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Trifluoromethylation

Trifluoromethylation of Alkenes with Concomitant Introduction of Additional Functional Groups

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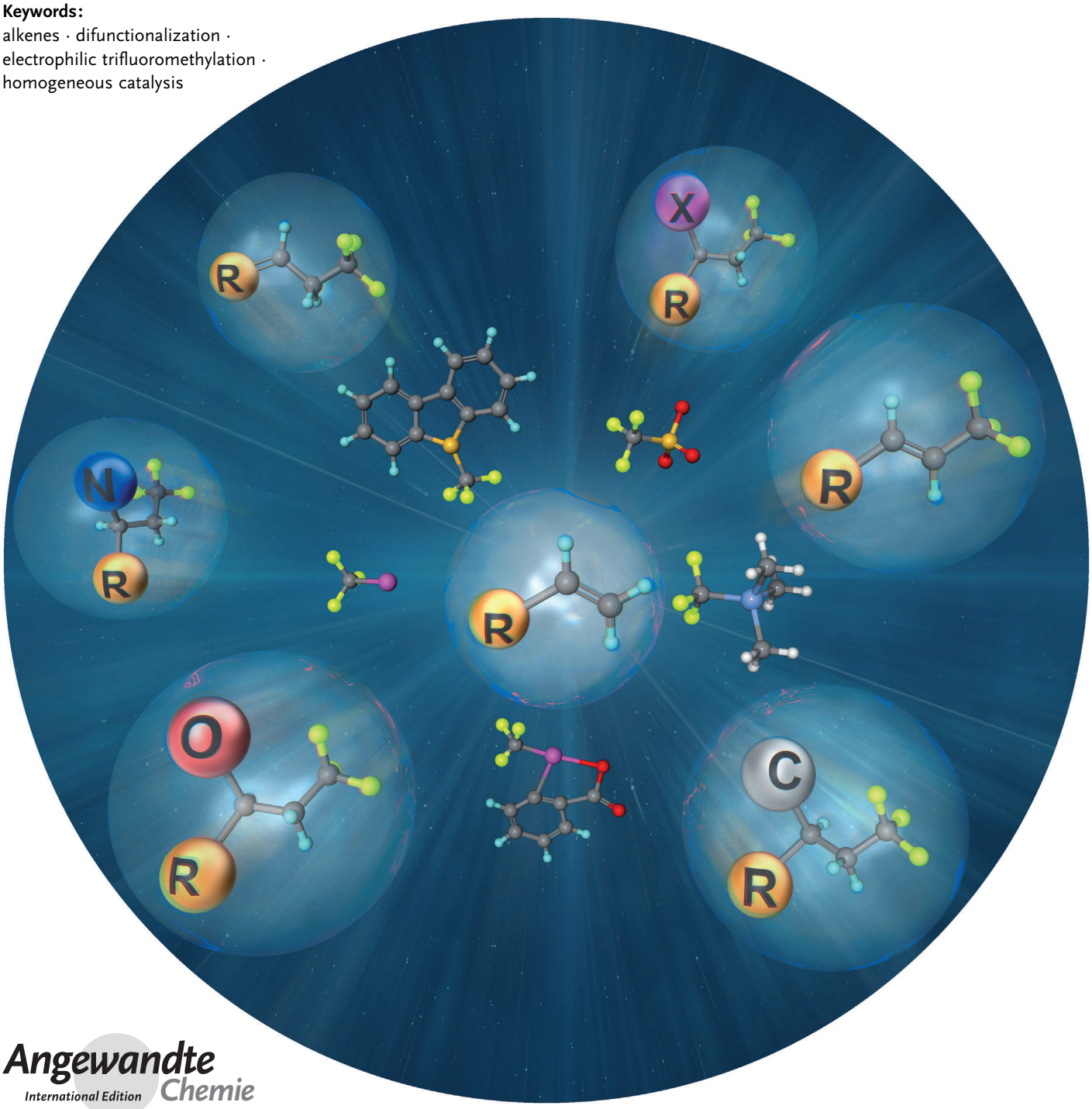

The trifluoromethyl group is found in many synthetic bioactive compounds, and the difunctionalization of a C=C bond, as a powerful strategy for the construction of compounds with various functional groups, has been intensively investigated. Therefore, the difunctionalizing trifluoromethylation of alkenes has attracted growing interest because of the potential of the products as building blocks for bioactive molecules. In this review, we focus on recent advances in the trifluoromethylation of alkenes with concomitant introduction of additional functional groups.

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1. Introduction

At present, about 20% of all pharmaceutical drugs and 30% of all agrochemicals contain one or more fluorine atoms,[1] and the trifluoromethyl group is used particularly widely. Fluorine is the second smallest atom after hydrogen, and the C–F bond is only 1.28 times longer than the C–H bond.[2] Nevertheless, the bond energy is much higher than that of the C–H bond (C–F bond: 105.4 kcal mol^{-1}, C–H bond: 98.8 kcal mol^{-1}).[3] Another feature of the fluorine atom is its strong electronegativity. In terms of electronic properties, fluorine is more similar to oxygen than to hydrogen (Pauling scale: F: 4.0, O: 3.5, H: 2.1),[3] and fluorine has been used as a functional quasi-isostere of oxygen.[1]

The trifluoromethyl group has been introduced into various organic frameworks in place of a methyl group in attempts to improve the properties of bioactive molecules, such as metabolic stability, lipophilicity, and selectivity. The size of the trifluoromethyl group is actually closer to that of an isopropyl group rather than a methyl group.[4] As expected, the trifluoromethyl group works as an electron-withdrawing group and has a significant influence on the pK_a values and the basicity of neighboring functional groups, such as alcohols, carboxylic acids, and amines.[5]

Many reactions have been developed for the construction of C–CF_3 bonds. Product molecules can be roughly classified into three types: alkynyl compounds with a C(sp)–CF_3 bond, aromatic or vinylic compounds with a C(sp^2)–CF_3 bond, and aliphatic compounds with a C(sp^3)–CF_3 bond. The introduction of a trifluoromethyl group into aryl and vinyl moieties has recently received much attention. Special attention has been paid to transition-metal-catalyzed or -mediated cross-coupling-type trifluoromethylations, which can be initiated by cleavage of not only a C–B or C–X (X = I, Br, Cl) bond, but also by cleavage of a C–H bond, and radical addition reactions using an in situ generated trifluoromethyl radical. These types of reactions have been reviewed elsewhere.[6]

Aliphatic compounds bearing a trifluoromethyl group are usually synthesized by utilizing carbonyl groups, that is, the trifluoromethyl group is introduced by nucleophilic attack of a trifluoromethyl anion equivalent on a carbonyl group, or by the reaction of enolates and enamines with an electrophilic trifluoromethylation reagent. Both non-asymmetric and asymmetric versions of these reactions have been reviewed in other publications.[7] On the other hand, the dual functionalization of alkenes is currently considered as one of the most promising approaches for the construction of multi-functional aliphatic compounds. Therefore, this review covers recent progress in the trifluoromethylation of alkenes with concomitant introduction of other functional groups.

2. Trifluoromethylation with C=C Bond Formation

2.1. Construction of Allylic Trifluoromethyl Compounds

The 1,1,1-trifluoro-3-butene framework has traditionally been synthesized by means of cross-coupling reactions or nucleophilic substitution.[8,9] For example, cross-coupling reactions of vinyl tin compounds with trifluoroethyl iodide under palladium-catalyzed conditions and reactions of allyl bromides with in situ generated nucleophilic Cu–CF_3 species have been reported.

In 2011, several groups independently made a breakthrough in this area,[10,11,12] reporting concise, environmentally benign methods for the formation of an allylic CF_3 bond from non-prefunctionalized alkenes. Buchwald and Parsons accomplished this trifluoromethylation with high regio- and stereoselectivity using a cationic copper(I) species, $[Cu(MeCN)_4]PF_6$, and Togni's reagent **1**[13] in MeOH at room temperature (Scheme 1a).[10] Their conditions could be

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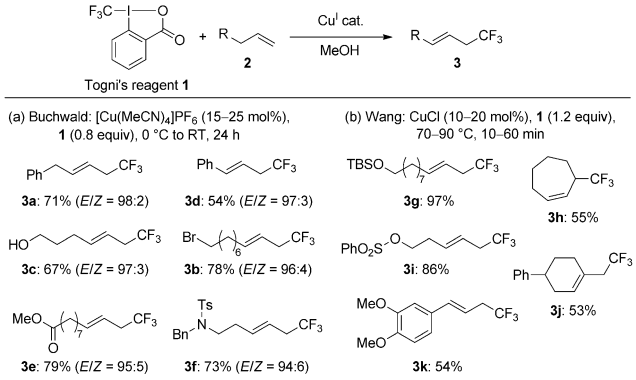
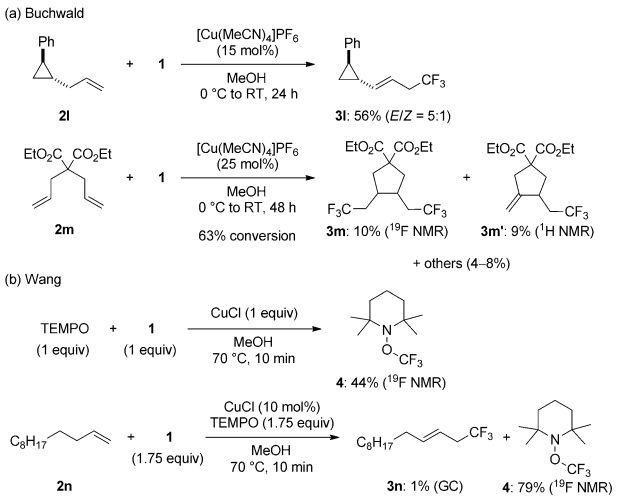


Scheme 1. Trifluoromethylation of simple alkenes using the Cu^{I}/Togni's reagent system.

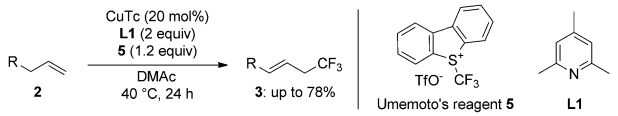


Scheme 2. Mechanistic studies by Buchwald and Wang.

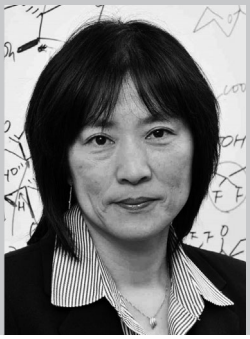
used for gram-scale synthesis without difficulty. Wang and co-workers also reported the same reaction in MeOH using CuCl as the catalyst (Scheme 1b).[11] Whereas a higher temperature was required under Wang's conditions, the reaction time was very short, and good to high yields were generally obtained. A notable finding is that this reaction can be applied to cyclic 1,2-disubstituted and 1,1-disubstituted alkenes (**3h**, **3j**), and various functional groups were tolerated under these reaction conditions.

The reaction mechanism of this trifluoromethylation is not yet clear, despite various mechanistic studies. Buchwald considered three types of mechanisms: 1) allylic oxidation and radical trifluoromethylation, 2) atom-transfer radical addition to the C=C bond, and 3) electrophilic trifluoromethylation via a cationic intermediate.[10] To investigate whether the generation of an allyl radical was possible, the reaction of radical-clock substrate **2l** was examined (Scheme 2a). The main product was the normal trifluoromethylation product and not the product of cyclopropane ring opening, suggesting that the allylic radical pathway was unlikely. They also examined diene **2m**, which bears a quaternary carbon center, and determined the structures of two cyclized products as bis(trifluoromethylated) compound **3m** and *exo*-methylene compound **3m′**. Other unidentified products were also formed in these reactions. Based on these results, Buchwald concluded that the mechanism of this reaction was complex and involved multiple pathways.[10] On the other hand, Wang et al. mentioned that a trifluoromethyl radical generated by the reaction of Togni's reagent with CuCl was likely to be the key species for this reaction, based on inhibition of the reaction by TEMPO.[11] Although trifluoromethylated TEMPO was detected, TEMPO could be converted into the trifluoromethylated product under standard conditions even in the absence of an alkene. Furthermore, no product of alkene-radical trapping was detected. Thus, simple experiments with a radical scavenger failed to elucidate the mechanism of trifluoromethylation using **1**.

Liu and co-workers developed the same reaction using CuTc (Tc = thiophenecarboxylate), collidine, and Umemoto's reagent **5**[14] in dimethylacetamide (DMAc; Scheme 3).[12] The scope of their reaction was almost the same as those of the transformations developed by the groups of Buchwald and Wang. The stereoselectivity (*E*/*Z*) of the resulting C=C bond depended on the substrate used, but good to high yields and stereoselectivities were generally observed. Interestingly, a mixture of regioisomers was obtained when [D$_4$]MeOH was used as the solvent. This clearly suggested that the reaction



Scheme 3. Trifluoromethylation of alkenes using Umemoto's reagent.



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Hiromichi Egami received his B.S., M.S., and Ph.D. degrees from Kyushu University under the supervision of Professor Tsutomu Katsuki. In 2009, he joined the ERATO Sodeoka Live Cell Chemistry Project as a Research Scientist and was promoted to Group Leader in 2012. Currently, he is working in Professor Yoshitaka Hamashima's group at the University of Shizuoka as an Assistant Professor.

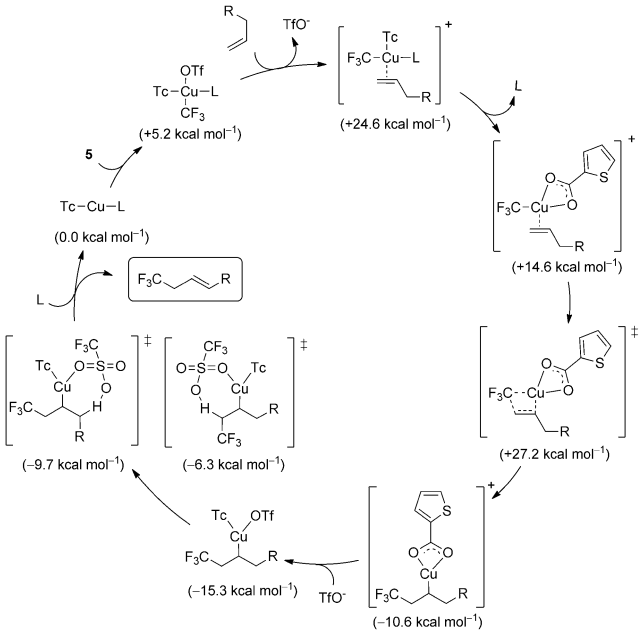
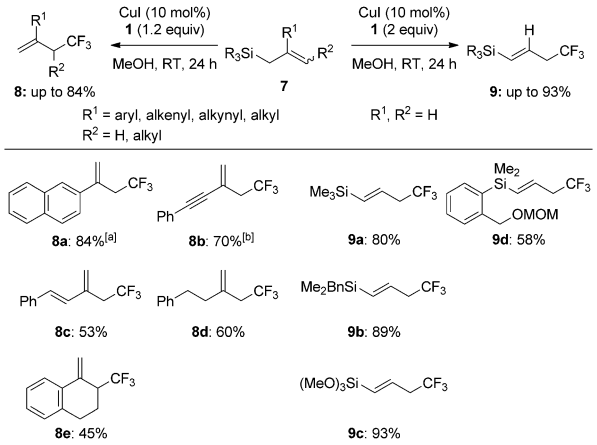


Figure 1. Reaction mechanism proposed by Liu.

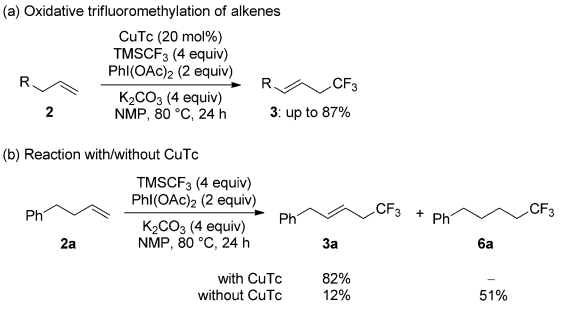


Scheme 5. Trifluoromethylation of allylsilanes. [a] Run for 72 h. [b] With CuI (50 mol%).

mechanism may be different from that of Buchwald and Wang's reactions. Based on theoretical calculations, Liu proposed the reaction mechanism shown in Figure 1: 1) generation of a Cu^{III}–CF_3 species, 2) coordination of the alkene, 3) insertion of the alkene into the Cu–CF_3 bond (Heck-like transition state with a four-membered ring), and 4) deprotonative reductive elimination.

In 2012, Qing and co-workers reported the copper-catalyzed oxidative trifluoromethylation of alkenes bearing allylic protons by using the combination of $TMSCF_3$/$PhI(OAc)_2$/K_2CO_3 (Scheme 4a).[15] Their conditions afforded allylic trifluoromethylated products in good yields. The substrate scope was broad, but epoxides and alkyl bromides were not tolerated because of side reactions. Interestingly, the reaction without a copper catalyst produced the trifluoromethylated allylic product **3a** (12%) and the aliphatic product **6a** (51%; Scheme 4b).[10–12] This suggests that the copper catalyst is crucial for the selectivity of this trifluoromethylation, but not for the reactivity, and that the reaction mechanism is likely to be different from that of the aforementioned reactions. Furthermore, it was observed that the signal of $PhI(CF_3)(OAc)$, which is an equivalent of Togni's reagent, was absent in the ^{19}F NMR spectrum.[16]

Sodeoka and co-workers focused on the trifluoromethylation of more nucleophilic allylsilanes (Scheme 5).[17,18] During independent studies on the trifluoromethylation of simple C=C bonds, which were based on their successful trifluoromethylation of indoles,[19] they had previously encountered a limited substrate scope, as was the case with the trifluoromethylations reported by the groups of Buchwald, Wang, and Liu. Using the newly established conditions, geminally disubstituted allylsilanes as well as trisubstituted allylsilanes were successfully converted into the corresponding desilylated products **8** in good yields even at room temperature. Interestingly, the use of mono-substituted allylsilanes (R^1, R^2 = H) that lack a substituent at the β-position afforded trifluoromethylated vinylsilane derivatives **9**. Based on their findings, Sodeoka and co-workers proposed that the stability of the carbocation at the β-position of the silicon atom was a key factor in determining the product. The proposed reaction mechanism is illustrated in Figure 2. The reaction of the 2-substituted allylsilane proceeds through generation of the cationic intermediate, and the silyl cation is generated and trapped by 2-iodobenzoate or methanol, with simultaneous formation of the C=C bond. If the substrate has no substituent at the β-position of the silicon atom, deprotonation at the allylic position, which would be preferable compared to the generation of a carbocation, occurs after



Scheme 4. Trifluoromethylation of alkenes under oxidative conditions.

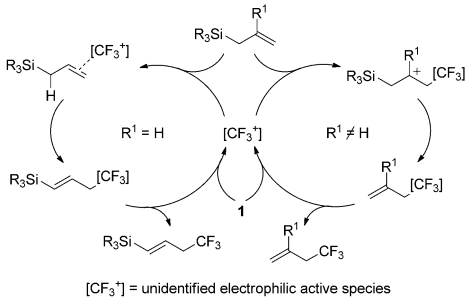
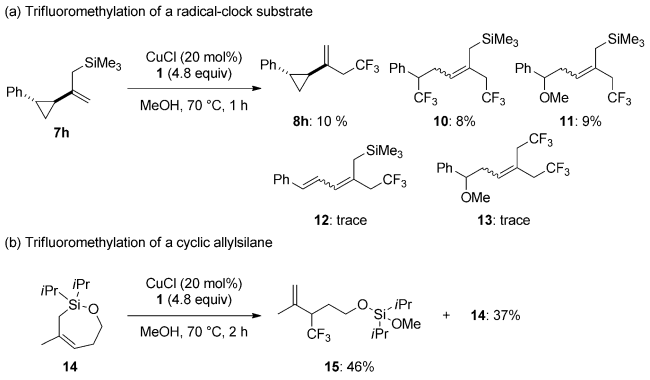


Figure 2. Reaction mechanism proposed by Sodeoka.

coordination of the alkene moiety to the unidentified electrophilic active species. Subsequently, the product is released by reductive elimination with C–CF_3 bond formation.

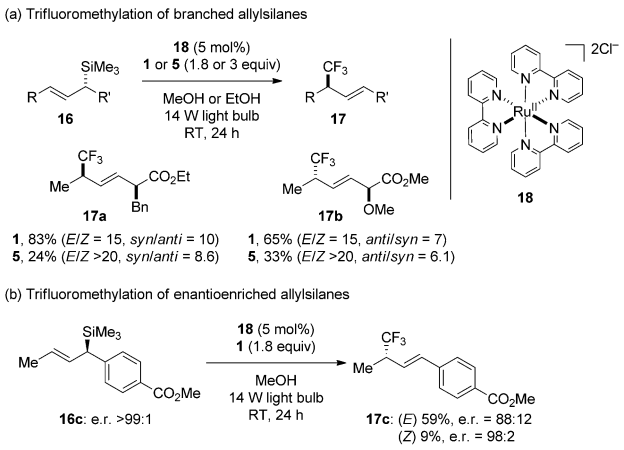
Gouverneur et al. independently reported the same reaction, but they focused in particular on more substituted allylsilanes.[20] A notable finding was that the use of Hünig's base suppressed undesired proto-desilylation and increased the product yields, especially in the reaction of trisubstituted allylsilanes. Gouverneur and co-workers also investigated the reaction mechanism using the radical-clock substrate **7h** (Scheme 6a). Their careful analysis revealed formation of



Scheme 6. Mechanistic studies by Gouverneur.

10% of normal trifluoromethylated product **8h**, 8% of bis(trifluoromethylated) product **10**, 9% of 1-trifluoromethyl-5-methoxy product **11**, and trace amounts of **12** and **13**. Furthermore, the fate of the silyl group was traced in the reaction of cyclic allylsilane **14**, and the product of methanol trapping, **15**, was obtained in 46% yield (Scheme 6b). As Gouverneur remarked, products **8h** and **11** as well as **15** suggest that a silicon-stabilized β-cation is likely to be a key intermediate, and these results agree with Sodeoka's mechanism. However, the formation of **10** implies that a radical pathway is operating. Therefore, a mechanism that involves addition of a trifluoromethyl radical generated by single electron transfer from Cu^I to Togni's reagent, followed by transfer to allylsilane and oxidation of the resulting carbon-centered radical could not be ruled out.

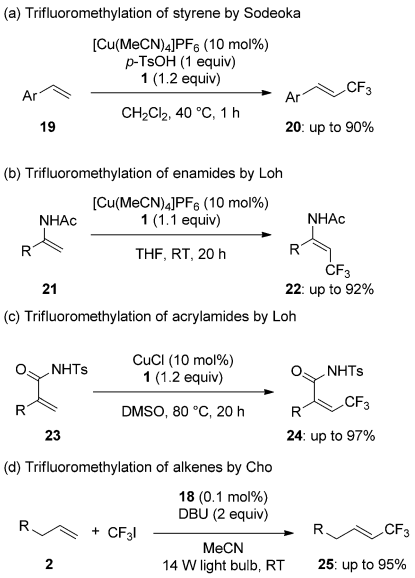
Further expansion of the substrate scope was achieved in 2013 by using a photoredox catalyst.[21] Gouverneur et al. addressed the formation of a stereogenic center containing a trifluoromethyl group, but the reaction system using a copper catalyst was not effective for internal allylsilanes. Therefore, photoredox catalyst **18** was utilized as a single-electron-transfer reagent to generate a trifluoromethyl radical from an electrophilic trifluoromethylation reagent (Scheme 7). This reaction proceeded in a highly stereospecific manner. Based on the correlation of stereochemistry between the allylsilanes and the corresponding products, it is likely that the reaction mode proceeds through *anti*-S_E2' addition. Gouverneur noted that the steric character of the allylsilanes significantly affected the regioselectivity of the addition of the trifluoromethyl radical.



Scheme 7. Trifluoromethylation of internal alkenes.

2.2. Construction of Trifluoromethyl-Substituted Alkenes

Trifluoromethyl-substituted alkenes are also key structural components in both pharmaceutical chemistry and materials chemistry.[1f] Methods for the synthesis of this unit have been actively researched,[8a,22] but the direct trifluoromethylation of non-prefunctionalized alkenes is still rare. A catalytic reaction for the introduction of a trifluoromethyl group has recently been achieved by using prefunctionalized substrates.[23] On the other hand, a direct trifluoromethylation of simple C=C bonds was accomplished in 2012. Sodeoka and co-workers reported the synthesis of β-trifluoromethyl styrenes from styrene derivatives (Scheme 8a).[24] While studying their oxy-trifluoromethylation reaction (Scheme 11), Sodeoka et al. found that the use of a Brønsted acid, such as *para*-toluenesulfonic acid (*p*-TsOH), in the reaction with Cu^I and Togni's reagent provided the corresponding product in high yield with high selectivity. They concluded that this



Scheme 8. Direct olefinic trifluoromethylation reactions.

reaction proceeded through oxy-trifluoromethylation and E1 reaction of 2-iodobenzoate. At the same time, Loh and Feng found that the reaction of an enamide with the Cu^{I}/Togni's reagent system in THF could provide trifluoromethyl-substituted olefins (Scheme 8b).[25] They proposed that the products were generated through trifluoromethylation of the enamide to provide the α-trifluoromethylated imine and subsequent imine/enamide tautomerization. In 2013, the same authors reported the trifluoromethylation of acrylamides under similar conditions (Scheme 8c). In this system, *Z* selectivity was observed. The reaction solvent, DMSO, worked as a ligand for the stabilization of the reaction intermediate, and the selectivity resulted from coordination of the amide moiety to the copper ion.[26]

Cho and co-workers utilized photoredox catalysis with a ruthenium complex for the construction of a trifluoromethylated alkene from simple alkenes at room temperature (Scheme 8d).[27] Similar to Stephenson's result (Scheme 28a),[28] the iodo-trifluoromethylation product was obtained in 95% yield when TMEDA or Et_3N was used as the base instead of DBU. It was reported that treatment of the iodo-trifluoromethylation product with DBU produced the trifluoromethyl-substituted alkene.[28] Using less than two equivalents of DBU decreased the product yield. It was assumed that DBU served as a reductive quencher for the photocatalyst and as a base for the E2 reaction.

In 2013, Szabó et al.[29] and Wang et al.[30] independently reported the trifluoromethylation of quinone derivatives (Scheme 9). The working hypotheses of these groups were

26 **27**

(a) Szabó: CuCN (1 equiv), **1** (1.5 equiv), B_2pin_2 (5 mol%), $CHCl_3$, RT, 18 h, up to 89%
(b) Wang: CuI (20 mol%), **1** (2 equiv), *t*BuOH–CH_2Cl_2, 55 °C, 12 h, up to 84%

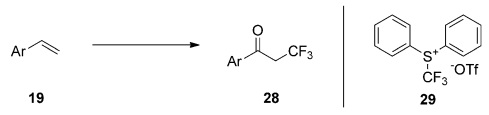
Scheme 9. Trifluoromethylation of quinones.

essentially the same: A trifluoromethyl radical generated from Togni's reagent and a Cu^{I} salt should couple with quinone derivatives. However, the reaction conditions are somewhat different. Szabó and co-workers accomplished this trifluoromethylation with a stoichiometric amount of CuCN and a catalytic amount of B_2Pin_2 at room temperature, whereas Wang et al. used a catalytic amount of CuI in *t*BuOH/CH_2Cl_2 at 55 °C.

3. Trifluoromethylation with C–O Bond Formation

In 1987, a pioneering oxy-trifluoromethylation reaction was reported by Fuchikami and co-workers.[31] A palladium-catalyzed oxy-trifluoromethylation of allylic alcohols was achieved using CF_3I. Later on, an electrochemical oxy-trifluoromethylation using trifluoroacetic acid (TFA) as the trifluoromethyl source[32] and an oxy-trifluoromethylation through iodo-trifluoromethylation using CF_3I and a radical initiator[33] were reported.

In 2011, Xiao et al. reported a method for the synthesis of α-trifluoromethyl ketone derivatives from styrenes by utilizing a trifluoromethyl radical that was generated by treatment of *S*-(trifluoromethyl)diphenylsulfonium triflate (**29**, Yagupolskii-type reagent) with $HOCH_2SO_2Na{\cdot}2H_2O$ as a reducing agent in air, albeit with low yield (Scheme 10a).[34] Xiao



19 **28** **29**

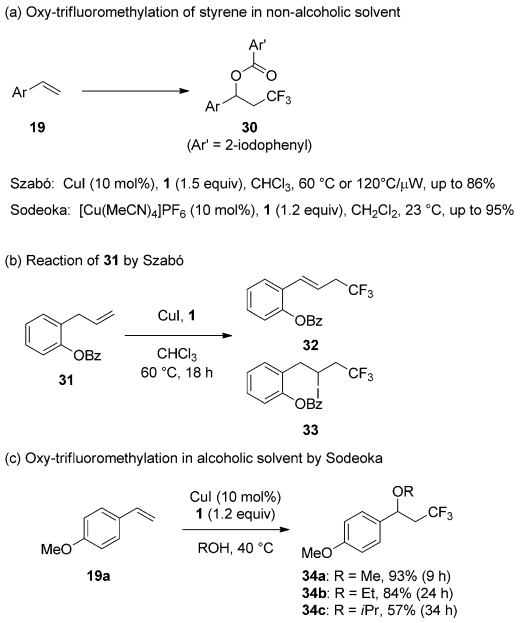
(a) Xiao: **29** (2 equiv), $HOCH_2SO_2Na{\cdot}2H_2O$ (6 equiv), air, DMF, 0 °C, 6 h, up to 42%
(b) Maiti: CF_3SO_2Na (2 equiv), $AgNO_3$ (20 mol%), $K_2S_2O_8$ (20 mol%), air, DMF, RT, 24 h, up to 95%

Scheme 10. Aerobic oxy-trifluoromethylation of styrenes.

confirmed that CF_3H and CF_3CF_3 were formed during the reaction, suggesting the generation of a trifluoromethyl radical. The source of oxygen in the products is molecular oxygen, because the use of $H_2{}^{18}O$ gave no ^{18}O-labeled products, and the desired product was not formed under a nitrogen atmosphere. Utilizing this transformation, Maiti et al. achieved the synthesis of α-trifluoromethyl ketones from styrene derivatives by using the Langlois reagent (CF_3SO_2Na)[35] in 2013 (Scheme 10a).[36] Under mild reaction conditions, good to high yields were obtained. This reaction was also applicable to internal styrenes. To confirm the oxygen source, isotopically labelled molecular oxygen was used, and the corresponding ^{18}O-containing product was detected by MS analysis. This result clearly indicated that the oxygen source of this reaction is molecular oxygen in air.

In 2012, Szabó and co-workers disclosed a remarkable copper-catalyzed trifluoromethylation of alkenes and alkynes along with concomitant C–O bond formation (Scheme 11a).[37] This reaction afforded β-trifluoromethyl ester derivatives in good yields, but microwave irradiation or a long reaction time were required. They noted that the reaction of an electron-rich substrate was faster, and that steric hindrance of the substrate affected the reaction rate. To investigate the reaction mechanism, the addition of a radical scavenger was examined. They found that TEMPO completely inhibited the reaction. Furthermore, the product of allylic trifluoromethylation, **32**, and iodo-trifluoromethylation product **33** were obtained in the reaction of **31** (Scheme 11b). Based on these findings, Szabó mentioned that both this reaction and the Buchwald and Wang trifluoromethylations proceed through the same intermediate, and that the mechanism may involve a trifluoromethyl radical. However, they did not exclude other possibilities, such as the formation of a Cu^{III}–CF_3 complex as an active species.

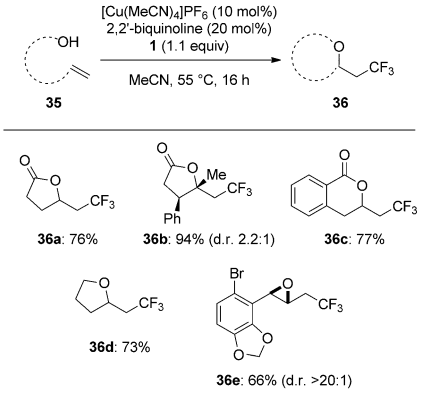
At the same time, Sodeoka and co-workers reported a similar oxy-trifluoromethylation of styrene derivatives (Scheme 11a).[24] In their report on allylsilane trifluoromethylation (Scheme 5), they had noted that the methoxy-trifluoromethylation product was obtained in the reaction of allylsilanes bearing an electron-rich aryl ring.[17] Conse-



Scheme 11. Oxy-trifluoromethylation reactions of styrenes.

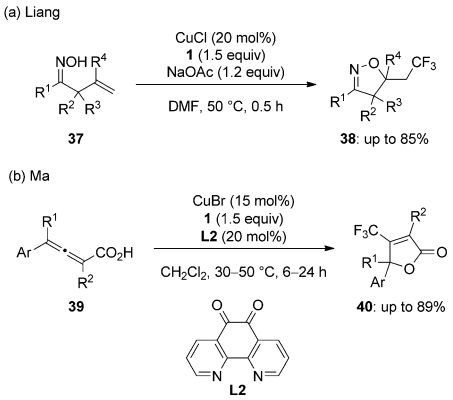
quently, they expected that trapping of the cationic intermediate with various oxygen nucleophiles would provide functionalized trifluoromethylated compounds. Interestingly, the reaction in an alcoholic solvent provided the trifluoromethylated alcohol adduct (Scheme 11c), whereas the reaction in CH_2Cl_2 afforded the 2-iodobenzoate adduct, as found by Szabó (Scheme 11a). Sodeoka's reaction conditions were found to be milder, with a broad reaction scope, and the product yields were generally high.

Elegant work on the intramolecular oxy-trifluoromethylation of simple alkenes was reported by Buchwald and Zhu (Scheme 12).[38a] It is well-known that an alkene bearing allylic protons affords the trifluoromethylated allylic product under electrophilic trifluoromethylation conditions (see Section 2.1).[10,11,17] This undesired competitive reaction was prevented by using 2,2′-biquinoline as a ligand. Carboxylic acids, phenols, or alcohols could be employed as nucleophiles in this oxy-trifluoromethylation. Three-, four-, five-, and six-membered rings were successfully formed under the standard conditions. Buchwald and Zhu proposed that the reaction mechanism involves atom-transfer radical addition. However, they did not establish the mechanism, because neither the TEMPO adduct derived from the trifluoromethyl radical nor the alkyl radical were detected during the reaction in the presence of TEMPO. More recently, the same authors reported an asymmetric version of this trifluoromethylation.[38b] This is the first example of a successful enantioselective trifluoromethylation of simple alkenes. Although the substrate scope was limited to styrene derivatives bearing a carboxyl group as a nucleophile, the enantioselectivity was good. Interestingly, similar results regarding the ratio of stereoisomers and enantioselectivity were obtained irrespective of the alkene stereochemistry.



Scheme 12. Intramolecular oxy-trifluoromethylation of alkenes.

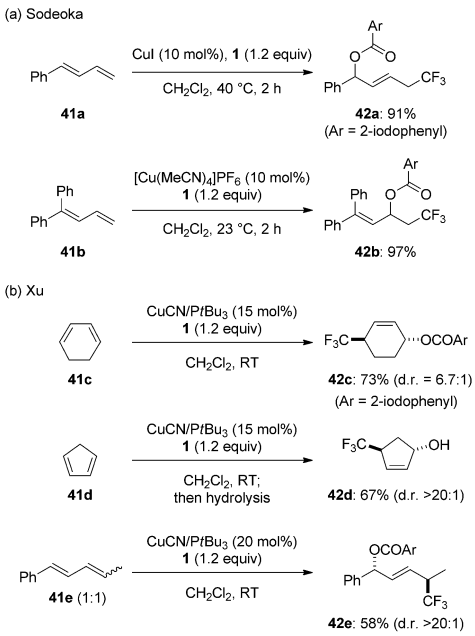
In 2013, a copper-catalyzed intramolecular oxy-trifluoromethylation was utilized for the synthesis of isoxazolines bearing a trifluoroethyl group by Liang and co-workers (Scheme 13a).[39] Various isoxazolines were obtained, and the yields were generally good. Later, Ma and Yu reported the intramolecular oxy-trifluoromethylation of 2,3-allenoic acids for the formation of butenolides bearing a trifluoromethyl group (Scheme 13b).[40] The substrate required an aryl ring to enhance the reactivity, and the butenolides were obtained in good to high yields.



Scheme 13. Intramolecular oxy-trifluoromethylation.

Cho et al. also reported an oxy-trifluoromethylation that proceeded through iodo-trifluoromethylation using photoredox catalyst **18**.[41] They focused on an intramolecular reaction to provide a trifluoromethylated epoxide from allylic alcohols and chose the reaction conditions as for their trifluoromethylation with C=C bond formation (Scheme 8d). This suggests that when allylic alcohols were used as a substrate, epoxide ring formation is faster than C=C bond formation by deprotonation at the α-position of the trifluoromethyl group under these reaction conditions.

Xu and co-workers recently reported a ligand effect in the oxy-trifluoromethylation of diene derivatives.[42] The oxy-trifluoromethylation of dienes had previously been achieved by using CuI/Togni's reagent system without any additive by Sodeoka et al.[24] In this case, 1-substituted 1,3-butadienes provided 1,4-addition products, whereas 1,1-disubstituted

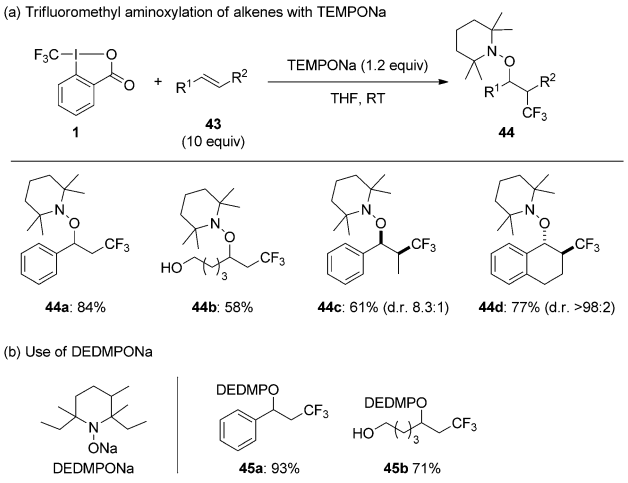


Scheme 14. Oxy-trifluoromethylation of dienes.

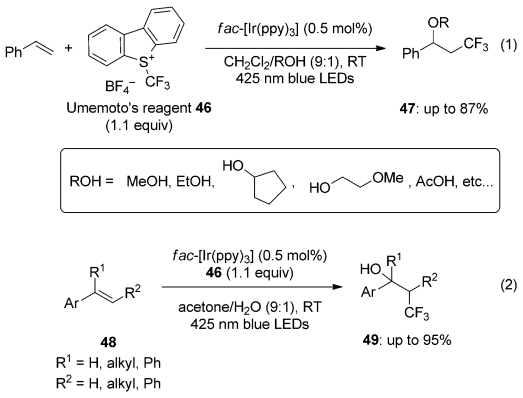
dienes afforded 1,2-oxy-trifluoromethylation products (Scheme 14a). However, the method was not suitable for internal dienes because of low product selectivity. To overcome this limitation, Xu et al. screened the reaction conditions and found that the combination of CuCN and P*t*Bu$_3$ provided the desired 1,4-oxy-trifluoromethylation product with good selectivity (Scheme 14b). For example, 1,4-adduct **42d** was obtained from cyclopentadiene with high diastereoselectivity. Xu and co-workers proposed that the active species was a Cu^{III} intermediate, and that the reaction proceeded via an allylic radical intermediate.

On the other hand, Studer and Li took a unique approach for the trifluoromethylation of alkenes through the addition of a trifluoromethyl radical (Scheme 15).[43] Although Togni's reagent was commonly utilized in the methods of Szabó, Sodeoka, and Buchwald, the trifluoromethyl radical was generated by treatment with TEMPONa, which worked as a single-electron-transfer reagent. Thus, their reaction could provide trifluoromethylated TEMPO adducts, and they called this reaction trifluoromethylaminoxylation. The N–O bond is easily cleaved under reducing conditions, and Studer and Li demonstrated that N–O bond cleavage with zinc in AcOH gave the corresponding alcohol derivatives. The scope of this reaction was broad. This unique approach was not only applicable to terminal alkenes but also to internal alkenes as well as to both conjugated and non-conjugated substrates. It is noteworthy that a higher diastereoselectivity was generally observed in the reaction of internal olefins. In the case of the copper-catalyzed trifluoromethylation reactions, TEMPO completely inhibited trifluoromethylation. However, the above reaction proceeded even though TEMPO would exist as an intermediate in the reaction mixture. The key point is presumably the slow addition of TEMPONa, because a low concentration of the nitroxide may ensure a low concentration of the TEMPO radical and prevent the formation of TEMPO–CF_3 by coupling of the CF_3 radical and the TEMPO radical. In line with this consideration, Studer and Li found that the use of DEDMPONa, which is bulkier than TEMPONa, increased the product yield and selectivity for the cycloaddition of diene substrates (Scheme 15b). More recently, Qing and co-workers also reported the copper-catalyzed three-component aminoxy-trifluoromethylation of alkenes using the Langlois reagent/*tert*-butyl hydroperoxide (TBHP) system[23h,44] and hydroxamic acid.[45]

Akita and Koike et al., who have recently focused on photoredox catalysis, achieved a three-component oxy-trifluoromethylation of C=C bonds using *fac*-[Ir(ppy)$_3$] as the catalyst (ppy = 2-phenylpyridine ; Scheme 16).[46] The choice of the trifluoromethylating reagent was important. Umemoto's reagent was selective for the desired reaction, whereas generation of olefinic side products was observed when Togni's reagent was used. From the viewpoint of the oxygen nucleophile, this reaction offers the broadest scope, and not only acetic acid, but also alcohols and water were successfully introduced into the products. Furthermore, this radical reaction was even applicable to an internal alkene, as was the case with the conditions developed by Studer and Li. Interestingly, instead of under blue LEDs, the reaction



Scheme 15. Oxy-trifluoromethylation with TEMPONa.



Scheme 16. Oxy-trifluoromethylation using photoredox catalysis.

proceeded smoothly under sunlight irradiation. Akita and Koike proposed that the reaction mechanism involves the following steps: 1) excitation of the photoredox Ir catalyst, 2) single electron transfer from the excited Ir complex to Umemoto's reagent, 3) generation of the CF_3 radical; 4) addition of the CF_3 radical to the alkene, 5) one-electron oxidation of the generated carbon-centered radical, and 6) trapping of the carbocation with alcohols or water (Figure 3).

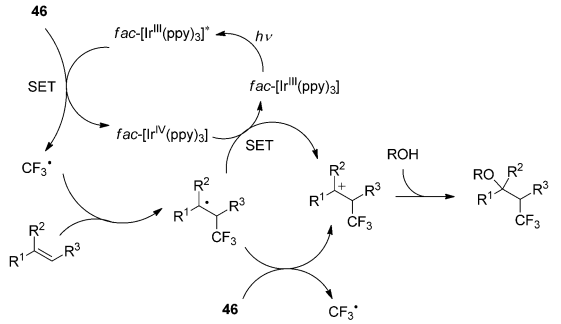
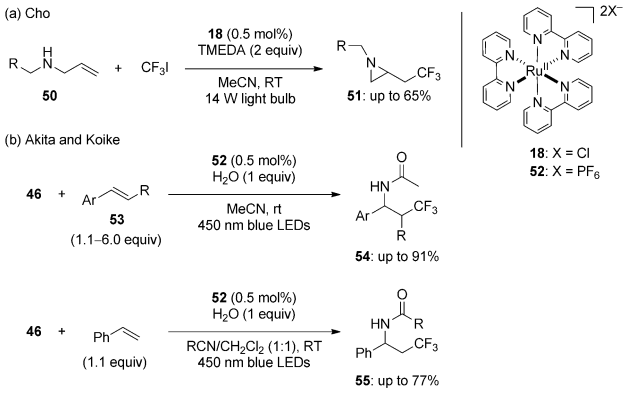


Figure 3. Reaction mechanism proposed by Akita and Koike.

4. Trifluoromethylation with C–N Bond Formation

In 2013, three groups independently accomplished the amino-trifluoromethylation of C=C bonds. In the wake of their trifluoromethylation with C=C[27] and C–O bond formation (see Scheme 8d), Cho and co-workers reported the amino-trifluoromethylation of allyl benzylamine to provide trifluoromethylated aziridines (Scheme 17a).[41] Their

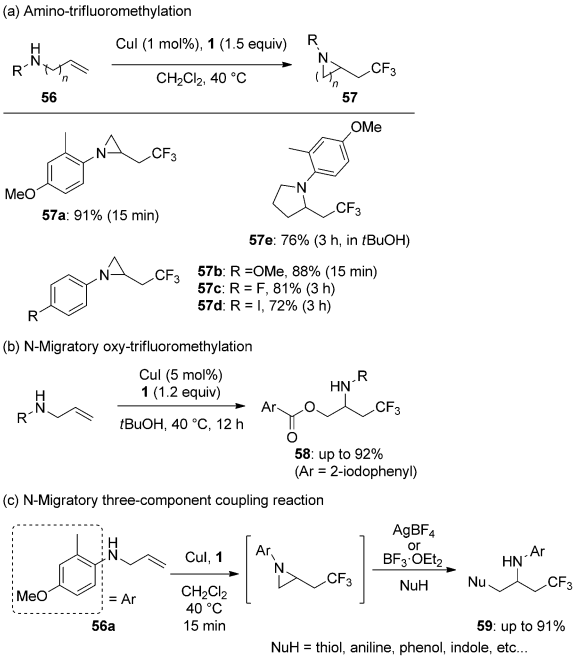


Scheme 17. Amino-trifluoromethylation with photoredox catalysts.

amino-trifluoromethylation is likely to proceed through iodo-trifluoromethylation and ring closure by substitution of the iodide with the amine unit. Unfortunately, the product yields were only moderate because of over-reaction and side reactions.

Akita and Koike reported the amido-trifluoromethylation of styrene derivatives utilizing a Ritter-type reaction (Scheme 17b).[47] Based on their oxy-trifluoromethylation (Scheme 16),[46] they hypothesized that a cationic intermediate generated during the reaction could be trapped by nitrile compounds to yield the corresponding amides after the addition of water. In this reaction system, oxy-trifluoromethylation was considered as an inherent side reaction. Indeed, the normal oxy-trifluoromethylation product was obtained as a major product when an excess amount of water was used. However, the use of one equivalent of water afforded the desired trifluoromethylation products.

Sodeoka and co-workers established an amino-trifluoromethylation of alkenyl amines to provide aziridines and pyrrolidines bearing a trifluoromethyl group and a sequential ring-opening reaction of the aziridines in situ (N-migratory oxy-trifluoromethylation and N-migratory three-component coupling reaction; Scheme 18).[48] The products, β-trifluoro-



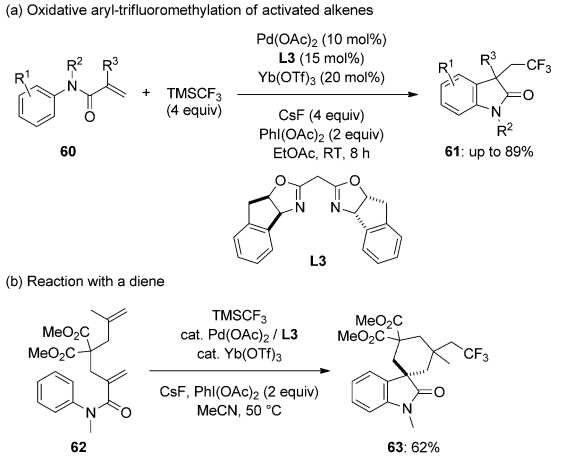
Scheme 18. Amino-trifluoromethylation of alkenyl amines.

methyl-substituted amines, were useful intermediates for the synthesis of bioactive compounds bearing a trifluoromethyl group.[49] Although additional Lewis acid was required for the aziridine ring-opening step in the three-component coupling reaction (except in the case of 2-iodobenzoate addition), good to high yields of the desired products were obtained (Scheme 18c). It is noteworthy that various nucleophiles, such as thiol, aniline, phenol, and indole, could be employed in this reaction.

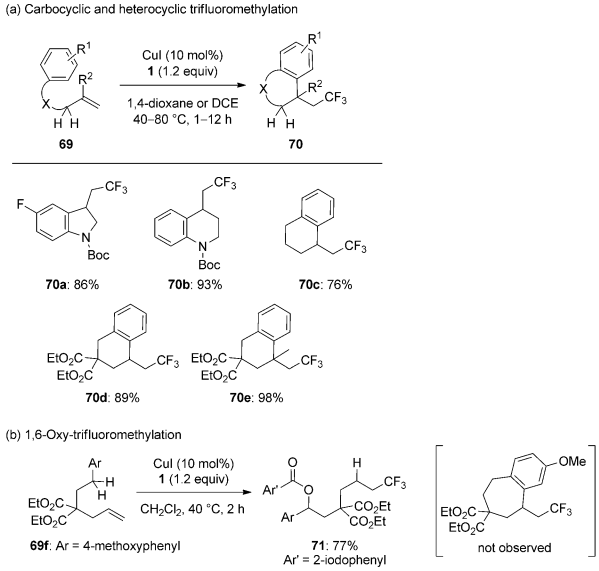
5. Trifluoromethylation with C–C Bond Formation

5.1. Construction of Carbocycles and Heterocycles

In early 2012, Liu and co-workers achieved the palladium/ytterbium-catalyzed aryl-trifluoromethylation of acrylanilide



Scheme 19. Carbo-trifluoromethylation under oxidative conditions.



Scheme 20. Carbo-trifluoromethylation of simple alkenes.

derivatives with $TMSCF_3$/CsF/$PhI(OAc)_2$.[50] This reaction afforded oxindoles with a trifluoromethyl group in good to high yields (Scheme 19). The scope of this reaction was broad, and various functional groups were tolerated. It is noteworthy that the spiro-oxindole derivative **63** was obtained in 62% yield as a single diastereomer from diene **62** under these conditions. The mechanism was well investigated by using deuterated substrates, ESI-MS analysis, and ^{19}F NMR spectroscopy. No kinetic isotope effect was observed for the intermolecular or intramolecular reaction. Furthermore, when a standard substrate and a substrate with an electron-donating or -withdrawing group were subjected to a competitive reaction, the corresponding products were formed in a ratio of 1:1. The results of these competitive reactions and the intermolecular kinetic isotope effect clearly suggest that the rate-determining step is not the C–H bond cleavage. The intramolecular kinetic isotope effect implies that C(Ar)–C(sp^3) bond formation may proceed through electrophilic aromatic substitution. Their proposed mechanism is illustrated in Figure 4. Intermediates **65** and **68** were detected by ESI-MS analysis, and intermediate **68** was also identified in a stoichiometric reaction by ^{19}F NMR spectroscopy. These findings are consistent with the data on aryl–Pd^{IV}–CF_3 species reported by Sanford and co-workers.[51]

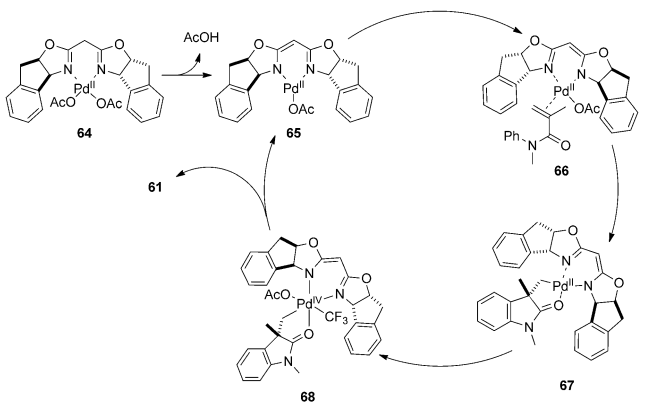
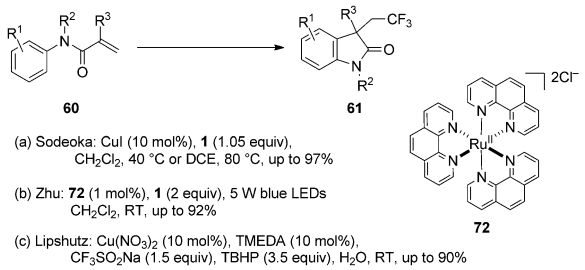


Figure 4. Reaction mechanism proposed by Liu.

The trifluoromethylation of simple alkenes with allylic protons, coupled with intramolecular C(Ar)–C(sp^3) bond formation, was reported by Sodeoka and co-workers in early 2013 (Scheme 20).[52] It is well known that trifluoromethylated allylic compounds are usually produced when simple alkenes bearing allylic protons are exposed to oxidative trifluoromethylation conditions (Scheme 1). Sodeoka and co-workers found that the choice of catalyst and solvent was very important for selective product switching, and the combination of a non-polar solvent and CuI as the catalyst afforded the desired carbo-trifluoromethylation products. Various functional groups were tolerated under these reaction conditions, and good to high yields were obtained. Reactions that lead to the formation of five- or six-membered rings proceeded smoothly.[53] Trifluoromethylation with formation of a seven-membered ring did not proceed, and 1,6-oxy-trifluoromethylation, which may occur through a 1,5-hydride shift, was observed instead of cyclization (Scheme 20b). The reaction rate of the formation of a six-membered ring was faster than for the formation of a five-membered ring. Based on these phenomena, it appears that the interaction between aryl ring and alkene is crucial for the reactivity and selectivity of this trifluoromethylation.

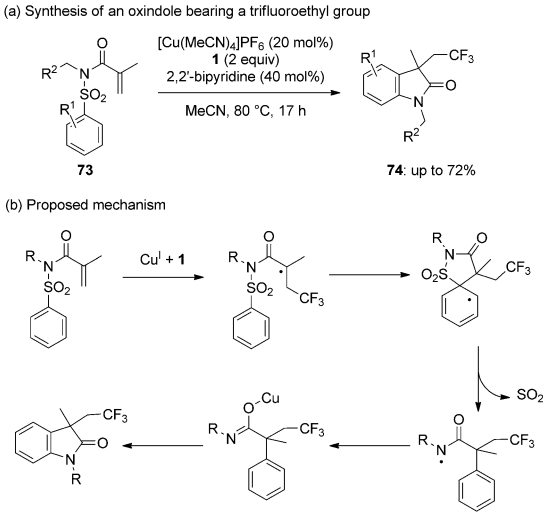
Using this reaction system, Sodeoka and co-workers also demonstrated the trifluoromethylation of acrylanilides with simultaneous construction of oxindole frameworks (Scheme 21a).[54] Liu et al. reported that oxindoles were not obtained when a palladium catalyst was used with Togni's or Umemoto's reagent,[50] whereas Sodeoka and co-workers found that copper iodide worked as an efficient catalyst for the desired reaction. This concise method generally provided oxindole derivatives bearing a 3-trifluoroethyl group in high to excellent yields, and various functional groups could tolerate the reaction conditions, as was the case with Liu's method. Later, Zhu and co-workers disclosed a similar



Scheme 21. Carbo-trifluoromethylation for the synthesis of oxindole derivatives using Togni's reagent.

reaction using the photoredox catalyst $[Ru(phen)_3]Cl_2$ (**72**) instead of a copper salt (Scheme 21 b),[55] and Lipshutz et al. reported a copper-catalyzed reaction using the combination of Langlois reagent and TBHP on water (Scheme 21 c).[56]

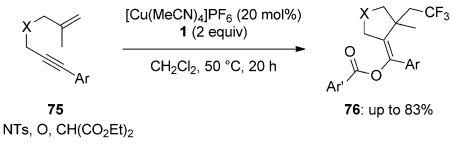
Nevado et al. recently demonstrated a trifluoromethylation coupled with a desulfonylative aryl migration/cyclization (Scheme 22 a).[57] Even though the trifluoromethylation of 3-



Scheme 22. Trifluoromethylation with desulfonylative aryl migration/cyclization.

substituted acrylanilides usually provides a mixture of 4- and 6-substituted oxindole derivatives, Nevado's method afforded a 6-substituted oxindole as the single product. Therefore, this trifluoromethylation could be a complementary method for the synthesis of 6-substituted oxindole derivatives. A major limitation of this method was the fact that the reaction afforded *N*-alkyl oxindoles (Scheme 26). The proposed reaction mechanism is shown in Scheme 22 b. The mechanism involves: 1) radical generation after $C-CF_3$ bond formation, 2) 5-*ipso* cyclization, 3) desulfonylation, 4) oxidation of the amidyl radical intermediate, and 5) formation of the oxindole framework (Scheme 22 b). More recently, the same authors revealed that an iodonium ion could function as the catalyst for these types of reactions.[58]

Liang and co-workers reported the trifluoromethylation of 1,6-enynes (Scheme 23).[59] This reaction provided carbo-

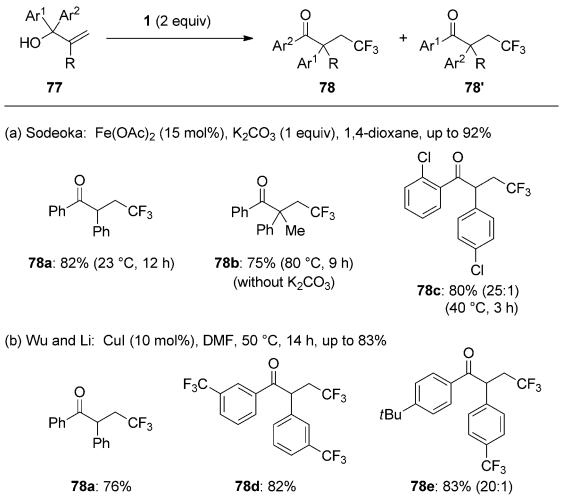


Scheme 23. Trifluoromethylation of 1,6-enynes.

cycles and heterocycles bearing a trifluoroethyl group on a quaternary carbon center and a vinyl ester moiety. Although the details of the reaction mechanism remain unclear, this trifluoromethylation may involve a carbocyclization triggered by trifluoromethylation and trapping of a vinyl cation equivalent by iodobenzoate.

5.2. Construction of β-Trifluoromethylated Carbonyl Compounds

Sodeoka and co-workers also achieved a carbo-trifluoromethylation with concomitant $C(sp^3)-C(Ar)$ bond formation by 1,2-migration of an aryl group.[60] In this reaction, α-substituted β-trifluoromethylated carbonyl compounds, which are important for the synthesis of bioactive compounds,[61] were successfully prepared from diaryl allylic alcohols with high efficiency (Scheme 24 a). It was found that iron(II) acetate was a better catalyst than copper ions, and that K_2CO_3 accelerated the reaction. In contrast to other trifluoromethylations, the reaction rate was faster for substrates with an electron-withdrawing group on the aryl ring than for substrates with an electron-donating group. In fact, an aryl ring bearing an electron-withdrawing group was a better migration unit, and selective migration was observed in the reaction of unsymmetric substrates. These results may be consistent with a free-radical-mediated neophyl rearrangement.[62] Furthermore, *ortho* substituents retarded aryl migration, probably because of steric hindrance. The product of alkyl-group migration could not be detected in the reaction of aryl–alkyl allylic alcohols. Based on these results, it is likely

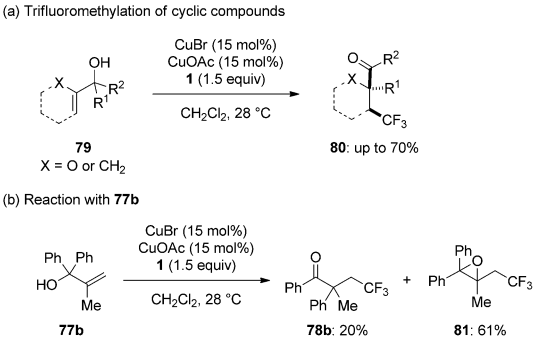


Scheme 24. Trifluoromethylation by 1,2-aryl migration.

that this reaction proceeds through a non-cationic intermediate with radical character.

Wu, Li, and co-workers independently studied the trifluoromethylation of α,α-diaryl allylic alcohols with radical 1,2-aryl migration (Scheme 24b).[63] After screening of the reaction conditions, they decided to use CuI as a catalyst in DMF. Wu et al. reported the trifluoromethylation of not only symmetric, but also unsymmetric substrates, and high selectivities were observed with unsymmetric substrates under their conditions. They also concluded that this reaction proceeded through a neophyl rearrangement after addition of the trifluoromethyl radical generated from Togni's reagent.

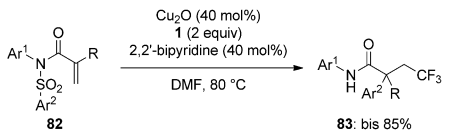
On the other hand, Tu and co-workers reported a copper-catalyzed trifluoromethylation with subsequent semipinacol rearrangement (Scheme 25).[64] The key feature of this work is



Scheme 25. Trifluoromethylation of cyclic alkenes by 1,2-rearrangement.

the use of dihydropyran derivatives. Interestingly, they found that the combination of CuOAc and CuBr provided better results than the use of either CuOAc or CuBr alone. Under Tu's conditions, the reaction of **77b** afforded epoxide **81** as the major product in 61% yield together with 20% of **78b** (Scheme 25b). In the reaction of unsymmetric substrates, an aryl group with an electron-withdrawing group migrated to provide the corresponding product. Based on their results, Tu et al. suggested that the reaction pathway depended on the substrate, and that the reactions of substrates with two aromatic rings proceeded through radical 1,2-migration (neophyl rearrangement).

While studying the trifluoromethylation through desulfonylative aryl-group migration (Scheme 22), Nevado and co-workers observed that α-aryl-β-trifluoromethyl amide derivatives were obtained when **82** bearing an *N*-aryl group was used (Scheme 26).[57] The authors concluded that the key factor for product selectivity is favorable hydrogen-atom

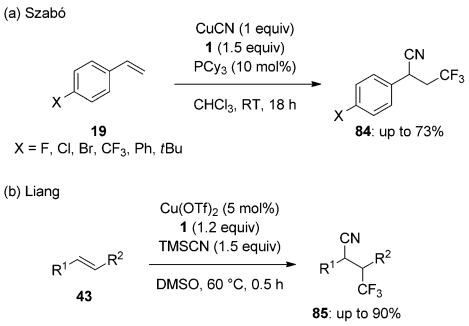


Scheme 26. Trifluoromethylation by desulfonylative aryl migration.

abstraction from the reaction medium when the substituent on the nitrogen atom is an aryl group.

5.3. Construction of β-Trifluoromethylated Nitriles

Cyano-trifluoromethylation of styrene derivatives using a stoichiometric amount of CuCN was achieved by Szabó and co-workers (Scheme 27a).[65] This reaction was efficient for substrates bearing an electron-withdrawing group on the aryl ring, and good yields were obtained. However, *para*-methoxystyrene, which is an electron-rich substrate, provided the oxytrifluoromethylation product. Very recently, a catalytic version of the cyano-trifluoromethylation using trimethylsilyl cyanide as the cyanide source was reported by Liang et al. (Scheme 27b).[66] Interestingly, this reaction could not only be successfully applied to styrene derivatives, but also to aliphatic alkenes.

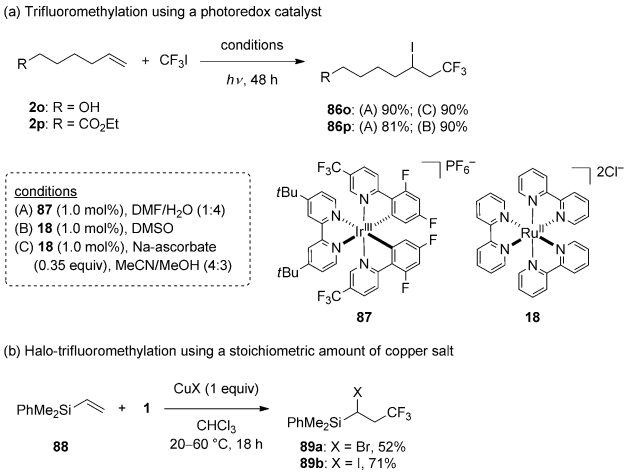


Scheme 27. Cyano-trifluoromethylation.

6. Trifluoromethylation with C–X Bond Formation

Halo-trifluoromethylation has been of interest for a long time, and the main focus of research on this difunctionalizing trifluoromethylation has been on atom-transfer radical reactions.[7] Representative methods for the generation of a trifluoromethyl radical are the use of CF_3I/photoirradiation, CF_3I/Me_3Al, CF_3I/Et_3B/air, and $CF_3SO_2Cl/[RuCl_2(PPh_3)_3]$ systems.[18,67] The products were utilized for further transformations. For example, an iodo-trifluoromethylation intermediate has been transformed in situ into an oxy-trifluoromethylation product by addition of an oxygen nucleophile to the C–X bond,[33,41] whereas hydrogenation conditions afforded trifluoromethylated alkanes.[67a,g]

In 2011, Stephenson and co-workers described the iodo-trifluoromethylation of simple alkenes using a combination of CF_3I and a photoredox Ir or Ru catalyst under visible-light irradiation during their work on atom-transfer radical additions (Scheme 28a).[28] From the viewpoint of green chemistry, the use of photoirradiation, especially sunlight, is a topic of growing interest. Photoredox catalysts have already been in use for trifluoromethylation reactions, but this was the first report of an iodo-trifluoromethylation of alkenes using a photoredox catalyst.



Scheme 28. Halo-trifluoromethylation of alkenes.

During their study on oxy-trifluoromethylation, Szabó et al. observed a halo-trifluoromethylation reaction of vinylsilane substrates (Scheme 11 a).[37] Although a stoichiometric amount of CuI or CuBr was required, and the substrates were limited to vinylsilanes, this reaction provided potent synthetic units (Scheme 28 b).

7. Conclusion

In this review, we have focused on recent progress in the trifluoromethylation of alkenes. Many powerful methods have recently been discovered, including deprotonative trifluoromethylation, oxy-trifluoromethylation, amino-trifluoromethylation, carbo-trifluoromethylation, and halo-trifluoromethylation. These methods serve to introduce a trifluoromethyl group into organic frameworks simultaneously with an additional functional group at the β-position of the trifluoromethyl group. Strategies for these reactions have mainly involved the use of electrophilic trifluoromethylation reagents,[68] oxidative reactions with nucleophilic trifluoromethylation reagent, and photoredox-catalyzed reactions generating a trifluoromethyl radical. In particular, the development of electrophilic trifluoromethylation reagents, such as Togni's reagents[13] and Umemoto's reagents,[14] has contributed enormously to the recent progress in this area, even though the real active species and reaction pathways remain to be established in most cases. Therefore, thorough mechanistic studies are needed to establish the reactivity and selectivity of these reaction systems and to expand their synthetic utility. We believe that these reactions will contribute to the development of novel pharmaceuticals and agrochemicals. Other methods for the trifluoromethylation of alkenes are still required to construct new frameworks with a trifluoromethyl group.

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