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Carbotrifluoromethylations of C–C Multiple Bonds (Excluding Aryl- and Alkynyltrifluoromethylations)

Klára Aradi[a] and Loránd Kiss*[a]

Abstract: Organofluorine chemistry has become an expanding area of research in organic chemistry and drug design. The synthesis of fluorine-containing molecules has received high significance in synthetic chemistry. Trifluoromethylative difunctionalizations of carbon-carbon multiple bonds with the simultaneous introduction of a CF_3 group and another function have considerable relevance. Because of the high importance of carbon-carbon bond-forming reactions in organic synthesis, carbotrifluoromethylations are considered to be a field of synthetic chemistry of increasing importance. Our current goal in this review is to summarize recent developments of various trifluoromethylation reactions (excluding aryl- and alkynyl-trifluoromethylations) taking into consideration several main approaches, such as alkenyltrifluoromethylation, alkyltrifluoromethylation, carbonyltrifluoromethylation, and cyanotrifluoromethylation reactions.

1. Introduction

The number of fluorine-containing drugs has been increasing continuously during the past decade,[1] as the introduction of fluorine into a chemical scaffold can affect the physicochemical and biological properties of a molecule.[2] The replacement of the C–H unit with a C–F unit in an organic compound can provide several advantages as shown, for example, in the case of *ezetimibe* and *cabotegravir* pharmaceuticals (Figure 1).[2,3] Since fluorine is the most electronegative element (EN = 3.98), it can change the polarity (lipophilicity/hydrophilicity balance) and the acid-base properties of a molecule. In addition, as the C–F bond is the strongest bond that carbon can form, the metabolic stability of fluoro-pharmaceuticals is often increased. It is important to mention that these beneficial effects, including improved bioactivity, bioavailability, and increased affinity, can be reached without drastically changing the parent structure, as fluorine is the second smallest atom after hydrogen (van der Waals radii: 1.47 Å for fluorine, 1.20 Å for hydrogen).[1,2,3]

Amongst the fluorinated pharmaceuticals, a significant part contains the trifluoromethyl group (CF_3). This group has high lipophilic and electron-withdrawing character; moreover, it is quite bulky and usually has good chemical stability.[4] Therefore, the introduction of the CF_3 group into biological molecules has promising metabolic effects.[5] Thanks to all these properties, trifluoromethylated (hetero)arenes are the second most common fluorinated motifs in drugs.[3,6] However, the development of new chemical entities including the aliphatic CF_3 group in the appropriate drug molecule has been still an ongoing challenge of organic syntheses.[5] As a consequence, only a limited number of drug molecules has been reported with trifluoromethylated non-aromatic systems (sp, sp^2, sp^3 carbon) (Figure 2).[3,5]

The synthesis of these compounds can be achieved by the employment of different trifluoromethylating reagents (Figure 3) having electrophilic, nucleophilic or radical character, concerning their reactivity in a given chemical process. Nevertheless, it is important to note that single-electron transfer (SET) reactions can generate CF_3 radicals from both electrophilic and nucleophilic trifluoromethylating agents.[4,5,7]

Beyond the construction of organic compounds bearing the CF_3 moiety, the simultaneous incorporation of a CF_3 group and another function to carbon-carbon multiple bonds is an area of high research interest of recent organic syntheses. The relevance of this strategy is, that via difunctionalization of alkenes and alkynes, complex architectural molecules can be constructed due to the synthetic versatility of these approaches.

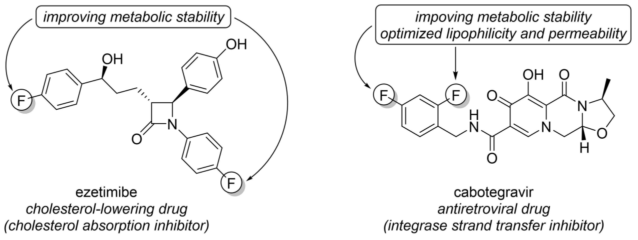

Figure 1. Fluoro-pharmaceuticals: benefits of fluorination in *ezetimibe* and *cabotegravir*.

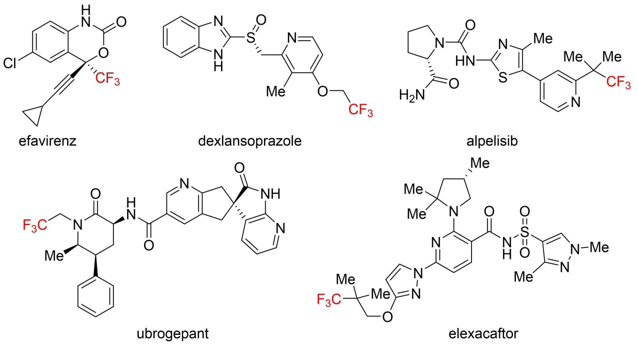

Figure 2. Structures of aliphatic Csp^3-CF_3-containing drugs.

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The trifluoromethyl group is usually introduced together with a heteroatom, but various carbotrifluoromethylation reactions (Scheme 1) were reported, too.[8] In these transformations, beyond the installation of the CF_3 group, the introduction of sp^2, sp, and sp^3 carbon atoms were all achieved via aryltrifluoromethylation, alkenyltrifluoromethylation, acyltrifluoromethylation, alkynyltrifluoromethylation, alkyltrifluoromethylation, and cyanotrifluoromethylation reactions.

Carbotrifluoromethylations concerning aryl- and alkynyltrifluoromethylation reactions of carbon-carbon multiple bonds were recently summarized and published by our research group.[8g,h] Therefore, our aim in this review is to collect the most important carbotrifluoromethylation reactions of alkenes and alkynes since 2013, in which the CF_3 group is introduced together with alkenyl, alkyl, carbonyl, and cyano groups.

Loránd Kiss completed his Ph.D. in 2002 in the Department of Organic Chemistry at the Faculty of Sciences, Debrecen University (Debrecen, Hungary) under the supervision of Prof. Sándor Antus. In 2003, he joined the research group of Prof. Ferenc Fülöp at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), where he started working in the area of cyclic β-amino acid chemistry. He followed postdoctoral research in the laboratories of Prof. Norbert De Kimpe at Ghent University (Ghent, Belgium), and Prof. Santos Fustero, University of Valencia. He is currently head of the Stereochemistry Research Group and director of the Institute of Organic Chemistry, Research Center for Natural Sciences (Budapest). His scientific interest is directed towards the selective functionalization unnatural amino acid derivatives and on the synthesis of highly functionalized fluorinated small molecular entities.

Klára Aradi was, born in 1989 in Budapest Hungary. She obtained a degree in pharmaceutical engineering at Budapest University of Technology and Economics in 2013. She completed her Ph.D. in 2016 at Eötvös Loránd University, Department of Organic Chemistry (Budapest, Hungary) under the supervision of Prof. Novák Zoltán. In 2017 and 2018, she was a postdoctoral researcher at University Paris Descartes in the group of Dr. Peter I. Dalko (Paris, France), then at University of Nice Sophia Antipolis in the group of Dr. Maria Duca (Nice, France). Since 2022 she has been working as a research fellow at Research Centre for Natural Sciences, Institute of Organic Chemistry (Budapest, Hungary). Her current research field has focused mainly on fluorine incorporation and selective functionalization of βamino acid derivatives.

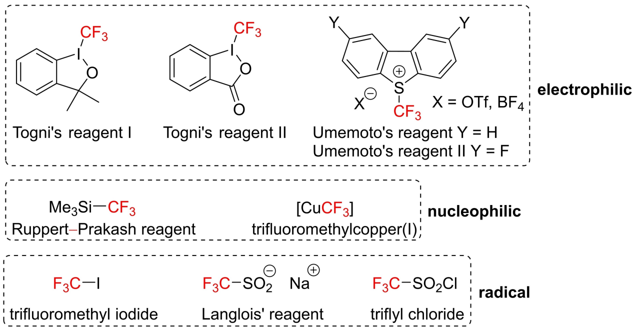
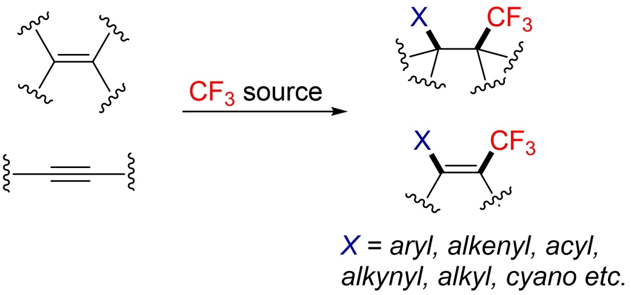
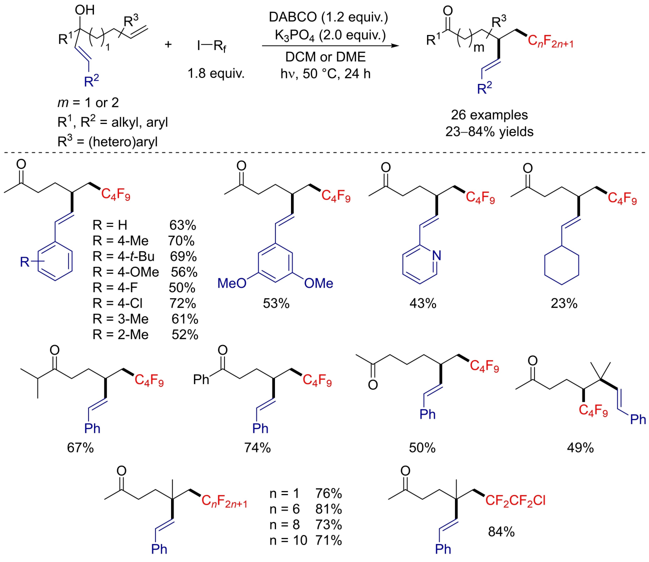


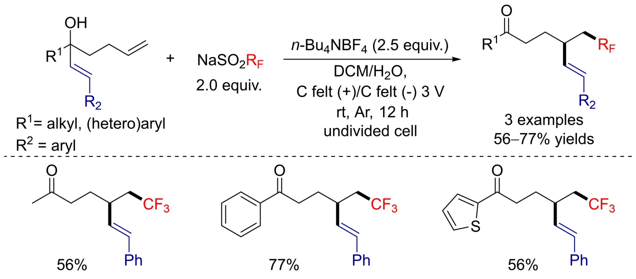
Figure 3. Commonly utilized trifluoromethylation reagents.



Scheme 1. Carbotrifluoromethylation of alkenes and alkynes.



Scheme 2. Perfluoroalkylation and β-alkenylation of allylic alcohols.



Scheme 3. Trifluoromethyl-alkenylation of olefins with Langlois' reagent.

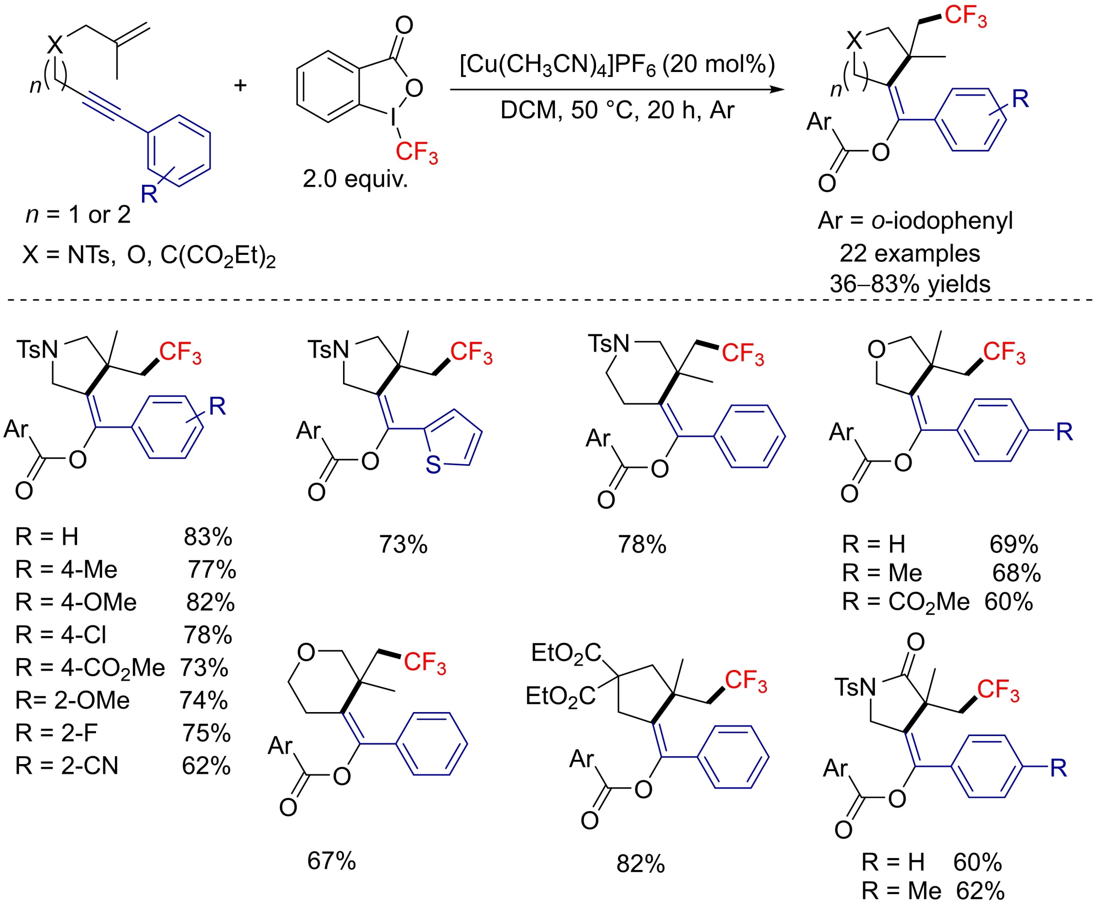
2. Alkenyltrifluoromethylation Reactions

2.1. Alkene functionalization

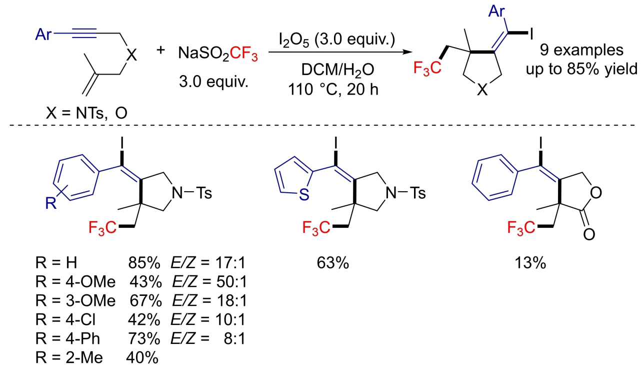
2.1.1. Reactions involving intramolecular alkenyl migration

In the last decade, two approaches have been elaborated for the alkenyltrifluoromethylation reactions of the carbon-carbon double bond involving intramolecular alkenyl migration. In 2018, Studer et al. developed a new, transition-metal-free method for the radical α-perfluoroalkylation of unactivated alkenes with accompanying β-alkenylation with the utilization of different perfluoroalkyl iodides, 1,4-diazabicyclo[2.2.2]octane (DABCO), and K_3PO_4 as base.[9] Aryl, heteroaryl, and cycloalkyl groups were all tolerated as substituents of the alkenyl moiety and the desired products were obtained in 23–84% yields (Scheme 2). Considering the mechanism of the reaction, after the construction of an unstrained cyclic intermediate via 5-*exo* or 6-*exo* cyclization from allylic alcohols, the radical cascade involves 1,4- or 1,5-alkenyl migration via SET providing the corresponding products.

One year later, Wang[10] and co-workers reported the electrochemically promoted (hetero)aryltrifluoromethylation of alkenes affording fluorinated (hetero)aryl ketones in the absence of a strong oxidant or a metal catalyst. Langlois' reagent or its CF_2H analogue ($NaSO_2CF_2H$) and tetrabutylammonium tetrafluoroborate (n-Bu_4NBF_4) were employed in the developed procedure and the desired products were synthesized in good yields with excellent regioselectivities. Beside aryltrifluoromethylation, alkenyltrifluoromethylation of the corresponding alkenes was also realized three examples in 56–77% yields (Scheme 3). According to the proposed mechanism, the reaction involves the formation of a cyclic nitrogen radical intermediate, generated from the CF_3 radical via anodic oxidation and addition of the tertiary alcohol. Then, fast ring opening followed by β-radical cleavage and another anodic



Scheme 4. Copper-catalyzed carbotrifluoromethyl-alkenylation of enynes.



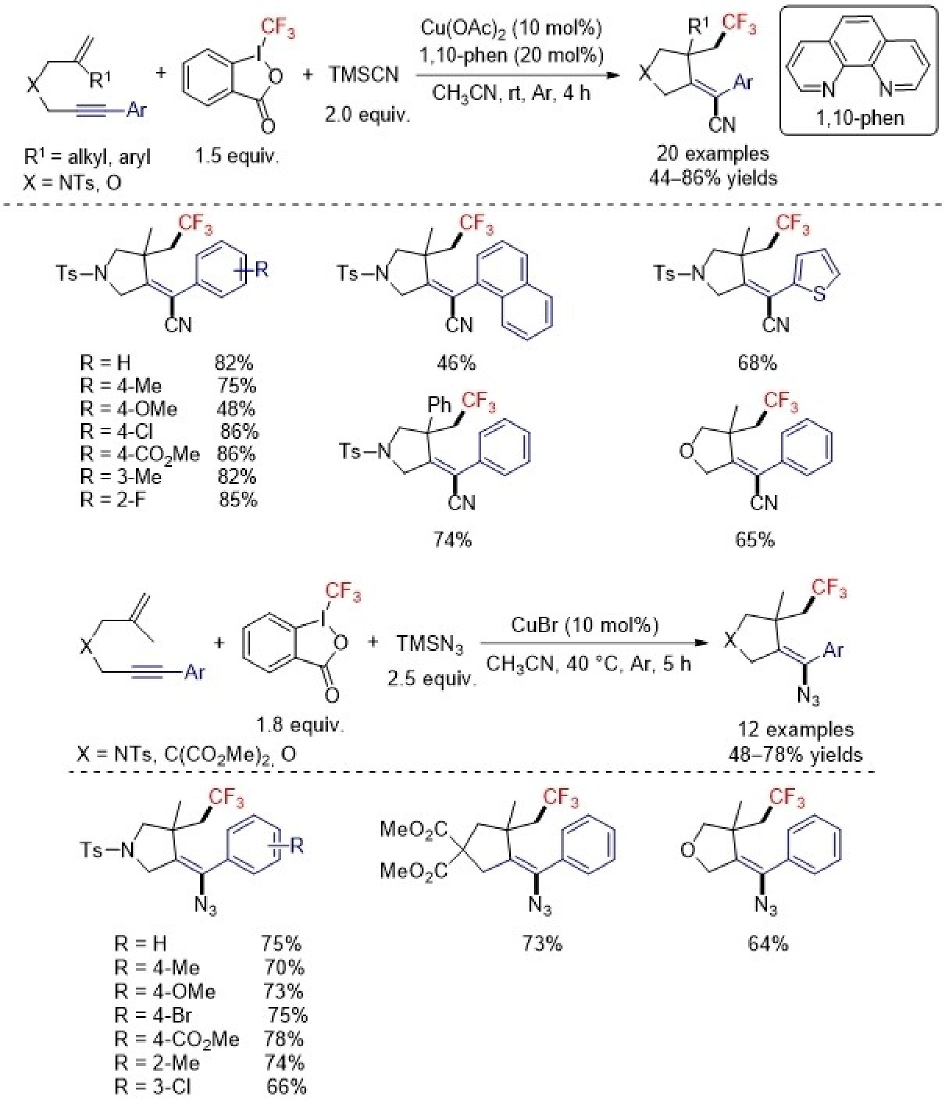
Scheme 5. I_2O_5-mediated trifluoromethylation-cyclization of enynes.

oxidation provides a carbocation, resulting in the final product after deprotonation.

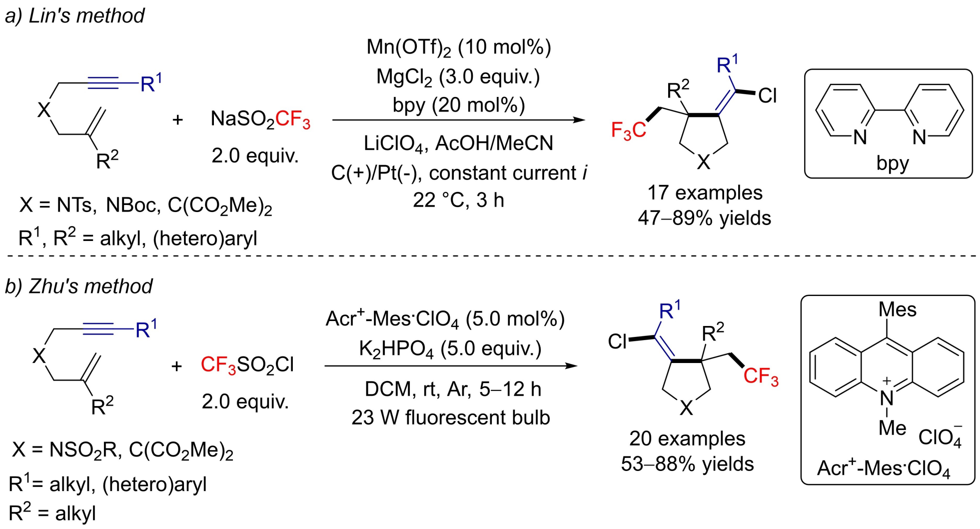
2.1.2. Intramolecular cyclizations

In the last decade, several carbotrifluoromethylation-alkenylation methodologies have been developed for the construction of diverse heterocyclic systems utilizing enynes as starting materials. Considering 1,*n*-enynes as radical acceptors, significant achievements have been made in the last ten years for 1,*n*-enyne-cyclizations triggered by carbon-, nitrogen-, and oxygen-centered radicals for the preparation of carbo- and heterocycles.[11]

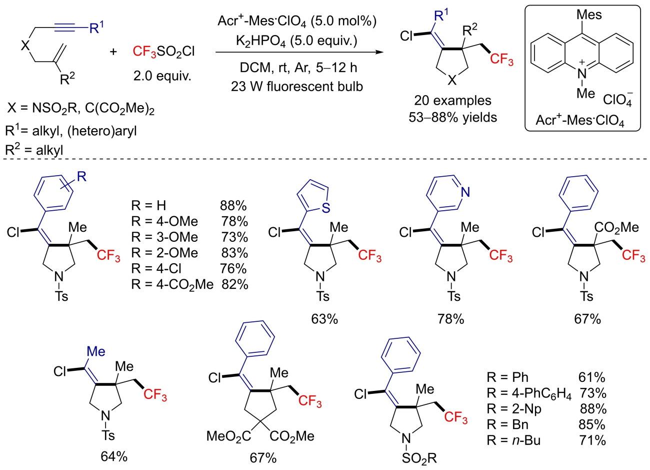
In 2013, Liang[12] and co-workers demonstrated the copper-catalyzed trifluoromethylation-cyclization of 1,6- and 1,7-enynes with Togni's reagent for the formation of trifluoromethylated carbocycles and heterocycles (Scheme 4). Aryl and heteroaryl substituents attached to the alkyne moiety were both tolerated in these transformations; however, no product was obtained when alkynes bearing a methyl or pyridyl group were employed



Scheme 6. Cyanotrifluoromethylation/Azidotrifluoromethylation and carbocyclization of 1,6-enynes.



Scheme 7. Electrocatalytic radical ene-yne cyclization for the synthesis of chlorotrifluoromethylated pyrrolidines.

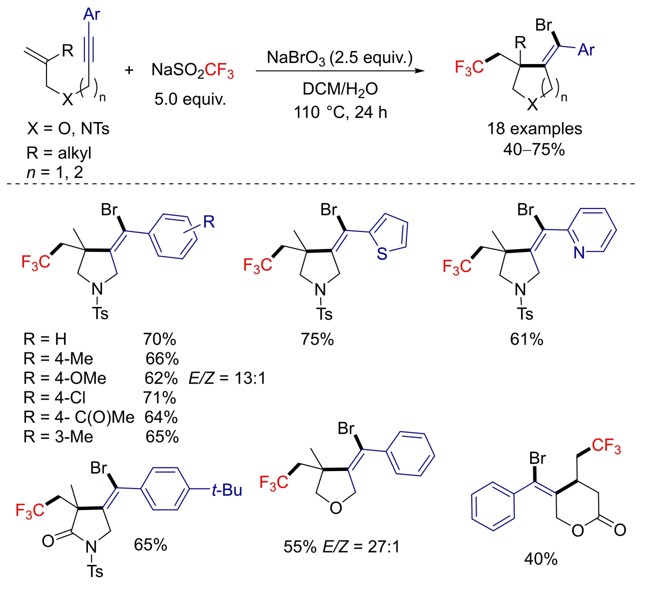


Scheme 8. Photocatalytic alkenyltrifluoromethylation of 1,6-enynes with triflyl chloride.

as starting materials. Regarding the plausible mechanism, the desired products were afforded via 5-*exo-dig* cyclization.

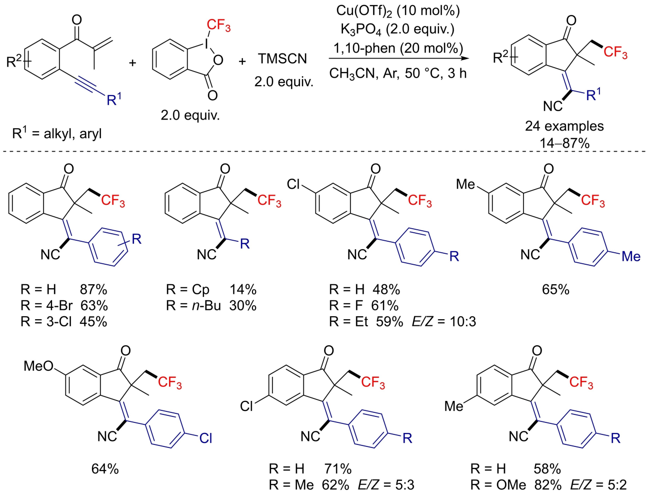
One year later another trifluorometylation-alkenylation approach was achieved by Liu[13] et al. for the synthesis of CF_3-containing pyrrolidines from enynes. Compared to Liang's method,[12] this transformation was realized in the absence of a transition metal and peroxide. Specifically, they worked with the Langlois reagent and I_2O_5 (Scheme 5). The appropriate products were isolated in yields up to 85%. The developed protocol was also extended for *N*-arylmethacrylamide substrates providing oxindoles as products of the aryltrifluoromethylation reaction. Concerning the mechanism of the transformations, in both cases, the expected skeletons are formed via a free-radical 5-*exo-dig* cyclization.

In the same year, the Liang group[14] reported another copper-catalyzed trifluoromethylation and carbocyclization reaction of the same 1,6-enynes in which cyano or azido

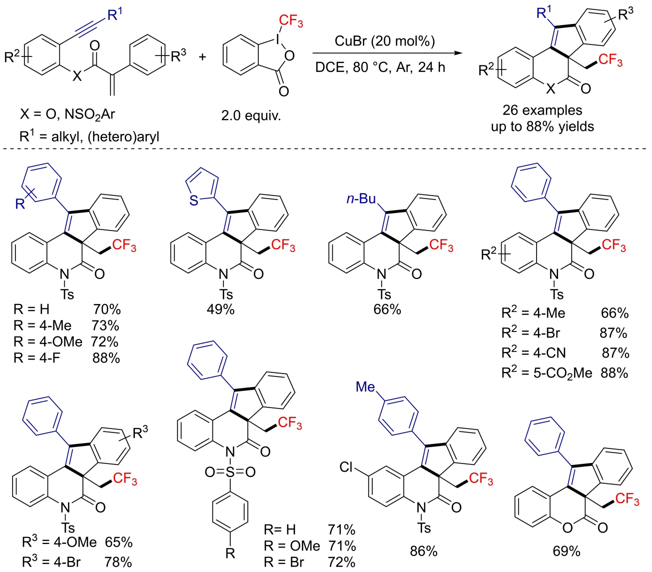


Scheme 9. $NaBrO_3$-mediated bromotrifluoromethylation of enynes.

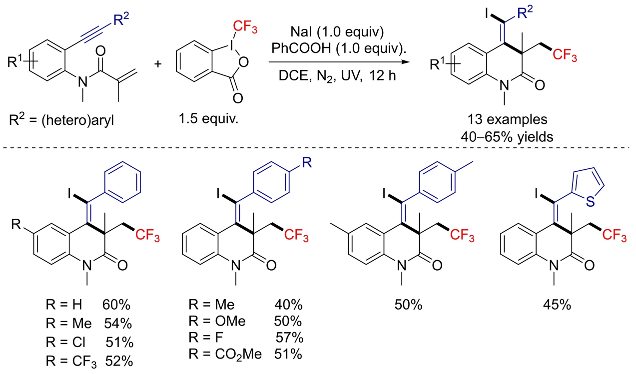
functional groups were also built into the cycloaddition products. In both transformations Togni's reagent served as the CF_3 source, and trimethylsilyl cyanide (TMSCN), $Cu(OAc)_2$, and 1,10-phenanthroline as ligand were utilized in the first (Scheme 6), whereas trimethylsilyl azide ($TMSN_3$) and CuBr were employed in the second protocol (Scheme 6). A broad substrate scope was presented with high functional-group tolerance leading to the desired alkenyl-trifluoromethylated products in good yields via 5-*exo-dig* cyclization. One year later, they extended the developed strategy to iododifluoromethylation involving the radical palladium-catalyzed carbocyclization of 1,6-enyne substrates in the presence of ethyl difluoroiodoacetate (ICF_2CO_2Et) for the construction of iodo-difluorinated pyrrolidines.[15]



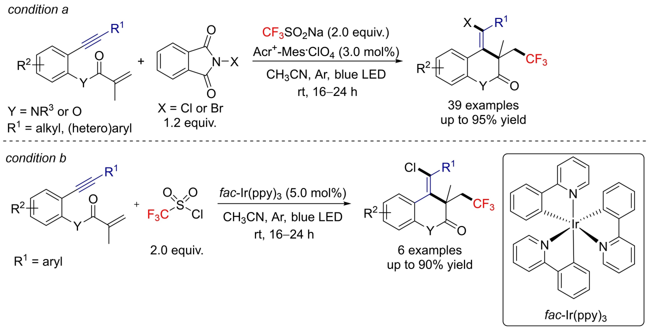
Scheme 10. Copper-catalyzed annulation-cyanotrifluoromethylation of 1,6-enynes.



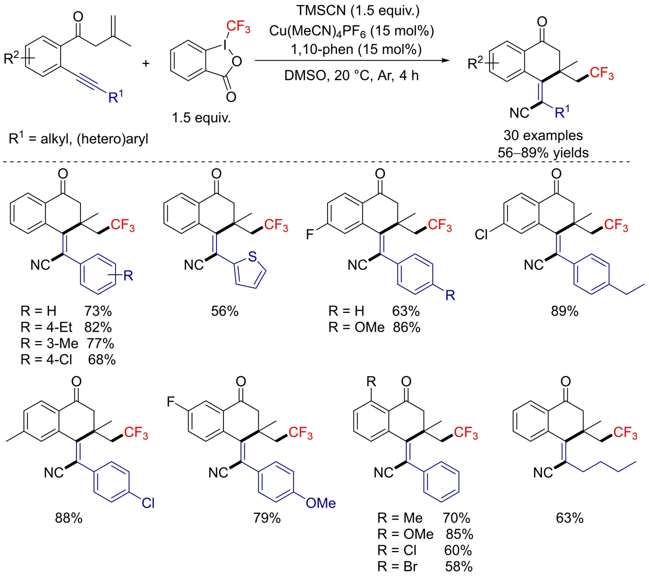
Scheme 11. Copper-catalyzed trifluoromethylation/bicyclization of 1,7-enynes.



Scheme 12. Photoinduced radical cyclization of benzene-tethered 1,7-enynes for the construction of trifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones.

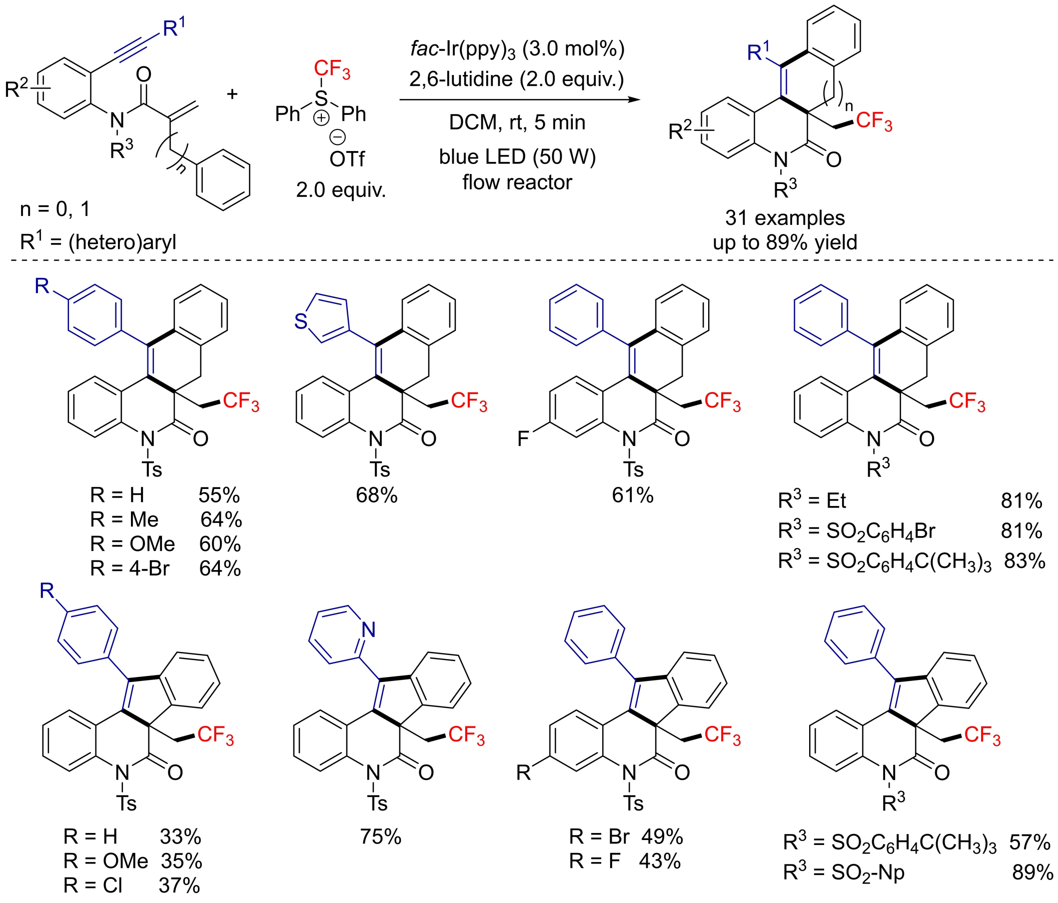


Scheme 13. Photoredox-catalyzed chloro- and bromo-trifluoromethylation of 1,7-enynes.

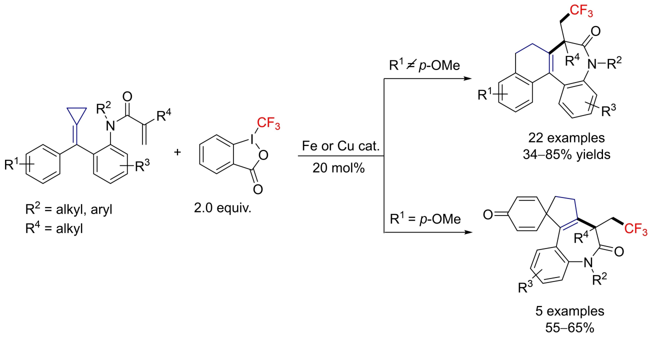


Scheme 14. Copper-catalyzed cyanotrifluoromethylation of 1,7-enynes.

In 2018, the stereoselective synthesis of chlorotrifluoromethylated pyrrolidines was described by Lin[16] et al. using anodically coupled electrolysis with 1,6-enyne substrates, employed in procedures described previously.[12–15] The reaction was performed in the presence of Langlois' reagent, $MgCl_2$, $Mn(OTf)_2$, and 2,2'-bipyridyl ligand (bpy), resulting in the observed stereoselectivity, namely, formation of the *Z* isomeric products in 47–89% yields (Scheme 7a). In addition, a visible-light-driven cyclization methodology for the construction of the same chlorotrifluoromethylated pyrrolidines from enynes and triflyl chloride (CF_3SO_2Cl) reagent was also published one year later by Zhu[17] and co-workers. In this procedure, 9-mesityl-10-methylacridinium perchlorate (Acr^+-Mes·ClO_4) as catalyst was applied with K_2HPO_4 as base, and the *Z* isomers of the corresponding products were obtained in 53–89% yields (Scheme 7b and Scheme 8). According to the plausible mecha-



Scheme 15. Visible-light-induced trifluoromethylation/cyclization of 1,7-enynes for the synthesis of benzo[*j*]phenanthridines and indeno[1,2-*c*]quinolones.



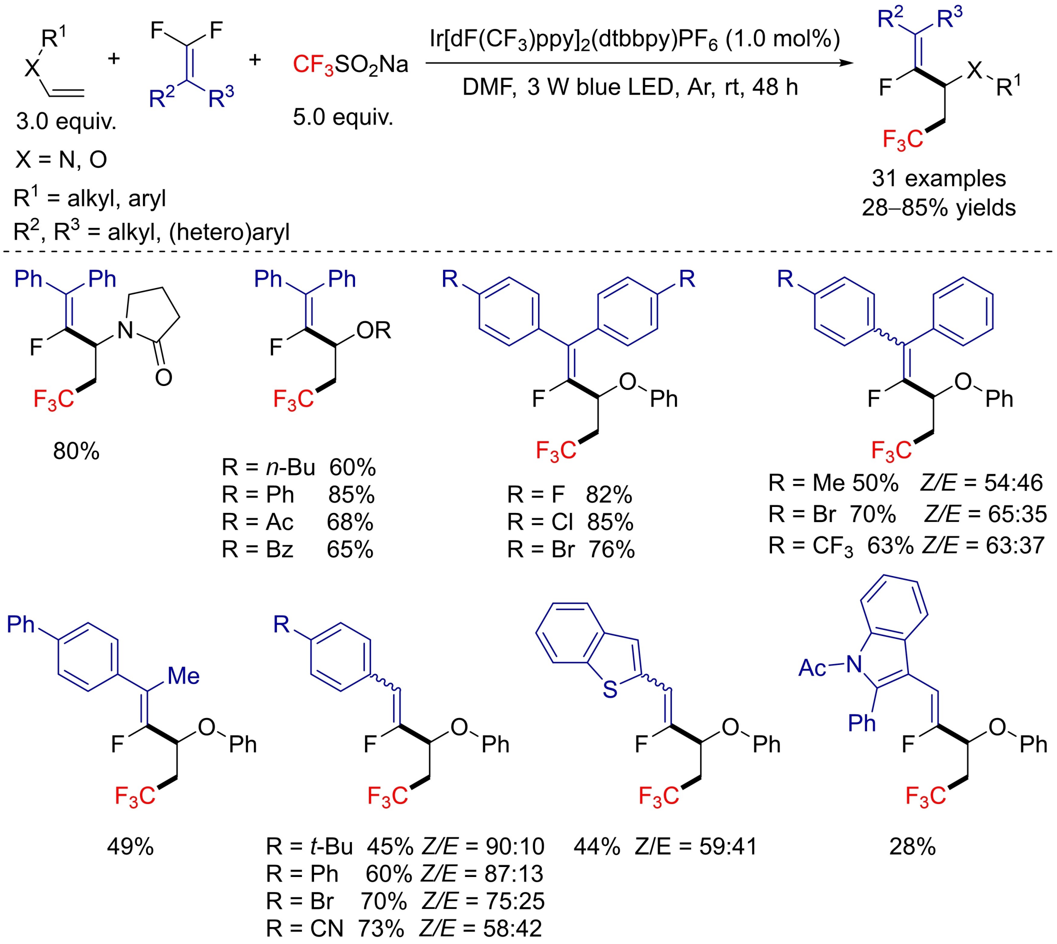
Scheme 16. Iron- or copper-catalyzed carbotrifluoromethylation of acrylamide-tethered alkylidenecyclopropanes for the synthesis of tetracyclic benzazepine derivatives.

nism of the transformations, the radical cascade reaction involves a 5-*exo-dig* cyclization.

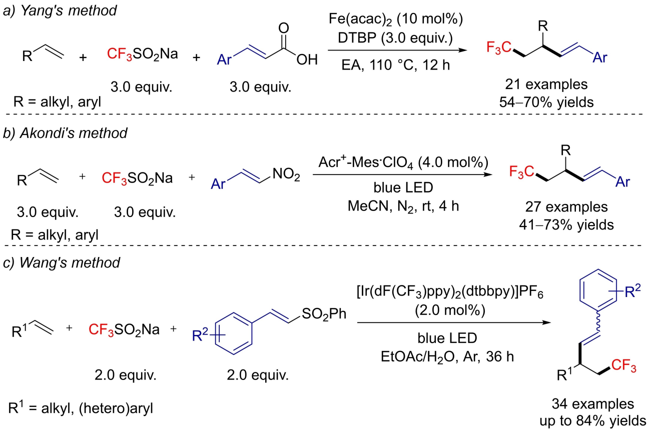
In 2018, the protocol described above by Lin[16] and Zhu[17] was also extended to the bromotrifluoromethylation of enynes by Liu[18] et al. The transition-metal-free free-radical cascade process was accomplished in the presence of $NaBrO_3$ and Langlois' reagent giving the *E* isomer of the appropriate products in 40–75% yields (Scheme 9). The developed procedure provides a facile access to a wide range of bromotrifluoromethylated five-membered heterocycles with high chemoselectivity via 5-*exo-dig* cyclization. In addition, the synthesis of the six-membered tetrahydropyran derivative was also achieved in a yield of 40% from the corresponding 1,7-enyne via 6-*exo-dig* cyclization.

In 2020, similar to Liang's work,[14] another cyanotrifluoromethylation process was realized by Jiang[19] et al. for the construction of 1-indanones from 1,6-enynes. The alkenyl-carbotrifluoromethylation reaction was effected in the presence of Togni's reagent as both the radical initiator and the CF_3 source, TMSCN as the nitrile source, $Cu(OTf)_2$ as catalyst, and K_3PO_4 as base utilizing 1,10-phenantroline ligand affording mostly the *E* isomer of the desired products in moderate to good yields (Scheme 10). The reaction was proposed to take place through a radical-triggered addition/5-*exo-dig* cyclization/oxidation/nucleophilic cascade.

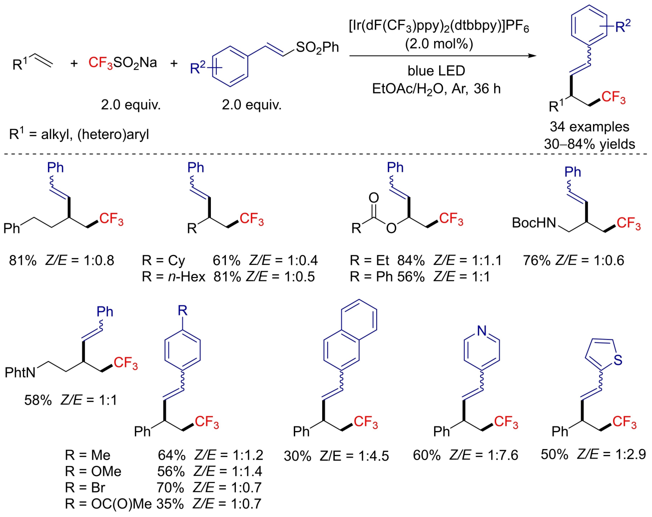
The employment of 1,7-enyne substrates in radical trifluoromethylation/cyclization processes enables a new pathway for the construction of fused heterocyclic systems via mostly 6-*exo-dig* cyclizations. Therefore, several approaches have been made in the last decade for the synthesis of diverse carbocycles and heterocycles. In 2016, Wang[20] and co-workers published the copper-catalyzed trifluoromethylation and bicyclization of 1,7-enynes leading to a wide range of trifluorometh-



Scheme 17. Trifluoromethyl-alkenylation of alkenes through radical-radical cross coupling.

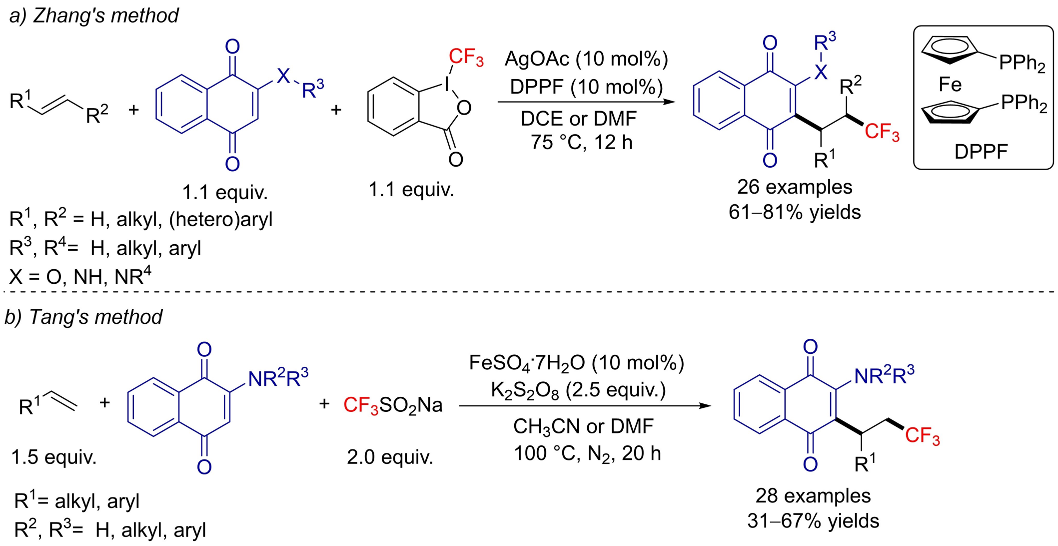


Scheme 18. Intermolecular trifluoromethyl-alkenylation reactions of alkenes with Langlois' reagent.

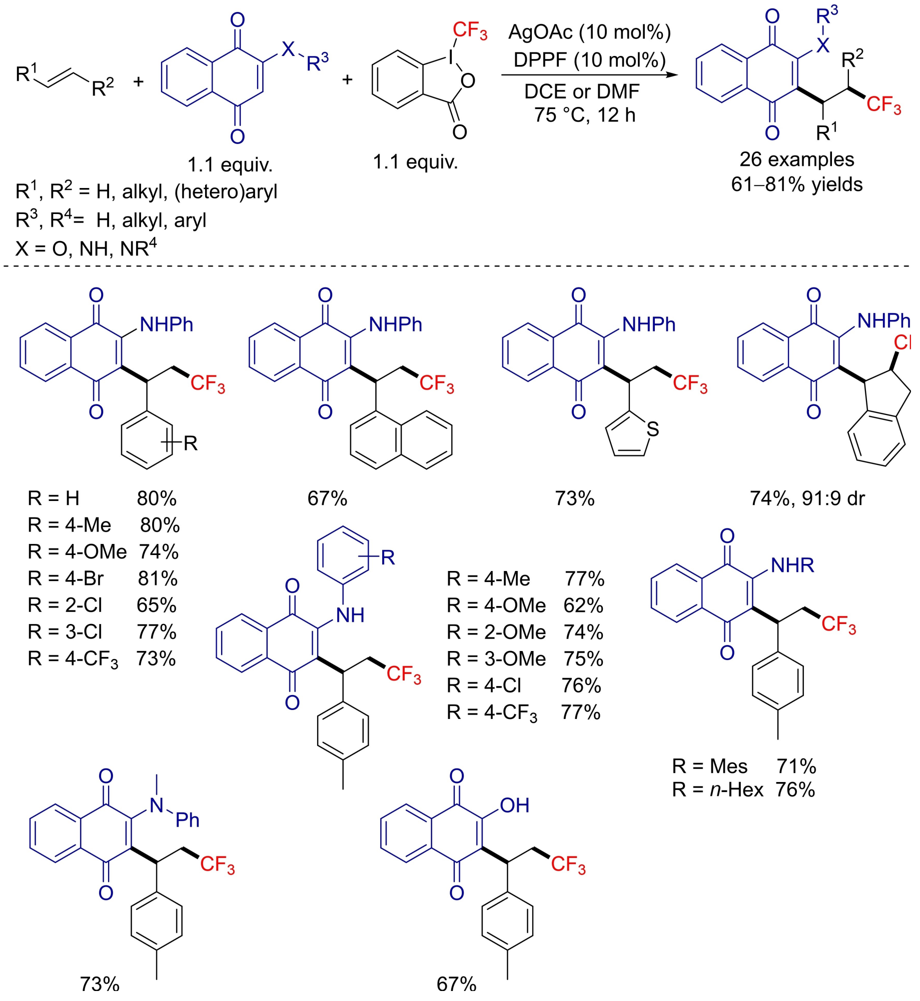


Scheme 19. Iridium-catalyzed trifluoromethyl-alkenylation of alkenes with sulfones.

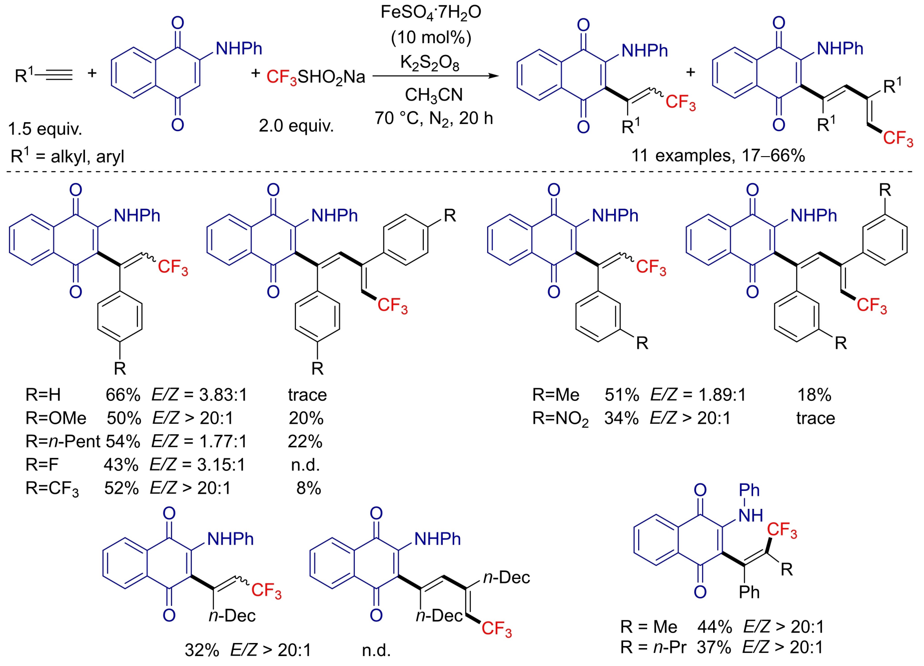
ylated heterocycles, namely, tetracyclic compounds with indene, dihydroquinolinone or dihydrocoumarin moieties. Reactions were implemented in the presence of Togni's reagent and CuBr catalyst resulting in the formation of the corresponding products in good yields (Scheme 11). Mechanistic investigations showed that radical trifluoromethylation and sequential 6-*exo-dig*/5-*endo-trig* bicyclization processes were involved in this protocol.



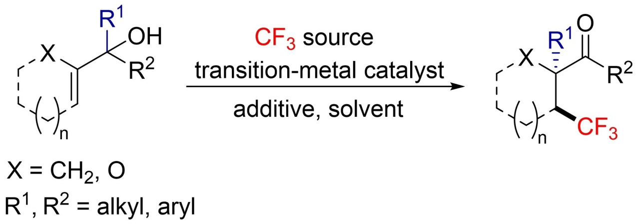
Scheme 20. Intermolecular trifluoromethyl-alkenylation reactions of alkenes with 2-amino- and 2-hydroxy-1,4-naphthoquinone derivatives.



Scheme 21. Silver-catalyzed trifluoromethyl-alkenylation of alkenes with 2-amino- and 2-hydroxy-1,4-naphthoquinone derivatives and Togni's reagent.



Scheme 22. Iron-catalyzed radical trifluomethyl-alkenylation reaction of alkynes with 2-amino-1,4-naphtoquinones and Langlois' reagent.



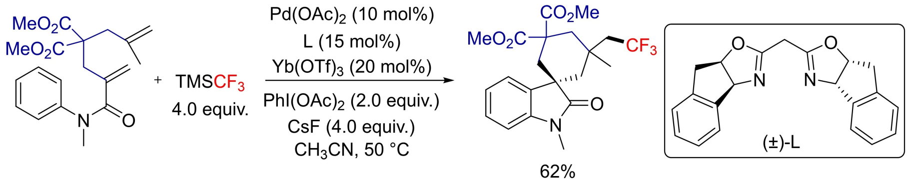
Scheme 23. Carbotrifluoromethylation of alkenes via intermolecular 1,2-carbon migration.

In the same year, Wu[21] and co-workers reported the synthesis of iodotrifluoromethylated 3,4-dihydroquinolin-2(1*H*)-ones via the photo-induced radical cyclization of benzene-tethered 1,7-enynes. Togni's reagent was employed as the CF_3 source, whereas benzoic acid and NaI were utilized as additives in the transition-metal-free transformation (Scheme 12). Under ultraviolet irradiation, the *Z* isomer of the dihydroquinoline derivatives was generated through a trifluoromethyl radical-triggered α,β-conjugate addition/intramolecular 6-*exo* cyclization/iodination process delivering the appropriate products in 40–65% yields. Interestingly, the iodotrifluoromethylated products of this transformation were isolated as by-product in Wang's method.[20]

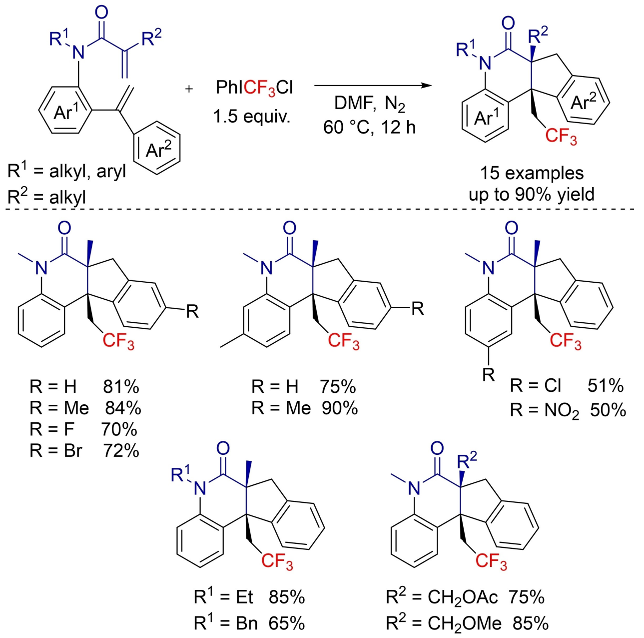
A few years later, Wu's work[21] was extended to chloro- and bromo-trifluoromethylation of 1,7-enynes utilizing mild conditions with visible-light catalysis by Guo[22] et al. The synthesis of 3,4-dihydroquinolin-2(1*H*)-ones was demonstrated over a broad substrate scope in good and excellent yields (Scheme 13).

Two types of reaction conditions were used. In one case, Langlois' reagent as the CF_3 source, *N*-chloro-/*N*-bromophthalimide as the Cl/Br source, and Acr^+-Mes·ClO_4 as the photocatalyst were applied. On the other hand, triflyl chloride, which could provide both the CF_3 radical and the Cl source in the presence of tris(2-phenylpyridine)iridium (*fac*-Ir(ppy)$_3$) photocatalyst was used. According to the proposed mechanism, the products are formed via 6-exo-*dig* cyclization.

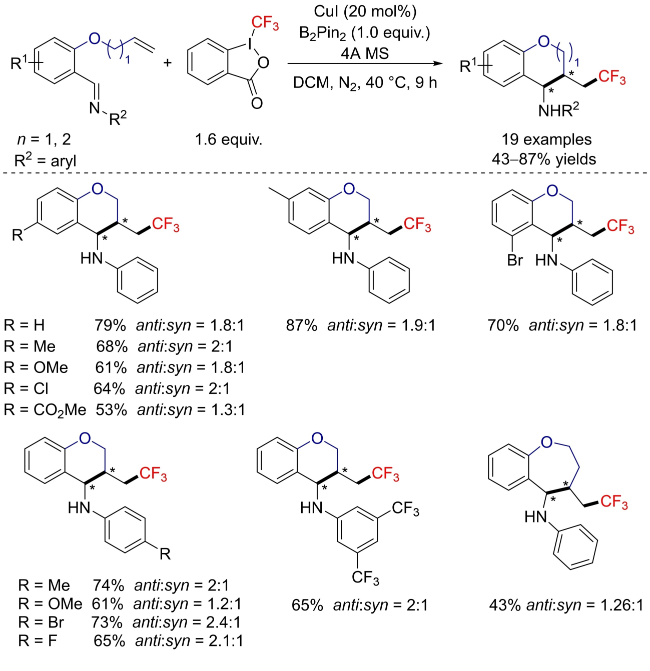
Two years later, after the halotrifluoromethylation methods reported by Wu and Guo, Jiang[23] demonstrated the copper-catalyzed annulation-cyanotrifluoromethylation of 1,7-enynes for the construction of (*Z*)-3,4-dihydronaphthalen-1(2*H*)-ones. Togni's reagent, TMSCN, tetrakis(acetonitrile)copper(I) hexafluorophosphate ($Cu(MeCN)_4PF_6$) as catalyst, and 1,10-phenan-



Scheme 24. Palladium-catalyzed alkyltrifluoromethylation of a diene via tandem cyclization.



Scheme 25. Catalyst-free domino biscyclization of dienes for the synthesis of trifluoroethylated tetrahydroindenoquinolinones.



Scheme 26. Copper-catalyzed alkyltrifluoromethylation of ene-imines for the construction of 3-trifluoroethylated 4-amino-chromans.

troline as ligand were utilized in the reaction leading to the corresponding products in 56–89% yields (Scheme 14). The reaction was proposed to undergo via a 6-*exo-dig* cyclization mechanism.

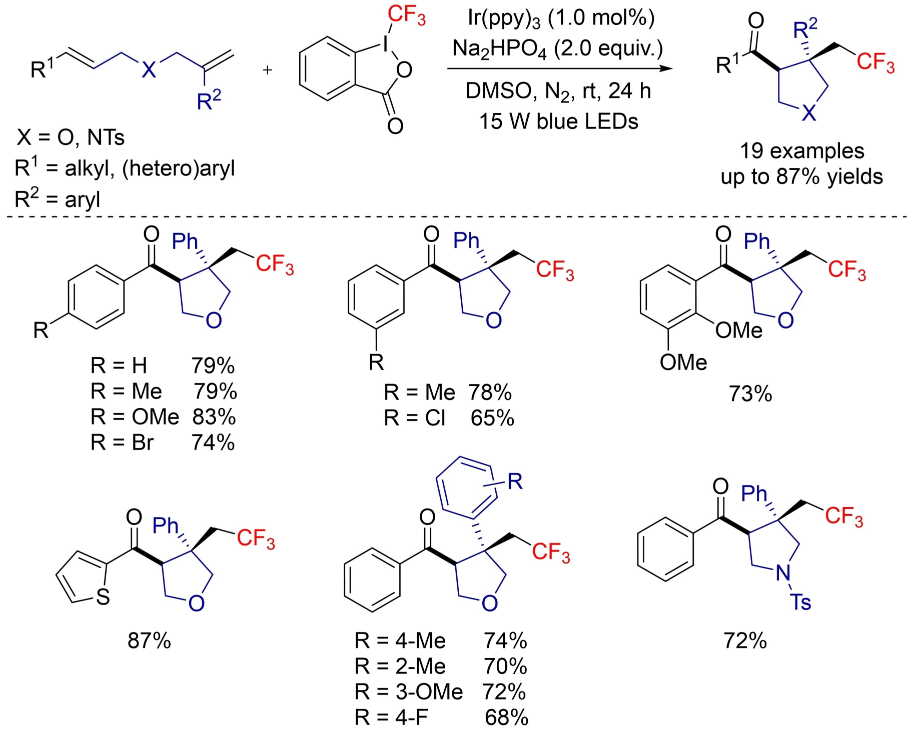
Guo and co-workers also presented the visible-light-induced trifluoromethylation/cyclization of 1,7-enynes in a continuous flow for the generation of several CF_3-containing heterocyclic scaffolds.[24] Ph_2SCF_3OTf, the Yagupolskii–Shreeve reagent, was employed as the trifluoromethylating agent, *fac*-Ir(ppy)$_3$ as the photocatalyst, and 2,6-lutidine as the base obtaining various benzo[*j*]phenanthridines and indeno[1,2-*c*]quinolines in moderate to good yields (Scheme 15). In accordance with mechanistic investigations, the formation of the *E* isomer of the appropriate products was realized, possibly controlled by the steric hindrance effect.

Trifluoromethylation reactions coupled with seven-membered ring formation are also possible and known in the literature. The iron- or copper-catalyzed trifluoromethylation of acrylamide-tethered alkylidenecyclopropanes for the construction of tetracyclic benzazepine derivatives under mild and convenient conditions was realized by Shi25 et al. in 2016. The reaction was implemented in the presence of Togni's regent and iron or copper catalysts ($FeCl_2$, $Cu(MeCN)_4PF_6$ or CuI) were used in the transformation affording the corresponding products in moderate to good yields (Scheme 16). When R^1 was a *para*-methoxy group of the benzene ring of the acrylamide-tethered alkylidenecyclopropane substrate, a spirocyclic product bearing both benzazepine and benzoquinone moieties was formed via a cyclization and dearomatization process.

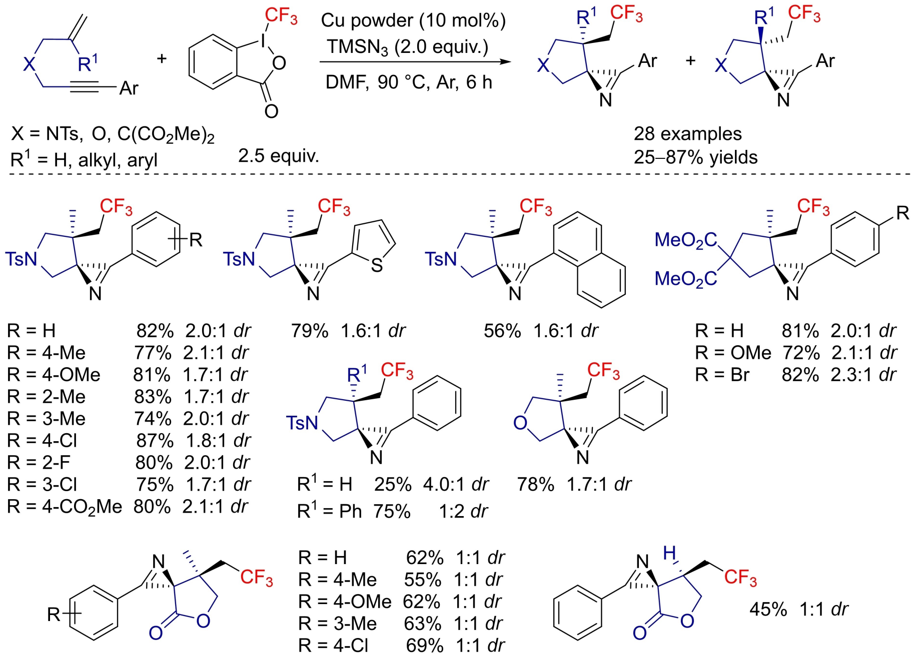
2.1.3. Intermolecular reactions

The difunctionalization of alkenes through intermolecular trifluoromethyl-alkenylation has been received increased attention in the last decade, as it converts simple and readily available alkenes into complex and valuable molecules. In 2019, Wang[26] et al. developed a method to the trifluoromethylation and monofluoroalkenylation of alkenes via radical-radical cross coupling providing allyl compounds in the presence of Langlois' reagent and an iridium photosensitizer catalyst. A broad substrate scope was presented with excellent functional group tolerance leading to the appropriate products in moderate to good yields (Scheme 17).

In the last three years, with the employment of Langlois' reagent, three similar approaches have been achieved by Yang, Akondi, and Wang. In 2020, Yang[27] demonstrated the iron-catalyzed radical difunctionalization of unactivated alkenes in which the CF_3 group of the Langlois' reagent and the styrene skeleton of the acrylic acid were added across the double bond. The developed methodology, in which Fe(acac)$_2$ catalyst and di-*tert*-butyl peroxide (DTBP) oxidant were applied, enables the synthesis of diverse trifluoromethylated aryl-substituted alkenes after decarboxylation, isolated in 54–70% yields (Scheme 18a). According to the proposed mechanism, the reaction undergoes an A–D-A–T (acceptor-donor-acceptor-terminal) type RDD (radical dual-difunctionalization) and cross-coupling process. Concerning the utilization of a transition metal catalyst, high temperature and a potentially explosive peroxide are limitations of Yang's method. Akondi[28] et al. accomplished the transition-metal-free and oxidant-free trifluoromethyl-alkenylation of alkenes under visible-light conditions at room temperature. This mild, three-component protocol uses readily available β-nitrostyrenes as the alkenyl source in the presence of Acr^+-Mes$\cdot$$ClO_4$



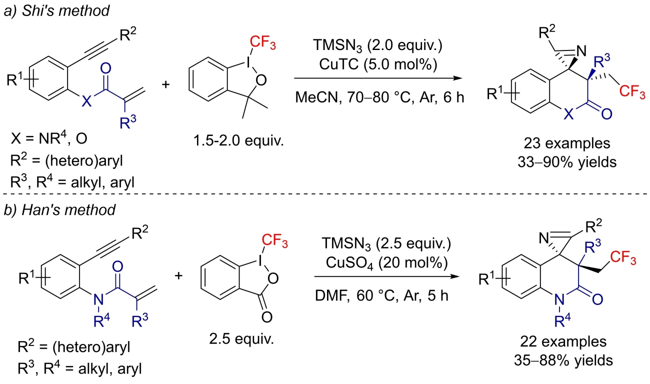
Scheme 27. Iridium-catalyzed tandem trifluoromethylation/cyclization/remote oxidation of 1,6-diene substrates under visible light.



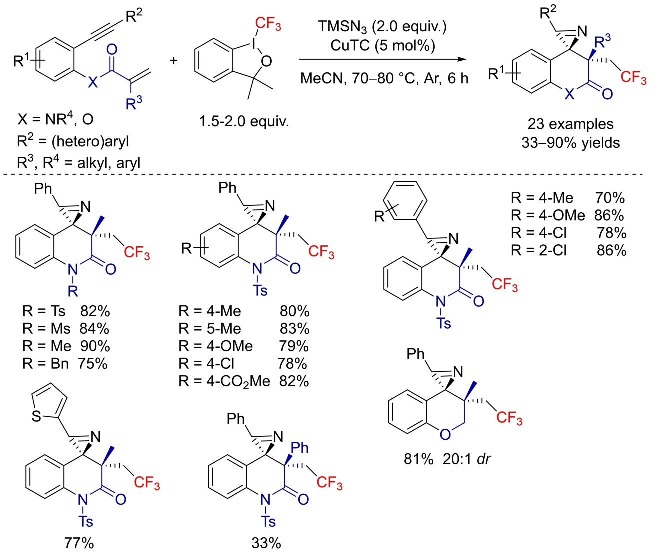
Scheme 28. Alkyltrifluoromethylation of 1,6-enynes for the synthesis of trifluoromethyl-substituted spiro-*2H*-azirines.

photocatalyst for the construction of the desired products with excellent functional group tolerance in 43–73% yields (Scheme 18b). Additionally, the applicability to late-stage functionalization of drug intermediates was also demonstrated in two examples.

In the case of the method of Wang,[29] the visible-light-induced reaction was implemented with the application of alkenyl source bearing a phenylsulfonyl group and iridium catalysis. A broad substrate scope was presented giving the appropriate products in yields up to 84% (Scheme 18c and



Scheme 29. Copper-catalyzed trifluoromethylazidation reactions of 1,7-enynes.

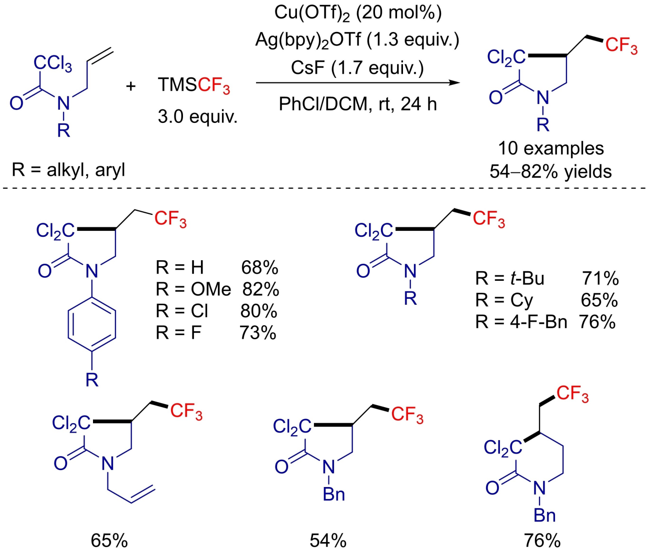


Scheme 30. CuTC-catalyzed trifluoromethylazidation of 1,7-enyne substrates with Togni's reagent I and TMSN$_3$.

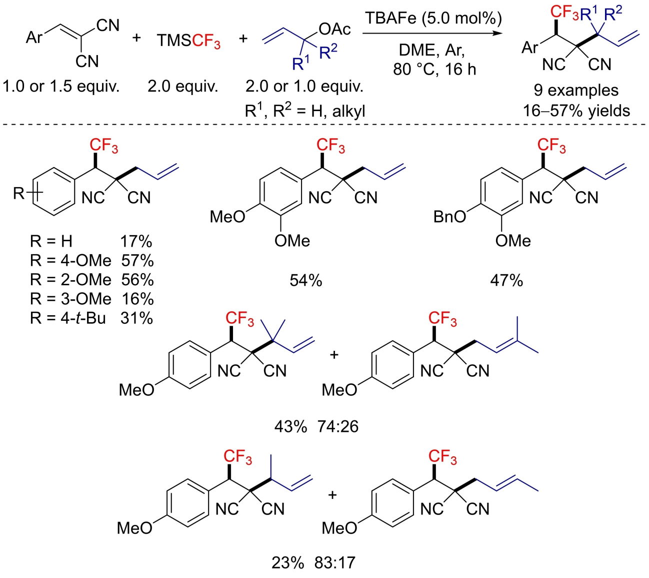
Scheme 19). Additionally, the methodology was also extended to the synthesis of a few alkynyltrifluoromethylated derivatives in the presence of acetylene sulfones.

Beyond the application of the Langlois reagent in intermolecular trifluoromethyl-alkenylation reactions, the utilization of Togni's reagent in these kinds of transformations was also demonstrated and published by Zhang[30] in 2019. The developed silver-catalyzed three-component radical difunctionalization of alkenes enables the synthesis of CF_3-functionalized alkyl-substituted 1,4-naphthoquinone derivatives in 61–81 % yields employing AgOAc and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) ligand (Scheme 20a and Scheme 21).

Furthermore, the employment of the same 1,4-naphthoquinone substrates in trifluoromethyl-alkenylation reaction was reported recently by Tang[31] and co-workers. In this procedure, Langlois' reagent was applied as the CF_3 source, $FeSO_4 \cdot 7H_2O$ as the catalyst, and $K_2S_2O_8$ as the oxidant providing the corresponding products in moderate to good yields (Scheme 20b).



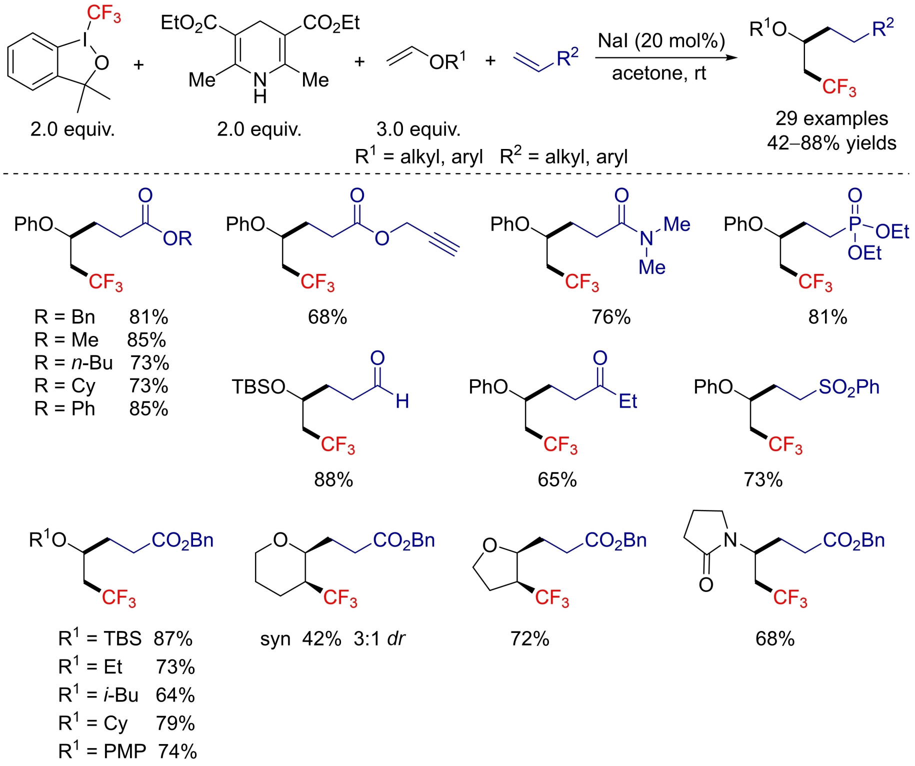
Scheme 31. Copper-catalyzed cyclization-trifluoromethylation of *N*-substituted *N*-allyltrichloroacetamides with $TMSCF_3$



Scheme 32. Iron-catalyzed tandem trifluormethylation-allylation of olefins.

2.2. Alkyne functionalization

Note, that the functionalization of the carbon-carbon double bond via trifluomethyl-alkenylation reactions is a highly researched area of the carbotrifluoromethylation reactions. In contrast, there is only a single publication in the literature regarding the functionalization of the carbon-carbon triple bond. Very recently, Tang[31] et al. reported the iron-catalyzed radical trifluomethyl-alkenylation reaction of alkenes with 2-



Scheme 33. Four-component radical cascade trifluoromethylation reaction of alkenes with Togni's reagent.

amino-1,4-naphtoquinones using Langlois' reagent, described above. The developed protocol was also suitable for the functionalization of acetylenes, enabling the highly regioselective synthesis of CF_3-substituted 1,4-naphthoquinones in the presence of terminal and internal alkynes with easily available and inexpensive reagents under simple reaction conditions. The reaction of phenylacetylene, Langlois' reagent, and 2-(phenylamino)naphthalene-1,4-dione gave the desired trifluoromethyl-alkenylated products as isomeric mixtures. However, the presence of electron-donating groups on the alkyne moiety generated not only the corresponding trifluoromethyl-alkenylated products, but afforded four-component coupling products as well (Scheme 22).

3. Alkyltrifluoromethylation Reactions

3.1. Alkene functionalization

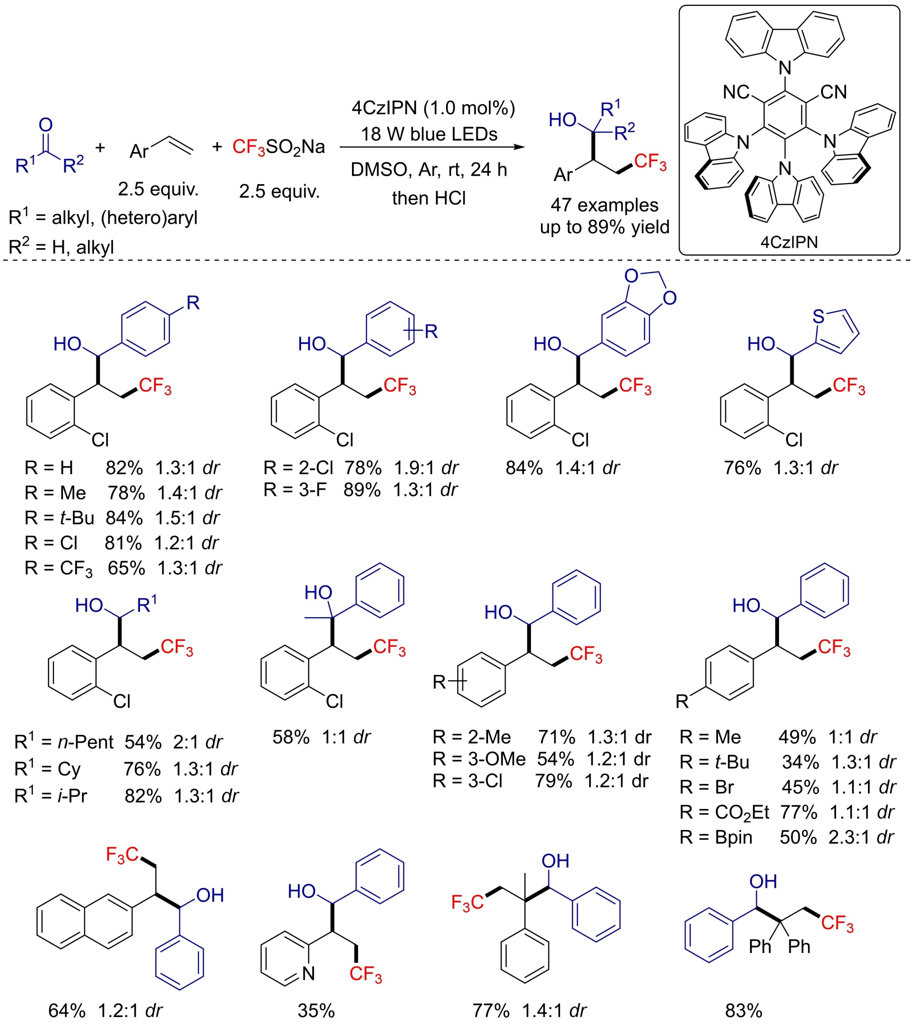
3.1.1. Reactions involving intramolecular alkyl migration

In the last decade, several approaches have been developed for the carbotrifluoromethylation of the carbon-carbon double bond involving intramolecular 1,2-carbon migration sequences[32] (Scheme 23). However, in these processes, beside the introduction of the trifluoromethyl group, the alkene moiety is equipped with a carbonyl group as well. Moreover, concerning the presented substrate scope of these syntheses, in most of the cases, the intramolecular migration implies aryl migration, and alkyl migration takes place only in a few cases. Therefore, related publications listed here are going to be discussed in Section 4.

3.1.2. Reactions involving intramolecular cyclization

Several applications have been reported in the last ten years for the carbotrifluoromethylation of alkenes involving intramolecular cyclization of dienes or 1,*n*-enyne substrates. In 2012, Liu[33] et al. developed the palladium-catalyzed aryltrifluoromethylation of activated alkenes in the presence of the Ruppert-Prakash reagent ($TMSCF_3$), CsF, $PhI(OAc)_2$ as oxidant, and a nitrogen-containing ligand. However, beside aryltrifluoromethylation, alkyltrifluoromethylation was also demonstrated in one example employing a diene substrate (Scheme 24). The tandem cyclization, in which CF_3^- was generated in situ from $TMSCF_3$ and CsF, afforded a spirocyclic product as a single diastereoisomer in 62% yield. According to the plausible mechanism, the corresponding product resulted from the arylpalladation of the alkene, followed by sequential alkene insertion and oxidative trifluoromethylation.

Another aryltrifluoromethylation approach including a new domino biscyclization of dienes as well was achieved by Wang[34] and co-workers in 2019. The additive- and catalyst-free method, in which $PhICF_3Cl$ was used as the trifluoromethylating agent, enables the construction of trifluoroethylated tetrahydroindenoquinolinones with *syn*-stereoselectivity in yields up to 90% (Scheme 25).



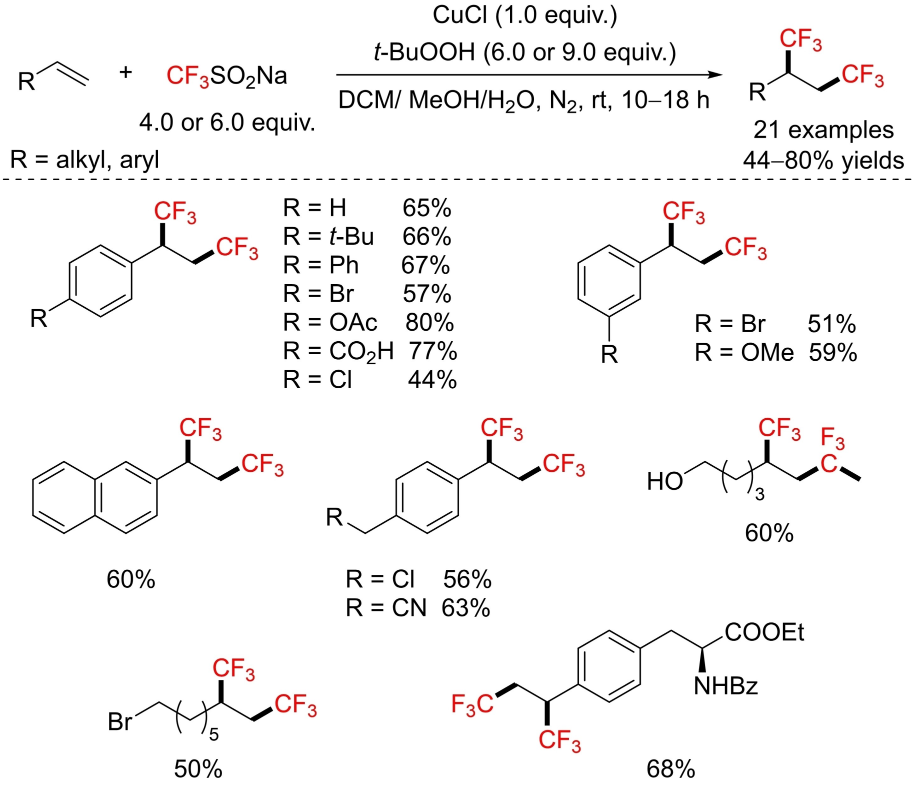
Scheme 34. Visible-light-mediated trifluoromethylation/benzylation of styrenes in the presence of Langlois' reagent.

After the application of Pd, a transition metal, in the method of Liu33, the copper-catalyzed synthesis for the formation of 3-trifluoroethylated 4-aminochromans via intramolecular carbotrifluoromethylation of ene-imines was also published by Deng[35] et al. in 2018. The reaction was implemented in the presence of Togni's reagent, CuI catalyst, and bis(pinacolato)diboron (B_2Pin_2) as additive providing the desired *anti-* and *syn*-products as isomers in 43–87% yields (Scheme 26).

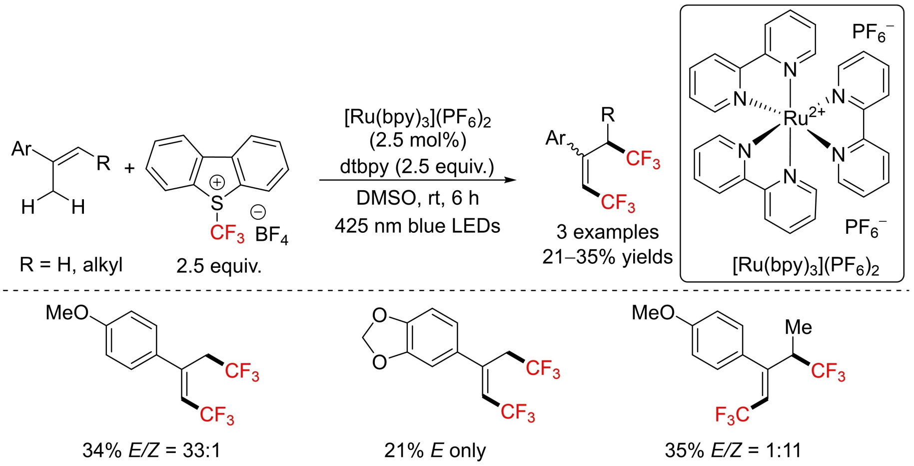
Three years later, the photoredox-catalyzed tandem trifluoromethylation/cyclization/remote oxidation of 1,6-diene substrates leading to CF_3-substituted five-membered heterocycles was developed by Zhu[36] and co-workers. Togni's reagent, $Ir(ppy)_3$, and Na_2HPO_4 were applied in the transformation giving the corresponding products with excellent diastereoselectivtiy in good yields (Scheme 27). Concerning the plausible reaction mechanism, the final product is formed from a carbocation, which reacts with DMSO via a deprotonation process, similar to that of Kornblum oxidation.

After the azidotrifluoromethylation and carbocyclization of 1,6-enynes reported by Liang[14] in 2014, the copper-catalyzed cascade cyclization of the same enyne substrates for the synthesis of trifluoromethyl-substituted spiro-*2H*-azirines was also realized by the same research group in the following year.[37] In the developed procedure, Togni's reagent, Cu powder, and $TMSN_3$ were utilized and the appropriate products were isolated as diastereoisomers in 25–87% yields (Scheme 28). Concerning the proposed mechanism, the procedure involves a 5-*exo-dig* cyclization.

After the pioneering studies of Liang, two similar copper-catalyzed trifluoromethylazidation reactions were published in 2017 with the application of 1,7-enyne substrates, Togni's reagent, and $TMSN_3$. In the method of Shi[38] Togni's reagent I and copper(I)-thiophene-2-carboxylate (CuTC) were applied (Scheme 29a and Scheme 30), whereas in the work of Han[39] Togni's reagent II and $CuSO_4$ (Scheme 29b) were employed. A broad substrate scope of CF_3-substituted azaspirocyclic dihydroquinolin-2-ones were presented in both cases, with excellent or good diastereoselectivities and in good isolated yields. Regard-



Scheme 35. Copper-mediated bis-trifluormethylation of alkenes with Langlois' reagent.



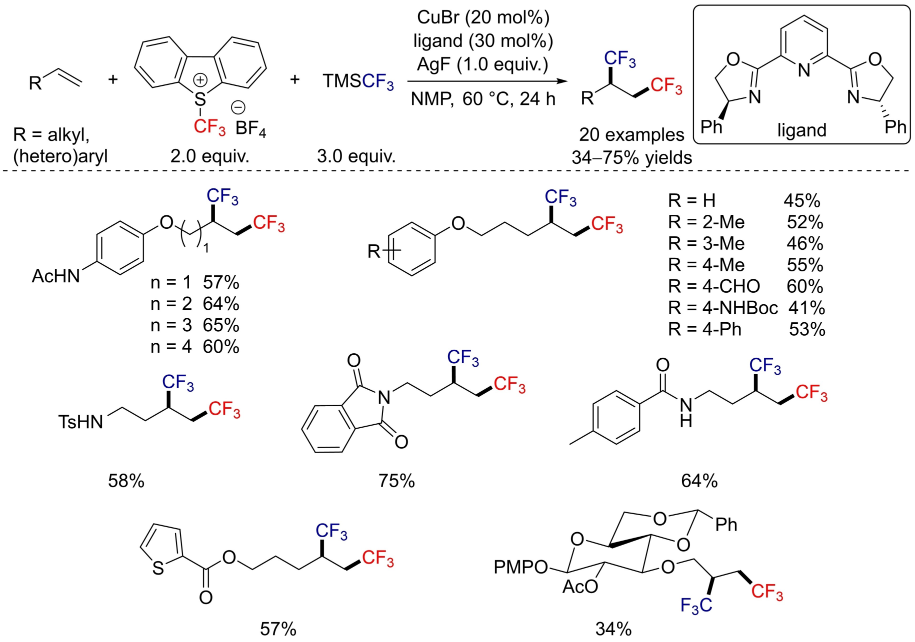
Scheme 36. Ruthenium-catalyzed double trifluoromethylation of styrenes with Umemoto's reagent.

ing the possible mechanism of the transformations, after the intramolecular cyclization, the desired products were synthesized from the appropriate vinyl azides after a thermal rearrangement.

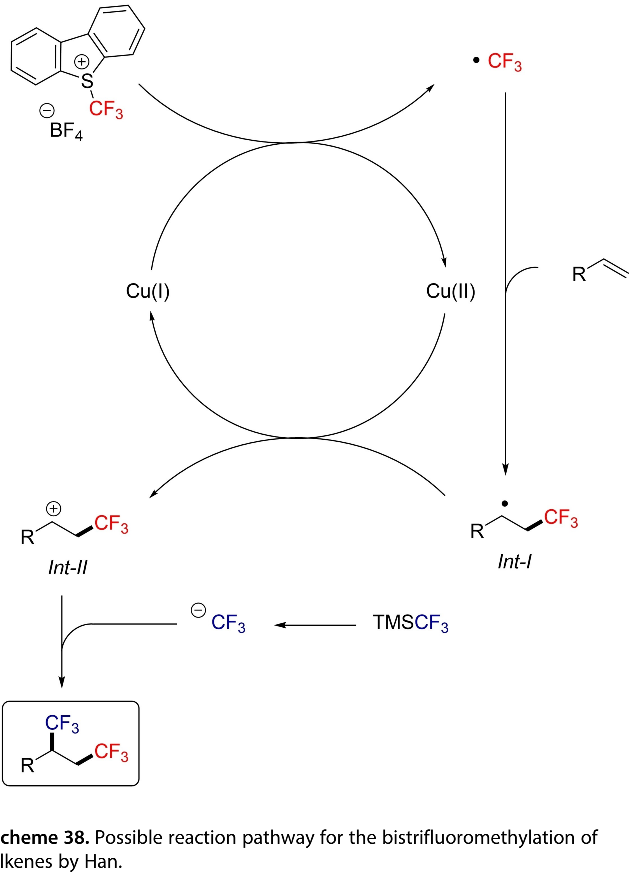
In 2019, the copper-catalyzed carbotrifluoromethylation of unactivated alkenes with CCl_3CF_3 as well as the copper-catalyzed alkyltrifluoromethylation of *N*-substituted *N*-allyltrichloroacetamides with $TMSCF_3$ were described by Li[40] et al. Both *N*-aryl- and *N*-alkylsubstituted *N*-allyltrichloroacetamides underwent efficient cyclization-trifluoromethylation, furnishing the corresponding products in 54–82% yields (Scheme 31). Mechanistic investigations revealed that the reaction undergoes via 5-*exo-trig* or 6-*exo-trig* cyclization.

3.1.3. Intermolecular reactions

The development of efficient methodologies for the construction of complex molecules via difunctionalization of olefins is a long-standing goal in synthetic organic chemistry associated to



Scheme 37. Copper-catalyzed bistrifluoromethylation of terminal alkenes with Umemoto's reagent and $TMSCF_3$.

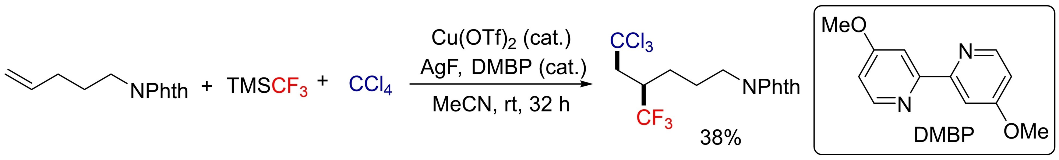


Scheme 38. Possible reaction pathway for the bistrifluoromethylation of alkenes by Han.

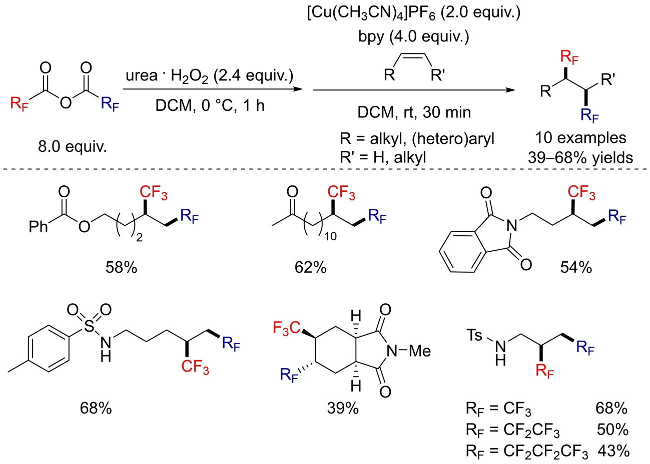
the chemo- and regioselectivitiy of these processes. However, only a few reports have been made in the last decade for the synthesis of diverse trifluoromethylated derivatives. In 2014, Plietker[41] published the iron-catalyzed tandem trifluormethylation-allylation of olefins with the employment of arylidene-malonitrile substrates, allylic acetate, $TMSCF_3$, and TBA[Fe] ($Bu_4N[Fe(CO)_3(NO)]$). Highly substituted allylic acetates were also proved to be reactive in the three-component coupling reaction affording the desired products in good regioselectivity, but only in poor to moderate yields (Scheme 32).

Another approach was realized by Chu[42] et al. in 2018 carrying out the metal-free four-component radical cascade trifluoromethylation reaction of alkenes. An electron-rich and an electron-deficient olefin, Togni's reagent, and the Hantzsch ester were utilized in the protocol, providing facile access to important δ-CF_3 carbonyls. Concerning the electron-deficient olefin, a wide range of important functional groups, such as esters, amides, phosphonates, ketones, sulfones, and aldehydes, were suitable for the transformation. In the case of electron-rich olefins, mostly alkyl-substituted or cyclo derivatives were employed. The multicomponent radical cascade, enabled by an EDA-complex between Togni's reagent and the Hantzsch ester, afforded the appropriate products under mild conditions in good yields and with excellent selectivity (Scheme 33). Additionally, the synthetic applicability of this protocol was demonstrated over the synthesis of the trifluoromethyl analogue of naftidrofuryl, a selective antagonist of 5-HT2 receptor.

The application of Langlois' reagent in the visible-light-mediated metal-free trifluoromethylation/benzylation of alkenes for the synthesis of β-trifluoromethyl-α-substituted alcohols with 4-CzIPN photocatalyst was developed by Liang[43] and co-workers in 2020. Various styrene derivatives were applied as the alkene substrates. According to the proposed mechanism, these are transferred to a benzylic carbanion through a SET process with the contribution of the 4-CzIPN photocatalyst and then



Scheme 39. Copper-catalyzed trifluoromethylation-trichloromethylation of alkene with $TMSCF_3$ and CCl_4.



Scheme 40. Copper-mediated bisperfluoralkylation of alkenes with perfluorocarboxylic anhydrides.

attacked by the carbonyl compound leading to the desired products. A broad substrate scope was demonstrated and the desired β-trifluoromethyl-α-substituted alcohols were isolated as diastereomers in moderate to good yields (Scheme 34).

3.1.4. Bistrifluoromethylation reactions

The double insertion of the trifluoromethyl group into an alkene has received increasing attention in organic syntheses in the last decades. However, only a few reports have been made for the construction of 1,2-bis(trifluoromethylated) compounds, because of the limited feasibility of these protocols. In 2015, Qing[44] et al. developed the copper-mediated radical 1,2-bis(trifluoromethylation) of alkenes employing Langlois' reagent, CuCl, and *t*-BuOOH. The chemoselectivity of the reaction was controlled by the amount of the initiator, aiming to reduce the dimerized by-product and providing the appropriate *bis*-CF_3 compounds in 44–80% yields (Scheme 35).

In the same year, Akita[45] and co-workers reported the ruthenium-catalyzed trifluoromethylation of aromatic alkenes by visible-light-driven photoredox catalysis in the presence of Umemoto's reagent and 2,6-di-*tert*-butylpyridine (dtbpy) as base. The double trifluoromethylation of styrene substrates was also achieved (3 examples); however, the appropriate products were isolated only in moderate yields (Scheme 36). According to the plausible mechanism, the reaction proceeds via the formation of the CF_3-allyl product, which is susceptible to a second trifluoromethylation leading to the final product after a deprotonation process.

The application of CuCl in bistrifluoromethylation reactions was already demonstrated by Qing[44]. Note, however, that it was employed in an equivalent amount. The first pioneering approach, using only a catalytic amount of copper, was achieved by Han[46] et al. in 2019. Double trifluoromethylation was realized with the utilization of Umemoto's reagent combined with $TMSCF_3$ in the presence of a pyridine-*bis*(oxazoline)-type ligand to transform a wide range of terminal alkenes to the desired products in 34–75% yields (Scheme 37).

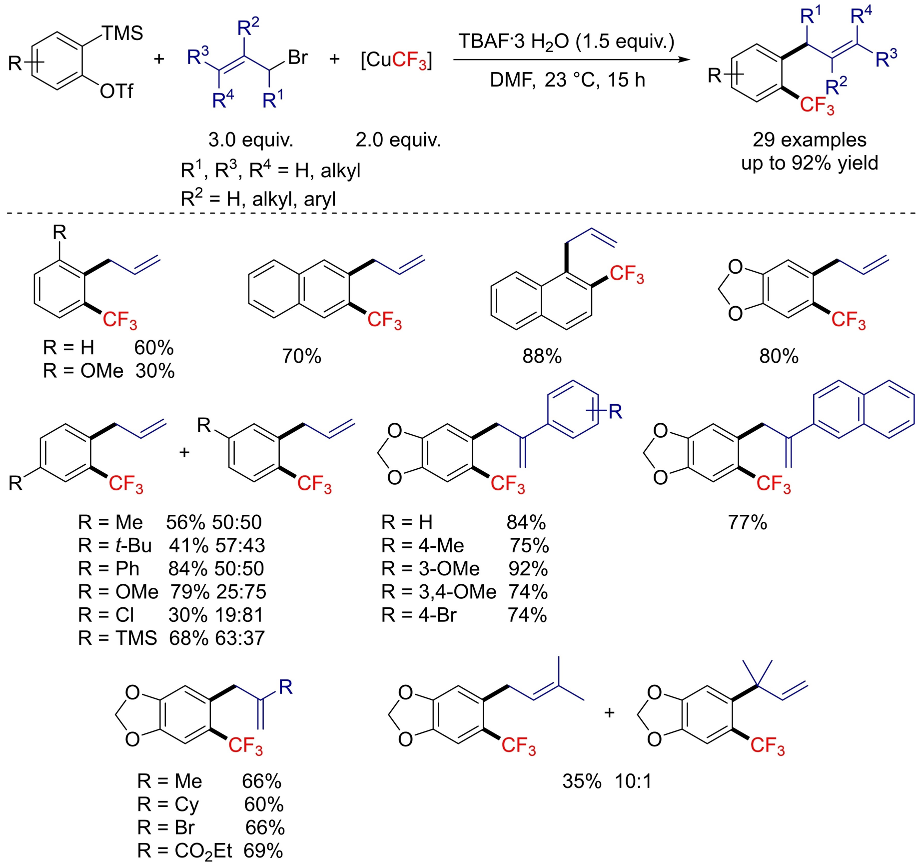
According to the proposed reaction mechanism, active CF_3 radicals generated from Umemoto's reagent with the aid of Cu(I), are readily trapped by the alkene. The resulting intermediate I is oxidized to the alkyl cation (Int-II) by Cu(II) and, finally, with the participation of nucleophilic CF_3, derived from $TMSCF_3$, the desired 1,2-bistrifluorometylated product is formed (Scheme 38).

Another copper-catalyzed transformation was developed by Zhang[47] and co-workers in 2019, in which the trifluoromethylation-trichloromethylation of an alkene substrate was accomplished with CCl_4 and $TMSCF_3$ reagents. The corresponding carbotrifluoromethylation product was isolated in 38% yield (Scheme 39).

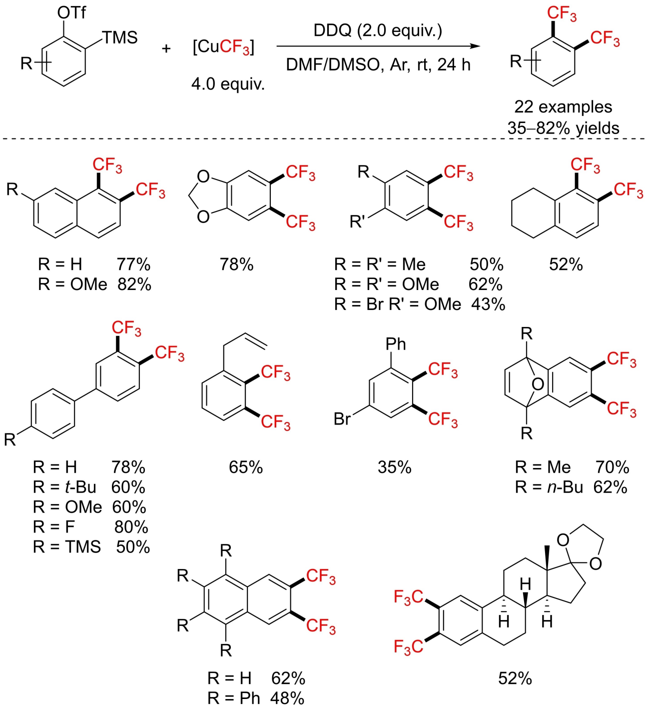
In the last year, Sodeoka[48] realized the copper-mediated synthesis of diverse bisperfluoroalkylated derivatives in moderate to good yields in the reaction of alkenes with perfluorocarboxylic anhydrides in the presence of H_2O_2 (Scheme 40). Mechanistic investigations revealed that the key step in this reaction is the formation of a stable perfluoroalkylcopper intermediate achieved with the aid of a bipyridyl ligand. The desired products were formed after the reaction of the intermediate with perfluoroalkyl-containing alkyl or vinyl radicals.

3.2. Functionalization of carbon-carbon triple bond

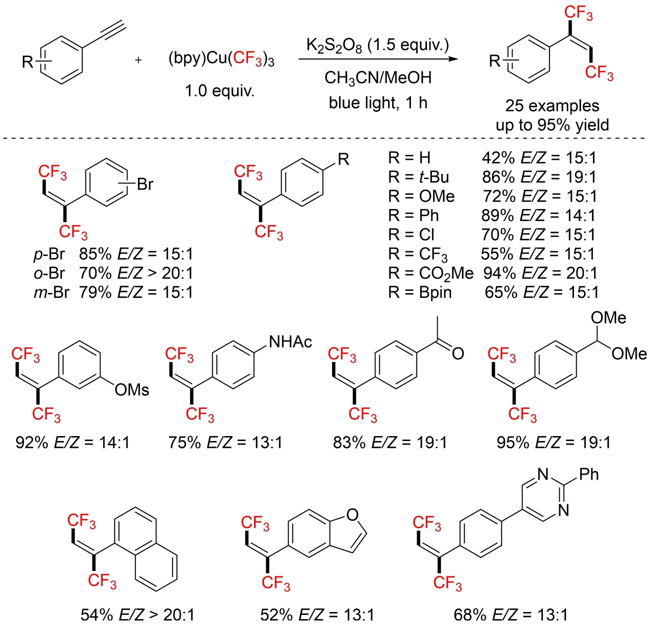
The difunctionalization of the carbon-carbon triple bond toward alkyltrifluoromethylation has received increased attention in organic syntheses in the last few years. In contrast to the single alkenyltrifluoromethylation reaction of alkynes reported recently by Tang[31], there are a few methodologies for the synthesis of alkyltrifluoromethylated derivatives. The majority of these protocols are bistrifluoromethylation reactions.



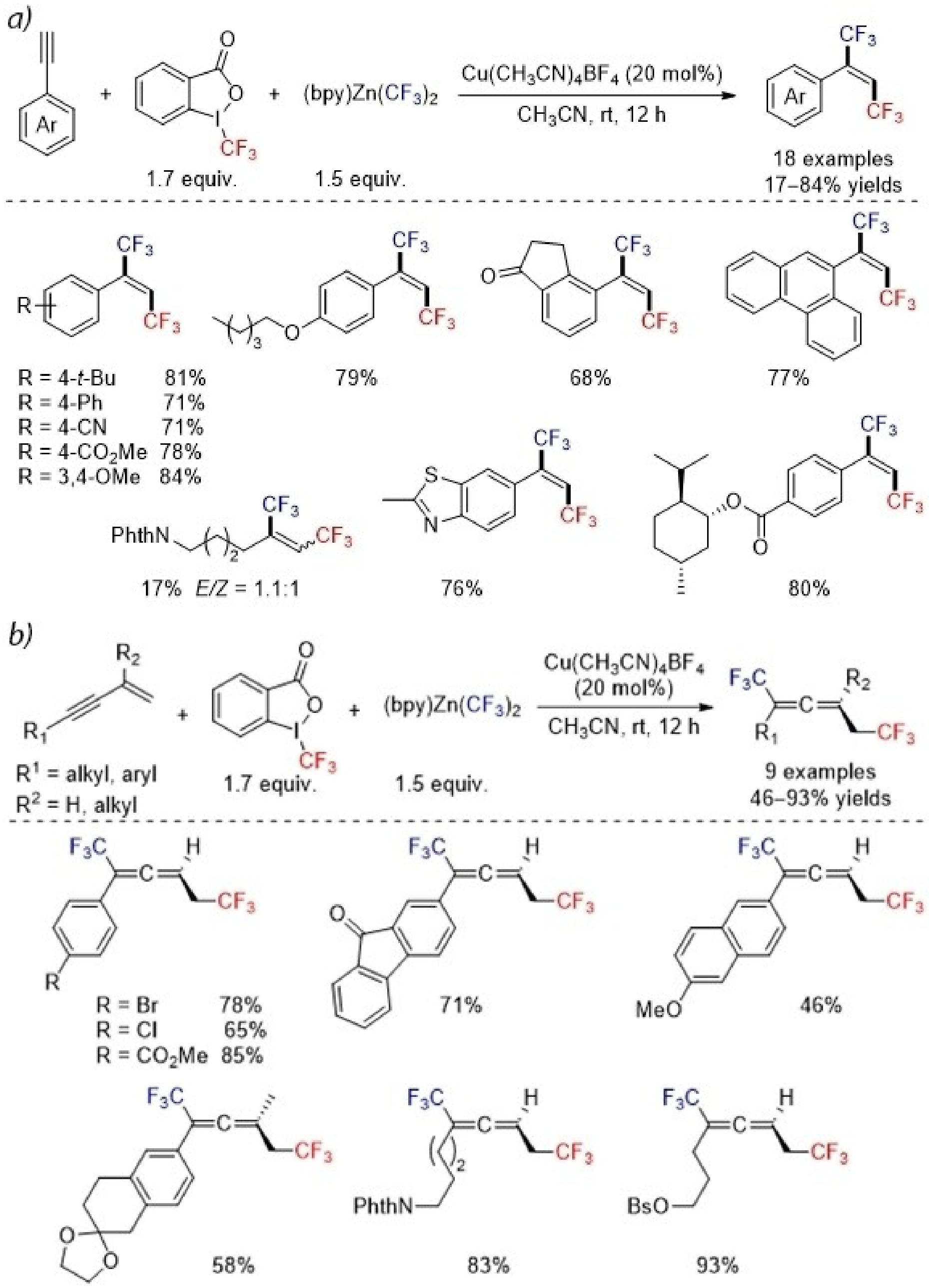
Scheme 41. Copper-mediated trifluoromethylation-allylation of arynes with $CuCF_3$.



Scheme 42. Copper-catalyzed bistrifluoromethylation of arynes with $CuCF_3$.



Scheme 43. Bistrifluoromethylation of aromatic and heteroaromatic alkynes with $(bpy)Cu(CF_3)_3$.

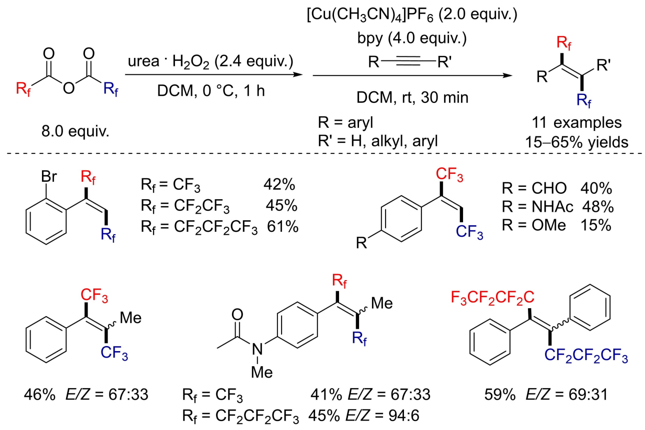


Scheme 44. Copper-catalyzed bistrifluormethylation of a) alkynes and b) 1,3-enynes with Togni's reagent and (bpy)Zn(CF_3)$_2$.

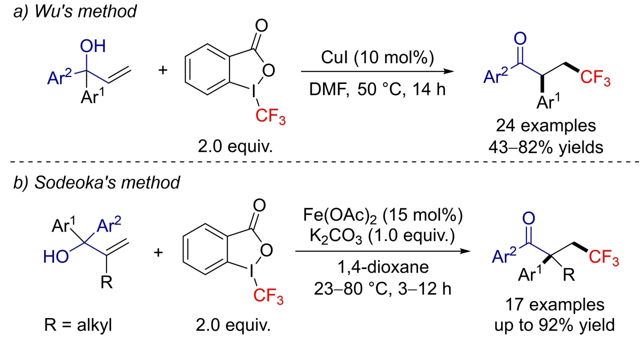
3.2.1. *Aryne functionalization*

The alkyltrifluoromethylation of aromatic alkynes is also known in the literature. In 2018, Tsui[49,50] et al. published two similar approaches employing the same aryne substrates and the [$CuCF_3$] reagent. In their first method,[49] the three-component copper-mediated vicinal trifluoromethylation-allylation of 2-(trimethylsilyl)aryl triflates as aryne precursors was executed in the presence of allyl bromides. The [$CuCF_3$] reagent was generated in situ from CuCl, *t*-BuOK, and CF_3H, then it was stabilized with HF-pyridine. The addition of tetra-*n*-butylammonium fluoride (TBAF) significantly inhibited the formation of the allyl-CF_3 byproduct leading to the desired products. In a single case, the mixture of regioisomers in yields up to 92 % was isolated (Scheme 41). Additionally, the applicability of the transformation was demonstrated in the expedient synthesis of the CF_3-containing analogue of the antispasmodic drug papaverine.

In their second publication,[50] the copper-catalyzed 1,2-bis(trifluoromethylation) of 2-(trimethylsilyl)aryl triflates was presented performed in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant. The synthesis enables the construction of diverse bistrifluoromethylated arenes in one step under mild reaction conditions in moderate



Scheme 45. Copper-mediated bisperfluoralkylation of alkynes with perfluorocarboxylic anhydrides.



Scheme 46. Cu- or Fe-catalyzed synthesis of β-trifluoromethyl-α-aryl ketones from diaryl allylic alcohols by Wu and Sodeoka.

to good yields (Scheme 42). Furthermore, bistrifluormethylation of an estrone derivative was also presented. Concerning the reaction mechanism, the formation of a Cu(III)-CF$_3$ species as key intermediate was proposed, which afforded the desired products through reductive elimination.

3.2.2. Alkyne functionalization

Aliphatic and aromatic alkynes were also proved to be suitable substrates in alkyltrifluoromethylation reactions. In 2019, the 1,2-bis(trifluoromethylation) of aromatic and heteroaromatic alkynes utilizing (bpy)Cu(CF$_3$)$_3$ and persulfate under blue light was developed by Cook[51] and co-workers. A broad substrate scope with high functional group tolerance was demonstrated leading to the appropriate *E*/*Z* isomeric mixture of hexafluorobutenes in good to excellent isolated yields with excellent *E* selectivities (Scheme 43). Moreover, the method was suitable for the late-stage bistrifluoromethylation of four bioactive molecules. Mechanistic investigations and DFT calculations showed that the first step of the process is the addition of the trifluoromethyl radical into the alkyne, then the formed allenyl radical recombines with the Cu(II) species. Finally, the desired product is formed through reductive elimination.

One year later, Li[52] reported the copper-catalyzed radical bistrifluormethylation of alkynes and 1,3-enynes with the employment of Togni's reagent and (bpy)Zn(CF$_3$)$_2$. The corresponding 1,2-bis(trifluoromethylated) alkenes were afforded in good yields with excellent *E* stereoselectivity (Scheme 44a), whereas under the same conditions the appropriate 1,4-bis(trifluoromethylated) allenes were obtained in 46–93 % yields (Scheme 44b). Concerning the proposed mechanism, the key step of the reaction is the formation of alkenyl and allenyl radicals, generated from the alkyne or 1,3-enyne by the addition of the trifluoromethyl radical derived from Togni's reagent.

Last year, the copper-mediated synthesis of diverse bisperfluoroalkylated derivatives from alkenes with perfluorcarboxylic anhydrides has been published by Sodeoka[48] et al. The method was extended for the double functionalization of alkynes as well providing the appropriate tetrasubstituted alkenes in acceptable yields (Scheme 45). Mechanistic investigations revealed that the bistrifluormethylation reaction proceeds via the formation of a vinyl radical, in a similar manner as proposed previously by Cook.[51]

4. Carbonyltrifluoromethylation Reactions

4.1. Alkene functionalization

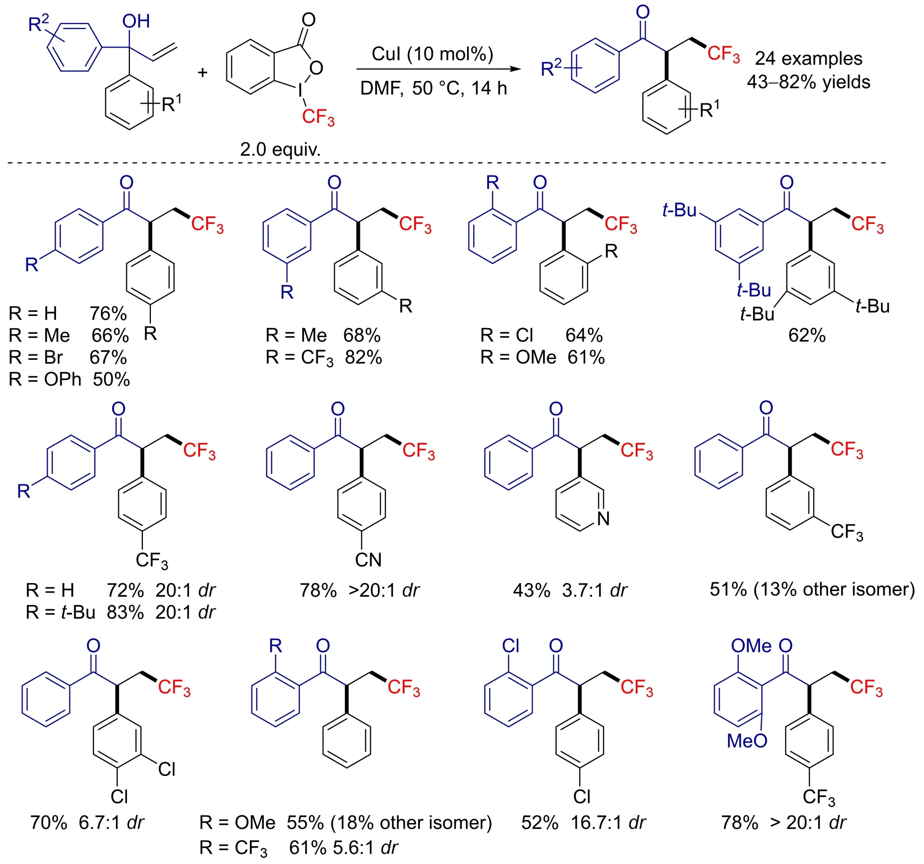
4.1.1. Reactions involving intramolecular carbon migration

The introduction of trifluoromethyl and carbonyl moieties onto alkenes via intramolecular carbon migration enables the transformation of allylic alcohols into β-trifluoromethyl ketones, which are potentially biologically active intermediates. Several methodologies have been developed in the last decade in the absence as well as in the presence of transition-metal catalysts (Cu, Ru, Ir) employing different trifluoromethylating agents. Concerning the type of the migrating moiety, the migration of aryl, alkyl, and formyl groups was described through a radical (neophyl) or a cationic (semipinacol) rearrangement.

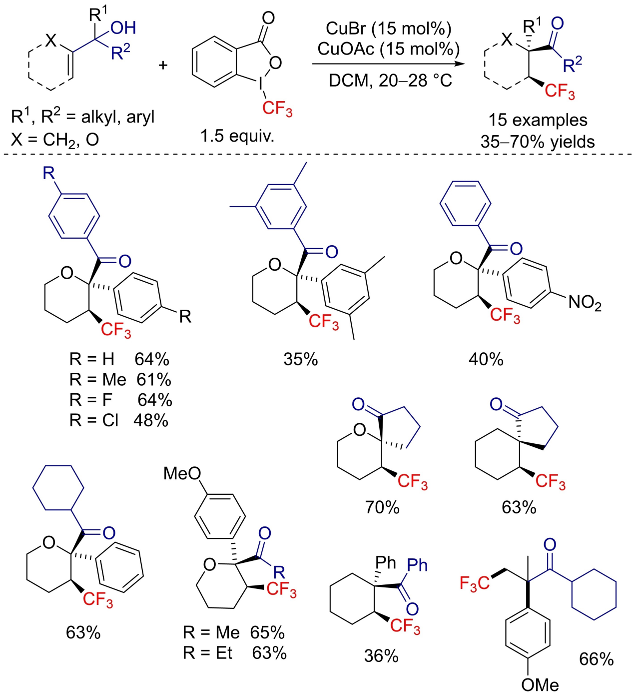
In 2013, two similar approaches were accomplished by Wu[32a] and Sodeoka[32b] for the synthesis of β-trifluoromethyl-α-aryl ketones from α,α-diaryl allylic alcohols and Togni's reagent via 1,2-migration of an aryl group. In the method of Wu, CuI was applied (Scheme 46a), whereas Sodeoka utilized Fe(OAc)$_2$ as the catalyst of the transformation, affording the desired products in good to high yields (Scheme 46b).

According to Wu's report, a radical pathway (neophyl rearrangement) for the 1,2-aryl migration was proposed. A wide substrate scope was presented providing the corresponding products in good yields. In the case of *meta*- and *para*-substituted unsymmetrical substrates, the migration of the more electron-deficient aryl group was observed, whereas *ortho*-substituted aryl rings migrated less effectively, leading to the appropriate products in lower yields (Scheme 47).

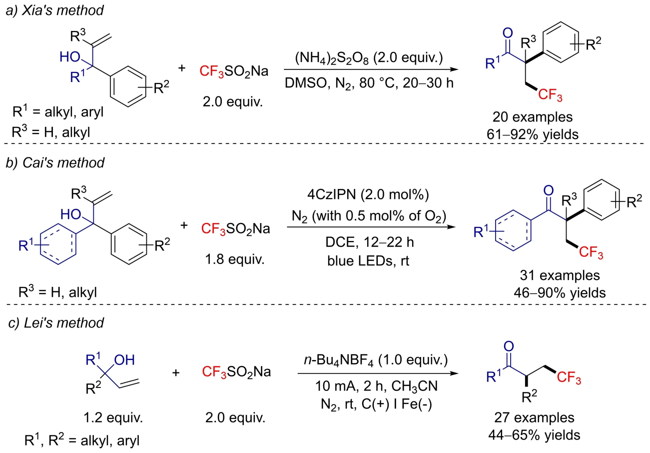
In the same year, another protocol with the utilization of Togni's reagent was published by Tu[32c] et al. describing the



Scheme 47. Copper-catalyzed synthesis of β-trifluoromethyl-α-aryl ketones from α,α-diaryl allylic alcohols and Togni's reagent.



Scheme 48. Copper-catalyzed tandem trifluoromethylation/semipinacol rearrangement of allylic alcohols with Togni's reagent.



Scheme 49. Transition-metal free, photoredox-catalyzed, and electrochemical oxidative syntheses of β-trifluoromethyl-α-aryl ketones from allylic alcohols with Langlois' reagent by Xia, Cai, and Lei.

copper-catalyzed tandem trifluoromethylation/semipinacol rearrangement of allylic alcohols for the synthesis of α-quaternary β-trifluoromethyl ketones. The method, in which CuOAc combined with CuBr as the catalyst was employed, affords the corresponding carbonyl-trifluoromethylated products in moderate to good yields (Scheme 48). Concerning the proposed

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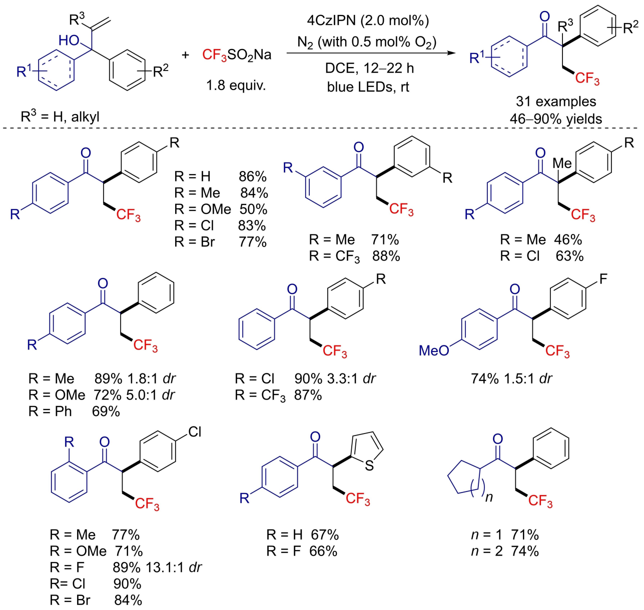
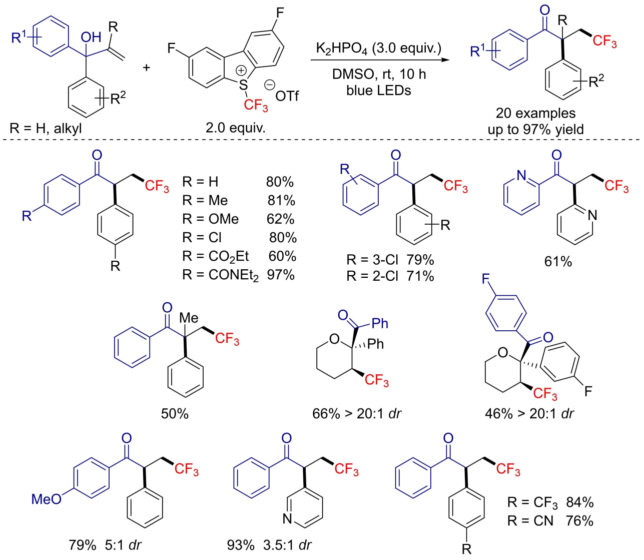


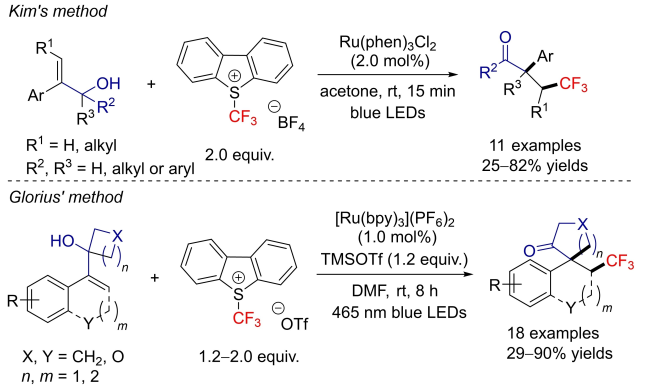
Scheme 50. Photoredox-catalyzed synthesis of β-trifluoromethyl-α-aryl ketones with Langlois' reagent.



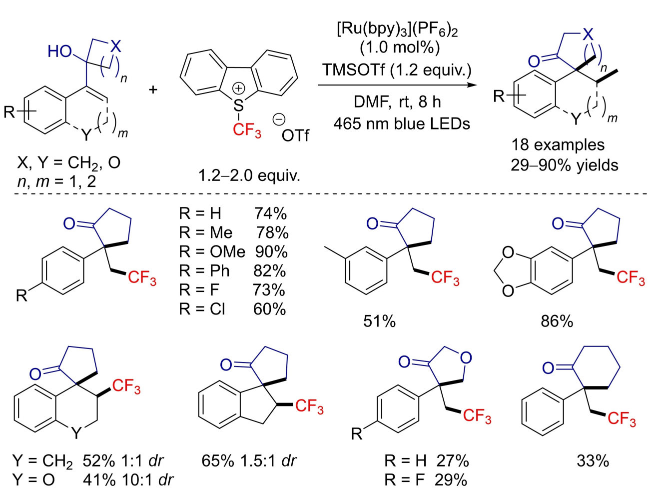
Scheme 51. Visible-light-induced carbonyltrifluoromethylation of diaryl allylic alcohols with Umemoto's reagent derivative.

mechanism, the transformation involves a 1,2-carbon migration through a cationic or a radical intermediate resulting in both the aryl- and alkyl-substituted products.

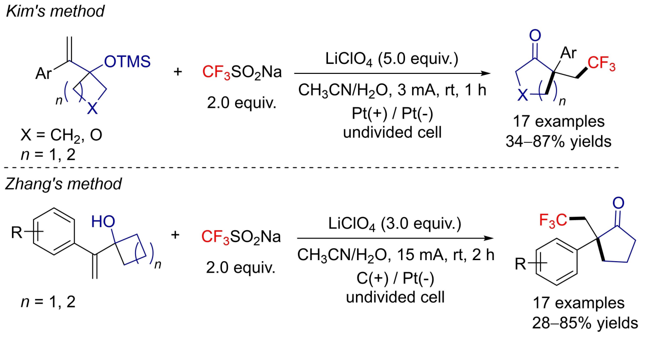
The application of Langlois' reagent in carbonyltrifluoromethylation reactions of allylic alcohols via 1,2-aryl or 1,2-alkyl migration was demonstrated by the groups of Xia, Cai, and Lei.[32d–f] The first transformation[32d] is a metal-free synthesis implemented in the presence of $(NH_4)_2S_2O_8$ resulting in the appropriate α-aryl-β-trifluoromethyl ketones after 1,2-aryl migration in good yields (Scheme 49a). The second reaction[32e] was promoted by organic photocatalyst 4CzIPN under visible-light irradiation (Scheme 49b), whereas the third protocol[32f] describes an electrochemical oxidative carbonyltrifluoromethylation reaction employing α,α-diaryl, α-alkyl-α-aryl or α,α-dialkyl allyl alcohols as substrates and Bu_4NBF_4 as the electrolyte (Scheme 49c). In the case of allyl alcohols bearing α-alkyl and α-



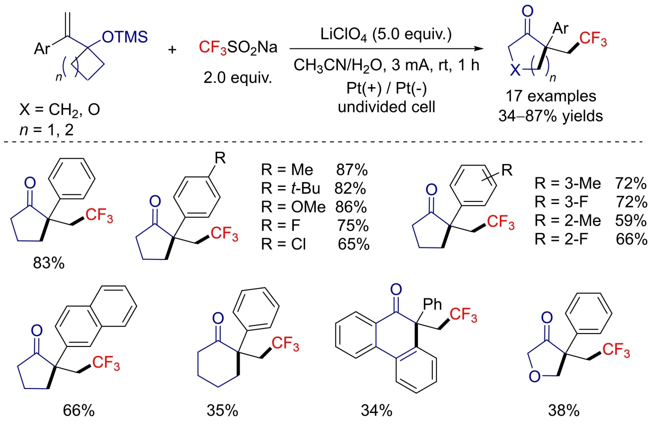
Scheme 52. Photoredox-catalyzed syntheses of trifluormethylated cyclic ketones with Umemoto's reagent by Kim and Glorius



Scheme 53. Visible-light-induced ruthenium-catalyzed synthesis of trifluormethylated cyclic ketones with Umemoto's reagent and TMSOTf.



Scheme 54. Electrochemical carbonyltrifluoromethylation of allylic cyclobutanols with Langlois' reagent by Kim and Zhang.

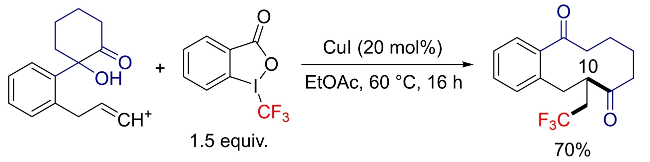


Scheme 55. Electrochemical synthesis of β-trifluoromethylated ketones with Langlois' reagent.

aryl substituents, the migration of the aryl moiety was observed.

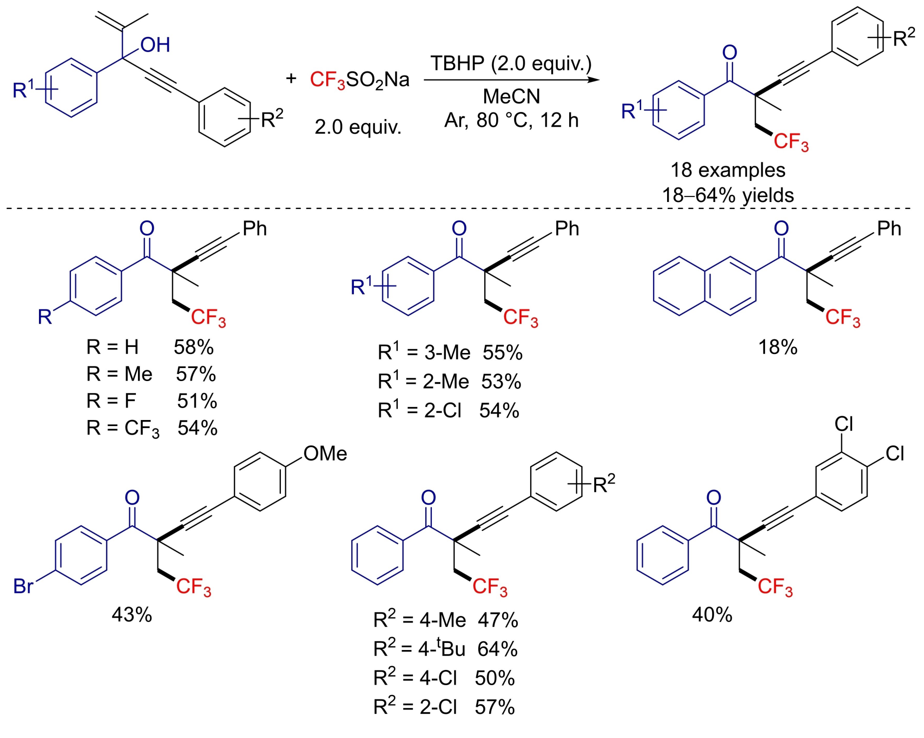
The efficiency and the high functional group tolerance of the method developed by Cai was tested over a wide substrate scope furnishing the desired products after 1,2-aryl migration in good to high yields (Scheme 50).

Concerning diaryl allylic alcohols presented above, Yu[32g] developed another transition-metal-free, visible-light-induced methodology for the construction of trifluoromethylated ketones. In this new version, Umemoto's reagent as the CF_3 source and K_2HPO_4 as the base were utilized. The synthesis of the desired carbonyltrifluoromethylated products via aryl migration was realized in isolated yields up to 97% yields (Scheme 51). Additionally, the protocol was also suitable for the preparation of (hetero)aryltrifluoromethylated products through distal heteroaryl migration.

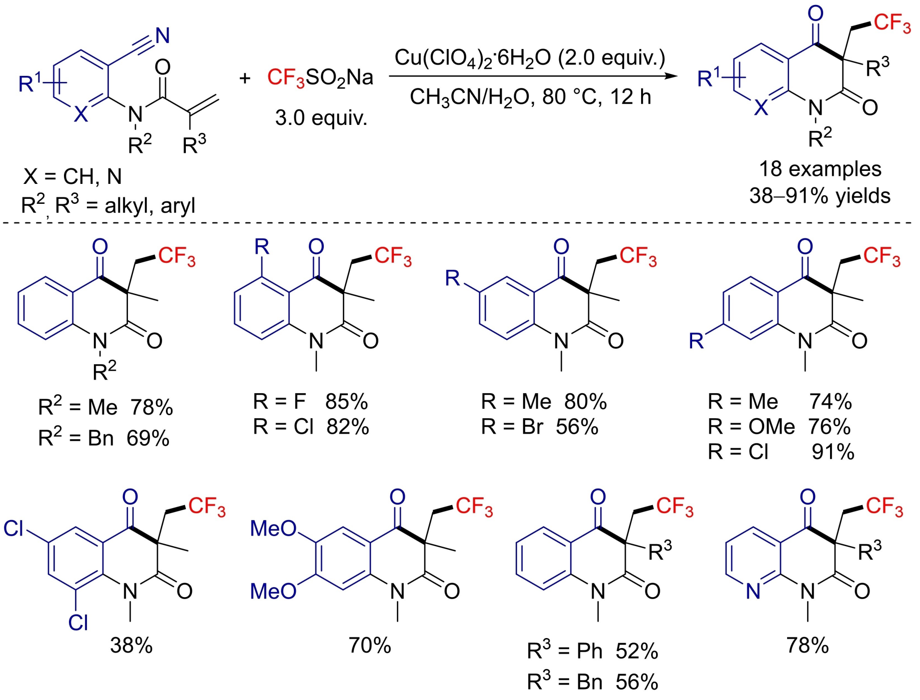


Scheme 57. Copper-catalyzed trifluoromethylcarbonylation of allylbenzene with Togni's reagent.

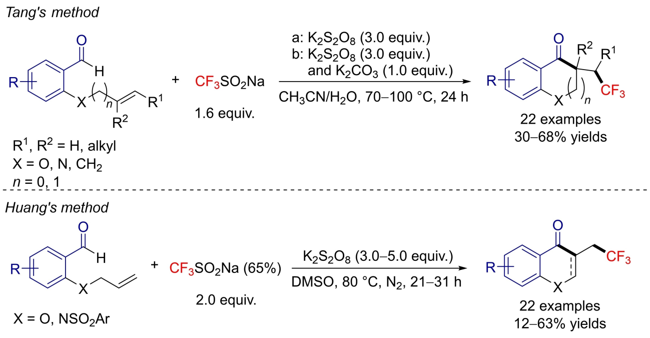
The employment of Umemoto's reagent was also demonstrated in two similar photoredox-catalyzed syntheses of CF_3-substituted cyclic ketones from 1-(1-arylvinyl)cyclobutanol derivatives, described by Kim[32h] and Glorius[32j] in 2015. In the first protocol,[32h] $Ru(phen)_3Cl_2$ was used as the catalyst of the transformation obtaining the corresponding products in 25–82% yields (Scheme 52a). According to the plausible mechanism of the reaction, the formation of a cationic intermediate was proposed to take place by single electron transfer, from which the desired cyclic ketones were generated via 1,2-carbon migration. In the method of Glorius32j, in addition to the utilization of Umemoto's reagent, TMSOTf was also applied in the reaction, realized in the presence of $[Ru(bpy)_3](PF_6)_2$ photocatalyst (Scheme 52b). The trifluoromethylation/ring expansion reaction proceeds via 1,2-alkyl migration delivering the desired cycloalkanones in moderate to good yields (Scheme 53).



Scheme 56. Carbonyltrifluoromethylation of 1,4-enynes with Langlois' reagent.



Scheme 58. Copper-mediated carbonyltrifluoromethylation of acrylamides with Langlois' reagent.



Scheme 59. Transition-metal-free carbonyltrifluoromethylation of 2-(allyloxy)arylaldehydes with Langlois' reagent by Tang and Huang.

Regarding the possible mechanism of the transformation, similar to Kim's proposal, radical trifluoromethylation and ionic ring expansion were suggested.

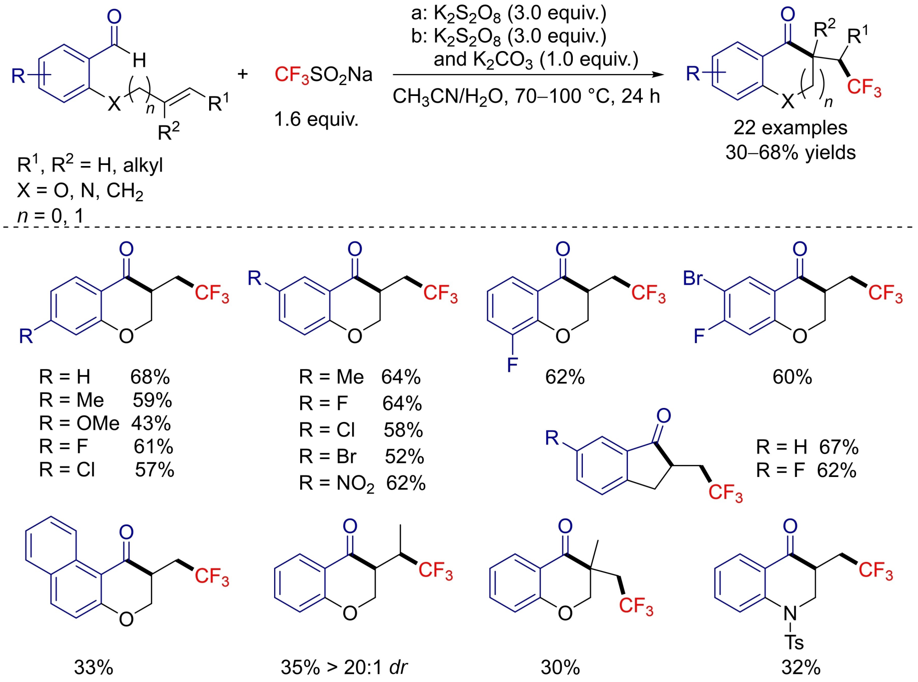
In 2019, two approaches were developed by Kim[32i] and Zhang[32k] in which the electrochemical carbonyltrifluoromethylation/semipinacol rearrangement of the same allylic cyclobutanol substrates with Langlois' reagent were achieved. In the method of Kim[32i] the TMS-substituted derivative of the alcohols was applied (Scheme 54a and Scheme 55), whereas in Zhang's protocol[32k] the allylic cyclobutanol was utilized (Scheme 54b). The desired β-trifluoromethylated ketones were afforded via 1,2-carbon migration in moderate to good yields. In both cases mechanistic investigations revealed that similar to the previous reports, radical trifluoromethylation and ionic ring expansion occur during the transformation.

In the same year, employing Langlois' reagent as the trifluoromethylating agent, Liang[32l] et al. reported the metal-free carbonyltrifluoromethylation of 1,4-enynes via 1,2-alkynyl migration. Reactions were carried out under mild conditions in the presence of *tert*-butyl hydroperoxide (TBHP) leading to the corresponding ketones in 18–64 % yields (Scheme 56). Additionally, difluoroalkylation of the appropriate 1,4-enyne substrates was also described using *N*-methylpiperidine as the base. Concerning the plausible mechanism of the transformations, a radical pathway was proposed through 3-*exo-dig* cyclization, followed by 1,2-alkynyl migration.

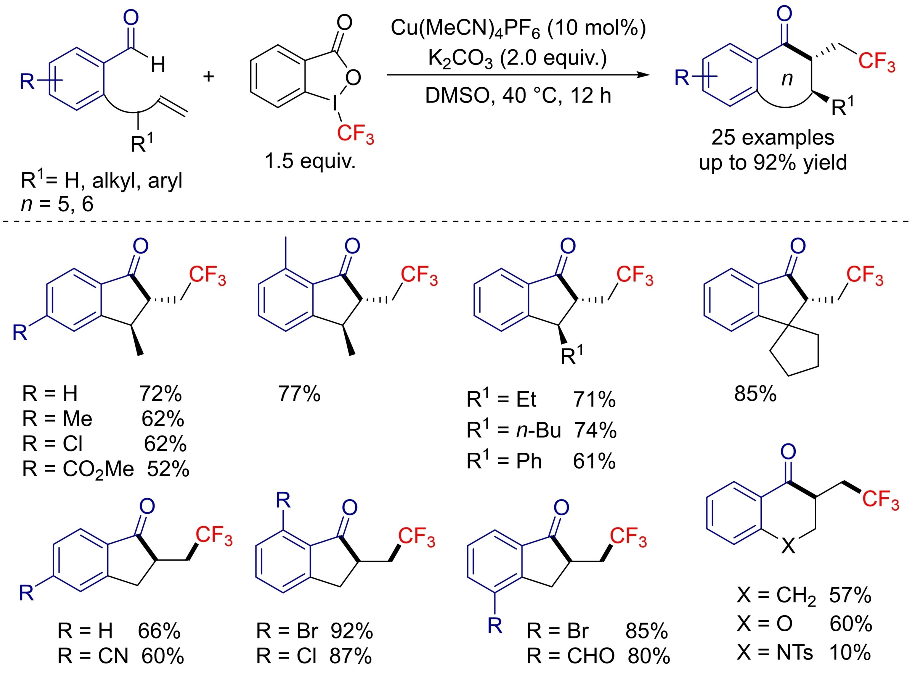
Furthermore, the radical-mediated copper-catalyzed trifluoromethylformylation of alkenes via 1,2(4,5)-formyl migration sequences was published by Liu[32m] in 2016 for the construction of diverse aromatic systems. The application describes the functionalization of an allylbenzene substrate for the synthesis of medium-sized molecules via 1,4- or 1,5-carbonyl migration processes. Scheme 57 shows an example about this trifluoromethylcarbonylation reaction in which Togni's reagent as the CF_3 source and CuI as the catalyst were applied furnishing the desired product through ring expansion in 70 % yield.

4.1.2. Reactions involving intramolecular cyclization

In the last decade, several approaches have been developed for the construction of different heterocyclic systems, such as quinolinones, chromanones or indanones, via intramolecular cyclization reactions employing Langlois' or Togni's reagent as the trifluoromethylating agent. In 2016, Li[53] and co-workers



Scheme 60. Transition-metal-free synthesis of chromane-4-ones and an 1-indanone with Langlois' reagent.

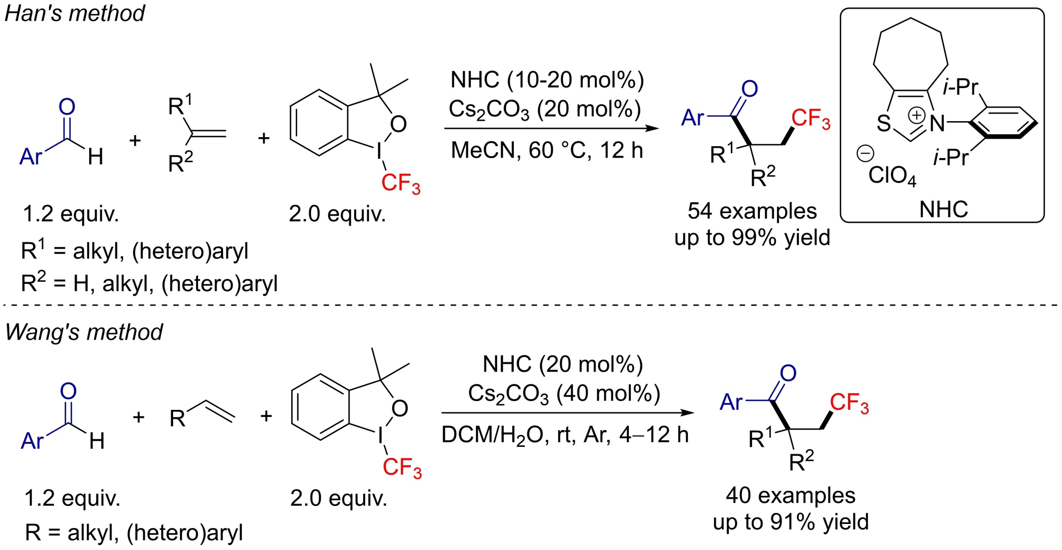


Scheme 61. Copper-catalyzed acyltrifluoromethylation of alkenes with Togni's reagent.

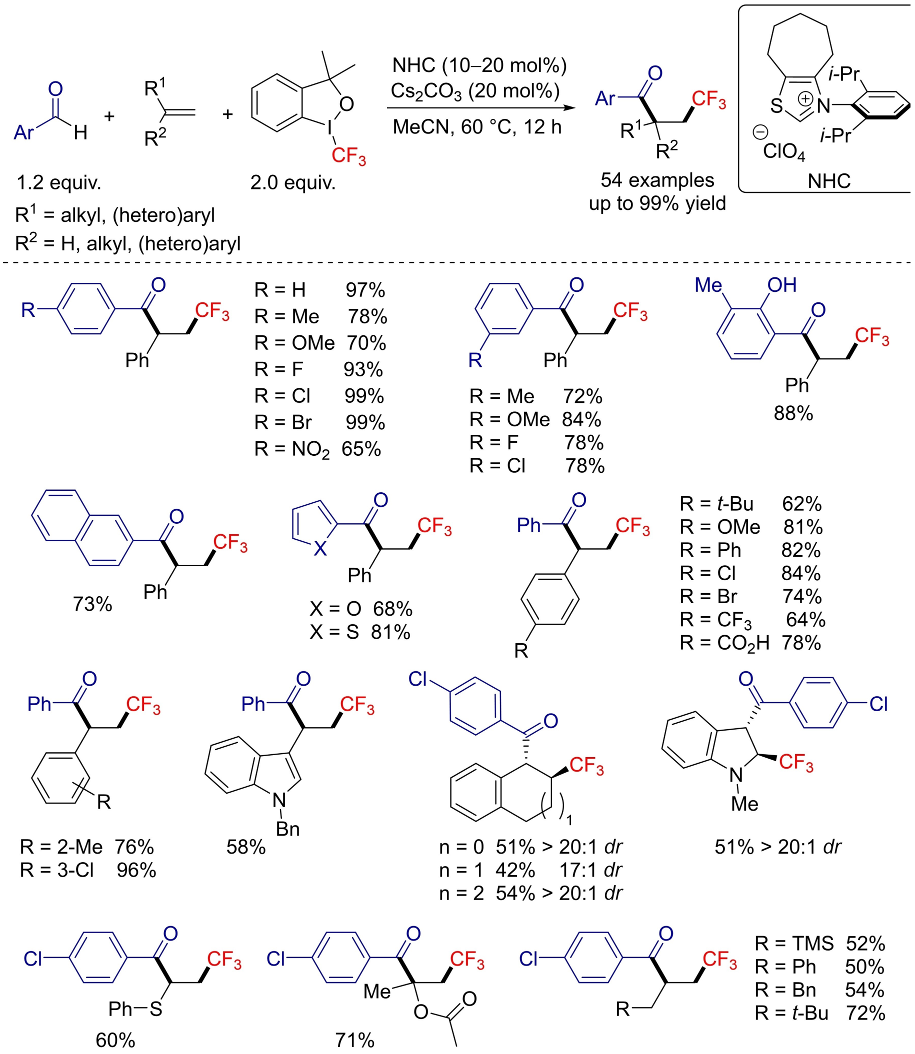
reported the copper-mediated oxidative radical addition/cyclization cascade of acrylamides in the presence of Langlois' reagent for the synthesis of trifluoromethylated quinolone-2,4(1*H*,3*H*)-diones. The desired carbonyltrifluoromethylated products were obtained in low to high yields (Scheme 58).

In 2018 and 2020, two similar transition-metal-free protocols were developed by Tang[54] and Huang[55] for the construction of chromane-4-one (Scheme 59a) and 4*H*-chromenone (Scheme 59b) scaffolds from 2-(allyloxy)arylaldehydes utilizing Langlois' reagent as the CF_3 source and $K_2S_2O_8$ as the oxidant of the transformations.

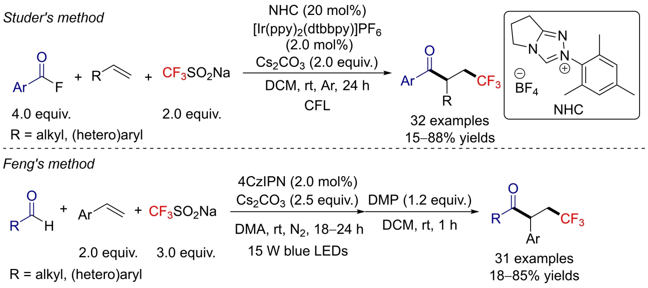
Additionally, the preparation of indanone derivatives from the corresponding vinyl-substituted arylaldehydes was also described by Tang (Scheme 60), whereas the method of Huang



Scheme 62. NHC-catalyzed three-component acyltrifluoromethylation reactions with Togni's reagent by Han and Wang.



Scheme 63. NHC-catalyzed three-component synthesis of β-trifluoromethylated ketones with Togni's reagent.



Scheme 64. Photoredox-catalyzed three-component trifluoromethylacylation of alkenes with Langlois' reagent by Studer and Feng.

includes the synthesis of 2,3-dihydroquinolin-4-ones as well from the appropriate nitrogen-substituted substrate. According to the plausible mechanism of the radical cascade cyclizations, the same reaction pathway was proposed in both cases with the only difference, that in Huang's transformation the appropriate 4*H*-chromenones are generated in the final oxidation step.

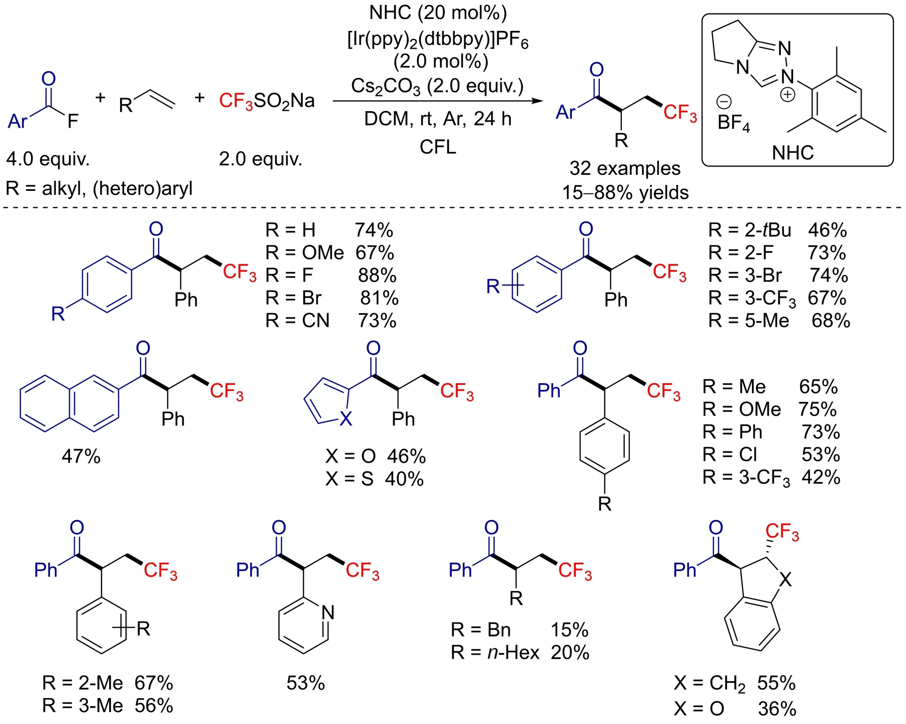
Another copper-mediated approach in which, in contrast to the method of Li,[53] only a catalytic amount of the catalyst was applied was published by Zhu[56] in 2017 executing the acyltrifluoromethylation of alkenes in the presence of Togni's reagent. The desired trifluoroethyl indanone, chromanone, and dihydroquinolinone derivatives were obtained in yields up to 92% (Scheme 61).

4.1.3. Intermolecular reactions

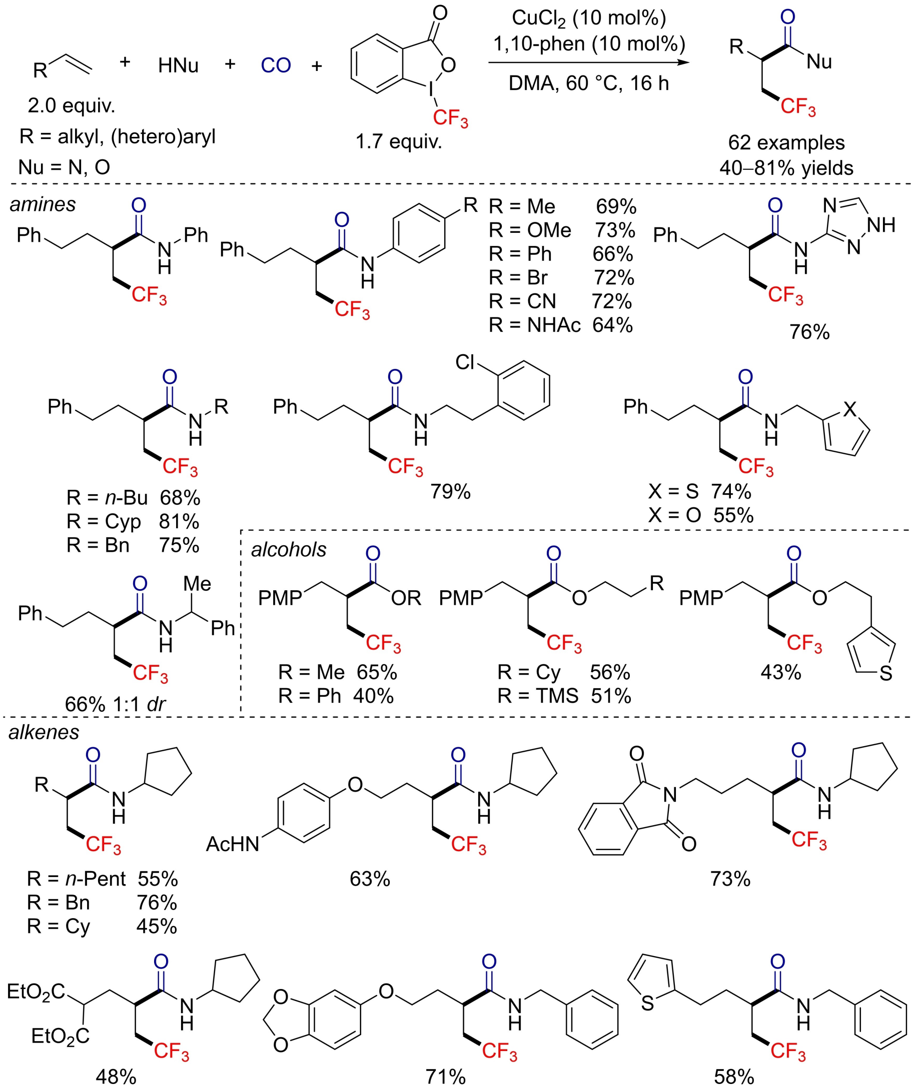
The carbonyltrifluoromethylation of alkenes via three-component coupling reactions, permitting the rapid assembly of more complex structures, has received intense interest in the last few years. In 2020, two very similar approaches were developed by Han[57] and Wang[58] for the radical acyltrifluoromethylation of styrene derivatives catalyzed by the NHC (N-heterocyclic carbene) organocatalyst employing Togni's reagent and (hetero)aromatic aldehydes (Scheme 62a and Scheme 62b). In both protocols, the cycloheptane-fused *N*-2,6-diisopropylphenyl-thiazolium salt as the NHC catalyst and Cs_2CO_3 as the base were applied, leading to the desired aromatic and heteroaromatic compounds in good to excellent yields.

The applicability of Han's method was demonstrated over a broad substrate scope with numerous examples. With the utilization of benzaldehydes, and styrene, 99% isolated yields were attained (Scheme 63). Additionally, the acyldifluoromethylation of alkenes was also achieved providing the corresponding products in good yields. Concerning the plausible mechanism of the reaction, the formation of a benzylic radical was assumed. Its recombination with a ketyl radical through a radical-radical cross-coupling pathway followed by the release of the NHC results in the final product.

The employment of Langlois' reagent in intermolecular carbonyltrifluoromethylation reaction of alkenes was accomplished by Studer[59] and Feng[60] in 2020 and 2022. In the first protocol the desired β-trifluoromethylated ketones were obtained via cooperative NHC and photoredox catalysis utilizing aroyl fluorides (Scheme 64a), whereas the second method was



Scheme 65. NHC- and photoredox-catalyzed carbonyltrifluoromethylation of alkenes with aroyl fluorides and Langlois' reagent.



Scheme 66. Copper-catalyzed carbonyltrifluoromethylation of unactivated alkenes with Togni's reagent for the preparation of trifluoromethylated aliphatic carboxylic acid derivatives.

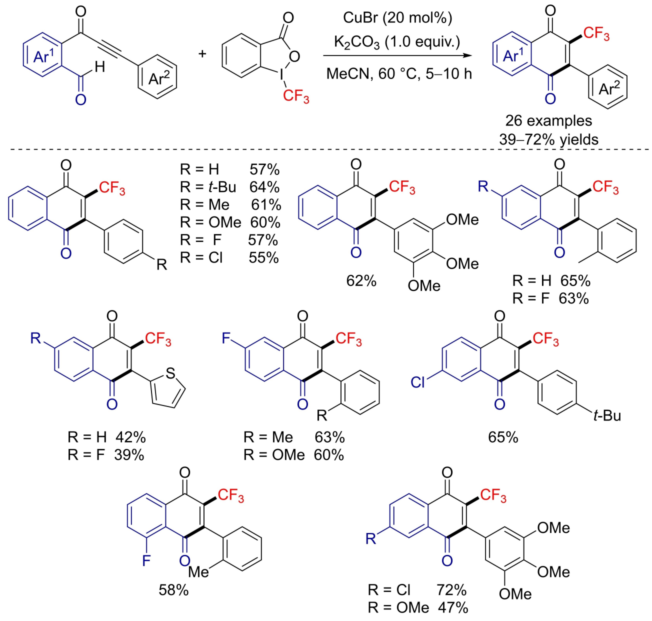
accomplished in the presence of aliphatic and (hetero)aromatic aldehydes, 4-CzIPN photocatalyst, and Dess-Martin periodinane (DMP) (Scheme 64b). In both cases Cs_2CO_3 was used as the base of the transformations.

Studer's work allows the synthesis of a variety of β-trifluoromethyl ketones with good functional group tolerance. The utilization of aromatic or heteroaromatic alkenes provided the corresponding products with good yields; however, in the case of aliphatic alkenes, only poor isolated yields were obtained (Scheme 65). Concerning the plausible mechanism of the reaction, similar to Han's and Wang's protocols,[57,58] the formation of the NHC-bound intermediate was proposed.

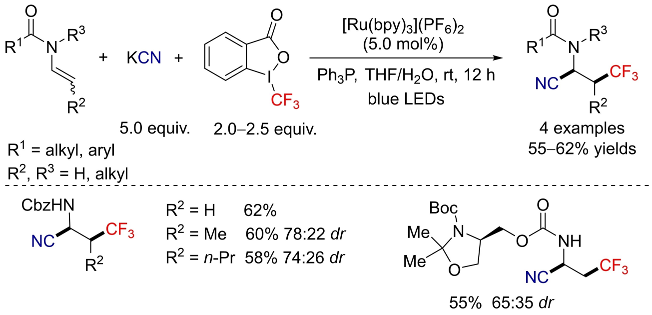
In the last year, the copper-catalyzed four-component carbonylative trifluoromethylation of unactivated alkenes with Togni's reagent and nitrogen (or oxygen) nucleophiles with the aid of CO was also realized by Wu[61] and co-workers. The developed procedure enables the synthesis of a variety of aromatic and aliphatic β-trifluoromethyl amides, esters, and acids with excellent functional group tolerance (Scheme 66). More than 60 examples were presented in good yields of the desired products.

4.2. Alkyne functionalization

Whereas several applications can be found for the functionalization of the carbon-carbon triple bond toward alkyltrifluoromethylation reactions, only a single approach has been reported for the carbonyltrifluoromethylation of alkynes. In 2017, Zhu[62] developed the first *trans*-acyltrifluoromethylation of internal alkynes for the synthesis of trifluoromethylated naphthoquinones via the CuBr-catalyzed intramolecular cyclization of 2-(3-arylpropioloyl)benzaldehydes with Togni's reagent. K_2CO_3 was employed as the base of the transformation providing the appropriate products in 39–72% yields under mild conditions (Scheme 67). Mechanistic investigations re-



Scheme 67. Copper-catalyzed cascade trifluoromethylation/cyclization of 2-(3-arylpropioloyl)-benzaldehydes with Togni's reagent.



Scheme 68. Ruthenium-catalyzed cyanotrifluormethylation of enecarbamates with Togni's reagent under visible-light.

vealed that the reaction comprise the formation of an alkoxyl radical, from which 1,2-hydrogen atom transfer followed by oxidation furnishes the corresponding trifluoromethylated naphthoquinone derivative.

5. Cyanotrifluoromethylation Reactions

The simultaneous addition of trifluoromethyl and cyano groups onto carbon-carbon double and triple bonds is a widely developed strategy of modern organic syntheses. In 2021, Han[63] et al. reported the recent advances on the halo- and cyanotrifluoromethylation of alkenes and alkynes summarizing the most significant contributions made in this area until 2021. Therefore, this chapter discusses only applications not included in this report.

In 2014, Masson[64] and co-workers published the photoredox-induced three-component oxy-, amino-, and carbotrifluoromethylation of enecarbamates utilizing Togni's reagent. Employing KCN as the nitrile source, the synthesis of four cyanotrifluormethylated products was realized in 55–62% yields (Scheme 68). According to the proposed reaction mechanism, a radical/cationic process was suggested involving the formation of an *N*-acyliminium cation, from which nucleophilic trapping of the nitrile provided the corresponding product.

In 2019, another photoredox-catalyzed approach was disclosed by Wang[65] for the dual-functional asymmetric cyanofluoroalkylation of aromatic alkenes in the presence of fluoroalkyl iodides and TMSCN induced by a chiral copper catalyst. The employment of bioxazoline ligand combined with CuI as the catalyst and dimethylbenzylamine (DMBA) as the base gave the best results. Beside the fluoroalkylation of several alkene substrates (introduction of C_4F_9, C_6F_{13}, and C_8F_{17} substituents), the synthesis of four cyanotrifluormethylated products was also demonstrated in 81–85% yields with excellent enantioselectivity (Scheme 69). Moreover, the protocol was suitable for the introduction of the difluoroethyoxycarbonyl group (CF_2CO_2Et) as well in good product yields. Mechanistic investigations revealed that the radical pathway includes the formation of a chiral Cu(III) species, which delivers the desired products in a subsequent reductive elimination.

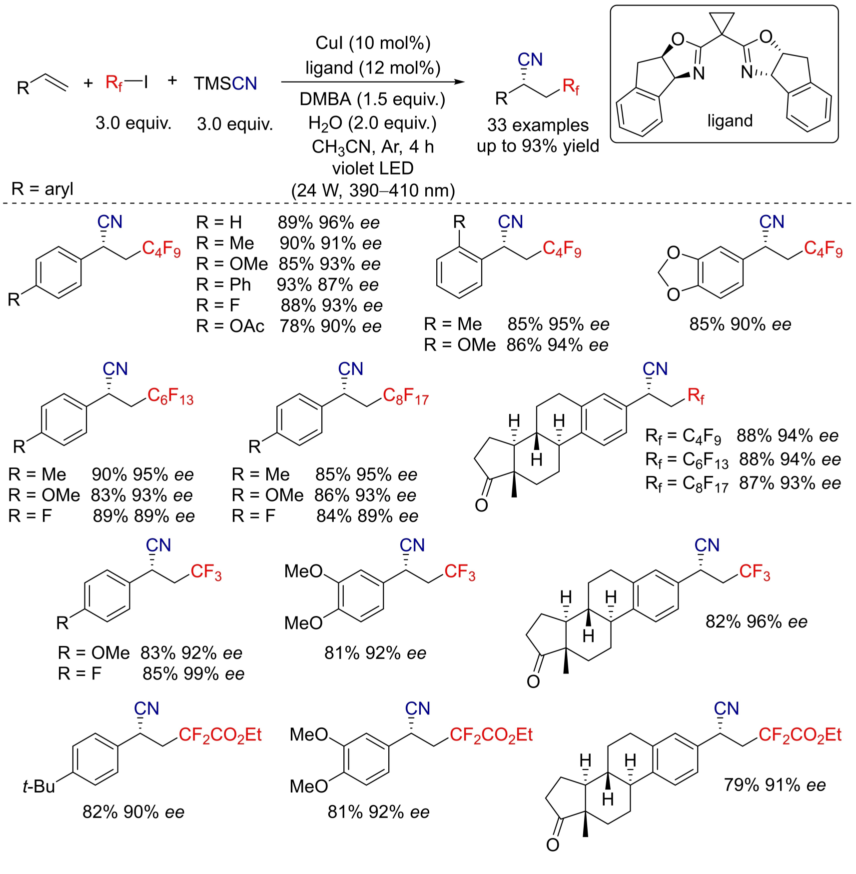
6. Summary and Outlook

In this report, we aimed to give a brief insight into the carbotrifluoromethylation reactions of carbon-carbon multiple bonds excluding aryl- and alkynyltrifluoromethylations. We can conclude that trifluoromethylation reagents presented here have been utilized for several applications in the last decade regarding the difunctionalization of alkene and alkyne moieties. Therefore, thanks to the unique chemical properties of these reagents, the construction of several diverse fluorine-containing aromatic, heteroaromatic, and non-aromatic systems were achieved.

It has been demonstrated that Togni's reagent and Langlois' reagent are the most commonly employed trifluoromethylation reagents, and they serve as excellent CF_3 sources for the difunctionalization of carbon-carbon double and triple bonds providing highly functionalized organofluorine derivatives. Due to their electrophilic, nucleophilic, and radical character, carbotrifluoromethylation reactions can take place under various circumstances. These protocols allow to build varied functionalities (alkenyl, alkyl, carbonyl, and cyano groups) into the corresponding organic scaffold.

Concerning the mechanism of these transformations, we can state that three reaction types were observed: intramolecular C-migration (alkenyl-, alkyl- or carbonyl), intramolecular cyclization, and intermolecular reactions. In the case of alkenyl- and alkyl-trifluoromethylations, the intramolecular cyclization is the most typical transformation. In the case of carbonyltrifluoromethylations, in turn, the intramolecular C-migration is proved to be the most typical reaction.

The carbotrifluoromethylation reactions summarized here were achieved both in the presence and in the absence of



Scheme 69. Copper-catalyzed cyanofluoroalkylation of aromatic alkenes with fluoroalkyl iodides and TMSCN under visible light irradiation.

transition metal catalyst. The most commonly used transition metal was copper. Furthermore, several accounts were published with the application of different iridium photocatalysts allowing the synthesis of the desired carbotrifluoromethylated product through visible-light-induced reaction.

The existing methods not only ensure easy access to highly functionalized organofluorine derivatives, but can also offer new mechanistic possibilities for the design of novel transformations in this intensively developing field of metal-free and transition-metal-catalyzed reactions in the future.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: addition · difunctionalization · fluorine · stereochemistry · trifluoromethylation

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