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Review

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Abstract

Over the years, the development of new methodologies for the introduction of various fluorinated motifs has gained a significant interest due to the importance of fluorine-containing molecules in the pharmaceutical and agrochemical industries. In a world eager to eco-friendlier tools, the need for innovative methods has been growing. To address these two challenges, copper-based reagents were developed to introduce CF_2H, CF_2R_F, CF_2CH_3, $CF_2PO(OEt)_2$ and CF_2SO_2Ph motifs on a broad range of substrates. Copper-based fluorinated reagents have the advantage of being inexpensive and generally in situ generated or prepared in a few steps, which make them convenient to use. In this review, an overview of the recent advances made for the synthesis of fluorinated molecules using copper-based fluorinated reagents will be given.

Introduction

In a society in which fluorinated molecules are playing a pivotal role in pharmaceutical and agrochemical industries as well as in materials science [1-4], the quest for innovation in the organofluorine chemistry field is of high importance. In that context, the development of new strategies is an important driving force [5-14], offering efficient and original tools to introduce a fluorine atom or a fluorinated moiety of unique properties [15]. Despite the tremendous advances made in that field, key synthetic challenges remain to synthesize fluorinated scaffolds. Among the different developed strategies to ravel synthetic issues, the use of inexpensive and readily available copper-based fluorinated reagents appeared over the years as a powerful tool in various transformations for the introduction of fluorinated moieties. Such strategy has already demonstrated a significant synthetic value for the trifluoromethylation of various compounds [16-27]. In contrast, available reagents for the incorporation of a CF_2R (R = H, alkyl, R_F, FG; FG = functional group) moiety remain restricted, despite the potential of these functionalized fluorinated moieties. In this review, the main contributions in the field of copper-based reagents for the introduction of CF_2H, CF_2FG, CF_2Me and CF_2R_F moieties over the last 5 years (period of 2014–2019) will be summarized. The design and the elaboration of either pre-formed or in situ-generated copper-based reagents was an efficient tool in several reactions. Note that only transformations involving the use of such copper-based reagents will be depicted and copper-catalyzed reactions are therefore beyond the scope of this review.

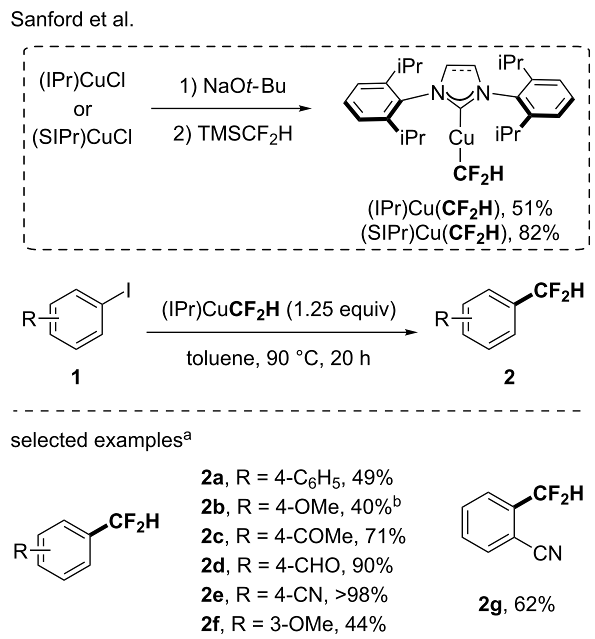
Review

Copper-based difluoromethylating reagents

In this section the key advances made to access copper-based difluoromethylating reagents are summarized. The CF_2H moiety [28-32], a well recognized alcohol and thiol bioisoster, is particularly attractive due to its unique features [33-36]. Besides, this residue is present in several bioactive compounds such as Deracoxib and Thiazopyr. In comparison with trifluoromethylcopper complexes, the difluoromethylcopper ones are less stable as demonstrated by the work of Burton in 2007 [37]. Investigations on the in situ synthesis of difluoromethylcopper from a difluoromethylcadmium source at low temperature and the study of its reactivity with various classes of compounds such as allylic halides, propargylic halides and tosylates, iodoalkynes and reactive alkyl halides were realized. It was established that $CuCF_2H$ readily decompose into 1,1,2,2-tetrafluoroethane and *cis*-difluoroethylene. From this pioneer work, attention was paid either to the design of new synthetic pathways for the synthesis of a well-defined copper-based reagent or to new tools for the in situ generation of an active $CuCF_2H$ species and its application in several transformations.

Pre-defined difluoromethylating reagents

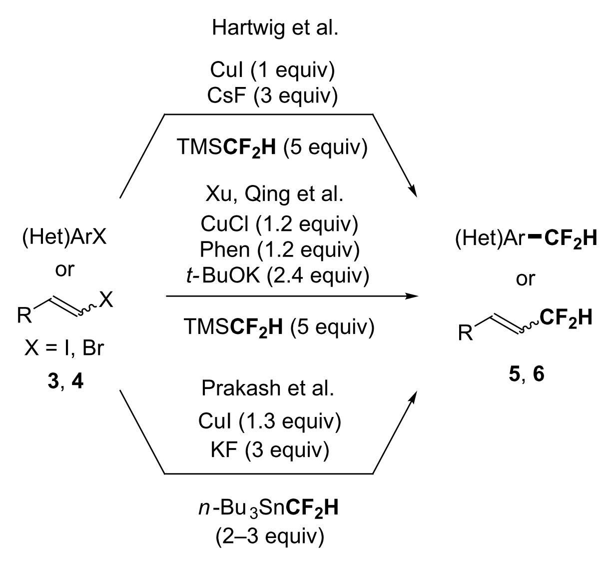
In the quest for well-defined and isolable MCF_2H species, Sanford depicted for the first time in 2017 the synthesis and characterization of isolable difluoromethylcopper(I) complexes [38]. The latter were prepared in a two-step sequence starting from the corresponding (NHC)CuCl as precursors in the presence of NaO*t*-Bu followed by the addition of $TMSCF_2H$ (Scheme 1). The latter was prepared in a one step synthesis after reduction of the Ruppert–Prakash reagent with sodium borohydride [39]. The key of success was the use of bulky IPr and SIPr ligands to stabilize the organometallic species. Indeed, in the case of IPr as a ligand, the complex was stable in solution at room temperature for at least 24 hours. The reactivity of the complex was then studied in stoichiometric reactions with aryl iodides and iodonium salts. The difluoromethylation reaction was smoothly carried out at 90 °C with electron-rich and electron-poor aryl iodides. However, the reaction was more efficient with electron-poor aryl iodides (Scheme 1). It is important to highlight that, in the course of their study for the synthesis of a stable and isolable $(NHC)CuCF_2H$ complex and the study of its reactivity, Sanford and co-workers demonstrated the possibility to develop a catalytic version of the reaction through the in situ generation of the active $(IPr)CuCF_2H$, starting from (IPr)CuCl [38].



Scheme 1: Synthesis of the first isolable $(NHC)CuCF_2H$ complexes from $TMSCF_2H$ and their application for the synthesis of difluoromethylated arenes from aryl iodides. [a]Yields were determined by ^{19}F NMR with fluorobenzene as the internal standard. [b]Reaction carried out at 120 °C.

In situ-generated copper-based difluoromethylating reagents

Although the review focused on the 2014–2019 period, a brief overview of seminal major advances should be given. In 2012, Hartwig and co-worker studied the difluoromethylation reaction of aryl and vinyl iodides by a copper-mediated transformation using $TMSCF_2H$ as the fluorinated source [39]. In this work, $CuCF_2H$ was suggested as the active species to promote the expected transformation. They highlighted that the formation of a cuprate species: $Cu(CF_2H)_2^-$, favoured by the presence of an excess of $TMSCF_2H$, might act as a reservoir of the unstable and reactive $CuCF_2H$ species. Xu and Qing reported a similar strategy for the difluoromethylation of electron-poor (hetero)aryl iodides at room temperature, using only 2.4 equivalents of $TMSCF_2H$ [40]. Note that the use of a strong base (*t*-BuOK) and 1,10-phenanthroline as a ligand was crucial in their system. In 2012, Prakash also studied the in situ generation of $CuCF_2H$ from $n\text{-}Bu_3SnCF_2H$, the presence of DMF being the key to stabilize the $CuCF_2H$ intermediate [41] (Scheme 2).

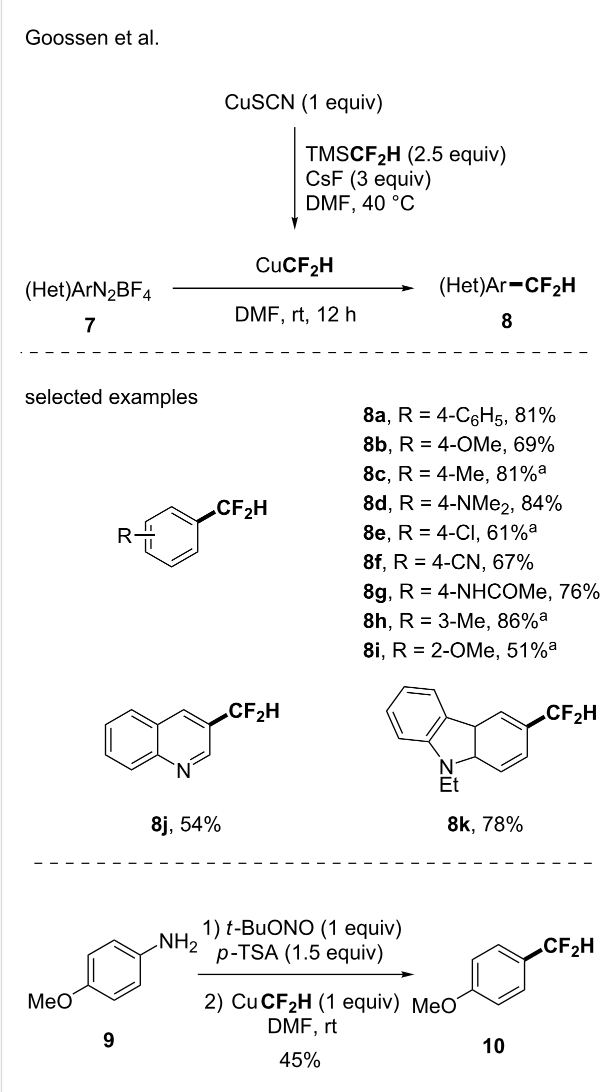


Scheme 2: Pioneer works for the in situ generation of $CuCF_2H$ from $TMSCF_2H$ and from $n\text{-}Bu_3SnCF_2H$. Phen = 1,10-phenanthroline.

From these seminal works, a handful of reports was then published by different research groups. In 2014, the group of Goossen astutely reported the in situ generation of the $CuCF_2H$ complex starting from $TMSCF_2H$, CuSCN and CsF as an activator in DMF. This approach was successfully applied in a Sandmeyer-type difluoromethylation reaction (Scheme 3) [42]. Starting from (hetero)aryldiazonium salts, a panel of difluoromethylated arenes and heteroarenes was obtained (26 examples, up to 84% yield). Note that the transformation was also carried out starting from 4-methoxyaniline followed by the in situ formation of the corresponding diazonium salt.

In the same vein, the authors used this in situ generation of a $CuCF_2H$ species to access high value-added difluoromethylthiolated molecules starting from organothiocyanates [43]. With this approach, they then developed a one pot, two-step sequence (generation of the organothiocyanates followed by the difluoromethylation step) for the functionalization of alkyl bromides, alkyl mesylates, aryldiazonium salts [43] as well as electron-rich arenes [44] (Scheme 4).

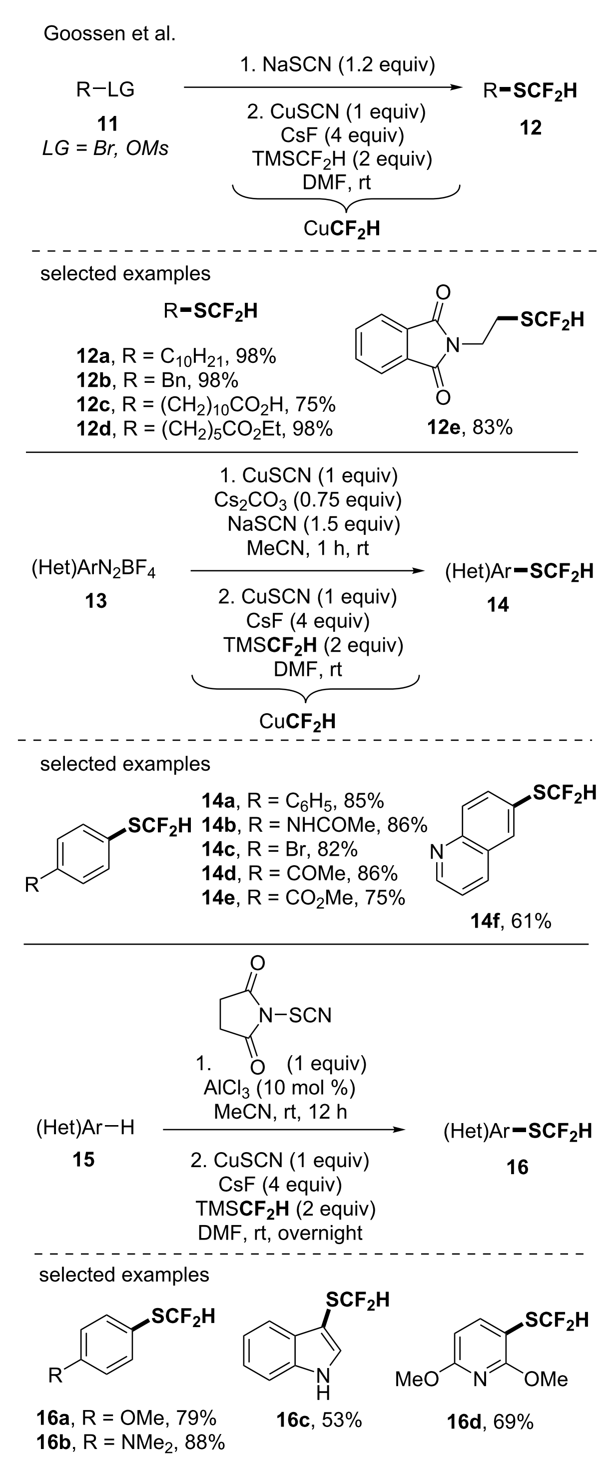
In 2015, the group of Qing investigated the oxidative difluoromethylation reaction of terminal alkynes with $TMSCF_2H$ via a copper-mediated reaction [45]. Using a stoichiometric amount of CuI, in the presence of *t*-BuOK and 9,10-phenanthraquinone, the functionalization of a panel of (hetero)aromatic and aliphatic terminal alkynes was achieved (Scheme 5). A good functional group tolerance was observed as alkynes bearing a cyano, ester, bromo or amino group among others were suitable substrates. Based on ^{19}F NMR studies, the authors suggested the following mechanism: first the in situ generation of a $CuCF_2H$



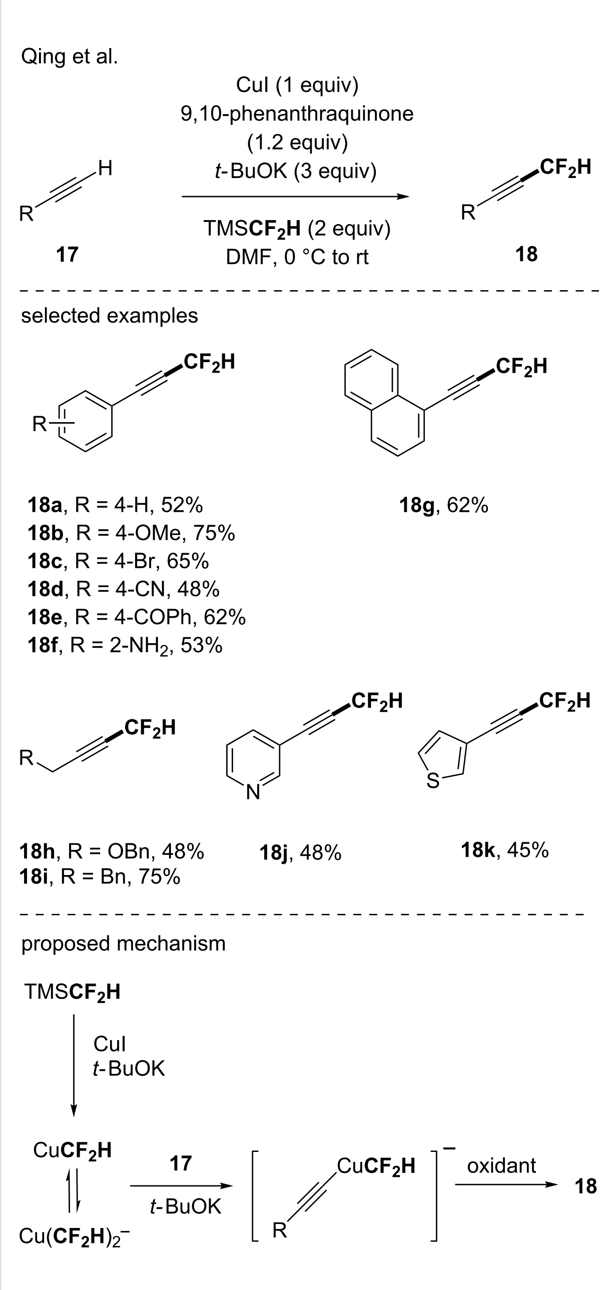
Scheme 3: A Sandmeyer-type difluoromethylation reaction via the in situ generation of $CuCF_2H$ from $TMSCF_2H$. [a] ^{19}F NMR yields determined using 2,2,2-trifluoroethanol as the internal standard.

complex from $TMSCF_2H$ in equilibrium with the corresponding cuprate ($Cu(CF_2H)_2^-$) occurred followed by the reaction with terminal alkynes under basic conditions. The resulting organocopper derivative was then oxidized resulting in the formation of the desired products.

Note that in 2018 the same group reported the copper-mediated oxidative difluoromethylation of heteroarenes under similar reaction conditions ($TMSCF_2H$, CuCN, 9,10-phenanthrenequinone, *t*-BuOK in NMP) [46]. Not only oxazoles (17 examples, up to 87% yield) were difluoromethylated but a variety of other heteroarenes turned out to be suitable such as pyridine, imidazole, benzo[*d*]thiazole, benzo[*b*]thiophene, benzo[*d*]oxazole, thiazole and thiophene derivatives (Scheme 6).



Scheme 4: A one pot, two-step sequence for the difluoromethylthiolation of various classes of compounds via the in situ generation of $CuCF_2H$ from $TMSCF_2H$.



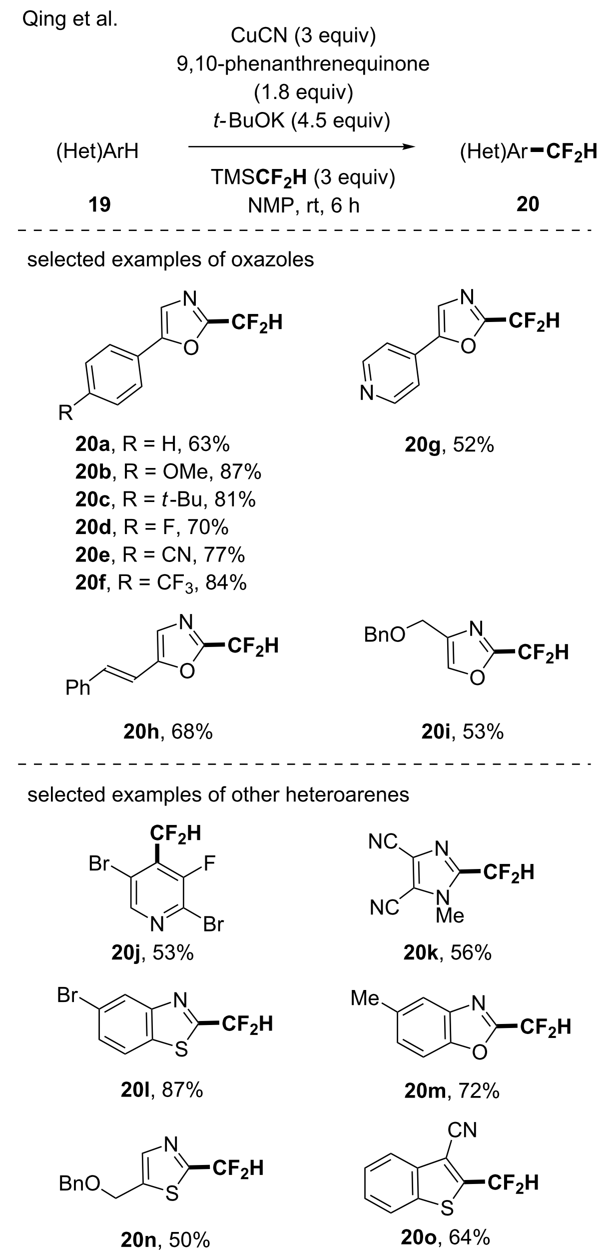
Scheme 5: A copper-mediated oxidative difluoromethylation of terminal alkynes via the in situ generation of a $CuCF_2H$ complex.

Copper-based CF_2FG-containing reagents

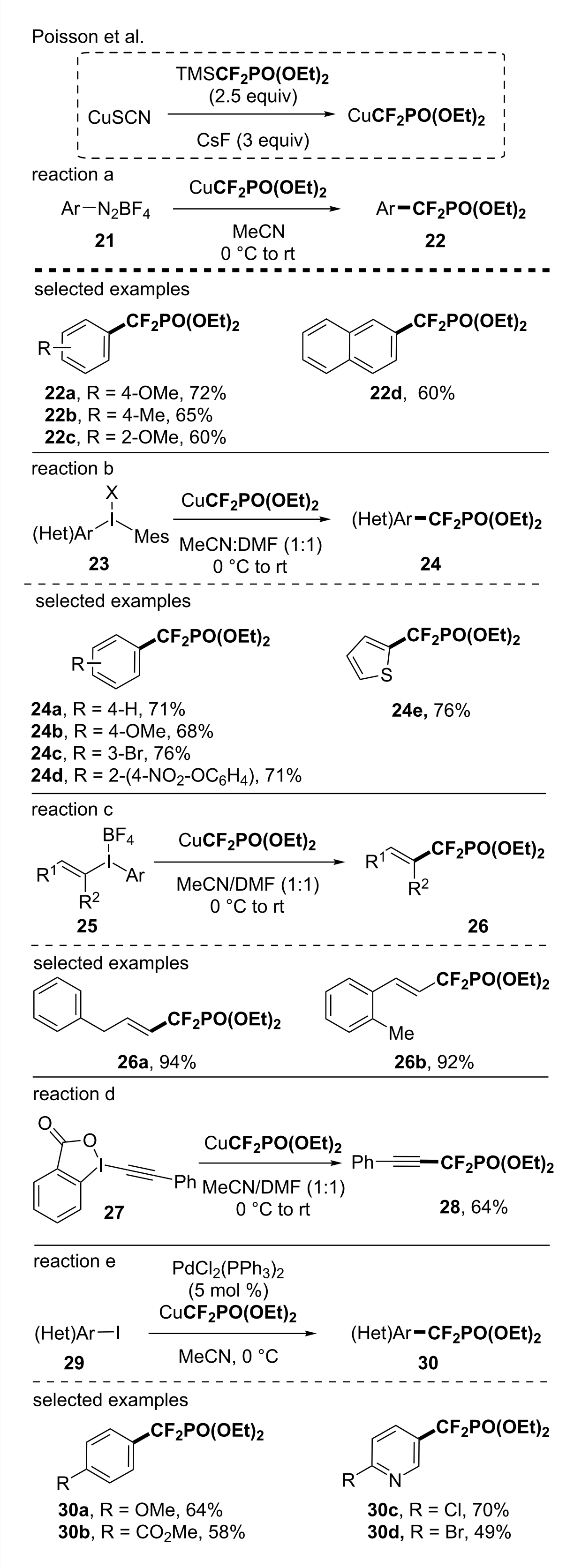
Besides the traditional CF_3 and CF_2H groups, a strong interest was devoted to other CF_2R groups (R = $PO(OEt)_2$, SO_2Ph and Me). In that aim, the development of copper-based reagents to introduce them onto molecules was studied over the last years and the major advances will be summarized in this section.

An in situ-generated copper-based $CF_2PO(OEt)_2$ reagent

As a bioisostere of the phosphonate group [47], a lot of attention was paid to the difluoromethylphosphonate residue as well as the development of efficient methodologies to introduce it onto molecules [48]. In that context, main contributions were made by the groups of Poisson and Goossen.



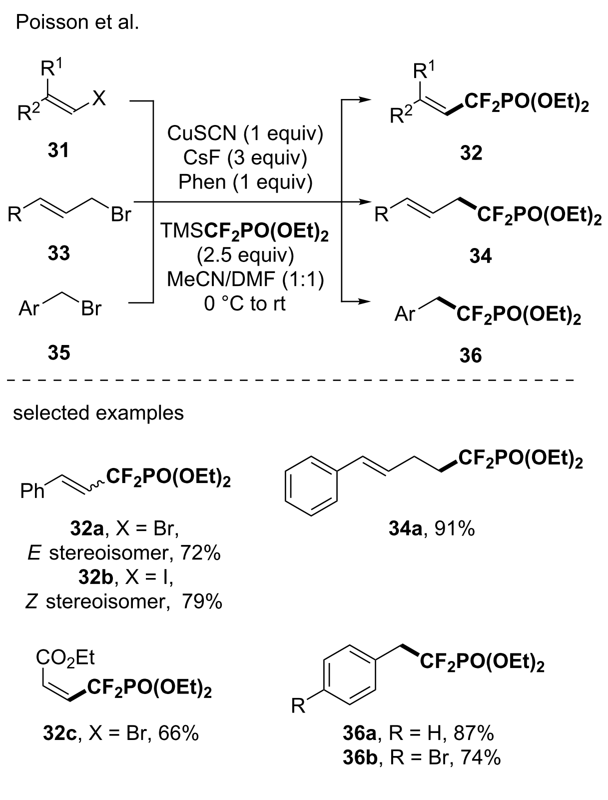
Scheme 6: A copper-mediated oxidative difluoromethylation of heteroarenes.



Scheme 7: Synthesis of difluoromethylphosphonate-containing molecules using the in situ-generated $CuCF_2PO(OEt)_2$ species.

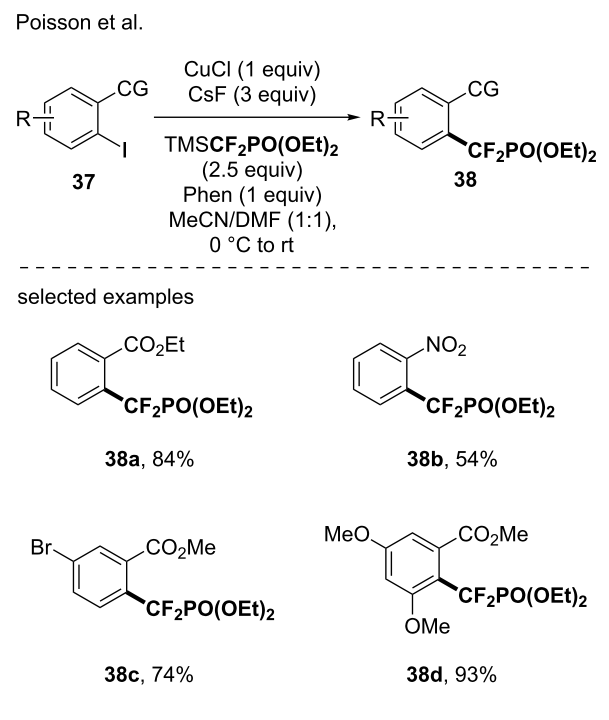
In the course of their study regarding the synthesis of difluoromethylphosphonate-containing molecules, Poisson and co-workers investigated the in situ generation of a $CuCF_2PO(OEt)_2$ species and its application to functionalize various classes of compounds [49-54]. The active species was prepared from $TMSCF_2PO(OEt)_2$, a copper salt and an activator. Note that the $TMSCF_2PO(OEt)_2$ was easily prepared from the commercially available $BrCF_2PO(OEt)_2$ and TMSCl under basic conditions [49]. The access to $CF_2PO(OEt)_2$-containing arenes was obtained after a Sandmeyer-type reaction (Scheme 7, reaction a) [49]. The reaction was efficient, although heteroaryl diazonium salts were reluctant in this reaction. To overcome these limitations, hypervalent iodinated species were used as substrates. The copper-mediated reaction with λ^3-iodanes demonstrated a large functional group tolerance and was efficiently applied to the synthesis of $CF_2PO(OEt)_2$-containing (hetero)arenes, alkenes and alkynes (Scheme 7, reactions b–d) [50]. Later on, the same group depicted the Pd-catalyzed introduction of the $CF_2PO(OEt)_2$ residue on (hetero)aryl iodides [51] by using an in situ-generated copper-based reagent (19 examples, up to 80% yield, Scheme 7e).

With a similar method and in the presence of 1,10-phenanthroline as a ligand, the functionalization of alkenyl halides (8 examples, up to 82% yield), allyl halides (7 examples, up to 99% yield) and benzyl bromides (6 examples, up to 87% yield) was investigated (Scheme 8) [52].



Scheme 8: Synthesis of difluoromethylphosphonate-containing molecules using in situ-generated $CuCF_2PO(OEt)_2$ species with 1,10-phenantroline as a ligand. Phen: 1,10-phenanthroline.

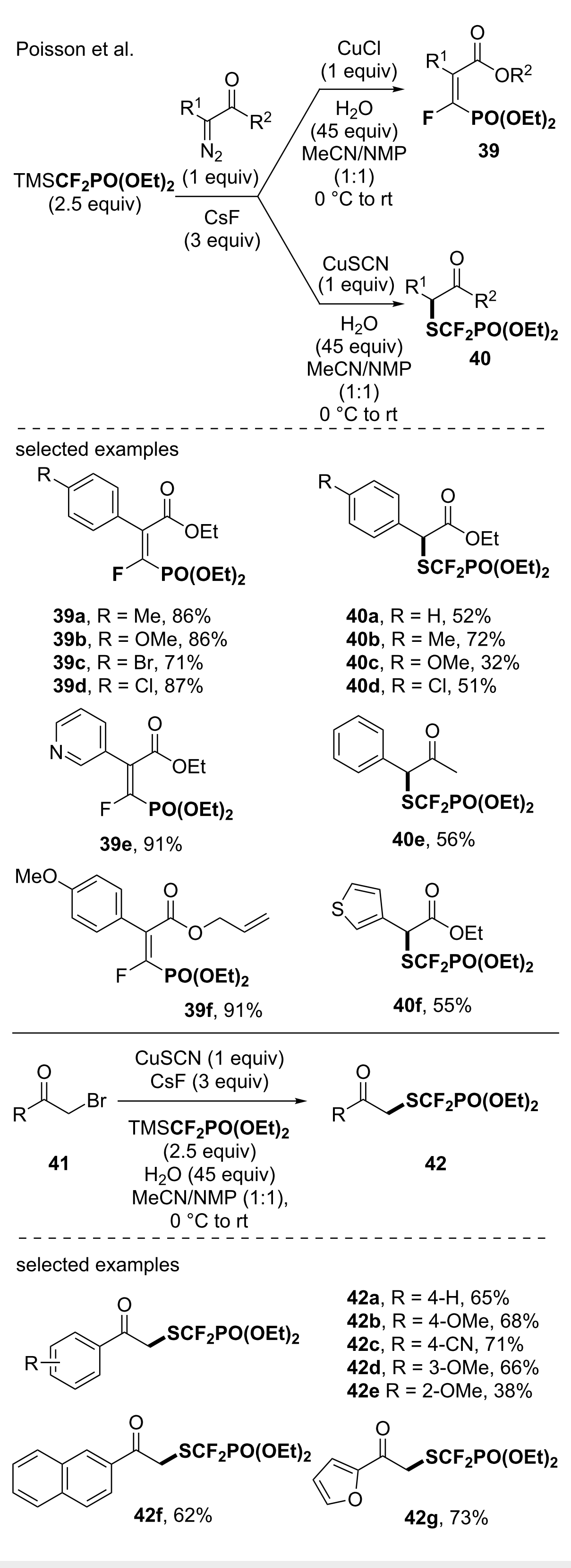
Finally, the Poisson's group developed a methodology for the Ullman cross-coupling reaction between the in situ-generated $CuCF_2PO(OEt)_2$ and aryl iodides containing a coordinating group (e.g., CO_2CH_3, $COCH_3$, NO_2), at the *ortho*-position of the halide [52]. This reaction broadened the portfolio of $CF_2PO(OEt)_2$-containing molecules leading to the corresponding compounds in good to excellent yields (Scheme 9). Note that the versatility of this methodology was further proved through its application to disulfides [52] with moderate to good yields.



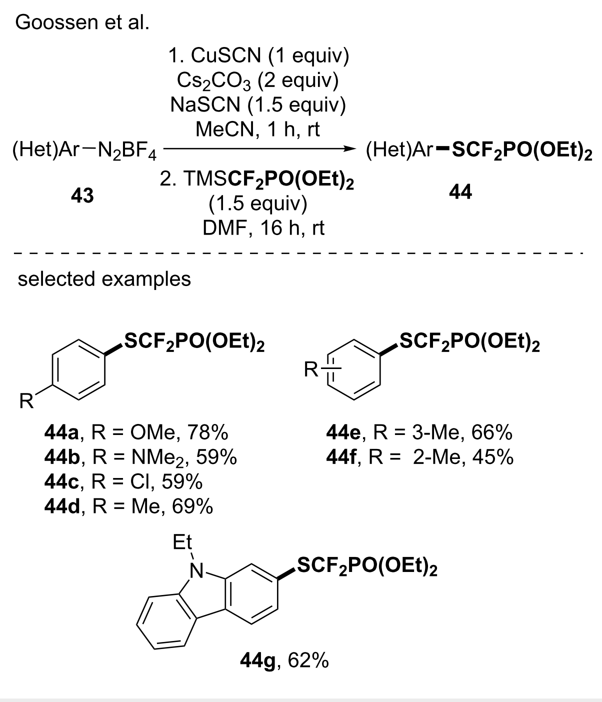
Scheme 9: Synthesis of difluoromethylphosphonate-containing molecules using in situ-generated $CuCF_2PO(OEt)_2$ species by an Ullman cross-coupling. CG = coordinating group.

Poisson and co-workers also reported the reaction of the $CuCF_2PO(OEt)_2$ reagent with α-diazocarbonyl derivatives. Depending on the copper salt used for the generation of the copper reagent, the reaction with α-diazocarbonyl derivatives provided either the α-fluorovinylphosphonate, in a stereoselective fashion, or the $SCF_2PO(OEt)_2$ derivatives [53]. In the same vein, the reaction of the $CuCF_2PO(OEt)_2$ species, generated from CuSCN, with α-bromoketones provided the α-$SCF_2PO(OEt)_2$-containing ketones [54] (Scheme 10).

In 2019, the group of Goossen developed an approach to access $SCF_2PO(OEt)_2$-containing arenes based on a Sandmeyer thiocyanation reaction followed by a Langlois-type nucleophilic substitution of the cyano group by the $CF_2PO(OEt)_2$ residue [55]. Several (diethylphosphono)difluoromethylthiolated products were obtained and this report further showcased the potential of using a copper-based reagent for the introduction of fluorinated moieties as this reaction involved the in situ generation of a suitable $CuCF_2PO(OEt)_2$ species (Scheme 11).



Scheme 10: Synthesis of (diethylphosphono)difluoromethylthiolated molecules using in situ-generated $CuCF_2PO(OEt)_2$ species. Phen: 1,10-phenanthroline.



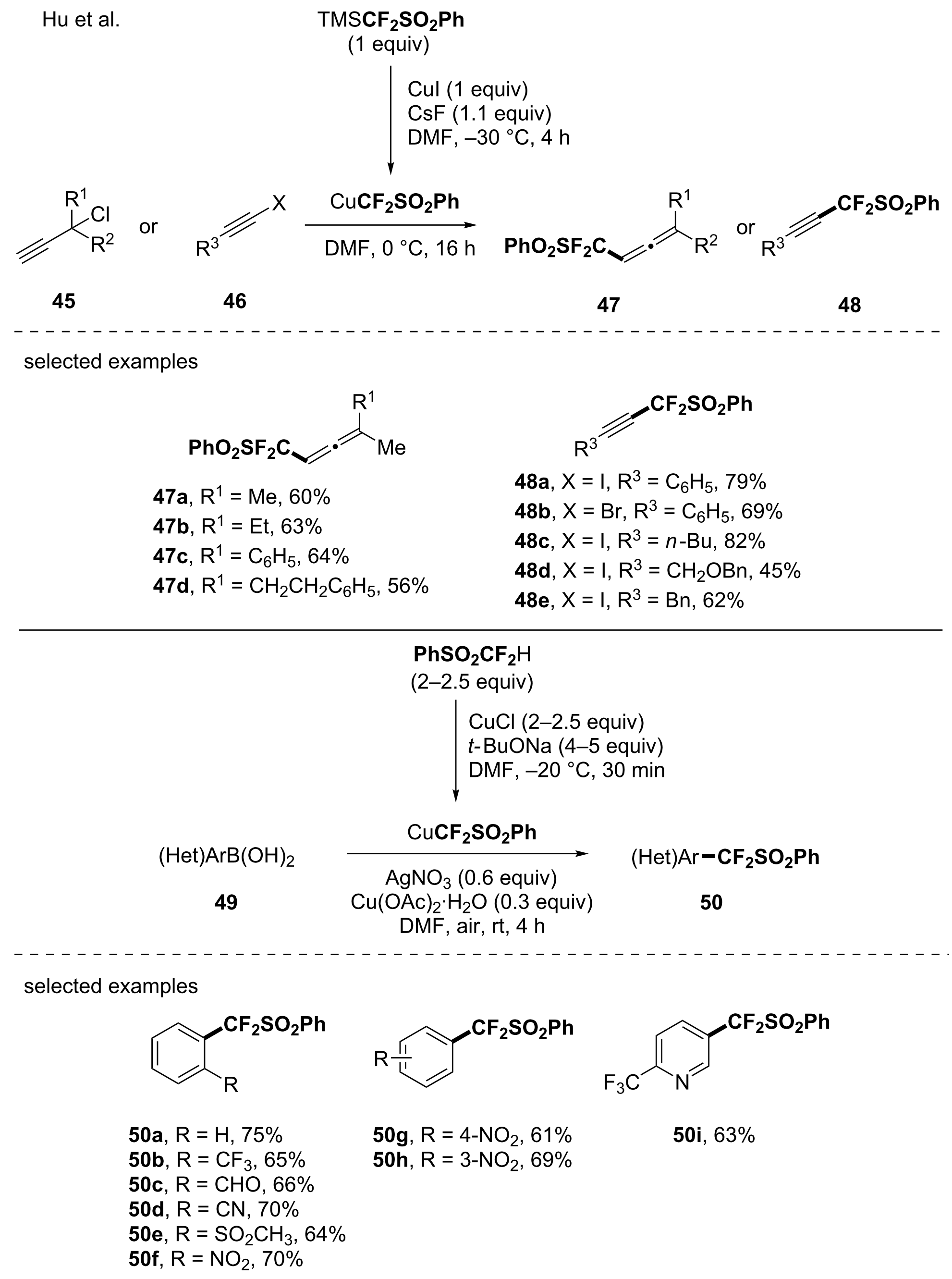
Scheme 11: Access to (diethylphosphono)difluoromethylthiolated molecules via the in situ generation of $CuCF_2PO(OEt)_2$ species.

An in situ-generated copper-based CF_2SO_2Ph reagent

As a long standing interest to the $PhSO_2CF_2$ moiety [56-60] thanks to its unique features, the group of Hu investigated the generation of the $PhSO_2CF_2Cu$ species from $PhSO_2CF_2TMS$, CuI and CsF in DMF [61] (Scheme 12). Note that $PhSO_2CF_2TMS$ was prepared from $PhSO_2CF_2Br$ after treatment with *n*-BuLi and TMSCl [61]. Due to its relatively low stability at room temperature, $PhSO_2CF_2Cu$ was in situ generated and applied to the (phenylsulfonyl)difluoromethylation reaction of propargyl chlorides and alkynyl halides, offering an access to the corresponding fluorinated allenes (6 examples) and alkynes (8 examples). In 2016, still interested by this versatile fluorinated moiety, the same authors demonstrated that the $PhSO_2CF_2Cu$ species might be prepared from difluoromethylphenylsulfone ($PhSO_2CF_2H$) and used it to functionalize an array of (hetero)aromatic boronic acids [62] (Scheme 12). The transformation showed a good functional group tolerance (aldehyde, CN, halogens). Note that the synthetic utility of the CF_2SO_2Ph group was further demonstrated by its conversion into the high value-added CF_2H moiety after treatment with Mg/AcOH/AcONa.

An in situ-generated copper-based CF_2CH_3 reagent

A strong interest was dedicated to the CF_2CH_3 residue, an important moiety in medicinal chemistry [63]. Among the different approaches developed to synthesize CF_2CH_3-containing

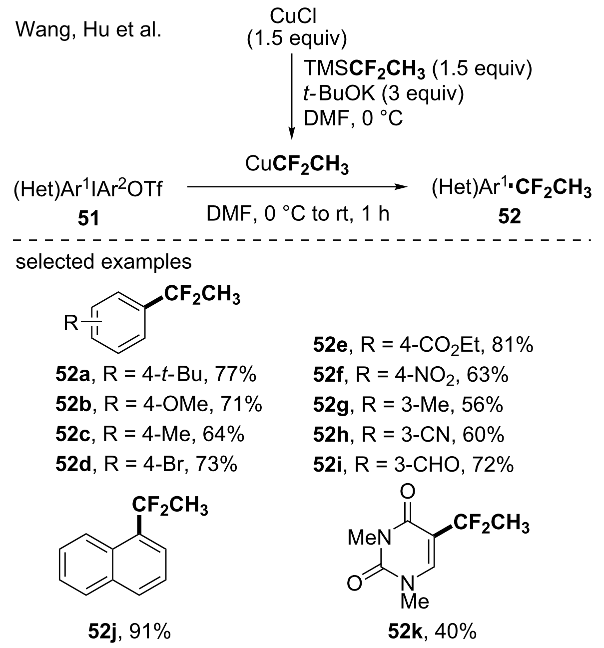


Scheme 12: Synthesis of (phenylsulfonyl)difluoromethyl-containing molecules via the in situ generation of $CuCF_2SO_2Ph$ species.

molecules, Wang, Hu and co-workers demonstrated the possibility to use 1,1-difluoroethylsilane ($TMSCF_2CH_3$) as a precursor for the in situ generation of the corresponding $CuCF_2CH_3$ species [64]. The synthetic utility of this copper-based reagent was illustrated through the 1,1-difluoroethylation of diaryliodonium salts, leading to the corresponding (1,1-difluoroethyl)arenes in moderate to high yields (Scheme 13). The transformation turned out to be functional group tolerant and even heteroaromatic compounds were functionalized.

Copper-based CF_2R_F reagents

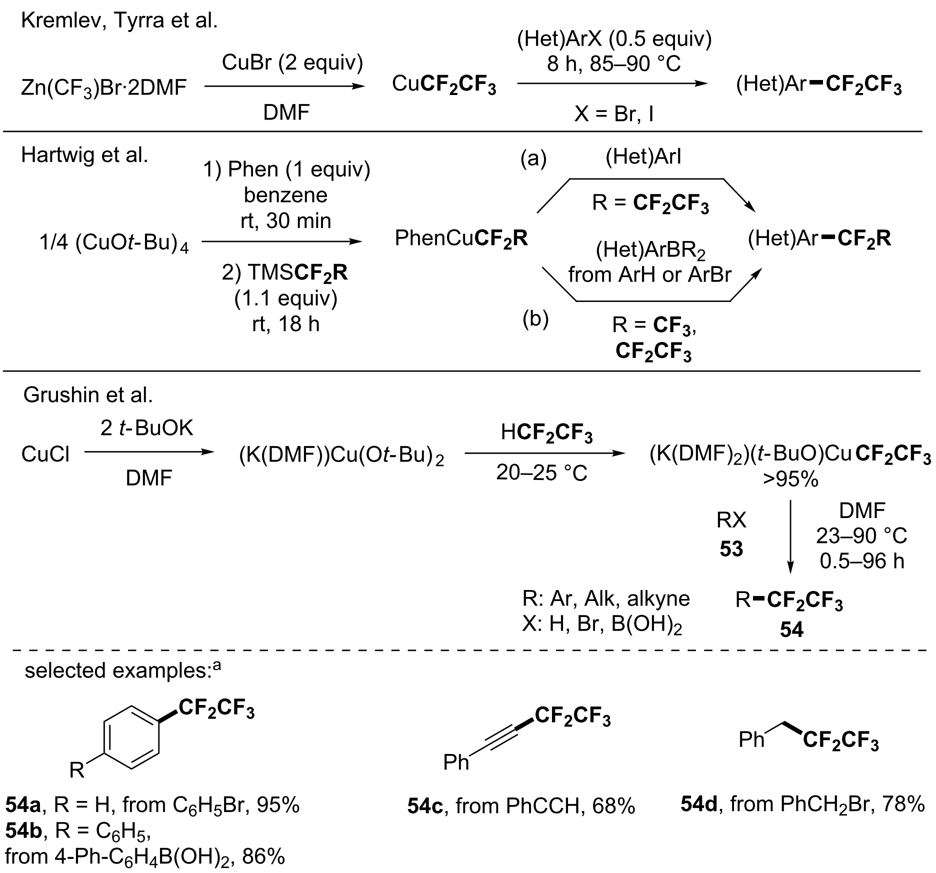
Due to the importance of perfluorinated moieties [2] and since their synthesis could not be achieved from the fluorination of the corresponding alkyl chains like in case of perfluoroalkyl arenes, several research groups investigated the synthesis of CF_2R_F-containing molecules via the use of perfluoroalkyl copper species. Before 2014, key contributions were made by the groups of Kremlev, Tyrra [65], Hartwig [66,67] and Grushin [68] as briefly summarized below. These major advances paved



Scheme 13: Copper-mediated 1,1-difluoroethylation of diaryliodonium salts by using the in situ-generated $CuCF_2CH_3$ species.

the way towards the synthesis of important pentafluoroethylated and more generally perfluoroalkylated molecules. Kremlev, Tyrra and co-workers depicted the in situ generation of a $CuCF_2CF_3$ species by mixing $Zn(CF_3)Br·2DMF$ and CuBr [65], and its application for the functionalization of (hetero)aryl halides (Scheme 14).

In the course of their studies to develop stable and well-defined copper reagents for perfluoroalkylation reactions [66], Hartwig developed in 2011 the $(Phen)CuCF_3$ and $(Phen)CuCF_2CF_2CF_3$ complexes from inexpensive reagents. Indeed, when mixing $(CuO\textit{t}\text{-}Bu)_4$, 1,10-phenanthroline and the corresponding $TMSR_F$, the perfluoroalkyl copper complexes were isolated for the first time (Scheme 14, a). One year later, they demonstrated that these copper-based reagents ($(Phen)CuCF_2R_F$, R_F = F, CF_3 and CF_2CF_3) were efficient in a two-step sequence reaction (borylation/perfluoroalkylation) allowing the functionalization of either sterically hindered arenes or aryl bromides with the CF_2CF_3 and $CF_2CF_2CF_3$ moieties (Scheme 14, b) [67]. In 2013, the group of Grushin reported the synthesis, characterization and application of a copper-based pentafluoroethylating reagent (Scheme 14) [68]. Using the cost-efficient pentafluoroethane as



Scheme 14: Pioneer works for the pentafluoroethylation and heptafluoropropylation using a copper-based reagent. Phen = 1,10-phenanthroline. [a] ^{19}F NMR yields determined using 1,3-bis(trifluoromethyl)benzene as the internal standard.

a precursor, the $(K(DMF)_2)(t\text{-BuO})Cu(CF_2CF_3)$ complex was prepared either from the pre-isolated $(K(DMF))Cu(Ot\text{-Bu})_2$ or in situ from CuCl, t-BuOK in DMF in a nearly quantitative yield. The copper reagent was used for the pentafluoroethylation of a panel of (hetero)aryl iodides and bromides (up to 99% ^{19}F NMR yield) and its synthetic utility was further demonstrated with the functionalization of different classes of compounds (benzyl and vinyl bromides, 4-biphenylboronic acid, phenylacetylene for instance).

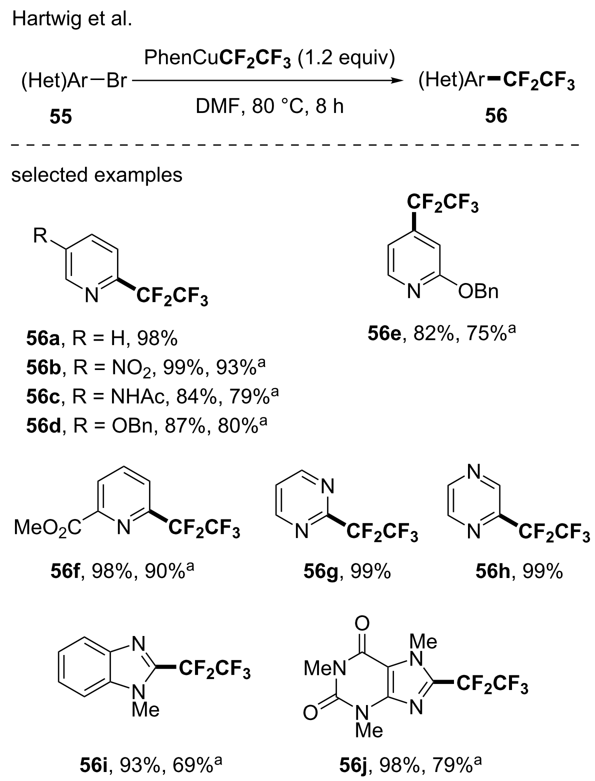
From these pioneering reports of perfluoroalkylation (trifluoromethylation, pentafluoroethylation and heptafluoropropylation), several groups studied the synthesis and/or the application of copper-based reagents in various transformations as depicted in this section. This latter will be organized into two sub-sections depending if the CuR_F-reagent was well-defined or in situ generated.

Well-defined pentafluoroethylating reagents

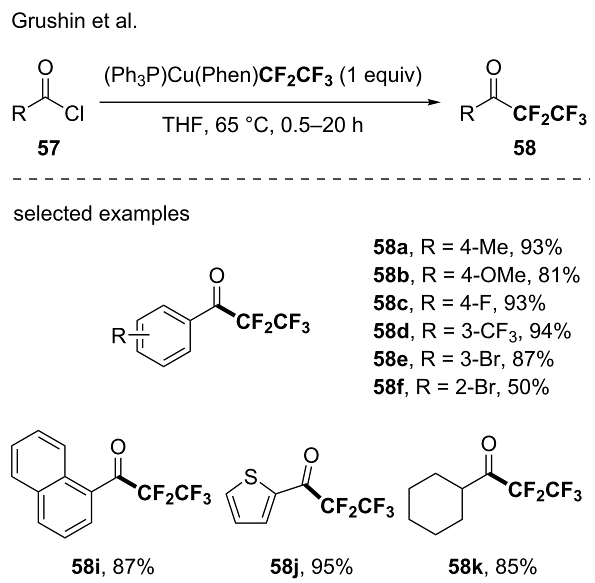
In 2014, a report from Hartwig dealt with the copper-mediated perfluororalkyaltion of (hetero)aryl bromides using the previously developed $PhenCuR_F$ [69]. Although the trifluoromethylation reaction was mainly studied, the methodology was efficiently extended to the pentafluoroethylation of various heteroarenes such as pyridine, pyrimidine and quinolone derivatives, for instance, when the $PhenCuCF_2CF_3$ complex was used as the pentafluoroethyl source (24 examples, up to 99% ^{19}F NMR yield and up to 93% isolated yield, Scheme 15). Note that a complete mechanistic study was recently reported to explain the reactivity of this well-designed complex [70].

In 2015, Grushin reported the generation of four well-defined CuC_2F_5 complexes, namely $(Ph_3P)_2CuCF_2CF_3$, $(bpy)CuCF_2CF_3$, $(IPr^*)CuCF_2CF_3$ and $(Ph_3P)Cu(Phen)CF_2CF_3$. The reactivity of the latter was studied for the synthesis of pentafluoroethyl ketones from acyl chlorides [71]. Indeed, the pentafluoroethylation of a large panel of acyl chlorides (23 examples) was achieved illustrating the synthetic utility and the efficiency of the newly designed $(Ph_3P)Cu(phen)CF_2CF_3$ reagent (Scheme 16).

Huang and Weng and co-workers reported the synthesis of air-stable perfluorocarboxylatocopper(I) complexes and their use in the perfluoroalkylation of (hetero)aryl halides [72]. By mixing t-BuOCu, in situ generated from CuCl and t-BuONa, with 1,10-phenanthroline, followed by a reaction with perfluorocarboxylic acids, four $(Phen)_2Cu(O_2CCF_2R_F)$ complexes were synthesized (R_F = CF_3, CF_2CF_3, $CF_2CF_2CF_3$ and $CF_2CF_2CF_2CF_3$). The reaction was efficient (65 examples, up to 97% yield), showed a good functional group tolerance (i.e., cyano, ester, ketone) and even heteroarenes such as pyridine,

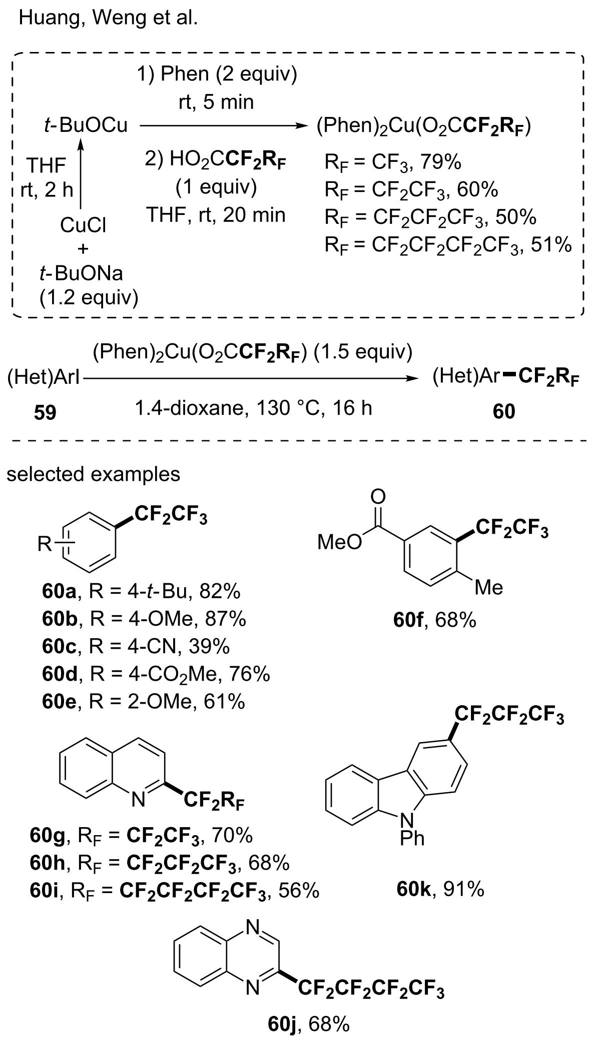


Scheme 15: Pentafluoroethylation of (hetero)aryl bromides using the $(Phen)CuCF_2CF_3$ complex. ^{19}F NMR yields were determined using 4-trifluoromethoxyanisole as the internal standard. [a]Isolated yields.



Scheme 16: Synthesis of pentafluoroethyl ketones using the $(Ph_3P)Cu(phen)CF_2CF_3$ reagent. ^{19}F NMR yields were given using 1,3-bis(trifluoromethyl)benzene as the internal standard.

quinoline and quinoxaline were functionalized with the four fluorinated moieties (Scheme 17).

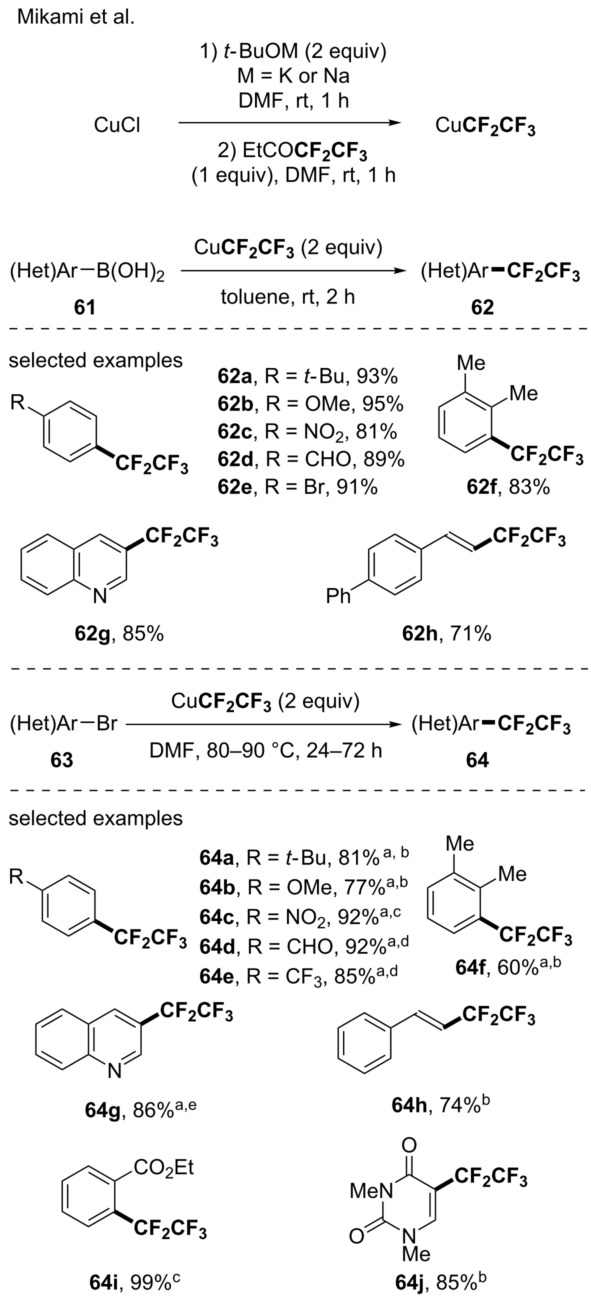


Scheme 17: Synthesis of $(Phen)_2Cu(O_2CCF_2RF)$ and functionalization of (hetero)aryl iodides.

In situ-generated copper-based pentafluoroethylating reagents

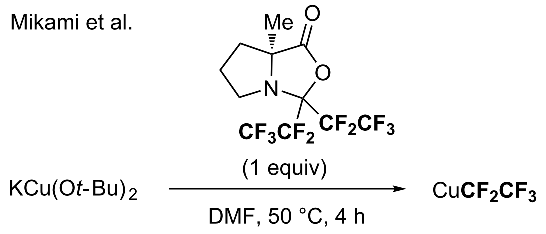
Several research groups investigated the generation of a $CuCF_2CF_3$ species from different fluorinated precursors offering various technological solutions.

In 2014, a study from Mikami reported the functionalization of a panel of (hetero)arylboronic acids (10 examples, up to 95% yield) and (hetero)aryl bromides (11 examples, up to 98% ^{19}F NMR yield) via the in situ generation of the suitable $CuCF_2CF_3$ from CuCl, KO*t*-Bu or NaO*t*-Bu and ethyl pentafluoropropionate [73]. Note that the methodology was also applied to the functionalization of a vinylboronic acid and a vinyl bromide (Scheme 18).



Scheme 18: Pentafluoroethylation of arylboronic acids and (hetero)aryl bromides via the in situ-generated $CuCF_2CF_3$ species from ethyl pentafluoropropionate and CuCl. [a]Yields were determined by ^{19}F NMR using benzotrifluoride (BTF) or trifluoromethoxybenzene as internal standards. [b]90 °C, 72 h. [c]80 °C, 24 h. [d]80 °C, 48 h. [e]90 °C, 48 h.

More recently, in the course of their investigation to generate a $CuCF_3$ reagent from a cyclic-protected hexafluoroacetone, an air-stable liquid trifluoromethylating reagent, and $KCu(Ot\text{-}Bu)_2$, the group of Mikami showed that a CF_2CF_3 analog (Scheme 19) was prepared in a similar way and applied for the pentafluoroethylation of aromatic derivatives [74] (2 examples).



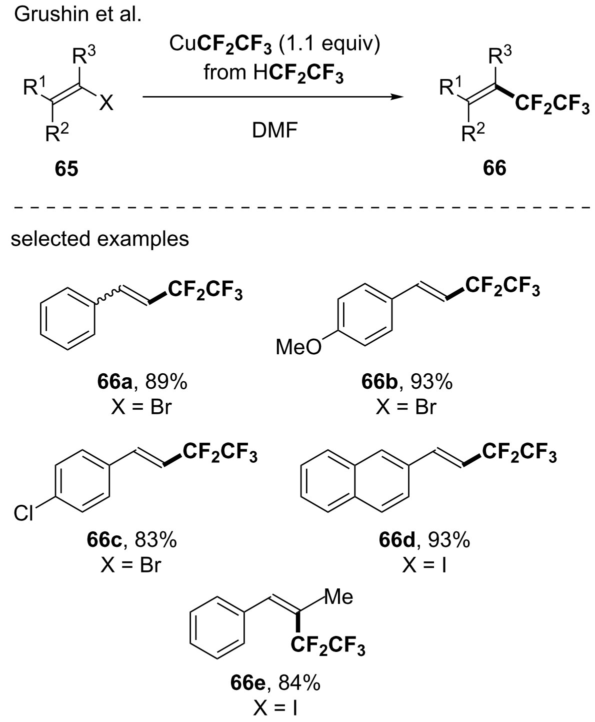
Scheme 19: In situ generation of $CuCF_2CF_3$ species from a cyclic-protected hexafluoroacetone and $KCu(Ot\text{-}Bu)_2$. ^{19}F NMR yields were determined using benzotrifluoride (BTF) as the internal standard.

In 2015, Grushin and co-workers further investigated the functionalization of vinyl halides with CuR_F reagents generated from inexpensive fluoroform ($R_F = CF_3$) and pentafluoroethane (CF_3CF_2H) [75]. Both trifluoromethylation and pentafluoethylation of vinyl bromides and iodides were efficiently achieved in high yields under mild reaction conditions. Noteworthy, the transformation turned out to be functional group tolerant and highly chemo- and stereroselective (Scheme 20).

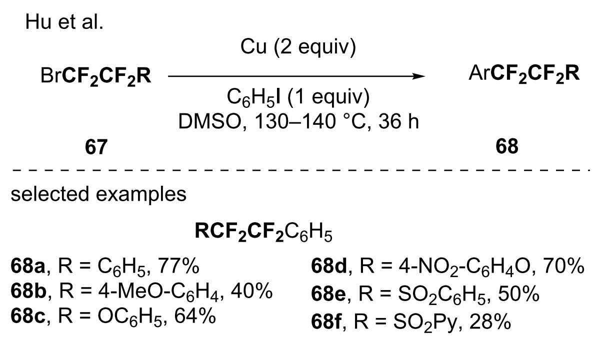
The group of Hu studied the fluoroalkylation of aryl halides. Indeed, a copper(0)-mediated reductive cross-coupling reaction between the iodobenzene and various 2-bromo-1,1,2,2-tetrafluoroethyl derivatives (RCF_2CF_2Br) was developed presumably involving a RCF_2CF_2Cu species (Scheme 21) [76].

In 2015, Yagupolskii and co-workers investigated the synthesis of perfluoroalkylcopper reagents [77]. Depending on the reaction conditions they were able to access to perfluoroorganolithium copper species or perfluroalkylcopper derivatives from iodoperfluoroalkanes in reaction with either *n*-BuLi or copper powder, respectively (Scheme 22).

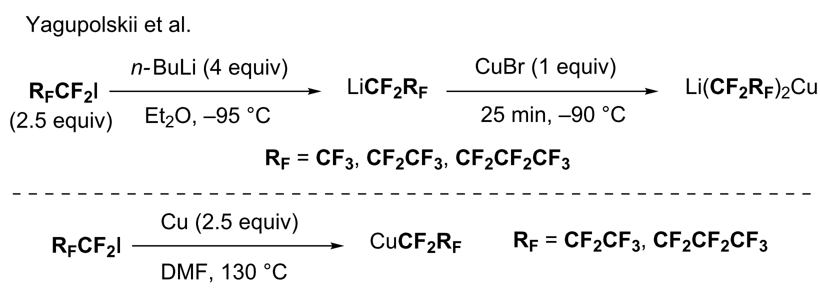
In 2017, the group of Hu offered an original synthetic route to the generation of the $PhenCuCF_2CF_3$ reagent [78]. Indeed, they demonstrated that the Ruppert–Prakash reagent was a suit-



Scheme 20: Pentafluoroethylation of bromo- and iodoalkenes. Only examples of isolated compounds were depicted.



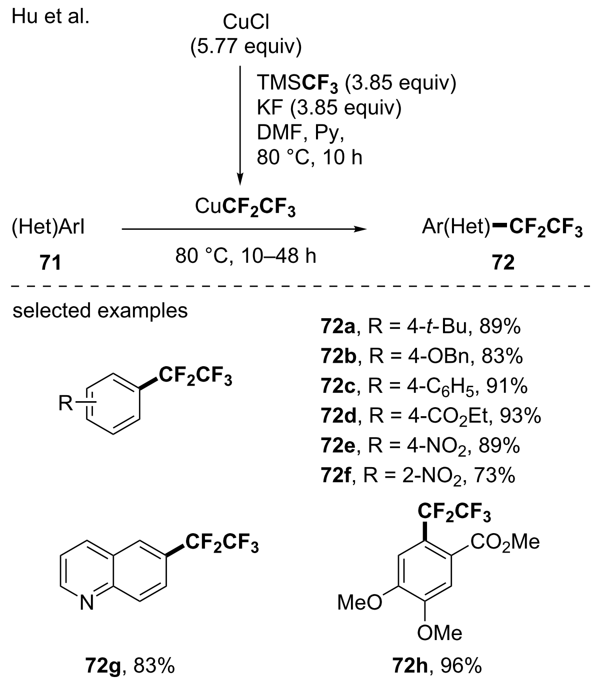
Scheme 21: Fluoroalkylation of aryl halides via a RCF_2CF_2Cu species.



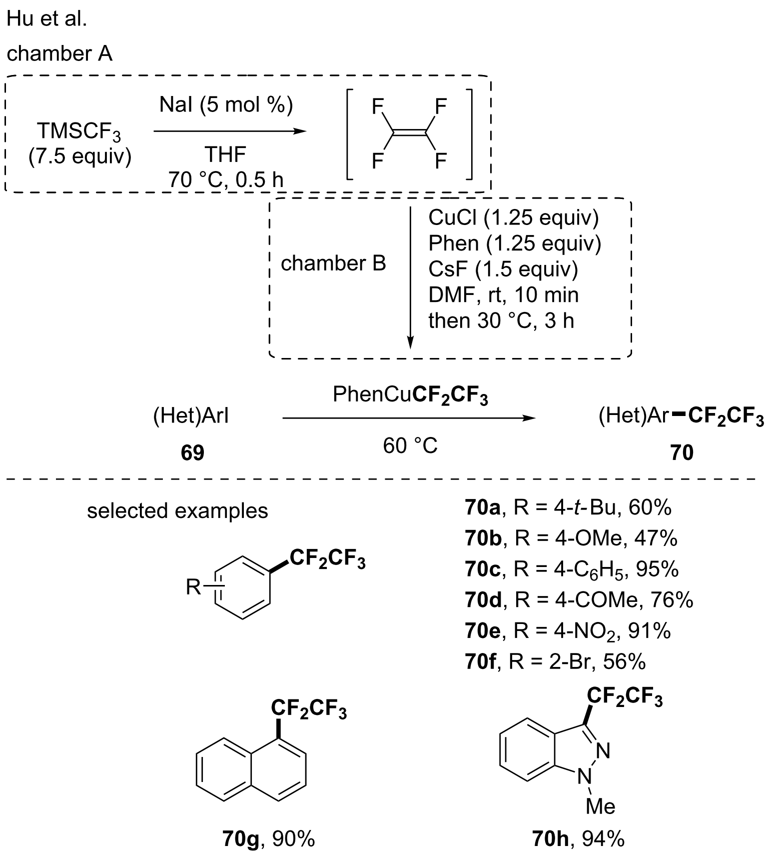
Scheme 22: Synthesis of perfluoroorganolithium copper species or perfluroalkylcopper derivatives from iodoperfluoroalkanes.

able source for the generation of tetrafluoroethylene in the presence of a catalytic amount of NaI. Then, the cupration of the tetrafluoroethylene led to the formation of the expected Phen-$CuCF_2CF_3$ reagent (Scheme 23). This constituted a complementary approach to the existing ones for its synthesis, as it avoided the use of $TMSCF_2CF_3$ or CF_3CF_2H. This copper-based reagent was then used for the pentafluoroethylation of iodoarenes [78]. The transformation was efficient and turned out to be functional group tolerant. The same group extended their protocol to the functionalization of aryldiazonium salts [79]. Very recently, a similar protocol was applied to the pentafluoroethylation of (hetero)aryl halides as well as alkenyl iodides derived from natural compounds (e.g., glycals, nucleosides and nucleobases) [80].

In 2018, Hu and co-workers reported a complementary approach for the pentafluoroethylation of aryl iodides using $TMSCF_3$ for the formation of $CuCF_2CF_3$ [81]. They suggested that in the presence of CuCl, KF and $TMSCF_3$, the corresponding $CuCF_3$ species will be formed and a subsequent homologation step involving a putative copper difluorocarbene will allow the formation of the $CuCF_2CF_3$ species. With this tool in hand, a panel of aryl iodides was functionalized (Scheme 24).



Scheme 24: Generation of a $CuCF_2CF_3$ reagent from $TMSCF_3$ and applications.



Scheme 23: Formation of the $PhenCuCF_2CF_3$ reagent by means of TFE and pentafluoroethylation of iodoarenes and aryldiazonium salts.

Conclusion

This review aims at providing an overview of the recent advances made since 2014 for the construction of CF_2R-containing molecules ($R \neq F$) using versatile and efficient copper-based reagents. Groundbreaking advances were made in the synthesis of well-defined copper-based reagents and innovative strategies were developed to generate in situ CuR_f complexes from various precursors. Unprecedented transformations were successfully achieved using these copper-based reagents and these efficient synthetic tools opened new perspectives in the very active research field of organofluorine chemistry. Nevertheless, this field is still in its infancy and milestones towards copper-based difluoromethylating reagents are expected in the upcoming years.

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References

1. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014,** *114,* 2432–2506. doi:10.1021/cr4002879
2. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008,** *37,* 320–330. doi:10.1039/b610213c
3. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015,** *58,* 8315–8359. doi:10.1021/acs.jmedchem.5b00258
4. Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014,** *57,* 2832–2842. doi:10.1021/jm401375q
5. Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013,** *52,* 8214–8264. doi:10.1002/anie.201206566
6. Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. – Eur. J.* **2014,** *20,* 16830–16845. doi:10.1002/chem.201404537
7. Ni, C.; Hu, J. *Chem. Soc. Rev.* **2016,** *45,* 5441–5454. doi:10.1039/c6cs00351f
8. Landelle, G.; Panossian, A.; Leroux, F. *Curr. Top. Med. Chem.* **2014,** *14,* 941–951. doi:10.2174/1568026614666140202210016
9. Besset, T.; Jubault, P.; Pannecoucke, X.; Poisson, T. *Org. Chem. Front.* **2016,** *3,* 1004–1010. doi:10.1039/c6qo00164e
10. Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015,** *115,* 9073–9174. doi:10.1021/cr500706a
11. Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014,** *43,* 6598–6608. doi:10.1039/c4cs00025k
12. Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014,** *53,* 8294–8308. doi:10.1002/anie.201309260
13. Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. – Eur. J.* **2015,** *21,* 12836–12865. doi:10.1002/chem.201501475
14. Song, H.-X.; Han, Q.-Y.; Zhao, C.-L.; Zhang, C.-P. *Green Chem.* **2018,** *20,* 1662–1731. doi:10.1039/c8gc00078f
15. O'Hagan, D. *Chem. Soc. Rev.* **2008,** *37,* 308–319. doi:10.1039/b711844a
16. Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* **2011,** *67,* 2161–2195. doi:10.1016/j.tet.2011.01.002
17. Jouvin, K.; Guissart, C.; Theunissen, C.; Evano, G. Emerging Areas in Copper-Mediated Trifluoromethylations: Catalytic and Oxidative Processes. In *Copper-Mediated Cross-Coupling Reactions;* Evano, G.; Blanchard, N., Eds.; John Wiley & Sons: Hoboken, NJ, USA, 2013; pp 515–530. doi:10.1002/9781118690659.ch14
18. Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2013,** *52,* 7972–7975. doi:10.1002/anie.201304276
19. Grushin, V. V. *Chim. Oggi* **2014,** *32* (3), 81–88.
20. Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015,** *115,* 683–730. doi:10.1021/cr400473a
21. Morstein, J.; Hou, H.; Cheng, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016,** *55,* 8054–8057. doi:10.1002/anie.201601163
22. Lin, X.; Hou, C.; Li, H.; Weng, Z. *Chem. – Eur. J.* **2016,** *22,* 2075–2084. doi:10.1002/chem.201504306
23. Zhang, C. *J. Chem. Sci.* **2017,** *129,* 1795–1805. doi:10.1007/s12039-017-1380-5
24. Kaplan, P. T.; Lloyd, J. A.; Chin, M. T.; Vicic, D. A. *Beilstein J. Org. Chem.* **2017,** *13,* 2297–2303. doi:10.3762/bjoc.13.225
25. Ye, Y.; Cheung, K. P. S.; He, L.; Tsui, G. C. *Org. Chem. Front.* **2018,** *5,* 1511–1515. doi:10.1039/c8qo00191j
26. Geri, J. B.; Wade Wolfe, M. M.; Szymczak, N. K. *Angew. Chem., Int. Ed.* **2018,** *57,* 1381–1385. doi:10.1002/anie.201711316
27. Li, G.-b.; Zhang, C.; Song, C.; Ma, Y.-d. *Beilstein J. Org. Chem.* **2018,** *14,* 155–181. doi:10.3762/bjoc.14.11
28. Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013,** *9,* 2476–2536. doi:10.3762/bjoc.9.287
29. Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009,** 7465–7478. doi:10.1039/b916463d
30. Gao, B.; Ni, C.; Hu, J. *Chimia* **2014,** *68,* 414–418. doi:10.2533/chimia.2014.414
31. Rong, J.; Ni, C.; Hu, J. *Asian J. Org. Chem.* **2017,** *6,* 139–152. doi:10.1002/ajoc.201600509
32. Levi, N.; Amir, D.; Gershonov, E.; Zafrani, Y. *Synthesis* **2019,** *51,* 4549–4567. doi:10.1055/s-0039-1690027
33. Meanwell, N. A. *J. Med. Chem.* **2011,** *54,* 2529–2591. doi:10.1021/jm1013693
34. Kirk, K. L. *Org. Process Res. Dev.* **2008,** *12,* 305–321. doi:10.1021/op700134j
35. Graton, J.; Wang, Z.; Brossard, A.-M.; Gonçalves Monteiro, D.; Le Questel, J.-Y.; Linclau, B. *Angew. Chem., Int. Ed.* **2012,** *51,* 6176–6180. doi:10.1002/anie.201202059
36. Giuffredi, G. T.; Gouverneur, V.; Bernet, B. *Angew. Chem., Int. Ed.* **2013,** *52,* 10524–10528. doi:10.1002/anie.201303766
37. Burton, D. J.; Hartgraves, G. A. *J. Fluorine Chem.* **2007,** *128,* 1198–1215. doi:10.1016/j.jfluchem.2007.05.015
38. Bour, J. R.; Kariofillis, S. K.; Sanford, M. S. *Organometallics* **2017,** *36,* 1220–1223. doi:10.1021/acs.organomet.7b00025
39. Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012,** *134,* 5524–5527. doi:10.1021/ja301013h

40. Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Org. Chem. Front.* **2014,** *1,* 774–776. doi:10.1039/c4qo00153b
41. Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012,** *51,* 12090–12094. doi:10.1002/anie.201205850
42. Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett.* **2014,** *16,* 5984–5987. doi:10.1021/ol5030037
43. Bayarmagnai, B.; Matheis, C.; Jouvin, K.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2015,** *54,* 5753–5756. doi:10.1002/anie.201500899
44. Jouvin, K.; Matheis, C.; Goossen, L. J. *Chem. – Eur. J.* **2015,** *21,* 14324–14327. doi:10.1002/chem.201502914
45. Zhu, S.-Q.; Xu, X.-H.; Qing, F.-L. *Org. Chem. Front.* **2015,** *2,* 1022–1025. doi:10.1039/c5qo00186b
46. Zhu, S.-Q.; Liu, Y.-L.; Li, H.; Xu, X.-H.; Qing, F.-L. *J. Am. Chem. Soc.* **2018,** *140,* 11613–11617. doi:10.1021/jacs.8b08135
47. Ivanova, M. V.; Bayle, A.; Besset, T.; Pannecoucke, X.; Poisson, T. *Chem. – Eur. J.* **2016,** *22,* 10284–10293. doi:10.1002/chem.201601310
48. Pannecoucke, X.; Poisson, T. *Synlett* **2016,** *27,* 2314–2326. doi:10.1055/s-0035-1562784
49. Bayle, A.; Cocaud, C.; Nicolas, C.; Martin, O. R.; Poisson, T.; Pannecoucke, X. *Eur. J. Org. Chem.* **2015,** 3787–3792. doi:10.1002/ejoc.201500373
50. Ivanova, M. V.; Bayle, A.; Besset, T.; Poisson, T.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2015,** *54,* 13406–13410. doi:10.1002/anie.201507130
51. Ivanova, M. V.; Besset, T.; Pannecoucke, X.; Poisson, T. *Synthesis* **2018,** *50,* 778–784. doi:10.1055/s-0036-1589140
52. Ivanova, M. V.; Bayle, A.; Besset, T.; Pannecoucke, X.; Poisson, T. *Chem. – Eur. J.* **2017,** *23,* 17318–17338. doi:10.1002/chem.201703542
53. Ivanova, M. V.; Bayle, A.; Besset, T.; Pannecoucke, X.; Poisson, T. *Angew. Chem., Int. Ed.* **2016,** *55,* 14141–14145. doi:10.1002/anie.201608294
54. Ivanova, M. V.; Bayle, A.; Besset, T.; Pannecoucke, X.; Poisson, T. *Eur. J. Org. Chem.* **2017,** 2475–2480. doi:10.1002/ejoc.201700182
55. Ou, Y.; Gooßen, L. J. *Asian J. Org. Chem.* **2019,** *8,* 650–653. doi:10.1002/ajoc.201800461
56. Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007,** *40,* 921–930. doi:10.1021/ar700149s
57. Zhang, W.; Zhu, J.; Hu, J. *Tetrahedron Lett.* **2008,** *49,* 5006–5008. doi:10.1016/j.tetlet.2008.06.064
58. Hu, J. *J. Fluorine Chem.* **2009,** *130,* 1130–1139. doi:10.1016/j.jfluchem.2009.05.016
59. He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012,** *51,* 3944–3947. doi:10.1002/anie.201200140
60. He, Z.; Hu, M.; Luo, T.; Li, L.; Hu, J. *Angew. Chem., Int. Ed.* **2012,** *51,* 11545–11547. doi:10.1002/anie.201206556
61. Zhu, J.; Wang, F.; Huang, W.; Zhao, Y.; Ye, W.; Hu, J. *Synlett* **2011,** 899–902. doi:10.1055/s-0030-1259676
62. Li, X.; Zhao, J.; Hu, M.; Chen, D.; Ni, C.; Wang, L.; Hu, J. *Chem. Commun.* **2016,** *52,* 3657–3660. doi:10.1039/c5cc10550a
63. Carbonnel, E.; Poisson, T.; Jubault, P.; Pannecoucke, X.; Besset, T. *Front. Chem. (Lausanne, Switz.)* **2019,** *7,* 111. doi:10.3389/fchem.2019.00111
64. Li, X.; Zhao, J.; Wang, Y.; Rong, J.; Hu, M.; Chen, D.; Xiao, P.; Ni, C.; Wang, L.; Hu, J. *Chem. – Asian J.* **2016,** *11,* 1789–1792. doi:10.1002/asia.201600577
65. Kremlev, M. M.; Tyrra, W.; Mushta, A. I.; Naumann, D.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2010,** *131,* 212–216. doi:10.1016/j.jfluchem.2009.10.011
66. Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011,** *50,* 3793–3798. doi:10.1002/anie.201100633
67. Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012,** *51,* 536–539. doi:10.1002/anie.201106668
68. Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2013,** *135,* 12584–12587. doi:10.1021/ja407017j
69. Mormino, M. G.; Fier, P. S.; Hartwig, J. F. *Org. Lett.* **2014,** *16,* 1744–1747. doi:10.1021/ol500422t
70. Kalkman, E. D.; Mormino, M. G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2019,** *141,* 19458–19465. doi:10.1021/jacs.9b10540
71. Panferova, L. I.; Miloserdov, F. M.; Lishchynskyi, A.; Martínez Belmonte, M.; Benet-Buchholz, J.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2015,** *54,* 5218–5222. doi:10.1002/anie.201500341
72. Huang, Y.; Ajitha, M. J.; Huang, K.-W.; Zhang, Z.; Weng, Z. *Dalton Trans.* **2016,** *45,* 8468–8474. doi:10.1039/c6dt00277c
73. Serizawa, H.; Aikawa, K.; Mikami, K. *Org. Lett.* **2014,** *16,* 3456–3459. doi:10.1021/ol501332g
74. Negishi, K.; Aikawa, K.; Mikami, K. *Eur. J. Org. Chem.* **2016,** 4099–4104. doi:10.1002/ejoc.201600711
75. Lishchynskyi, A.; Mazloomi, Z.; Grushin, V. V. *Synlett* **2015,** *26,* 45–50. doi:10.1055/s-0034-1379497
76. Zhu, J.; Ni, C.; Gao, B.; Hu, J. *J. Fluorine Chem.* **2015,** *171,* 139–147. doi:10.1016/j.jfluchem.2014.08.011
77. Kremlev, M. M.; Mushta, A. I.; Tyrra, W.; Yagupolskii, Y. L.; Naumann, D.; Schäfer, M. *Dalton Trans.* **2015,** *44,* 19693–19699. doi:10.1039/c5dt02925b
78. Li, L.; Ni, C.; Xie, Q.; Hu, M.; Wang, F.; Hu, J. *Angew. Chem., Int. Ed.* **2017,** *56,* 9971–9975. doi:10.1002/anie.201705734
79. Xing, B.; Li, L.; Ni, C.; Hu, J. *Chin. J. Chem.* **2019,** *37,* 1131–1136. doi:10.1002/cjoc.201900268
80. Mestre, J.; Castillón, S.; Boutureira, O. *J. Org. Chem.* **2019,** *84,* 15087–15097. doi:10.1021/acs.joc.9b02001
81. Xie, Q.; Li, L.; Zhu, Z.; Zhang, R.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2018,** *57,* 13211–13215. doi:10.1002/anie.201807873

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