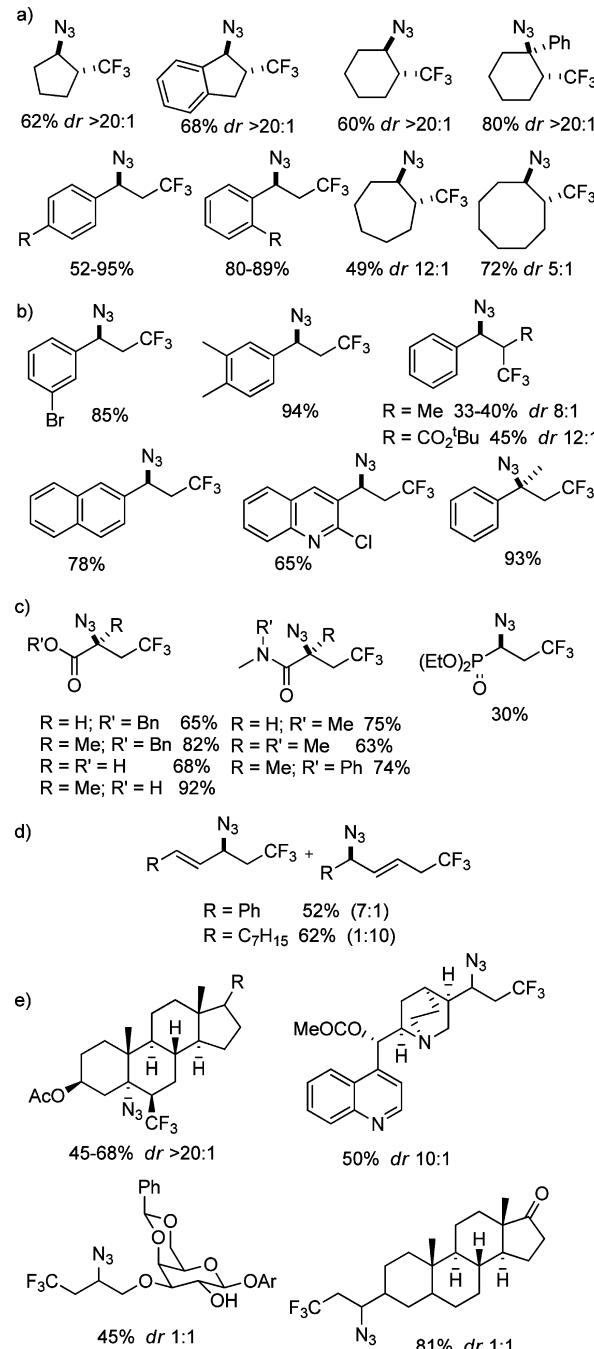
An elegant novel copper-catalyzed intermolecular trifluoromethylazidation of a wide range of unactivated and activated alkenes 135 has been recently developed<sup>225</sup> (Scheme 128). In this process, 187 (Tr2)<sup>80</sup> was used as trifluoromethylating agent and oxidant, [Cu(MeCN)<sub>4</sub>]PF<sub>6</sub> as Cu(I)-catalyst, and the nitrogen nucleophile TMSN<sub>3</sub> as azide source in *N,N*-dimethylacetamide (DMA) at room temperature to

Scheme 128



give a broad variety of substituted organoazides 303 (Scheme 128). Unactivated alkenes such as monoalkyl 135 (R<sup>1</sup> = R<sup>3</sup> = H) and 1,1-dialkyl-substituted olefins 135 (R<sup>1</sup> = H) were suitable, and functional groups such as ether, imide, and ester were tolerated.

Likewise, cyclic unactivated alkenes 135 (R<sup>1</sup>R<sup>2</sup> = (CH<sub>2</sub>)<sub>n</sub>, n = 3–6) can be used for the preparation of five-, six-, and seven-membered cyclic trifluoromethylated organoazides 303 with high *E*-stereoselectivity, while moderate diastereoselectivity was observed for the eight-membered cyclic organoazide (Scheme 128, Figure 6a). The reaction was extended to terminal 135 (R<sup>2</sup> = Ar, R<sup>3</sup> = R<sup>1</sup> = H) and 1,1-disubstituted styrenes 135 (R<sup>2</sup> = Ar,



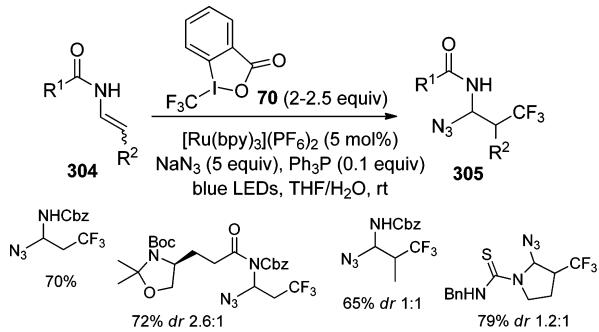
**Figure 6.** Trifluoromethylated organoazides 303 obtained from alkenes 135.

$R^1 = H$ ), the reaction being compatible not only with electron-donating but also with electron-withdrawing groups in the aryl group. Moreover, functional groups such as ester, carboxylic acid, halogen, nitro, nitrile, phenol, or aldehyde were tolerated, and even a functionalized azide containing a quinoline group can also be obtained. However, lower reactivity was observed for 1,2-disubstituted internal styrenes **135** ( $R^2 = Ar$ ,  $R^3 = H$ ), and azides **303** were obtained in low yields (Scheme 128 and Figure 6b).

Activated alkenes **135** ( $R^2 = CO_2R$ ,  $CONR_2$ ,  $PO(OR)_2$ ) containing electron-withdrawing groups such as  $\alpha,\beta$ -unsaturated carboxylates, amides, or phosphonates can also be used in this process, although when conjugated dienes **135** ( $R^2 = RCH=CH-$ ,  $R^3 = R^1 = H$ ) were used as starting olefins, a mixture of 1,2- and 1,4-additions compounds was observed (Scheme 128, Figure 6c,d). Moreover, the preparative utility of this synthetic strategy was outlined with complex molecules containing an alkenyl group such as steroids, alkaloids derived from cinchonine, sugars, and estrone with formation of the corresponding trifluoromethylated azide derivatives with moderate-good yields (Figure 6e). The authors suggested that the mechanism may be explained through the formation of radical or cationic intermediates in this catalytic process by means of the addition of  $Cu(I)$  and the  $CF_3$  source to the olefin and subsequent C–N bond formation involving an azide radical or anion.

A photoredox-catalyzed intermolecular three-component azidotrifluoromethylation of enecarbonates **304** with the trifluoromethylating agent **70** ( $Tr1^{80}$ ) and  $NaN_3$  as nitrogen nucleophile has been achieved (Scheme 129).<sup>167</sup> The

Scheme 129

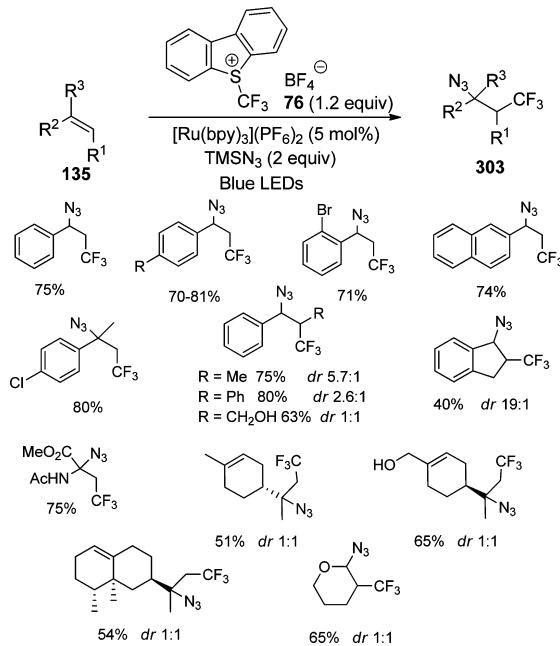


irradiation of a  $THF/H_2O$  solution of the three components with  $[Ru(bpy)_3](PF_6)_2$  as photocatalyst in the presence of  $Ph_3P$  gave the corresponding adducts **305** in good yields. A radical/cationic mechanism was suggested by the authors.

Finally, a photoredox-catalyzed regioselective three-component azidotrifluoro-methylation of alkenes **135**, with **76** ( $Ur^{84}$ ) and  $TMSN_3$  as trifluoromethyl ( $CF_3$ ) and azide ( $N_3$ ) sources in the presence of  $[Ru(bpy)_3](PF_6)_2$  as photocatalyst, has been developed for the preparation of trifluoromethylated azides **303** (Scheme 130).<sup>221</sup>

Terminal **135** ( $R^2 = Ar$ ,  $R^3 = R^1 = H$ ) and 1,1-disubstituted styrenes **135** ( $R^2 = Ar$ ,  $R^1 = H$ ) were compatible with this transformation, and similar reactivity was observed for 1,2-disubstituted internal styrenes **135** ( $R^2 = Ar$ ,  $R^3 = H$ ) with the generation of the corresponding azides in good yields (Scheme 130). The reaction can be extended to activated alkenes such as a methyl 2-acetamidoacrylate or dihydropyran. Moreover, unactivated alkenes were also compatible with this photoredox

Scheme 130



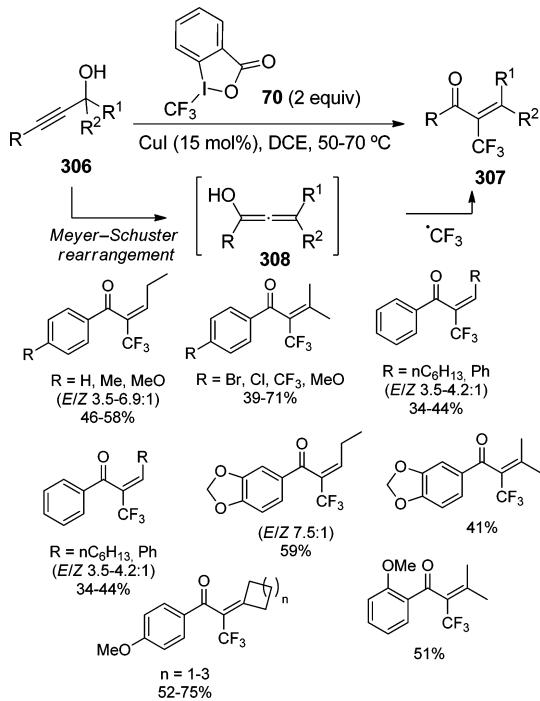
process, and trifluoromethylated azides **303** derived from (*R*)-limonene, (*S*)(*−*)-perillyl alcohol, and valencene can be prepared in a regioselective fashion involving the exocyclic terminal olefin without trifluoromethylation of the trisubstituted internal carbon–carbon double bond.

**2.5.6. Miscellaneous.** As it has been observed previously, propargylic alcohols may suffer Meyer–Schuster rearrangement to give allenol derivative intermediates, which may be trapped with electrophiles.<sup>226</sup> Taking into account this observation, Tan, Liu et al.<sup>227</sup> developed a domino copper-catalyzed trifluoromethylating reaction of propargylic alcohols **306** with Togni's reagent **70** ( $Tr1^{80}$ , Scheme 131). In this case, starting from propargylic alcohols **306**, several  $\alpha$ -trifluoromethylated enones **307** have been prepared with moderate to good yields and good stereoselectivity with *E*-isomers as major products. The formation of these compounds may be explained by an initial Meyer–Schuster rearrangement of propargylic alcohols **306** to give allenol derivatives **308**, whose subsequent reaction with  $CF_3$  would afford corresponding  $\alpha$ -trifluoromethylated enones **307**. As the authors observed, a radical  $CF_3$  may be involved in the reaction, and the direct C–H trifluoromethylation of enone can be ruled out.

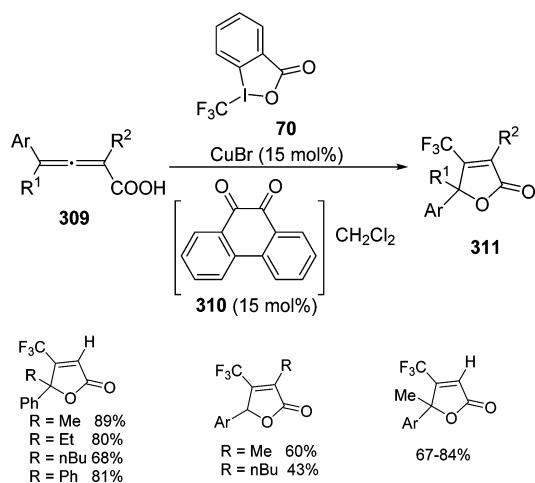
An intramolecular acyloxytrifluoromethylation of 2,3-allenic acids **309** has been described by Ma et al.<sup>228</sup> The reaction of activated allenes with Togni reagent **70** ( $Tr1^{80}$ ) in the presence of  $CuBr$  as catalyst and a dicarbonyl ligand **310** led to the formation of cyclic  $\beta$ -trifluoromethylated butenolide **311** (Scheme 132) in moderate to good yields.

The trifluoromethylation of vinyl azides **312** in the absence of metal catalysis has been reported.<sup>229</sup> The process involves a  $PhI(OAc)_2$ -mediated radical oxidative trifluoromethylation with **14** ( $RPr^{47}$ ) as trifluoromethyl source in the presence of  $CsF$  to produce  $\alpha$ -trifluoromethylated azines **314**, which were efficiently transformed into  $\alpha$ -trifluoromethylated ketones **268** or  $\beta$ -trifluoromethyl *N*-acylamines **315** (Scheme 133). A radical mechanism was proposed by the authors with formation of the trifluoromethyl radical through a SET process and subsequent addition of the radical to the vinyl azide to generate an iminyl

Scheme 131



Scheme 132

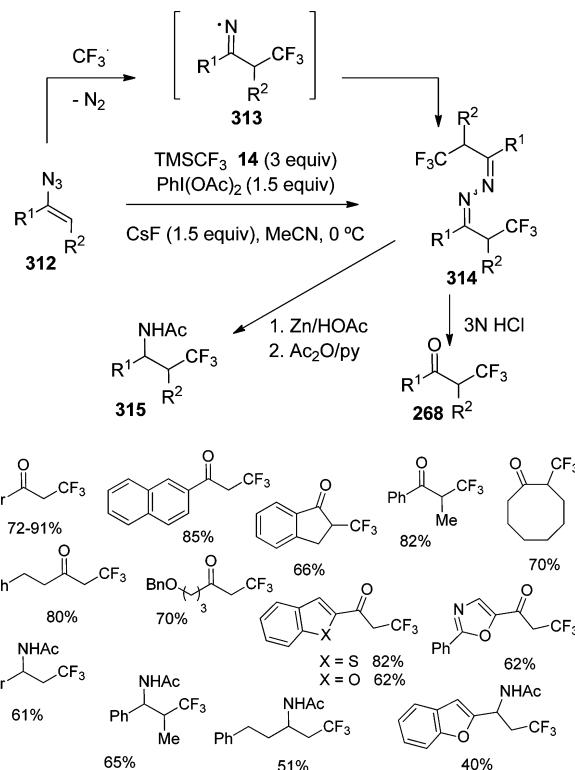


radical intermediate **313**, which dimerizes to obtain the trifluoromethylated azines **314**.

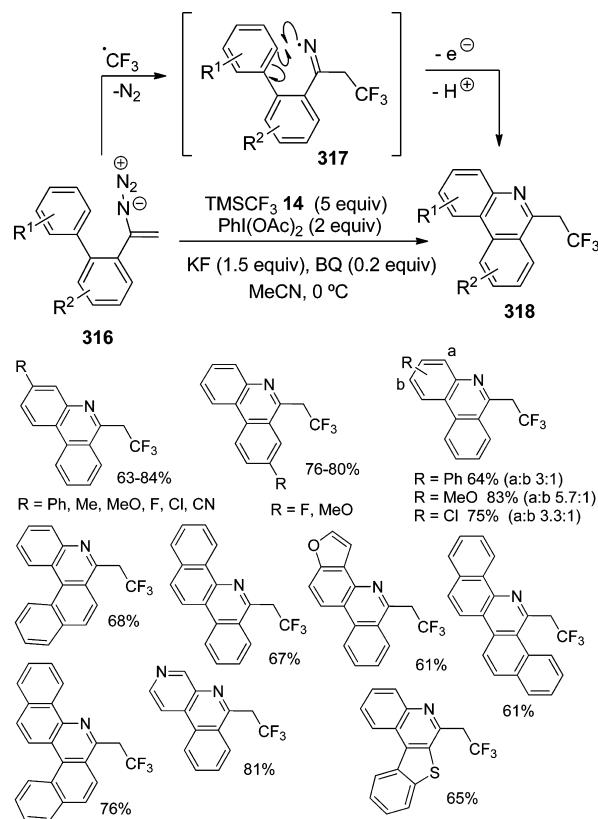
The same group reported the radical trifluoromethylation of azides containing a biphenyl group **316** for the preparation of trifluoroethyl aza-polycyclic aromatic hydrocarbons (aza-PAHs) **318** (Scheme 134).<sup>230</sup> Commercially available  $\text{TMSCF}_3$  **14** ( $\text{RPr}$ )<sup>47</sup> was employed as the source of trifluoromethyl radicals upon oxidation with  $\text{PhI(OAc)}_2$  and the assistance of KF and a catalytic amount of benzoquinone (BQ). The addition of trifluoroalkyl radical to biarylvinyl azides **316** generates the corresponding iminyl radicals **317**, which now intramolecularly cyclize with the arene moiety instead of the dimerization (vide supra, Scheme 133), furnishing aza-PAH skeletons **318** having a trifluoroethyl group.

A particular case of trifluoromethylation of nickel complex **319** afforded the corresponding heterocyclic compounds **320** with a  $\text{CF}_3$  substituent via a  $\text{Csp}^3-\text{CF}_3$  bond formation. In this example, modified trifluoromethylated porphyrin **320** has been

Scheme 133



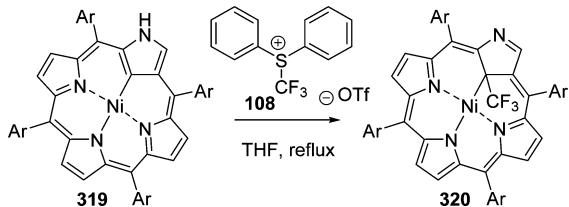
Scheme 134



prepared employing trifluoromethylating reagents. This type of Ni(II)-functionalized *N*-confused porphyrines **320** had already been prepared using perfluoroalkyl iodides, with large excess (100 equiv) of reagent and high temperatures, but only when

perfluoroalkyl derivatives other than trifluoromethyl were used.<sup>231</sup> However, when sulphonium reagent **108**<sup>97</sup> was employed, trifluoromethyl porphyrines **320** were synthesized in good yields with only 10 equiv of reagent and mild conditions (Scheme 135).<sup>232</sup>

Scheme 135

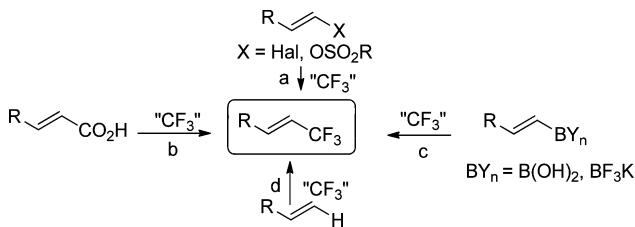


### 3. $\text{Csp}^2\text{—CF}_3$ BOND FORMATION

#### 3.1. Alkene Trifluoromethylation

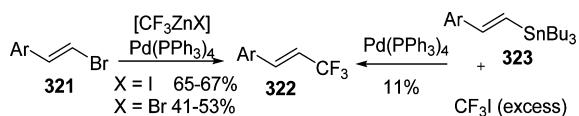
The obtention of vinyl trifluoromethyl compounds<sup>111b,d</sup> can be achieved either from functionalized alkenes through a formal substitution reaction of halides or sulfonates (Scheme 136a), carboxylic acids (Scheme 136b), boronic acids or trifluoroborates (Scheme 136c), or by direct olefinic C–H trifluoromethylation (Scheme 136d).

Scheme 136



**3.1.1. From Vinyl Halides or Sulfonates.** The preparation of alkenyl trifluoromethyl derivatives **322** mediated by palladium-catalyzed trifluoromethylation reaction of vinyl bromides **321** with trifluoromethyl zinc halides, which were generated *in situ* from trifluoromethyl halides and ultrasonically dispersed zinc power, has been described (Scheme 137).<sup>54,154</sup>

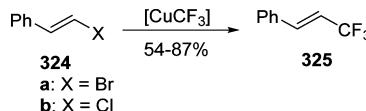
Scheme 137



On the other hand, palladium-catalyzed cross-coupling reaction between vinyl-stannanes **323** and trifluoromethyl iodide has also been reported but with very low yield.<sup>56</sup> The process may be considered as a two-step preparation of trifluoromethyl derivatives **322** from vinyl halides, given that vinyl-stannanes **323** can be prepared from halides.<sup>57</sup>

Alternatively, trifluoromethylation of  $\beta$ -bromostyrene **324a** (X = Br, Scheme 138) with a trifluoromethyl copper complex prepared either from  $\text{CF}_3\text{Cl}$  and Cu powder (62%)<sup>42</sup> or by electro-reduction of bromotrifluoromethane in the presence of a Cu anode (87%)<sup>60</sup> has been described. Furthermore, sodium triflate in the case of  $\beta$ -bromostyrene **324a** (54%)<sup>233</sup> and methyl 3-oxa- $\omega$ -fluorosulfonyl-perfluoropentanoate<sup>62</sup> or methyl

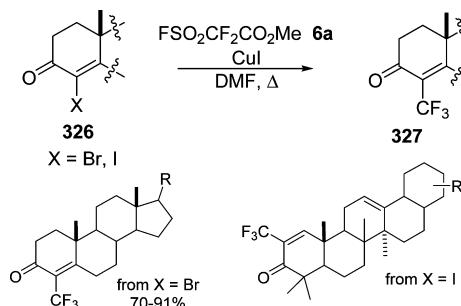
Scheme 138



halodifluoroacetate<sup>61</sup> in the presence of copper(I) iodide were used as the source of trifluoromethyl group, which replaced the halogen in alkenyl halides **324a,b** to produce the corresponding trifluoromethyl derivatives **325** (67–70%).

Methyl fluorosulfonyldifluoroacetate **6a**,<sup>43</sup> in the presence of CuI, was also utilized as the source of a trifluoromethyl group for the trifluoromethylation of 1,2-diiodoalkenes to give excellent yields (72–91%) of the useful fluorinated synthetic intermediates *trans*, *vicinal* trifluoromethyl iodo alkenes.<sup>234</sup> This strategy has been applied to the trifluoromethylation of flavonoids and to the preparation of antitumor trifluoromethylated flavonoid derivatives,<sup>136</sup> as well as for the introduction of the trifluoromethyl group in the cyclohexenone group of bromo-<sup>235</sup> and iodo-steroidal molecules **326** with formation of trifluoromethyl steroids **327** (Scheme 139).<sup>236</sup>

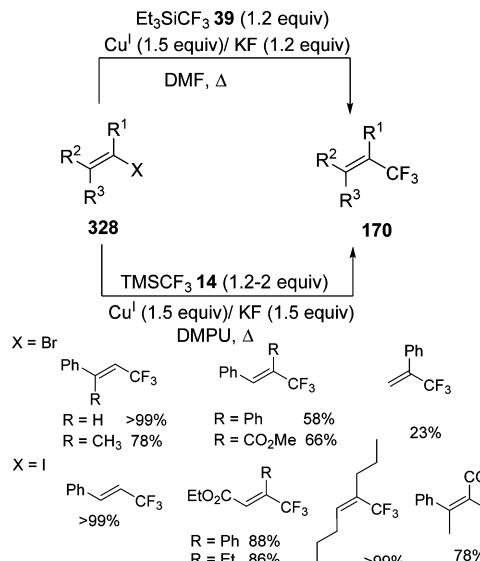
Scheme 139



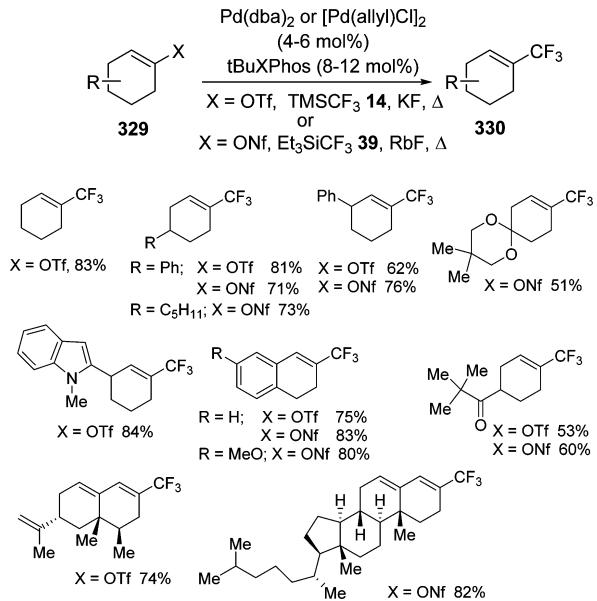
Furthermore, fluoride ion-induced cross-coupling reaction of alkenyl halides **328** with trifluoromethyltriethylsilane **39** in the presence of Cu(I) salts and KF under mild reaction conditions gave the corresponding trifluoromethylated products **170** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ; 51% from bromide;  $\text{R}^1 = \text{C}_8\text{H}_{17}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ; 90% from iodide) in moderate-good yields (Scheme 140).<sup>64</sup> Similarly, an efficient trifluoromethylation of activated and nonactivated alkenyl halides **328** (X = Br, I) was achieved with **14** ( $\text{RPr}$ )<sup>47</sup> in the presence of Cu(I) salts and KF in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) as chelating solvent.<sup>237</sup> Terminal bromides **328** ( $\text{R}^1 = \text{H}$ , X = Br) afforded good-excellent yields of the corresponding trifluoromethylated olefins **170**, while in the case of more complex substrates the yields decreased. However, iodides **328** (X = I) reacted more smoothly, and excellent yields were obtained (78–99%) when di- and also trisubstituted olefins were used, and even in the case of quaternary olefin a good yield was observed.

Buchwald et al.<sup>238</sup> developed the first palladium-catalyzed process for the trifluoromethylation of cyclic vinyl derivatives. Cyclohexenyl trifluoromethanesulfonate **329** (X = OTf) was used as substrate, and the process was achieved with **14** ( $\text{RPr}$ )<sup>47</sup> as trifluoromethyl anion source with KF as activator, in the presence of the palladium catalysts  $\text{Pd}(\text{dba})_2$  or  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  in combination with bulky biphenyl-based ligand  $t\text{BuXPhos}$ , and derivatives **330** were obtained (Scheme 141). In the case of vinyl nonaflates **329** (X = ONF =  $\text{OSO}_2\text{C}_4\text{F}_9$ ), however, the

Scheme 140



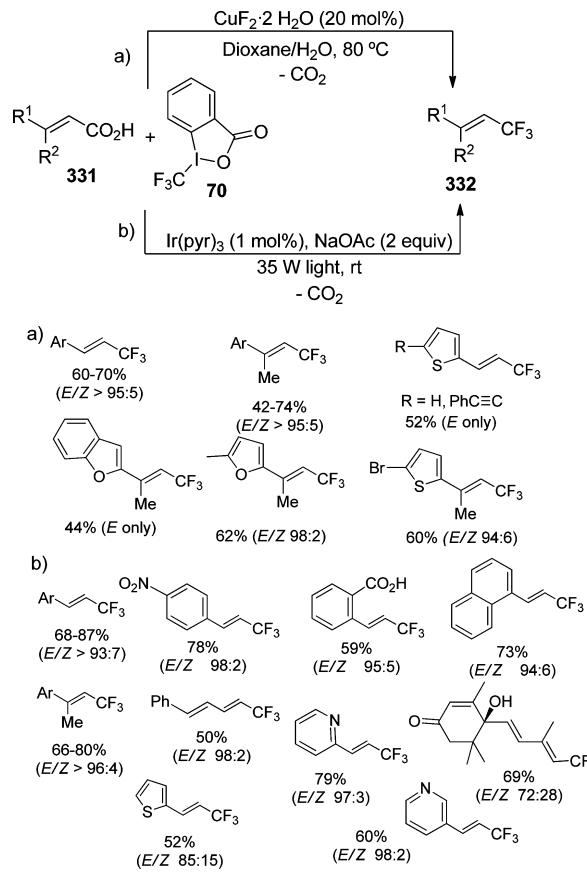
Scheme 141



combination of trifluoromethyltriethylsilane **39** as trifluoromethyl anion source with RbF as activator was used. The scope of the process was not restricted to simple and 3- or 4-substituted cyclohexene derivatives, but also ketal, amide, and heteroaromatic rings were tolerated under the reaction conditions. Likewise, conjugated alkenyl sulfonates such as those derived from 2-tetralone, (+)-nootkatone, and cholesterol can be used as substrates.

**3.1.2. From Vinyl Carboxylic Acids.** The transformation of a carboxylic group into a trifluoromethyl group has been reported<sup>239</sup> and, for example, has been applied to acrylic (45–54%) or fumaric acid (95%)<sup>240</sup> by means of the use of a fluorinating agent such as SF<sub>4</sub>. Vinyl trifluoromethyl derivatives can also be obtained from  $\alpha,\beta$ -unsaturated carboxylic acids **331** with copper catalysis through a decarboxylative fluoroalkylation reaction (Scheme 142a).<sup>241</sup> Thus, by using **70** (Tr1),<sup>80</sup> trifluoromethyl olefins **332** have been prepared with moderate to good yields and high *E* stereoselectivities, although a large

Scheme 142

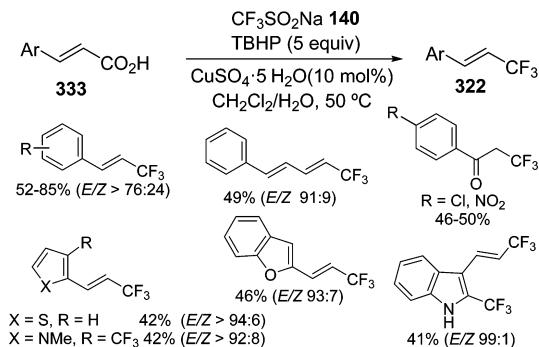


excess of carboxylic compound **331** was needed. The Lewis acid CuF<sub>2</sub> plays a double role in this reaction: on one hand enhancing the reactivity of the **70** (Tr1) and on the other facilitating decarboxylation. The scope of the process is not limited to aromatic acids **331** ( $\text{R}^1 = \text{Ar}$ ) given that trifluoromethylvinyl derivative conjugated with heterocycles **332** ( $\text{R}^1 = \text{Het}$ ) such as thiophene, furane, and benzofurane can also be prepared.

The same trifluoromethylating agent **70** (Tr1)<sup>80</sup> was used for a visible-light-induced decarboxylative trifluoromethylation of  $\alpha,\beta$ -unsaturated carboxylic acids **331** to obtain alkenyl trifluoromethanes **332** at room temperature with moderate to good yields, very high *E* stereoselectivities and tolerance to a wide range of functional groups (Scheme 142b).<sup>242</sup> The scope of the process is not limited to disubstituted aromatic acids **331** ( $\text{R}^1 = \text{Ar}$ ,  $\text{R}^2 = \text{H}$ ) including the nitro (NO<sub>2</sub>) group, which is usually not tolerated in catalytic photoredox processes, given that trisubstituted compounds **332** ( $\text{R}^1 = \text{Ar}$ ,  $\text{R}^2 = \text{Me}$ ) and the corresponding trifluorosubstituted compound derived from (+) abscisic acid (69%; *E/Z* 72:28) can be obtained. Likewise, the process was extended to trifluoromethylvinyl derivatives conjugated with heterocycles **332** ( $\text{R}^1 = \text{Het}$ ) such as thiophene and pyridine compounds with moderate yields and good *E* stereoselectivities.

Another copper-catalyzed decarboxylative trifluoromethylation of various  $\alpha,\beta$ -unsaturated carboxylic acids **333** by using the stable and inexpensive solid **140** (Lr)<sup>127</sup> was reported (Scheme 143).<sup>243</sup> The decarboxylative coupling reactions of various cinnamic acids **333** with **140** (Lr) were studied, using TBHP as the radical initiator and CuSO<sub>4</sub>·5H<sub>2</sub>O, which was found to be more efficient than other copper(II) salts (Scheme

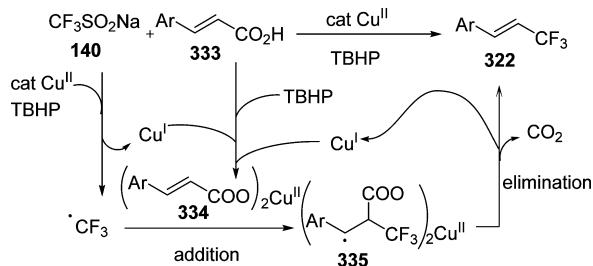
Scheme 143



143). The reaction is stereospecific providing  $\text{CF}_3$ -substituted *E*-alkenes 322. Cinnamic acids bearing electron-donating groups afforded the corresponding products 322 in moderate to high yields, while heteroarene-substituted acrylic acids such as benzene, pyrrole, benzofuran, or indole also gave the corresponding products.

A plausible mechanism involving a trifluoromethyl radical may explain the formation of the  $\text{CF}_3$ -substituted *E*-alkenes 322 (Scheme 144). The trifluoromethyl radical may be generated by

Scheme 144



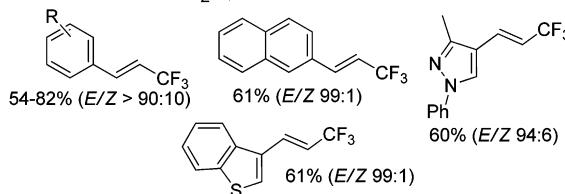
the reaction of TBHP with 140 (Lr) and Cu(II). Reaction of the  $\alpha,\beta$ -unsaturated acid 333 with Cu(I) reduced from the former step would generate a salt of Cu(II) carboxylate 334 in the presence of TBHP. Addition of the trifluoromethyl radical at the  $\alpha$ -position of cupric carboxylate would give radical 335, which then proceeds via an elimination of carbon dioxide and Cu(I) to generate product 322. Oxidation of Cu(I) by the hydroxyl radical in the presence of  $\alpha,\beta$ -unsaturated acid would regenerate the cupric carboxylate 334.

Similarly, other metals were also used for the decarboxylative trifluoromethylation of  $\alpha,\beta$ -unsaturated carboxylic acids 333 with 140 (Lr)<sup>127</sup> as trifluoromethylating agent. For example, an iron-mediated ( $\text{FeCl}_3$ ) reaction<sup>244</sup> was described, and the process tolerated aryl, naphthyl, and heterocycles under mild reaction conditions (Figure 7a).

In another example, a copper/silver-catalyzed decarboxylative trifluoromethylation of 333 with an excess of 140 (Lr, 3 equiv)<sup>127</sup> has also been developed.<sup>245</sup> The Ag(I) ( $\text{Ag}_2\text{CO}_3$ , 0.6 equiv) seemed to be essential in the presence of TBHP. Although yields are moderate, very high stereoselectivities were observed (Figure 7b).

**3.1.3. From Vinyl Boronic Acids or Vinyl Trifluoroborates.** Other methods of making vinyl trifluoromethyl derivatives start from vinyl boronic compounds by means of a copper-catalyzed trifluoromethylation process. The first example of preparation of trifluoromethylated alkenes was the cross-coupling of alkenylboronic acids 336 with 14 ( $\text{RPr}$ )<sup>47</sup> and

a) Conditions: 140 (3 equiv),  $\text{FeCl}_3$  (1 equiv),  $\text{K}_2\text{S}_2\text{O}_8$  (4 equiv) MeCN/H<sub>2</sub>O, 50 °C



b) Conditions: 140 (3 equiv), TBHP (5 equiv),  $\text{CuCl}$  (20 mol%),  $\text{Ag}_2\text{CO}_3$  (0.6 equiv), DCE

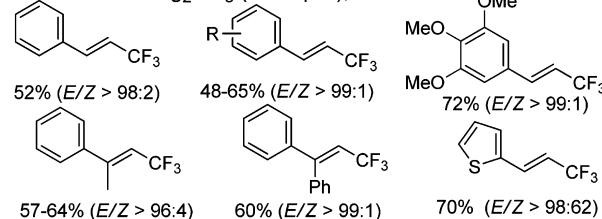
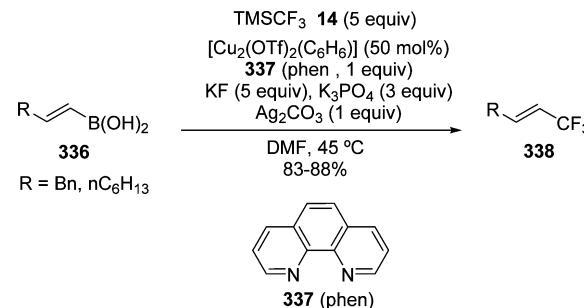


Figure 7. Reaction conditions employed and trifluoromethylated compounds 322 obtained from  $\alpha,\beta$ -unsaturated carboxylic acids 333.

mediated with Cu(I), in the presence of  $\text{Ag}_2\text{CO}_3$ , 1,10-phenanthroline 337 (phen), KF, and  $\text{K}_3\text{PO}_4$ , providing trifluoromethyl compounds 338 (Scheme 145).<sup>246</sup>

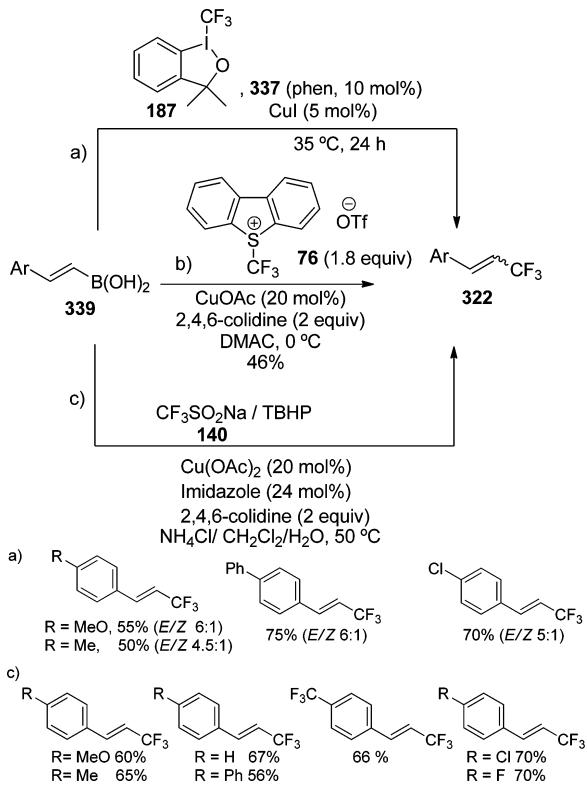
Scheme 145



In another example, Liu et al. used aromatic alkenylboronic acids 339 (Scheme 146a) and hypervalent iodine(III) Togni's reagent 187 ( $\text{Tr}2$ )<sup>80</sup> in the presence of 337 (phen, 10 mol %) as a ligand and CuI as a catalyst to make trifluoromethylated alkenes 322 as a mixture of *E/Z* stereoisomers ( $E/Z = 4.5–6:1$ ).<sup>247</sup> Similarly, a copper-catalyzed process for trifluoromethylation of vinyl boronic acid 339 ( $\text{Ar} = 4-\text{PhC}_6\text{H}_4$ ) with 76 ( $\text{Ur}$ )<sup>84</sup> was described<sup>248</sup> (Scheme 146b), and the corresponding trifluoromethylstyryl derivative 322 ( $\text{Ar} = 4-\text{PhC}_6\text{H}_4$ ) was obtained in moderate yield with a higher proportion of the *E* isomer ( $E/Z = 17:1$ ). The selective trifluoromethylation of arylvinylboronic acids 339 with 140 (Lr)<sup>127</sup> in the presence of copper catalysts and TBHP has also been recently reported.<sup>249</sup> The process (Scheme 146c) can be performed at room temperature under an air atmosphere, with exclusive *E* isomer formation and in moderate-good yields.

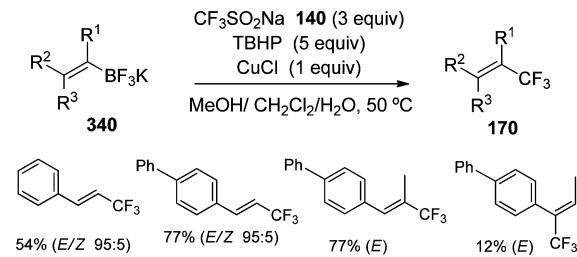
Potassium organotrifluoroborates have advantages in cross-coupling reactions as compared to their boronic acid and boronic ester counterparts in terms of easier preparation procedures and greater nucleophilicity.<sup>250</sup> To evaluate these advantages, a simple and efficient copper-mediated radical trifluoromethylation of unsaturated organotrifluoroborates 340 with 140 (Lr)<sup>127</sup> in the presence of copper and TBHP was reported.<sup>251</sup> The substitution pattern in the starting olefin

Scheme 146



seems to play an important role in the process. Simple styrenes **340** ( $\text{R}^2 = \text{Ar}$ ,  $\text{R}^3 = \text{R}^1 = \text{H}$ ) and  $\beta$ -substituted styrene derivatives **340** ( $\text{R}^2 = \text{Ar}$ ,  $\text{R}^3 = \text{H}$ ;  $\text{R}^1 = \text{CH}_3$ ) led to the formation of the trifluoromethylated di- and trisubstituted compounds **170** in moderate to good yields and high *E*-stereoselectivity (Scheme 147). However, trisubstituted olefin

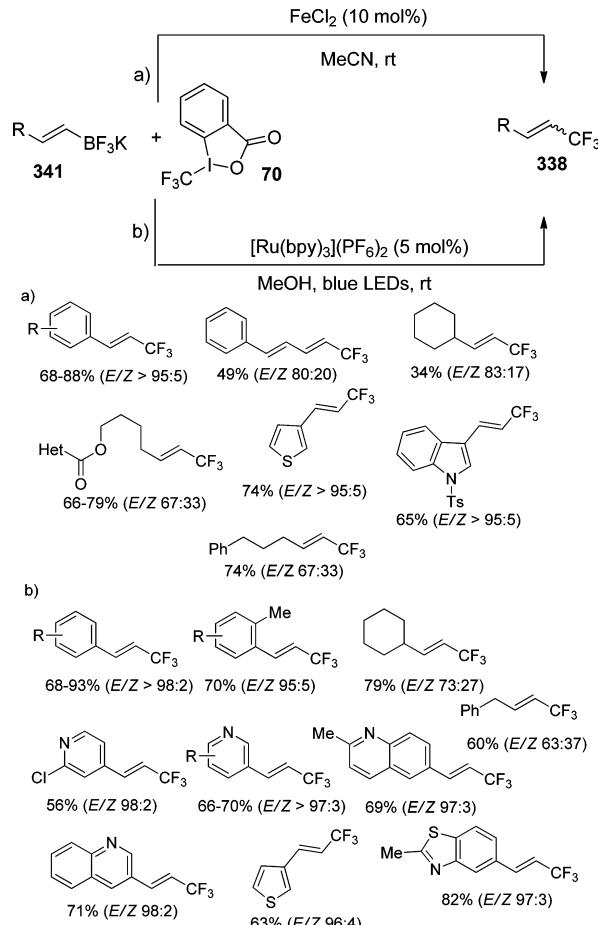
Scheme 147



with the trifluoromethyl group in  $\alpha$ -position **170** ( $\text{R}^2 = \text{Ar}$ ,  $\text{R}^3 = \text{CH}_3$ ;  $\text{R}^1 = \text{H}$ ) was obtained in very low yield, and no reaction was observed in a cyclic olefin. A little later, the same trifluoromethylating agent (**140**, Lr),<sup>127</sup> similar substrates, and reaction conditions were used for the Cu-mediated trifluoromethylation of vinyl trifluoroborates **340**.<sup>252</sup> In the case of disubstituted trifluoroborates **340** ( $\text{R}^2 = \text{Ar}$ ,  $\text{R}^1 = \text{R}^3 = \text{H}$ ), good yield and stereoselectivities were observed and even a cyclic vinyl trifluoromethane **170** ( $\text{R}^1\text{R}^2 = (\text{CH}_2)_4$ ,  $\text{R}^3 = \text{H}$ , 60%) was prepared.

Buchwald employed vinyltrifluoroborates **341** as substrates and iron(II) catalysis with **70** (Tr1)<sup>80</sup> (Scheme 148a).<sup>253</sup> The conditions are mild and can be applied to aryl, cinnamyl, alkyl, or heteroaryl derivatives, with good yields and excellent *E/Z* ratio. The reaction also worked quite well with other Lewis acid

Scheme 148

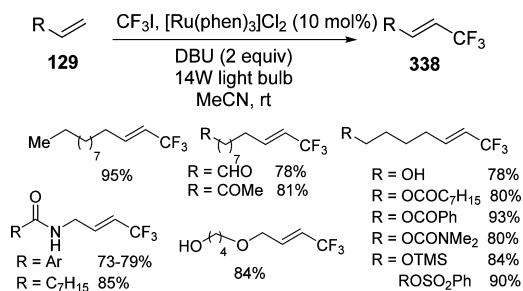


catalysts instead of  $\text{FeCl}_2$ ,  $\text{Sn}(\text{OTf})_2$  being the best one. The limitations are that electron-deficient substrates give low yields of trifluoromethylated alkenes **338**, as do trisubstituted vinyltrifluoroborate salts. Moreover, the reaction showed no stereospecificity because even starting from the *Z* isomer, the *E* isomer is obtained almost exclusively. These results suggest that trifluoromethylation is not proceeding through a transmetalation/reductive elimination pathway and that the Lewis acid could promote the formation of a cationic intermediate, although a radical-type mechanism cannot be ruled out.

Vinyltrifluoroborates **341** have also been trifluoromethylated with **70** (Tr1)<sup>80</sup> through a facile visible-light-induced synthesis using the photoredox catalyst  $[\text{Ru}(\text{bpy})_3](\text{PF}_6)_2$  (5 mol %) (Scheme 148b).<sup>254</sup> Reagent **70** (Tr1)<sup>80</sup> serves as a  $\text{CF}_3$  radical precursor, likely through a SET process. This new photocatalytic protocol can be applicable to a wide variety of arylvinylborates **341** containing electronically diverse substituents such as aromatics and heteroaromatic derivatives, as well as for the preparation of benzyl- and cyclohexyltrifluoromethyl derivatives **338** with stereoselective formation of the *E* isomer.

**3.1.4. Direct C–H Olefinic Trifluoromethylation.** Direct C–H olefinic trifluoromethylation of unactivated alkenes has been developed by visible light photoredox catalysis with trifluoromethyl iodide ( $\text{CF}_3\text{I}$ ) as the source of the trifluoromethyl group,  $[\text{Ru}(\text{phen})_3]\text{Cl}_2$  as catalyst, and with a 14 W household lamp.<sup>93</sup> The reaction is stereoselective providing only the *E* isomer and works especially well with terminal alkenes **129** (Scheme 149).

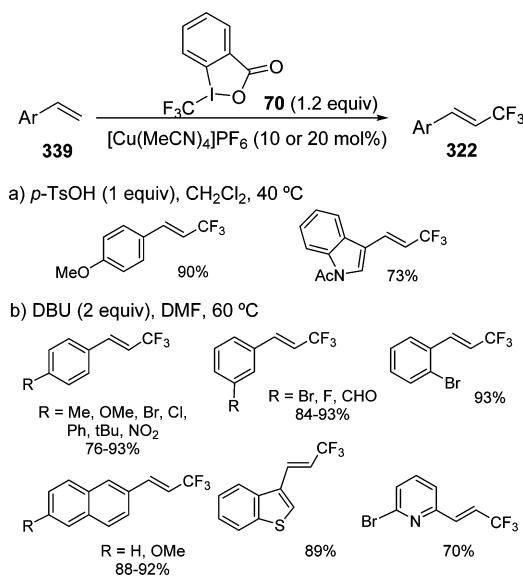
Scheme 149



The process tolerates a wide range of functional groups in the alkene, including aldehyde, ketone, unprotected alcohol, ester, carbamate, amide, silyl ether, and sulfonate. Although the process for terminal alkenes is regio- and stereoselective, in the case of internal alkenes a mixture of *E* and *Z* isomers is formed. For example, the reaction of *trans*-*S*-decene gave a mixture of *E* and *Z* isomers (1.4:1) in 80% yield. The authors suggested that the reaction may be explained through a radical  $\text{CF}_3$  intermediate formed from  $\text{CF}_3\text{I}$  favored by the visible light and the Ru catalyst.

Electrophilic trifluoromethylating reagent **70** ( $\text{Tr1}$ )<sup>80</sup> and catalytic conditions worked for the direct trifluoromethylation of styrene and ethenylindole derivative **339** (Scheme 150a) to

Scheme 150

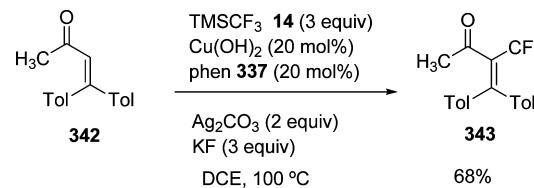


obtain the corresponding trifluoromethyl alkenes **322** in good yields.<sup>198</sup> Likewise, another copper-mediated process with the same trifluoromethylating reagent **70** ( $\text{Tr1}$ )<sup>80</sup> has been developed for the efficient trifluoromethylation of terminal alkenes **339** under mild conditions.<sup>255</sup> Substituents in *ortho*, *meta*, and *para* of the phenyl group are tolerated, and trifluoromethylated naphthyl, benzotriophene, and pyridine derivatives can also be prepared (Scheme 150b).

The first example for the introduction of the trifluoromethyl group in the  $\alpha$ -position of enones was described in the 1970s in the context of the cyclohexenone ring functionalization of steroids.<sup>256</sup> This photocatalyzed reaction was performed by irradiation of a mixture of the steroid dienones with trifluoromethyl iodide in the presence of pyridine with

ultraviolet light (3500 Å) at room temperature. However, the yields were low (32–42%). Another regioselective  $\alpha$ -trifluoromethylation of  $\alpha,\beta$ -unsaturated ketones has been achieved by means of a Cu(II)-catalyzed trifluoromethylation of ketone **342** using **14** ( $\text{RPr}$ )<sup>47</sup> as trifluoromethyl source and KF in the presence of catalytic amounts of  $\text{Cu}(\text{OH})_2$ , **337** (phen), and  $\text{Ag}_2\text{CO}_3$  (Scheme 151).<sup>257</sup> A mechanism involving radicals was suggested for this process based on a TEMPO-quenching experiment.

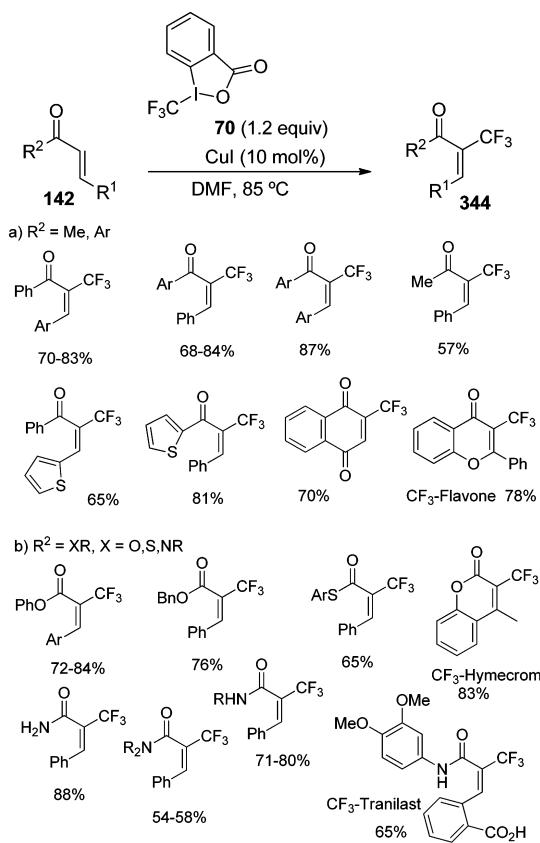
Scheme 151



Likewise, a catalytic regioselective  $\alpha$ -trifluoromethylation of conjugated ketones using trifluoromethylating reagent **70** ( $\text{Tr1}$ )<sup>80</sup> has been also developed.<sup>258</sup> Copper(I) iodide was used as catalyst, yields are moderate-good, and the trifluoromethyl group is localized in the *E*  $\alpha$ -position with respect to the  $\beta$ -substituent (Scheme 152a). The scope of the process is not restricted to aryl ketones **142** ( $\text{R}^2 = \text{Ar}$ ) given that an example of methyl ketone **142** ( $\text{R}^2 = \text{Me}$ ) and a quinone is described. The process has been outlined with the trifluoromethylation of biologically active molecules such as a flavone.

This copper-catalyzed  $\alpha$ -trifluoromethylation was extended to  $\alpha,\beta$ -unsaturated esters, thioesters, and amides **142** ( $\text{R}^2 = \text{XR}$ ,

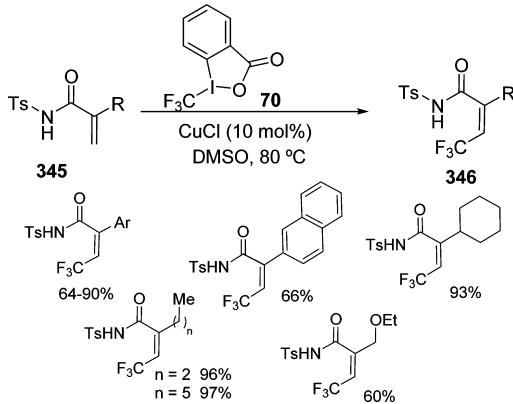
Scheme 152



$X = O, S, NR$ ) using trifluoromethylating reagent **70** (Tr1)<sup>80</sup> and copper(I) iodide as catalyst to obtain  $\alpha$ -trifluoromethylated derivatives **344** (Scheme 152b).<sup>258</sup> Moderated yields were obtained for esters and thioesters, and the process also applied to primary, secondary, and tertiary  $\alpha,\beta$ -unsaturated amides. This methodology was successfully employed for the trifluoromethylation of Hymecromone and Tranilast.

*N*-Tosylated acrylamides **345** treated in similar conditions with **70** (Tr1)<sup>80</sup> and the aid of a Cu(I) salt in DMSO produced however the *cis* stereospecific  $\beta$ -trifluoromethylation leading to compounds **346** (Scheme 153).<sup>259</sup> The reaction tolerates a

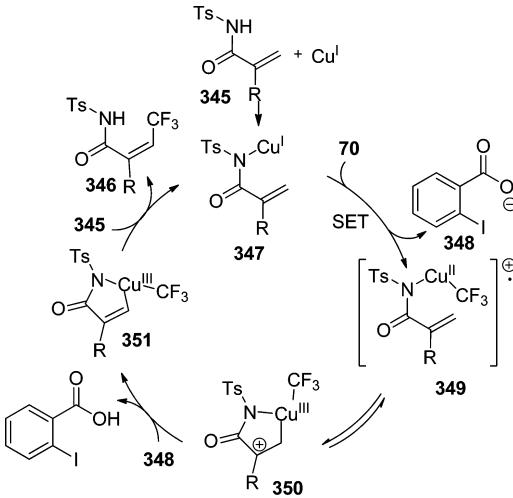
Scheme 153



wide variety of substituents, and the tosylamido group not only activates the starting olefinic substrates but also seems to act as a directing group for the stereospecific formation of *cis*-trifluoromethylated derivatives **346**.

The authors proposed a mechanism based on an initial formation of a copper(I)-complex **347** (Scheme 154) generated

Scheme 154

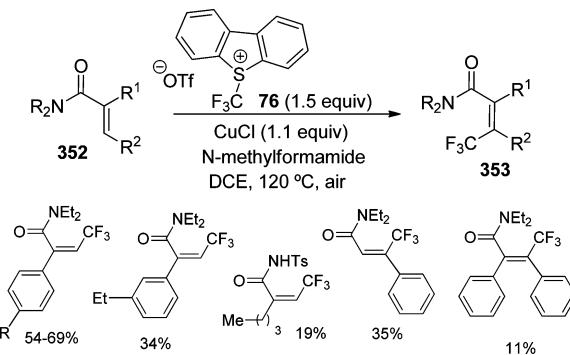


by reaction of acrylamide and  $CuI$  catalyst, followed by oxidation and intramolecular SET to give the anion **348** and the cation radical **349**. Intramolecular cyclization of this intermediate may afford a metal–carbon bond construction with formation of cyclic Cu(III) carbocation **350** and subsequent hydrogen elimination to produce cyclic intermediate **351**. Reductive elimination and transmetalation with a molecule of acrylamide **345** gives trifluoromethyl derivatives **346** and

regenerates the Cu(I)-complex **347** ready for the next catalytic cycle.

Similarly, a copper-catalyzed direct *cis* stereospecific trifluoromethylation on *N,N*-diethylacrylamides **352** with **76** (Ur)<sup>84</sup> as trifluoromethyl source for the regio- and diastereoselective preparation of *Z*- $\beta$ -trifluoromethyl-substituted acrylamides **353** was reported (Scheme 155).<sup>260</sup> The method was not restricted

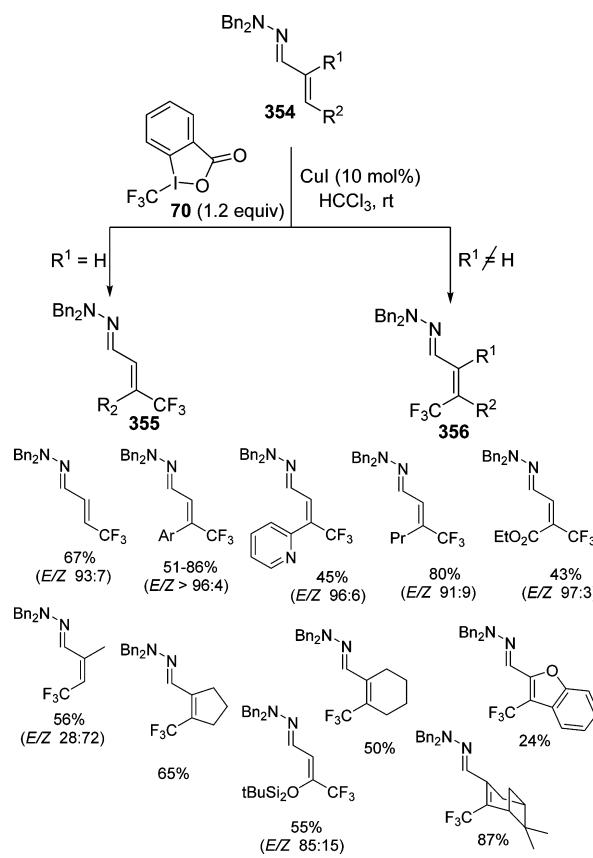
Scheme 155



to terminal alkenes **352** ( $R^2 = H$ ), given that  $\beta$ -substituted alkenes **352** ( $R^2 = Ph$ ) can also be used, although in this latter case the yields were low.

Copper-catalyzed  $\beta$ -trifluoromethylation of  $\alpha,\beta$ -unsaturated aldehyde *N,N*-dibenzylhydrazones **354** (Scheme 156) using hypervalent iodine reagent **70** (Tr1)<sup>80</sup> and copper(I) iodide as catalyst has been also described.<sup>261</sup> When hydrazones without substituent in  $\alpha$ -position **354** ( $R^1 = H$ ) were used, *E*- $\beta$ -

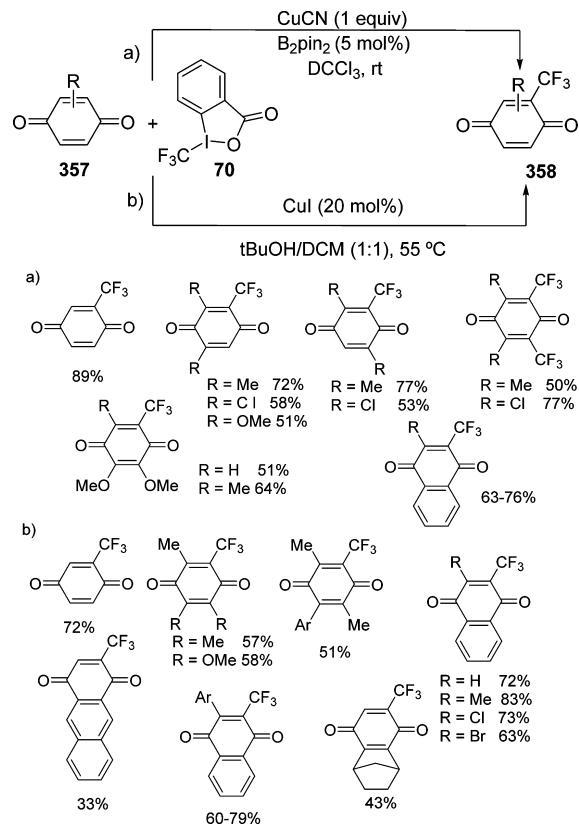
Scheme 156



trifluoromethylated derivatives **355** were obtained with very high *E* stereoselectivity. Various substituents and functional groups such as aryl, pyridyl, propyl, carboxylic ester, or silyloxytrialkyl derivatives were tolerated (Scheme 156). The effect of substitution at the  $\alpha$ -position of the hydrazones was also explored, and under similar reaction conditions the reaction of  $\alpha$ -substituted hydrazones **354** ( $R^1 \neq H$ ) gave *Z*- $\beta$ -trifluoromethylated  $\alpha,\beta$ -unsaturated hydrazones **356**. Five- and six-membered cycloalkenyl hydrazones worked well, and even trifluoromethyl-substituted (-)-Myrtenal dibenzylhydrazone can be prepared in excellent yield. The authors suggested a radical mechanism, following addition–elimination pathways with the formation of the corresponding alkene.

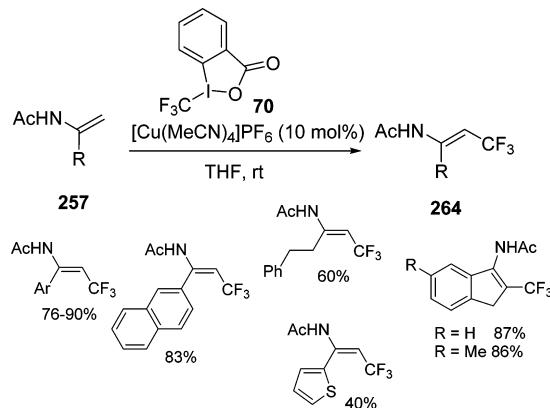
Quinones **357** may be considered as functionalized alkenes, and copper-mediated oxidative reaction involving the C–H trifluoromethylation of these substrates for the formation of trifluoromethylated quinones **358** with **70** (Tr1)<sup>80</sup> can be achieved.<sup>262</sup> Copper cyanide (CuCN) was used as Cu(I) source, and the addition of bis(pinacolato)diboron ( $B_2\text{Pin}_2$ ) accelerated the trifluoromethylation. This strategy is suitable for the preparation of alkyl-, chloro-, methoxy-, and naphthoquinones (Scheme 157a). In the presence of TEMPO the reaction

Scheme 157



Copper-catalyzed direct C–H olefinic trifluoromethylation has been also described on enamides **257** with **70** (Tr1)<sup>80</sup> and assistance of a Cu(I) salt (Scheme 158). The reaction is

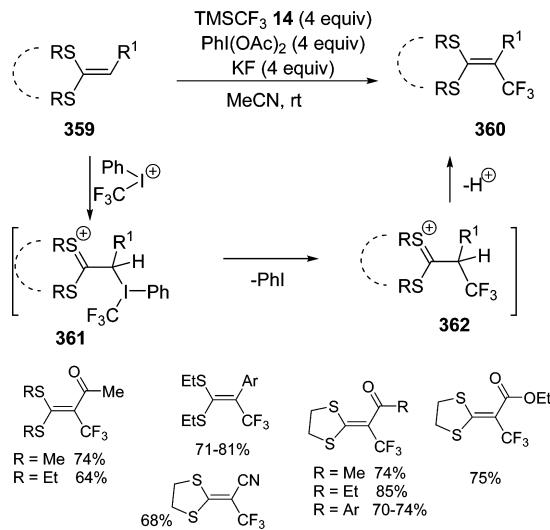
Scheme 158



stereoselective providing the *E* isomer of enamide **264** with the location of  $\text{CF}_3$  group in  $\beta$ -position. Many different aryl substituents and some alkyl moieties can survive the soft reaction conditions. The exclusive formation of *E* isomers may be explained from steric interaction between the trifluoromethyl group and metal bound amido group.

Liu et al.<sup>264</sup> reported the introduction of the trifluoromethyl group in activated olefins such as ketene dithioacetals under mild transition-metal-free conditions. The electrophilic acyclic hypervalent iodide trifluoromethylating species  $[\text{PhICF}_3]^+$  was generated *in situ* from  $\text{PhI(OAc)}_2$ , **14** (RPr),<sup>47</sup> and KF and reacted with ketene dithioacetals **359** to afford trifluoromethylated compounds **360** (Scheme 159). The process tolerates a

Scheme 159

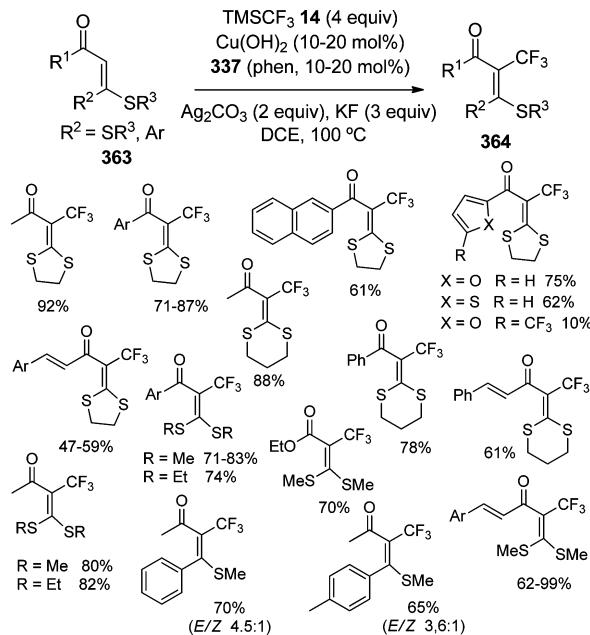


is inhibited; therefore, a radical process may be involved in the formation of these trifluoromethylated quinones **358**. The first catalytic direct trifluoromethylation of quinones **357** has also been described, leading to trifluoromethylated quinones and naphthoquinones **358** with a wide range of substituents (Scheme 157b).<sup>263</sup> In this case, the same electrophilic trifluoromethylation reagent **70** was used, and the process was performed in the presence of CuI in  $t\text{BuOH}/\text{CH}_2\text{Cl}_2$ .

variety of functional groups such as ketone, carboxylic ester, or nitrile, and the products are obtained in moderate-good yields. The formation of compounds **360** may be explained by nucleophilic addition of the ketene to the electrophilic trifluoromethylating agent  $[\text{PhICF}_3]^+$  to give the thionium intermediate **361** followed by reductive elimination of phenyl iodide (PhI), construction of the C–CF<sub>3</sub> bond, and subsequent loss of the acidic proton from **362**.

Finally, the functionalization of internal olefins can be achieved by means of an efficient Cu(II)-catalyzed trifluoromethylation of dithioalkyl  $\alpha$ -oxoketene acetals **363** ( $R^2 = SR^3$ ) with **14** ( $RPr$ )<sup>47</sup> as trifluoromethyl reagent in the presence of catalytic amounts of  $Cu(OH)_2$ .<sup>257</sup> Five- and six-membered cyclic and acyclic  $\alpha$ -oxoketene dithiocacetals **363** ( $R^2 = SR^3$ ) were used, and alkyl, aryl, naphthyl, cinnamyl, and heterocyclic substituents were tolerated (Scheme 160). Moreover, the

Scheme 160



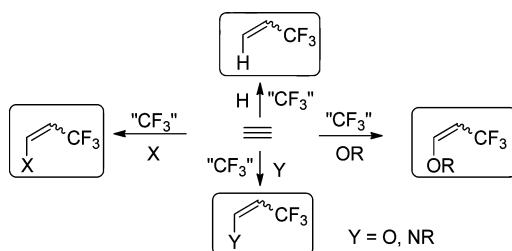
process can be extended to  $\alpha$ -oxoketene monothioacetals **363** ( $R^2 = Ar$ ,  $R^3 = Me$ ), and the corresponding trifluoromethyl derivatives **364** ( $R^2 = Ar$ ,  $R^3 = Me$ ) were obtained in good yields and with a major proportion of the *E*-isomers. The push–pull effect from the polarized starting olefins seems to favor the internal trifluoromethylation. A mechanism involving radicals was suggested on the basis of a TEMPO-quenching experiment.

### 3.2. Trifluoromethylation of Alkynes

Addition reactions of trifluoromethyl reagents onto alkynes are also a suitable approach for the preparation of vinyl trifluoromethyl compounds and involve halo-, hydro-, carbo-, oxy-, and aminotrifluoromethylation processes (Scheme 161). Parts of these type of reactions have been reviewed recently by Shimuzu and Kanai.<sup>265</sup>

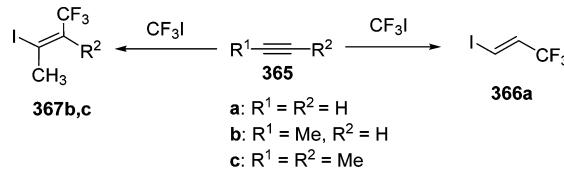
**3.2.1. Halotrifluoromethylation Reactions.** Trifluoromethyl radicals react also with alkynes, predominantly at the

Scheme 161



least substituted carbon to yield alkenes.<sup>32</sup> In the context of kinetic studies on the photochemical reaction with  $CF_3I$ , different isomers were generated depending upon the substrate. When acetylene **365a** ( $R^1 = R^2 = H$ ) was used, the *E* isomer **366a** is formed, whereas propyne **365b** ( $R^1 = CH_3$ ,  $R^2 = H$ ) and but-2-yne **365c** ( $R^1 = R^2 = CH_3$ ) yielded predominantly the *Z* isomers **367b,c** respectively (Scheme 162).<sup>266</sup> Trifluor-

Scheme 162



methyl iodide in the presence of a Lewis acid as triethylborane has also been used as precursor of trifluoromethyl radical for the addition of terminal and internal alkynes.<sup>114</sup> In this case, however, the adducts have the iodine and the trifluoromethyl group in a *trans* relationship.

Furthermore, iodotrifluoromethylalkenyl derivatives have been prepared from terminal alkynes **368** and  $CF_3I$  under visible-light photoredox catalysis.<sup>267</sup> The corresponding trifluoromethylated compounds **369** were obtained in the presence of  $[Ru(phen)_3]Cl_2$  and TMEDA and isolated as *E* isomers (Scheme 163a). Analogously, a variety of alkynes **368** have been trifluoromethylated also with  $CF_3I$  but with iron transition-metal catalysis (Scheme 163b).<sup>121</sup> The advantage of this Fe-catalyzed reaction is the wider substrate scope and higher functional-group tolerance than those observed for radical trifluoromethylations. Moreover, the metal used is cheaper and environmentally friendlier than ruthenium.

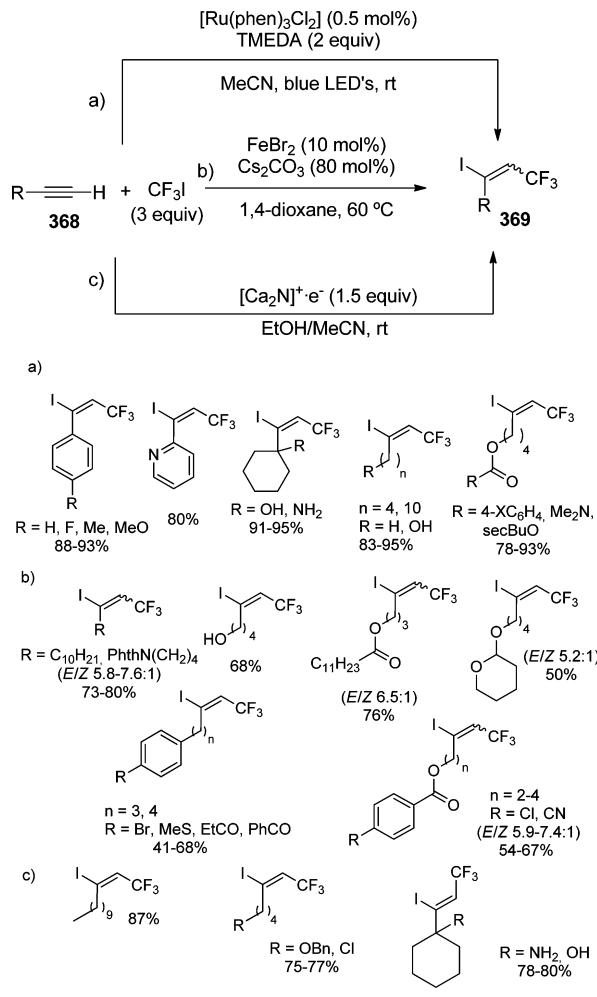
Likewise, an inorganic electrode (calcium nitride) has been used for the iodotrifluoromethylation of terminal alkynes **368** (Scheme 163c).<sup>152</sup> Whereas linear alkynes **368** led stereoselectively to the formation of *E*-isomers **369**,  $\alpha$ -branched acetylenes afforded exclusively the *Z*-isomers **369**.

Another procedure for the halotrifluoromethylation of alkynes has been developed where trifluoromethylating reagent **140** ( $Lr$ ),<sup>127</sup> easier to handle than  $CF_3I$  gas, is used in the presence of iodine pentoxide ( $I_2O_5$ ).<sup>126</sup> In this report, the iodotrifluoromethylation of several aryl- and alkyl-substituted alkynes **368** with  $CF_3SO_2Na/I_2O_5$  and the assistance of  $NaHCO_3$  is described, yielding the corresponding *E*-isomers of alkenyl iodides **369** (Scheme 164). A radical mechanism may explain the formation of these products **369** as authors have experimentally observed.

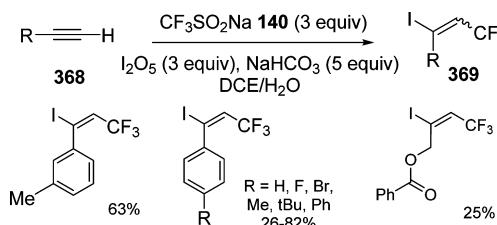
**3.2.2. Hydro- and Carbotrifluoromethylation Reactions.** Ultrasound-promoted hydrotrifluoromethylation of terminal alkynes **368** with trifluoromethyl-cuprates, formed in situ from trifluoromethyl iodides or bromides and zinc in the presence of copper(I) iodide, has been reported.<sup>154</sup> Moderate-good yields of *Z* olefins **338** (*Z/E* 1.9:1–3.2:1) as major components are obtained (Scheme 165). Moreover, catalase and urease enzymes have been used for the regio- and stereoselective hydrotrifluoromethylation of alkynes **368** giving rise to the formation of *E*-trifluoromethylated alkenes **338**, although the yields are low (Scheme 165).<sup>268</sup>

Trifluoromethylated alkenes **338** were obtained by hydrotrifluoromethylation of alkynes **368** when  $CF_3I$  was used as trifluoromethylating reagent under visible-light irradiation in

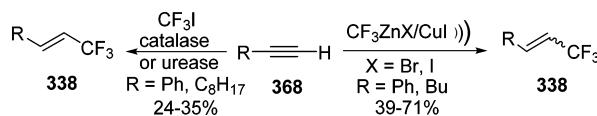
Scheme 163



Scheme 164



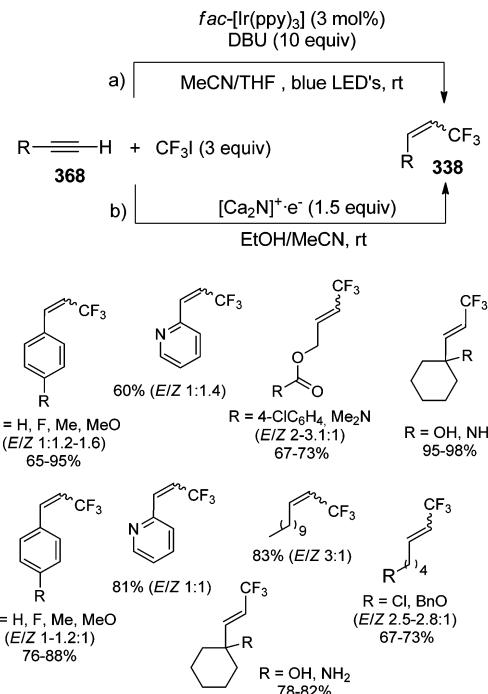
Scheme 165



the presence of *fac*-[Ir(ppy)<sub>3</sub>] in catalytic amounts and DBU (Scheme 166a).<sup>267</sup> The scope of the process is not restricted to aryl alkynes 368 given that olefins with pyridyl, cyclohexyl, and alkoxy substituents can also be prepared.

A new procedure by using the same trifluoromethylating agent (CF<sub>3</sub>I) and ionic crystals (calcium nitride) as electride has been reported (Scheme 166b).<sup>152</sup> Aryl, pyridyl, and aliphatic substituted alkenes 338 were obtained as a mixture of *E* and *Z* isomers. However, only *E*-alkenes were prepared

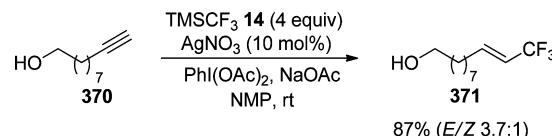
Scheme 166



when departing from *α*-branched hydroxyl- or amino acetylenes 368.

A single example is known of **14** (RPr)<sup>47</sup> reagent having been used for hydrotrifluoromethylation of alkynes (Scheme 167).<sup>153</sup>

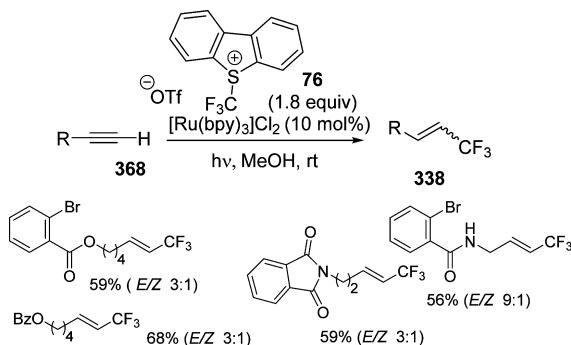
Scheme 167



In this case, substrates **370** reacted in the presence of silver salt (AgNO<sub>3</sub>) and hypervalent iodine derivative (PhI(OAc)<sub>2</sub>) giving rise to an alkene **371** with good yield and low selectivity.

A visible-light-catalyzed reductive intermolecular hydrotrifluoromethylation of unactivated alkynes **368** was reported (Scheme 168).<sup>156</sup> In this case, **76** (Ur)<sup>84</sup> as the CF<sub>3</sub> source and MeOH as the reductant and solvent were used. This process operates in a regioselective manner with a higher proportion of the *E* isomers at room temperature in the presence of

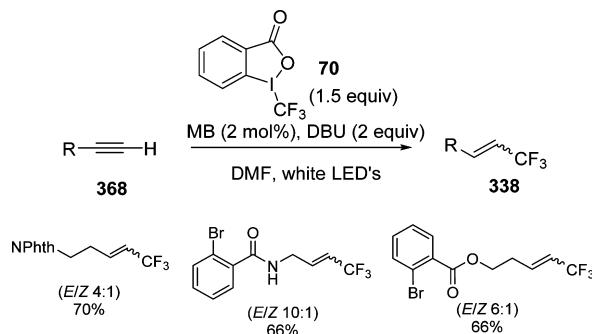
Scheme 168



$[\text{Ru}(\text{bpy})_3]\text{Cl}_2$  (10 mol %) and shows good functional group tolerance.

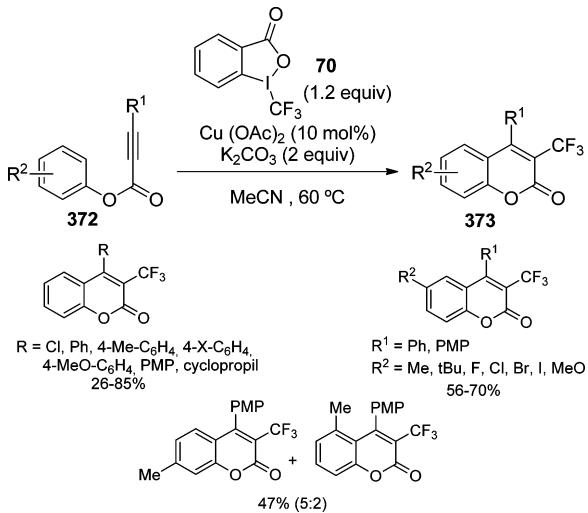
An organocatalytic hydrotrifluoromethylation procedure of terminal alkynes **368** with **70** ( $\text{Tr1}$ )<sup>80</sup> based on methylene blue (MB, vide supra, Scheme 69) photocatalyst has been developed also under visible light irradiation.<sup>155</sup> Low catalyst loading (2 mol %) was sufficient for the effective radical trifluoromethylation of starting substrates giving corresponding products **338** with good yields and high stereoselectivity (Scheme 169).

Scheme 169



On the other hand, a novel carbotrifluoromethylation process has been reported. Thus, internal alkynes **372** have been trifluoromethylated by a copper-catalyzed process using **70** ( $\text{Tr1}$ )<sup>80</sup> as  $\text{CF}_3$  source to give trifluoromethylated coumarins **373** (Scheme 170).<sup>269</sup> The formation of these compounds **373**

Scheme 170

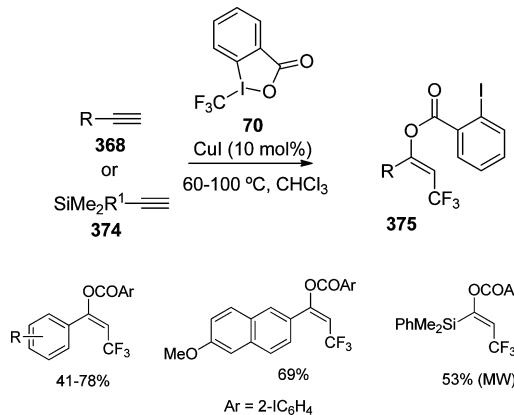


may be explained by an initial  $\text{CF}_3$  addition to triple bond via a radical mechanism followed by intramolecular cyclization. Togni's reagent **70** resulted in the most effective trifluoromethylating reagent under these conditions, and the corresponding heterocyclic compounds **373** were obtained with good functional group tolerance.

**3.2.3. Oxy- and Aminotrifluoromethylation Reactions.** Besides being useful in synthesizing trifluoromethylated alkenes from olefins (vide supra, section 3.1), **70** ( $\text{Tr1}$ )<sup>80</sup> has also been employed for the addition of the  $\text{CF}_3$  moiety to alkynes as it has been shown in the previous section. In a similar reaction, the Cu-catalyzed addition of the hypervalent iodine reagent **70** ( $\text{Tr1}$ ) to terminal aryl alkynes **368** took place with high regio-

and stereoselectivity, placing the  $\text{CF}_3$  in the terminal carbon of the alkyne and 2-iodobenzoate from **70** in the other one to furnish **375** (a formal trifluoromethyl-benzoyloxylation, Scheme 171).<sup>197</sup> The process may be extended to silyl acetylene

Scheme 171

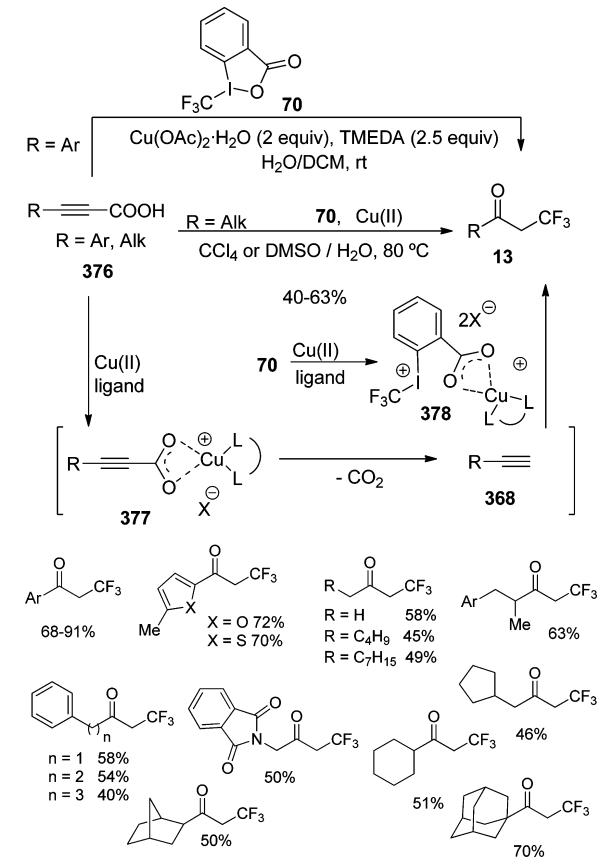


derivative **374** ( $\text{R}^1 = \text{Ph}$ ), but in this case the reaction was conducted by microwave irradiation (MW) and moderate yields were obtained. The use of the other Togni's reagent **187** ( $\text{Tr2}$ )<sup>80</sup> and copper catalysis with aryl acetylenes in the presence of base gave substitution (C–H trifluoromethylation) instead of addition (vide infra, section 4). The reaction with **70** ( $\text{Tr1}$ )<sup>80</sup> has been extended to other ethynyl benzene derivatives **368** using  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$  (30 mol %) under mild conditions, with the formation of adducts **375** ( $\text{R} = \text{Ar}$ , 70–91%).<sup>198</sup> Additionally, in the case of silyl acetylene derivatives **374** ( $\text{R}^1 = \text{Me, Bn, Ph}$ ) with  $\text{CuI}$  (30 mol %) as catalyst, the corresponding oxytrifluoromethylated compounds **375** ( $\text{R} = \text{SiMe}_2\text{R}^1$ , 53–63%) were reported.

A formal decarboxylative oxytrifluoromethylation of propionic acids **376** provides a new strategy for the preparation of  $\alpha$ -trifluoromethyl ketones **13** (Scheme 172).<sup>270</sup> When arylpropionic acids were used, the process was performed with  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  as the appropriate metal salts in the presence of TMEDA as additive and  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  as solvent, and a wide range of electron-rich, electron-poor aryl, or heteroaryl-substituted trifluoromethyl ketones **13** can be prepared in good yields (Scheme 172). Reagent **77** ( $\text{Ur}$ )<sup>84</sup> was also explored, but the process gave lower yields. In the case of alkylpropionic acids **376** ( $\text{R} = \text{Alk}$ ), however, different reaction conditions were necessary (Scheme 172). Indeed, copper(II) gluconate or tartrate were used as  $\text{Cu}(\text{II})$  salts in  $\text{CCl}_4/\text{H}_2\text{O}$  or  $\text{DMSO}/\text{H}_2\text{O}$  as mixed solvent system at 80 °C, although lower yields than in the case of arylpropionic acids were reported. The authors suggested a mechanism based on copper intermediates **377** and **378** generated from carboxylic acids **376** and trifluoromethylating agent **70** ( $\text{Tr1}$ ), respectively. After decarboxylation of copper complex **377**, addition of copper intermediate **378** onto **368** may give ketones **13**.

Nucleophilic trifluoromethylating reagents are also appropriate for the introduction of trifluoromethyl group into alkynyl precursors. For example, Langlois reagent **140** (**Lr**) has been used in a silver-catalyzed protocol in the presence of  $\text{O}_2$  to prepare aliphatic, aromatic, and heteroaromatic  $\alpha$ -trifluoromethyl ketones **13** in a regioselective way (Scheme 173).<sup>271</sup> This oxytrifluoromethylation of terminal alkynes **368** may be explained by a radical mechanism, where  $\text{CF}_3$  radical adds to

Scheme 172



the triple bond followed by an oxygen radical addition to form an enol derivative, which finally isomerizes to the corresponding trifluoromethylated ketone 13. The scope of the process is quite general because alkyl, aryl, and heterocyclic derivatives were tolerated.

The first example of aminotrifluoromethylation of alkynes has been reported in 2014. In this example, Umemoto's reagent 76 ( $\text{Ur}^{84}$ ) has been used in a  $\text{CuBr}$ -catalyzed domino cyclization-trifluoromethylation of homopropargyl amines 379 (Scheme 174) to produce 4-trifluoromethyl-2,3-dihydropyrrolium salts 380 in high yields.<sup>272</sup> The authors suggested the formation of a copper complex followed by an intramolecular ring closure and trifluoromethylation.

#### 4. $\text{Csp}-\text{CF}_3$ BOND FORMATION. ALKyne TRIFLUOROMETHYLATION

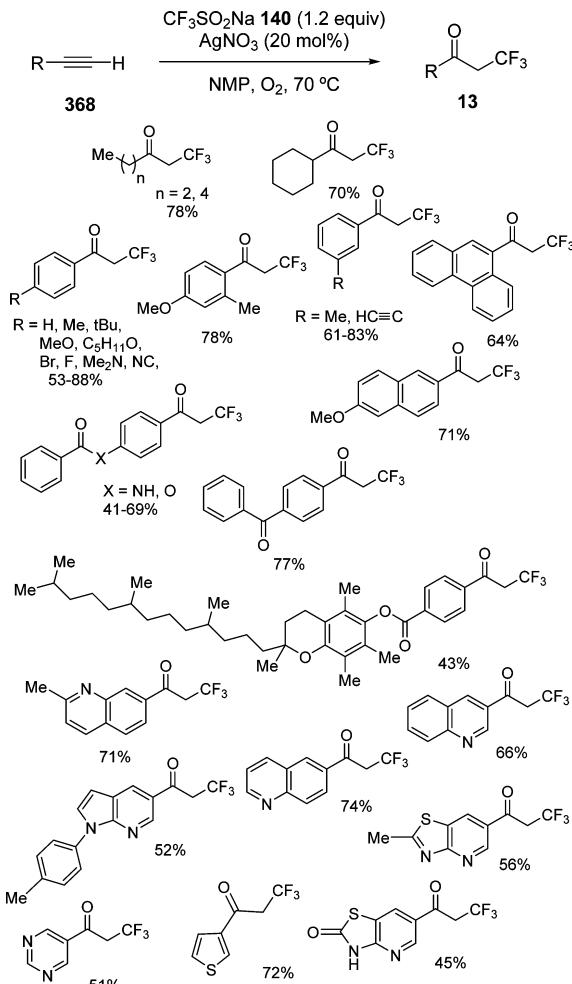
Trifluoromethylated acetylenes have found applications as building blocks in agrochemicals, pharmaceuticals, and as functional materials.<sup>273</sup> They can be made from metal-functionalized alkynes or by direct C–H trifluoromethylation (Scheme 175).

##### 4.1. From Metalated Alkynes

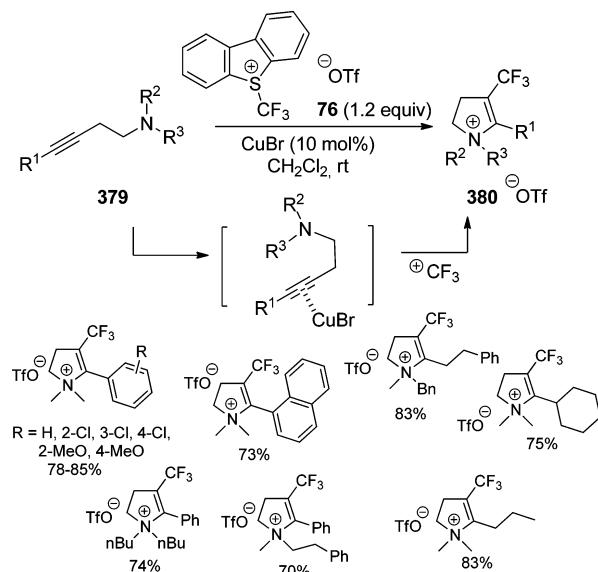
The first example of preparation of trifluoromethylalkynyl derivatives involved the photoreaction of (trimethylstannyl)-phenyl acetylene 381 with trifluoromethyl iodide (Scheme 176).<sup>274</sup>

Additionally, electrophilic trifluoroalkylating agents have been used for the C–C bond construction of trifluoromethylalkynyl derivatives with lithium acetylides 383. The S-, Se-, and Te-trifluoromethylated dibenzoheterocyclic onium salts 76

Scheme 173

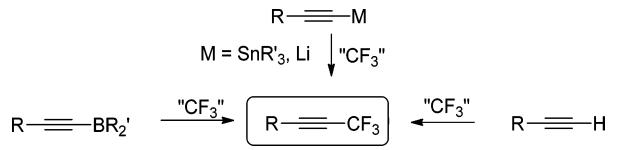


Scheme 174

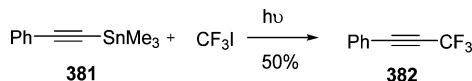


( $\text{Ur}$ )<sup>84</sup> 385a, and 385b were used as trifluoromethylating agents, which reacted with lithium phenyl acetylene 383 to give the corresponding trifluoromethyl derivative 382 (Scheme 177).<sup>275</sup> Later, electrophilic fluoroalkylating agents based on

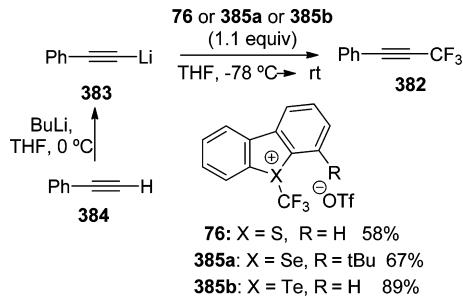
Scheme 175



Scheme 176



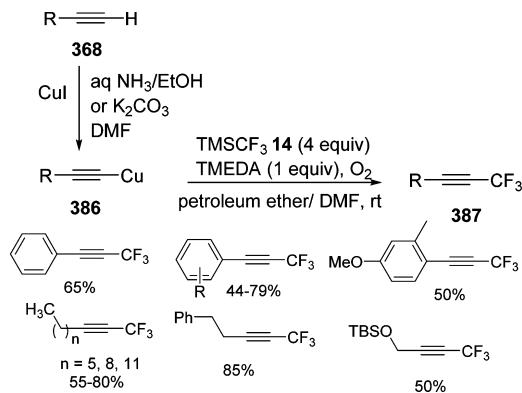
Scheme 177



the sulfoximine skeleton were also evaluated with acetylides to give trifluoromethylalkynyl derivatives,<sup>276</sup> although with low-moderate yields in the case of aryl acetylides (12–53%) and even lower for alkyl acetylides (<16%).

A simple and practical method for the oxidative copper(I)-mediated trifluoromethylation of copper acetylides **386** (Scheme 178), easily prepared from terminal alkynes **368** and

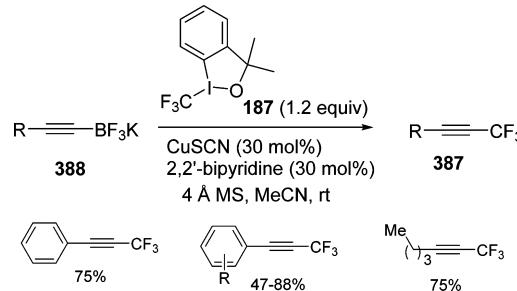
Scheme 178



$\text{CuI}^{277}$  with **14** ( $\text{RPr}^4$ )<sup>47</sup> as trifluoromethyl reagent in the presence  $\text{O}_2$  and TMEDA has been described.<sup>278</sup> The method proceeded at room temperature, and very mild conditions and trifluoromethyl arylalkynyl and alkylalkynyl derivatives **387** were prepared in moderate-good yields. Even some common protecting groups such as silyl ethers were tolerated.

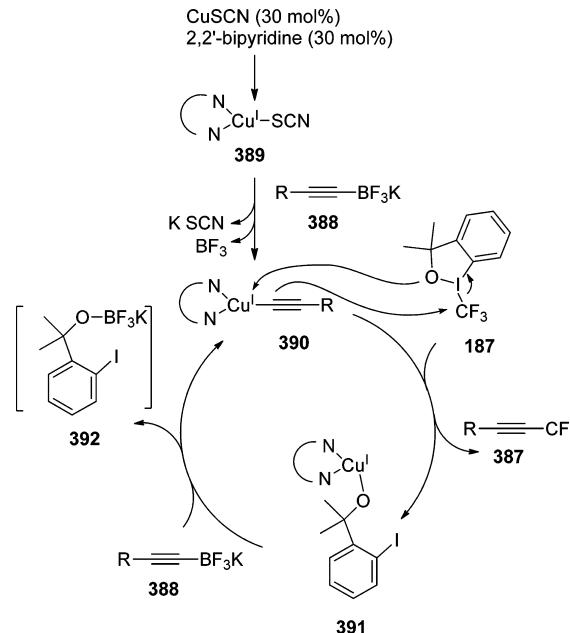
A new method<sup>279</sup> for the synthesis of trifluoromethylated acetylenes **387** (Scheme 179) involves the copper-catalyzed trifluoromethylation of alkynyltrifluoroborates **388** with **187** ( $\text{Tr2}$ ).<sup>80</sup> The results show that the catalytic reaction proceeds smoothly at room temperature without addition of an oxidant. Aryl and alkyl trifluoromethylated acetylenes **387** can be prepared, and a variety of functional groups, such as alkyl, alkoxy, and halides, were tolerated in the aryl group.

Scheme 179



A plausible mechanism for this reaction is shown in Scheme 180. Initial complexation of CuSCN with 2,2'-bipyridine forms

Scheme 180



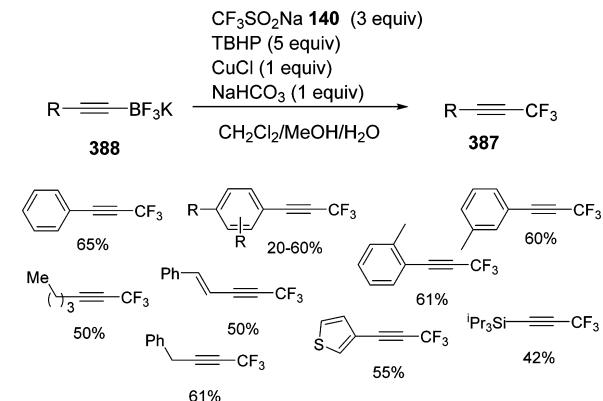
the  $\text{Cu(1)}$ -thiocyanate complex **389**. Subsequent transmetalation of **389** with the alkynyltrifluoroborate **388** generates copper(I)-acetylide species **390** as the key intermediate. Nucleophilic attack of the alkynyl group of **390** at the  $\text{CF}_3$  moiety is assumed to occur next, to generate the trifluoromethylated acetylene product **387**, along with  $\text{Cu(1)}$ -alkoxide complex **391**. This undergoes further reaction with the alkynyltrifluoroborate **388** to regenerate **390** and complete the catalytic cycle.

Potassium alkynyl trifluoroborates **388** can also be used as starting substrates for a copper-mediated trifluoromethylation process with trifluoromethyl radicals generated from **140** ( $\text{Lr}$ )<sup>127</sup> as trifluoromethylating agent for the synthesis of trifluoromethylated alkynes **387** (Scheme 181).<sup>280</sup> The method tolerates a wide range of substituted aryl groups, as well as thiophene, alkyl, benzyl, trialkylsilyl, or cinnamyl groups. Likewise, a couple of examples of trifluoromethylation of potassium alkynyl trifluoroborates **388** in similar reaction conditions with moderate yields have been reported.<sup>251</sup>

#### 4.2. Direct C—H Trifluoromethylation

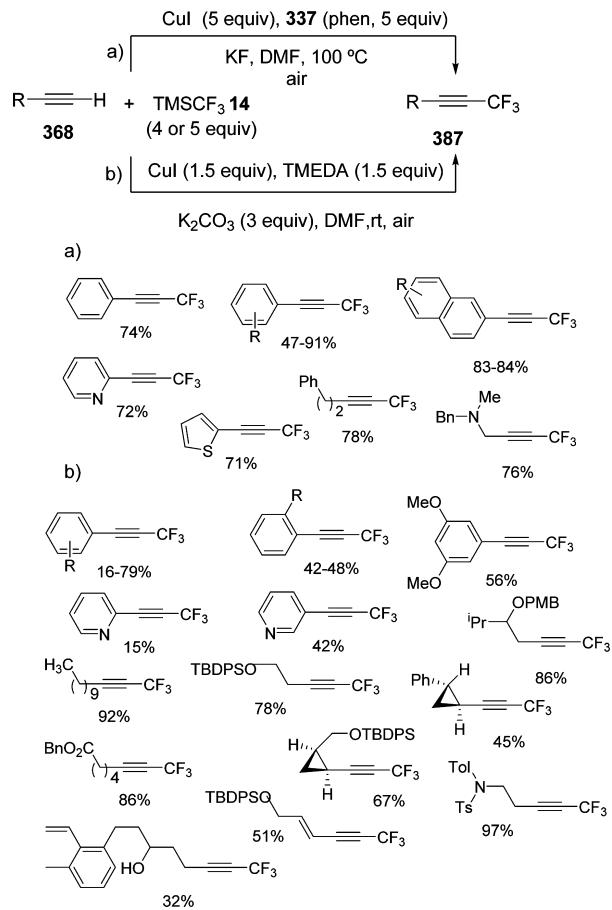
Terminal alkynes **368** have been successfully functionalized with  $\text{CF}_3$  moiety by copper-mediated  $\text{Csp}^2-\text{Csp}^3$  oxidative trifluoromethylation with nucleophilic trifluoromethyltrimethyl-

Scheme 181



silane **14** ( $\text{RPr}$ )<sup>47</sup> stoichiometric amounts of copper reagents, and **337** (phen, Scheme 182a).<sup>281</sup> Both aromatic and aliphatic

Scheme 182

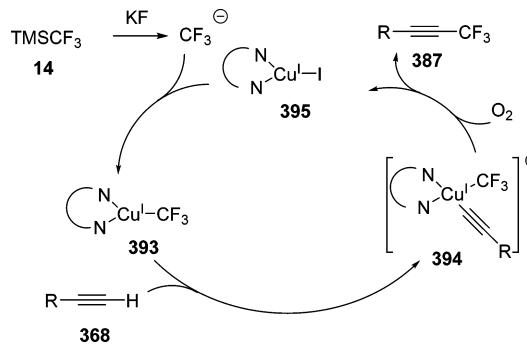


alkynes were effective, and a variety of functionalities such as amino, methoxy, ethyl carboxylate, bromide, and nitro were tolerated under the reaction conditions. This reaction represents the first example of  $\text{Csp}-\text{CF}_3$  bond formation via transition-metal-mediated C–H oxidative trifluoromethylation. This group has also developed an improved procedure for the Cu-mediated oxidative trifluoromethylation of terminal alkynes **368** by using  $[(\text{phen})\text{Cu}(\text{CF}_3)]$  complex generated in situ from trifluoromethylating reagent **14** ( $\text{RPr}$ ) and oxygen as oxidant.<sup>282</sup>

A similar method for the oxidative copper(I)-mediated trifluoromethylation of terminal alkynes **368** (Scheme 182b) with **14** ( $\text{RPr}$ )<sup>47</sup> as trifluoromethyl source in the presence  $\text{CuI}$ , air,  $\text{K}_2\text{CO}_3$ , and TMEDA has been reported.<sup>278</sup> The reaction proceeded at room temperature and very mild conditions, and not only aryl- but also alkyl-alkynyl derivatives were synthesized in moderate-good yields. This methodology tolerates molecules with functional groups such as 1,3-enynes, ketones, unprotected alcohols, cyclopropane rings, and some protecting group such as benzyl and silyl ethers. Likewise, a copper-promoted trifluoromethylation of terminal alkynes with excess of *S*-trifluoromethyl diarylsulfonium salt **108** (2 equiv) in the presence of equimolecular amounts of  $\text{CuI}$ , bipyridine (bpy), and  $\text{K}_2\text{CO}_3$  was reported.<sup>283</sup>

The catalytic version of the direct oxidative trifluoromethylation of C–H bonds in terminal alkynes has also been accomplished.<sup>284</sup> The limitation of the use of stoichiometric amounts of copper reagent was avoided by using an excess of **14**/KF and catalytic amounts (20 mol %) of both  $\text{CuI}$  and **337** (phen). The catalytic reaction could be carried out with a series of electron-rich and electron-poor aryl alkynes, as well as terminal alkyne containing a pyridine skeleton. The authors proposed that the oxidative trifluoromethylation of terminal alkyne **368** proceeds by the formation of trifluoromethyl anion (Scheme 183), which undergoes generation of complex **393**.

Scheme 183

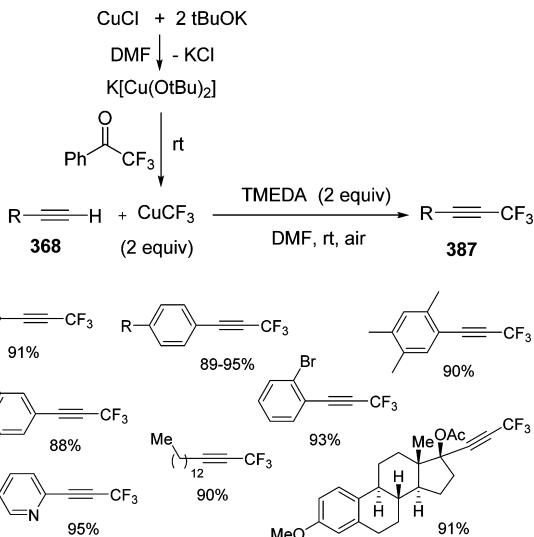


The subsequent reaction with acetylene **368** to afford another Cu(I) complex **394**, and oxidation followed by reductive elimination, delivered the trifluoromethylacetylene **387** and regenerated copper(I) catalyst **395**.

A new useful strategy for the preparation of a trifluoromethylating agent starting from trifluoromethyl ketone derivatives and cuprate has been developed.<sup>285</sup> The  $[\text{CuCF}_3]$  was prepared from potassium bis(2-methyl-2-propanolate)cuprate(I) ( $\text{K}[\text{Cu}(\text{O}^+\text{Bu})_2]$ ), generated in situ from  $\text{CuCl}$  and  $\text{KOtBu}$ , and 2,2,2-trifluoroacetophenone (Scheme 184). This reagent  $[\text{CuCF}_3]$  in the presence of tetramethylenediamine (TMEDA) and air at room temperature was used for the oxidative trifluoromethylation of terminal alkynes **368** to give the corresponding alkynyl trifluoromethanes **387** in excellent yields (Scheme 184). To increase the yields, a slow addition of the alkynes with a syringe pump was used, and the scope of the process is not limited to electron-donating and electro-withdrawing aromatic substituents, because trifluoromethylated aliphatic alkynes and a steroid derivative were also prepared.

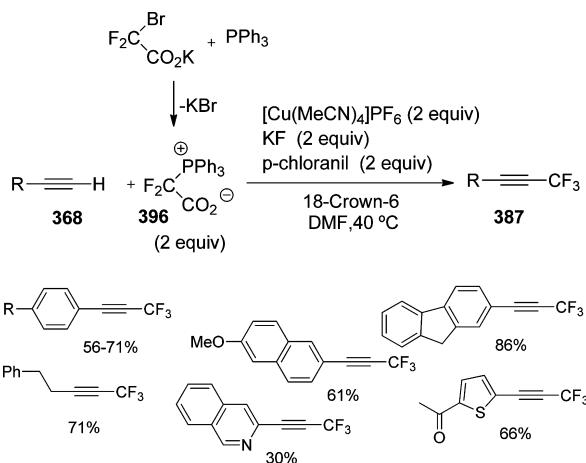
A new difluorocarbene reagent such as difluoromethylene phosphobetaine **396** ( $\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$ , PDFA), prepared from triphenyl phosphine ( $\text{Ph}_3\text{P}$ ) and potassium bromodifluoroacetate,<sup>286</sup> was reported for the Cu-mediated oxidative trifluor-

Scheme 184



omethylation of terminal alkynes **368** to give alkynyl trifluoromethanes **387** in moderate yields (Scheme 185).<sup>287</sup> The

Scheme 185



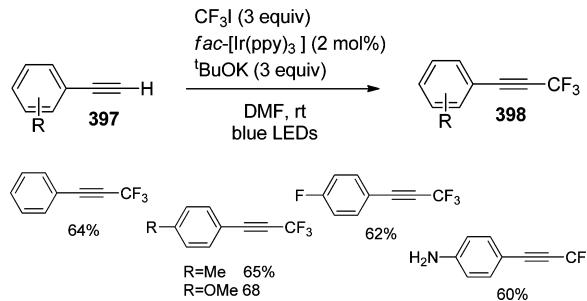
process was applicable to aliphatic alkyne **368** ( $\text{R} = \text{CH}_2\text{CH}_2\text{Ph}$ ) and a wide range of substituted aryl groups, although in the case of heterocyclic substituents low yield was observed for isoquinoline derivative.

A visible-light photoredox catalysis for the trifluoromethylation of terminal aryl alkynes **397** with  $\text{CF}_3\text{I}$  as trifluoromethylating reagent for the preparation of trifluoromethylated alkynes **398** was described.<sup>267</sup> The process required both an iridium photocatalyst such as *fac*-[Ir(ppy)<sub>3</sub>] and a visible light source in the presence of a base (KOtBu, Scheme 186). The process is limited to both electron-poor and electron-rich phenyl alkynes because aliphatic alkynes are not effective for the preparation of the corresponding substituted alkynes.

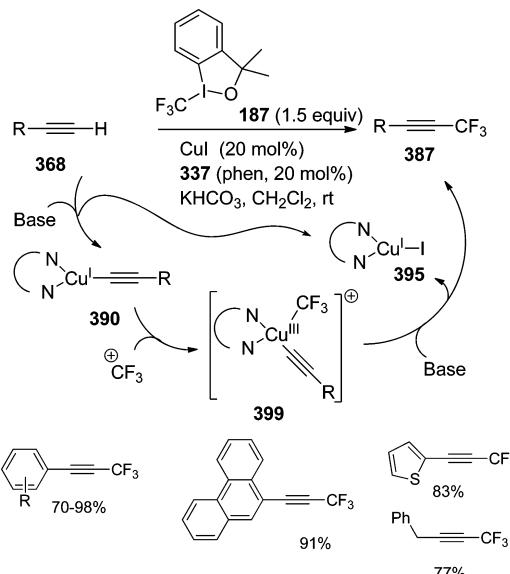
Catalytic processes for the trifluoromethylation of terminal alkynes **368** with **187** ( $\text{Tr}_2$ )<sup>80</sup> have also been developed affording trifluoromethylated acetylenes **387** in good to excellent yields (Scheme 187).<sup>288</sup>

The reaction is conducted at room temperature and exhibits tolerance to a range of functional groups (amine, alkoxy, or halide). It is noteworthy that, as stated in the previous section (vide supra, section 3.2.3), the other Togni reagent **70** ( $\text{Tr}_1$ )<sup>80</sup>

Scheme 186



Scheme 187



in the absence of base added to aryl alkynes **368** instead of direct C–H activation. Initial deprotonation of alkyne **368** and complexation of the resulting acetylide with Cu(I) and **337** (phen) followed by oxidative addition of  $\text{CF}_3^+$  cation would form a Cu(III) alkynyltrifluoromethyl complex **399**. The mechanism would continue by reductive elimination to produce the trifluoromethylated alkyne **387**, thus closing the catalytic cycle (Scheme 187).

Finally, another electrophilic reagent such as thiophenium triflate **77** (Ur)<sup>84</sup> and a Cu(I) catalyst have been used to trifluoromethylate terminal alkynes **368** bearing several functionalities including ester, nitro, halide, or alcohol. TMP was used as a ligand, and several new derivatives **387** were made (Scheme 188).<sup>289</sup>

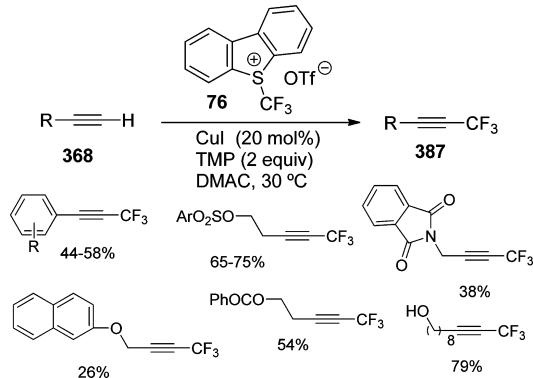
## 5. $\text{Csp}^2$ AROMATIC– $\text{CF}_3$ BOND FORMATION

Arenes and heteroarenes bearing trifluoromethyl groups have become important structural motifs found in compounds used in medicinal, agricultural, and material sciences. A large number of existing pharmaceutical candidates contain trifluoromethyl group introduced into an aromatic cycle because these moieties can favorably affect the physical and biological properties of a compound.<sup>1–3,290,291</sup>

### 5.1. Trifluoromethylation of Aryl Compounds

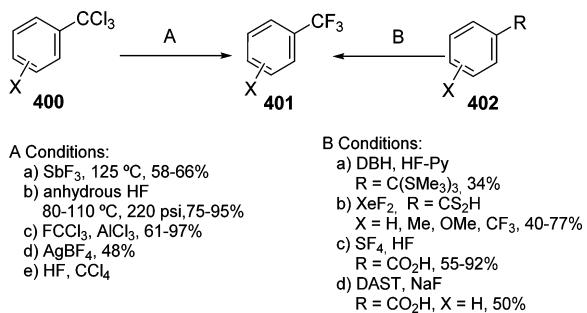
At the end of the 19th century, Swarts developed a good method for the preparation of trifluoromethyl aromatic compounds **401** from benzotrichloride with antimony tri-

Scheme 188



fluoride as fluorination reagent (Scheme 189, strategy A, a).<sup>292</sup> Afterward, some other methods were developed for the

Scheme 189

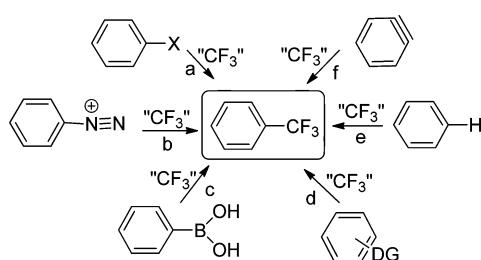


synthesis of arenes **401** departing from aromatic halomethanes **400** in the presence of fluorinating reagents such as hydrogen fluoride,<sup>293</sup> aluminum trichloride/fluorotrichloromethane,<sup>294</sup> silver tetrafluoroborate,<sup>295</sup> or HF/CCl<sub>4</sub>.<sup>296</sup>

Furthermore, different carbon-functionalized substrates **402** such as acids or their *ortho*-diester derivatives have also been used to yield the corresponding benzotrifluorides **401** (Scheme 189, strategy B) by fluorination reactions.<sup>32c</sup> However, these aforementioned methods turn out to be inappropriate due to toxicity and/or the relatively high cost of some reagents and harsh conditions employed, among other drawbacks.

Accordingly, the development of methods to introduce the trifluoromethyl group into aromatic compounds has become increasingly important.<sup>37,297</sup> Considerable progress has been made in the trifluoromethylation of prefunctionalized aromatic substrates including three general strategies that can be used toward this goal, trifluoromethylation of aryl halides (Scheme 190a), aryl diazonium salts (Scheme 190b), and aryl boronic derivatives (Scheme 190c). Moreover, two additional ap-

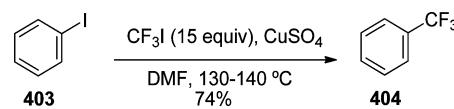
Scheme 190



proaches have been developed involving the direct trifluoromethylation of aryl compounds either bearing (Scheme 190d) or not (Scheme 190e) a directing group (DG). Likewise, arynes can be used for this purpose (Scheme 190f).

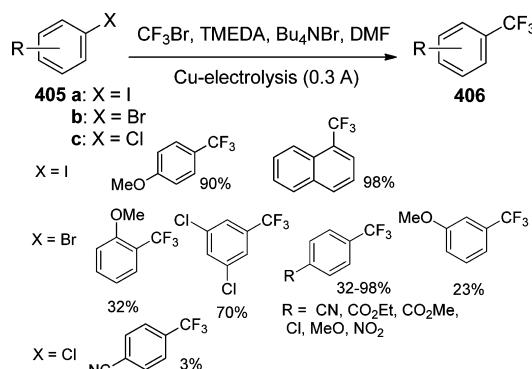
**5.1.1. From Haloaryl Derivatives.** Several synthetic methods starting from aryl halides for the introduction of a CF<sub>3</sub> moiety onto aromatic compounds with metals, mainly copper, have been developed over many years.<sup>37,297</sup> Since the original pioneering works of Kobayashi and Kumadaki<sup>298</sup> and those of McLoughlin and Thrower,<sup>299</sup> both in 1969, preparation of trifluoromethylated derivatives has been widely achieved by cross-coupling of aromatic halides with stoichiometric amounts of trifluoromethyl copper complexes generated in situ. For example, trifluoromethylbenzene **404** was obtained from iodobenzene **403** and CF<sub>3</sub>I in the presence of CuSO<sub>4</sub> (Scheme 191).<sup>298</sup>

Scheme 191



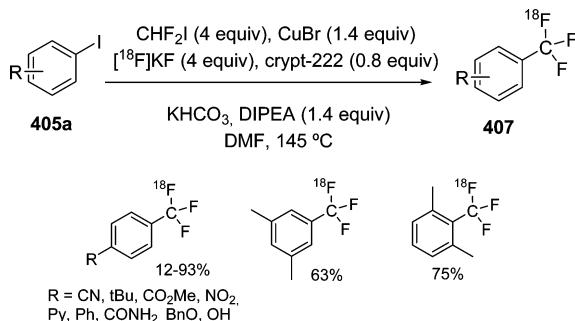
Since the ground-breaking investigations of Wiemers and Burton,<sup>41,58</sup> where the first NMR evidence of the formation of [CuCF<sub>3</sub>] species was reported, a great deal of effort has been expended in devising convenient strategies for generating trifluoromethyl copper complexes, which are presumed to be key intermediates in many copper-mediated trifluoromethylation processes. Different reagents have been used for the in situ generation of trifluoromethyl copper complexes. For example, an electrochemical cross-coupling of bromotrifluoromethane with aromatic halides **405** has been successfully achieved in a one-step procedure (Scheme 192). The [CuCF<sub>3</sub>] intermediate reacted with halides **405** to give the corresponding trifluoromethylated products **406** under mild conditions, and with reasonable yields.<sup>300</sup>

Scheme 192



Cu(I)-mediated <sup>18</sup>F-trifluoromethylation reactions of haloarenes in the presence of DIPEA have been reported.<sup>301</sup> The [<sup>18</sup>F]trifluoromethyl arenes **407** were obtained in moderate to good yields by using an operationally convenient protocol, suitable for straightforward automation (Scheme 193). Difluoroiodomethane (CHF<sub>2</sub>I), copper-ligand system (CuBr-DIPEA) in the presence of cryptand (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan, crypt-222), K<sub>2</sub>CO<sub>3</sub>, and a <sup>18</sup>F anion were selected as the starting materials to provide a

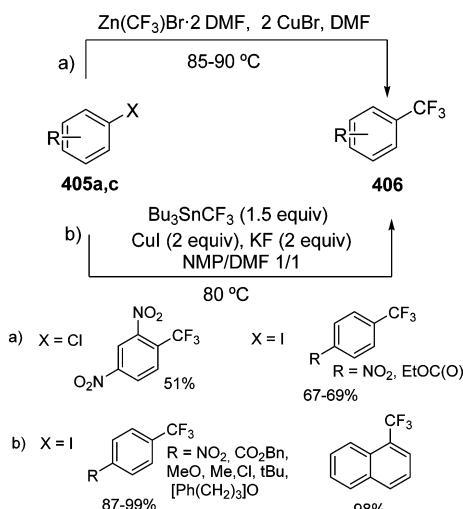
Scheme 193



convenient source of  $\{\text{Cu}^{[18]\text{F}}\text{CF}_3\}$  allowing the highly efficient, direct, and rapid conversion of iodoarenes **405** bearing diverse functional groups.  $[^{18}\text{F}]$ -Radiolabeled trifluoromethylated aromatic compounds **407** were obtained, interesting derivatives to be used for positron emission tomography (PET).

Yagupolski et al. prepared trifluoromethyl copper species conveniently via the combination of the solid complex  $[\text{Zn}(\text{CF}_3)\text{Br}\cdot 2\text{DMF}]$  with CuBr in DMF.<sup>302</sup> The reaction with activated aryl iodides **405a** ( $X = \text{I}$ ) and chlorides **405c** ( $X = \text{Cl}$ ) gave the corresponding trifluoromethylated compounds **406** in good yields (Scheme 194a).

Scheme 194

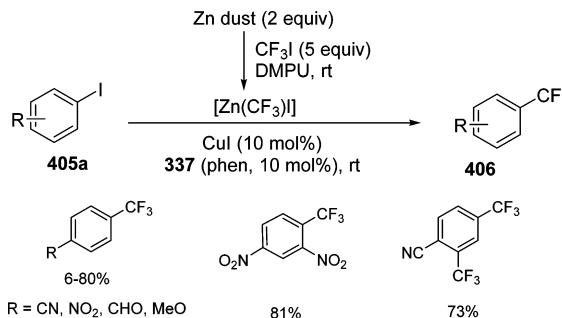


Similarly, reagents such as  $\text{Bu}_3\text{SnCF}_3$  were effective in trifluoromethylation reactions of aryl iodides also via the intermediacy of  $[\text{CuCF}_3]$  species.<sup>303</sup> Thus, using CuI,  $\text{Bu}_3\text{SnCF}_3$ , and KF along with coordinating solvents, such as the mixture DMF/NMP, led to the conversion of various electron-rich as well as electron-deficient aryl iodides **405a** into trifluoromethylated products **406** under relatively mild conditions and with good yields (Scheme 194b).

Trifluoromethylzinc reagent prepared in situ from trifluoromethyl iodide and Zn was used for the trifluoromethylation of aryl iodides **405a** in DMPU at 50 °C in the presence of a catalytic amount of CuI and 337 (phen). The reaction provided the corresponding aromatic trifluoromethylated products **406** in moderate to high yields (Scheme 195).<sup>304</sup>

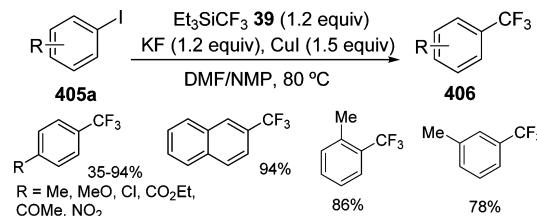
The transient trifluoromethyl copper species can be also generated under particularly mild conditions when using

Scheme 195



trifluoromethylsilyl reagents. For instance, silylated reagent  $\text{Et}_3\text{SiCF}_3$  **39** in combination with a base (e.g., KF, TBAF, or KOtBu) was applied for the trifluoromethylation of aryl iodides **405a** (Scheme 196).<sup>64</sup> Copper was used in stoichiometric

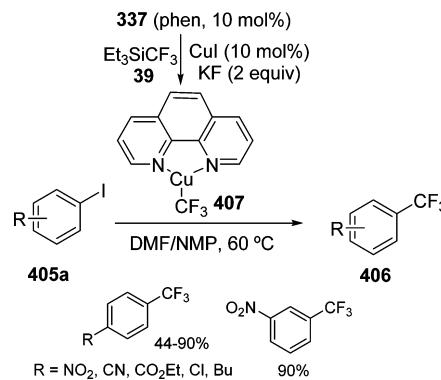
Scheme 196



quantities because the copper-mediated substitution of iodide by  $\text{CF}_3$  groups on the aryl iodide substrates proceeded much more slowly than the generation of the  $[\text{CuCF}_3]$  species.

The first copper-catalyzed trifluoromethylation process of aryl iodides **405a** (Scheme 197) was disclosed by Amii et al. in

Scheme 197

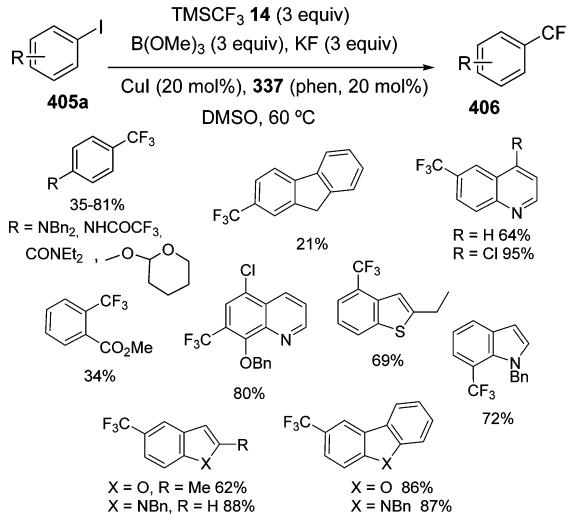


2009.<sup>305</sup> This group demonstrated that the effectiveness of Cu-mediated reactions can be improved by the addition of chelating ligands such as 337 (phen). Thus, employing a CuI/337 catalytic system and a mixture of **39** and KF, aryl iodides **405a**, particularly those bearing electron-withdrawing functions, were transformed into the benzotrifluoromethanes **406**. The authors suggested that the reaction proceeded through a phenanthroline-ligated Cu(I) complex  $[\text{Cu}(\text{phen})\text{CF}_3]$  **407**.

Afterward, the same group reported that this Cu(I) complex could be generated from the easily available O-silylated hemiaminal derivative of trifluoroacetaldehyde in the presence of cesium fluoride.<sup>306</sup>

An efficient copper-catalyzed trifluoromethylation of aromatic iodides has been achieved with  $\text{TMSCF}_3$  14 ( $\text{RPr}$ )<sup>47</sup> as a readily available  $\text{CF}_3$  source and trialkyl borates as Lewis acid for the temporary trapping of the  $\text{CF}_3$  anion generated by KF from the trifluoromethylating agent (Scheme 198). The

Scheme 198



method has been used for the trifluoromethylation of a diverse set of aromatic iodides 405a containing both electron-donating and electron-withdrawing groups. However, in the latter case the reactions were faster. The trifluoromethyl-substituted derivatives 406 were obtained in moderate to good yields, but free hydroxyl and amino groups (including indoles) should be protected.

Some studies provide direct evidence for  $[\text{CuCF}_3]$  species as trifluoromethylating agents, particularly when reactions have been carried out from preformed complexes. Hartwig et al. prepared  $[(\text{phen})\text{CuCF}_3]$  complex 407, commercialized as Trifluoromethylator, using 337 (phen), 14 ( $\text{RPr}$ ),<sup>47</sup> and  $\text{CuOtBu}$  (Scheme 199).

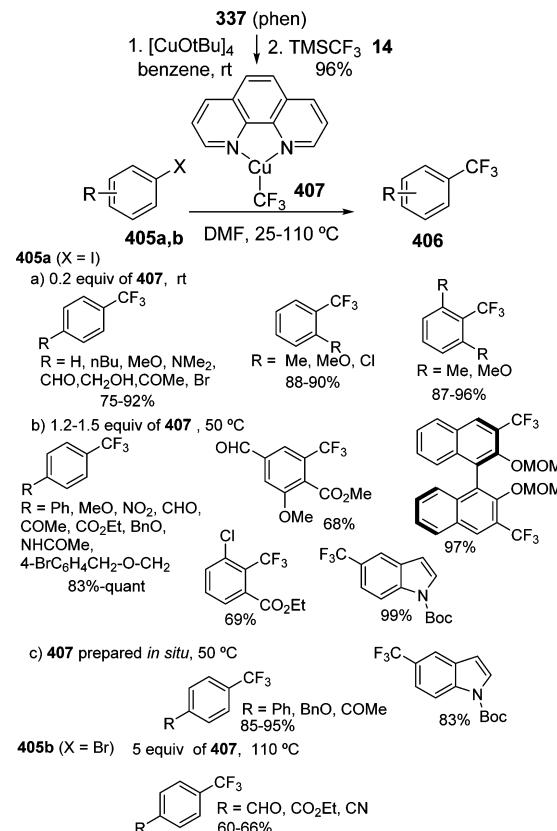
This complex reacted under mild conditions with prefunctionalized aryl iodides and bromides 405a,b to afford trifluoromethylated arenes 406 in high yields including the trifluoromethylation of the aryl group of an indole derivative (Scheme 199). Furthermore, this complex reacts with hindered substrates, and the process tolerates a wide range of functional groups, such as basic heterocycles.

Moreover, other ligands have been used for the preparation of copper complexes. For example, Vicic et al. used NHC copper complexes 408 and 14 ( $\text{RPr}$ )<sup>47</sup> for the preparation of new trifluoromethylated air-sensitive complexes of the type  $[(\text{NHC})\text{Cu}(\text{CF}_3)]$  409a–d and demonstrated their ability to trifluoromethylate iodoarenes 410 (Scheme 200) for the preparation of aryl derivatives 411.<sup>309</sup>

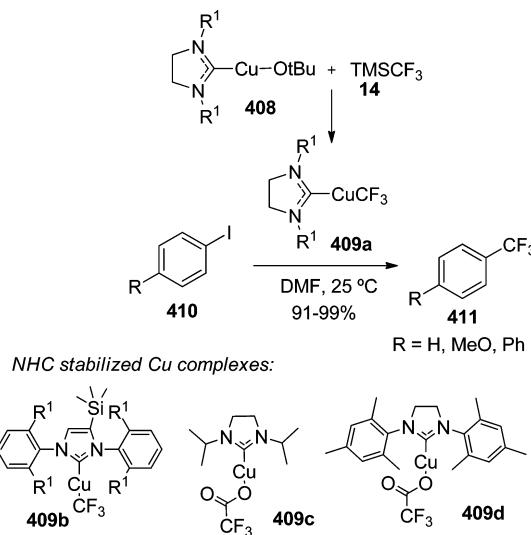
Triphenylphosphane-ligated trifluoromethyl copper complex 46  $[(\text{Ph}_3\text{P})_3\text{Cu}(\text{CF}_3)]$ ,<sup>67</sup> prepared from 14 ( $\text{RPr}$ ),<sup>47</sup> reacted also with aryl iodides 410 to afford trifluoromethylated arenes 411 (Scheme 201).

A ligand-free method to obtain  $[\text{CuCF}_3]$  trifluoromethylating reagent has been developed for the trifluoromethylation of 405a–c via the reaction of silver fluoride,  $\text{TMSCF}_3$  14 ( $\text{RPr}$ ),<sup>47</sup> and copper powder. In this case,  $\text{AgCF}_3$  may be first generated, and subsequent redox transmetalation with elemental copper

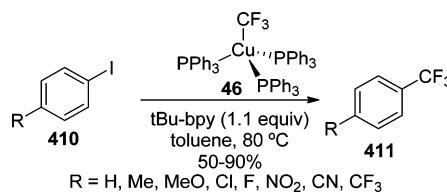
Scheme 199



Scheme 200

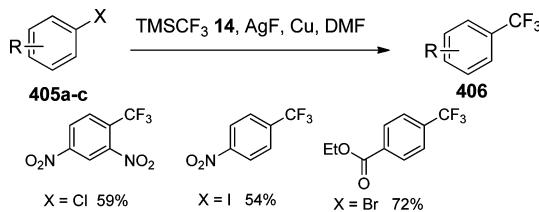


Scheme 201



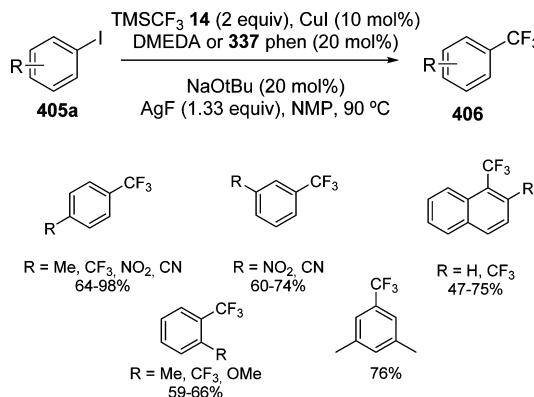
would afford the active trifluoromethyl copper species to obtain compounds 406 (Scheme 202).<sup>102</sup>

Scheme 202



Catalytic amounts of copper iodide were sufficient in a cooperative catalytic model of silver-assisted copper-catalyzed trifluoromethylation of activated and unactivated aryl iodides **405a**.<sup>310</sup> The transformation was performed using  $\text{TMSCF}_3$  **14** in the presence of  $\text{CuI}$ ,  $\text{AgF}$ ,  $\text{NaOtBu}$ , and  $\text{DMEDA}$  or **337** (phen, Scheme 203). Both  $\text{CuI}$  and  $\text{AgF}$  seemed to

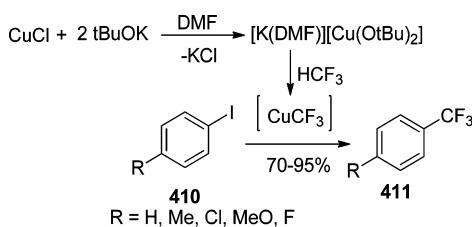
Scheme 203



be essential for efficient catalysis.  $\text{AgF}$  may promote the reaction due to the high affinity between the silver cation and the iodide as well as that between the fluoride ion and silicon. Indeed, other fluoride sources, such as  $\text{KF}$ , were inefficient. Under the mentioned conditions, electron-poor and electron-rich substituted trifluoromethylated aromatics **406** were obtained in moderate to excellent yields. Functional groups such as cyano, nitro, acetals, and the trifluoromethyl group were well tolerated.

Starting from a different  $\text{CF}_3$  source, such as fluoroform, Daugulis et al. communicated the trifluoromethylation of ethyl 2-iodobenzoate in a 51% yield.<sup>311</sup> In this case,  $\text{TMP}_2\text{Zn}$  was used as a base and copper chloride/**337** (phen) as a catalytic system. Also using fluoroform, Grushin et al. accomplished the preparation of  $[\text{CuCF}_3]$  complex in the absence of additional ligands (Scheme 204). Moreover, they showed that this complex is a highly reactive trifluoromethyl copper species for the trifluoromethylation of electrophiles such as aryl iodides **410**, and compounds **411** can be prepared.<sup>313</sup>

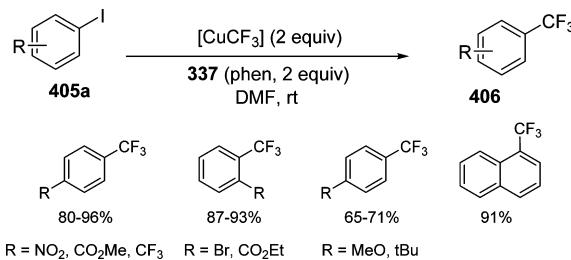
Scheme 204



The cupration of fluoroform in a flow manner for the production of  $[\text{CuCF}_3]$  in up to 94% yield has been reported, and this complex was used to trifluoromethylate aryl halides with excellent efficiency and yields (85–89%) comparable to those previously observed for the same reagent prepared by other methodologies.<sup>314</sup>

On the other hand,  $[\text{CuCF}_3]$  reagent can be directly prepared<sup>285</sup> from 2,2,2-trifluoro acetophenone (vide supra, Scheme 184) and  $\text{K}[\text{Cu}(\text{OtBu})_2]$ . In this sense, the trifluoromethylation of aryl iodides **405a** in the presence of **337** (phen, Scheme 205) has been accomplished almost

Scheme 205

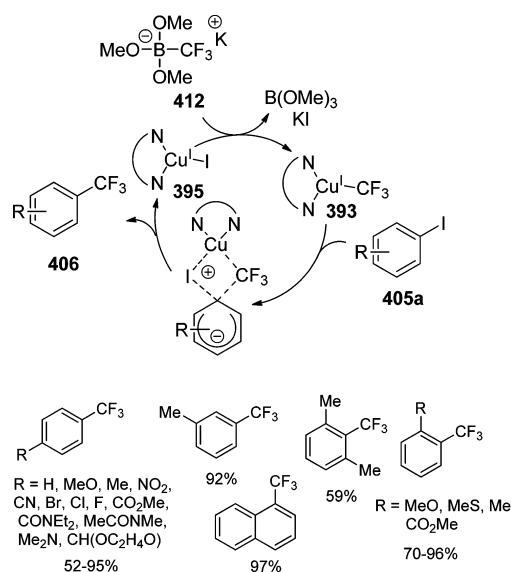


quantitatively. The use of the electron-deficient aryl iodides **405a** led to the corresponding products **406** in good to excellent yields even at room temperature, while decreased yields were found for iodides with demanding *ortho*-substituent. In the latter case, increasing the reaction temperature up to 50 °C improved the reactivity to give good yields.

As an alternative, Gooßen et al. developed another trifluoromethylating agent, the potassium (trifluoromethyl)-trimethoxyborate **412**, which allowed the conversion of various aryl iodides **405a** into the corresponding benzotrifluorides **406** in high yields under mild, base-free conditions in the presence of catalytic quantities of a  $\text{CuI}/\text{337}$  (20 mol %) complex **395** (Scheme 206).<sup>315</sup>

This new reagent can be used for the trifluoromethylation of both electron-rich and -poor aryl iodides **405a**, and it is sufficiently mild to be tolerated by substrates containing moderately reactive carbon electrophiles, for example, ester,

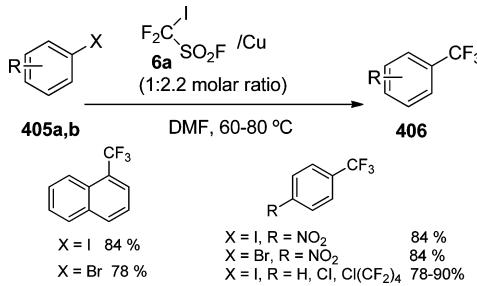
Scheme 206



amide, and nitrile (Scheme 206). However, aryl iodides **405a** containing particularly reactive carbonyl groups, ketones and aldehydes, could be used only in their protected form.

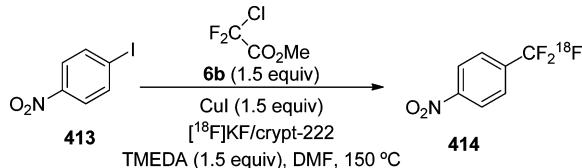
Other attractive sources of trifluoromethyl moiety for copper-mediated couplings with aryl iodides are Chen's methyl fluorosulfonyldifluoroacetate **6a**<sup>43</sup> and fluorosulfonyldifluoromethyl iodide.<sup>316</sup> For example, treatment of aryl halides **405a,b** with the latter reagent in the presence of copper in DMF at 60–80 °C gave high yields of the trifluoromethylated product **406** (Scheme 207).

Scheme 207



Gouverneur, Passchier et al.<sup>317</sup> reported the use of the trifluoromethylating reagent **6b** and developed a method for the [<sup>18</sup>F]trifluoromethylation of aryl iodides **413** allowing the preparation of a molecule containing unnatural radiolabeled isotope fluorine-18 **414** (Scheme 208), which can be used for positron emission tomography (PET).

Scheme 208

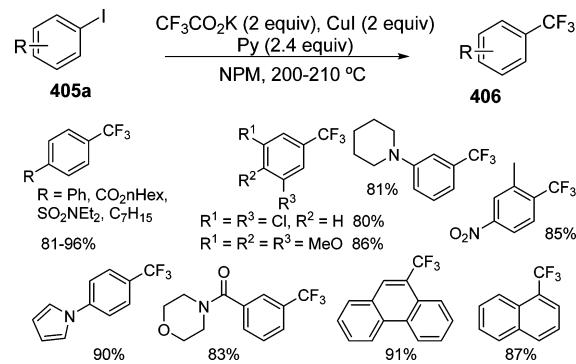


Trifluoroacetate salts could also be used as trifluoromethyl sources. For instance, a ligand-free copper-mediated decarboxylative trifluoromethylation of aryl halides with sodium trifluoroacetate has been reported by Matsui et al.,<sup>318</sup> Chambers et al.,<sup>233</sup> and Vicic et al.<sup>319</sup> However, this reagent presents the drawback of low solubility; therefore, it must be used generally in excess. Some other examples with the copper-catalyzed version and Ag<sub>2</sub>O as a promoter<sup>320</sup> can be found in the literature.

Similarly, but using CF<sub>3</sub>CO<sub>2</sub>K as the CF<sub>3</sub> source, aromatic trifluoromethylation was conducted under flow conditions (Scheme 209).<sup>321</sup> Rapid decarboxylation occurs in the presence of copper iodide and facilitates the generation of the [CuCF<sub>3</sub>] intermediate. Pyridine (Py) proved to be the optimal ligand, and very short reaction times were required to achieve full conversion of a wide spectrum of aryl iodides **405a** into the corresponding trifluoromethylated aromatic compounds **406**.

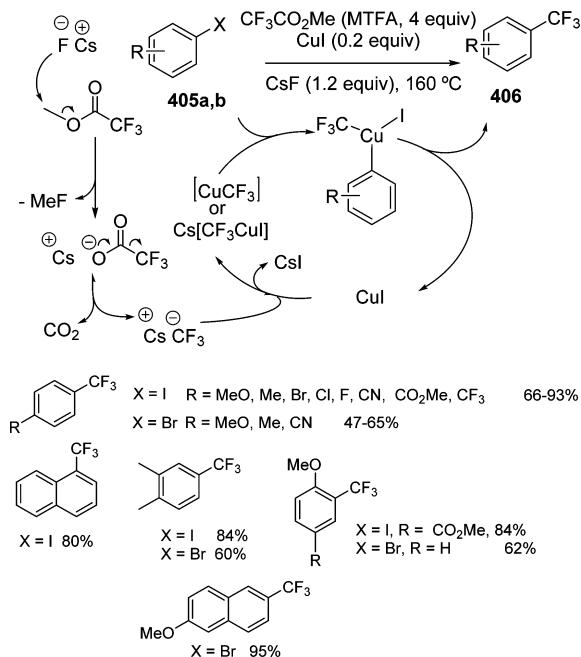
A similar reagent, such as methyl trifluoroacetate (CF<sub>3</sub>CO<sub>2</sub>Me, MTFA) can also be used as reagent for the copper-catalyzed trifluoromethylation of aryl halides. This reagent is more easily available than methyl chlorodifluoroacetate **6b** and is more soluble than trifluoroacetate salts. In this way, Langlois and co-worker<sup>322</sup> reported the trifluoromethylation of several aromatic iodides and bromides. Further-

Scheme 209



more, MTFA can be used not only with stoichiometric but also with catalytic amounts of copper iodide as Beller et al. reported.<sup>323</sup> Thus, a variety of substituted aryl iodides **405a** and bromides **405b** reacted with MTFA in the presence of CsF to give the trifluoromethyl-substituted arenes **406** (Scheme 210).

Scheme 210

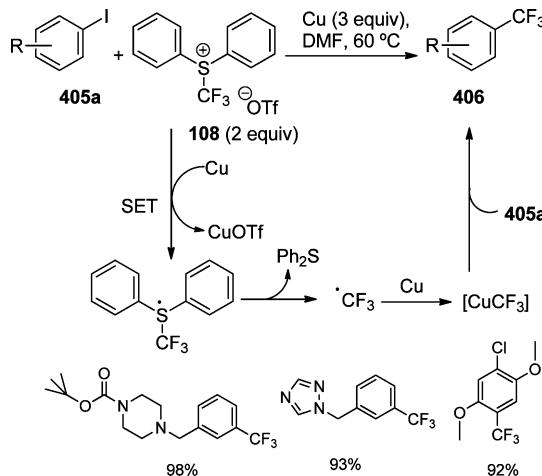


The mechanism of the reaction could be explained via fluoride-induced decarboxylation, copper complex formation, and subsequent transfer of CF<sub>3</sub> to the aromatic halide **405a,b** leading to the trifluoromethylated product **406** and starting copper iodide.

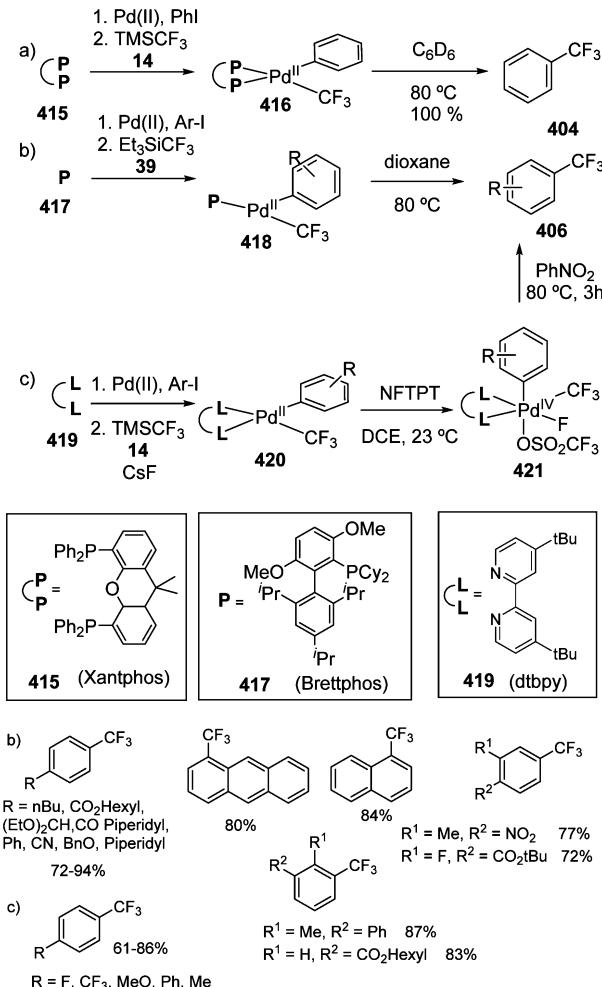
In 2011, Xiao et al.<sup>324</sup> confirmed by <sup>19</sup>F NMR spectroscopy and ESI-MS the formation of [CuCF<sub>3</sub>] complex in trifluoromethylation reactions of aromatic iodides **405a** when using trifluoromethylsulfonium salt **108**<sup>97</sup> in the presence of copper, affording the corresponding trifluoromethylated compounds **406** in high yields via a SET mechanism (Scheme 211).

Transition metals other than copper have also been used for carbon–CF<sub>3</sub> bond formation. For example, palladium-based systems have been applied to the trifluoromethylation of aryl iodides or activated aryl bromides.<sup>297,325</sup> However, due to the inertness of the Pd–CF<sub>3</sub> bond, most [Pd(II)(Aryl)(CF<sub>3</sub>)]

Scheme 211



Scheme 212



complexes have limited application in aryl–CF<sub>3</sub> bond-forming reductive elimination processes, requiring temperatures higher than 150 °C.<sup>326</sup> To avoid such harsh conditions, two strategies can be found in the literature. The first one focuses on aryl–CF<sub>3</sub> bond-construction by means of reductive elimination from Pd(II) via steric and electronic modification of phosphine ligands **415** and **417** at [(L)nPd(II)(Aryl)(CF<sub>3</sub>)] complexes **416** and **418** obtained from TMSCF<sub>3</sub> **14** (RPr)<sup>47</sup> and Et<sub>3</sub>SiCF<sub>3</sub> **39** (Scheme 212). For example, pioneering work of Grushin et al.<sup>327</sup> described the use of Pd catalysts for stoichiometric transformations of [Pd–CF<sub>3</sub>] complexes into the corresponding trifluoromethylated aromatic derivatives. The diphosphine ligand used in this case, **415** (Xantphos), facilitates high yielding formation of trifluoromethylbenzene **404** through [(Xantphos)-Pd(II)(Ph)(CF<sub>3</sub>)] complex **416** at 80 °C (Scheme 212a). Later, this group reported an experimental and computational study of this process.<sup>328</sup>

In a similar fashion, Buchwald and co-workers<sup>329</sup> developed the sterically large monodentate phosphine ligand **417** (Brettphos), which promotes stoichiometric aryl–CF<sub>3</sub> coupling from [(Brettphos)Pd(II)(Aryl)(CF<sub>3</sub>)] complex **418** at 80 °C (Scheme 212b). In this sense, the palladium-catalyzed trifluoromethylation of aryl bromides has been achieved in micellar media using the Brettphos ligand **417**, along with [cinnamylPdCl]<sub>2</sub>, **14** (RPr),<sup>47</sup> and CsF as the fluoride source.<sup>330</sup> Application of the micellar trifluoromethylation reaction to various aryl bromides with electron-withdrawing or electron-donating functionalities gave the corresponding ArCF<sub>3</sub> **406** in good yields.

Furthermore, there is a second complementary strategy for achieving aryl–CF<sub>3</sub> bond-forming reductive elimination from palladium, which consists of changing its oxidation state, rather than the ancillary ligand environment. For example, the key Pd(IV) intermediate [(dtbpy)Pd(IV)(Aryl)(CF<sub>3</sub>)(F)-(OTf)] **421** can be generated via oxidation of a preassembled [(dtbpy)Pd(II)(Aryl)(CF<sub>3</sub>)] **420** with N-fluoro-1,3,5-trimethylpyridinium triflate (NFTPT).<sup>331</sup> Thermolysis of this complex at 80 °C resulted in aryl–CF<sub>3</sub> bond-formation to **406** (Scheme 212c). DFT calculations carried out by Sanford et al.<sup>332</sup> revealed that the transition state for aryl–CF<sub>3</sub> bond formation involves the CF<sub>3</sub> acting as an electrophile with the aryl ligand serving as a nucleophilic coupling partner.

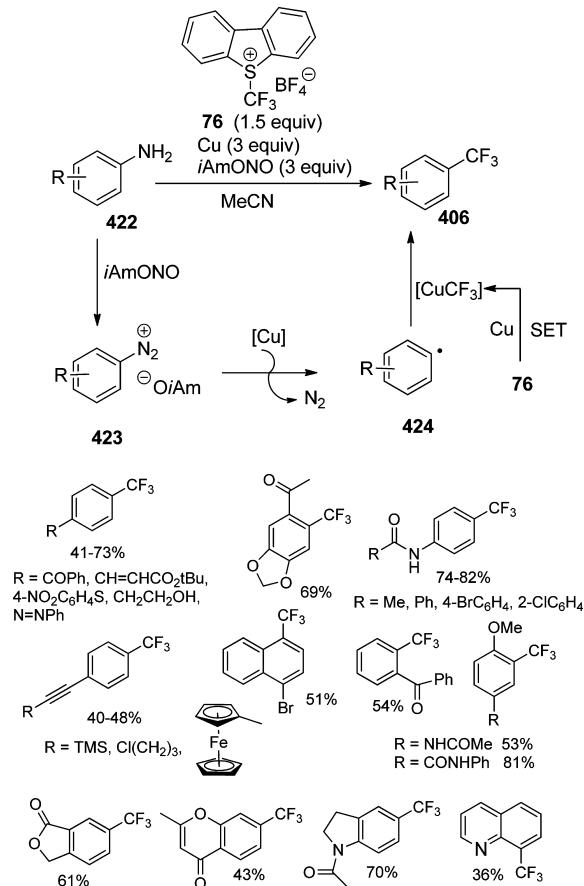
### 5.1.2. From Nitrogen-Functionalized Aryl Derivatives.

The aromatic amino group could be also converted into a

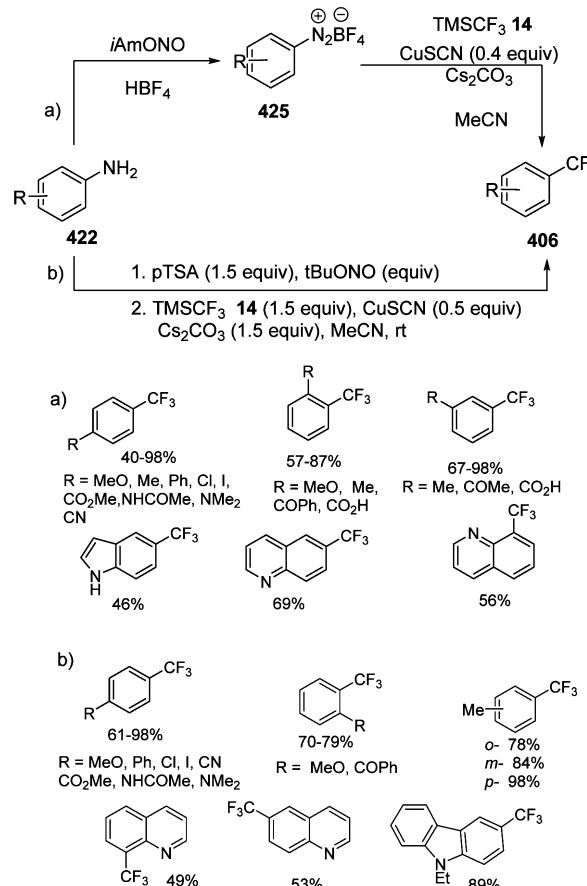
trifluoromethyl group by means of diazonium salts based on Sandmeyer reactions<sup>333</sup> of these substrates. In 2013, Fu et al.<sup>334</sup> described the first example of the trifluoromethylation reaction of aromatic amines by a copper-promoted Sandmeyer strategy.<sup>333</sup> Diazonium salts **423** were generated by reaction of arylamines **422** and alkynitrile (*i*AmONO, Scheme 213). The sulphonium salt **76** (Ur)<sup>84</sup> was used as the trifluoromethylating agent along with isoamyl nitrite (*i*AmONO) and Cu powder, to convert the amino group of aromatic amines **422** through the diazonium salts **423** into the trifluoromethyl compounds **406** (Scheme 213). A variety of aryl amines can be successfully trifluoromethylated to the corresponding products **406** in modest to good yields. Electron-donating as well as electron-withdrawing groups presented good tolerance under the reaction conditions. The reaction may proceed through a copper-mediated SET where a CF<sub>3</sub> radical, produced from **76**, combined with copper would afford [CuCF<sub>3</sub>]. This complex reacted with the aryl radical **424** generated from the aryl diazonium ion **423** to provide the product **406** (Scheme 213).

Similarly, various arenediazonium tetrafluoroborates **425**, prepared from arylamines **422** and organic nitrites, have been converted into the corresponding benzotrifluorides **406** in high yields by a combination of **14** (RPr),<sup>47</sup> CuSCN (0.4 equiv), and Cs<sub>2</sub>CO<sub>3</sub>.<sup>335</sup> Both electron-rich and electron-deficient substrates gave similar yields, and also the aryl group of indoles and

Scheme 213



Scheme 214



quinoline derivatives can be trifluoromethylated (Scheme 214a). The reaction seems to proceed, as in the previous example, analogously to Sandmeyer reactions<sup>333</sup> of diazonium salts via radical intermediates.

Afterward, a practical one-pot procedure Sandmeyer-type trifluoromethylation of diversely substituted aromatic amines **422** has been developed by Gooßen et al.<sup>336</sup> The diazotization with 1 equiv of *tert*-butyl nitrite and 1.5 equiv of anhydrous pTSA in acetonitrile followed by the slow addition of copper thiocyanate, cesium carbonate, and TMSCF<sub>3</sub> **14** to the in situ formed mixture gave the corresponding benzotrifluorides **406** in near quantitative yields without isolating the diazonium salts via radical intermediates (Scheme 214b).

On the basis of the oxidizing properties of aryl diazonium salts, Wang et al. proposed<sup>337</sup> that oxidative addition of diazonium salts **426** generated from anilines **422** could be favored with an electron-rich silver center of  $[\text{AgCF}_3]$  complex, prepared from AgF and **14** (RPr),<sup>47</sup> affording an intermediate **427**, which under reductive elimination formed a Caryl–CF<sub>3</sub> bond. The expected trifluoromethylated products **406** were obtained in moderate to excellent yields departing either from electron-withdrawing or from -donating substituted anilines **422**, and the process is applied not only to simple and functionalized arenes with a wide range of functionalized groups but also to the aryl group of indoles and benzofuran derivatives (Scheme 215).

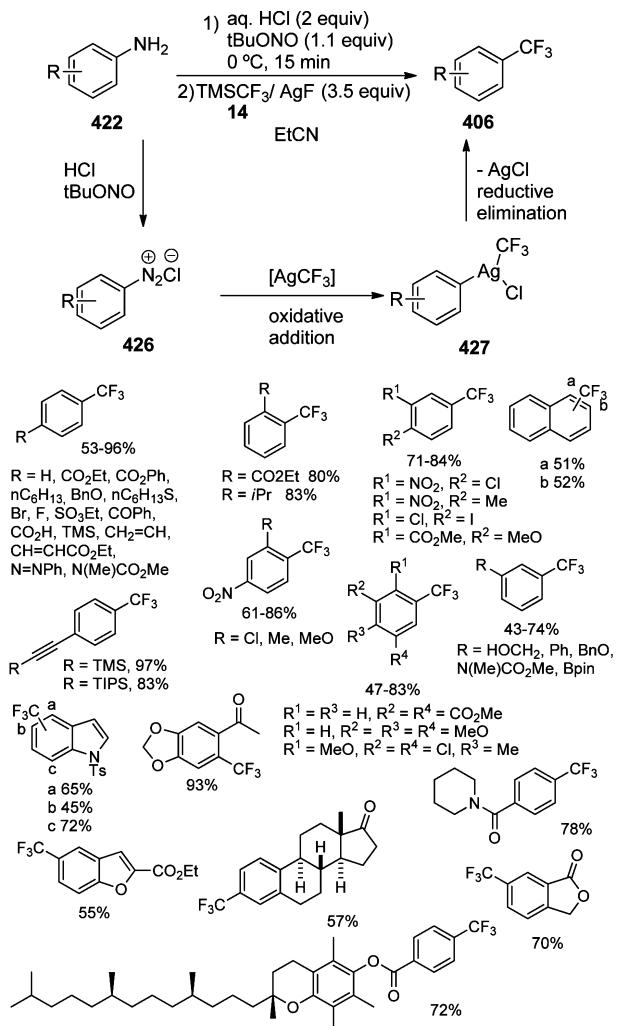
The trifluoromethylation of arendiazonium salts with fluoroform derived  $[\text{CuCF}_3]$  under aqueous conditions has been reported by Grushin et al.<sup>338</sup> Diazonium salts were generated by reaction of a variety of arylamines **422** and

NaNO<sub>2</sub> with aqueous HF (Scheme 216). Premixing a freshly generated aqueous solution of the diazonium salt with MeCN prior to the addition of  $[\text{CuCF}_3]$  benefited both the yield and the selectivity of the reaction. The trifluoromethylation reaction of arendiazonium salts in the aqueous medium to provide the product **406** may be governed by a radical mechanism and tolerates a broad variety of functional groups with both electron-donating and -withdrawing functional groups (Scheme 216).

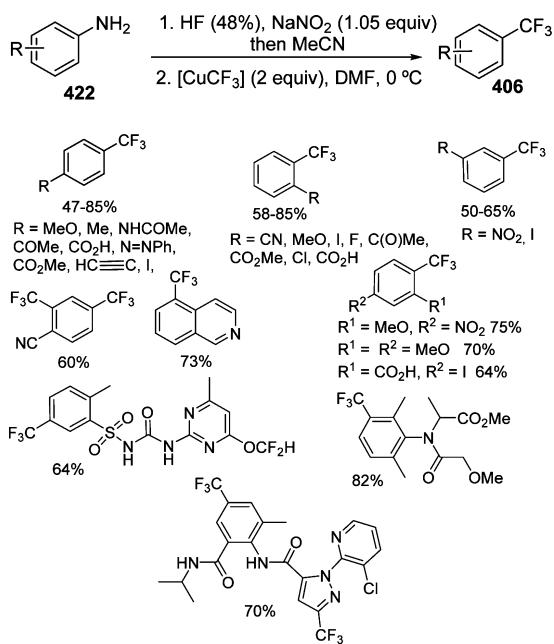
Alternatively, Bräse and co-worker reported the trifluoromethylation of aryltriazenes,<sup>339</sup> easily prepared from aniline derivatives.<sup>340</sup> This strategy was carried out by using **14** (RPr),<sup>47</sup> potassium fluoride, and copper iodide as trifluoromethylating system in the presence of **337** (phen). Various functionalized aromatic diisopropyltriazenes **428** have been transformed into the corresponding trifluoromethyl-substituted arenes **406** with good yields in a two-step, one-pot synthesis procedure involving initially iodination of triazenes with MeI followed by the trifluoromethylation process (Scheme 217).

**5.1.3. From Aryl Boronic Derivatives.** Apart from the previously mentioned functionalizations, oxidative trifluoromethylation protocols have been also developed for aryl boronic acids or borates. One of these methodologies implies the use of trifluoromethyl radicals. For example, a mild and general method for the cross-coupling of aryl boronic acids **429** with CF<sub>3</sub>I via visible-light photocatalysis (to generate CF<sub>3</sub> radical) and Cu catalysis (to generate reactive Cu–aryl species) has been reported by Sanford et al.<sup>341</sup> for the preparation of aryl compounds **406** (Scheme 218). Aromatic boronic acids bearing either electron-donating or electron-withdrawing substituents

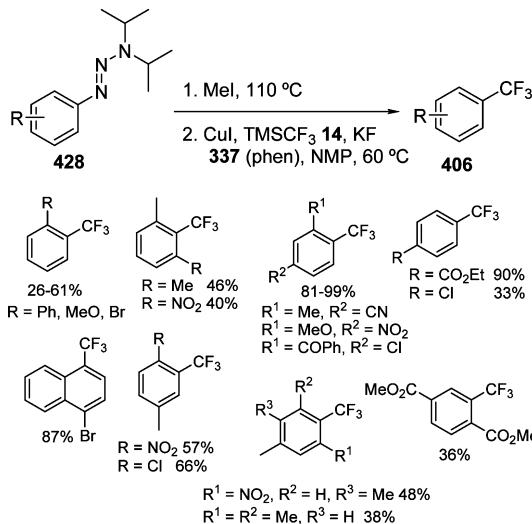
Scheme 215



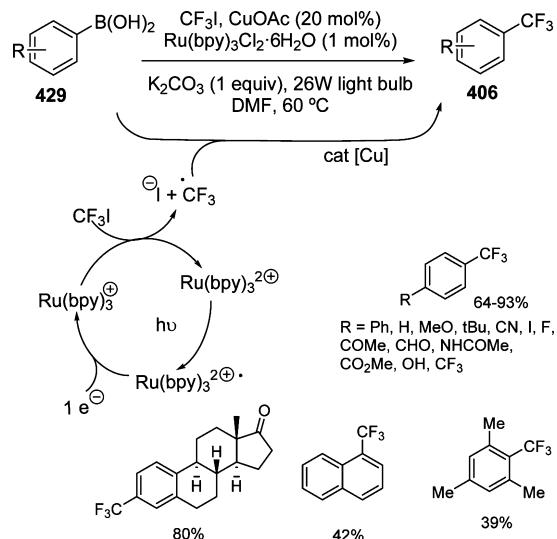
Scheme 216



Scheme 217



Scheme 218

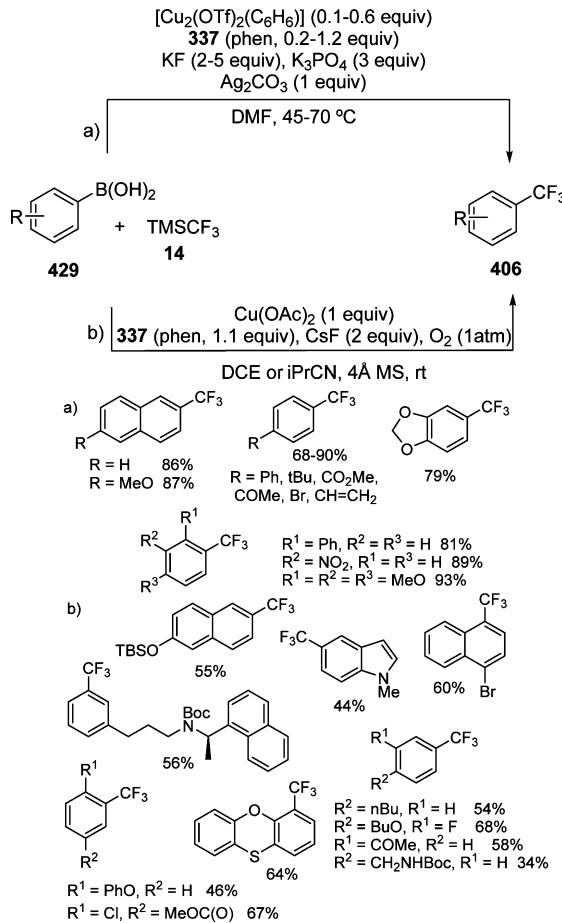


underwent trifluoromethylation in high yield and with good functional group tolerance.

Nucleophilic trifluoromethylating reagents can also be used for the preparation of trifluoromethyl arenes from aryl boronic acid derivatives. Chu and Qing<sup>246,284</sup> reported the first example of oxidative trifluoromethylation of aryl boronic acids 429 to afford the Csp<sup>2</sup>-CF<sub>3</sub> products 406 in high yields. The reaction occurred smoothly in high yields for a variety of aryl boronic acids 429 with 14 (RPr, 5 equiv)<sup>47</sup> in the presence of [CuOTf]<sub>2</sub>·C<sub>6</sub>H<sub>6</sub>, 337 (phen), K<sub>3</sub>PO<sub>4</sub>, and Ag<sub>2</sub>CO<sub>3</sub> as an oxidant in DMF (Scheme 219a). Buchwald et al.<sup>342</sup> disclosed an improved protocol, still more economical, using only a 2-fold excess of 14 (2 equiv) and dry O<sub>2</sub>, as oxidant, in place of the silver salt. Proceeding under mild conditions, the method tolerates a range of functional groups, allowing access to a variety of trifluoromethyl arenes 406 including the aryl ring of indole and phenoxathiine derivatives (Scheme 219b).

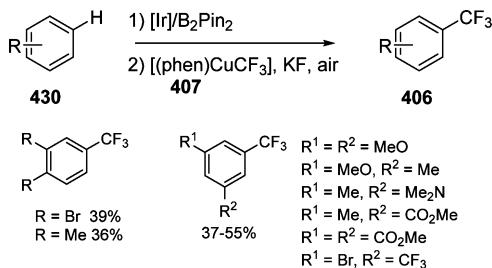
Moreover, Hartwig et al. reported<sup>343</sup> an oxygen-based oxidative trifluoromethylation of intermediate aryl boronic acid pinacol esters with [(phen)CuCF<sub>3</sub>] 407 (Trifluoromethylator).<sup>308</sup> The aryl boronate ester generated in situ by iridium-

Scheme 219



catalyzed borylation of arenes **430** is then converted to the trifluoromethylarene **406** by reaction with **407** in air. This system reacts under mild conditions and tolerates a wide range of functional groups (Scheme 220). Similar results were

Scheme 220

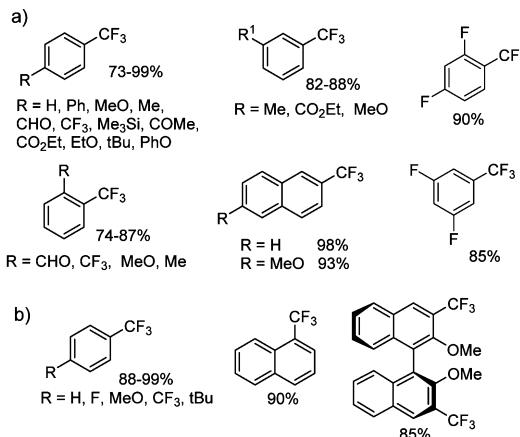
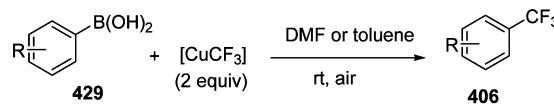


obtained by palladium-catalyzed borylation<sup>343</sup> of aryl bromides and subsequent trifluoromethylation of the intermediate aryl boronate ester obtaining corresponding trifluoromethylated compounds **406** in moderate-good yields (53–88%).

Likewise, Grushin et al. prepared a well-defined copper complex from fluoroform and used it for the selective trifluoromethylation of aryl boronic acids **429** in nondried air (Scheme 221).<sup>344</sup>

The reaction occurs smoothly in the absence of any extra ligands/additives at room temperature and 1 atm of air as the oxidant, and afforded trifluoromethylated aromatic compounds **406** in up to 99% yield with high selectivity. The method has a

Scheme 221

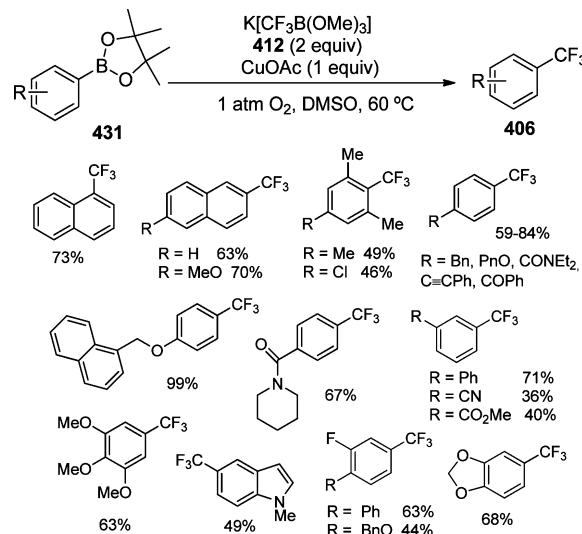


broad scope and tolerates various functionalities, including not only simple alkyl or aryl groups but also alkoxy, aryloxy, carbalkoxy, silyl, and even formyl groups.

$[\text{CuCF}_3]$  reagent prepared from 2,2,2-trifluoroacetophenone, as it has been previously described (vide supra, sections 4.2 and 5.1.1),<sup>285</sup> can be applied also to the trifluoromethylation of aromatic boronic acids **429** bearing both electron-withdrawing and -donating substituents providing the corresponding products **406** in high yields (Scheme 221b).

Potassium trifluoromethyltrimethoxyborate **412**, previously reported for the trifluoromethylation of aryl halides (vide supra, section 5.1.1), can also be useful for the placement of trifluoromethyl group into borates **431** (Scheme 222), as

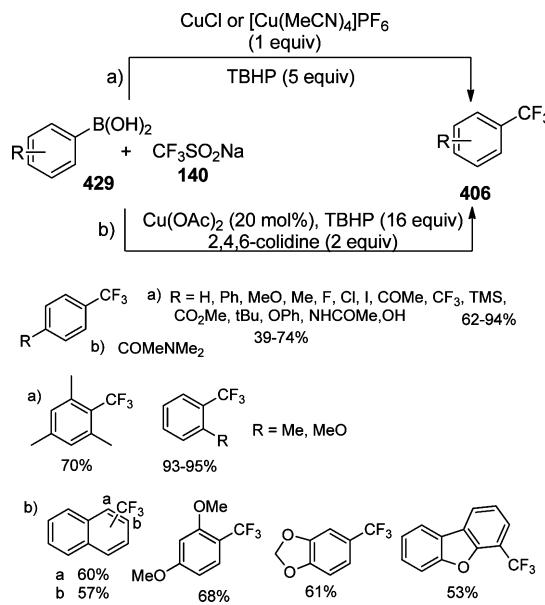
Scheme 222



described by Goossen et al.<sup>345</sup> In this case, the reagent is combined with copper acetate and molecular oxygen for the conversion of aryl boronic acid pinacol esters **431** into the corresponding simple and functionalized benzotrifluorides **406** including the trifluoromethylation of the aryl ring of indoles.

Alternatively, sodium trifluorosulfinate **140** ( $\text{Lr}$ )<sup>127</sup> is able to react with a variety of aryl boronic acids **429** in the presence of copper derivatives to afford trifluoromethylated arenes **406** (Scheme 223). In this context, Sanford et al.<sup>346</sup> described the

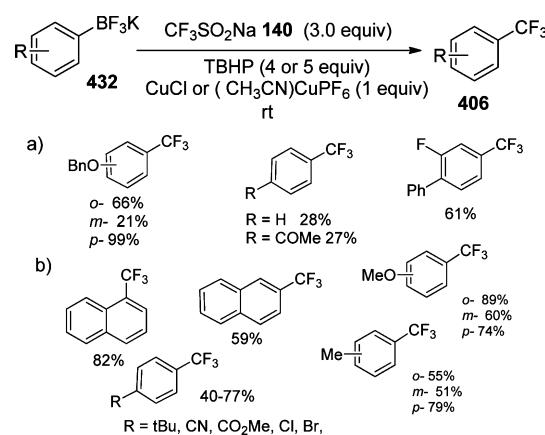
Scheme 223



trifluoromethylation of boronic derivatives **429** using TBHP and stoichiometric amounts of  $\text{CuCl}$  or  $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$  as copper source (Scheme 223a), and Beller et al.<sup>249</sup> employed catalytic amounts of  $\text{Cu}(\text{OAc})_2$  (20 mol %) as efficient copper catalyst (Scheme 223b). This strategy allowed the preparation of trifluoromethyl arenes and the trifluoromethylation of the aryl ring of dibenzofurane.

A copper-mediated radical trifluoromethylation with sodium trifluorosulfinate **140** ( $\text{Lr}$ )<sup>127</sup> and TBHP allowed the introduction of trifluoromethyl group into a variety of aryl potassium trifluoroborates **432** (Scheme 224).<sup>251</sup> Electron-rich substrates were efficiently trifluoromethylated, but a decreased yield was observed in the case of *ortho*-substituted products, which may be attributed to steric hindrance. The reaction performed with *meta*-substituted potassium trifluoroborate led to a poor yield. Electron-poor arenes required the use of modified conditions such as the use of  $(\text{CH}_3\text{CN})\text{CuPF}_6$ . The

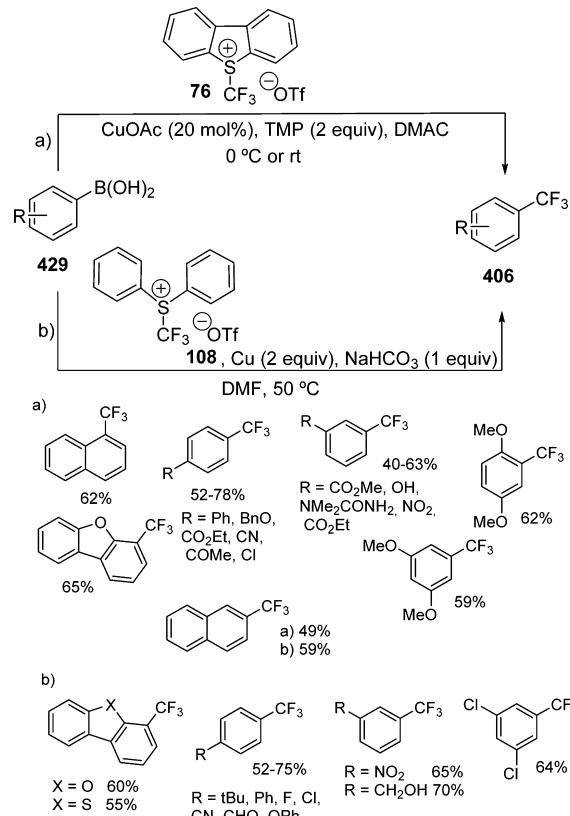
Scheme 224



same procedure has been used<sup>252</sup> by other authors for the preparation of trifluoromethylarenes **406** (Scheme 224).

Electrophilic reagents have also been used for the catalytic trifluoromethylation of nucleophilic substrates such as boronic acids or boranes. For example, dibenzothiophenium salt **76** ( $\text{Ur}$ )<sup>84</sup> can be used in the presence of TMP as ligand and  $\text{CuOAc}$  (20 mol %) for the general synthesis of aryl trifluoromethanes **406** in very mild conditions starting from aryl boronic acid derivatives **429** (Scheme 225a).<sup>248</sup> The same

Scheme 225

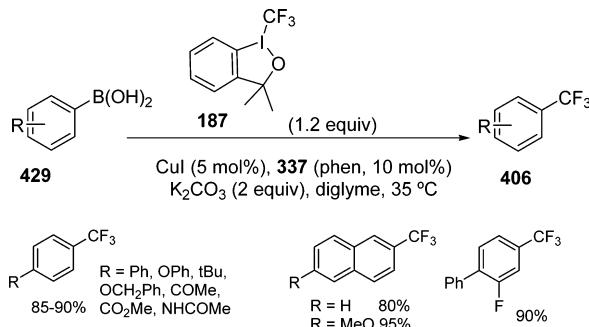


reaction, but using **108**<sup>97</sup> instead of **76**, was disclosed a few months later by Xiao et al.<sup>347</sup> Heating and 2 equiv of Cu powder were needed for the reaction to proceed, but, unlike in the previous reaction, no ligand was required (Scheme 225b). The scope of the reaction is wide, tolerating functional groups such as aldehyde, halogen, alcohol, and ether and the introduction of the trifluoromethyl moiety into the phenyl group of dibenzofuran and dibenzothiophene.

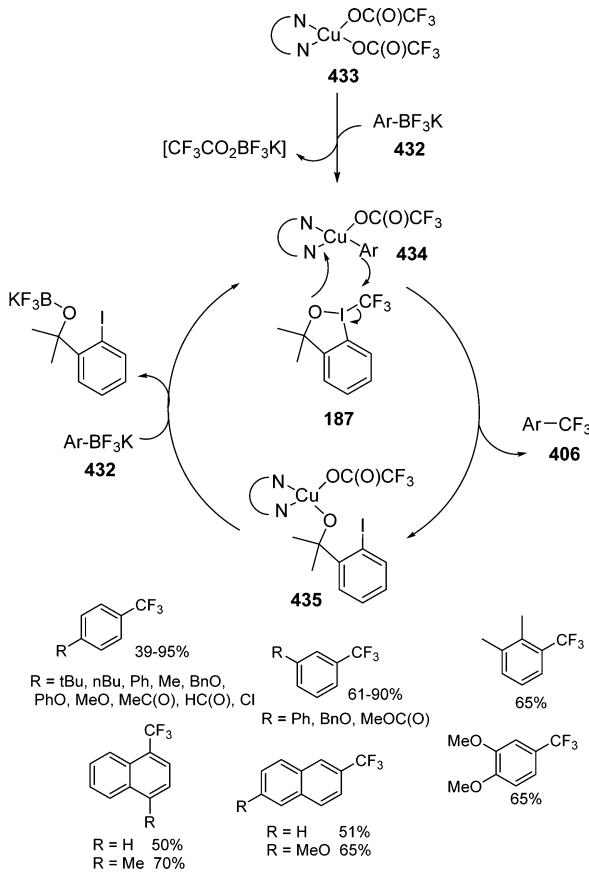
Another method using the reagent **187** ( $\text{Tr}2$ )<sup>80</sup> was published at the same time.<sup>247</sup> This procedure also used  $\text{Cu(I)}$  catalysis and the basic ligand **337** (phen), in a way similar to that reported using **76** ( $\text{Ur}$ )<sup>84</sup> for the trifluoromethylation of boronic acid compounds **429**, but provided much better yields of aryl derivatives **406** (Scheme 226).

The extension of this methodology from boronic acid derivatives **429** to aryl borates **432** was reported by Huang et al.<sup>348</sup> through an effective copper catalyst system, consisting of **187** ( $\text{Tr}2$ ),<sup>80</sup>  $\text{Cu}(\text{TFA})_2$ , and 2,2'-bipyridine. It is noteworthy that the reaction occurs smoothly at room temperature in the absence of either base or oxidant to afford trifluoromethyl arenes **406** in good to excellent yields and can tolerate a variety of functionalities (Scheme 227). Electron-donating groups on

Scheme 226



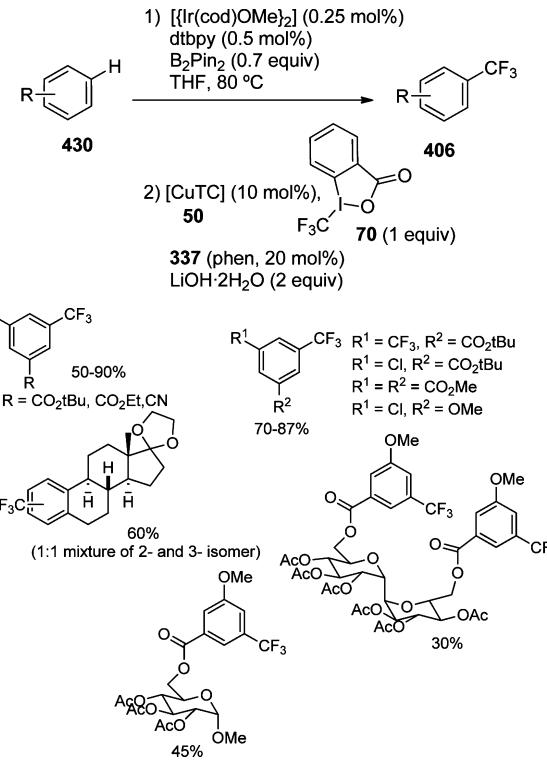
Scheme 227



the phenyl or naphthalyl rings did not reduce the reactivity. A plausible mechanism is proposed in Scheme 227. The bipyridine ligated  $[(N,N\text{-Cu}(\text{CF}_3\text{CO}_2)_2)]$  complex 433 could be initially generated in situ. Next, 433 undergoes reaction with potassium arylborate 432 to give a copper(II) intermediate 434. Subsequent nucleophilic attack of the aryl group of 434 to the  $\text{CF}_3$  moiety in the reagent 187 (Tr2) might proceed to form the product 406 and a Cu-alkoxide complex 435, which can further react with potassium arylborate to regenerate 434 and complete the catalytic cycle.

Similarly to Scheme 220 (vide supra), Shen disclosed<sup>349</sup> a sequential iridium-catalyzed C–H activation-borylation with bis(pinacolate)diboron ( $\text{B}_2\text{Pin}_2$ ) in the presence of  $[\{\text{Ir}(\text{cod})\text{OMe}\}_2]$  and di-*tert*-butylpyridine (dtbpy) and subsequent copper-catalyzed trifluoromethylation of the aryl boronate esters using the trifluoromethylating reagent 70<sup>80</sup> and CuTC 50 (Scheme 228). This methodology can be applied to arenes

Scheme 228

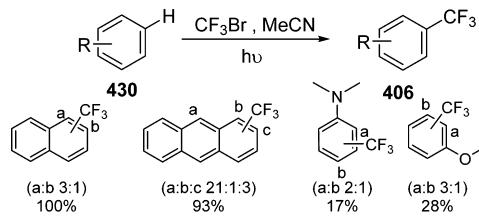


430 bearing a variety of functional groups, and a wide range of trifluoromethyl derivatives 406 can be obtained. This strategy can even be used for the introduction of the  $\text{CF}_3$  group in a steroid or carbohydrates.

#### 5.1.4. Direct C–H Aryl Trifluoromethylation.

**5.1.4.1. Without Directing Group Assistance.** Although we have seen above that significant progress has been made in the trifluoromethylation of functionalized aromatic derivatives, the most effective route for the preparation of  $\text{CF}_3$ -substituted arenes would be the direct trifluoromethylation of C–H bonds in aromatic substrates. Nevertheless, mixtures of regioisomers of trifluoromethylated derivatives are obtained when departing from substituted aromatic substrates. A number of pioneering methods for the direct radical trifluoromethylation of arene C–H moieties included  $\text{CF}_3\text{I}$ ,<sup>350</sup>  $(\text{CF}_3)_2\text{Te}$ ,<sup>351</sup> and  $\text{CF}_3\text{Br}/\text{Na}_2\text{S}_2\text{O}_4$ .<sup>352</sup> In 1998, Akiyama et al.<sup>353</sup> reported the results of a one-step photochemical trifluoromethylation of some aromatic compounds 430 by irradiation with a high-pressure mercury lamp under bubbling  $\text{CF}_3\text{Br}$  to obtain 406 (Scheme 229). The mechanistic study of the reaction indicates that it may proceed via the electron transfer from the excited singlet state of substrate to  $\text{CF}_3\text{Br}$  and then the formation of a  $\text{CF}_3$  radical.

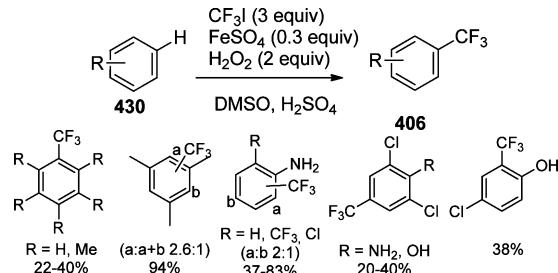
Scheme 229



Gas-phase perfluoroalkylation of naphthalene with an excess of  $\text{CF}_3\text{I}$  reagent, high-temperature gas-phase, solvent- and catalyst-free, has been used for the first time by Popov et al.<sup>354</sup> to produce a series of highly trifluoromethylated naphthalene products.

Kino et al. also generated trifluoromethyl radicals from  $\text{CF}_3\text{I}$  with the aid of a Fe(II) compound,  $\text{H}_2\text{O}_2$ , and DMSO in the presence, or not, of  $\text{H}_2\text{SO}_4$  (Scheme 230).<sup>355</sup> As the authors

Scheme 230

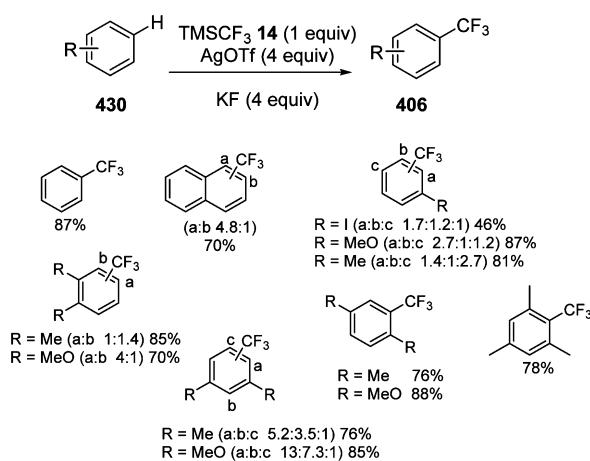


stated, the orientation of trifluoromethylated position could be predicted by the general trend of substitution on aromatic compounds 430, although this rule could not be applicable in all cases, because sometimes mixtures of regiosomers of 406 were obtained. As can be deduced from the generally low yields of this reaction, the transition-metal-catalyzed trifluoromethylation of aryl C–H bonds is not easy, probably due to the slowness of aryl/CF<sub>3</sub> reductive elimination and a lack of ligands that are mutually compatible for both the reductive elimination and the C–H activation steps.

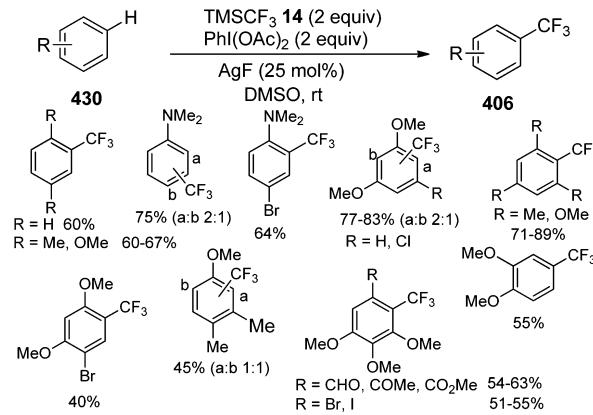
Nevertheless, Sanford et al.<sup>356</sup> proposed the trifluoromethylation of unfunctionalized arenes 430 via silver complexes obtained by the combination of AgOTf, KF, and 14 (RPr),<sup>47</sup> and got better results for compounds 406. Even the formation of *o*-trifluoromethylmethoxy derivatives 406 (R = OMe) as major products when substrates 329 (R = OMe) were treated under mild conditions was observed (Scheme 231).

Similarly, trifluoromethylation of arenes can be performed with 14 (RPr)<sup>47</sup> and silver metal as Sanford et al. established two years earlier, but with PhI(OAc)<sub>2</sub> and under catalytic conditions (AgF, 25 mol %).<sup>357</sup> Indeed, electron-rich arenes 430 afforded the corresponding trifluoromethylated products 406 in moderate to good yields (Scheme 232). The reaction was

Scheme 231



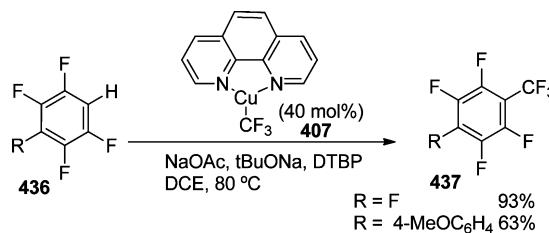
Scheme 232



also effective for unactivated arenes, while for unsymmetrical substrates isomeric mixtures were generally observed. A possible mechanism suggested that 14 could be oxidized to the CF<sub>3</sub> radical, followed by subsequent addition, a second one electron oxidation, and proton loss to give the trifluoromethylated product 406.

Furthermore, a copper-mediated oxidative strategy also succeeded for the direct C–H trifluoromethylation of arenes. Thus, Qing et al. described<sup>358</sup> a method for copper-catalyzed oxidative trifluoromethylation via C–H activation of electron-deficient polyfluoroarenes with nucleophilic 14 (RPr)<sup>47</sup> in the presence of a catalytic amount of Cu(I) complex 407, prepared from Cu(OAc)<sub>2</sub> and 337 (phen), cobases tBuONa/NaOAc, and di-*tert*-butyl peroxide (DTBP) as an oxidant. The oxidative trifluoromethylation of electron-deficient arenes such as pentafluorobenzene 436 (R = F) or tetrafluorobenzene derivative 436 (R = 4-MeOC<sub>6</sub>H<sub>4</sub>) gave products 437 in excellent or moderate yield (Scheme 233).

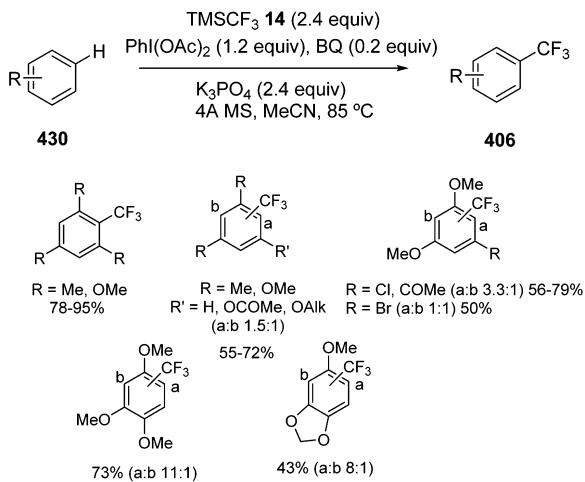
Scheme 233



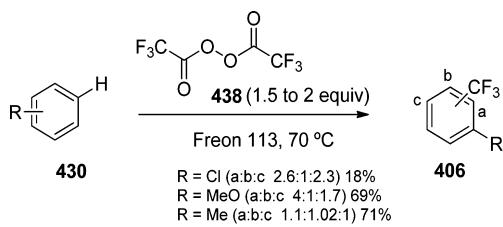
One year later, the same group achieved the PhI(OAc)<sub>2</sub>-mediated oxidative trifluoromethylation of arenes with 14 (RPr)<sup>47</sup> under metal-free conditions.<sup>359</sup> Either electron-rich or electron-withdrawing arenes 430 became suitably trifluoromethylated, affording the corresponding products 406 in moderate to excellent yields (Scheme 234).

Trifluoromethyl acetate derivatives have been used also for the trifluoromethylation of unfunctionalized arenes, as, for example, CF<sub>3</sub>CO<sub>2</sub>H/XeF<sub>2</sub><sup>360</sup> or bis(trifluoroacetyl) peroxide.<sup>361</sup> In the latter case, when an arene 430 and trifluoroacetyl derivative 438 were heated in Freon 113, trifluoromethylated compounds 406 were obtained (Scheme 235). In these transformations, the CF<sub>3</sub> radical may be generated by homolysis of the peroxide and subsequent thermal elimination of CO<sub>2</sub> from the trifluoromethylcarboxyl radical intermediate. As expected, substituted benzene derivatives 430 delivered the

Scheme 234



Scheme 235

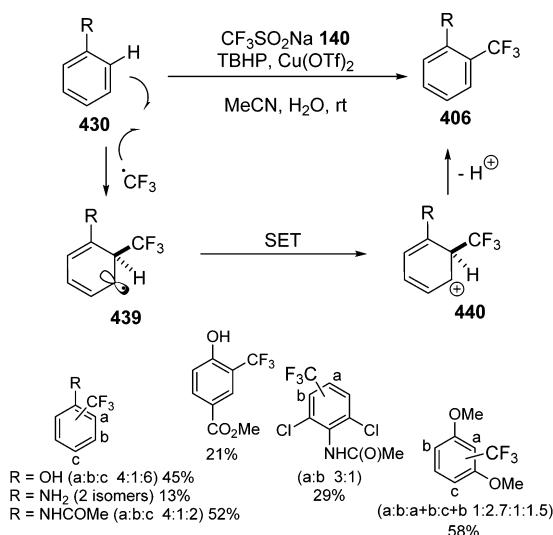


homolytic aromatic substitution products **406** as mixture of regioisomers.

On the other hand, Langlois et al. showed that **140** (Lr)<sup>127</sup> could be used to generate the CF<sub>3</sub> radical upon oxidation with catalytic amounts of Cu(OTf)<sub>2</sub> in the presence of an excess of TBHP as stoichiometric oxidant and ambient air and moisture (Scheme 236).

Various mono-, di-, and trisubstituted electron-rich benzene derivatives **430** were successfully transformed into the corresponding trifluoromethylated arenes **406**, which were isolated as mixtures of regioisomers (Scheme 236). The same group carried out the electrochemical oxidation of CF<sub>3</sub>SO<sub>2</sub>K

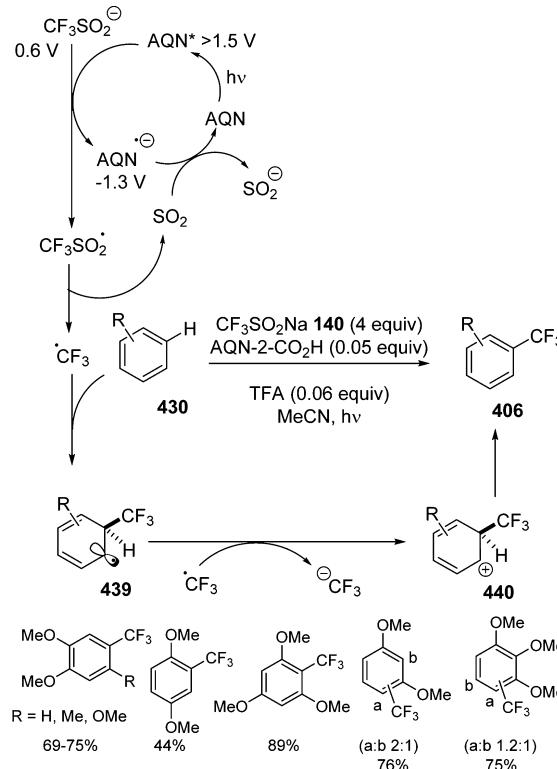
Scheme 236



**140** (Lr) in the presence of electron-rich arenes, which allowed the formation of the corresponding trifluoromethylated derivatives, in a metal-free strategy.<sup>149</sup> Intermediate radical **439** underwent a second SET event affording cyclohexadienyl cation **440** whose deprotonation gave the product **406**.

The same trifluoromethylating reagent **140** (Lr)<sup>127</sup> has also been used in metal-free conditions for the direct trifluoromethylation of arenes using a photoredox-based process under visible light irradiation with an organocatalyst.<sup>362</sup> A catalytic amount of anthraquinone-2-carboxylic acid AQN-2-CO<sub>2</sub>H (0.05 equiv) and acetonitrile were the most effective photosensitizer and solvent, respectively (Scheme 237). The addition

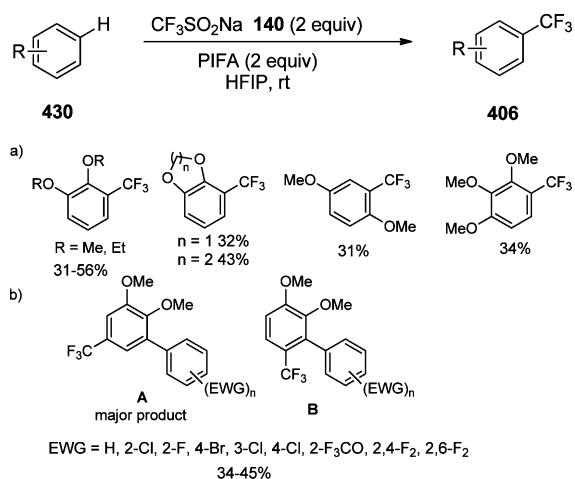
Scheme 237



of TFA (0.06 equiv) accelerated the reaction rate, and electron-rich arenes **430** gave the corresponding products **406** in good yields (Scheme 237). The authors suggested that the ground and excited redox states of AQN, an electron-transfer mediator, were important for the formation of the electron-deficient trifluoromethyl radical, which oxidized the substrate **430** to afford the corresponding trifluoromethyl arenes **406** following the catalytic cycle described in Scheme 237.

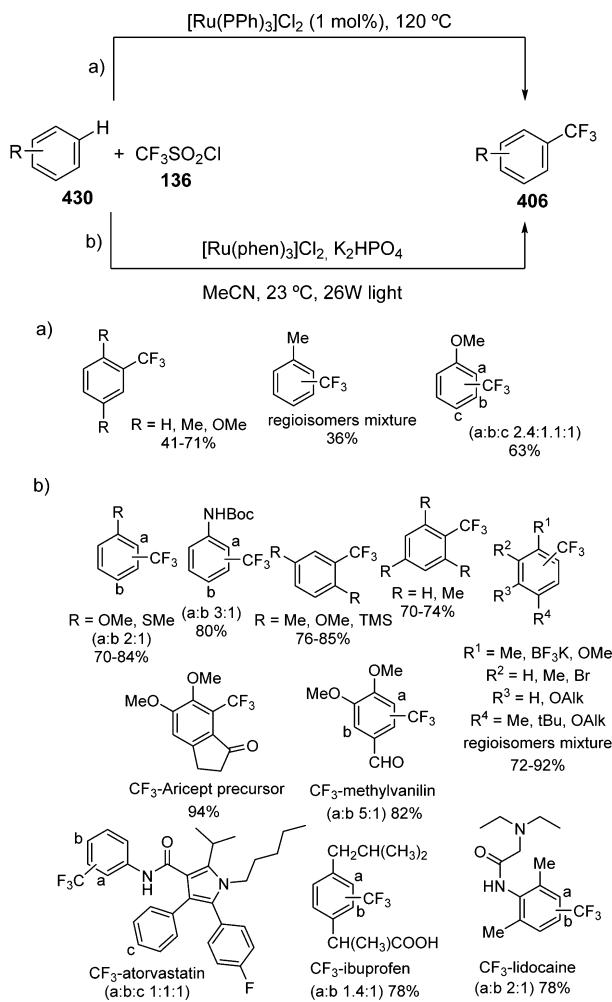
Similarly, Shibata et al. used the combination of CF<sub>3</sub>SO<sub>2</sub>Na **140** (Lr)<sup>127</sup> and phenyliodine bis(trifluoroacetate) (PIFA) in 1,1,1,3,3-hexafluoro-2-propanol (HFIP) for the transition-metal-free direct oxidative trifluoromethylation of arenes (Scheme 238a) and unsymmetrical biaryls (Scheme 238b).<sup>363</sup> The presence of electron-donating substituents on the aromatic system seems to be crucial for the regioselective trifluoromethylation of symmetric substrates **430** (Scheme 238a). It is noteworthy that trifluoromethylation of unsymmetrical biaryl substrates **430** (Scheme 238b) occurred selectively on their electron-rich cycle. In addition, a moderate 4,5-regioselectivity was observed, with the C-5 regioisomer obtained as major product (Scheme 238b).

Scheme 238



Another trifluoromethylating reagent, such as trifluoromethanesulfonyl chloride **136**, has been used in the presence of ruthenium(II) phosphine complex,  $[\text{Ru}(\text{PPh}_3)_3]\text{Cl}_2$  (1 mol %), to introduce the  $\text{CF}_3$  group into unfunctionalized aromatics **430** (Scheme 239a).<sup>364</sup> As expected for a homolytic aromatic substitution, the reactions of toluene and anisole provided the corresponding products **406** as mixtures of regioisomers. Later,

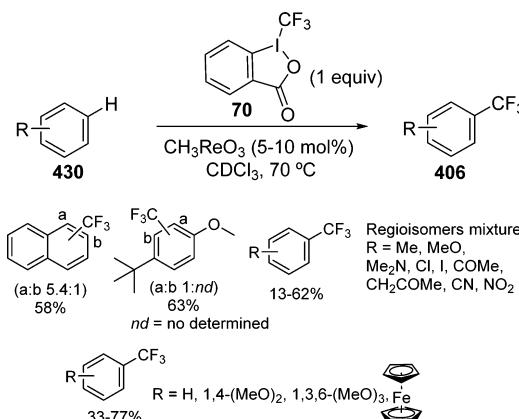
Scheme 239



MacMillan et al.<sup>365</sup> used the same reagent with the aid of a photosynthesis-inspired redox catalysis. In this case, trifluoromethyl electrophilic radicals were obtained in a mild and efficient way by SET reduction of  $\text{CF}_3\text{SO}_2\text{Cl}$  **136** concurrently with oxidation of  $\text{Ru}(\text{phen})_3^{2+}$  (Scheme 239b). In all of these examples, the electron-deficient radical  $\text{CF}_3$  added to the most electron-rich position of arenes in a way similar to that described in Scheme 236 (vide supra) to provide the product **406**. Therefore, these photoredox protocols allowed, at room temperature, direct incorporation of trifluoromethyl group into a broad range of aromatic systems without aryl ring preactivation.

Electrophilic trifluoromethylating derivatives, such as **70** (Tr1),<sup>80</sup> can be also used for the incorporation of  $\text{CF}_3$  group into unfunctionalized arenes. Indeed, direct trifluoromethylation of nonfunctionalized arenes via electrophilic substitution and deprotonation reactions by using **70** (Tr1) and zinc salts was developed by Togni et al.<sup>366</sup> Another method, also developed by the same group, included the use of the same trifluoromethylating agent **70** (Tr1) with the aid of rhenium as transition metal catalyst (Scheme 240).<sup>367</sup> A large range of

Scheme 240



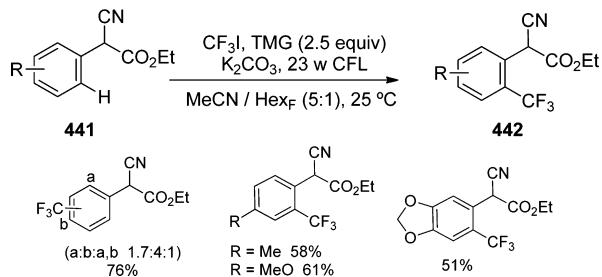
arenes, activated and unactivated, have been submitted to the reaction, although the yields and regioselectivities of trifluoromethyl arenes **406** were modest, particularly in the case of substrates bearing electron-withdrawing substituents.

**5.1.4.2. With Directing Group Assistance.** As it has been described so far in this section, direct aromatic C–H trifluoromethylation of substituted arenes generally leads to a mixture of regioisomers. To avoid these mixtures, a good alternative is the use of arenes bearing different directing groups.

In this sense, the direct trifluoromethylation of  $\alpha$ -cyano arylacetates **441** at ambient temperature and under visible-light irradiation has been carried out with trifluoromethyl iodide.<sup>368</sup> The reaction was conducted in MeCN and in the presence of  $\text{K}_2\text{CO}_3$  to favor the formation of the corresponding enolate. Immediately after mixing with the iodide, the solution developed a marked yellow-orange color, while its optical absorption spectrum showed a bathochromic displacement in the visible spectral region, diagnostic of an electron donor–acceptor (EDA) complex (Scheme 241).

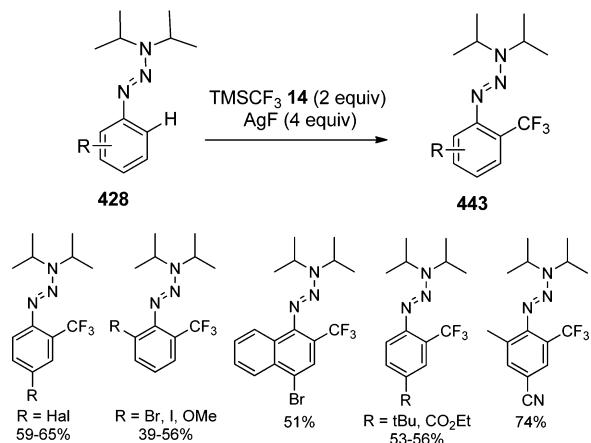
On the other hand, the triazene moiety in conjunction with nucleophilic trifluoromethylating reagents has been used for direct aromatic C–H trifluoromethylation of arenes.<sup>369</sup> In this case, the aromatic triazenes **428** were trifluoromethylated with a

Scheme 241



high *ortho*-selectivity by silver-mediated reaction using **14** ( $\text{RPr}$ )<sup>47</sup> to obtain trifluoromethylated triazene derivatives **443** (Scheme 242). This reaction tolerated a broad range of functional groups, especially iodides and bromides.

Scheme 242

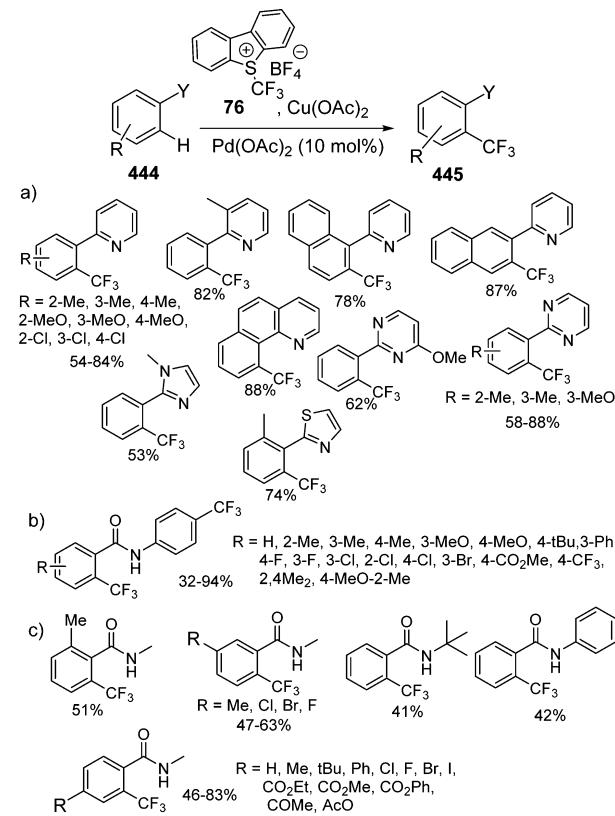


Under palladium-assisted systems, some research groups have reported an elegant Pd(II/IV)-catalyzed ligand-directed C–H trifluoromethylation with different trifluoromethylating reagents. For example, Yu et al.<sup>370</sup> used **76** ( $\text{Ur}$ )<sup>84</sup> on aromatic substrates **444** ( $\text{Y} = \text{heterocycle}$ , Scheme 243a) with several heterocycles, including pyridine, pyrimidine, imidazol, and thiazol, as directing groups for the trifluoromethylation in the *ortho* position and selective formation of compounds **445**.

The same research group extended the reaction to arenes **444** bearing amides as directing groups ( $\text{Y} = \text{C(O)NHC}_6\text{H}_4-p\text{-CF}_3$ , Scheme 243b). In this case, **76**, triflate, or tetrafluoroborate, worked similarly well, but it was necessary to add 15 equiv of *N*-methylformamide (NMF), as a weak base, and to increase the amount of Cu(II) salt up to 2 equiv.<sup>371</sup> Later, Shi et al.<sup>372</sup> expanded the process to the trifluoromethylation of arenes activated with an amido group **444** ( $\text{Y} = \text{CONHR}^1$ , Scheme 243c) to obtain derivatives **445** in similar reaction conditions.

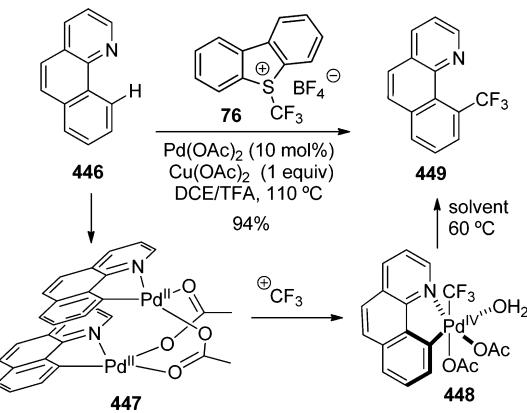
In a related approach, Sanford et al. used also this electrophilic reagent **76** ( $\text{Ur}$ )<sup>84</sup> for the generation of trifluoromethyl cation and the introduction of the  $\text{CF}_3$  group into the aryl group of benzo[*h*]quinoline.<sup>373</sup> The aromatic heterocycle **446** with the assistance of the vicinal heterocyclic nitrogen atom of the pyridyl group in *ortho* position and  $\text{Pd}(\text{OAc})_2$  would form the corresponding palladium complex **447**. The latter species reacted with trifluoromethyl cation, and after isolation of a new palladium complex **448** and reductive

Scheme 243



elimination, the formation of the corresponding trifluoromethylated derivative **449** (Scheme 244) was accomplished.

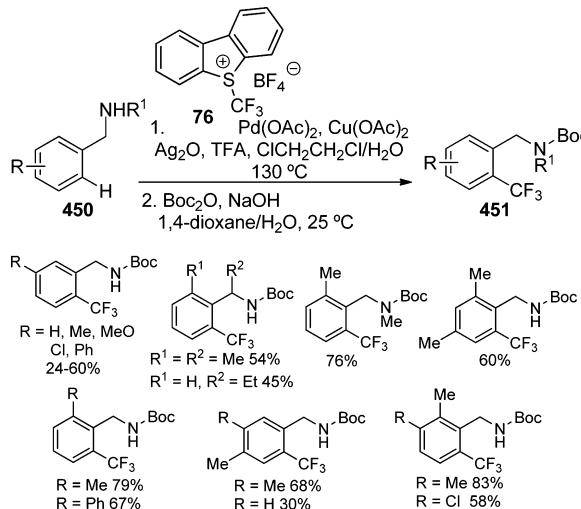
Scheme 244



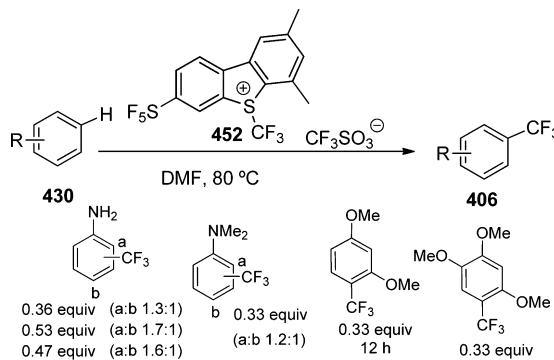
The same trifluoromethylating system, **76** ( $\text{Ur}$ )<sup>84</sup>/ $\text{Pd}(\text{OAc})_2$ , was also used by Yu et al. for the trifluoromethylation of benzylamines **450** via palladium-catalyzed C–H activation.<sup>374</sup> Nevertheless, in this case, the addition of  $\text{H}_2\text{O}$  and  $\text{Ag}_2\text{O}$  proved to be crucial for this transformation, and *ortho*-trifluoromethylated benzylamines **449** were regioselectively obtained with good yields (Scheme 245).

In 2014, the synthesis in two steps and isolation of **452**, the  $\text{SF}_5$ -analog of Umemoto salt **76**, starting from the  $\text{SF}_5-\text{C}_6\text{H}_4-\text{N}_2^+$   $\text{BF}_4^-$  salt have been reported.<sup>375</sup> The reagent **452** has been used for the trifluoromethylation of aromatic amines and anisol derivatives **430** (Scheme 246). The organic phase of the reaction was separated and analyzed as a mixture directly by <sup>1</sup>H

Scheme 245



Scheme 246

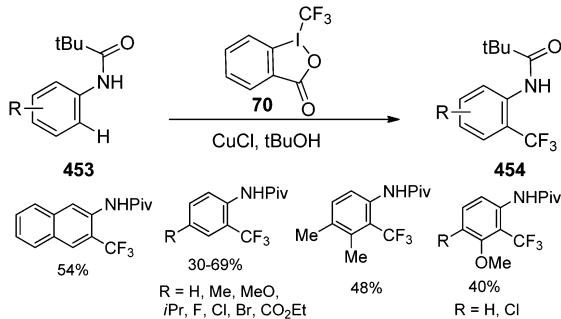


and <sup>19</sup>F NMR. In the case of anisole derivatives, an excess of arene 430 was used, and the reactions were monitored directly by <sup>19</sup>F NMR without isolation.

Not only 76 but also 70 (Tr1),<sup>80</sup> as CF<sub>3</sub> source, can be used for the C–H direct trifluoromethylation of, for example, pivalamido arenes 453.<sup>376</sup> The reaction proceeded in a novel Cu-catalyzed radical pathway directed by a pivalamido group and afforded trifluoromethylated pivalamido arenes 454 with high selectivity at the *ortho*-position (Scheme 247). The authors proposed an oxidative addition between CuCl and 70 (Tr1) to generate the CF<sub>3</sub> radical.

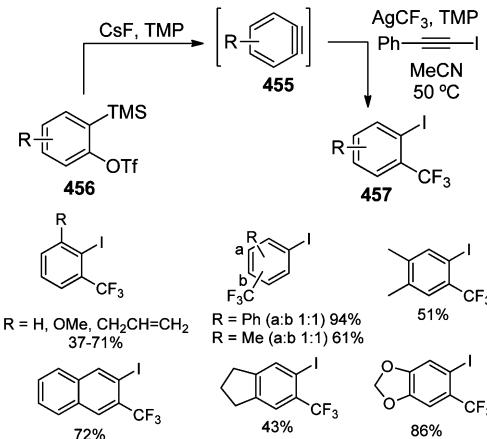
**5.1.5. From Aryne Derivatives.** An unprecedented silver-mediated vicinal trifluoromethylation–iodination of prefunctionalized arynes that quickly introduces CF<sub>3</sub> and iodide groups

Scheme 247



into aromatic rings in a single step to give *o*-trifluoromethyl iodoarenes has been developed.<sup>377</sup> The method uses a variety of structurally diverse arynes 455 generated by means of CsF and silylated aryl triflates 456 (Scheme 248). The in situ-

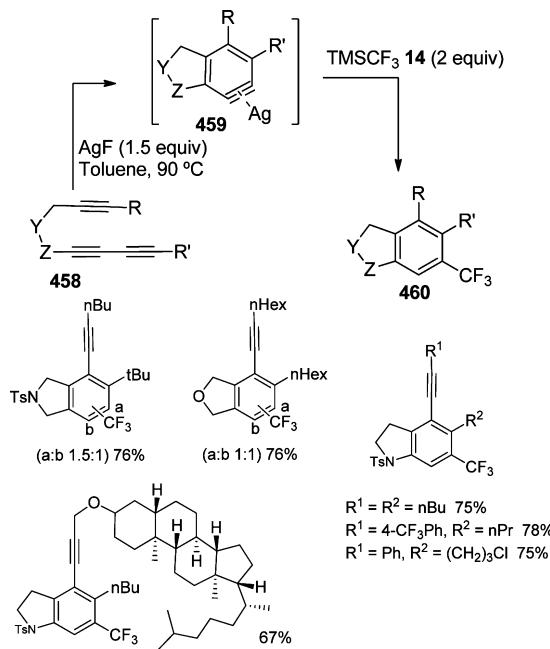
Scheme 248



generated arynes 455 reacted with AgCF<sub>3</sub>·TMP via a carboagation step and subsequent reaction with iodophenylacetylene to afford *o*-iodotri fluoromethylbenzenes 457.

The electrophilic nature of arynes has been exploited in a general approach to obtain trifluoromethylated aromatic compounds through the formal silver-mediated addition of nucleophilic CF<sub>3</sub> anion onto aryne intermediates directly generated from nonaromatic building blocks.<sup>378</sup> The addition of trifluoromethyl group nucleophile from 14 (RPr)<sup>47</sup> onto aryne intermediates was efficiently promoted by silver fluoride to allow the highly efficient and regioselective trifluoromethylation of various arynes 458 including indoline and isoindoline derivatives (Scheme 249). While primary alkyl group-substituted symmetrical bis-1,3-diyne and substrate possessing an oxygen linkage provided mixtures of regioisomers, primary

Scheme 249

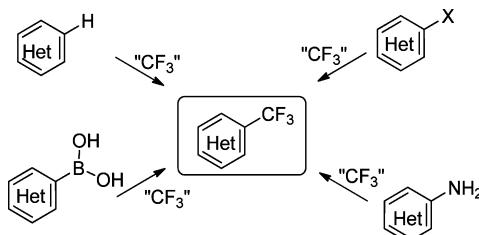


alkyl group-substituted bis-1,3-diyne provided trifluoromethylated indolines as single regioisomers in good yields, whereas terminal and bis-1,3-diyne containing dihydrocholesterol group provided structurally indoline derivatives **460**. A concerted thermal hexadehydro-Diels–Alder reaction of alkynes **458** followed by silver complexation to give intermediate **459**, and addition of nucleophilic  $\text{CF}_3$ , may explain the formation of trifluoromethylated aromatic compounds **460** (Scheme 249).

### 5.2. Trifluoromethylation of Heteroarenes

Trifluoromethylated heteroarenes are, analogously to arenes, important derivatives due to their presence in pharmaceuticals<sup>1–3</sup> and agrochemicals.<sup>17</sup> In this section, we focus on methods for the introduction of  $\text{CF}_3$  moiety into the heterocyclic ring, although some of them are quite similar to trifluoromethylation reactions of arenes (vide supra, section 5.1). These strategies can be divided into four sections taking into account the nature of starting substrates, heteroaryl halides, amines, boronic derivatives, and for the direct trifluoromethylation processes (Scheme 250).

**Scheme 250**

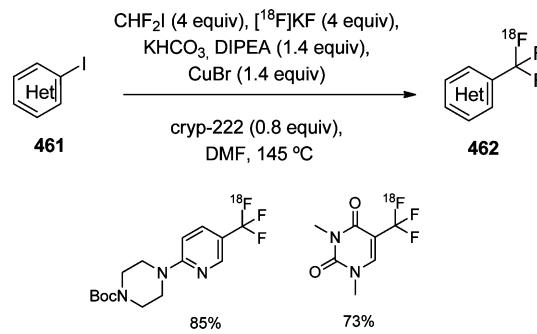


**5.2.1. From Heteroaryl Halides.** As in the case of trifluoromethylation of arenes, prefunctionalized heteroarenes can be used as starting materials in the preparation of trifluoromethylated derivatives. Several synthetic methods for the introduction of a  $\text{CF}_3$  moiety into heteroaromatic compounds have been developed starting from heteroaryl halides. First, Kobayashi and Kumadaki<sup>298</sup> reported the preparation of trifluoromethyl quinolines by cross-coupling of heteroaromatic halides with a stoichiometric amount of trifluoromethyl copper complex generated in situ from  $\text{CF}_3\text{I}$  in the presence of  $\text{CuSO}_4$ . Since the pioneering work of Wiemers and Burton,<sup>41</sup> various methods were published regarding the generation of  $[\text{CuCF}_3]$  species, a key intermediate in many copper-mediated heterocyclic trifluoromethylation processes. Such transformations generally occur via reaction of heteroaryl halides with highly reactive trifluoromethyl copper species, usually formed in situ. For example, heterocyclic halides were trifluoromethylated by electrolysis with a copper anode and  $\text{CF}_3\text{Br}$  in DMF; the best results were obtained when TMEDA was used as a ligand.<sup>379</sup>

Suitable candidates for PET as  $[^{18}\text{F}]\text{-trifluoromethylthymine}$  and  $[^{18}\text{F}]\text{-trifluoromethyl-Boc-protected piperazine}$  have been efficiently synthesized from heterocyclic iodides and  $\{\text{Cu}[^{18}\text{F}]\text{-CF}_3\}$  species.<sup>301</sup> For this purpose, radiolabeled  $\{\text{Cu}[^{18}\text{F}]\text{CF}_3\}$  species has been prepared by reaction of a copper-ligand system ( $\text{CuI-DIPEA}$ ) and  $\text{CHF}_2\text{I}$  in the presence of crypt-222,  $\text{K}_2\text{CO}_3$ , and a  $^{18}\text{F}$  anion (Scheme 251).

Trifluoromethyl copper species has been also prepared from  $[\text{Zn}(\text{CF}_3)\text{Br}\text{-2DMF}]$  reagent and copper bromide. However, trifluoromethylation reactions under these conditions yielded

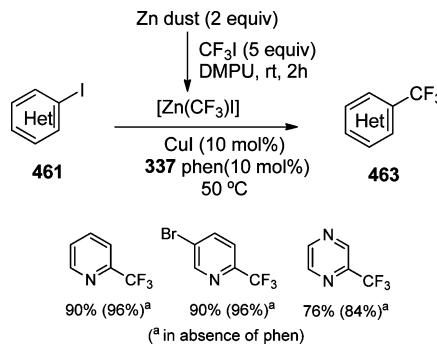
**Scheme 251**



mixtures of trifluoromethylated heterocycles and pentafluoroethylated derivatives.<sup>302</sup>

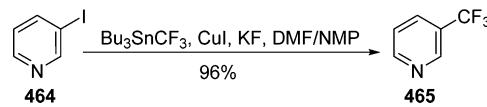
Mikami et al. also developed Cu-catalyzed trifluoromethylation of aryl iodides **461** preparing trifluoromethyl copper(I) species, but in this case, with trifluoromethylzinc reagent obtained in situ from trifluoromethyl iodide and Zn dust (Scheme 252).<sup>304</sup> It is noteworthy that the reaction of heterocyclic substrates without a ligand led to higher yields than reaction conditions with a ligand such as **337** (phen).

**Scheme 252**



Tributyl(trifluoromethyl)stannane,  $\text{Bu}_3\text{SnCF}_3$ , has been also used as an effective reagent in copper-mediated trifluoromethylation reaction of pyridine **464**, along with KF and coordinating solvents such as DMF/NMP to give **465** (Scheme 253).<sup>303</sup>

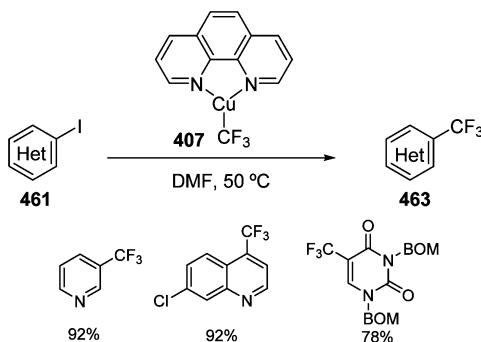
**Scheme 253**



Hartwig et al. used Trifluoromethylator reagent **407**,  $[(\text{phen})\text{CuCF}_3]$  (vide supra, section 5.1), obtained from **14** ( $\text{RPr}$ )<sup>47</sup> as the trifluoromethyl source, for the trifluoromethylation of heteroaromatic iodides **461** under very mild conditions<sup>308</sup> and the preparation of corresponding five- and six-membered heterocycles **463** (Scheme 254).

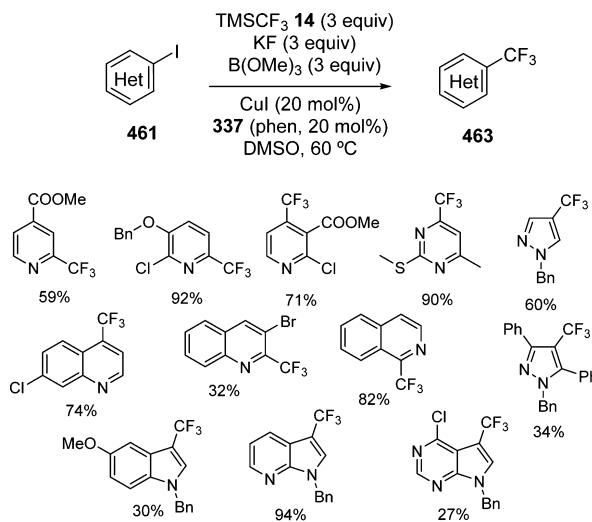
Stoichiometric amounts of copper were necessary in the previous work probably to compensate the slowness of catalytic cycle with respect to the rapid production of  $\text{CF}_3$  anion. In this sense, Kotschy, Novák et al. developed a new Lewis-base enabled approach for the catalytic copper trifluoromethylation of heteroaromatic iodides.<sup>307</sup> These trifluoromethylation

Scheme 254



reactions were achieved with TMSCF<sub>3</sub> 14 (3 equiv), KF (3 equiv), CuI (20 mol%), and 337 (phen, 20 mol%) in the presence of trimethylborate (3 equiv), used as Lewis acid to avoid the rapid decomposition of in situ generated trifluoromethyl anion (Scheme 255). This strategy allowed the

Scheme 255



synthesis of several trifluoromethylated heteroaromatic molecules 463, as pyridine derivatives bearing different functional groups, pyrimidine, pyrazole, quinoline, isoquinoline, indole, 7-azaindole, and 7-deazapurine derivatives, in good to excellent yields.

The use of trifluoromethylsilyl reagents constitutes one of the most widely applied methods to form [CuCF<sub>3</sub>]. For example, a kinase inhibitor 466 shown in Figure 8 was prepared

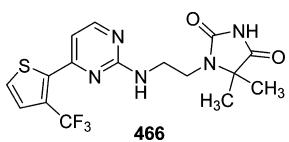


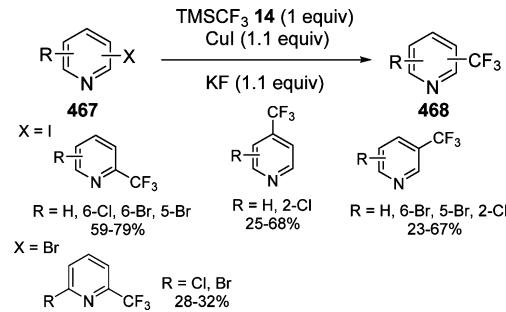
Figure 8. Kinase inhibitor.

by trifluoromethylation of thiophene halide with trifluoromethyltriethylsilyl reagent 39<sup>380</sup> either starting from copper halides and an alkali fluoride or from copper and silver fluoride.

Schlosser et al.<sup>381</sup> reported the trifluoromethylation of pyridine halides 467 with [CuCF<sub>3</sub>] generated in situ from 14

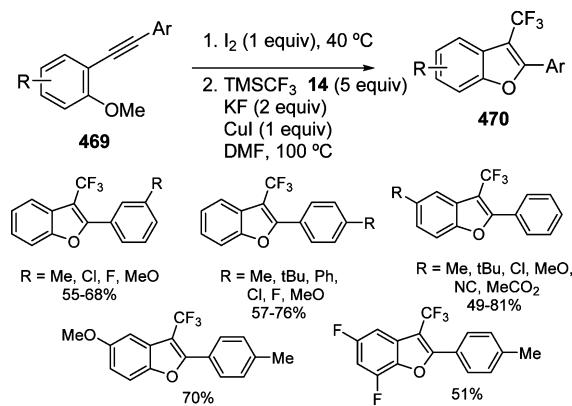
(RPr)<sup>47</sup> in the presence of copper iodide and potassium fluoride (Scheme 256) leading to the formation of 468.

Scheme 256



Similar trifluoromethylation conditions have been used for the preparation of 3-trifluoromethylbenzofurans 470 from 2-alkynylanisoles 469 (Scheme 257).<sup>382</sup> This transformation

Scheme 257

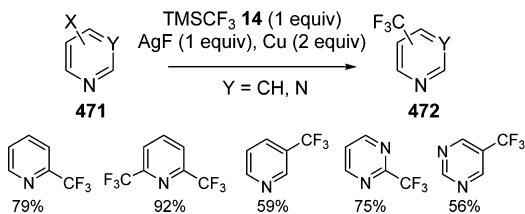


occurred via two-step, one-pot tandem reaction of 2-alkynylanisoles 469 with elemental iodine and subsequent trifluoromethylation with 14 (RPr)<sup>47</sup> in the presence of KF, stoichiometric amounts of CuI, and DMF as the best solvent. It is noteworthy that reaction of 2-alkynylanisole bearing alkyl groups did not work, probably because iodocyclization did not occur. However, when using 2-alkynylanisoles bearing aromatic groups, the corresponding products 470 were obtained in moderate to excellent yields.

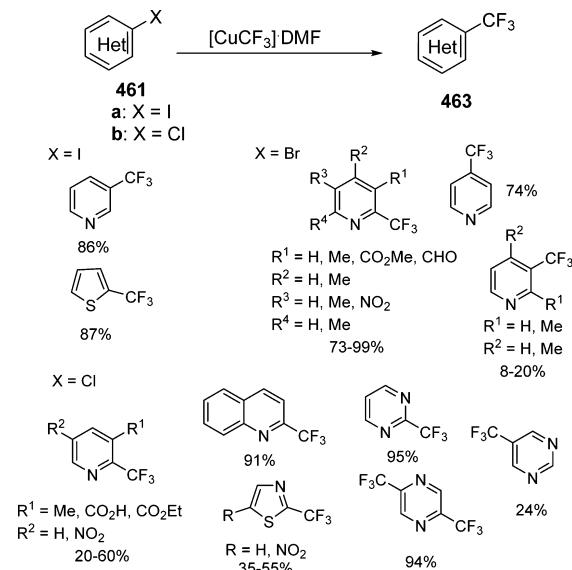
Another method to obtain [CuCF<sub>3</sub>] reagent has been developed via the reaction of silver fluoride and 14 (RPr)<sup>47</sup> followed by a redox transmetalation with elemental copper. This trifluoromethyl copper exhibited excellent reactivity and selectivity in the substitution of iodine and bromine atoms bonded to heterocyclic compounds 471 in the absence of additional catalyst to furnish heterocycles 472 with one or two nitrogen atoms such as pyridines or pyrimidines (Scheme 258).<sup>102</sup>

Alternatively, simple trifluoromethyl copper species can be obtained easily by direct cupration of fluoroform with CuCl and tBuOH as it has been shown by Grushin et al.<sup>312</sup> In this case, heteroaryl halides 461, derived from pyridine, pyrimidine, pyrazine, or thiazole, could be trifluoromethylated with [CuCF<sub>3</sub>] with excellent yields in the absence of additional ligands (Scheme 259).<sup>313</sup> A wide variety of heteroaryl halides undergo smooth trifluoromethylation under these conditions to

Scheme 258



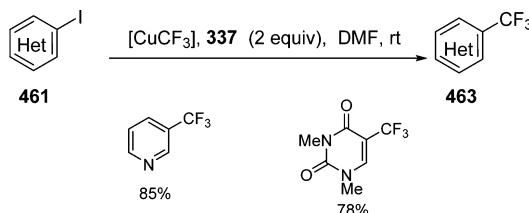
Scheme 259



afford the corresponding trifluoromethylated five- and six-membered heterocycles 463 in good yields (Scheme 259). In contrast with other methodologies, different halide substitution was not restrictive for trifluoromethylation. Although heteroaryl iodides 461a remain most reactive, also heteroaryl bromides and chlorides 461b could also be trifluoromethylated as well under these conditions. Moreover, *ortho*-substituted substrates showed an enhanced reactivity toward [CuCF<sub>3</sub>], mostly with electron-withdrawing substituents.

By the strategy developed by Mikami et al.,<sup>285</sup> where [CuCF<sub>3</sub>] complex is generated *in situ* from CuCl and KOTBu, and 2,2,2-trifluoroacetophenone (vide supra, Scheme 184), the trifluoromethylation of heteroaromatic iodides 461a has been accomplished (Scheme 260). In this case, the reaction

Scheme 260

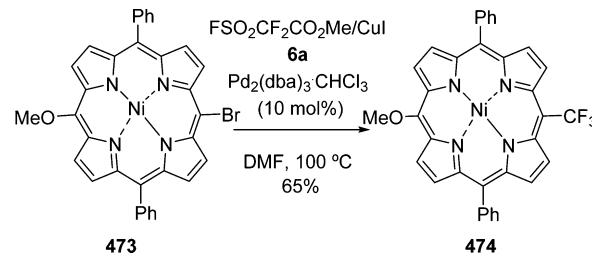


proceeded smoothly when conducted in DMF with 1,10-phenanthroline 337 (phen), which was more efficient than TMEDA, as previously indicated for the trifluoromethylation of aromatic halides (vide supra, sections 4.2 and 5.1.1).

Brominated porphyrines 473 could be trifluoromethylated with fluorinated ester reagent 6a along with CuI and in the

presence of catalytic amounts of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (Scheme 261).<sup>383</sup> This trifluoromethylation reaction can be applied to

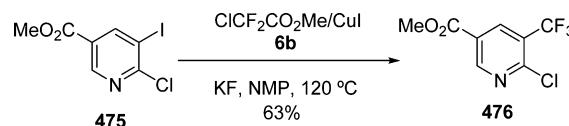
Scheme 261



give trifluoromethylated porphyrine 474 in good yield. The same trifluoromethylating reagent 6a in the presence of copper was also used by both Takeda et al.<sup>384</sup> and Liu et al.<sup>385</sup> for the specific synthesis of interesting trifluoromethylated quinolines.

Another difluoroacetate derivative, such as 6b (ClCF<sub>2</sub>CO<sub>2</sub>Me), in the presence of copper iodide and potassium fluoride, has been used by Mulder et al. for the trifluoromethylation of a heterocyclic iodide derivative 475.<sup>386</sup> It is worth noting the versatility of the procedure for the synthesis in kilogram scale of methyl 6-chloro-5-(trifluoromethyl)nicotinate 476, an intermediate in the synthesis of novel anti-infective agents (Scheme 262).

Scheme 262

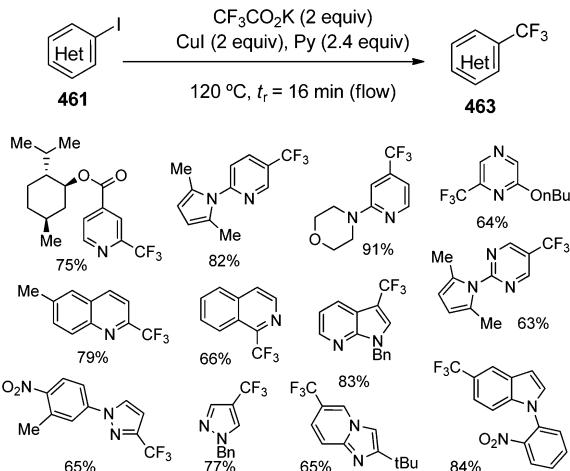


Trifluoromethyl acetate salts have also been used for the trifluoromethylation of heterocycles. For example, a pioneering work of Matsui's et al.<sup>318</sup> described the trifluoromethylation of 2-bromopyridine with sodium trifluoromethyl acetate and copper iodide in a 41% yield. Later, potassium trifluoromethyl acetate was used as the CF<sub>3</sub> source and pyridine in NMP as optimal ligand for an efficient heteroaromatic trifluoromethylation process under flow conditions of heterocycles 461 to afford products 463 of *para*-, *meta*-, and *ortho*-substituted heteroaryl substrates and with electron-deficient, electron-neutral, and electron-rich substituents in good to excellent yields (Scheme 263).<sup>321</sup> A broad spectrum of heterocycles 463, such as pyridines, pyridazines, pyrimidines, quinolines, isoquinolines, indoles, and pyrazoles, can be obtained.

Similar reagent, such as methyl trifluoroacetate (CF<sub>3</sub>CO<sub>2</sub>Me, MTFa), can be used for the copper-catalyzed trifluoromethylation of heteroaryl halides. This reagent is more easily available than methyl chlorodifluoroacetate 6b and more soluble than trifluoroacetate salts. In this way, Langlois et al.<sup>322</sup> reported the trifluoromethylation of 2-bromopyridine in a 42% yield.

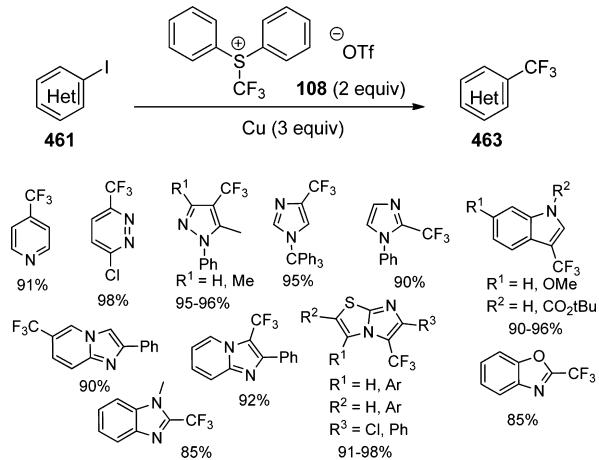
The idea of using a reducing agent to generate a CF<sub>3</sub> radical and then a CF<sub>3</sub> anion, starting from an electrophilic reagent, was used in the trifluoromethylation of iodo-substituted heterocycles 461 (pyridines, pyridazines, pyrazoles, pyrimidines, indoles, among others) to give heterocycles 463. In this case, copper metal was the reducing agent, and, according to the authors, the reduction of the sulfonium salt 108 went further through the CF<sub>3</sub> radical to generate the CF<sub>3</sub> anion in

Scheme 263



the form of  $[\text{CuCF}_3]$ , which may be the intermediate proposed for this efficient reaction (Scheme 264).<sup>324</sup>

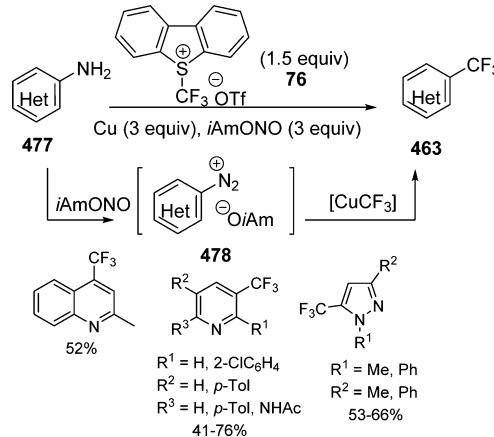
Scheme 264



**5.2.2. From Heteroaryl Amines.** As it has been described, heterocyclic derivatives as heteroaryl halides can be used as precursors of trifluoromethylated compounds by transition-metal-promoted trifluoromethylation reactions. However, other functionalized compounds, such as amino derivatives, can also be applied for the conversion of functional groups into  $\text{CF}_3$ . Taking advantage of the Sandmeyer reaction,<sup>333</sup> where aromatic amino groups can be converted into numerous functional groups such as hydrogen, halide, hydroxyl, cyano, or azido, two research groups applied Sandmeyer-type reaction conditions in the preparation of trifluoromethylated heterocyclic derivatives from amino precursors.

For example, when Fu et al. used **76** ( $\text{Ur}^{84}$ ) as the trifluoromethylating agent, a variety of heteroaryl amines **477** were successfully trifluoromethylated into the products **463** in modest to good yields through generation in situ of the corresponding diazonium salts **478** by reaction of amines **477** and isoammonium nitrite ( $i\text{AmONO}$ ) and subsequent trifluoromethylation (Scheme 265).<sup>334</sup> The reaction has been used with pyridines, quinolines, and pyrazoles. As proved by the authors, the Cu-promoted Sandmeyer trifluoromethylation reaction may proceed through a radical mechanism, where a  $\text{CF}_3$  radical is generated from **76** by copper-mediated SET. This radical may

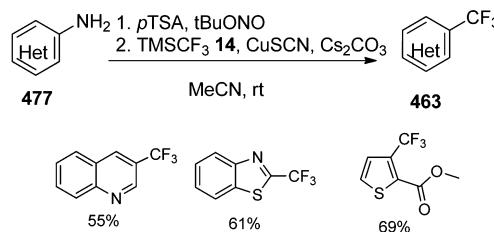
Scheme 265



combine with copper to give trifluoromethyl copper species  $[\text{CuCF}_3]$ , which reacted with the heteroaryl radical generated from the heteroaryldiazonium ion **478**.

Gooßen et al. have also used a copper-promoted Sandmeyer trifluoromethylation reaction of heteroaromatic amines **477** (Scheme 266). In first attempts,<sup>335</sup> diazonium salts obtained

Scheme 266

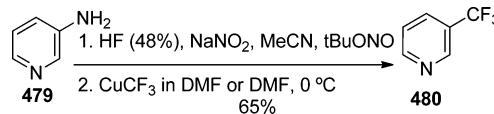


with iso-amyl nitrite had to be generated prior to the coupling with  $[\text{CuCF}_3]$  species generated from the Ruppert–Prakash reagent **14** ( $\text{RPr}^{47}$ ) in the presence of 0.5 equiv of copper thiocyanate, and afforded the corresponding 3-trifluoromethylquinoline in 74% yield. Subsequently, efficient in situ diazotization-trifluoromethylation sequence was developed by using *tert*-butyl nitrite as diazotization reagent.<sup>336</sup> In this sense, the straightforward conversion of the corresponding heteroaromatic amines **477** into trifluoromethylated heterocycles **463** was accomplished in good yields.

A similar strategy in aqueous media has been reported by Grushin et al. for the preparation of trifluoromethylated heterocycles **480** from amino pyridine **479**.<sup>338</sup> In this case,  $[\text{CuCF}_3]$  species, generated from fluoroform, reacted with in situ preformed diazonium salts obtained by reaction of heterocyclic amine **479** with  $\text{NaNO}_2$  in the presence of aqueous solution of HF in MeCN (Scheme 267).

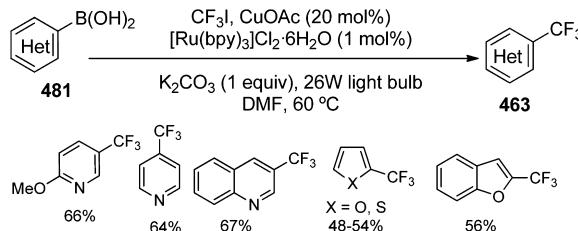
**5.2.3. From Heteroaryl Boronic Derivatives.** Not only prefunctionalized derivatives such as heterocyclic halides or heteroaryl diazonium salts have been trifluoromethylated, but also heteroarenes bearing a boronic acid group. For instance, a

Scheme 267



mild method for the cross-coupling of arylboronic acids **481** with  $\text{CF}_3\text{I}$  via the merger of photoredox  $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$  and  $\text{Cu}(\text{I})$  catalysis under light irradiation has been reported by Sanford et al.<sup>341</sup> (Scheme 268).

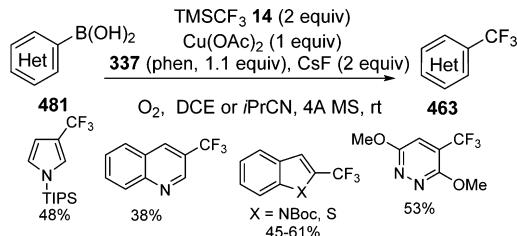
Scheme 268



In this manner, the boronic acid substrate **481** reacted under conditions reported by Baran<sup>387</sup> and MacMillan<sup>365</sup> to promote C–H trifluoromethylation reactions by means of in situ generation of trifluoromethyl radical. Boronic acids **481** derived from pyridine, quinoline, furan, and thiophene all underwent trifluoromethylation to obtain heterocycles **463** in modest to good yields (Scheme 268).

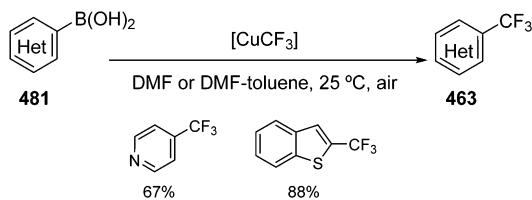
Alternatively, another protocol using **14** ( $\text{RPr}$ )<sup>47</sup> as nucleophilic trifluoromethylating reagent, and dry  $\text{O}_2$ , as oxidant, was disclosed.<sup>342</sup> The trifluoromethylation of five- and six-membered heteroaryl boronic acids **481** (Scheme 269) to prepare substituted heterocycles **463** such as pyrroles, indoles, benzothiophenes, quinolines, and pyridazines was accomplished.

Scheme 269



Fluoroform was also used for the synthesis of trifluoromethyl copper species in the trifluoromethylation of heteroaryl boronic acids **481** (Scheme 270).<sup>344</sup> The reaction occurred at room

Scheme 270

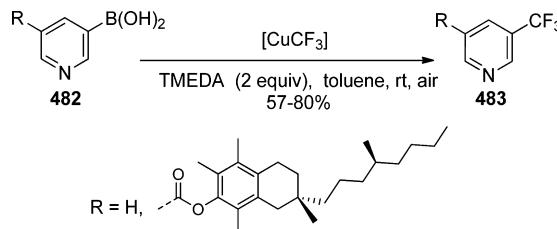


temperature, with air as oxidant and in the absence of additional additives to afford trifluoromethylated heteroaromatic compounds **463** in high yield and selectivity.

Mikami et al. reported as well the trifluoromethylation of pyridine boronic acids **482** by using  $[\text{CuCF}_3]$  preformed complex from cuprate and trifluoromethylacetophenone (vide supra, Scheme 184).<sup>285</sup> In this case, the oxidative coupling reaction at a  $\text{sp}^2$ -carbon of heterocyclic core proceeded

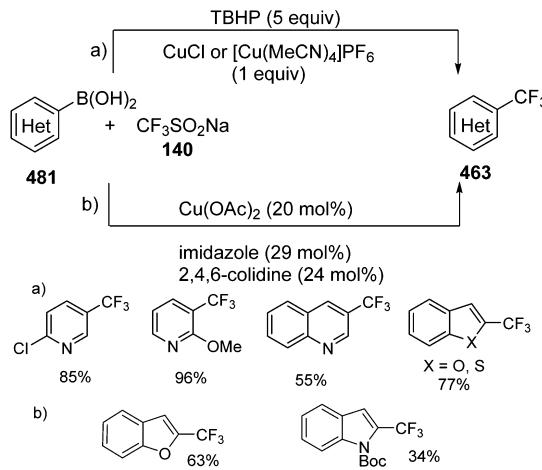
smoothly in toluene as the best solvent without any ligand, yielding the corresponding products **483** in good yields (Scheme 271).

Scheme 271



Trifluoromethylsulfinate salts proved to be appropriate for the generation of  $\text{CF}_3$  radical in the presence of a copper salt. For example, the combination of **140** ( $\text{Lr}$ )<sup>127</sup> and TBHP in a copper-mediated trifluoromethylation of a variety of heteroaryl boronic acids **481** afforded the corresponding derivatives **463** including pyridines, quinoline, benzofuran, and benzothiophene derivatives in good to excellent yields (Scheme 272a).<sup>346</sup>

Scheme 272



Alternatively, reagent **140** ( $\text{Lr}$ )<sup>127</sup> can also be used for the preparation of trifluoromethylbenzofuran and indole compounds **463** from heteroaryl boronic acid derivatives **481** in the presence of catalytic amounts of  $\text{Cu}(\text{OAc})_2$  (20 mol %) as it has been reported by Beller et al. (Scheme 272b).<sup>249</sup>

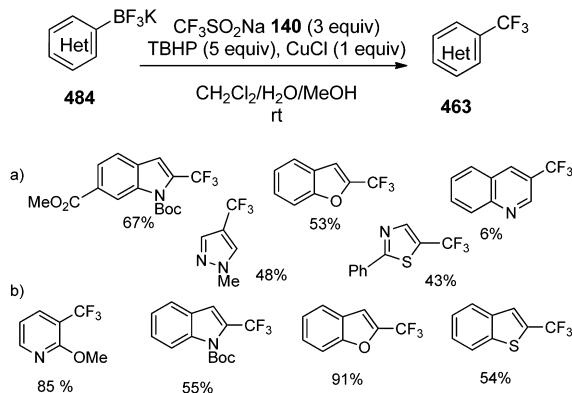
Two different groups reported simultaneously the use of the same trifluoromethylating conditions **140** ( $\text{Lr}$ ),<sup>127</sup> TBHP, and  $\text{CuCl}$  for the radical trifluoromethylation of heteroaromatic trifluoroborates **484** (Scheme 273).<sup>251,252</sup> The active trifluoromethylating radical agent  $\text{CF}_3$ , generated in situ, gave the corresponding heterocycles **463** as pyridine, pyrazole, thiazole, quinoline, indole, benzofuran, and benzothiophene in good yields.

#### 5.2.4. Direct C–H Heteroaryl Trifluoromethylation.

Several protocols can be found in recent literature where the hydrogen of C–H heteroaromatic bond is replaced by a trifluoromethyl group, thus providing a straightforward access to trifluoromethylated heterocyclic compounds without the need for prefunctionalized substrates such as heteroaryl halides, amines, and boronic acid derivatives.

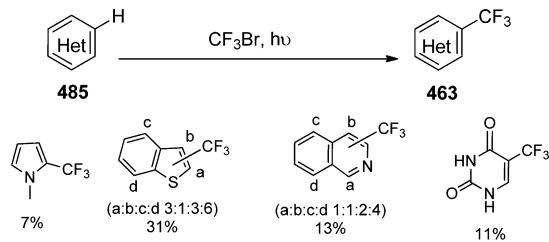
Pioneering works reported the use of different trifluoromethylating reagents, such as  $\text{CF}_3\text{I}$ <sup>350</sup> or  $(\text{CF}_3)_2\text{Te}$ ,<sup>388</sup> for the

Scheme 273



direct C–H substitution in heterocyclic substrates. For example, imidazole ring of histidine in a peptide chain may be photochemically trifluoromethylated with  $\text{CF}_3\text{I}$ .<sup>389</sup> Under these conditions, imidazole residues undergo trifluoromethylation more readily than either benzenes or indoles, leading to the application of this technique for the preparation of modified peptides. In a similar way, a variety of heteroaromatic compounds **485** were trifluoromethylated by a one-step photochemical trifluoromethylation reaction with  $\text{CF}_3\text{Br}$  (Scheme 274).<sup>353</sup> However, in general, low yields and a mixture of regioisomers of the corresponding trifluoromethylated compounds **463** were obtained.

Scheme 274

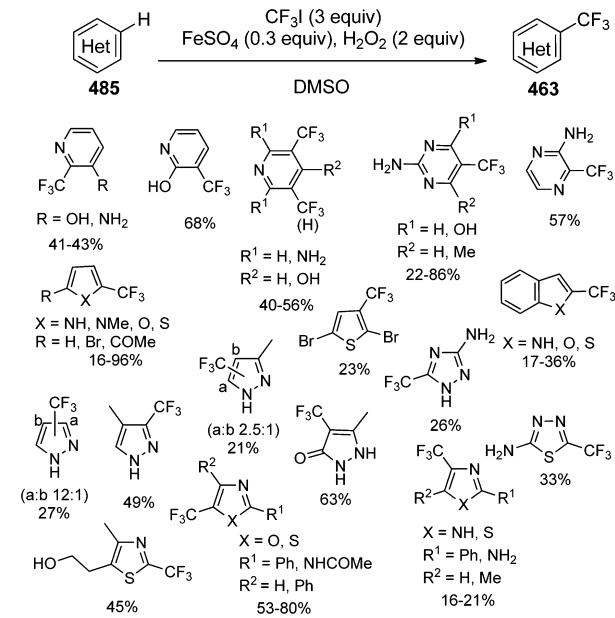


Nevertheless, the combination of  $\text{CF}_3\text{I}$  in the presence of  $\text{FeSO}_4$ ,  $\text{H}_2\text{O}_2$ , and DMSO was successful for the regioselective synthesis of trifluoromethylated heteroarenes **463** from heterocycles **485** (Scheme 275).<sup>355</sup> The process can be applied not only to six-membered heterocycles such as pyridines, pyrimidines, and pyrazines, but also to a wide range of pentagonal heterocycles such as pyrroles, furans, thiophenes, indoles, pyrazoles, 1,3-oxazoles, 1,3-diazoles, and 1-thia-3,4-diazoles, although the yields in most cases are low-moderate.

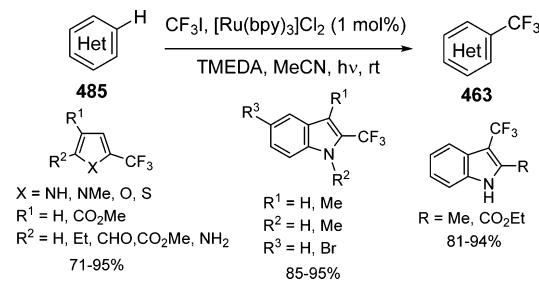
Later, Cho et al.<sup>390</sup> reported a visible light-induced trifluoromethylation of a variety of electron-rich heterocycles **485** by using  $\text{CF}_3\text{I}$  as the trifluoromethyl radical source and  $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$  as the photocatalyst under mild reaction conditions (Scheme 276). A variety of heterocycles, including indoles, pyrroles, thiophenes, and furans, were used in the reaction and resulted in the formation of trifluoromethylated heterocycles **463** in good to excellent yields. Although electron-deficient heterocycles were not reactive, several functional groups were tolerant under the reaction conditions including bromide, aldehyde, ester, and amine.

Trifluoromethylated heteroaromatic systems can be enhanced in continuous microflow of  $\text{CF}_3\text{I}$  under visible-light photoredox catalysis.<sup>391</sup> The optimal gas flow rate was found to

Scheme 275



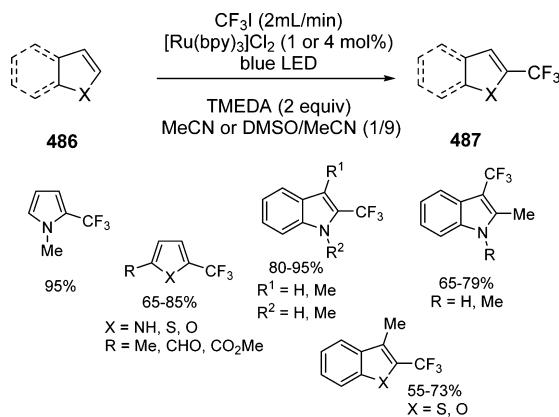
Scheme 276



be  $2 \text{ mL min}^{-1}$  (4 equiv of  $\text{CF}_3\text{I}$ ), and TMEDA was the most effective base to be used along with a polypyridyl organometallic complex as  $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ . Under these conditions, a selection of pyrrole and indole derivatives **486** was efficiently trifluoromethylated (Scheme 277).

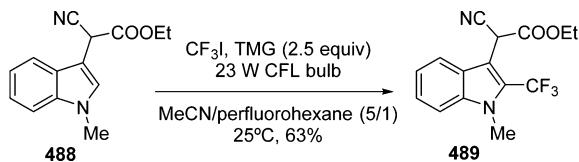
In 2014, Melchiorre et al.<sup>368</sup> developed a direct and effective metal-free approach to install trifluoromethyl groups within the aromatic ring of  $\alpha$ -cyano arylacetates. As the authors suggested, the enolate generated in situ from the starting  $\alpha$ -cyano arylacetate **488** may act as a powerful electron-releasing

Scheme 277



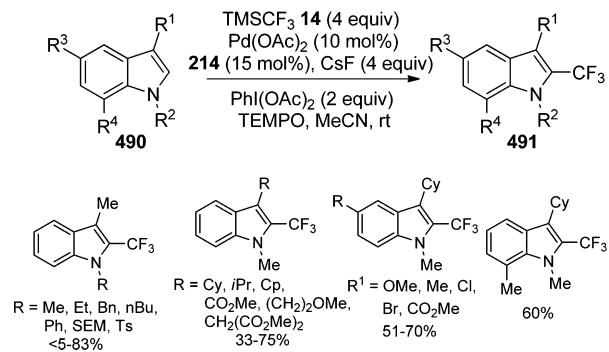
group reacting with trifluoromethyl iodide under photochemical conditions to give the corresponding trifluoromethylated indole **489** (Scheme 278).

Scheme 278



A novel Pd-catalyzed oxidative trifluoromethylation of a variety of indoles **490** at room temperature, in which  $\text{PhI(OAc)}_2$  was used as an oxidant and **14** ( $\text{RPr}$ )<sup>47</sup> as a  $\text{CF}_3$  source, for the generation of substituted indoles **491** was reported (Scheme 279).<sup>392</sup> Addition of the bidentate nitrogen-

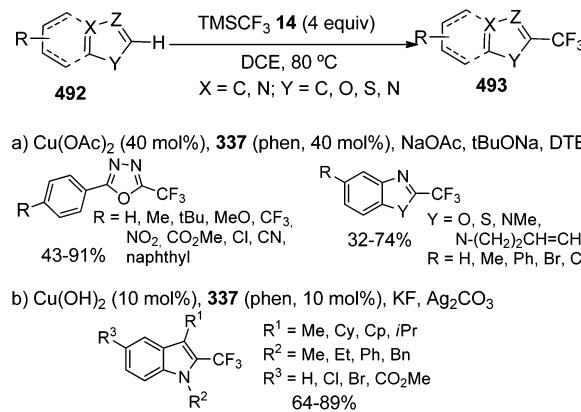
Scheme 279



containing ligand such as oxazolidine **214** (vide supra, Scheme 86) resulted beneficial to the reaction. When the reaction was performed with indoles unsubstituted at 3-position, the corresponding 3-trifluoromethylated indoles were selectively obtained but in moderate yields (39–66%).

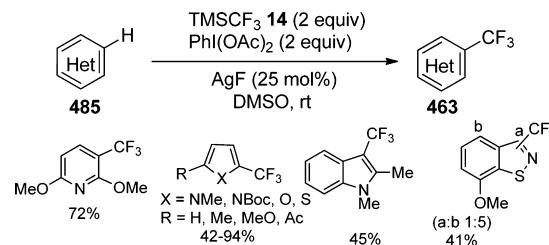
In 2012, Qing and co-worker reported the first copper-catalyzed oxidative trifluoromethylation of heteroarenes **492** also with **14** ( $\text{RPr}$ )<sup>47</sup> by deprotonation of a heteroaryl C–H bond.<sup>358</sup> In the presence of a combination of catalyst  $\text{Cu(OAc)}_2$ , ligand **337** (phen), and cobases *tert*-BuONa/NaOAc, oxidative trifluoromethylation of 1,3,4-oxadiazoles **492** ( $\text{Y} = \text{O}$ ,  $\text{X} = \text{Z} = \text{N}$ ) proceeded smoothly using either air or DTBP as an oxidant to give the corresponding trifluoromethylated 1,3,4-oxadiazoles **493** in high yields (Scheme 280a). Similarly, heterocycles **493** ( $\text{X} = \text{C}$ ,  $\text{Y} = \text{O}$ ,  $\text{S}$ ,  $\text{NR}$ ;  $\text{Z} = \text{N}$ ) were obtained. DTBP was also chosen as the suitable oxidant for oxidative trifluoromethylation of 1,3-azoles, while  $\text{Cu(OH)}_2$  and  $\text{Ag}_2\text{CO}_3$  were the best catalyst and oxidant, respectively, for the direct oxidative trifluoromethylation of indoles **492** ( $\text{Y} = \text{N}$ ,  $\text{X} = \text{Z} = \text{C}$ ) (Scheme 280b). Using this method, a wide range of heterocycles, including 1,3,4-oxadiazoles, benzo[*d*]oxazoles, benzo[*d*]thiazole, benzo[*d*]imidazoles, and indoles, were converted into their corresponding trifluoromethylated derivatives in moderate to excellent yields. Importantly, most common functionalities, such as ester, nitro, nitrile, and bromine, were well-tolerated. Preliminary mechanistic investigations indicated that the catalytic cycle occurred via the generation of a  $[\text{CuCF}_3]$  complex as the key intermediate.

Scheme 280



One year later, Greaney et al. developed<sup>357</sup> a novel silver-catalyzed oxidative trifluoromethylation reaction for electron-rich heteroaromatic substrates **485** with **14** ( $\text{RPr}$ ).<sup>47</sup> Oxidizing conditions obtained by the combination of  $\text{PhI(OAc)}_2$  and  $\text{AgF}$  were highly effective, while  $\text{AgF}$  alone was unable to generate  $\text{CF}_3$  radical (Scheme 281). The reaction was compatible with

Scheme 281

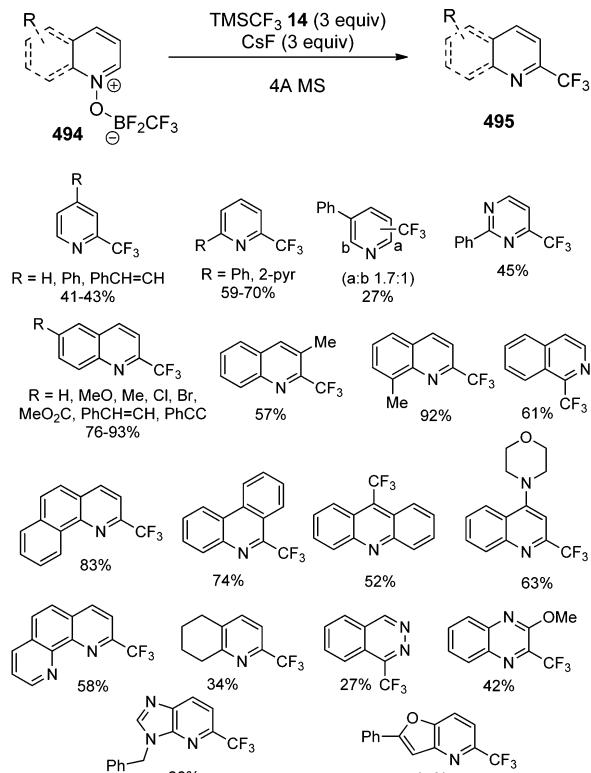


electron-withdrawing groups, and heterocycles such as pyridines, furans, thiophenes, indoles, and benzothiazoles were suitable for trifluoromethylation under these oxidizing conditions, affording the corresponding derivatives **463** with good selectivity.

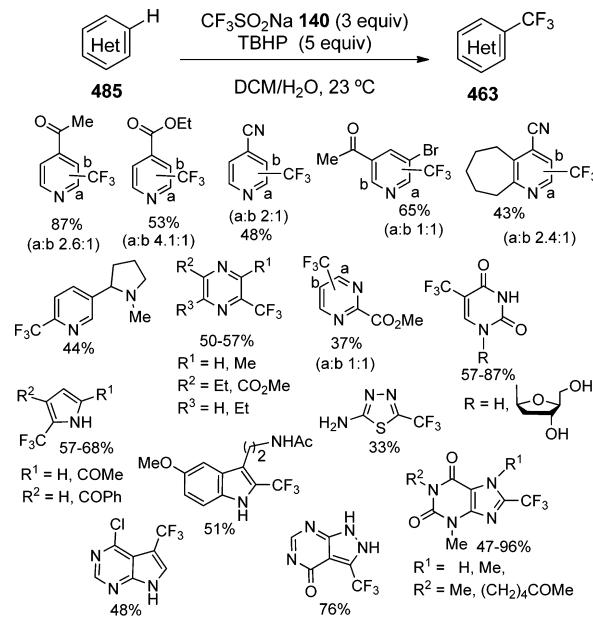
Lewis acid activation of six-membered *N*-heteroaromatic compounds as *N*-oxide– $\text{BF}_2\text{CF}_3$  complexes with trifluoromethylidifluoroborane ( $\text{BF}_2\text{CF}_3$ ) has allowed the regioselective C–H trifluoromethylation reaction of heteroaromatic substrates.<sup>393</sup> This methodology started with the electrophilic activation of *N*-oxide heterocycles **494** with  $\text{BF}_2\text{CF}_3$ , prepared from  $\text{K}[\text{BF}_3\text{CF}_3]$  and  $\text{BF}_3\cdot\text{OEt}_2$  (Scheme 282). Subsequent nucleophilic addition of the trifluoromethyl group to electrophilically activated *N*-oxide– $\text{BF}_2\text{CF}_3$  complexes **494** with  $\text{TMSCF}_3$  reagent **14** ( $\text{RPr}$ )<sup>47</sup> in the presence of  $\text{CsF}$  activator yielded corresponding trifluoromethylated heterocycles **495** in general in a regioselective way at the carbon adjacent to the nitrogen atom.

Trifluoromethyl acetate reagent, such as bis(trifluoroacetyl) peroxide **438**, was found to trifluoromethylate five-membered heterocycles at low temperature (Scheme 283).<sup>394</sup> Thus, when pyrrole derivatives **496** and trifluoroacetyl derivative **438** were heated in Freon 113, the corresponding trifluoromethylated compounds **497** were obtained in moderate yields. In these transformations, the  $\text{CF}_3$  radical was generated by homolysis of the peroxide and subsequent elimination of  $\text{CO}_2$  from the trifluoromethylcarboxyl radical intermediate.

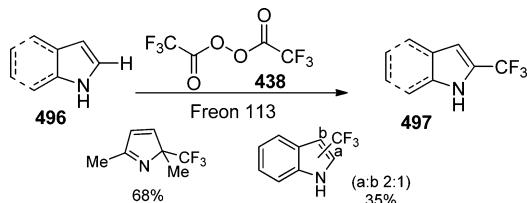
Scheme 282



Scheme 284



Scheme 283

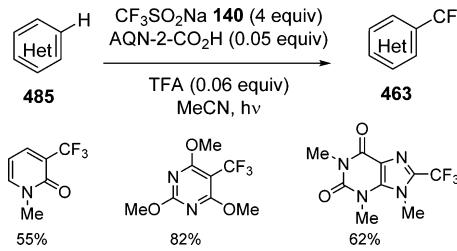


Baran et al.<sup>387</sup> described the direct transition metal-free trifluoromethylation of unsubstituted heterocycles by relying on reagent 140 (Lr) as the source of radical  $\text{CF}_3$  and TBHP. Under optimized conditions, several heterocycles 485, among them common pharmaceutical and natural products, could be directly trifluoromethylated with a simple procedure (Scheme 284). For example, this group successfully achieved C–H trifluoromethylation of natural product derivatives dihydroquinine and caffeine and the drug Chantix (veranicline, used to combat nicotine addiction).

The same system,  $\text{CF}_3\text{SO}_2\text{Na}/\text{TBHP}$ , was used by Montesarchio et al. for the trifluoromethylation of several nucleosides derived from cytidine, adenosine, guanosine, and inosine.<sup>395</sup> Despite some substrates showing poor results due to acidic pH conditions, the biphasic system  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  proved to be the best solvent combination to perform the reaction at room temperature.

Reagent 140 (Lr) has been also used for a convenient photoredox- and organocatalyzed-based direct trifluoromethylation of heteroarenes 485 under visible light irradiation (Scheme 285).<sup>362</sup> Anthraquinone-2-carboxylic acid (AQN-2- $\text{CO}_2\text{H}$ ) turned out to be the most effective organocatalyst for the reaction, and the use of TFA as additive enhanced the reaction rate. Under these conditions, some mono- and

Scheme 285

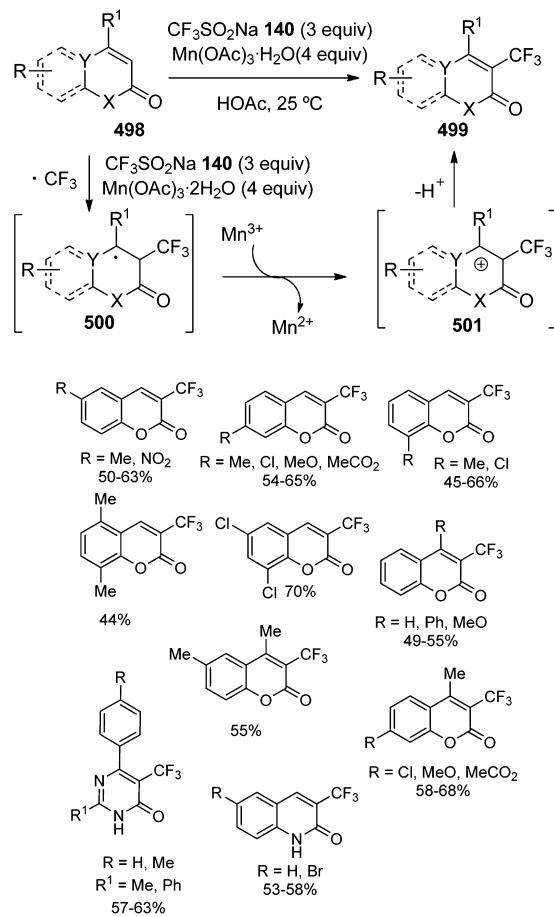


bicyclic-substituted heteroarenes 463 were obtained in moderate-good yields. Their formation may be explained by a radical mechanism with the anthraquinone derivative playing as an electron transfer mediator to allow the formation of the electron-deficient trifluoromethyl radical.

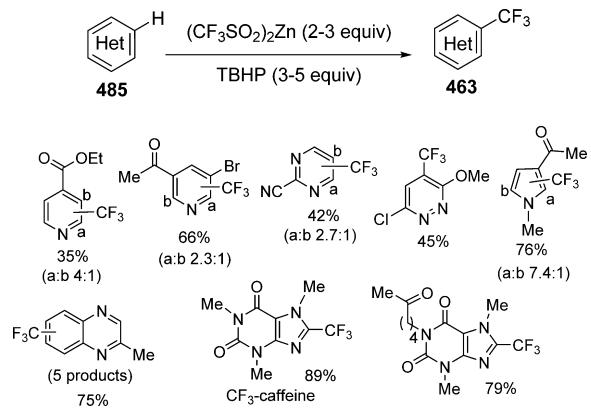
Selective direct trifluoromethylation in position 3 of coumarins 498 was achieved by the reaction of the trifluoromethylating agent 140 (Lr)<sup>127</sup> with coumarins in the presence of  $\text{Mn}(\text{OAc})_3$  under mild conditions in air<sup>396</sup> (Scheme 286). This strategy can be applied to coumarins with electron-donating and electron-withdrawing groups. A radical mechanism involving the selective addition of trifluoromethyl radical to the 3-position of the coumarins with initial formation of the radical intermediate 500 followed by oxidation with Mn(III) salt and deprotonation of carbocation 501 may explain the formation of substituted coumarins 499. It is noteworthy that with this methodology, trifluoromethyl group has been straightforwardly inserted into not only coumarins but also into quinolinones and pyrimidinones by a direct C–H functionalization.

Zinc sulphinate salts and TBHP have been used to transfer alkyl radicals to a wide range of five- and six-membered nitrogenated compounds 485, through a mild direct and operationally simple C–C bond formation leading to trifluoromethylated heterocycles 463 containing 1, 2, or 4 heteroatoms (Scheme 287).<sup>397</sup> The practicality, versatility, and functional group tolerance of this innate functionalization of heterocycles make it a valuable addition to the range of C–H

Scheme 286



Scheme 287

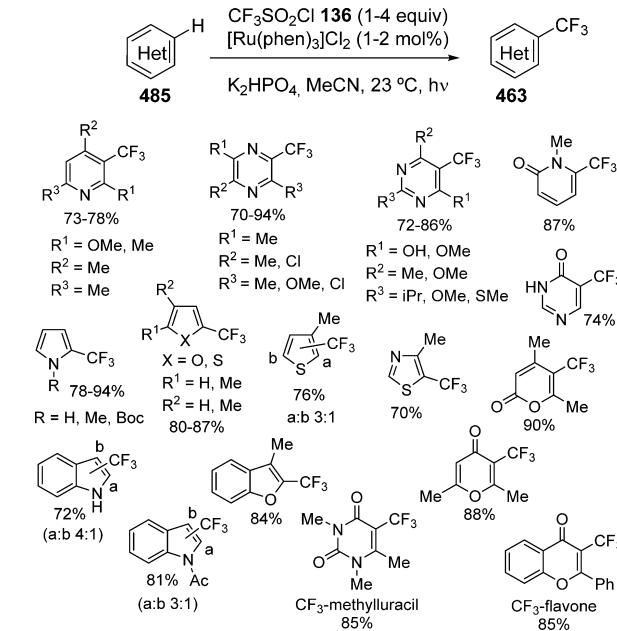


functionalization methods that could be used to construct pharmaceutically important targets, as, for example, trifluoromethylated caffeine. Blackmond et al. monitored the trifluoromethylation reaction of caffeine under the conditions previously developed by Baran's group to study this radical reaction mechanism.<sup>398</sup> The reaction profile seemed to be characterized by two regimes, rapid and slow, that could be modulated by different additives, as  $\text{FeSO}_4$ , and neither caffeine concentration nor oxidant concentration seem to affect the reaction rate.

MacMillan et al.<sup>365</sup> used **136** ( $\text{CF}_3\text{SO}_2\text{Cl}$ ) as trifluoromethylating reagent in the presence of  $\text{K}_2\text{HPO}_4$  and a ruthenium catalyst in a photosynthesis-inspired redox catalysis process.

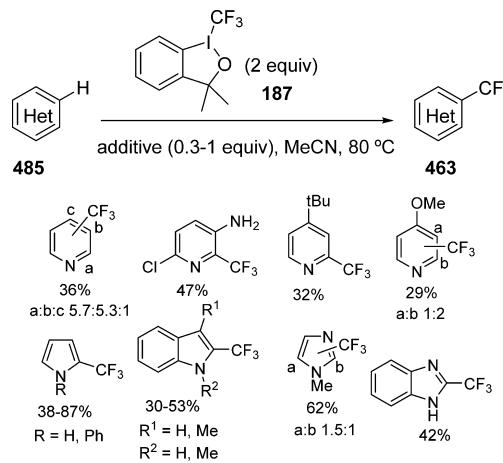
This approach allowed the direct incorporation of trifluoromethyl group into a broad range of heteroaromatic systems **485** without the need for ring preactivation to obtain pentagonal heterocycles containing N, O, or S as heterocycles and six-membered heterocycles, such as pyridines, pyridine-2-ones, pyridazines, pyrimidine derivatives, as well as chromones and coumarines (Scheme 288).

Scheme 288



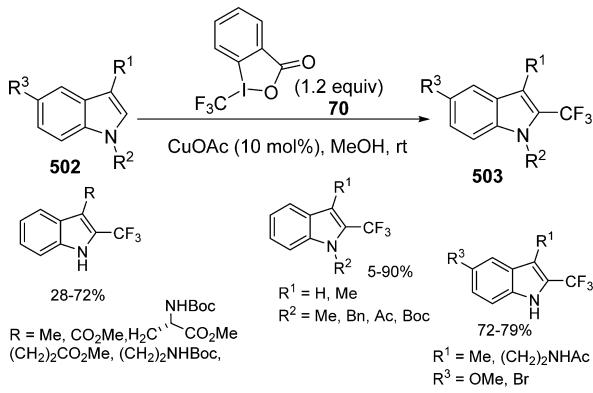
Electrophilic hypervalent iodine trifluoromethylating reagents were also successfully used for the trifluoromethylation of heterocycles. For example, Togni's group developed a method for the direct trifluoromethylation of nonfunctionalized heteroarenes **485** under mild conditions by using **70** (Tr1)<sup>80</sup> or **187** (Tr2),<sup>80</sup> with several additives, such as  $\text{ZnBr}_2$ ,  $\text{Zn}(\text{OTf})_2$ , or tris(trimethylsilyl)silyl chloride (TTMSSCl) as promoters to obtain heterocycles **463** (Scheme 289).<sup>366</sup> Better results were obtained when reagent **187** (Tr2) was used, and trifluoromethylated pyridines as well as substituted pyrroles, indoles, imidazoles, and benzimidazoles **463** were prepared.

Scheme 289



Moreover, reagent **70** ( $\text{Tr1}^{80}$ ) also proved to be a suitable  $\text{CF}_3$  source for the regioselective trifluoromethylation of heterocycles by a transition-metal-catalyzed reaction. In this sense, Sodeoka et al. reported<sup>399</sup> the copper-catalyzed direct C2-regioselective trifluoromethylation of indoles **502** to give heterocycles **503** under mild conditions and with good tolerance of some functional groups such as ester, amide, or bromide (Scheme 290).

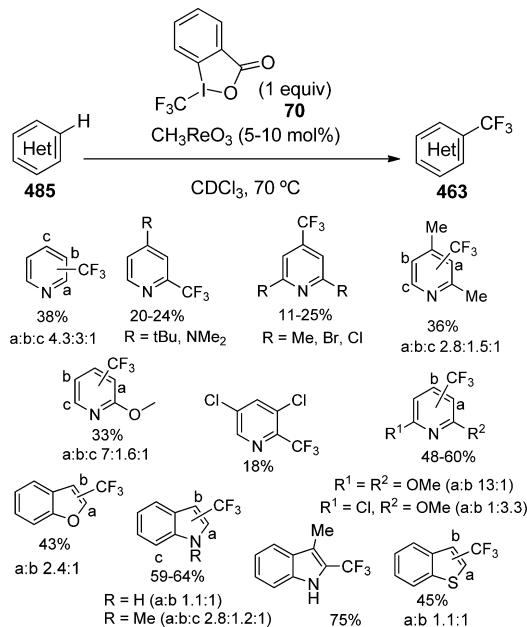
Scheme 290



However, this group found that protection of indole nitrogen atom with TMS or TBDSM affected the reactivity and selectivity of the reaction.<sup>400</sup> Indeed, better results from TMS-protected substrates supported the hypothesis that the silyl cation may be an activator. In fact, when this reaction was performed under previously established mild conditions (**70**,  $\text{CuOAc}$  at rt) but using  $\text{TMSOTf}$  as a catalyst (20 mol %), a very fast (5 min) trifluoromethylation of indoles was observed.

Later, the same reagent **70** ( $\text{Tr1}^{80}$ ) was used with rhenium instead of Cu(I) as transition-metal catalyst (Scheme 291).<sup>367</sup> A wide range of heteroarenes **485**, including pyridines, benzofuran, benzothiophene, and indoles, activated and inactivated, have been submitted to the reaction to give **463**,

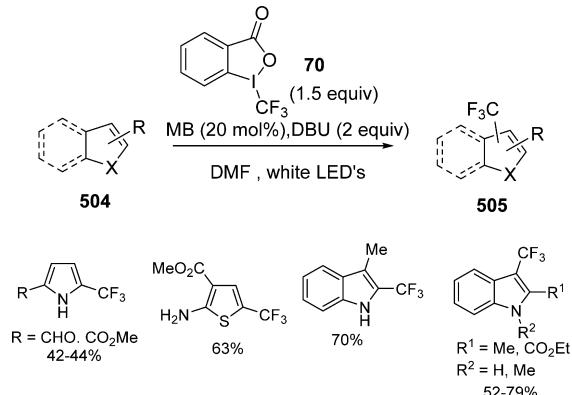
Scheme 291



although the yields and regioselectivities are modest, particularly in the case of substrates bearing electron-withdrawing substituents.

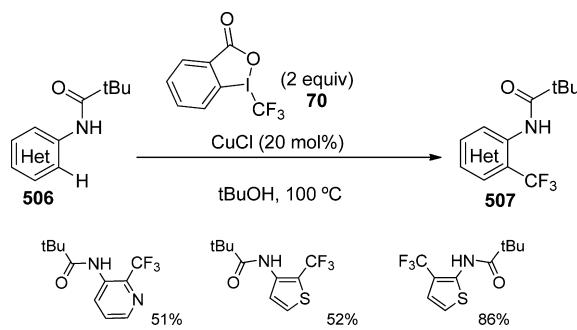
Also, with Togni's reagent **70** as the  $\text{CF}_3$  source, but with methylene blue (MB, vide supra, Scheme 69) as organocatalytic photocatalyst, the trifluoromethylation of electron-rich heterocycles under visible light irradiation has been accomplished.<sup>155</sup> Low catalyst loading (0.02 equiv) was sufficient for the effective radical trifluoromethylation of starting substrates **504** giving corresponding products **505** with good yields (Scheme 292).

Scheme 292



Finally, Xi et al.<sup>376</sup> developed a similar process for heterocycles **506** bearing a pivalamido directing group ( $\text{NHCOtBu}$ ) by using reagent **70** ( $\text{Tr1}^{80}$ ) to carry out an innate heterocyclic trifluoromethylation in a regioselective fashion. The corresponding trifluoromethylated pyridine and thiophenes **507** were obtained with high selectivity at the *ortho*-position through a novel Cu-catalyzed radical pathway (Scheme 293).

Scheme 293



## 6. SUMMARY

Many biologically active compounds contain a trifluoromethyl group as the essential motif, and the trifluoromethyl group has been particularly difficult to install, in part because the reactive intermediates that are generated during trifluoromethylation reactions are unstable under the conditions necessary for the reactions to proceed. Therefore, the introduction of this moiety is a challenging topic, and the development of highly efficient methodologies for trifluoromethylation is of significant importance and with special incidence in medicinal chemistry, agrochemistry, and materials science and technology.

A lot of ground has been covered from pioneering works on carbon trifluoromethylation of prefunctionalized hydrocarbons and heteroarenes mediated by transition metals, mainly copper, in stoichiometric amounts and using  $\text{CF}_3$  radical sources. In the past decade, an outstanding advance in the trifluoromethylation reaction of aliphatic and aromatic hydrocarbons as well as heterocycles occurred not only by the use of new prefunctionalized substrates such as boron and silicon derivatives but also by the discovery of new catalytic processes mediated by transition metals ( $\text{Cu}$ ,  $\text{Fe}$ ,  $\text{Ag}$ , ...), including photocatalysts and metal-free methods.

Likewise, recently the direct trifluoromethylation of unsaturated substrates such as allyl, alkene, and alkyne derivatives in both stoichiometric and catalytic reactions has attracted special interest. Nevertheless, the direct trifluoromethylation of aromatic systems has often the drawback of generating mixtures of regioisomers. The use of new prefunctionalized aromatic compounds bearing directing groups improves the reliability (yields and reaction conditions) and increases the regioselectivity of these processes in some cases.

Despite that the synthetic tools described in this account are becoming more suitable toward  $\text{C}-\text{CF}_3$  bond building, current methods still lack enough efficiency for their general use in practical large-scale manufacturing. Excellent challenges for the future imply a better understanding of their mechanism pathways along with the development of new simple trifluoromethylating agents, the design of new cheap catalytic systems and metal-free strategies, to improve not only the regioselectivity, especially in the case of aromatic substrates, but also the enantioselectivity in these trifluoromethylation processes.

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### Notes

The authors declare no competing financial interest.

### Biographies



Concepción Alonso was born in Vitoria-Gasteiz, Spain, in 1968. She had received her B.Sc. degree in Chemistry from the University of Valladolid in 1991, and Ph.D. degrees in Chemistry from the University of Basque Country in 1998, the latter under the supervision of Prof. Francisco Palacios. She stayed at the University of California at Davis as a postdoctoral fellow under the supervision of Prof. Mark J. Kurth for two years. After her return to Spain, she has been working as a postdoctoral fellow and as research associate with Prof. Francisco Palacios at the University of Basque Country. She became Associate

Professor in 2012 in Organic Chemistry at the same University. Her research has been focused in the development of new reactions and methods for the synthesis of small organophosphorus molecules by solid-phase and combinatorial chemistry. Nowadays, her current interest is focused on the development of new methodologies in organic synthesis of heterocyclic compounds containing phosphorus, nitrogen, and fluorine substituents.



Eduardo Martínez de Marigorta was born in 1961 in Vitoria-Gasteiz. He graduated in Chemistry in 1984 and received his Ph.D. at the University of Basque Country under the guidance of Dr. Esther Domínguez on the chemistry of isoquinolines and protoberberines. In 1991–92 and 1996 he worked with Dr. Ian Fleming at the University of Cambridge on the use of silyl anions in synthesis. By the end of 1996, he joined the Faculty of Pharmacy and Dr. Palacios' group at the University of Basque Country where he is now Associate Professor of Organic Chemistry. His research interests include the chemistry of fluorine- and phosphorus-containing compounds and their applications to the conventional and solid-phase synthesis of cyclic and acyclic compounds.



Gloria Rubiales was born in Aranda de Duero (Burgos, Spain). She graduated in Chemistry from the University of Valladolid and received her Ph.D. degree in Chemistry from the University of the Basque Country under the supervision of Prof. Claudio Palomo and Prof. Fernando Cossío. She has worked at the University of the Basque Country as Assistant Professor and Associate Professor. Since 1995 she was appointed as an Associate Professor in Organic Chemistry at the same University, where she is working in Dr. Palacios' group. Her current research interest is focused on the development of new methodology in organic synthesis of heterocyclic compounds containing phosphorus, nitrogen, and fluorine substituents, as well as on the design and development of enzyme inhibitors, molecular modeling, and computational chemistry.



Francisco Palacios was born in Vitoria, Spain (1951). He graduated in Chemistry from the University of Zaragoza, and he received his Ph.D. degree at the University of Oviedo in 1977 under the supervision of Prof. José Barluenga. After two years (1979–1981) of Post Doctoral work with Prof. Dr. Rolf Huisgen at the Organic Chemistry Institute of the Ludwig University (Munich, Germany) working on cycloaddition reactions, he came back to the University of Oviedo as Assistant Professor and he became Associate Professor in 1983 at the same University. Since 1991 he has been full Professor of Organic Chemistry at the University of the Basque Country (Faculty of Pharmacy). He has held Visiting Professorships at the Ecole Nationale Supérieure de Chimie de Montpellier (France, 2003) and at the Department of Chemistry of the University of Coimbra (Portugal, 2005, 2006, 2008, 2010, 2011). His research interests are organic synthesis, organophosphorus chemistry, fluorine chemistry, heterocyclic chemistry, cycloaddition reactions, design and development of enzyme inhibitors, and solid-phase synthesis.

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Financial support from the Dirección General de Investigación del Ministerio de Ciencia e Innovación (CTQ2012-34323) and by Gobierno Vasco and Universidad del País Vasco (GV, IT 422-10; UPV, UFI-QOSYC 11/12) is gratefully acknowledged.

## ABBREVIATIONS

AAA	asymmetric allylic alkylation	(DHQD) <sub>2</sub> -PHAL	dihydroquinidine 1,4-phthalazinediyl diether
AIBN	azobisisobutironitrile	(DHQD) <sub>2</sub> -PYR	2,5-diphenyl-4,6-pyrimidine diyl diether
Alk	alkyl	DMAC	dimethylacetamide
AQN	anthraquinone	DME	dimethoxyethane
ATRA	atom transfer radical addition	DMEDA	N,N'-dimethylethylenediamine
Ar	aryl	DMF	dimethylformamide
Boc	butoxycarbonyl	DMPU	N,N'-dimethylpropylene urea
BQ	1,4-benzoquinone	DMSO	dimethyl sulfoxide
BPO	benzoyl peroxide	DTBP	di- <i>tert</i> -butylhydroperoxide
bpy	2,2'-bipyridine	equiv	equivalents
Bs	besylate	ESI-MS	electro spray ionization-mass spectrometry
1,4-CHD	1,4-cyclohexadiene	FDA	Food and Drug Administration
cod	cyclooctadiene	FBDD	fragment based drug discovery
crypt	cryptand	GO	graphene oxide
Cy	cyclohexyl	Hal	halogen
DABCO	1,4-diazabicyclo[2.2.2]octane	HFIP	1,1,1,3,3-hexafluoro-iso-propanol
DAST	diethylamino sulfur trifluoride	HMPA	hexamethylphosphoramide
DBH	1,3-dibromo-5,5-dimethylhydantoin	HMPT	hexamethylphosphorus triamide
DBU	1,4-diazabicyclo[5.4.0]undec-7-ene	IL	ionic liquid
DCE	1,2-dichloroethane	iPrCN	isopropyl cyanide
DCM	dichloromethane	KHMDS	potassium hexamethyldisilazide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone	LED	light emitting diodes
DFT	density functional theory	Ln	ligand
		Lr	NaSO <sub>2</sub> CF <sub>3</sub> , Langlois reagent
		MB	methylene blue
		MOM	methoxymethyl
		MS	molecular sieves
		MTBE	methyl tertbutyl ether
		MTFA	methyl trifluoroacetate
		MW	microwave
		naphth	naphthyl
		nd	not determined
		Nf	nonaflate
		NFTPT	N-fluoro-1,3,5-trimethylpyridinium triflate
		NMP	N-methylpyrrolidinone
		PAH	polycyclic aromatic hydrocarbons
		PET	positron emission tomography
		PG	protecting group
		phen	1,10-phenanthroline
		pin	pinacol
		Piv	pivalamido
		Phth	phthaloyl
		PIFA	phenyliodine bis(trifluoroacetate)
		PMP	<i>p</i> -methoxyphenyl
		Py	pyridine
		quant	quantitative
		RB	rose bengal
		RPr	trifluoromethyltrimethylsilane, Ruppert-Prakash reagent
		SET	single-electron transfer
		TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
		TBHP	<i>tert</i> -butyl hydroperoxide
		TBAF	tetra- <i>n</i> -butylammonium fluoride
		TBDMS	<i>tert</i> -butyldimethylsilyl chloride
		TBS	<i>tert</i> -butyldimethylsilyloxy
		TC	thiophene-2-carboxylate
		TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
		Tf	triflyl
		THF	tetrahydrofuran
		TIPS	tri-isopropylsilyl
		TMEDA	tetramethylethylenediamine

TMG	tetramethylguanidine
TMP	2,4,6-trimethylpyridine
TMS	trimethyl silane
Tr1	1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one, Togni's reagent 1
Tr2	3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, Togni's reagent 2
Ts	tosyl
TTMSS	tris(trimethylsilyl)silane
Ur	S-(trifluoromethyl)dibenzothiophenium tetrafluoroborate, Umemoto's reagent

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