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Louise Ruyet, Tatiana Besset. Copper-based fluorinated reagents for the synthesis of CF<sub>2</sub> R-containing molecules (R ≠ F). *Beilstein Journal of Organic Chemistry*, 2020, 16, pp.1051-1065. 10.3762/bjoc.16.92 . hal-02615098

**HAL Id: hal-02615098**

**<https://normandie-univ.hal.science/hal-02615098v1>**

Submitted on 22 May 2020

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# Copper-based fluorinated reagents for the synthesis of CF<sub>2</sub>R-containing molecules (R ≠ F)

Louise Ruyet and Tatiana Besset\*

## Review

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### Keywords:

copper; difluoromethylation; fluorinated reagents; fluorine chemistry; synthetic methodologies

*Beilstein J. Org. Chem.* **2020**, *16*, 1051–1065.

doi:10.3762/bjoc.16.92

Received: 19 March 2020

Accepted: 29 April 2020

Published: 18 May 2020

This article is part of the thematic issue "Copper-catalyzed reactions for organic synthesis".

Guest Editor: O. Riant

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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<sub>2</sub>H, CF<sub>2</sub>R<sub>F</sub>, CF<sub>2</sub>CH<sub>3</sub>, CF<sub>2</sub>PO(OEt)<sub>2</sub> and CF<sub>2</sub>SO<sub>2</sub>Ph 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<sub>2</sub>R (R = H, alkyl, R<sub>F</sub>, 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  $\text{CF}_2\text{H}$ ,  $\text{CF}_2\text{FG}$ ,  $\text{CF}_2\text{Me}$  and  $\text{CF}_2\text{R}_F$  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

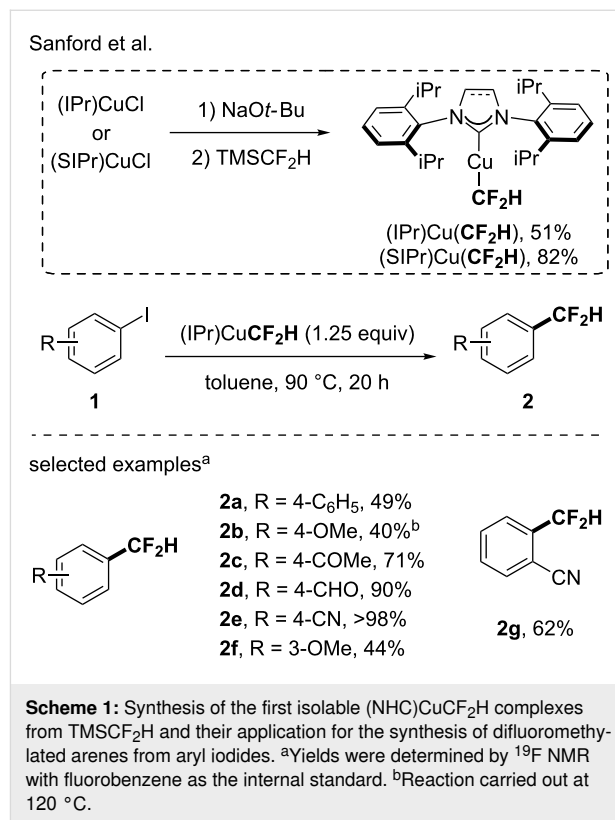
### Copper-based difluoromethylating reagents

In this section the key advances made to access copper-based difluoromethylating reagents are summarized. The  $\text{CF}_2\text{H}$  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  $\text{CuCF}_2\text{H}$  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  $\text{CuCF}_2\text{H}$  species and its application in several transformations.

#### Pre-defined difluoromethylating reagents

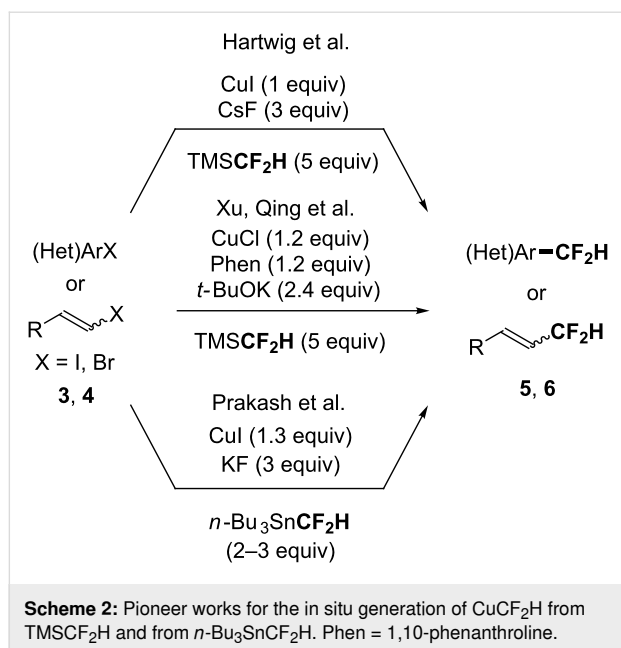
In the quest for well-defined and isolable  $\text{MCF}_2\text{H}$  species, Sanford depicted for the first time in 2017 the synthesis and characterization of isolable difluoromethylcopper(I) complexes [38]. The latter were prepared in a two-step sequence starting from the corresponding (NHC)CuCl as precursors in the presence of  $\text{NaOt-Bu}$  followed by the addition of  $\text{TMSCF}_2\text{H}$  (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 synthe-

sis of a stable and isolable (NHC)CuCF<sub>2</sub>H 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<sub>2</sub>H, starting from (IPr)CuCl [38].



#### In situ-generated copper-based difluoromethylating reagents

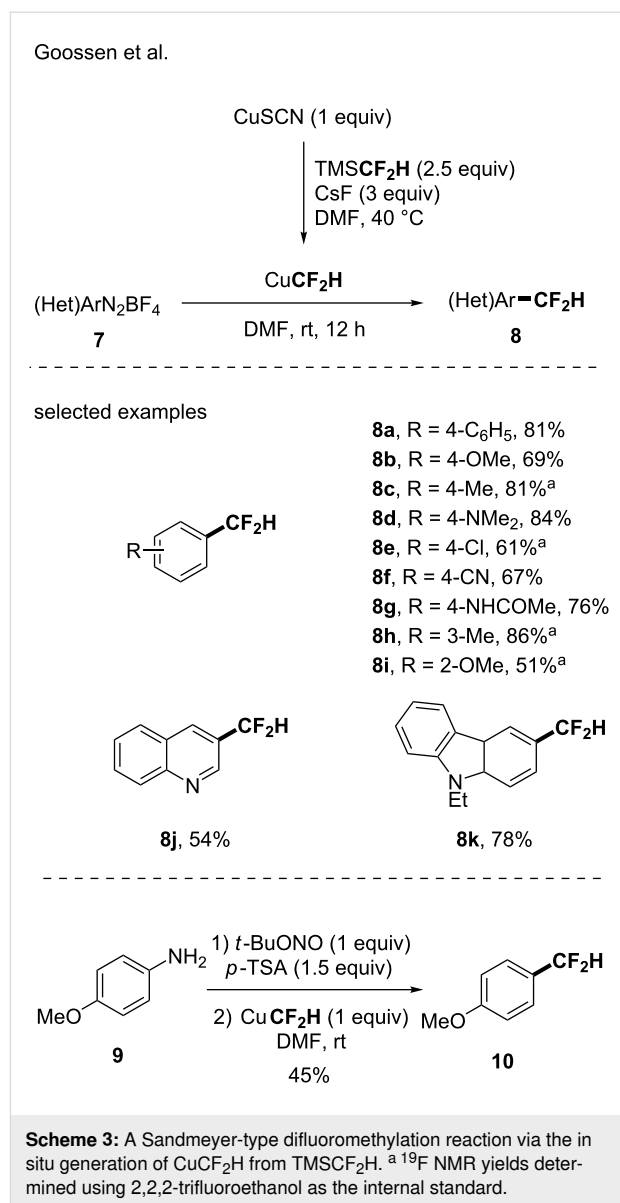
Although the review focused on the 2014–2019 period, a brief overview of seminal major advances should be given. In 2012, Hartwig and co-worker studied the difluoromethylation reaction of aryl and vinyl iodides by a copper-mediated transformation using  $\text{TMSCF}_2\text{H}$  as the fluorinated source [39]. In this work,  $\text{CuCF}_2\text{H}$  was suggested as the active species to promote the expected transformation. They highlighted that the formation of a cuprate species:  $\text{Cu}(\text{CF}_2\text{H})_2^-$ , favoured by the presence of an excess of  $\text{TMSCF}_2\text{H}$ , might act as a reservoir of the unstable and reactive  $\text{CuCF}_2\text{H}$  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  $\text{TMSCF}_2\text{H}$  [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  $\text{CuCF}_2\text{H}$  from *n*-Bu<sub>3</sub>SnCF<sub>2</sub>H, the presence of DMF being the key to stabilize the  $\text{CuCF}_2\text{H}$  intermediate [41] (Scheme 2).



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  $\text{CuCF}_2\text{H}$  complex starting from  $\text{TMSCF}_2\text{H}$ ,  $\text{CuSCN}$  and  $\text{CsF}$  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.

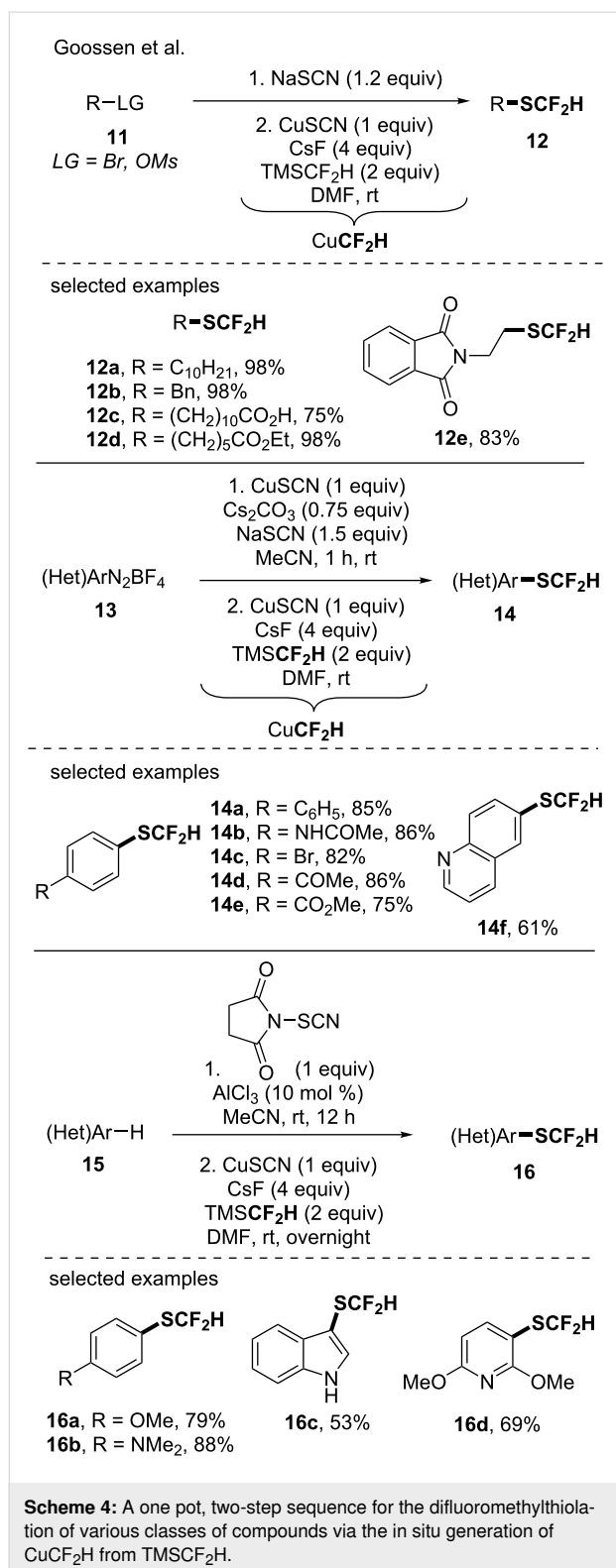
In the same vein, the authors used this in situ generation of a  $\text{CuCF}_2\text{H}$  species to access high value-added difluoromethylthiolated molecules starting from organothiocyanates [43]. With this approach, they then developed a one pot, two-step sequence (generation of the organothiocyanates 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  $\text{TMSCF}_2\text{H}$  via a copper-mediated reaction [45]. Using a stoichiometric amount of  $\text{CuI}$ , in the presence of  $t\text{-BuOK}$  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  $^{19}\text{F}$  NMR studies, the authors suggested the following mechanism: first the in situ generation of a  $\text{CuCF}_2\text{H}$



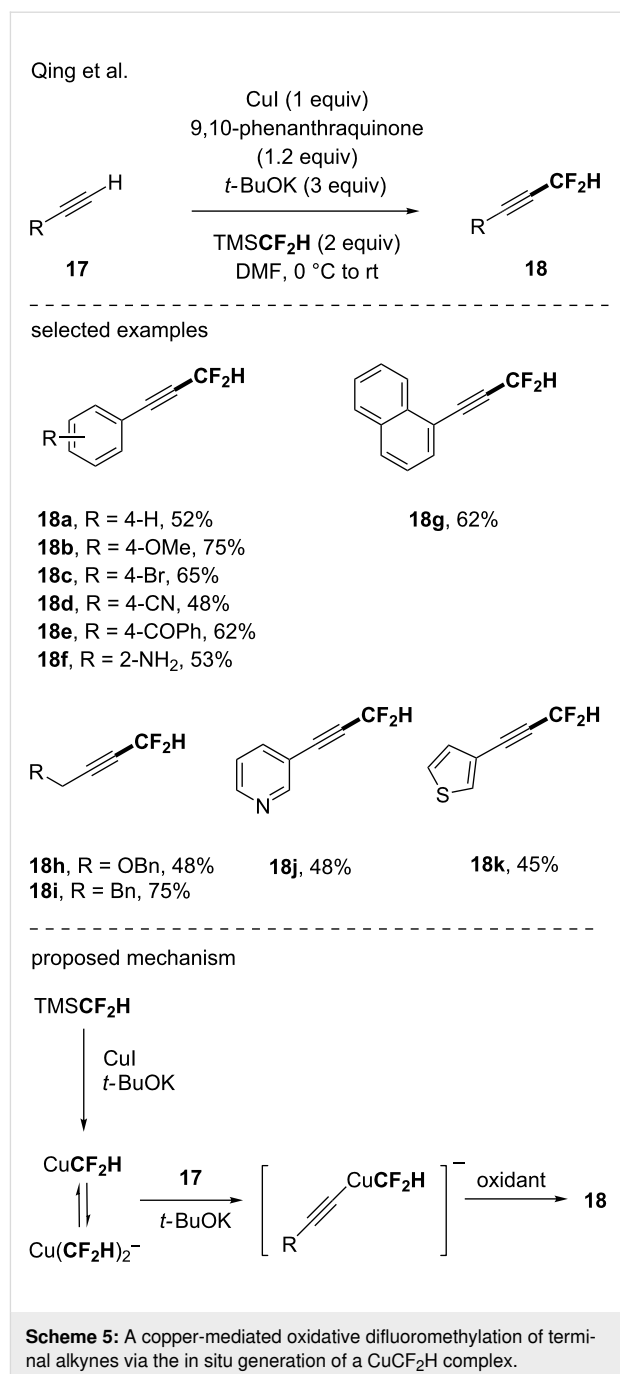
complex from  $\text{TMSCF}_2\text{H}$  in equilibrium with the corresponding cuprate ( $\text{Cu}(\text{CF}_2\text{H})_2^-$ ) occurred followed by the reaction with terminal alkynes under basic conditions. The resulting organocopper derivative was then oxidized resulting in the formation of the desired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

Note that in 2018 the same group reported the copper-mediated oxidative difluoromethylation of heteroarenes under similar reaction conditions ( $\text{TMSCF}_2\text{H}$ ,  $\text{CuCN}$ , 9,10-phenanthrenequinone,  $t\text{-BuOK}$  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).



### Copper-based CF<sub>2</sub>FG-containing reagents

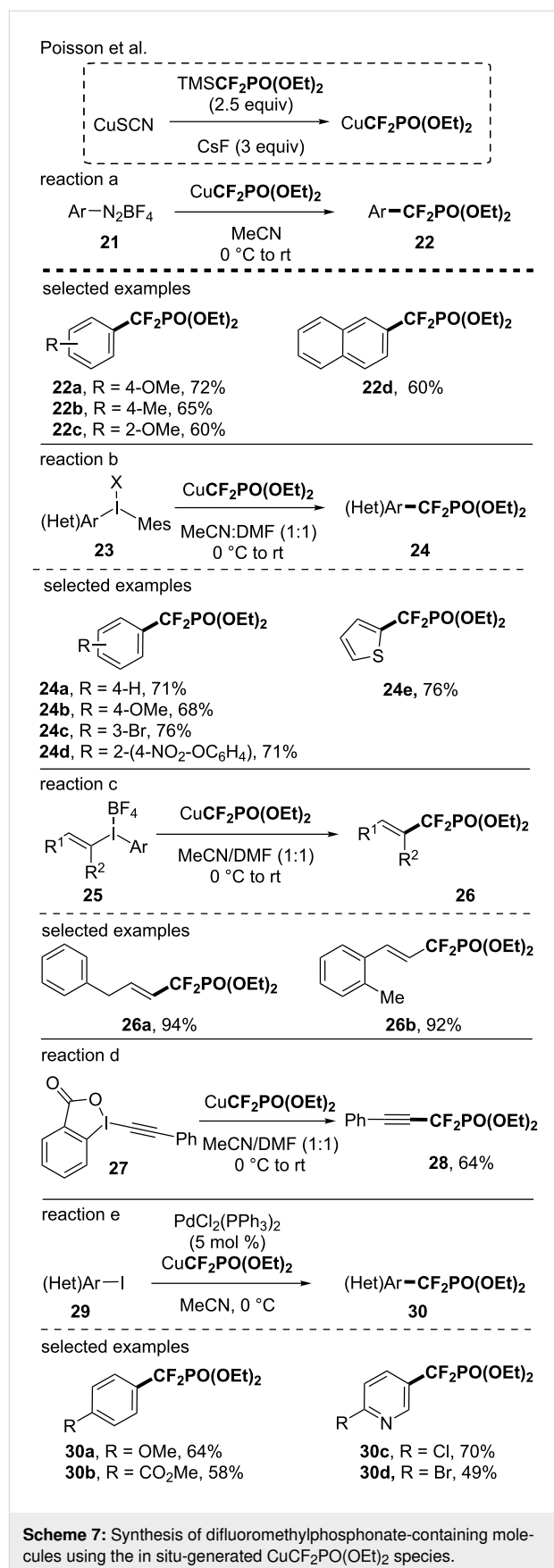
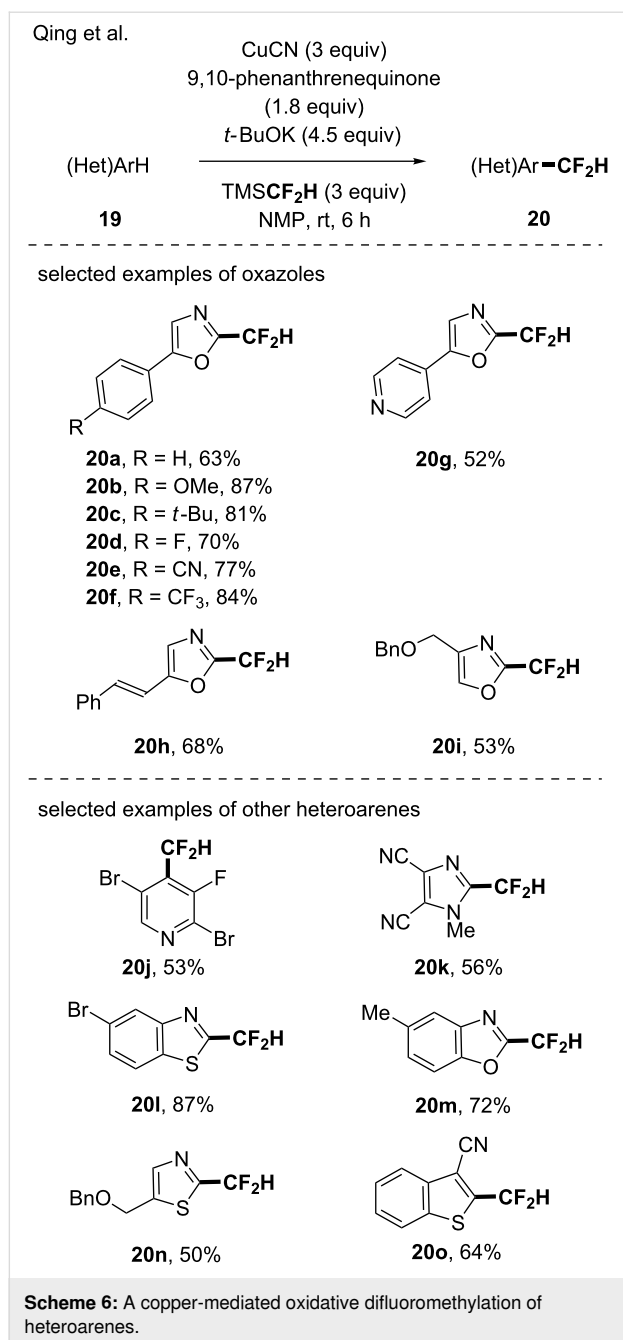
Besides the traditional CF<sub>3</sub> and CF<sub>2</sub>H groups, a strong interest was devoted to other CF<sub>2</sub>R groups (R = PO(OEt)<sub>2</sub>, SO<sub>2</sub>Ph and Me). In that aim, the development of copper-based reagents to



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<sub>2</sub>PO(OEt)<sub>2</sub> reagent

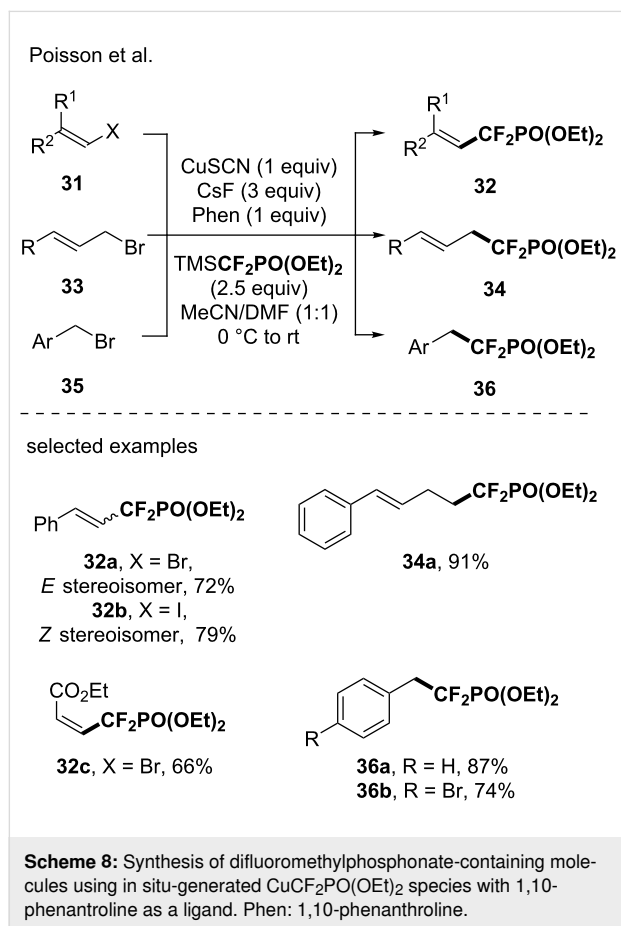
As a bioisostere of the phosphonate group [47], a lot of attention was paid to the difluoromethylphosphonate residue as well as the development of efficient methodologies to introduce it onto molecules [48]. In that context, main contributions were made by the groups of Poisson and Goossen.



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<sub>2</sub>PO(OEt)<sub>2</sub> species and its application to functionalize various classes of compounds [49–54]. The active species was prepared from TMSCF<sub>2</sub>PO(OEt)<sub>2</sub>, a copper salt and an activator. Note that the TMSCF<sub>2</sub>PO(OEt)<sub>2</sub> was easily prepared from the commercially available BrCF<sub>2</sub>PO(OEt)<sub>2</sub> and TMSCl under basic conditions [49]. The access to CF<sub>2</sub>PO(OEt)<sub>2</sub>-containing arenes was obtained after a Sandmeyer-type reaction (Scheme 7, reaction a) [49]. The reaction was efficient, al-

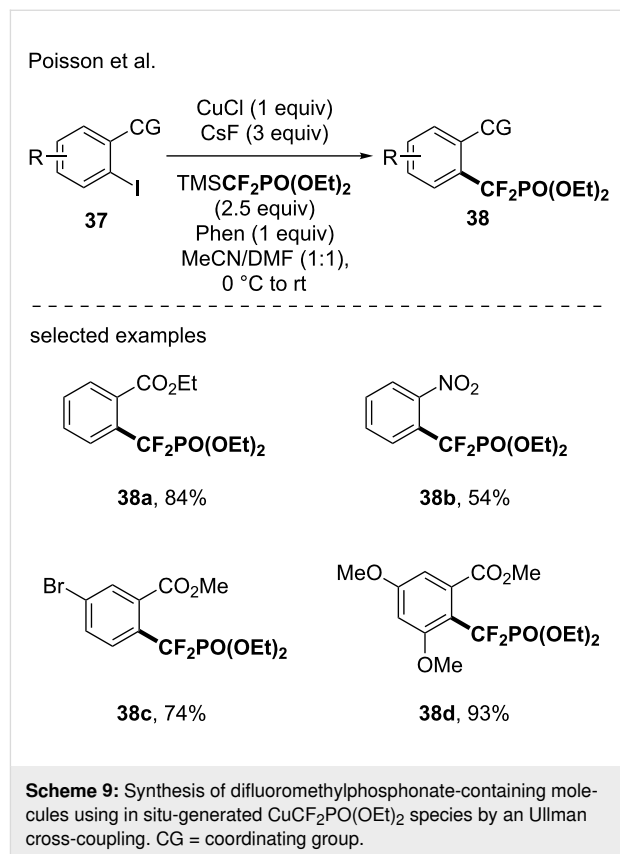
though heteroaryl diazonium salts were reluctant in this reaction. To overcome these limitations, hypervalent iodinated species were used as substrates. The copper-mediated reaction with  $\lambda^3$ -iodanes demonstrated a large functional group tolerance and was efficiently applied to the synthesis of  $\text{CF}_2\text{PO}(\text{OEt})_2$ -containing (hetero)arenes, alkenes and alkynes (Scheme 7, reactions b–d) [50]. Later on, the same group depicted the Pd-catalyzed introduction of the  $\text{CF}_2\text{PO}(\text{OEt})_2$  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].



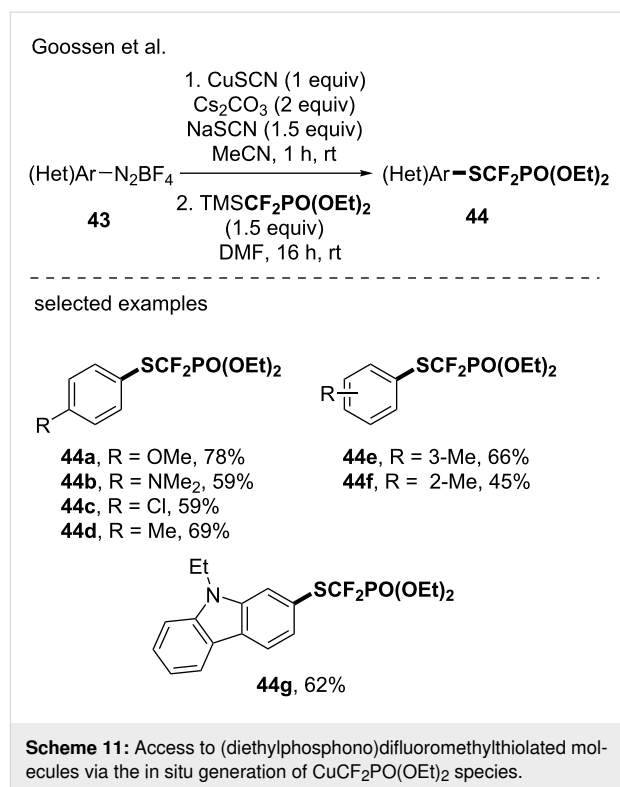
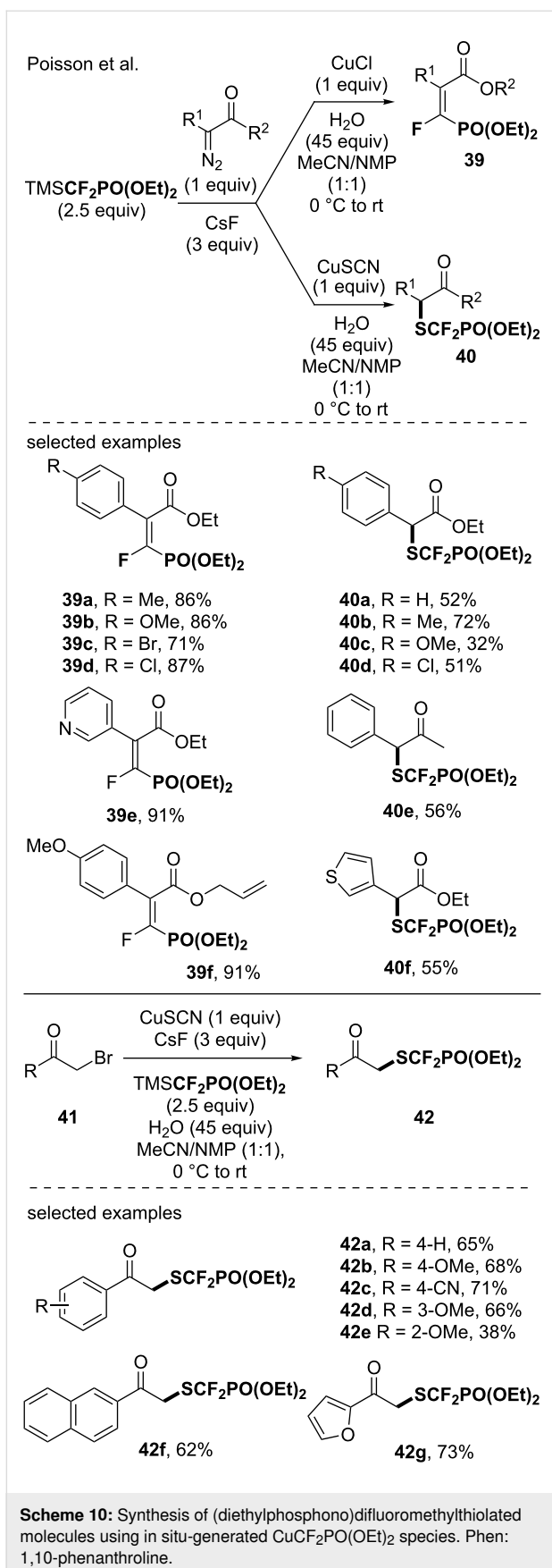
Finally, the Poisson's group developed a methodology for the Ullman cross-coupling reaction between the in situ-generated  $\text{CuCF}_2\text{PO}(\text{OEt})_2$  and aryl iodides containing a coordinating group (e.g.,  $\text{CO}_2\text{CH}_3$ ,  $\text{COCH}_3$ ,  $\text{NO}_2$ ), at the *ortho*-position of the halide [52]. This reaction broadened the portfolio of

$\text{CF}_2\text{PO}(\text{OEt})_2$ -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.



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

In 2019, the group of Goossen developed an approach to access  $\text{SCF}_2\text{PO}(\text{OEt})_2$ -containing arenes based on a Sandmeyer thiocyanation reaction followed by a Langlois-type nucleophilic substitution of the cyano group by the  $\text{CF}_2\text{PO}(\text{OEt})_2$  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  $\text{CuCF}_2\text{PO}(\text{OEt})_2$  species (Scheme 11).



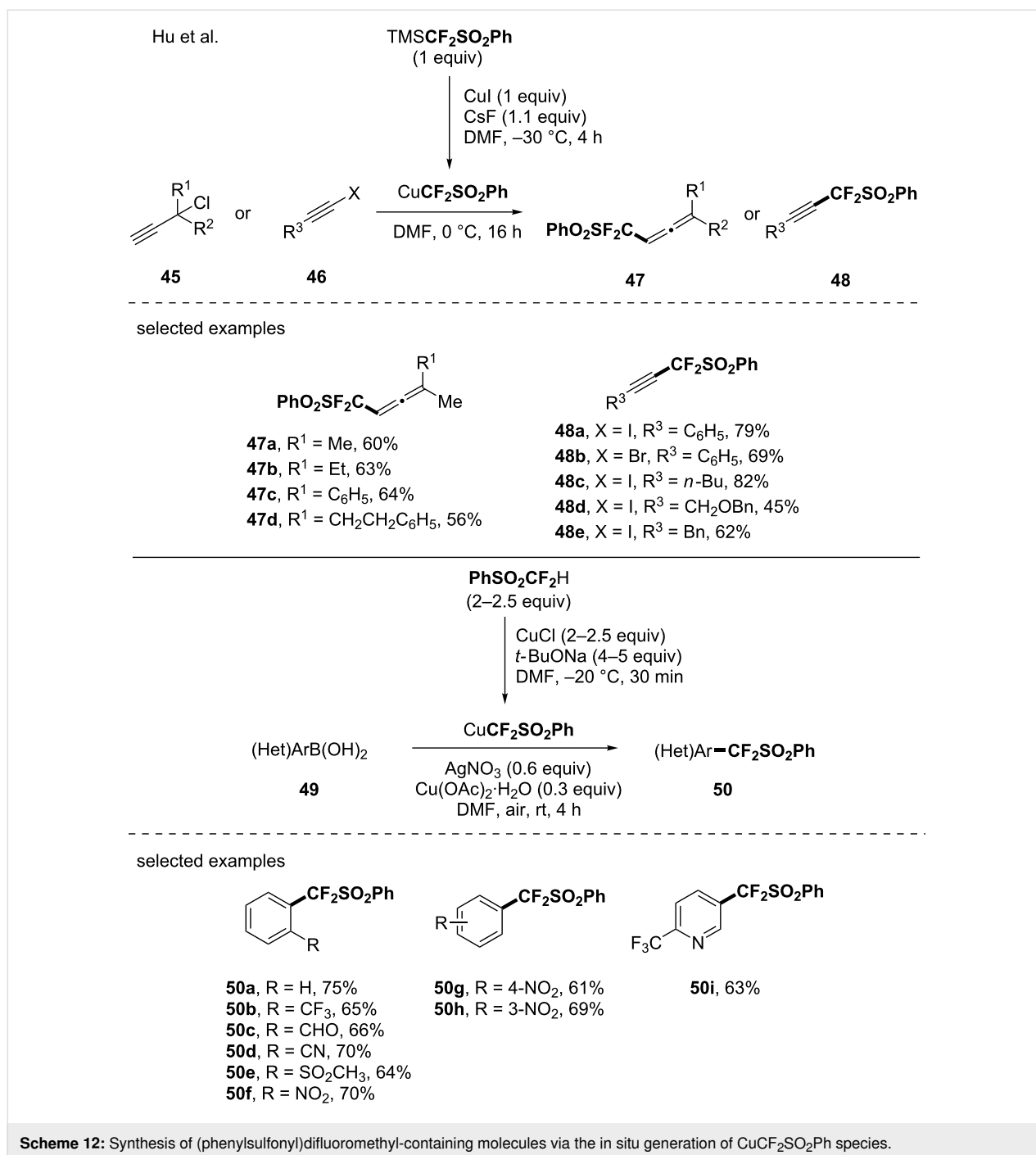
### An in situ-generated copper-based $\text{CF}_2\text{SO}_2\text{Ph}$ reagent

As a long standing interest to the  $\text{PhSO}_2\text{CF}_2$  moiety [56-60] thanks to its unique features, the group of Hu investigated the generation of the  $\text{PhSO}_2\text{CF}_2\text{Cu}$  species from  $\text{PhSO}_2\text{CF}_2\text{TMS}$ ,  $\text{CuI}$  and  $\text{CsF}$  in  $\text{DMF}$  [61] (Scheme 12). Note that  $\text{PhSO}_2\text{CF}_2\text{TMS}$  was prepared from  $\text{PhSO}_2\text{CF}_2\text{Br}$  after treatment with *n*-BuLi and  $\text{TMSCl}$  [61]. Due to its relatively low stability at room temperature,  $\text{PhSO}_2\text{CF}_2\text{Cu}$  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  $\text{PhSO}_2\text{CF}_2\text{Cu}$  species might be prepared from difluoromethylphenylsulfone ( $\text{PhSO}_2\text{CF}_2\text{H}$ ) 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  $\text{CF}_2\text{SO}_2\text{Ph}$  group was further demonstrated by its conversion into the high value-added  $\text{CF}_2\text{H}$  moiety after treatment with  $\text{Mg}/\text{AcOH}/\text{AcONa}$ .

### An in situ-generated copper-based $\text{CF}_2\text{CH}_3$ reagent

A strong interest was dedicated to the  $\text{CF}_2\text{CH}_3$  residue, an important moiety in medicinal chemistry [63]. Among the different approaches developed to synthesize  $\text{CF}_2\text{CH}_3$ -containing

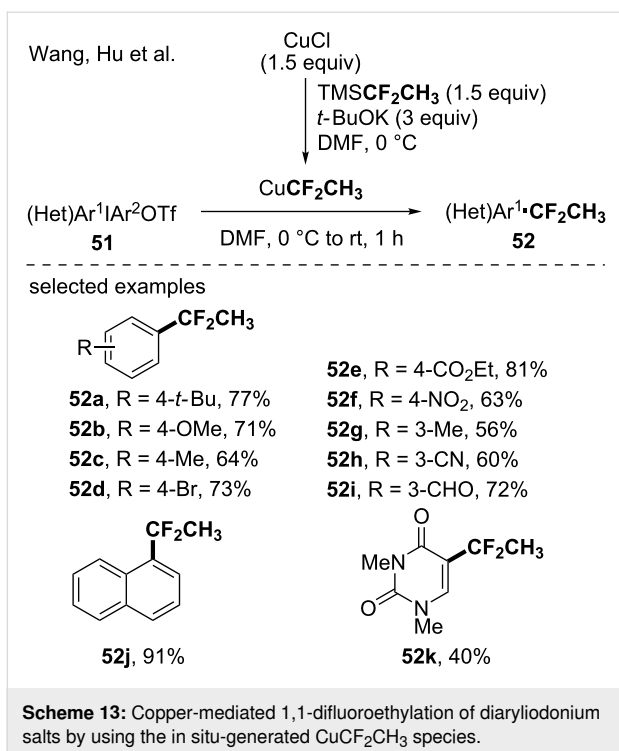




molecules, Wang, Hu and co-workers demonstrated the possibility to use 1,1-difluoroethylsilane ( $\text{TMSCF}_2\text{CH}_3$ ) as a precursor for the in situ generation of the corresponding  $\text{CuCF}_2\text{CH}_3$  species [64]. The synthetic utility of this copper-based reagent was illustrated through 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.

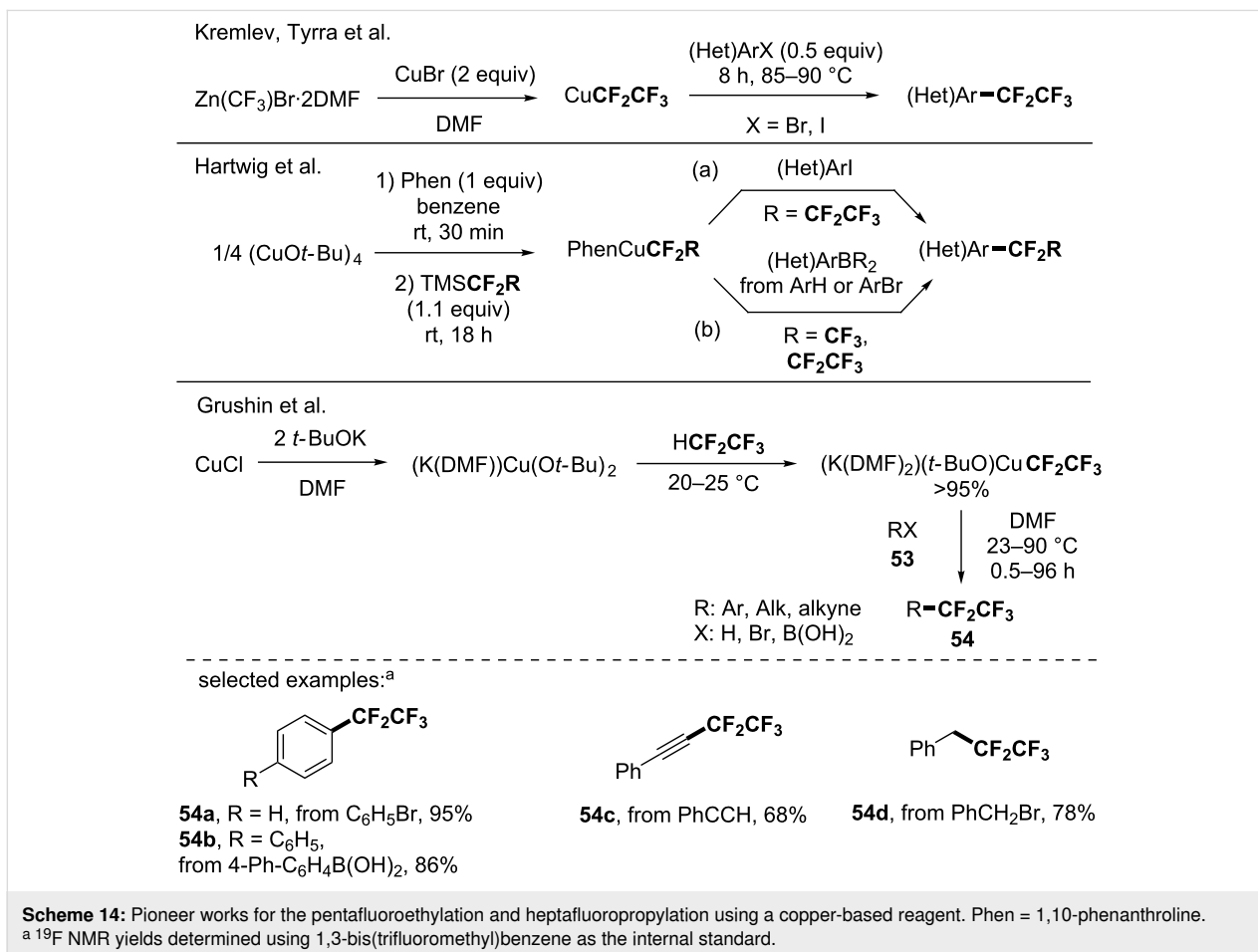
### Copper-based $\text{CF}_2\text{R}_F$ reagents

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  $\text{CF}_2\text{R}_F$ -containing molecules via the use of perfluoroalkyl copper species. Before 2014, key contributions were made by the groups of Kremlev, Tyrre [65], Hartwig [66,67] and Grushin [68] as briefly summarized below. These major advances paved



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  $\text{CuCF}_2\text{CF}_3$  species by mixing  $\text{Zn}(\text{CF}_3)\text{Br}\cdot 2\text{DMF}$  and  $\text{CuBr}$  [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  $(\text{Phen})\text{CuCF}_3$  and  $(\text{Phen})\text{CuCF}_2\text{CF}_2\text{CF}_3$  complexes from inexpensive reagents. Indeed, when mixing  $(\text{CuOt-Bu})_4$ , 1,10-phenanthroline and the corresponding  $\text{TMSR}_F$ , the perfluoroalkyl copper complexes were isolated for the first time (Scheme 14, a). One year later, they demonstrated that these copper-based reagents ( $(\text{Phen})\text{CuCF}_2\text{R}_F$ ,  $\text{R}_F = \text{F}$ ,  $\text{CF}_3$  and  $\text{CF}_2\text{CF}_3$ ) were efficient in a two-step sequence reaction (borylation/perfluoroalkylation) allowing the functionalization of either sterically hindered arenes or aryl bromides with the  $\text{CF}_2\text{CF}_3$  and  $\text{CF}_2\text{CF}_2\text{CF}_3$  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



a precursor, the  $(\text{K}(\text{DMF})_2)(t\text{-BuO})\text{Cu}(\text{CF}_2\text{CF}_3)$  complex was prepared either from the pre-isolated  $(\text{K}(\text{DMF}))\text{Cu}(\text{O}t\text{-Bu})_2$  or in situ from  $\text{CuCl}$ ,  $t\text{-BuOK}$  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%  $^{19}\text{F}$  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).

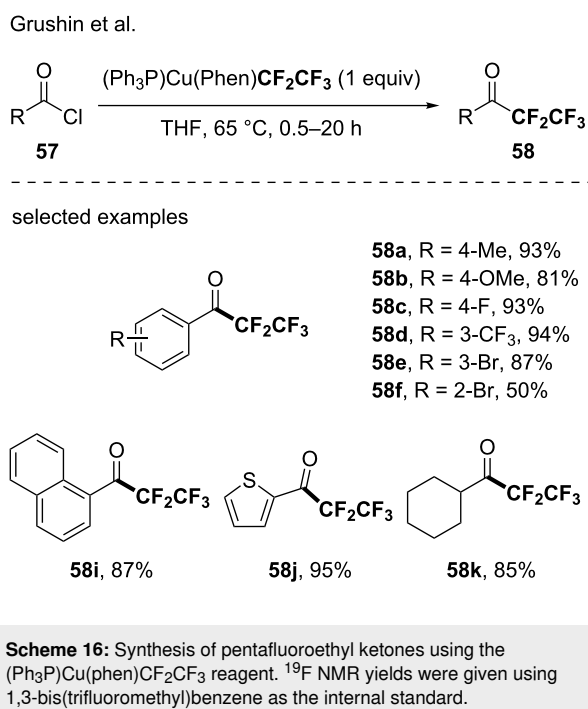
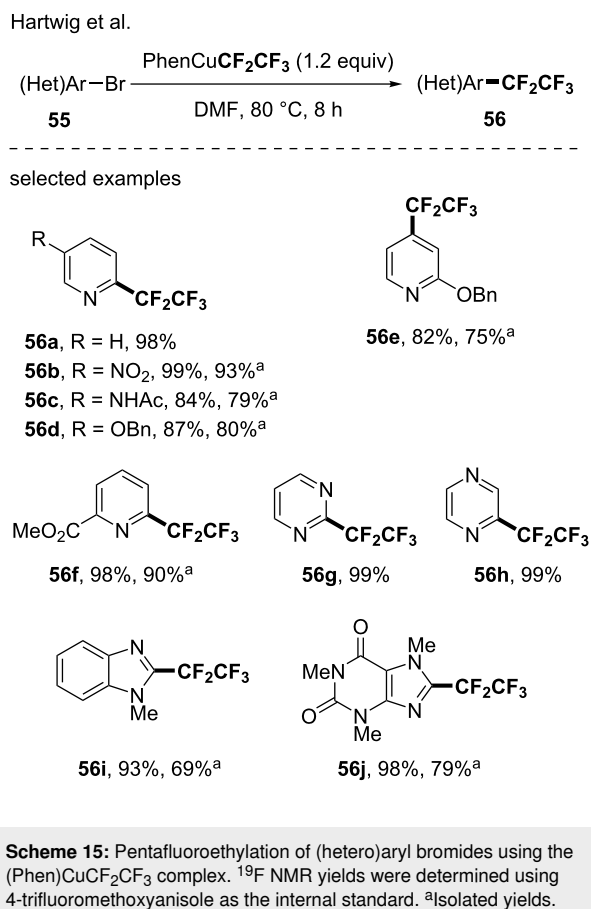
From these pioneering reports of perfluoroalkylation (trifluoromethylation, pentafluoroethylation and heptafluoropropylation), several groups studied the synthesis and/or the application of copper-based reagents in various transformations as depicted in this section. This latter will be organized into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

### Well-defined pentafluoroethylating reagents

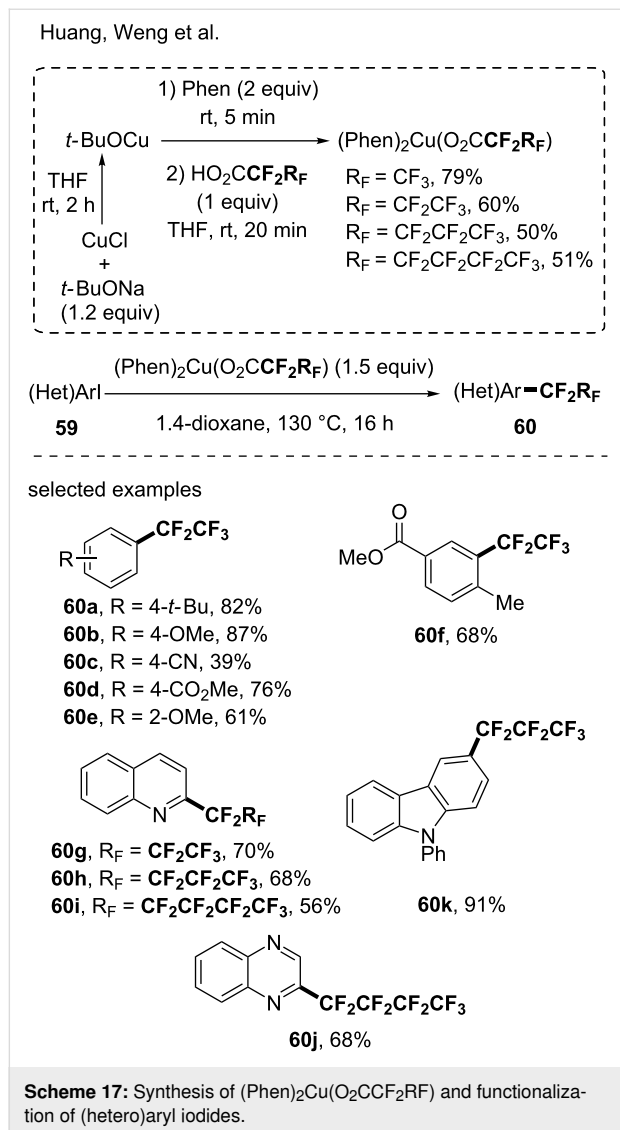
In 2014, a report from Hartwig dealt with the copper-mediated perfluoroalkylation of (hetero)aryl bromides using the previously developed  $\text{PhenCuR}_\text{F}$  [69]. Although the trifluoromethylation reaction was mainly studied, the methodology was efficiently extended to the pentafluoroethylation of various heteroarenes such as pyridine, pyrimidine and quinolone derivatives, for instance, when the  $\text{PhenCuCF}_2\text{CF}_3$  complex was used as the pentafluoroethyl source (24 examples, up to 99%  $^{19}\text{F}$  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  $\text{CuC}_2\text{F}_5$  complexes, namely  $(\text{Ph}_3\text{P})_2\text{CuCF}_2\text{CF}_3$ ,  $(\text{bpy})\text{CuCF}_2\text{CF}_3$ ,  $(\text{IPr}^*)\text{CuCF}_2\text{CF}_3$  and  $(\text{Ph}_3\text{P})\text{Cu}(\text{Phen})\text{CF}_2\text{CF}_3$ . 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  $(\text{Ph}_3\text{P})\text{Cu}(\text{phen})\text{CF}_2\text{CF}_3$  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  $t\text{-BuOCu}$ , in situ generated from  $\text{CuCl}$  and  $t\text{-BuONa}$ , with 1,10-phenanthroline, followed by a reaction with perfluorocarboxylic acids, four  $(\text{Phen})_2\text{Cu}(\text{O}_2\text{CCF}_2\text{R}_\text{F})$  complexes were synthesized ( $\text{R}_\text{F} = \text{CF}_3$ ,  $\text{CF}_2\text{CF}_3$ ,  $\text{CF}_2\text{CF}_2\text{CF}_3$  and  $\text{CF}_2\text{CF}_2\text{CF}_2\text{CF}_3$ ). 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,



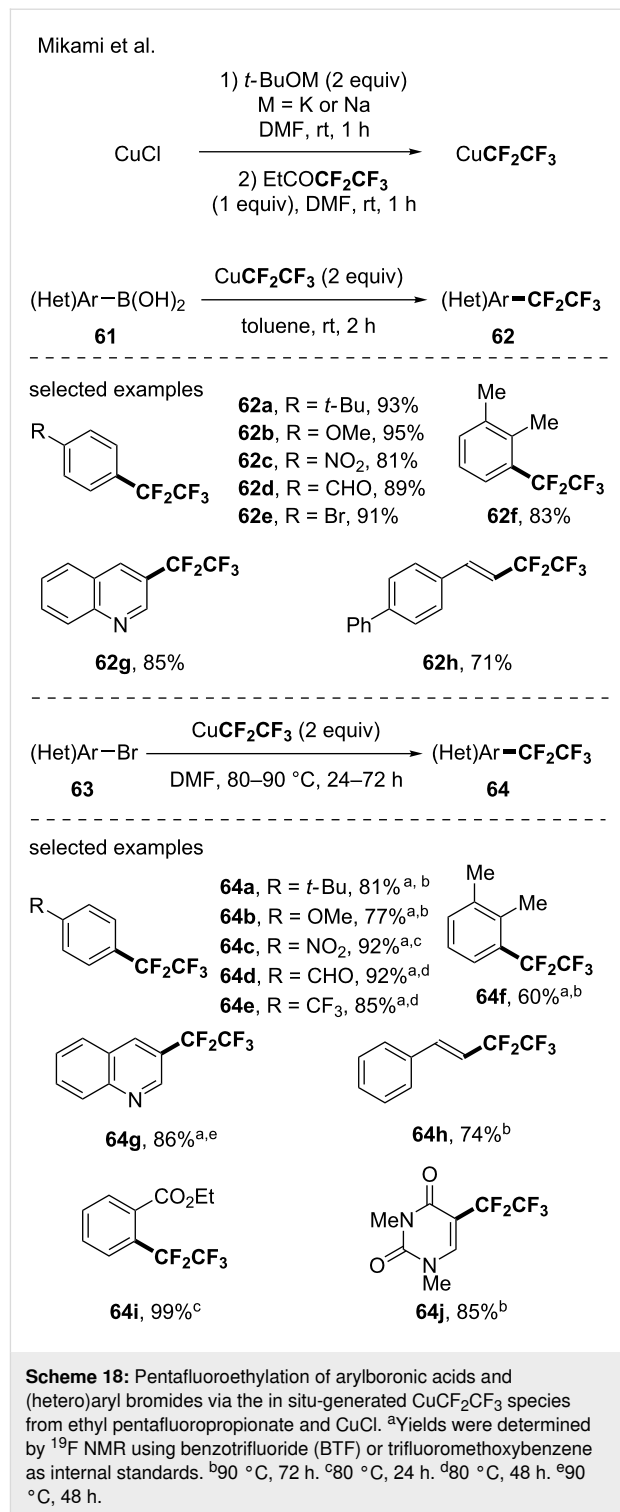
quinoline and quinoxaline were functionalized with the four fluorinated moieties (Scheme 17).



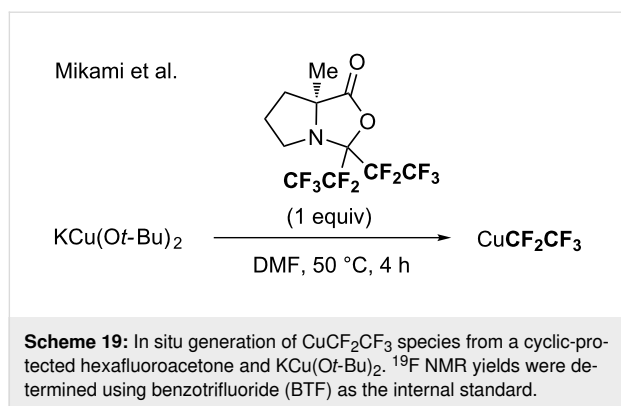
### In situ-generated copper-based pentafluoroethylating reagents

Several research groups investigated the generation of a CuCF<sub>2</sub>CF<sub>3</sub> 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% <sup>19</sup>F NMR yield) via the in situ generation of the suitable CuCF<sub>2</sub>CF<sub>3</sub> 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).



More recently, in the course of their investigation to generate a CuCF<sub>3</sub> reagent from a cyclic-protected hexafluoroacetone, an air-stable liquid trifluoromethylating reagent, and KCu(O*t*-Bu)<sub>2</sub>, the group of Mikami showed that a CF<sub>2</sub>CF<sub>3</sub> analog (Scheme 19) was prepared in a similar way and applied for the pentafluoroethylation of aromatic derivatives [74] (2 examples).

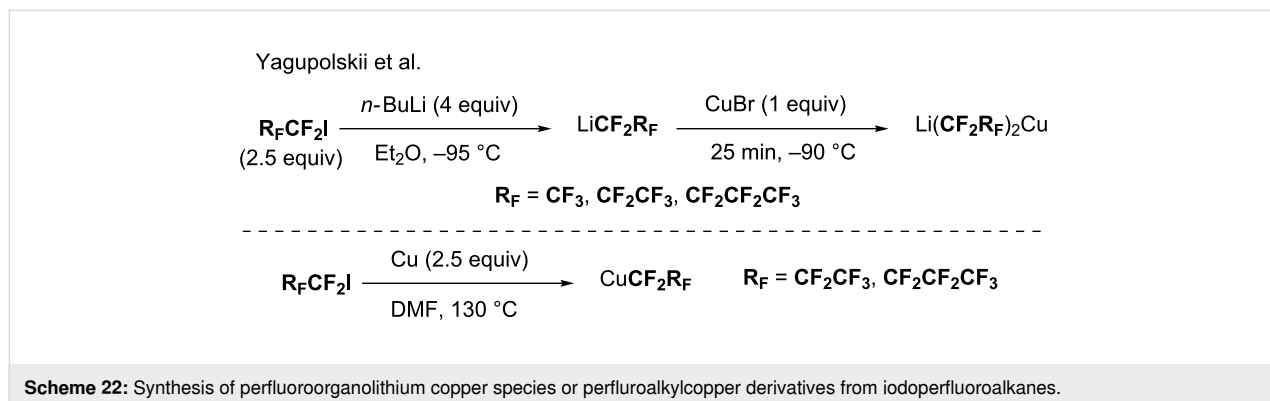
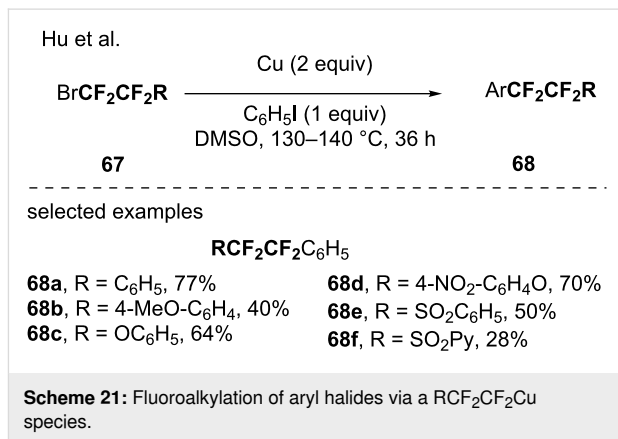
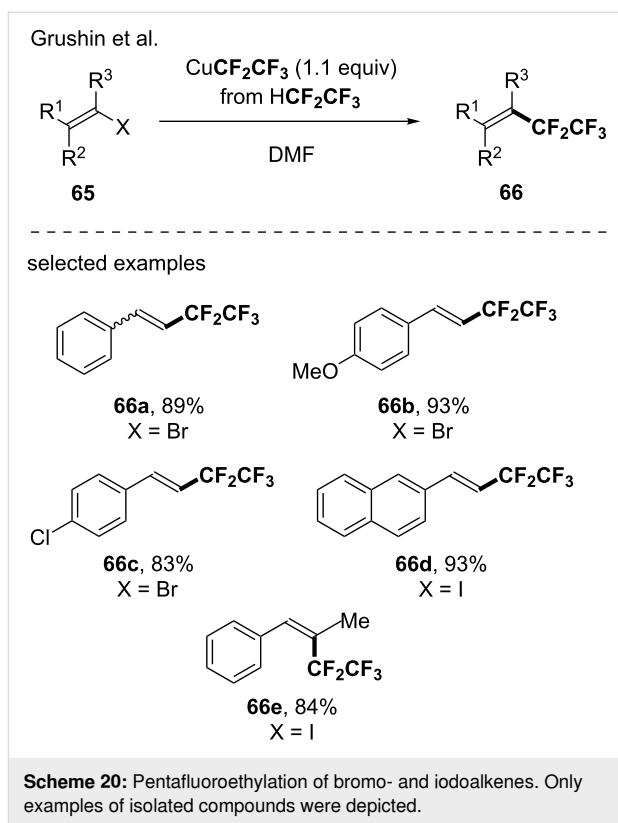


In 2015, Grushin and co-workers further investigated the functionalization of vinyl halides with  $\text{CuR}_F$  reagents generated from inexpensive fluoroform ( $\text{R}_F = \text{CF}_3$ ) and pentafluoroethane ( $\text{CF}_3\text{CF}_2\text{H}$ ) [75]. Both trifluoromethylation and pentafluoroethylation 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 stereoselective (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 ( $\text{RCF}_2\text{CF}_2\text{Br}$ ) was developed presumably involving a  $\text{RCF}_2\text{CF}_2\text{Cu}$  species (Scheme 21) [76].

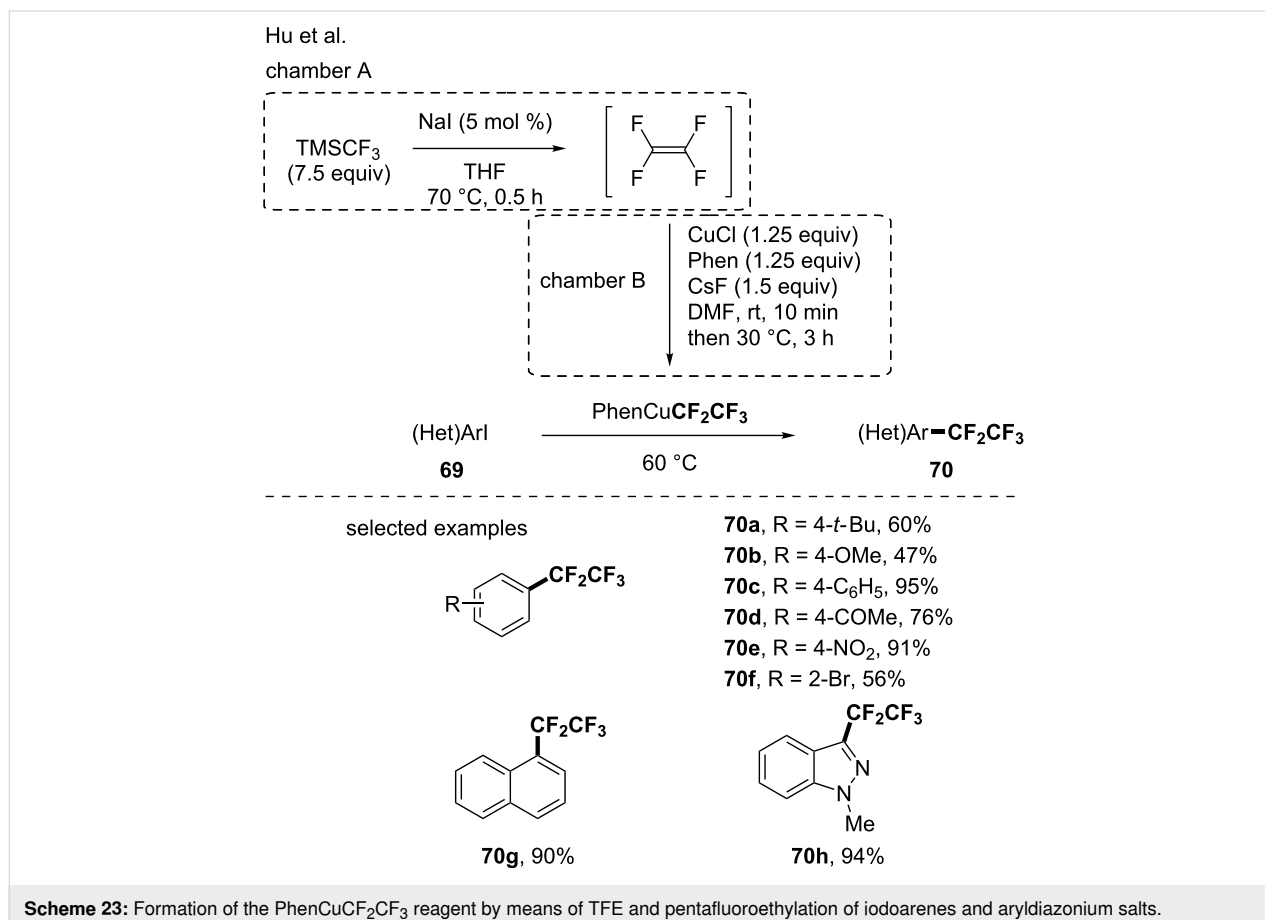
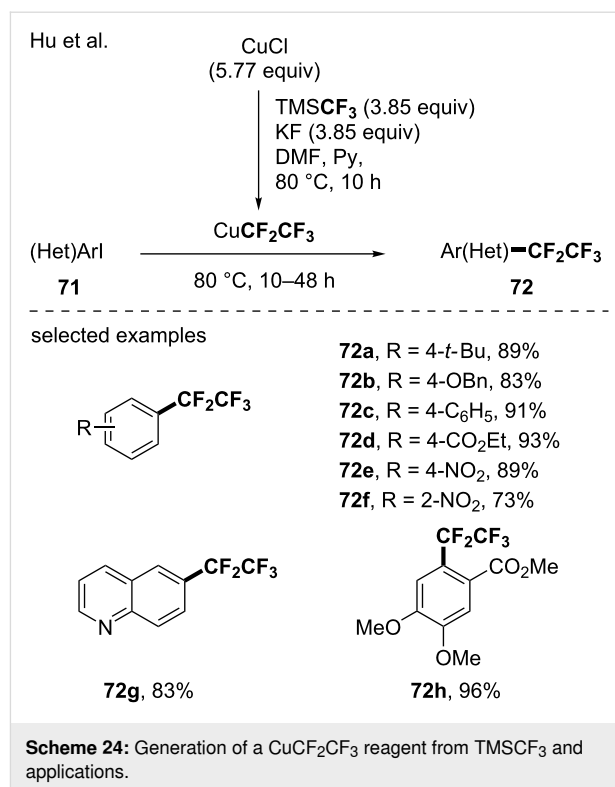
In 2015, Yagupolskii and co-workers investigated the synthesis of perfluoroalkylcopper reagents [77]. Depending on the reaction conditions they were able to access to perfluoroorganolithium copper species or perfluoroalkylcopper derivatives from iodoperfluoroalkanes in reaction with either *n*-BuLi or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

In 2017, the group of Hu offered an original synthetic route to the generation of the  $\text{PhenCuCF}_2\text{CF}_3$  reagent [78]. Indeed, they demonstrated that the Ruppert–Prakash reagent was a suit-



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  $\text{PhenCuCF}_2\text{CF}_3$  reagent (Scheme 23). This constituted a complementary approach to the existing ones for its synthesis, as it avoided the use of  $\text{TMSCF}_2\text{CF}_3$  or  $\text{CF}_3\text{CF}_2\text{H}$ . 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  $\text{TMSCF}_3$  for the formation of  $\text{CuCF}_2\text{CF}_3$  [81]. They suggested that in the presence of  $\text{CuCl}$ ,  $\text{KF}$  and  $\text{TMSCF}_3$ , the corresponding  $\text{CuCF}_3$  species will be formed and a subsequent homologation step involving a putative copper difluorocarbene will allow the formation of the  $\text{CuCF}_2\text{CF}_3$  species. With this tool in hand, a panel of aryl iodides was functionalized (Scheme 24).



## Conclusion

This review aims at providing an overview of the recent advances made since 2014 for the construction of CF<sub>2</sub>R-containing molecules (R ≠ 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<sub>f</sub> 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.

## Funding

This work was partially supported by Normandie Université (NU), the Région Normandie, the Centre National de la Recherche Scientifique (CNRS), Université de Rouen Normandie (URN), INSA Rouen Normandie, Labex SynOrg (ANR-11-LABX-0029) and Innovation Chimie Carnot (I2C). L.R. and T.B. thanks the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no. 758710) and especially L.R. for a doctoral fellowship.

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