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Difluoromethylation and Difluoroalkylation of (Hetero) Arenes: Access to Ar(Het)–CF_2H and Ar(Het)–CF_2R

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1.1 Introduction

The difluoromethylation of arenes has been given increasing attention due to the unique properties of the difluoromethyl group (CF_2H), which is considered as a bioisostere of hydroxyl and thiol groups and also as a lipophilic hydrogen bond donor [1]. Thus, the incorporation of CF_2H into an aromatic ring has become an important strategy in medicinal chemistry [2]. Conventional method for the synthesis of difluoromethylated arenes relies on the deoxyfluorination of aromatic aldehydes with diethylaminosulfur trifluoride (DAST) [3]. However, this method has a modest functional group tolerance and high cost. Transition-metal-catalyzed cross-coupling difluoromethylation is one of the most efficient strategies to access this class of compounds. Over the past few years, impressive achievements have been made in this field [4]. In this chapter, we describe three modes of difluoromethylation of aromatics: nucleophilic difluoromethylation, catalytic metal difluorocarbene-involved coupling reaction (MeDIC), and radical difluoromethylation.

1.2 Difluoromethylation of (Hetero)aromatics

1.2.1 Transition-Metal-Mediated/Catalyzed Nucleophilic Difluoromethylation of (Hetero)aromatics

Copper is the first transition metal that has been used for mediating nucleophilic difluoromethylation of (hetero)aromatics. In 1990, Burton et al. synthesized the first difluoromethyl copper complex by metathesis reaction between [$Cd(CF_2H)_2$] and CuBr [5]. However, the instability of this complex restricts its further synthetic applications [6]. In 2012, Hartwig and coworker found that using $TMSCF_2H$ (5.0 equiv) as source of fluorine to generate difluoromethyl copper *in situ* could

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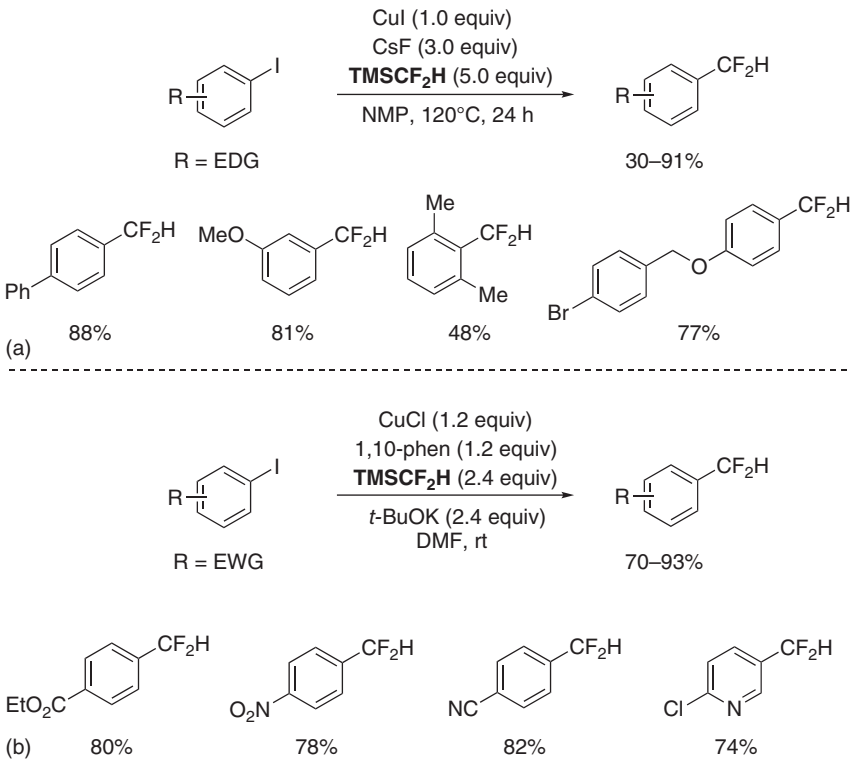
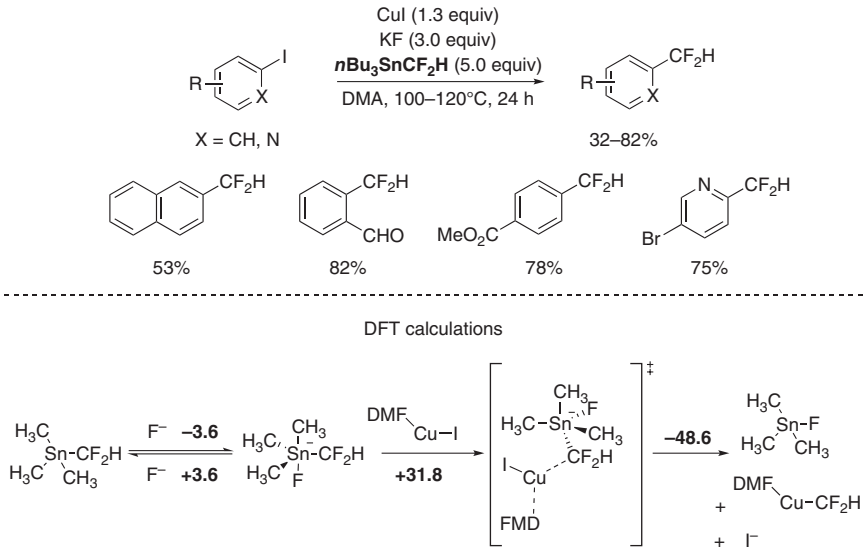


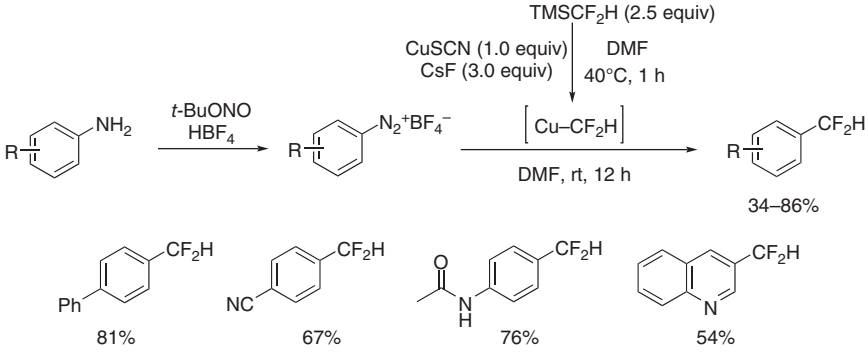
Scheme 1.1 Copper-mediated difluoromethylation of aryl iodides with $TMSCF_2H$.

lead to the difluoromethylation of aryl iodides efficiently (Scheme 1.1a) [7], representing the first example of copper-mediated difluoromethylation of aromatics. In this reaction, however, only electron-rich and -neutral aryl iodides were suitable substrates. A difluoromethylcuprate species $[Cu(CF_2H)_2]^-$ was proposed in the reaction. To overcome this limitation, Qing and coworkers reported a 1,10-phen-promoted copper-mediated difluoromethylation of electron-deficient (hetero)aryl iodides with $TMSCF_2H$ (Scheme 1.1b) [8]. The role of the ligand is to stabilize the difluoromethyl copper species. In 2012, Prakash et al. also reported a copper-mediated difluoromethylation of aryl iodides, employing *n*-Bu_3SnCF_2H, instead of $TMSCF_2H$, as the difluoromethylation reagent (Scheme 1.2) [9]. This method allowed difluoromethylation of electron-deficient (hetero)aryl iodides, but electron-rich partners produced low yields. A transmetalation between *n*-Bu_3SnCF_2H and CuI to generate $CuCF_2H$ species was proposed. Using similar strategy, Goossen and coworkers reported a Sandmeyer-type copper-mediated difluoromethylation of (hetero)arenediazonium salts with $TMSCF_2H$ (Scheme 1.3) [10].

In addition to the difluoromethylation of prefunctionalized aromatics, the copper-mediated direct C—H bond difluoromethylation of heteroaromatics has also been reported, representing a more straightforward and atom/step-economic approach. Inspired by the oxidative trifluoromethylation reaction of



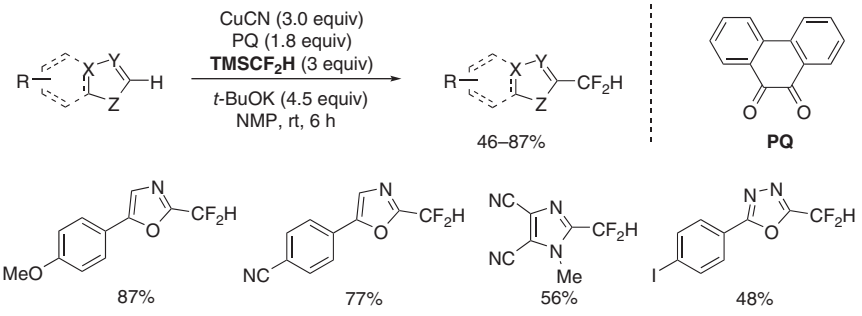
Scheme 1.2 Copper-mediated difluoromethylation of (hetero)aryl iodides with *n*-Bu_3SnCF_2H.



Scheme 1.3 Copper-mediated difluoromethylation of (hetero)arenediazoniums.

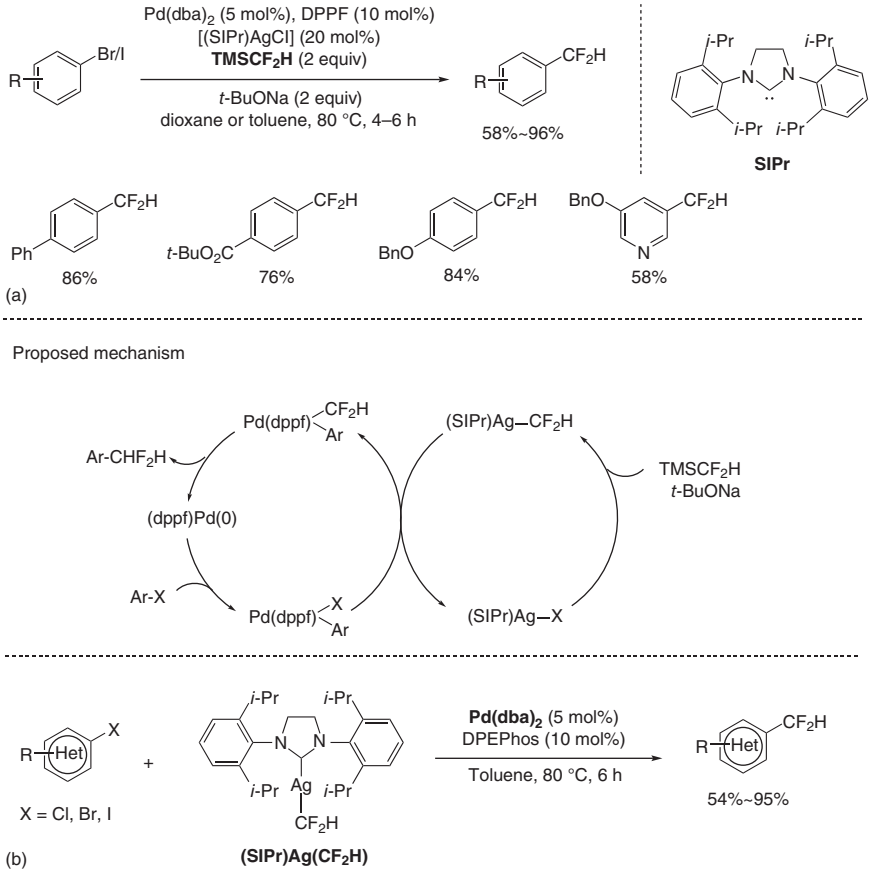
heteroaromatics [11], Qing and coworkers reported a copper-mediated direct oxidative difluoromethylation of C—H bonds on electron-deficient heteroarenes with $TMSCF_2H$ (Scheme 1.4) [12]. The use of 9,10-phenanthrenequinone (PQ) as an oxidant was essential for the reaction. Regioselective difluoromethylation was favorable to the more acidic C—H bond, which was readily deprotonated by *t*-BuOK base, to provide the desired products.

These copper-mediated difluoromethylation reactions paved a new way to access difluoromethylated arenes. In these reactions, however, more than stoichiometric amount of copper salts were required. A more efficient and attractive alternative is the catalytic difluoromethylation. In 2010, Buchwald and coworkers reported the first example of palladium-catalyzed trifluoromethylation of aryl chlorides with $TESCF_3$ [13]. Direct adaptation of this strategy to difluoromethylation resulted in inefficient transmetalation between the palladium



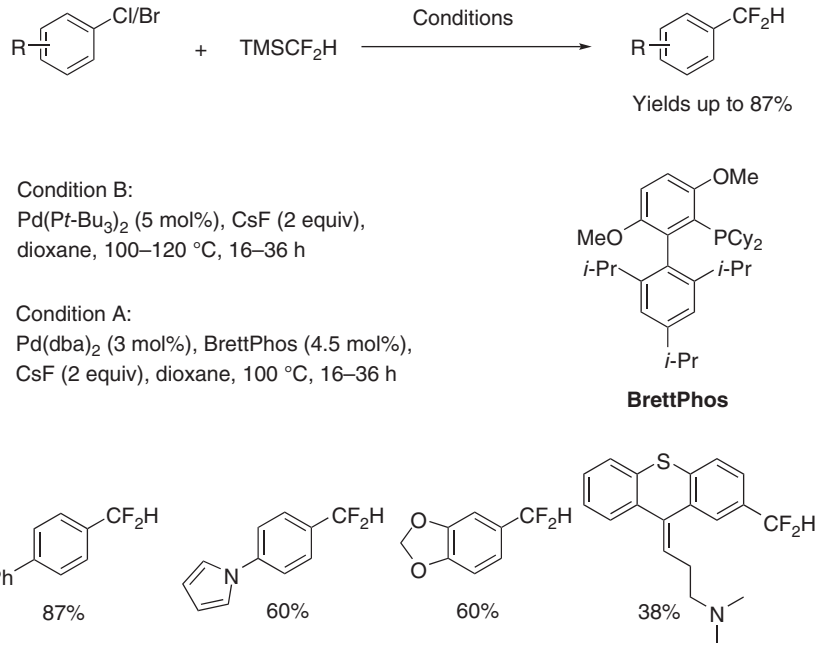
Scheme 1.4 Copper-mediated oxidative difluoromethylation of heteroarenes.

catalyst and $TMSCF_2H$. In 2014, Shen and coworkers developed a cooperative dual palladium/silver catalytic system with both bidentate phosphine 1,1′-bis(diphenylphosphino)ferrocene (dppf) and *N*-heterocyclic carbene (NHC) SIPr as the ligands (Scheme 1.5a) [14]. This system enabled difluoromethylation of electron-rich and electron-deficient aryl bromides and iodides with $TMSCF_2H$



Scheme 1.5 Palladium-catalyzed difluoromethylation of aryl halides with $(SIPr)Ag(CF_2H)$.

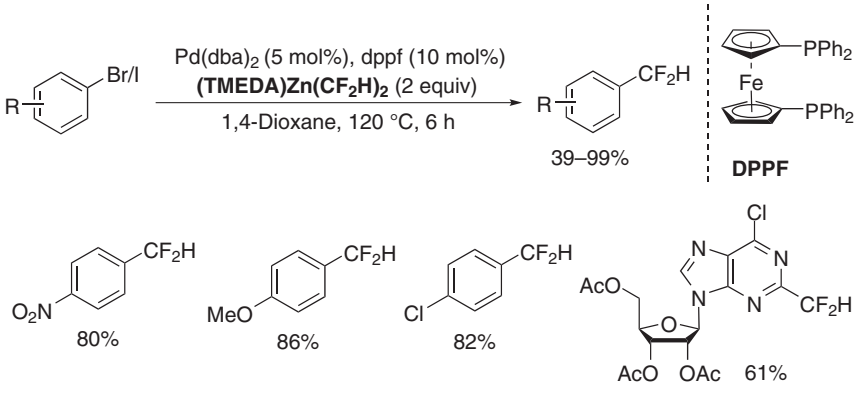
efficiently. An *in situ* generated difluoromethyl silver complex (SIPr)Ag(CF_2H) was found to promote the transmetalation step and facilitate the catalytic cycle. Stoichiometric reaction showed that the reductive elimination of aryldifluoromethyl palladium complex [Ar–Pd(L_n)–CF_2H] is faster than that of aryltrifluoromethyl palladium complex [Ar–Pd(L_n)–CF_3], suggesting the different electronic effect between CF_3 and CF_2H. The method can also be extended to heteroaryl halides [15] and triflates (Scheme 1.5b) [15b], including pharmaceutical and agrochemical derivatives. Very recently, Sanford and coworkers demonstrated that the use of $TMSCF_2H$ can also lead to difluoromethylated arenes under palladium catalysis (Scheme 1.6) [16]. The use of electron-rich monophosphine ligands [BrettPhos and P(*t*-Bu)$_3$] allowed difluoromethylation of a series of electron-rich (hetero)aryl chlorides and bromides.



Scheme 1.6 Palladium-catalyzed difluoromethylation of aryl halides with $TMSCF_2H$.

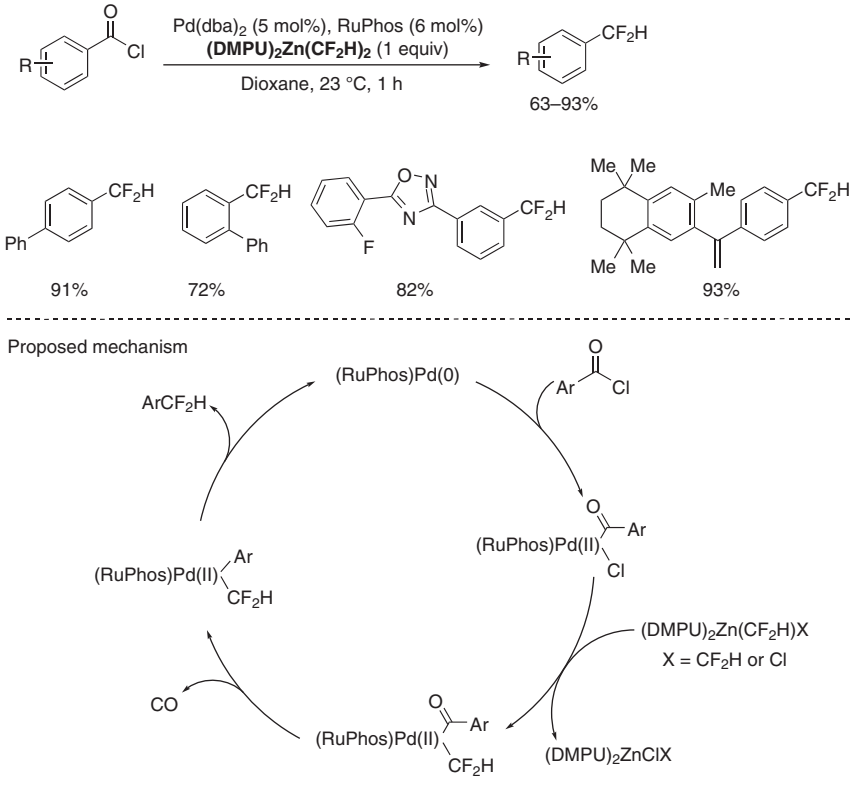
Using more reactive transmetalating zinc reagent $(TMEDA)_2Zn(CF_2H)_2$ as fluorine source, Mikami and coworkers developed a palladium-catalyzed difluoromethylation of (hetero)aryl iodides and bromides (Scheme 1.7) [17]. Similar to Shen's work, dppf was employed as the ligand in the reaction. This method exhibited broad substrate scope, where both electron-rich and electron-deficient aryl iodides were suitable substrates.

Besides the aryl halides, benzoic acid chlorides were also a competent coupling partner. With $(DMPU)_2Zn(CF_2H)_2$ as the difluoromethylating reagent, Ritter and coworkers developed a palladium-catalyzed decarbonylative difluoromethylation of benzoic acid chlorides (Scheme 1.8) [18]. This reaction proceeded under



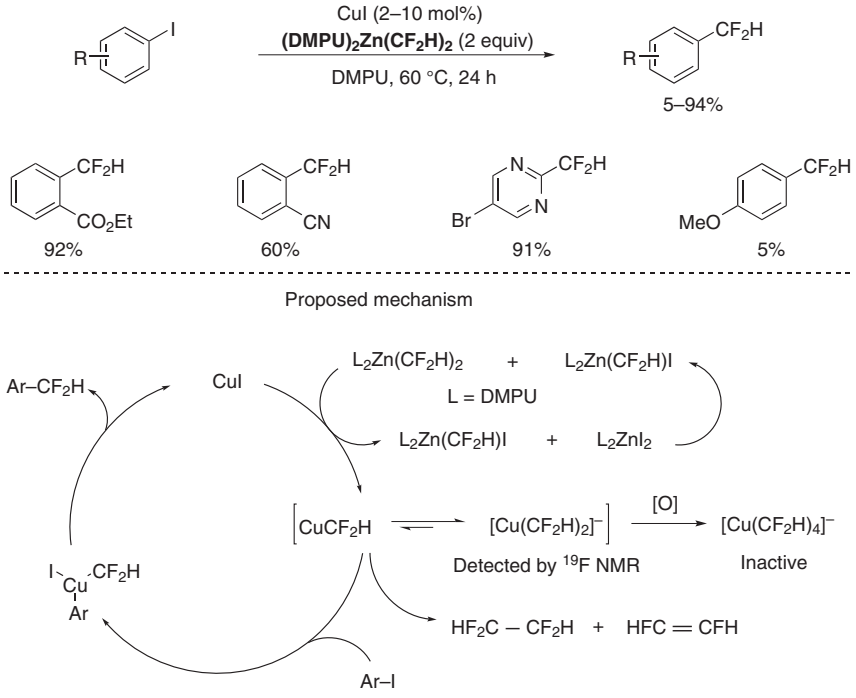
Scheme 1.7 Palladium-catalyzed difluoromethylation of aryl bromides/chlorides with $(TMEDA)Zn(CF_2H)_2$.

mild reaction conditions with good functional group tolerance. The use of monophosphine ligand RuPhos is critical in promoting the decarbonylation and subsequent difluoromethylation.



Scheme 1.8 Palladium-catalyzed decarbonylative difluoromethylation of benzoic acid chlorides with $(DMPU)_2Zn(CF_2H)_2$.

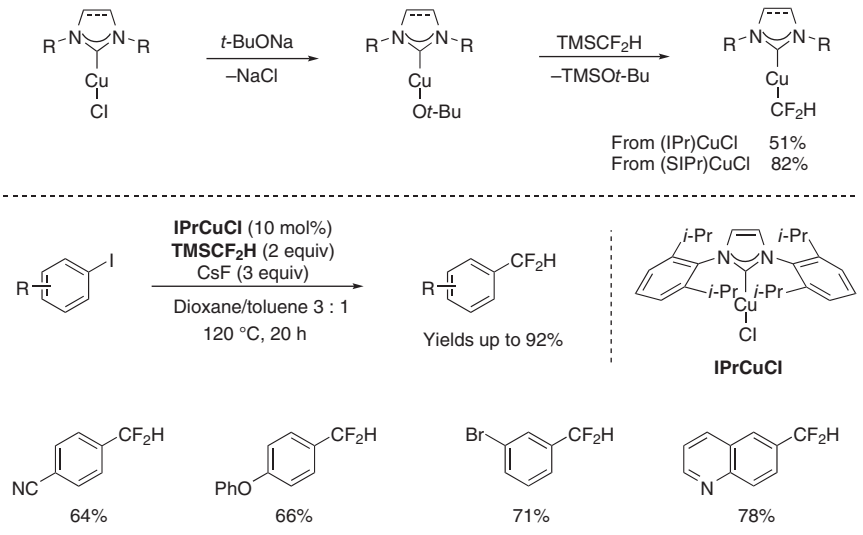
Copper can also be used as the catalyst for the difluoromethylation. In 2016, Mikami and coworkers reported a ligand-free copper-catalyzed difluoromethylation of (hetero)aryl iodides (Scheme 1.9), in which a cuprate $[Cu(CF_2H)_2]^-$ species may be involved in the reaction [19], in agreement with Hartwig's hypothesis [7].



Scheme 1.9 Copper-catalyzed difluoromethylation of aryl iodides with $(DMPU)_2Zn(CF_2H)_2$.

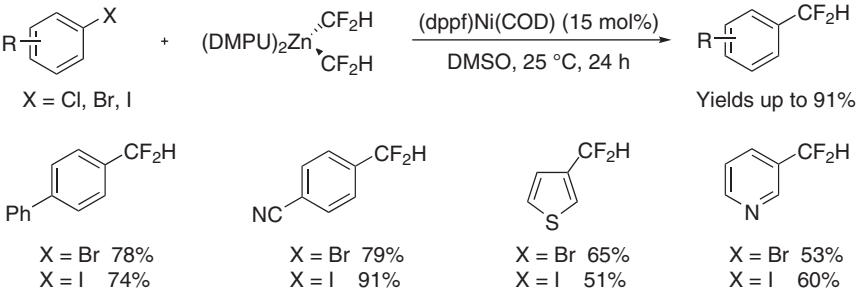
For all these copper-mediated or catalyzed difluoromethylation reactions, a difluoromethyl copper species was proposed as the key intermediate. However, the nature and properties of the unstable copper species have not been systematically investigated. In 2017, Sanford and coworkers reported the synthesis, reactivity, and catalytic applications of an isolable $(IPr)Cu(CF_2H)$ complex (Scheme 1.10) [20]. Unlike the previous supposition [5, 6], this complex is stable in solution at room temperature for at least 24 hours, suggesting that the bimolecular decomposition pathway is relatively slow. A variety of aryl electrophiles could react with this $(IPr)Cu(CF_2H)$ complex to furnish the corresponding difluoromethylated arenes smoothly. Based on this fundamental research, a copper-catalyzed difluoromethylation of aryl iodides with $TMSCF_2H$ has been developed by employing IPrCuCl as the catalyst.

Although palladium- and copper-catalyzed nucleophilic difluoromethylation reactions have been developed, the development of fluoroalkylation catalyzed by earth-abundant transition metals remains appealing. In 2016, Vicic and coworker reported a nickel-catalyzed difluoromethylation of (hetero)aryl iodides,



Scheme 1.10 (NHC)CuCl-catalyzed difluoromethylation of aryl iodides with $TMSCF_2H$.

bromides, and triflates with $(DMPU)_2Zn(CF_2H)_2$ (Scheme 1.11) [21]. This is the first example to use $(DMPU)_2Zn(CF_2H)_2$ as the difluoromethylation reagent. The reaction underwent difluoromethylation smoothly with electron-deficient substrates, but electron-rich aryl iodides or aryl bromides were not applicable to the reaction.



Scheme 1.11 Nickel-catalyzed difluoromethylation of aryl halides with $(DMPU)_2Zn(CF_2H)_2$.

1.2.2 Catalytic Metal-Difluorocarbene-Involved Coupling (MeDIC) Reaction

Difluorocarbene is an electrophilic ground-state singlet carbene. As an important intermediate, difluorocarbene has privileged applications in various areas [22]. However, the intrinsic electrophilic nature of difluorocarbene limits its reaction types [23]. Usually, difluorocarbene is used to react with heteroatom nucleophiles (O, S, N, P) to produce heteroatom-substituted difluoromethylated compounds [24] or to react with alkenes/alkynes to prepare *gem*-difluorocyclopropanes

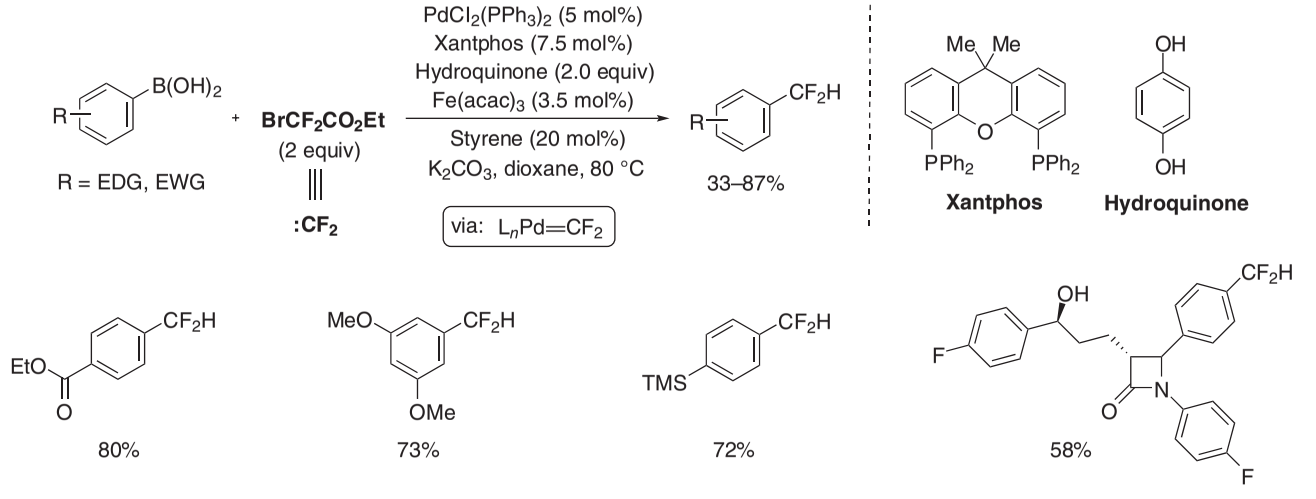
/*gem*-difluorocyclopropenes [25]. The use of transition metal to tune the reactivity of difluorocarbene would provide a promising strategy to develop new types of difluorocarbene transfer reaction. However, because of the inherently low reactivity of known isolated metal-difluorocarbene complexes compared to their nonfluorinated counterparts [26], it is of great challenge to apply metal-difluorocarbene to the catalytic cross-coupling. The catalytic MeDIC reaction had not been reported until Zhang and coworkers reported a palladium-catalyzed difluoromethylation of arylboronic acids with $BrCF_2CO_2Et$ in 2015 (Scheme 1.12) [27]. This reaction represents the first example of a catalytic MeDIC reaction by exhibiting excellent functional group tolerance (even toward bromide and hydroxyl groups) and being compatible with both electron-rich and electron-deficient arylboronic acids. Compared to the catalytic nucleophilic difluoromethylation of aromatics, the advantages of this reaction are broad substrate scope and the use of inexpensive and readily available fluorine source without requiring a multistep synthetic procedure. The combination of bidentate phosphine ligand Xantphos and additive hydroquinone is essential for reaction efficiency. Kinetic studies showed that a potassium salt $BrCF_2CO_2K$ was generated *in situ* at the initial stage, which served as a difluorocarbene precursor in the reaction. Mechanistic studies revealed that an aryl group migration to the palladium difluorocarbene carbon pathway was not involved in the reaction.

Inspired by this palladium-catalyzed MeDIC reaction, Zhang and coworkers employed $ClCF_2H$ as the fluorine source for the difluoromethylation (Scheme 1.13) [28]. $ClCF_2H$ is an inexpensive and abundant industrial chemical used for the production of fluorinated polymers [22], representing an ideal and the most straightforward difluoromethylating reagent. The reaction allowed difluoromethylation of a wide range of (hetero)arylboronic acids and esters and was used for difluoromethylation of a series of biologically active molecules, including pharmaceuticals, agrochemicals, and natural products. Most remarkably, the late-stage difluoromethylation of biologically active molecules through a sequential C–H/C–CN borylation [29] and difluoromethylation process proceeded smoothly, thus providing a straightforward route for applications in drug discovery and development. Deuterium-labeling experiments demonstrated that arylboronic acids, hydroquinone, $ClCF_2H$, and even water were the proton donors.

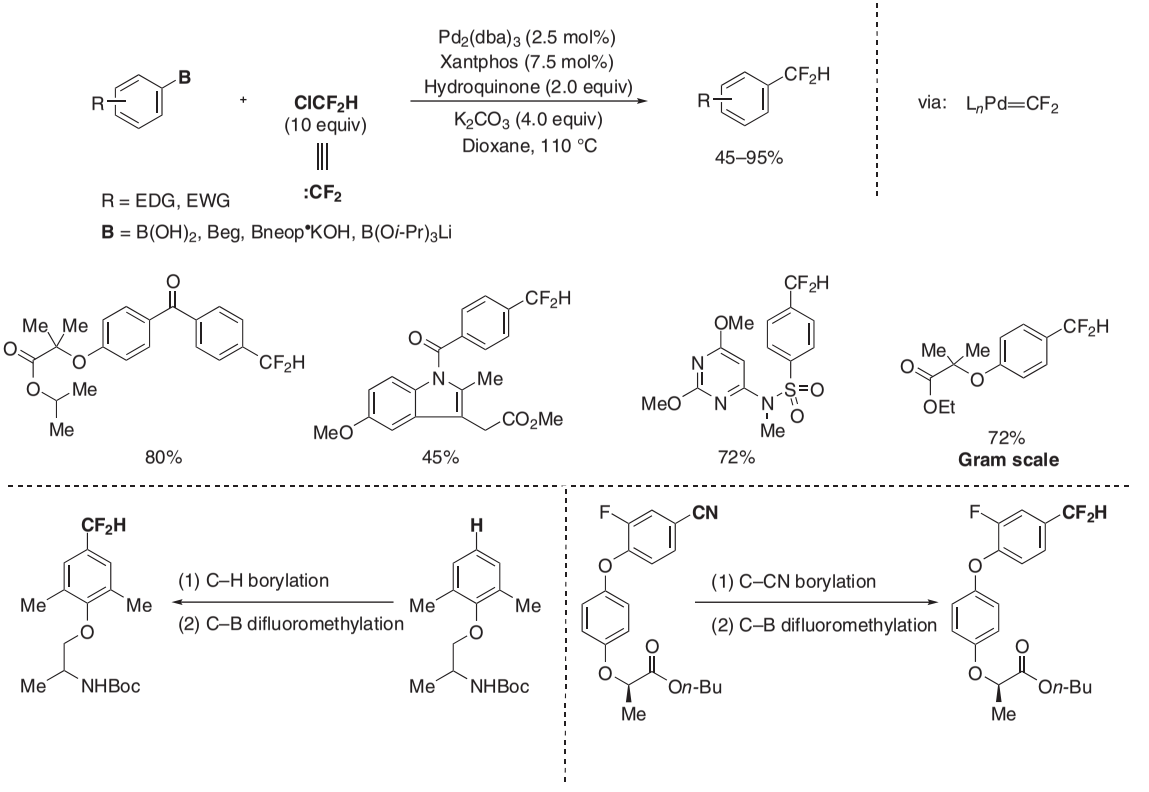
Xiao and coworkers reported a difluoromethylation of arylboronic acids with $Ph_3P^+CF_2COO^-$ (PDFA), but electron-deficient arylboronic acids were not suitable substrates (Scheme 1.14) [30]. A palladium(0) difluorocarbene trimer $[Pd(CF_2)(PPh_3)]_3$ was isolated. Stoichiometric reaction of this $[\{Pd(CF_2)(PPh_3)\}_3]$ complex with arylboronic acid demonstrated that this palladium difluorocarbene cluster was not an active species in the reaction.

1.2.3 Transition-Metal-Catalyzed Radical Difluoromethylation of (Hetero)aryl Metals/Halides and Beyond

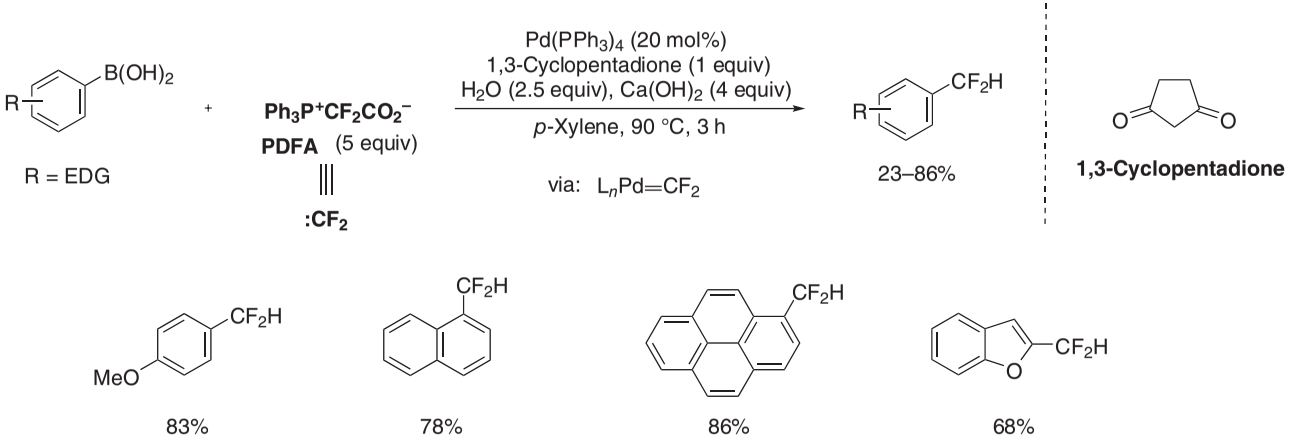
Owning to the electron-withdrawing effect of fluorine atom, perfluoroalkyl halides can be readily initiated by a low-valent transition metal to generate a radical via a single electron transfer (SET) pathway [31]. A nickel-catalyzed perfluoroalkylation of aromatics with perfluoroalkyl iodides was reported in



Scheme 1.12 Palladium-catalyzed difluoromethylation of arylboronic acids with bromodifluoroacetate via a difluorocarbene pathway.

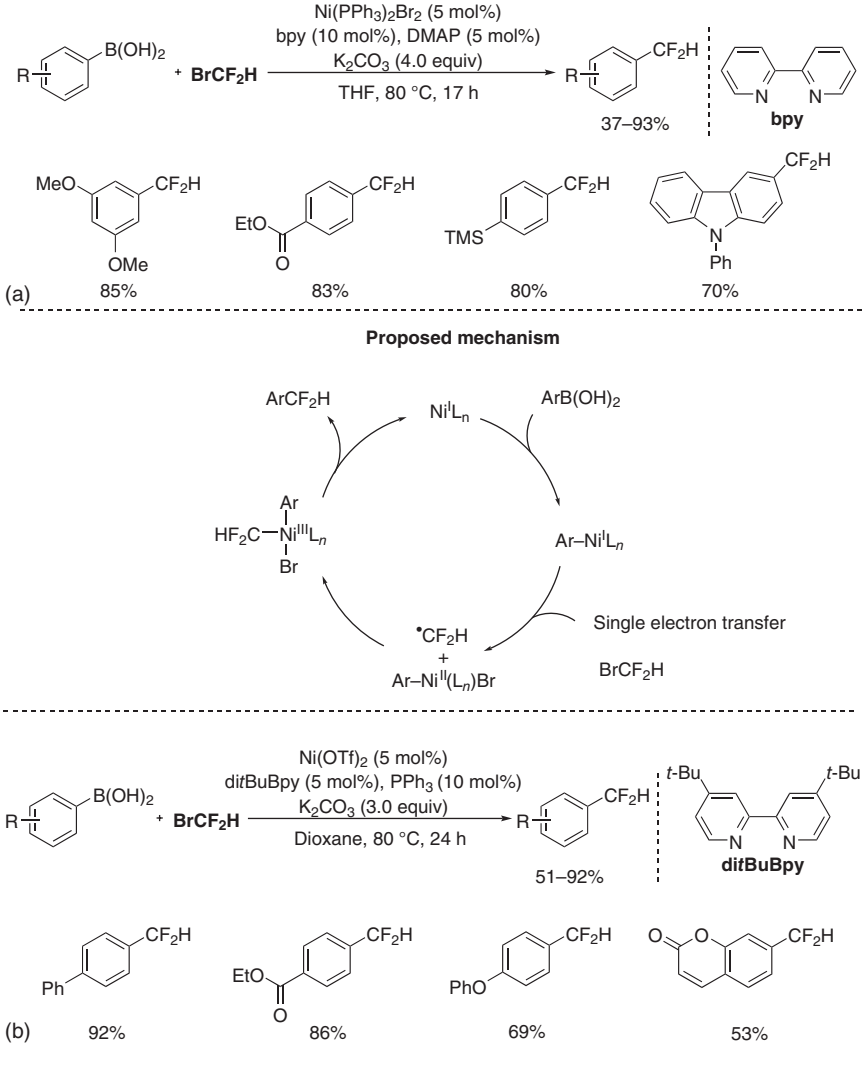


Scheme 1.13 Palladium-catalyzed difluoromethylation of aryl borons with chlorodifluoromethane via a difluorocarbene pathway.



Scheme 1.14 Palladium-catalyzed difluoromethylation of arylboronic acids with PDFA via a difluorocarbene pathway.

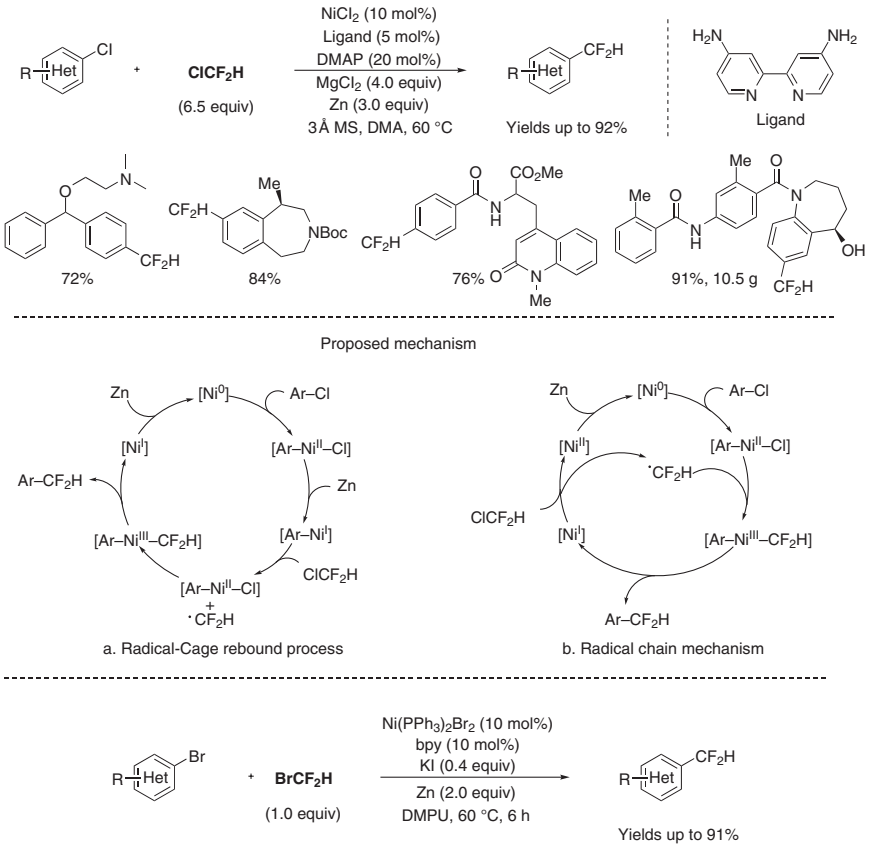
1989 by Huang and coworker [32]. A radical initiated by nickel(0) was involved in the reaction, but no fluoroalkyl nickel species was generated. A nickel-catalyzed radical difluoromethylation of aromatics (Scheme 1.15a) was reported in 2018 by Zhang and coworkers [33] on the basis of their previous work on the nickel-catalyzed difluoroalkylation of arylboronic acids with difluoroalkyl halides [34]. The reaction exhibited high functional group tolerance and allowed difluoromethylation of a variety of arylboronic acids with simple and readily available bromodifluoromethane ($BrCF_2H$) as the fluorine source. A combined (2 + 1) ligand system [34b,c] (a bidentate ligand and a monodentate ligand) was employed to promote the relatively low reactivity of $BrCF_2H$ and facilitate catalytic cycle. Radical inhibition, radical clock, and electron paramagnetic resonance (EPR)



Scheme 1.15 Nickel-catalyzed difluoromethylation of arylboronic acids with bromodifluoromethane.

experiments demonstrated that a difluoromethyl radical was involved in the reaction. Based on the mechanistic studies and previous reports [35], a Ni(I/III) catalytic cycle involving a radical was proposed. Similar to Zhang's studies, Wang and coworkers reported a nickel-catalyzed cross-coupling of $BrCF_2H$ with arylboronic acids using PPh_3 as the co-ligand (Scheme 1.15b) [36].

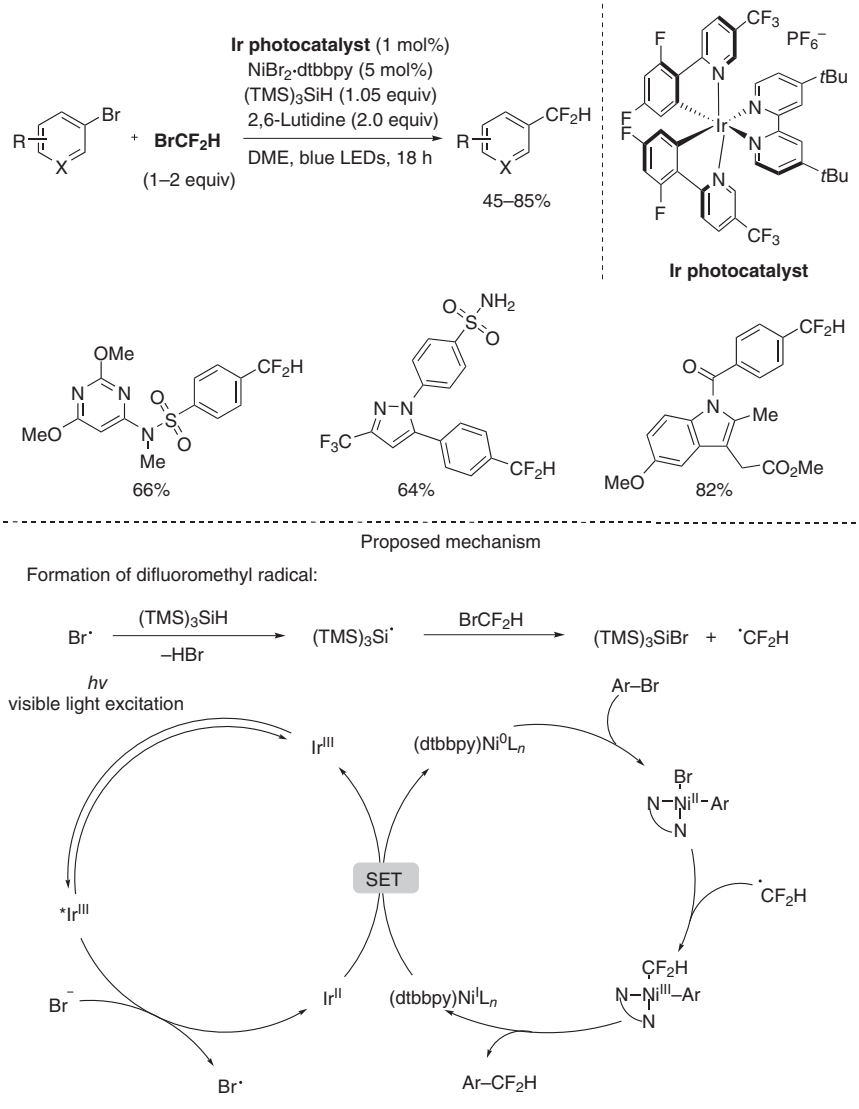
Later on, Zhang and coworkers extended this (2 + 1) ligand system to the nickel-catalyzed cross-coupling between (hetero)aryl chlorides/bromides and $ClCF_2H$ [37], representing the first example of nickel-catalyzed reductive cross-coupling between organoelectrophiles and fluoroalkyl halides (Scheme 1.16). The reaction exhibited remarkably broad substrate scope, including a range of pharmaceuticals, without preformation of aryl metals. The reaction can be scaled up to 10 g scale without loss of reaction efficiency, providing a practical application of $ClCF_2H$ in life and materials sciences. Radical clock and control experiments revealed that a difluoromethyl radical generated by direct cleavage of C—Cl bond in $ClCF_2H$ was involved in the reaction. Stoichiometric reaction of aryl nickel complex [ArNi(di*t*BuBpy)X] with $ClCF_2H$ and reaction of difluoromethyl nickel complex [HCF_2Ni(di*t*BuBpy)X] with aryl chloride showed that the reaction started from the oxidative addition of aryl halides to Ni(0). This is in



Scheme 1.16 Nickel-catalyzed reductive difluoromethylation of aryl chlorides and bromides.

contrast to palladium-catalyzed difluoromethylation of arylboronic acids and esters with $ClCF_2H$, in which a difluorocarbene pathway is involved in the reaction [28]. This nickel-catalyzed reductive process can also be applied to $BrCF_2H$ with high efficiency and good functional group tolerance (Scheme 1.16) [38].

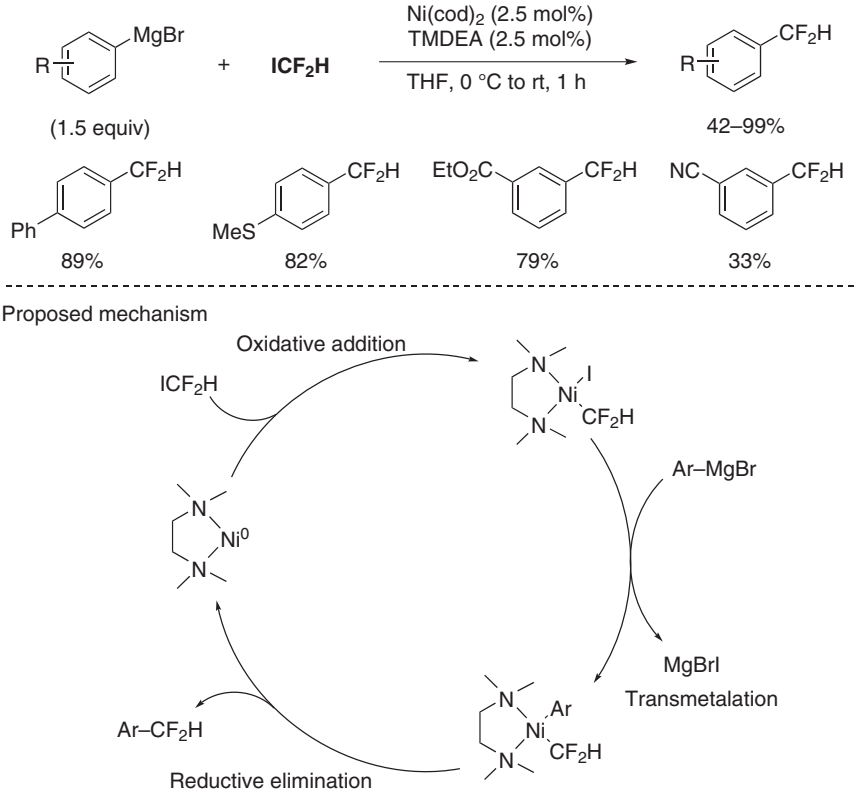
The nickel-catalyzed reductive difluoromethylation has also been extended to photoredox catalysis. Recently, McMillan and coworkers reported a method to access difluoromethylated (hetero)arenes through cross-coupling of (hetero)aryl bromides with $BrCF_2H$ by combining nickel catalysis ($NiBr_2$·4,4′-di-*tert*-butyl-2,2′-bipyridine [dtbbpy]) with iridium photocatalysis {[Ir(dF(C_{F3})ppy)$_2$(dtbbpy)]PF_6} (Scheme 1.17) [39]. A pathway involving silyl radical-medi-



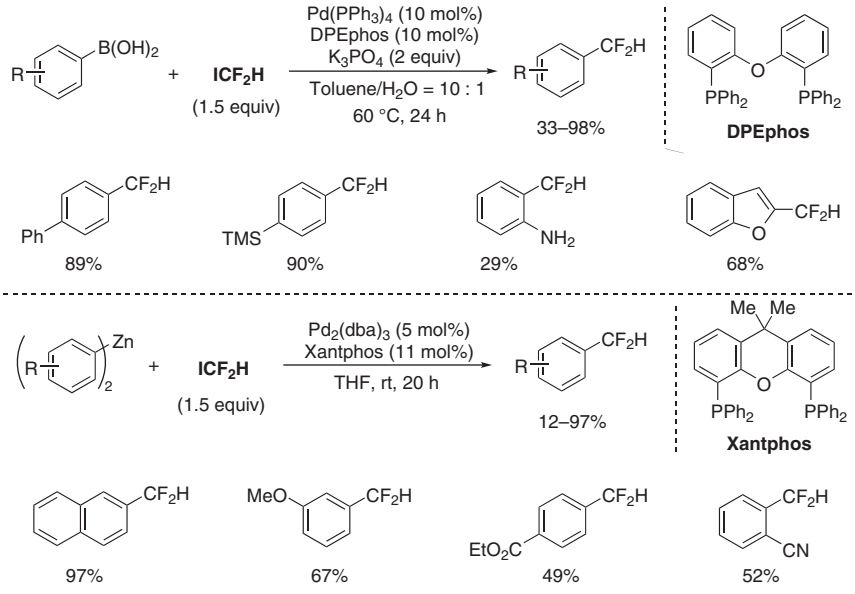
Scheme 1.17 Metallaphotoredox difluoromethylation of aryl bromides with bromodifluoromethane.

ated halogen abstraction to generate difluoromethyl radical was proposed. One advantage of this method is that various N-containing heteroaromatics were applicable to the reaction, providing an alternative access to difluoromethylated (hetero)aromatics.

The nickel-catalyzed difluoromethylation of arylmetals with difluoromethyl halides has also been applied to the cross-coupling between arylmagnesium bromides and difluoroiodomethane (ICF_2H) (Scheme 1.18) [40]. In contrast to the previous difluoromethylation via a Ni(I/III) catalytic cycle [33], a Ni(0/II) catalytic cycle was proposed by Mikami and coworkers [40] to be likely involved in the reaction. This plausible mechanism was supported by the stoichiometric reaction of a difluoromethyl nickel(II) complex with PhMgBr. Radical clock experiment showed that the free difluoromethyl radical was unlikely involved in the reaction. They also used ICF_2H as the difluoromethylating reagent and developed a palladium-catalyzed difluoromethylation of arylboronic acids with ICF_2H (Scheme 1.19) [41]. Preliminary mechanistic studies revealed that the reaction started from the oxidative addition of ICF_2H to $Pd(PPh_3)_4$; the resulting square-planar *trans*-$(PPh_3)_2Pd(II)(CF_2H)I$ complex underwent transmetalation to provide *cis*-$(PPh_3)_2Pd(CF_2H)Ph$, which subsequently underwent a ligand



Scheme 1.18 Nickel-catalyzed difluoromethylation of aryl magnesium reagents with iododifluoromethane.



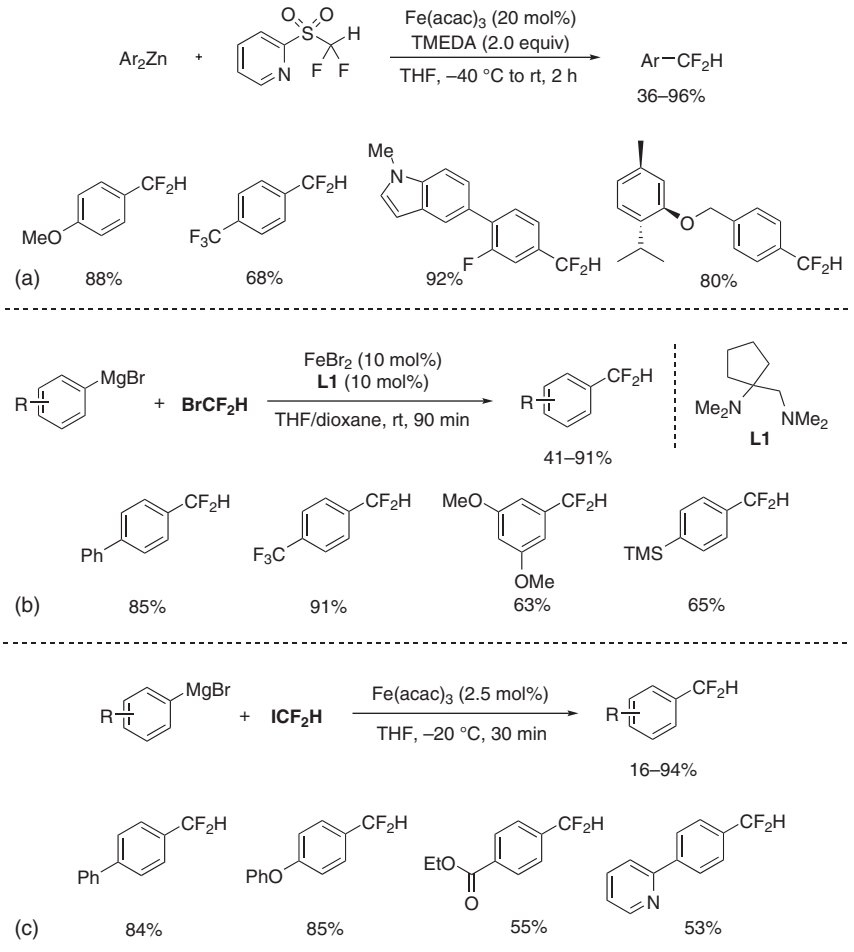
Scheme 1.19 Palladium-catalyzed difluoromethylation of arylboronic acids or aryl zinc reagents.

exchange with DPEphos, followed by reductive elimination to produce the difluoromethylated aromatics.

In addition to the nickel-catalyzed radical difluoromethylation, the use of inexpensive, nontoxic, and environmentally benign iron as the catalyst has also been given increasing attention. In 2018, Hu and coworkers reported an iron-catalyzed difluoromethylation of arylzinc reagents with difluoromethyl 2-pyridyl sulfone (Scheme 1.20a) [42]. Generally, moderate to high yields were obtained with electron-rich substrates, but less reactivity was showed by electron-deficient substrates. Preliminary mechanistic studies showed that a difluoromethyl radical, generated via SET pathway from difluoromethyl 2-pyridyl sulfone, was involved in the reaction. In the same year, Zhang and coworkers also developed an iron-catalyzed difluoromethylation (Scheme 1.20b) [43], in which a bulky diamine ligand with a butylene group substituted at one carbon atom of ethylene backbone in *N,N,N′,N′*-tetramethyl-ethane-1,2-diamine (TMEDA) was used to promote the reaction. During the reaction/catalysis process, the corresponding iron complex can be changed from five-coordinate to more electron-deficient four-coordinate, thus improving its catalytic efficiency. This iron-catalyzed difluoromethylation has later been extended to ICF_2H by Mikami and coworkers (Scheme 1.20c) [44]. In contrast, no ligand was required in this reaction, mainly owing to the different reactivity between $BrCF_2H$ and ICF_2H.

1.2.4 Radical C—H Bond Difluoromethylation of (Hetero)aromatics

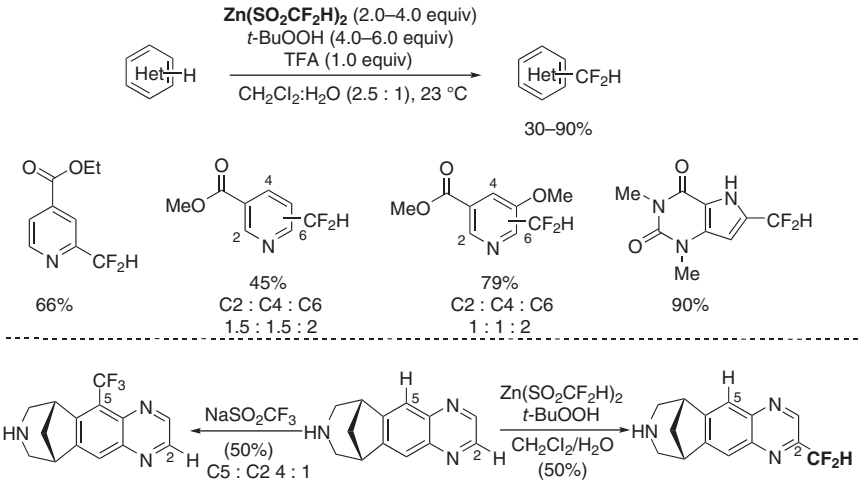
The direct C—H bond difluoromethylation of (hetero)aromatics represents a more straightforward alternative. Over the past a few years, important progress has been made in this field, providing synthetically convenient routes for



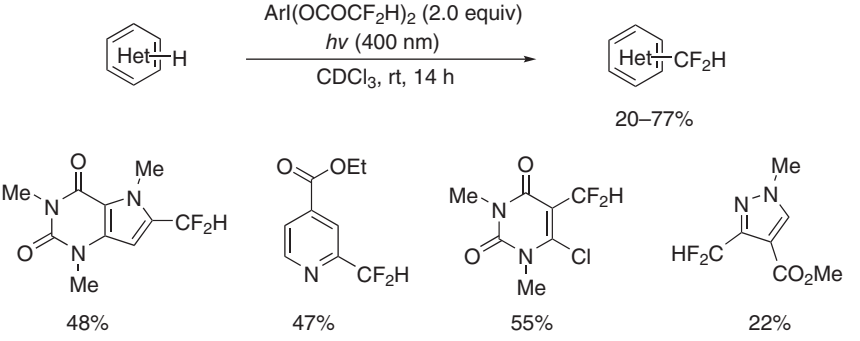
Scheme 1.20 Iron-catalyzed difluoromethylation of aryl zinc reagents or aryl magnesium reagents.

applications in organic synthesis. In 2012, Baran and coworkers developed a new difluoromethylating reagent $Zn(SO_2CF_2H)_2$ (DMFS) that allowed difluoromethylation of a range of N-containing heteroarenes in the presence of *t*-BuOOH via a radical pathway (Scheme 1.21) [45]. Regiochemical comparisons showed that the difluoromethylation preferred to occur at relatively more electron-deficient carbon, suggesting a nucleophilic character of the difluoromethyl radical generated from DMFS.

The use of inexpensive and readily available difluoromethylating reagents via the C—H bond difluoromethylation would be more attractive in terms of cost efficiency. In 2017, Maruoka and coworkers developed a hypervalent iodine reagent with readily available difluoroacetic acid as the ligand (Scheme 1.22) [46]. Upon irradiation of this difluoromethylating reagent with UV, a series of *N*-heteroarenes can be difluoromethylated at relatively more electron-deficient carbons via a difluoromethyl radical process. The regioselectivity of this reaction



Scheme 1.21 Radical difluoromethylation of heteroarenes with $Zn(SO_2CF_2H)_2$.

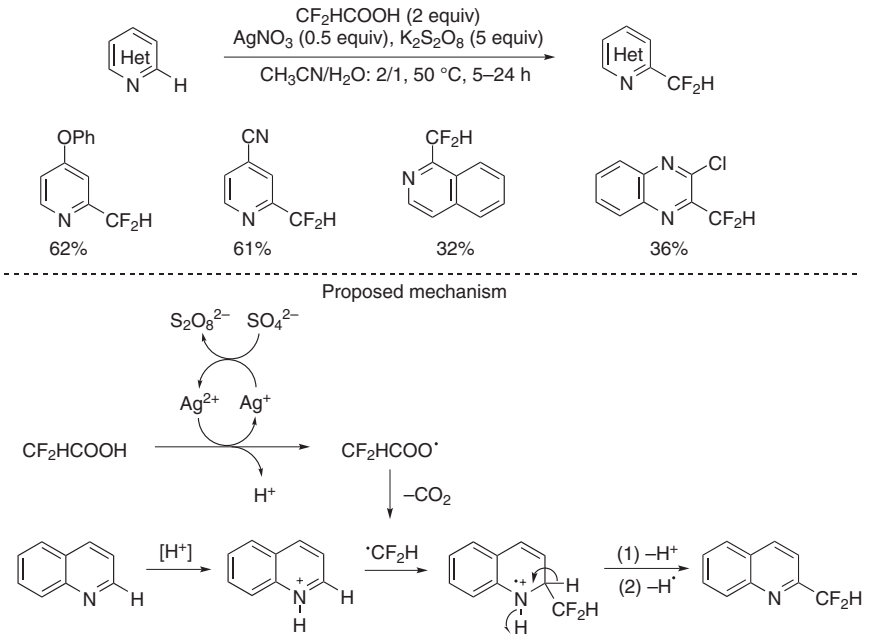


Scheme 1.22 Radical difluoromethylation of heteroarenes with $ArI(OCOCF_2H)_2$.

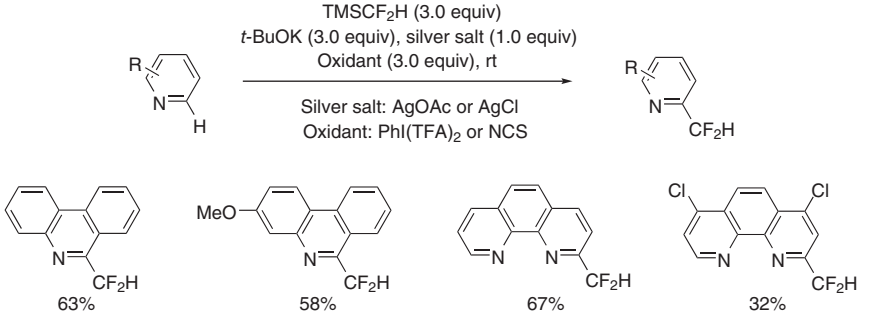
is same as that of Baran's method [45], implying the same nucleophilic character of difluoromethyl radical generated from these two new reagents. However, only low to moderate yields were obtained.

The direct use of difluoroacetic acid as the difluoromethylating reagent has also been reported almost contemporaneously. Nielsen and coworkers employed $AgNO_3/K_2S_2O_8$ as the oxidants to generate difluoromethyl radical from difluoroacetic acid (Scheme 1.23) [47]. This process allowed difluoromethylation at electron poor carbons adjacent to the nitrogen atom in *N*-heteroarenes. Similarly, low to moderate yields were obtained. Further investigation showed that a bis-difluoromethylation could also be occurred by increasing the reaction temperature.

In parallel to Nielsen's work, Qing and coworkers described a direct difluoromethylation of phenanthridines and 1,10-phenanthrolines with $TMSCF_2H$ (Scheme 1.24) [48]. The reaction used $PhI(OCOCF_3)_2$ or N-Chlorosuccinimide (NCS) as the oxidant, and silver salt as the additive, providing the corresponding difluoromethylated heteroarenes in low to moderate yields. A pathway was pro-



Scheme 1.23 Radical difluoromethylation of heteroarenes with HCF_2COOH.



Scheme 1.24 Oxidative difluoromethylation of phenanthridines and 1,10-phenanthrolines with $TMSCF_2H$.

posed for the reaction to involve a nucleophilic addition of difluoromethyl anion to the heteroarenes, followed by aromatization process, but a difluoromethyl radical pathway cannot be ruled out.

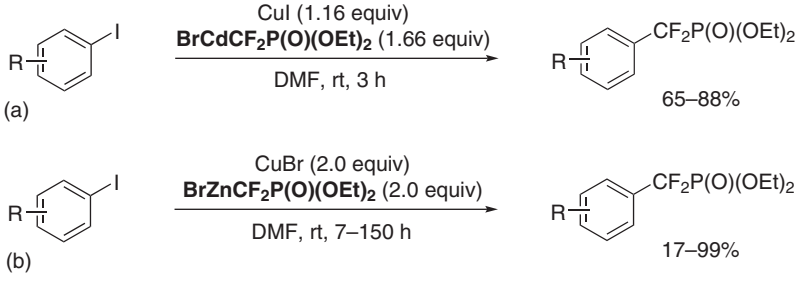
1.3 Difluoroalkylation of Aromatics

In addition to difluoromethylated aromatics, other difluoroalkylated aromatics also have important applications in medicinal chemistry and materials science due to the unique properties of difluoromethylene group (CF_2). The incorporation of CF_2 at the benzylic position not only can improve the metabolic stability

of biologically active molecules but also can enhance the acidity of its neighboring groups [49]. However, except for the conventional difluorination of ketoaromatics with DAST, general and efficient methods for highly selective introduction of CF_2R into organic molecules to access these valuable compounds had been less explored before 2012 [4]. The transition-metal-catalyzed cross-coupling difluoroalkylation would be an attractive strategy, as it can directly construct (Het)Ar—CF_2R bonds in an efficient and controllable manner. In particular, this strategy can enable late-stage difluoroalkylation of biologically active molecules without the need of multistep synthesis. Nevertheless, the difficulty in selectively controlling the catalytic cycle to access the desired difluoroalkylated aromatics posed problems with such strategy. Difluoroalkylated metal species have a different instability compared with their non-fluorinated counterparts due to decomposition or protonation to generate by-products [50]; this has increased attention on the subject and impressive achievements have been made over the past a few years [4]. Here, we specifically focus on the transition-metal-catalyzed difluoroalkylation of aromatics, including phosphonyldifluoromethylation and difluoroacetylation. The direct difluoroalkylation of C—H bond via a radical process will not be discussed in this session, as comprehensive reviews have been described previously [4].

1.3.1 Transition-Metal-Catalyzed Phosphonyldifluoromethylation of (Hetero)aromatics

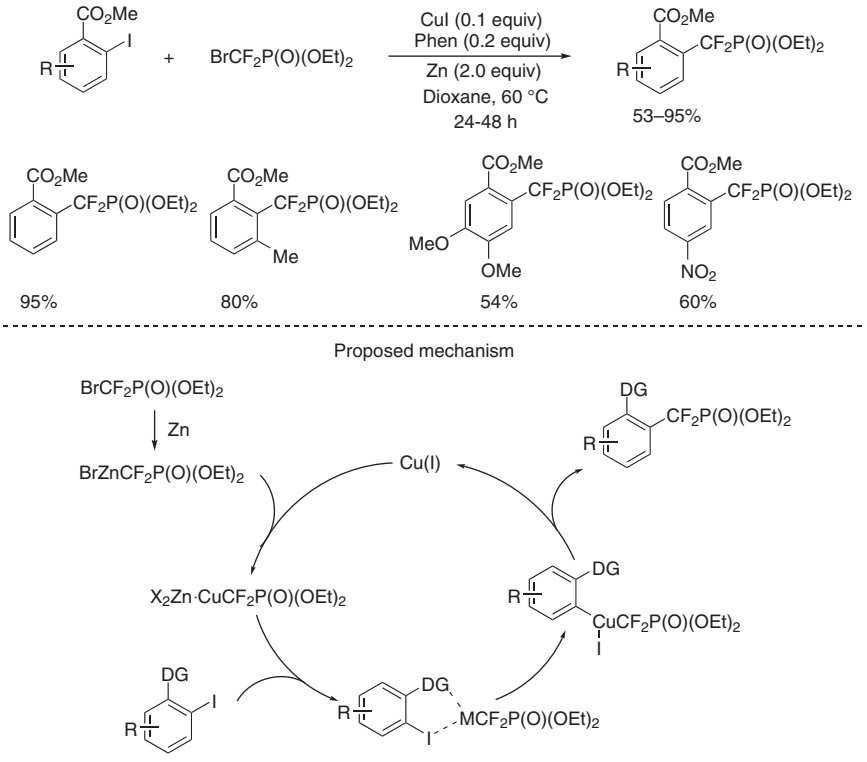
Phosphonyldifluoromethyl groups ($CF_2PO(OR)_2$) have important applications in medicinal chemistry and chemical biology because CF_2 is a bioisopolar and bioisostere of oxygen and replacing the oxygen atom of phosphoryl ester with CF_2 results in a phosphate mimic that can protect against hydrolysis. For instance, an aromatic ring bearing this functional group can act as a protein tyrosine phosphatase (PTPase) inhibitor with significant bioactivity [51]. However, only a few methods to access aryldifluoromethylphosphonates have been developed before 2012 [52]. In 1996, Burton and coworker reported the first example of copper-mediated phosphonyldifluoromethylation of aryl iodides with bromocadmiumdifluoromethylphosphate ($BrCdCF_2PO(OEt)_2$) (Scheme 1.25a) [52a]. The reaction was carried out under mild conditions and exhibited good functional group compatibility. However, the use of excessive toxic



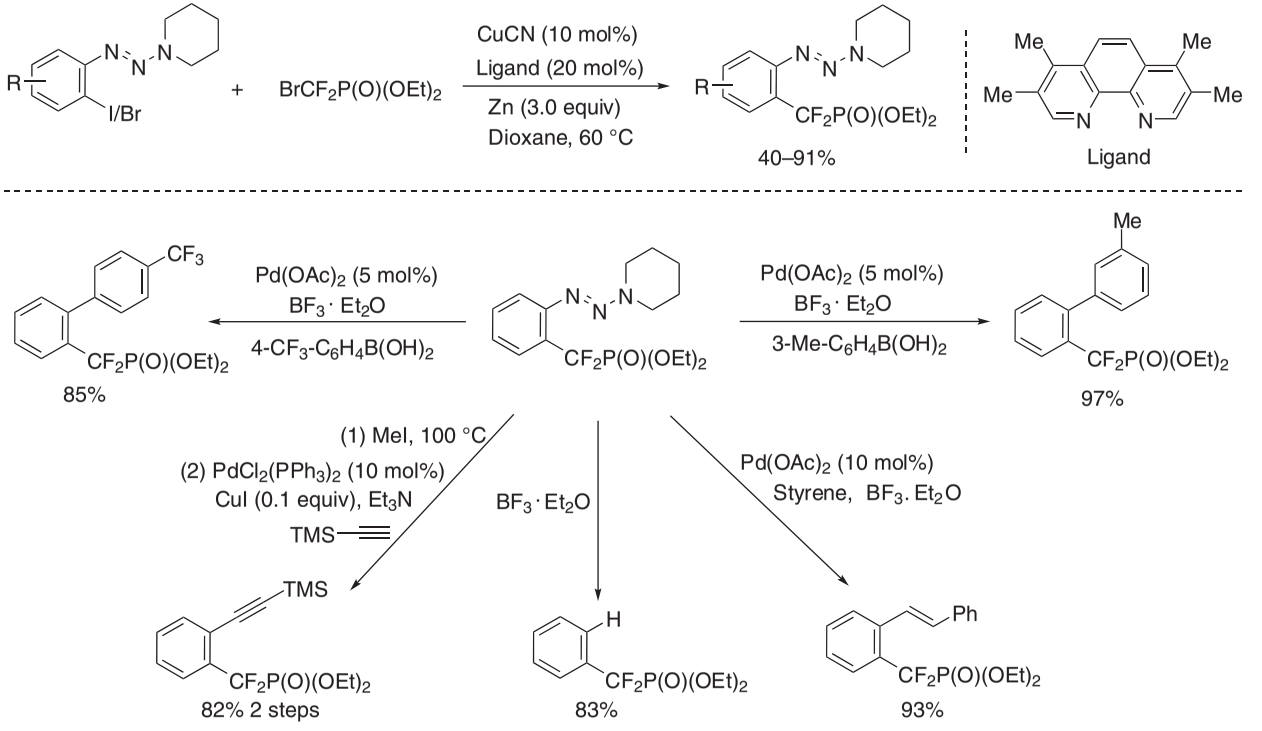
Scheme 1.25 Copper-mediated phosphonyldifluoromethylation of aryl iodides with difluoromethylphosphonyl cadmium or zinc reagents.

cadmium reagents restricts its widespread synthetic applications. In this context, Shibuya and coworkers replaced $BrCdCF_2PO(OEt)_2$ with a zinc analogue ($BrZnCF_2PO(OEt)_2$) reagent and furnished the corresponding $Ar–CF_2PO(OEt)_2$ smoothly (Scheme 1.25b) [52b]. This reaction required 2.0 equiv of copper salt due to the instability of the difluoromethylphosphonate copper–zinc complex.

To overcome this limitation, in 2012 Zhang and coworkers reported the first example of copper-catalyzed cross-coupling of iodobenzoates with $BrZnCF_2PO(OEt)_2$ (Scheme 1.26) [53]. To stabilize the difluoromethylphosphonate copper–zinc complex, 1,10-phenanthroline (Phen) was used as the ligand and an ester group was employed as a chelating group *ortho* to the iodide to facilitate the oxidative addition of copper to the Ar—I bond. The reaction showed high reaction efficiency and excellent functional group tolerance. A Cu(I/III) catalytic cycle was proposed for this reaction, which was further supported by computational studies by Jover [54], in which the Zn(II) salt can act as a linker to connect both the chelating group and the copper catalyst. When replacing the ester on aromatic ring with a removable and versatile triazene group, the aryl bromides were also suitable substrates for this reaction. The resulting triazene-containing products could serve as a good platform for diversity-oriented synthesis, providing a wide range of $Ar–CF_2PO(OEt)_2$ that are otherwise difficult to prepare (Scheme 1.27) [55].



Scheme 1.26 Copper-catalyzed cross-coupling of bromozinc-difluorophosphonate with 2-iodobenzoates.



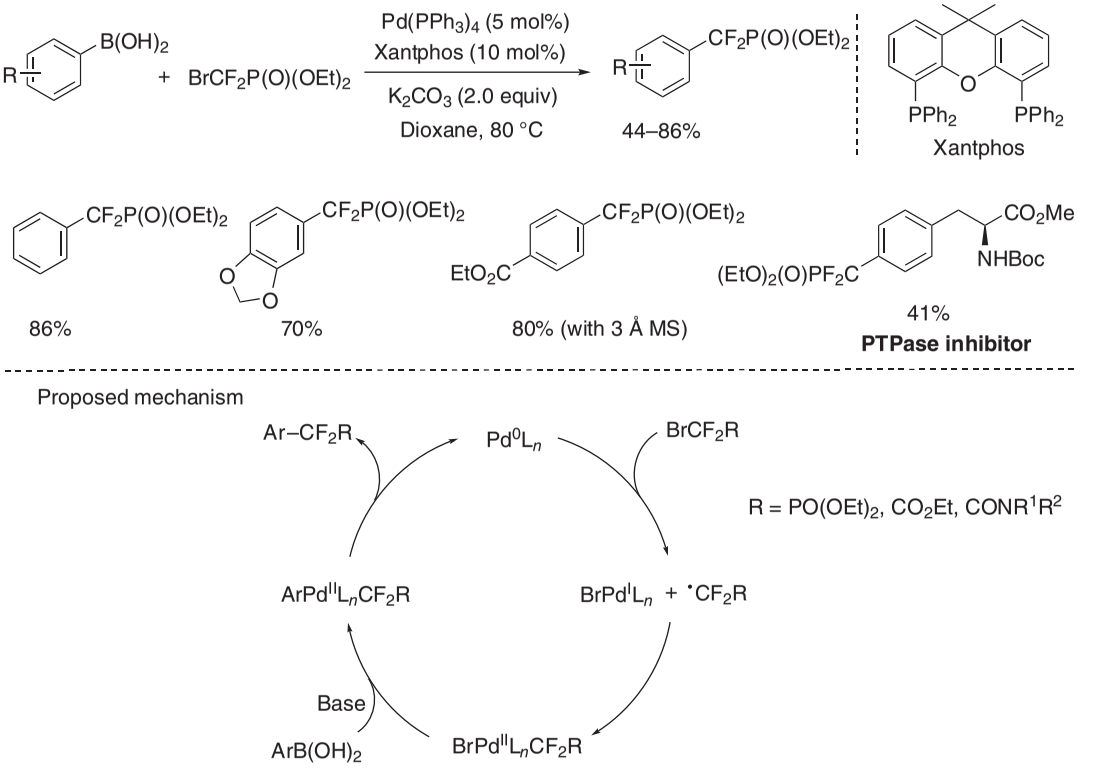
Scheme 1.27 Copper-catalyzed cross-coupling of bromozinc-difluorophosphonate with iodo/bromo-aryl triazenes and further transformations.

Chelating group free transition-metal-catalyzed phosphonyldifluoromethylation of (hetero)aromatics would be a more attractive strategy. In 2014, Zhang and coworkers developed a palladium-catalyzed cross-coupling of $BrCF_2PO(OEt)_2$ with arylboronic acids (Scheme 1.28) [56], representing the first example of catalytic difluoroalkylation of organoborons. The use of bidentate ligand Xantphos was essential in the promotion of the reaction probably due to the wide bite angle of Xantphos. This method paved a new way for the selective difluoroalkylation of aromatics. The reaction allowed the preparation of a variety of $Ar–CF_2PO(OEt)_2$, including a PTPase inhibitor. Preliminary mechanistic studies showed that a difluoroalkyl radical generated via an SET pathway was involved in the reaction. Recently, Poisson and coworkers also reported a palladium-catalyzed phosphonyldifluoromethylation to prepare $Ar–CF_2PO(OEt)_2$ (Scheme 1.29) [57]. The reaction employed aryl iodides as the coupling partner, and stoichiometric amount of phosphonyldifluoromethyl copper ($CuCF_2PO(OEt)_2$) was needed.

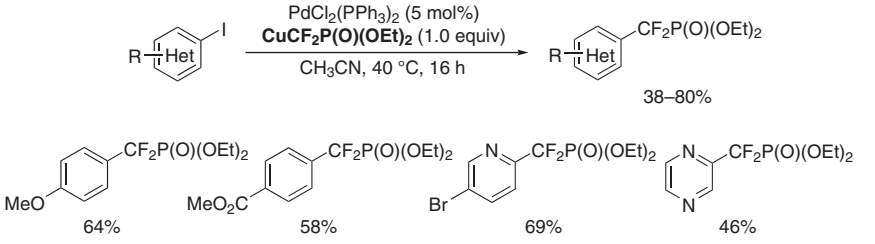
As an alternative, Qing and coworkers reported a copper-mediated oxidative cross-coupling between arylboronic acids and $TMSCF_2PO(OEt)_2$ (Scheme 1.30) [58]. Stoichiometric copper complex CuTc and excess of Ag_2CO_3 were needed. This strategy can also be extended to oxidative cross-coupling of $PhSO_2CF_2Cu$ with arylboronic acids [59]. Later on, Poisson and coworkers employed (hetero) aryl iodonium and aryl diazonium salts as the coupling partners, enabling the phosphonyldifluoromethylation (Scheme 1.31) [60]. Vinyl and alkynyl iodonium salts were also suitable substrates, thus demonstrating the generality of this method. In 2018, Amii and coworkers replaced (hetero)aryl iodonium salts with (hetero)aryl iodides and developed a copper-mediated cross-coupling between (hetero)aryl iodides and $TMSCF_2PO(OEt)_2$ (Scheme 1.32) [61]. They investigated the catalytic phosphonyldifluoromethylation, but only three electron-deficient (hetero)aryl iodides with 42–69% yields were obtained by using 0.1–0.2 equiv CuI.

1.3.2 Transition-Metal-Catalyzed Difluoroacetylation of (Hetero) aromatics and Beyond

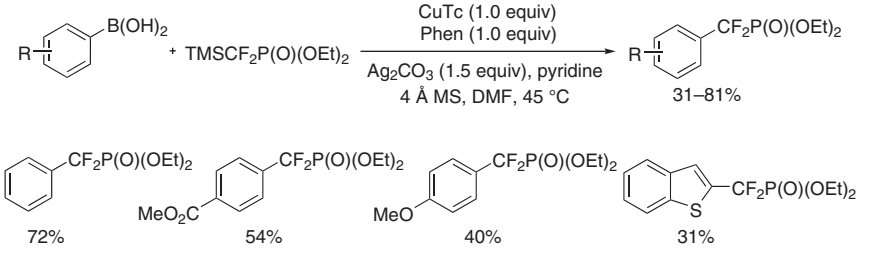
The versatile synthetic utility of ester moiety led to the increased attention on the difluoroacetylation of aromatics. In 1986, Kobayashi and coworkers reported the first example of copper-mediated difluoroacetylation of aryl halides with difluoroacetate iodide (Scheme 1.33a) [62]. The reaction underwent difluoroacetylation under mild conditions with good functional group compatibility. Several copper-mediated difluoroacetylations of various aryl halides and aryl boronic acids have been reported [63]. However, excess of copper was needed. Later on, Amii and coworkers reported a copper-catalyzed cross-coupling of aryl iodides with $TMSCF_2CO_2Et$ (Scheme 1.33b) [64]. The reaction facilitated the synthesis of difluoroacetylated arenes in 40–71% yields but was limited to electron-deficient substrates. The resulting difluoroacetylated arenes were further used to prepare difluoromethylated arenes by sequential hydrolysis and decarboxylation. To overcome the substrate scope limitation of Amii's method, Hartwig and coworker employed α-silyldifluoroamides as the coupling partners and 18-crown-6 as the additive, enabling the efficient synthesis of aryl difluoroacetamides (Scheme 1.34) [65]. Both electron-rich and electron-deficient aryl iodides were



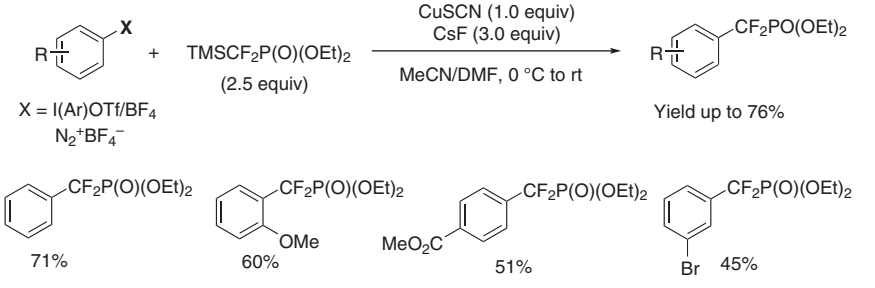
Scheme 1.28 Palladium-catalyzed phosphonyldifluoromethylation of arylboronic acids with bromodifluorophosphonate.



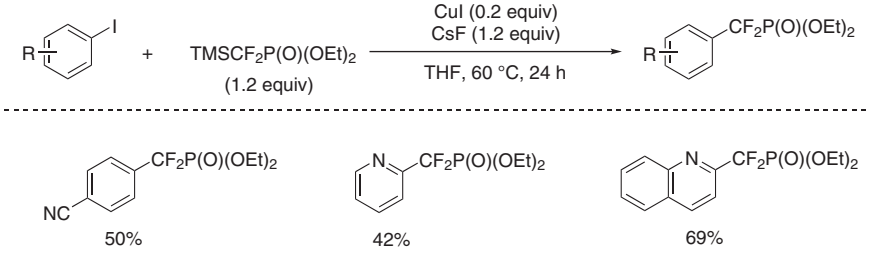
Scheme 1.29 Palladium-catalyzed phosphonyldifluoromethylation of aryl iodides with difluorophosphonyl copper reagents.



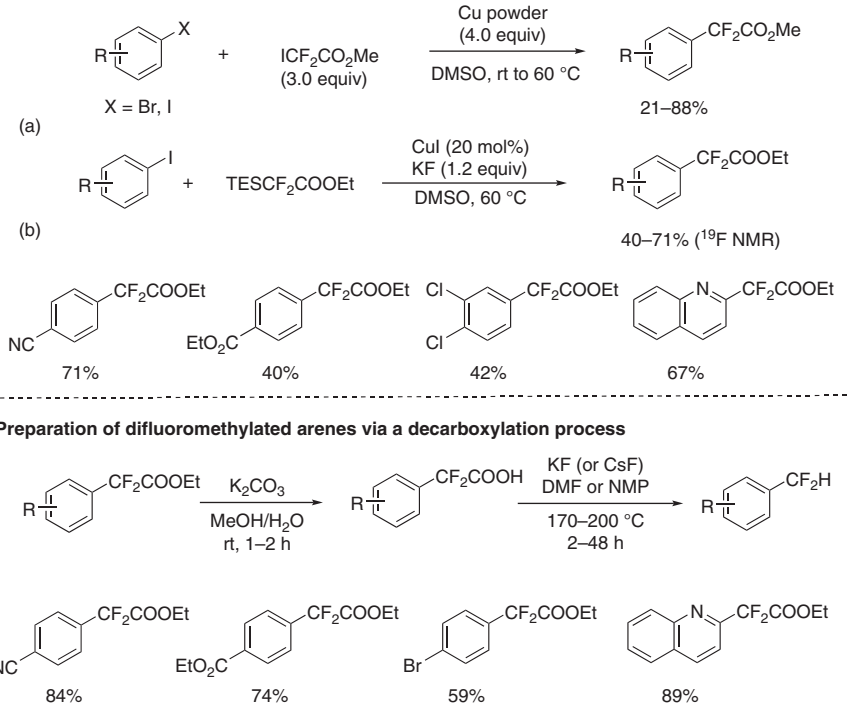
Scheme 1.30 Copper-mediated oxidative phosphonyldifluoromethylation of arylboronic acids with $TMSCF_2PO(OEt)_2$.



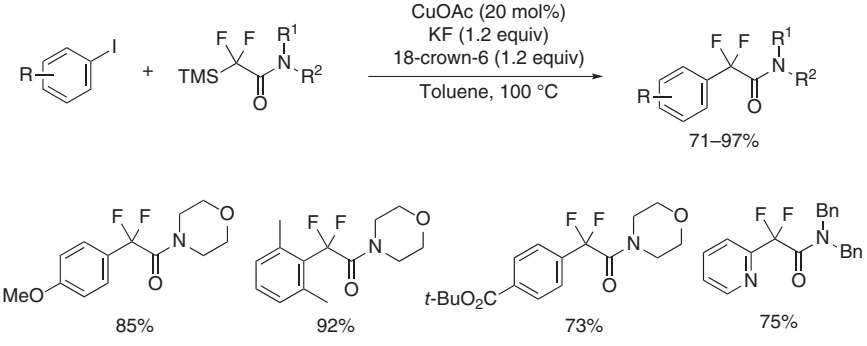
Scheme 1.31 Copper-mediated phosphonyldifluoromethylation of aryl hypervalent iodides or aryl diazoniums with $TMSCF_2PO(OEt)_2$.



Scheme 1.32 Copper-catalyzed phosphonyldifluoromethylation of (hetero)aryl iodides with $TMSCF_2PO(OEt)_2$.

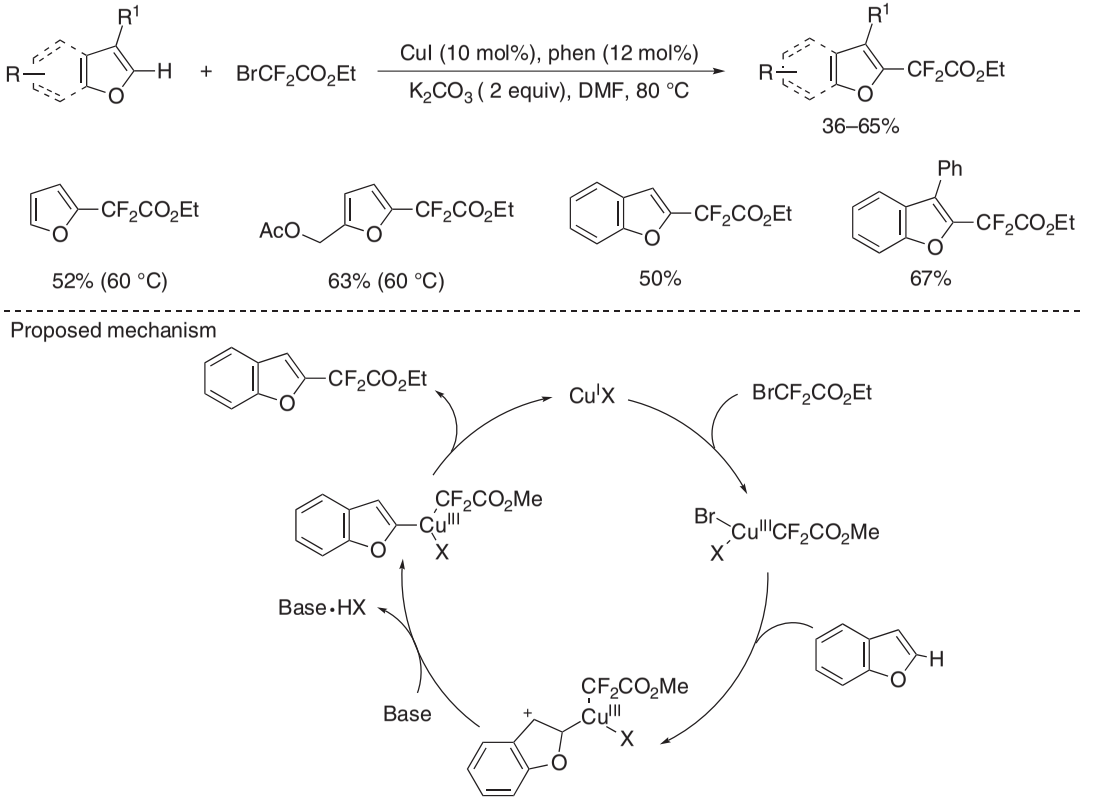


Scheme 1.33 Copper-mediated/catalyzed difluoroacetylation of aryl iodides/bromides and applications in the synthesis of difluoromethylated arenes.



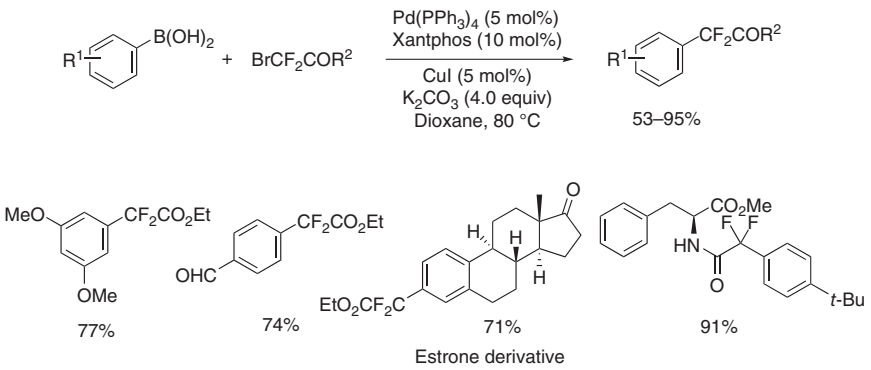
Scheme 1.34 Copper-catalyzed cross-coupling of aryl iodides with α-silyldifluoroamides.

applicable to the reaction, providing an alternative access to difluoroacetylated arenes. The copper-catalyzed C—H bond difluoroacetylation of furans and benzofurans with difluoroacetate bromide has also been reported by Poisson and coworkers (Scheme 1.35) [66]. A Cu(I/III) catalytic cycle was proposed based on no inhibition of the reaction by addition of radical inhibitor (*tert*-butylhydroxytoluene) or scavenger tetramethylpiperidinooxy (TEMPO) to the reaction.



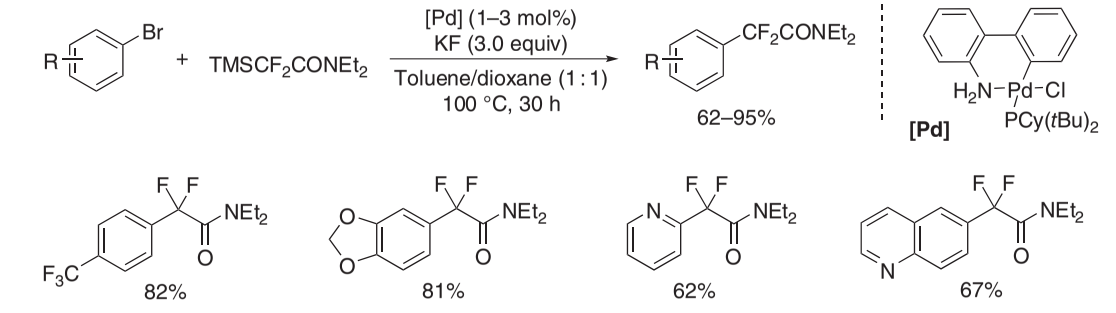
Scheme 1.35 Copper-catalyzed difluoroacetylation of furans and benzofurans with bromodifluoroacetates and the possible mechanism.

The first example of palladium-catalyzed difluoroacetylation of aromatics was reported by Zhang and coworkers in 2014 (Scheme 1.36) [56]. The combination of $Pd(PPh_3)_4$/Xantphos with CuI provided an efficient catalytic system to prepare difluoroacetylated arenes from arylboronic acids and difluoroacetate bromide. The reaction allowed difluoroacetylation of a variety of arylboronic acids with excellent functional group tolerance. Mechanistic studies revealed that a difluoroacetyl radical via an SET pathway was involved in the reaction. This strategy can also be extended to (hetero)aryl bromides. Later on, Hartwig and coworkers developed a palladium cross-coupling of α-trimethylsilyldifluoroacetamides with (hetero)aryl halides (Scheme 1.37a) [67]. Contrary to Zhang's method, a palladacyclic complex containing $PCy(t\text{-}Bu)_2$ was used as the pre-catalyst in this reaction. The mechanistic studies of the reductive elimination from arylpalladium difluoroacetate complexes showed that Xantphos with a wide bite angle facilitates the reductive elimination [68]. Recently, Liao, Hartwig, and coworkers also developed a palladium-catalyzed cross-coupling of aryl electrophiles with difluoroacetylzinc generated *in situ* from the reaction of $BrCF_2CO_2Et$ with zinc (Scheme 1.37b) [69], providing an alternative route for applications in the synthesis of aryl difluoroacetates.

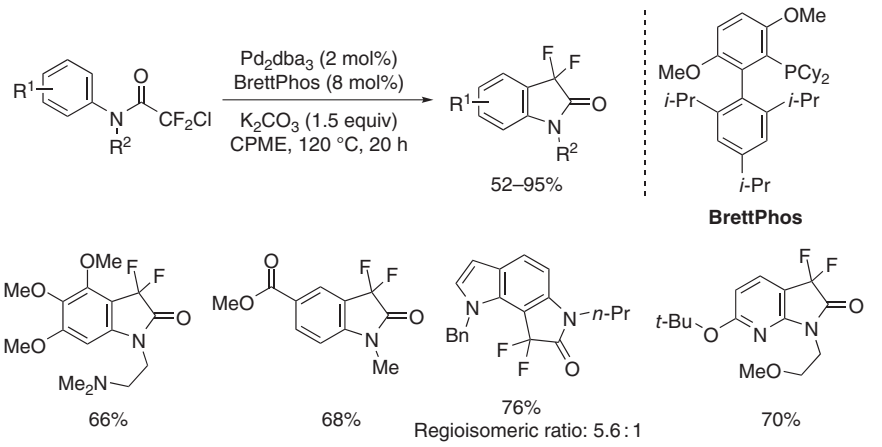


Scheme 1.36 Palladium-catalyzed cross-coupling of arylboronic acids with bromodifluoroacetate and bromodifluoroacetamides.

In addition to palladium-catalyzed difluoroacetylation of prefunctionalized (hetero)arenes, Buchwald and coworker described a palladium-catalyzed intramolecular C—H bond difluoroalkylation from chlorodifluoroacetamides with BrettPhos as the ligand (Scheme 1.38) [70]. An intermolecular ruthenium-catalyzed C–H difluoroacetylation of aromatics was reported by Ackermann and coworkers in 2017 (Scheme 1.39a) [71], in which a cooperative phosphine and carboxylate ligand system was used to promote the C–H difluoroacetylation. The reaction showed high meta-selectivity with pyridine as the directing group. Mechanistic studies showed that an *ortho* C–H metalation was the initial step. Subsequently, the resulting ruthenium(II) complex reacted with the difluoroacetyl radical generated via an SET pathway from Ru(II) species to provide meta-difluoroacetylated arenes. Simultaneously to Ackermann's work, Wang and



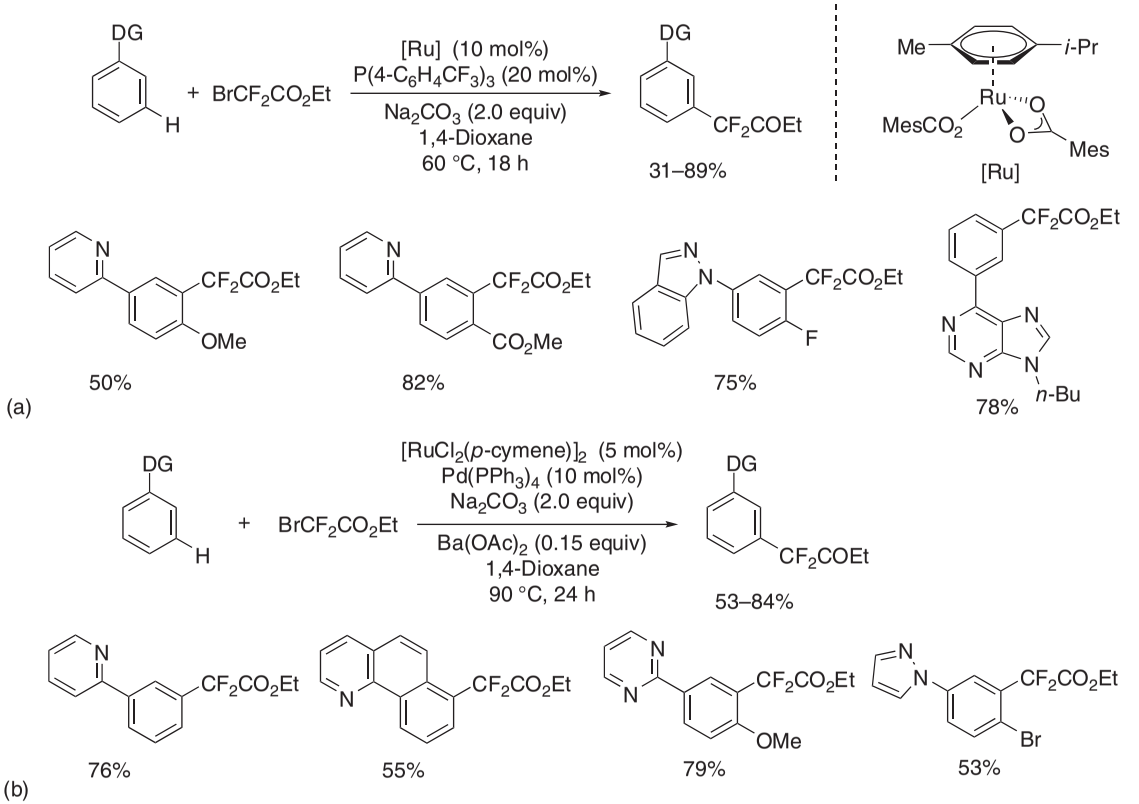
Scheme 1.37 Palladium-catalyzed difluoroacetylation of aryl bromides/triflates.



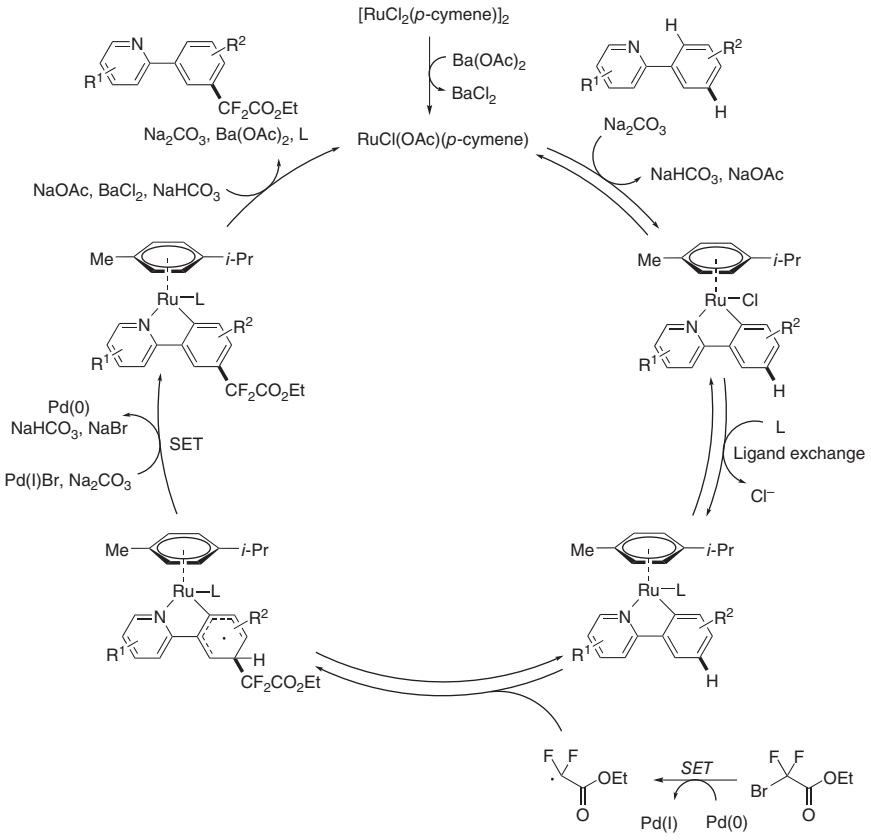
Scheme 1.38 Palladium-catalyzed intramolecular C—H bond difluoroalkylation with the aid of chlorodifluoroacetamides.

coworkers developed a ruthenium and palladium co-catalyzed meta-selective difluoroacetylation (Scheme 1.39b) [72]. Similarly, the ortho C–H metalation by ruthenium(II) was the initial step, but $Pd(PPh_3)_4$ was used as the radical initiator for the SET process (Scheme 1.40). Recently, a para-selective difluoroacetylation of arenes has been reported by Zhao and coworkers with aniline derivatives as the coupling partners, in which a radical process was also involved in the reaction (Scheme 1.41) [73].

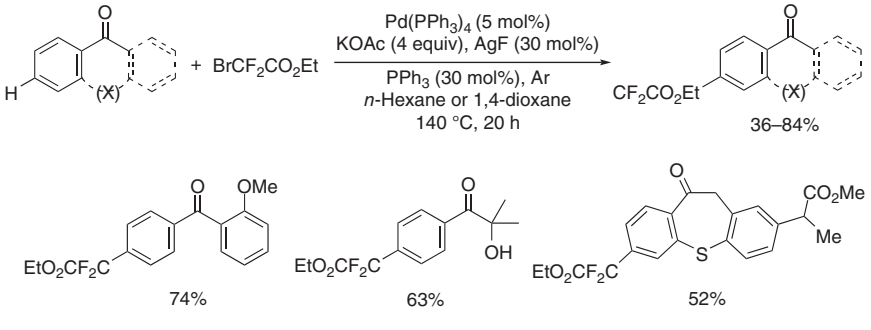
Although impressive achievements have been made in copper- and palladium-catalyzed trifluoromethylation and difluoroalkylation of aromatics, the use of earth-abundant nickel as a catalyst has been less explored due to the thermal stability of arylnickel(II) fluoroalkyl complexes [74]. In 2014, Zhang and coworkers reported the first example of a nickel-catalyzed difluoroacetylation of arylboronic acids with $Cl/BrCF_2CO_2Et$ (Scheme 1.42) [34a]. The reaction exhibited broad substrate scope including drug derivatives and excellent functional tolerance, with inexpensive $Ni(NO_3)_2{\cdot}6H_2O$ as the catalyst and readily available bipyridine (bpy) as the ligand. Notably, a wide range of difluoroalkyl bromides ($BrCF_2R$, R = CO_2Et, $CONR^1R^2$, COAr, COR^1, HetAr) were applicable to the reaction. A Ni(I/III) catalytic cycle was proposed for the reaction, in which a nickel(III) facilitates the reductive elimination of the arylnickel(III) fluoroalkyl complex. Recently, Sanford and coworkers confirmed that arylnickel(III) trifluoromethyl complexes [$(Ar)(CF_3)Ni(III)L_nX$] are favorable for reductive elimination [75]. Compared to the palladium- and copper-catalyzed difluoroalkylation, the advantage of nickel-catalyzed process is more general in terms of the substrate scope of difluoroalkyl halides and functional group tolerance. This strategy has also been applied to the nickel-catalyzed cross-coupling of bromodifluoroacetamides with arylzinc reagents by using bisoxazoline as the ligand (Scheme 1.43) [76]. In addition to the nickel-catalyzed difluoroacetylation, the cobalt-catalyzed cross-coupling of arylzinc reagents with bromodifluoroacetate has also been reported by Inoue and coworker(Scheme 1.44) [77].



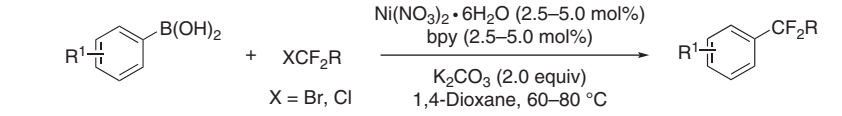
Scheme 1.39 Directing-group promoted ruthenium-catalyzed meta-difluoroacetylation of arenes.

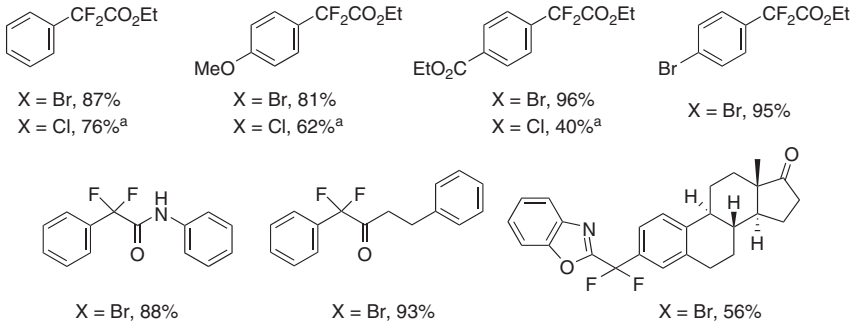


Scheme 1.40 Possible mechanism of ruthenium/palladium co-catalyzed meta-difluoroacetylation of arenes with direction groups.

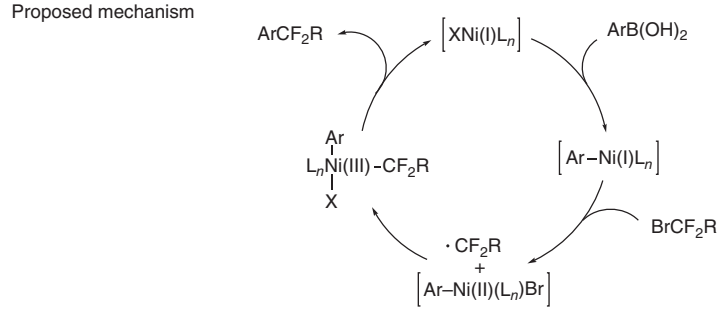


Scheme 1.41 Palladium-catalyzed para-selective C—H bond difluoroacetylation of aryl ketones.

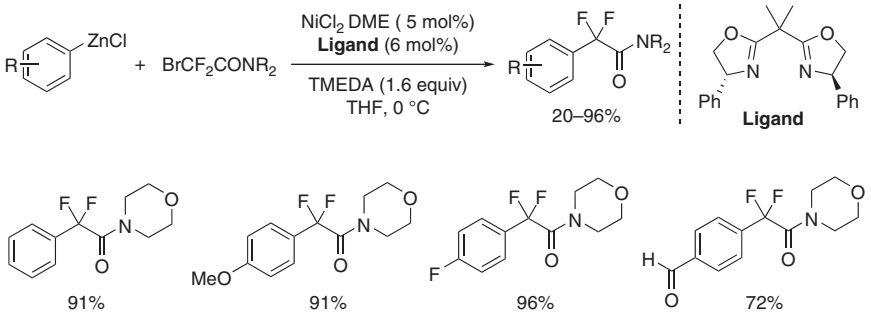




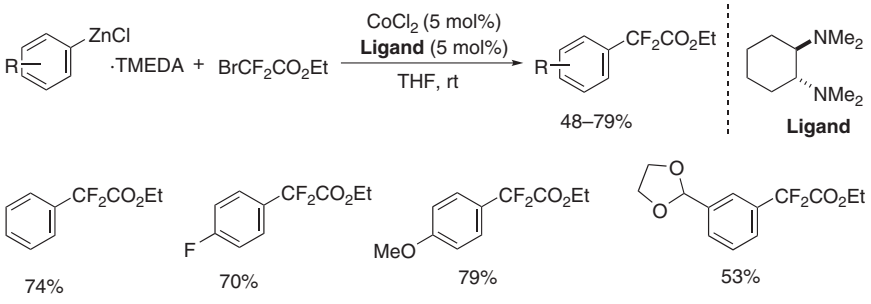
[a]5 mol% PPh_3 was added.



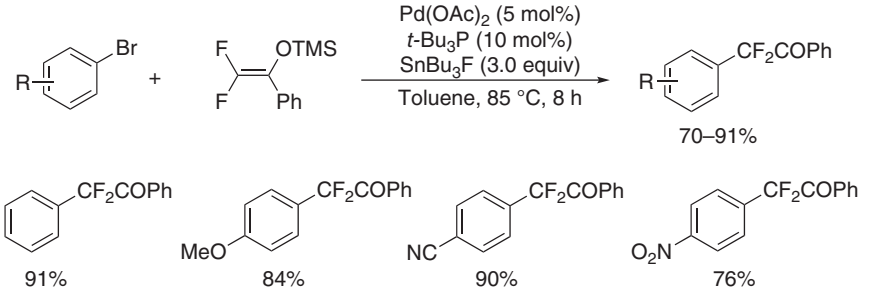
Scheme 1.42 Nickel-catalyzed cross-coupling of arylboronic acids with functionalized difluoroalkyl bromides and chlorides.



Scheme 1.43 Nickel-catalyzed cross-coupling of aryl zinc reagents with bromodifluoroacetamides.



Scheme 1.44 Cobalt-catalyzed cross-coupling of aryl zinc reagents with bromodifluoroacetates.

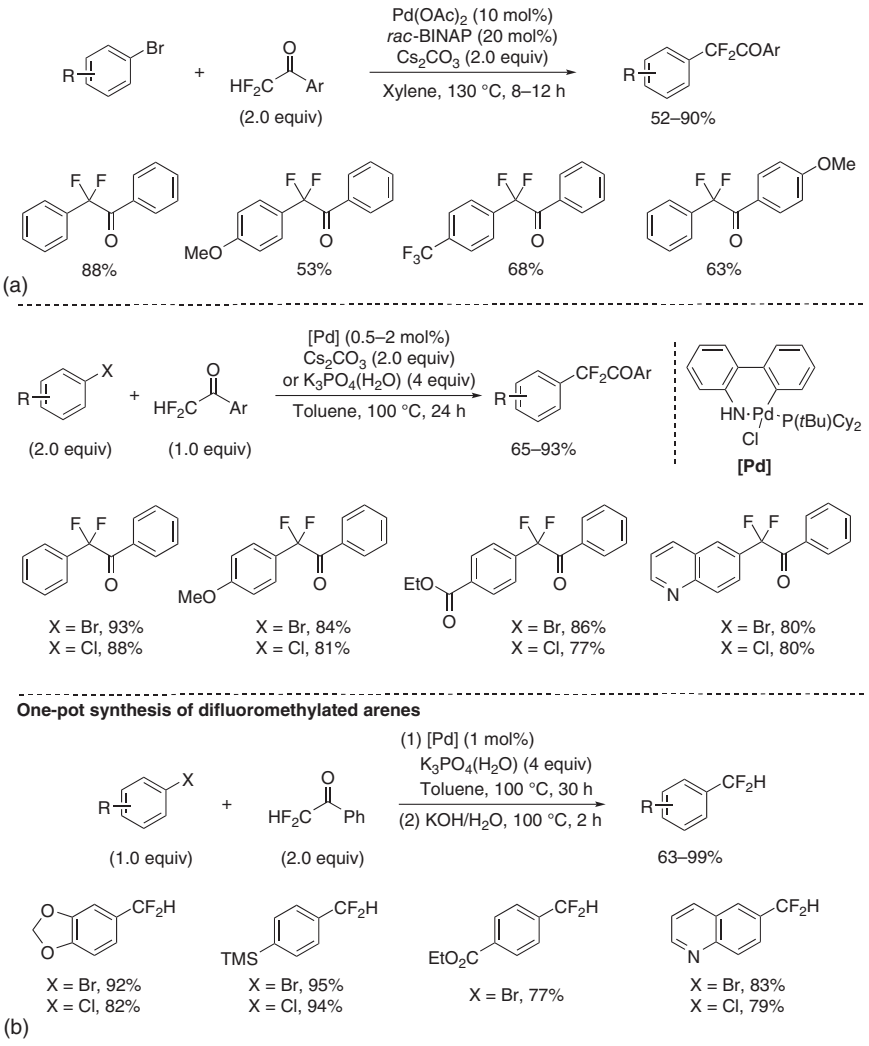


Scheme 1.45 Palladium-catalyzed cross-coupling of aryl bromides with difluoroenol silyl.

1.3.3 Other Catalytic Difluoroalkylations of (Hetero)aromatics

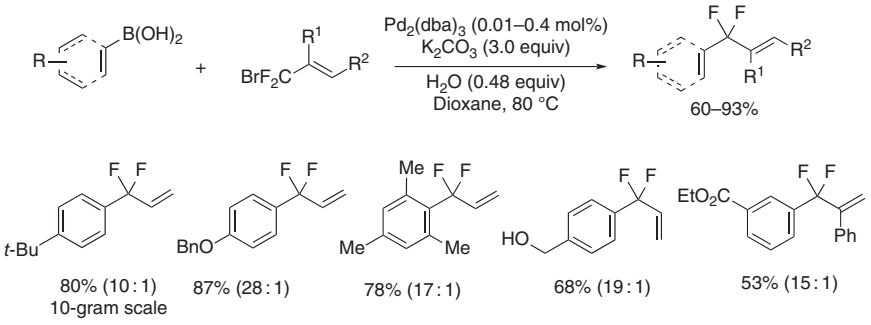
In 2007, Shreeve and coworker reported the first example of a palladium-catalyzed cross-coupling between aryl bromides and difluoroenol silyl ether with a bulky electron-rich monophosphine P(*t*Bu)$_3$ as the ligand (Scheme 1.45) [78]. However, toxic tin reagent was needed to promote the reaction and the substrate scope was relatively limited. In this context, Qing and coworkers developed a palladium-catalyzed cross-coupling of difluoromethyl phenyl ketone with aryl bromides in the presence of a base (Scheme 1.46a) [79]. This method is synthetically convenient: no need to prepare difluoroenol silyl ether and use toxic tin reagent. Hartwig and coworkers found that the use of a cyclopalladium species as the catalyst could enable the difluoroalkylation with high efficiency and broad scope, even aryl chlorides were suitable substrates (Scheme 1.46b) [80]. Notably, the method can also be used for the preparation of difluoromethylated arenes by debenzoylation of the resulting products ArCF$_2$COPh (Scheme 1.46).

In addition to the preparation of ArCF$_2$COAr, the catalytic *gem*-difluoroallylation of aromatics has also been reported. In 2014, Zhang and coworkers developed a palladium-catalyzed highly α-selective *gem*-difluoroallylation of arylboronic acids and esters with bromodifluoromethylated alkenes



Scheme 1.46 Palladium-catalyzed cross-coupling of aryl bromides/chlorides with α,α-difluoroketones and one-pot synthesis of difluoromethylated arenes.

(Scheme 1.47) [81]. Contrary to previous works using $BrCF_2PO(OEt)_2$ and $BrCF_2CO_2Et$ as the coupling partners, this reaction was presumed to occur via a formal electrophilic difluoroalkylation pathway, probably because of stabilization of palladium intermediate by coordination with alkene, thus facilitating the oxidative addition step via a two-electron transfer process. The high α-regioselectivity of this reaction ($\alpha/\gamma > 37 : 1$) may be ascribed to the strong electron withdrawing effect of the CF_2 group, which strengthens the Pd—CF_2R bond. Remarkably, even when the Pd catalyst loading was decreased to 0.02 mol%, high α-regioselectivity and good yield of *gem*-difluoroallylated arene was still obtained on the 10 g scale reaction, thus demonstrating the good practicality of this protocol. This reaction can also be extended to *gem*-difluoropropargylation



Scheme 1.47 Palladium-catalyzed *gem*-difluoroallylation of organoborons with bromodifluoromethylated alkenes.

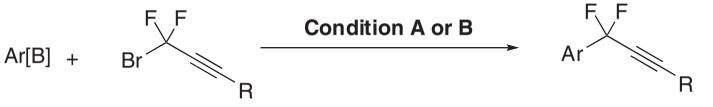
of arylboronic acids and esters with high efficiency and regioselectivity (Scheme 1.48) [82]. Since carbon–carbon double bond and triple bond are synthetically versatile functional groups, these resulting difluoroalkylated arenes could serve as useful building blocks for diversity-oriented synthesis, thus offering good opportunities for applications in the organic synthesis and related chemistry.

Although impressive progress has been made in the catalytic difluoroalkylation of aromatics, a π-system adjacent to CF_2 is required to activate the difluoroalkylating reagents [4a, 83]. In 2013, Baran and coworkers developed a type of sodium α,α-difluoroalkylsulfinate ($NaSO_2CF_2$alkyl) reagents for direct difluoroalkylation of heteroarenes (Scheme 1.49) [84]. Similar to the difluoromethylating reagent DMFS, the reaction required *t*BuOOH to furnish the difluoroalkylated heteroarenes via a radical process. Zinc chloride was found to be critical for the reaction. The advantage of this protocol is the synthetic simplicity. However, the modest regioselectivity of this approach restricts its widespread synthetic applications.

In 2016, Zhang and coworkers reported a nickel-catalyzed difluoroalkylation of (hetero)arylboronic acids with unactivated difluoroalkyl bromides ($BrCF_2$–alkyl) (Scheme 1.50a) [34b]. A combined (2 + 1) ligand system was used to facilitate the formal oxidative addition of nickel to the $BrCF_2$–alkyl. The reaction showed broad substrate scope with high efficiency. A nickel-catalyzed reductive cross-coupling between (hetero)aryl bromides and $BrCF_2$–alkyl [85] and an iron-catalyzed cross-coupling of arylmagnesiums with $BrCF_2$–alkyl have been reported by the same group (Scheme 1.50b,c) [43]. In 2018, Baran and coworkers also reported nickel-catalyzed difluoroalkylation of arylzincs with difluoroalkyl sulfones, providing an alternative access to difluoroalkylated arenes (Scheme 1.51) [86].

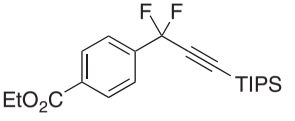
1.4 Outlook

We have comprehensively summarized the transition-metal-mediated/catalyzed difluoromethylation and difluoroalkylation of (hetero)aromatics. Several new types of difluoroalkylation reactions were developed and provided synthetically

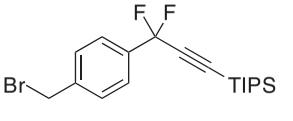


Condition A: **$Pd_2(dba)_3$** (0.1–2.5 mol%), P(*o*-Tol)$_3$ (0.6–15 mol%),
K_2CO_3 or Cs_2CO_3 (3.0 equiv), dioxane or toluene, 80 °C, 24 h

[B] = $B(OH)_2$



80%, gram scale



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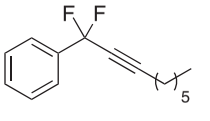

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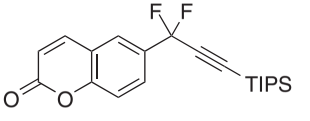
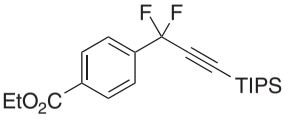
[B] = Bpin



60%

Condition B: **$NiCl_2$·dppe** (2.5 mol%), bpy (2.5 mol%), K_2CO_3 (2.0 equiv), dioxane, 80 °C, 24 h

[B] = $B(OH)_2$



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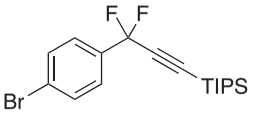

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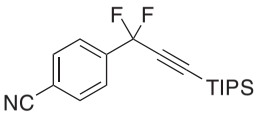

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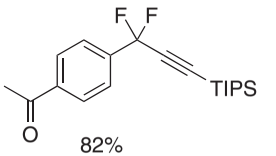

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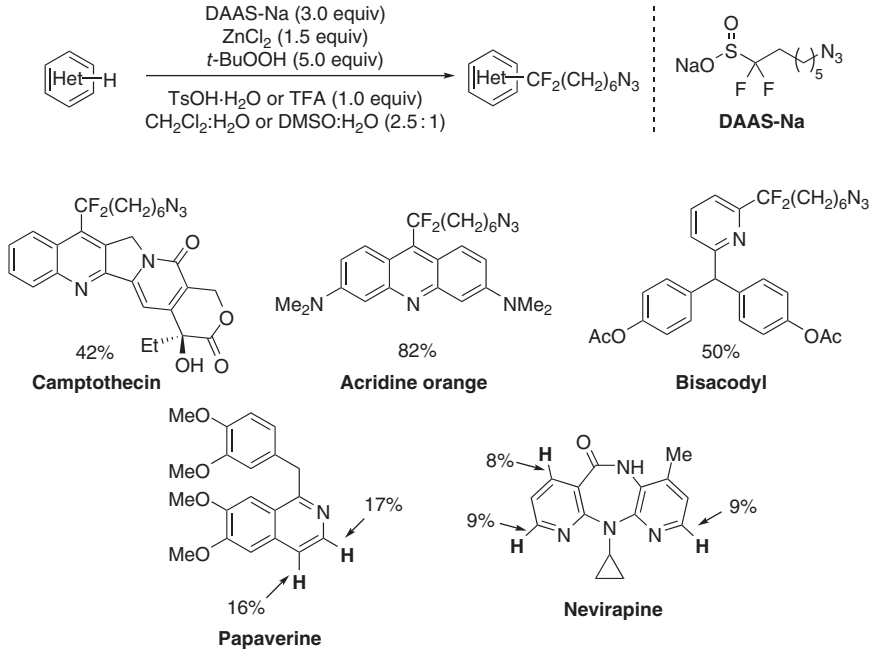
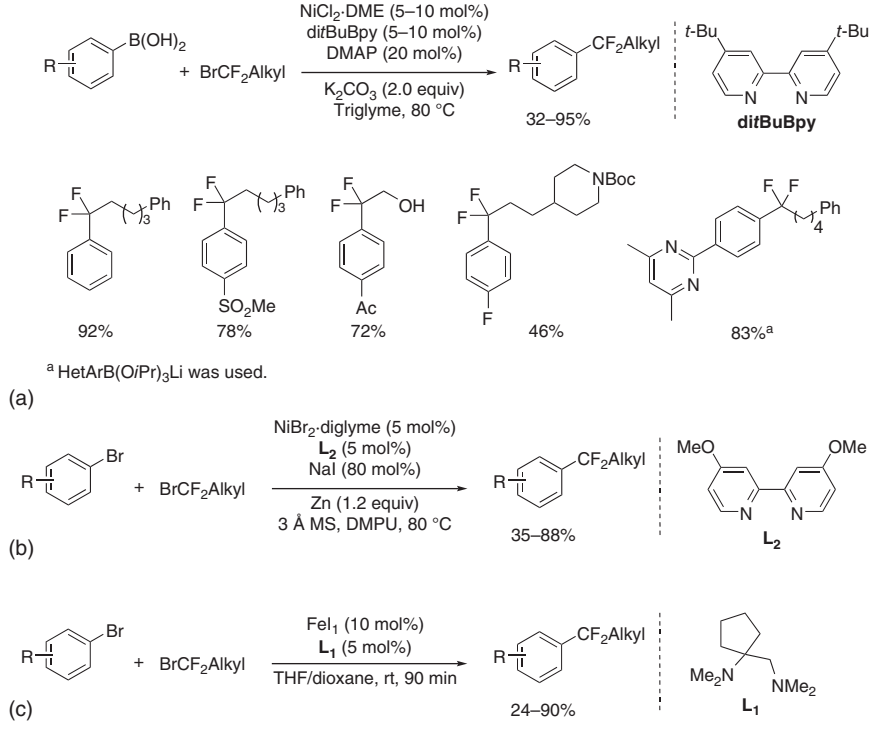
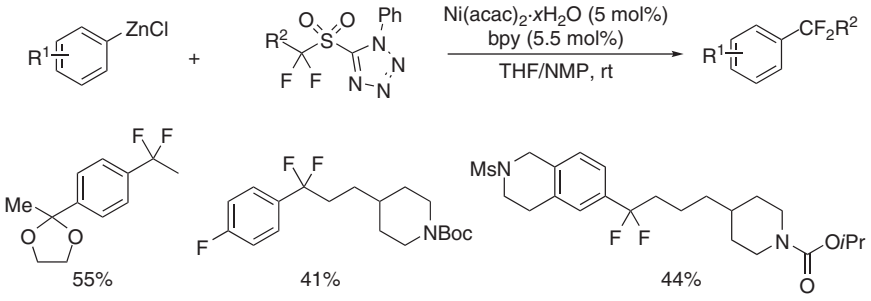
Scheme 1.48 Palladium- or nickel-catalyzed *gem*-difluoropropargylation of arylboronic reagents.



Scheme 1.49 C—H bond difluoroalkylation of heteroarenes with DAAS-Na.



Scheme 1.50 Nickel- or iron-catalyzed difluoroalkylation of aromatics with unactivated difluoroalkyl bromides.



Scheme 1.51 Nickel-catalyzed difluoroalkylation of aryl zinc reagents with difluoroalkylated sulfones.

convenient and cost-efficient methods to prepare difluoroalkylated arenes that are of great interest in life and materials sciences. In particular, a new mode of difluoromethylation reaction, i.e. catalytic MeDIC, has been developed, which expands our understanding of metal difluorocarbene chemistry, and should influence future thinking in the field. Mechanistic studies on difluoroalkylation reactions showed the differences between organofluorine chemistry and classical C–H chemistry, and thus it is imperative to develop new chemistry for fluoroalkylation reactions. In future works, the development of environmental benign, cost-efficient, and highly regioselective difluoroalkylation reactions from inexpensive fluorine sources remains necessary. In particular, the direct C–H difluoroalkylation of heteroarenes with high regioselectivity and broad substrate scope should be considered in pharmaceutical, agrochemical, and advanced material applications. To meet the increasing demand from life science, such as design of bioactive peptides, protein engineering, probes for the investigation of enzyme kinetics, diagnosing neurodegenerative diseases and so on, the development of biocompatible fluoroalkylations, including site-selective fluoroalkylation of peptides, proteins, oligocarbohydrates and DNA, would be a promising research area.

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