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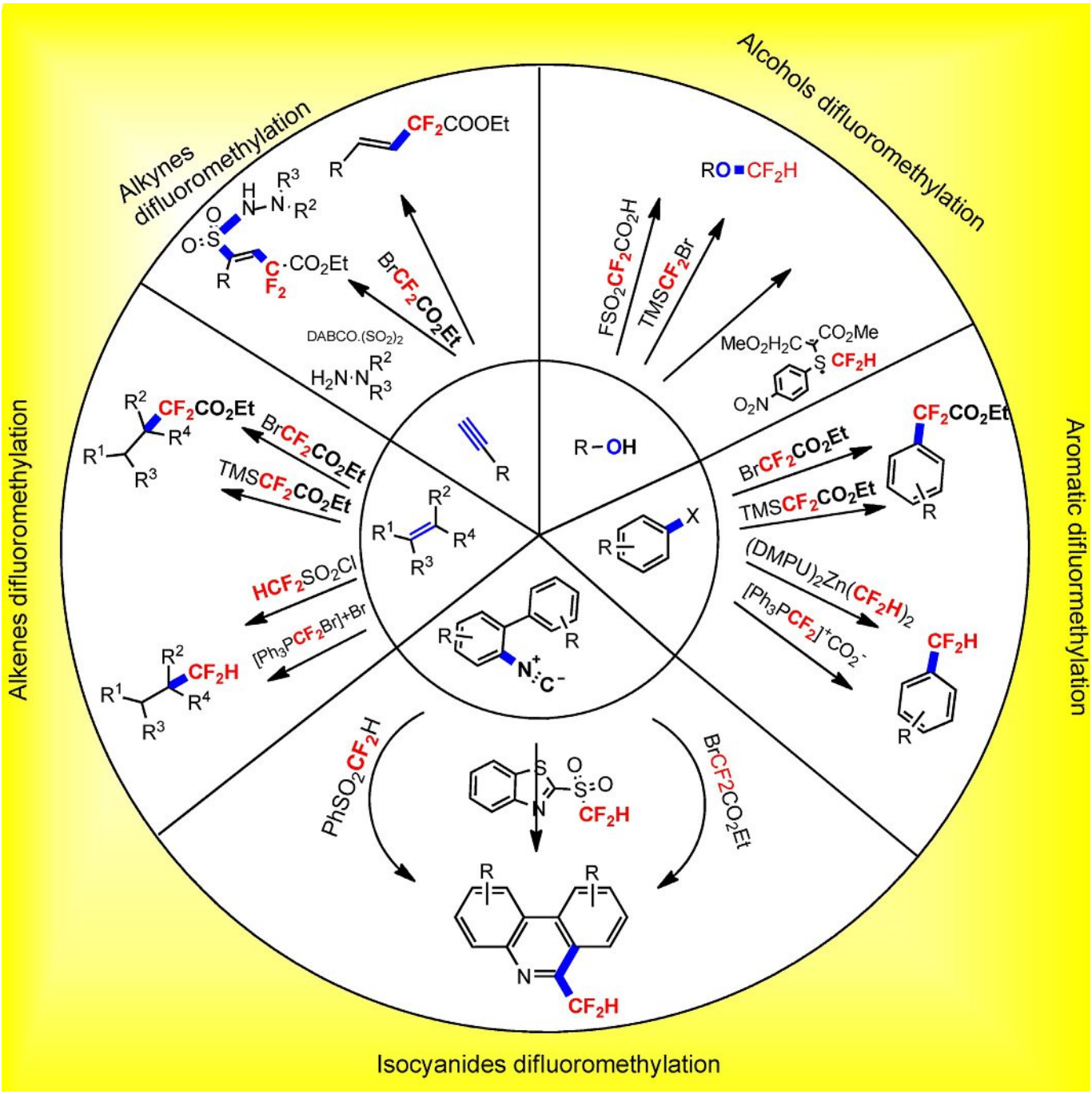
Fluorination

Difluoromethylation Reactions of Organic Compounds

Damian E. Yerien, Sebastian Barata-Vallejo, and Al Postigo*[a]



Abstract: The relevance of the -CF_2H moiety has attracted considerable attention from organic synthetic and medicinal chemistry communities, because this group can act as a more lipophilic isostere of the carbinol, thiol, hydroxamic acid, or amide groups. Being weakly acidic, the CF_2H moiety can establish hydrogen-bonding interactions to improve the binding selectivity of biologically active compounds. Therefore, the hydroxyl, amino, and thio substituents of lead structures are routinely replaced by a CF_2H motif in drug discovery, with great benefits in the pharmacological activity of drugs and drug candidates and agrochemicals. Consequently, the late-stage introduction of CF_2H is a sought-after strategy in designing bioactive compounds. Secondly, but nonetheless relevant and meaningful, is the study of synthetic pathways to introduce a CF_2–Y moiety (Y ≠ H, F) into organic substrates because compounds that contain a CF_2–Y functionality have also found vast applications in medicinal chemistry and in other areas, such as that of fungicides, insecticides, etc., and thus, this functionality deserves special attention. Although emphasis is made on difluoromethylation strategies to functionalize different families of organic compounds, three main methodological protocols will be presented in this review article for the late-stage introduction of a CF_2H or CF_2Y moieties into organic substrates: i) a metal-photoredox catalysis; ii) through transition metal-catalyzed thermal protocols; and iii) from transition-metal-free strategies.

Introduction

The preparation of compounds with difluoromethyl groups CF_2R (R = H, alkyl/aryl, CO_2R, SO_2R, etc.) has attracted considerable attention, and various approaches have been reported for the difluoroalkylation of organic substrates. Particularly, the -CF_2H group is of great importance because it can act as a more lipophilic isostere[1] of the carbinol, thiol, hydroxamic acid, or amide group.[2] Therefore, the hydroxyl, amino, and thio substituents of lead structures are routinely replaced by the CF_2H group in drug discovery.[3]

In contrast to the lipophilic CF_3 group, a CF_2H group has special physicochemical properties. The CF_2H group is weakly acidic[1] and can establish hydrogen-bonding interactions to improve the binding selectivity of biologically active compounds.[2] As a consequence, the CF_2H group is widely utilized in the design of pharmaceuticals and agrochemicals (Figure 1). For instance, Roflumilast®[4] is used for treatment of obstructive pulmonary disease; AstraZeneca has come up with a β-secretase 1 inhibitor (BACE-inhibitor); Pantoprazol II®, is a commercial drug used in therapy for patients with gastro-esophageal reflux disease; various insecticides such as Sedaxane; fungicides such as Isopyrazam, Benzovindiflurpyr, Fluzapyroxad; and agrochemicals such as Bixafen®, Thiazopir®, etc., all possess a CF_2H motif in their structures, as observed from Figure 1.

Difluoromethylated compounds have traditionally been prepared through diverse reactions, such as the deoxyfluorination of aldehydes with SF_4, *N*,*N*′-diethylaminosulfur trifluoride (DAST), with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor),[5] and other related reagents.[6] However, these syntheses require harsh reaction conditions, the CF_2 sources

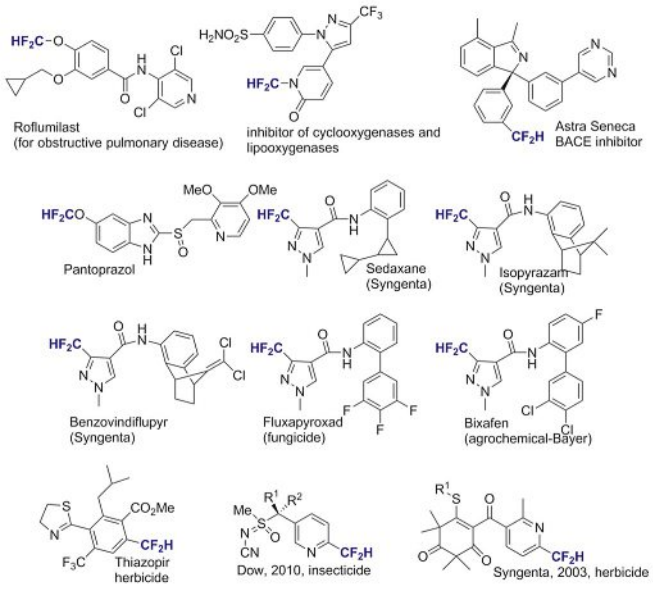


Figure 1. Difluoromethylated compounds used as therapeutic drugs, herbicides, fungicides, agrochemicals.

are too volatile, toxic, or compromise the presence of functional groups in the compounds to functionalize. Direct difluoromethylation of lithium/potassium enolates with CF_3H,[7–10a] or using difluoromethylation reagents such as $TMSCF_2H$,[10b] Bu_3SnCF_2H, or $(HCF_2SO_2)_2Zn$[11,12] together with metal catalysis effectively leads to CF_2H-substituted compounds.[13] Recently, the Hu's reagent, that is, *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine,[14] has been employed to introduce CF_2H functionality.

Transition metals can also be used in difluoromethylation reactions, not only exclusively as part of CF_2H reagents (such as in Bu_3SnCF_2H, or $(HCF_2SO_2)_2Zn$) but also as catalysts, mediators, or additives. These metals play various roles, including stabilizing the difluoromethyl anion (as difluoromethyl carriers), promoting the formation of difluoromethyl free radical (such as transition-metal photoredox catalysts), and facilitating formation of HF_2C–C and HF_2C–X bonds (through reductive elimina-

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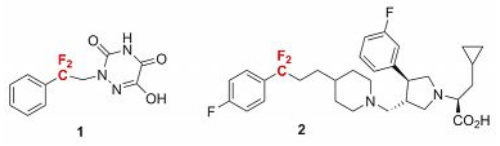


Figure 2. Compounds with the CF_2 functionality.

tion of difluoromethyl-metal complexes).[15] Applications of the use of CF_2Y compounds ($Y \neq H,F$) can also be found in medicinal chemistry and in other areas, such as fungicides, insecticides, etc. For instance, compound **1** (Figure 2) is an inhibitor of D-aminoacid oxidase, and compound **2** is a potent antiviral agent against HIV.

Difluoromethylation can also be accomplished through difluoromethyl reagents of the type Z-CF_2-Y (where $Z,Y \neq H$, F), such as R_3SiCF_2COOEt,[16] $BrCF_2COOEt$,[17,18] FSO_2CF_2COOH, $TMSCF_2SO_2Ph$,[16] $BrCF_2SO_2Ph$,[19–21] $BrCF_2P(O)OEt_2$,[22–24,17,12] or ICF_2SO_2Ph.[25–39,19,20] These reagents (Z–CF_2Y, in which $Z,Y \neq H$, F) append to organic molecules as CF_2Y groups, and can ultimately be reduced to a CF_2H motif.[40,41] In 2014, Xiao and colleagues[42] described most difluoromethylating reagents Z–CF_2Y in a review article.[43] More recent examples on the synthesis and applications of these reagents and others will be presented here.

A series of phosphonium difluoroalkyl sources such as $Ph_3P^+CF_2CO_2^-$, $(Me_2N)_3P^+CF_2CO_2^-$,[44a] have recently been shown to introduce a CF_2Y moiety into alkenes,[24] alkynes, phenols, thiols, carboxylic acids, and heterocyclic amines.[45] These recently reviewed methods[46–49,23] are not included in this review article. Unlike a thorough or exhaustive revision of the literature on difluoromethylation reactions, a discussion on the recent progress in the field and new reactions is intended, with a view towards future perspectives, outlining established methods for difluoromethylation of functional groups along with the recent developments (2015–present), which will include the late-stage introduction of CF_2H and CF_2Y moieties into organic molecules.

While describing such methodologies, difluoromethylation reactions of diverse families of organic substrates such as (hetero)aromatic compounds, olefins,[24,18] isocyanides,[17] alkynes, carbonyl compounds,[48,20] alcohols, hydrazones, tertiary amines, sulfides, and azo compounds will be presented. The methodology described for such reactions will include metal-mediated photocatalytic[50–52] and thermal processes, as well as metal-free methodologies. The two tables presented critically summarize all reagents employed either for late stage CF_2H (Table 1) or CF_2Y (Table 2) group introduction into organic compounds.

Late-stage introduction of CF_2H and CF_2Y groups into organic molecules

Synthesis of $C_{Ar(Het)}$–CF_2H and $C_{Ar(Het)}$–CF_2Y compounds

Vicic and colleagues[53] introduced the use of zinc reagent $(DMPU)_2Zn(CF_2H)_2$ for the direct difluoromethylation of Ar–X (X = I,[54,27] Br, OT_f), using $Ni(COD)_2$ as catalyst, and DPPF (1,1′-bis(diphenylphosphino)ferrocene) as ligand in DMSO as solvent. The scope of the transformation is illustrated in Scheme 1. The reagent $(DMPU)_2Zn(CF_2H)_2$ was synthesized according to Scheme 2.

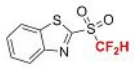
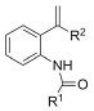
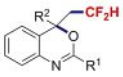
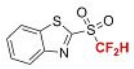
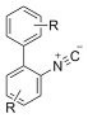
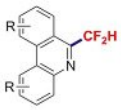
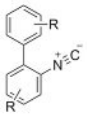
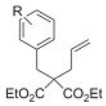
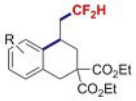
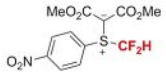
Generally, electron-poor aryl substrates render better yields than electron-rich aryl compounds. Perhaps the most impressive feature of the methodology is the reactivity with ArBr. Until this report, the only other known method for catalytically difluoromethylating ArBr operated at 80 °C,[55] whereas the method reported by Vicic[53] operates at room temperature. Scheme 1 shows that ArBr (**7**–**9**) substrates afford cross-coupled products in yields that are roughly identical to those seen for the ArI counterparts (**3**–**6**). However, this method suffers

Damian E. Yerien was born in Buenos Aires (Argentina) and holds a degree in Biochemistry (2013). He is currently a Ph.D. student at the University of Buenos Aires, studying radical fluorination and fluoroalkylation reactions in heterogeneous and microheterogeneous media under the direction of Professor Dr. Alberto Postigo. He is a holder of a National Research Council Scholarship (Conicet) at the Faculty of Pharmacy and Biochemistry, University of Buenos Aires.

Sebastián Barata-Vallejo was born in General Villegas (Argentina) and holds degrees in Pharmacy (2007) and Biochemistry (2010). He obtained his Ph.D. degree (2012) at the University of Buenos Aires, studying radical reactions in aqueous and microheterogeneous media under the direction of Professor Dr. Alberto Postigo. He has been a research fellow at Istituto per la Sintesi Organica e la Fotoreattivita (ISOF), Consiglio Nazionale delle Ricerche (CNR), Bologna, Italia, under the supervision of Dr. C. Chatgilialoglu. He is currently a Researcher at the National Council for Scientific and Technical Investigation, CONICET (Argentina and a Lecturer at the Organic Chemistry Department, Faculty of Pharmacy and Biochemistry, University of Buenos Aires.

Al Postigo was born in Argentina and obtained his M.Sc. degree from University of Buenos Aires in 1986. He moved to Canada in 1990, and obtained his Ph.D. degree from McMaster University in 1994, under the direction of Professor Dr. William J. Leigh. After postdoctoral positions in Canada, he returned to Argentina and worked with Professor Dr. Roberto Rossi at University of Córdoba in the area of radical ion reactions. He held assistant and associate professorship positions at University of Córdoba, University of Buenos Aires, and University of Belgrano. He is currently Full Professor of Organic Chemistry at the Department of Organic Chemistry, Faculty of Pharmacy and Biochemistry, University of Buenos Aires. His interests are in the areas of radical chemistry, both carbon-centered radicals and metal-centered radicals. He is devoted to studying radical reactions of these species in water and non-conventional media.

Table 1. Reagents used for the late-stage introduction of CF_2H. *hν* refers to illuminated conditions, whereas Δ denotes thermal reactions.

Reagent	Conditions 1	Conditions 2	Group modification	Target class of compounds	Ref.
	*hν*	*fac*-[Ir(ppy)$_3$], Na_2CO_3, MeCN, 5 W blue LED			[74]
	*hν*	[Ru(bpy)$_2$Cl$_2$·6H$_2$O 6 W blue LED, DMSO, Na_2CO_3, N_2, r.t.			[75]
HCF_2SO_2Cl	*hν*	*fac*-[Ir(ppy)$_3$], Na_2CO_3 1,4-dioxane, H_2O			[77] [65]
HCF_2SO_2Cl	*hν*	*fac*-[Ir(ppy)$_3$], $NaHPO_4$, MeCN, r.t. blue LED			[76]
	*hν*	*fac*-[Ir(ppy)$_3$], acetone/H_2O, r.t., 24 h 425 nm blue LED			[14]
$[Ph_3PCF_2Br]^+Br$	*hν*	*fac*-[Ir(ppy)$_3$], acetone/H_2O, r.t., 24 h 425 nm blue LED			[70]
$[Ph_3PCF_2Br]^+Br^-$	*hν*	*fac*-[Ir(ppy)$_3$], Ph_3P, NaI, $KHCO_3$ H_2O, THF			[67]
$[Ph_3PCF_2H]^+Br^-$	*hν*	*fac*-[Ir(ppy)$_3$], CuBr, DMF			[71]
$[Ph_3PCF_2H]^+Br^-$	Δ	Cs_2CO_3, DMC, r.t.	ArCO–R		[104]
Me_3SiCF_2H	Δ	1) CsF/18-crown-6, DME, r.t. overnight 2) TBAF, r.t., 1 h, 3) HCl, r.t., 1 h			[109]
$(DMPU)_2Zn(CF_2H)_2$	Δ	(dppf)Ni(COD)$_2$, DMSO, 20 °C, 24 h			[53]
$(TMEDA)Zn(CF_2H)_2$	Δ	Pd(dba)2, DPPF 1,4-dioxane, 120 °C, 6 h			[56]
$[Ph_3PCF_2]^+CO_2^-$	Δ	*p*-xylene	PhOH	$PhOCF_2H$	[95]
$FSO_2CF_2CO_2H$	Δ	CuI in MeCN, 50 °C	ROH	$ROCF_2H$	[99]
	Δ	$LiBF_4$, CH_2Cl_2 30 °C, 1 h	alkyl–OH	alkyl–OCF_2H	[97]
$TMSCF_2Br$	Δ	Additive: CH_2Cl_2/H_2O Additive: NaOH method A KOAc method B KHF_2 method C			[98] [121]
$(EtO)_2P(O)CF_2Br$	Δ	CsF, MeOH DCM, r.t.	RR^1R^2N	$RR^1R^2NCF_2H^+$ Br^-	[112]

from a high catalyst loading of Ni complex (15 mol%) and the turnover number of the catalytic reaction is not high enough.

Mikami and co-workers[56] have used the difluoromethylating reagent $(TMEDA)Zn(CF_2H)_2$ (2 equiv) in the presence of $Pd(dba)_2$ (5 mol%) as catalyst, DPPF (10 mol%) as ligand, in 1,4-dioxane as solvent, at 120 °C, for six hours to difluoromethylate ArX (X = I, Br). The reagent $(TMEDA)Zn(CF_2H)_2$ is synthesized in an analogous manner as reagent $(DMPU)_2Zn(CF_2H)_2$. However, in this method, reactions of non-activated heteroaryl iodides or heteroaryl bromides occurred with much less efficiency.

Boronic acids have also been useful as leaving groups in the difluoromethylation reaction of arylboronic acids through the use of a $PdCl_2(PPh_3)_2$ catalyst and $BrCF_2CO_2Et$ as difluorometh-

Table 2. Reagents used for the introduction of CF_2–Z groups through Y-CF_2-Z synthons; *hν* refers to illuminated conditions, whereas Δ denotes thermal reactions.

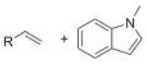
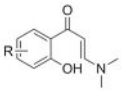
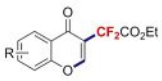
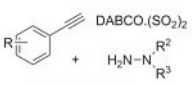
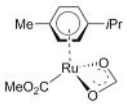
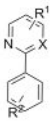
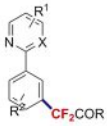
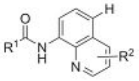
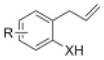
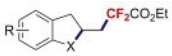
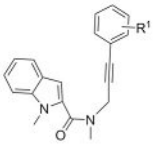
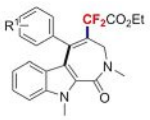
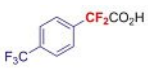
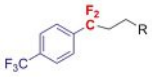
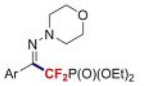
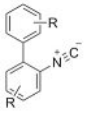
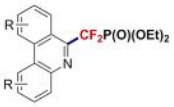
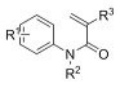
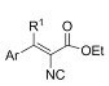
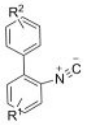
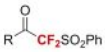
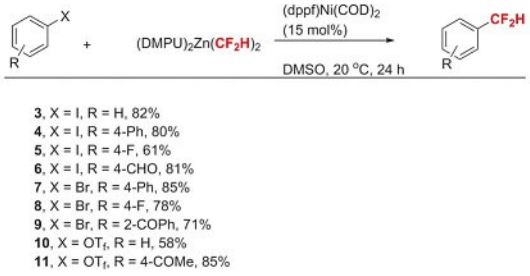
Reagent	Conditions 1	Conditions 2	Group modification	Target class of compounds	Ref.
$BrCF_2CO_2Et$ and $BrCF_2CONEt_2$	*hν*	*fac*-[Ir(ppy)$_3$], K_2HPO_4, DMSO, r.t., 24 h, 12 W blue LED			[66]
$BrCF_2CO_2Et$	*hν*	*fac*-[Ir(ppy)$_3$], AgOAc, DCM, r.t.			[79]
$BrCF_2CO_2Et$	*hν*	*fac*-[Ir(ppy)$_3$], NaOAc, acetone, r.t. 24 h			[126]
$BrCF_2CO_2Et$	Δ	$CuBr_2$,B_2pin_2 DTBDPy, KOAc, 1,4-dioxane			[89]
$BrCF_2CO_2Et$	*hν*	Mes-Acr$^+$, DMF, r.t.			[91]
$BrCF_2CO_2Et$	Δ	 $P(4\text{-}C_6H_4CF_3)_3$, Na_2CO_3 1,4-dioxane, 60 °C, 18 h			[61]
$BrCF_2CO_2Et$	Δ	$RuCl_2$(*p*-cymene)$_2$, $Pd(PPh_3)_4$, Na_2CO_3 $Ba(OAc)_2$, 1,4-dioxane, 90 °C, 24 h			[59]
$BrCF_2CO_2Et$	Δ	Ni(dppf)Cl_2, $KHCO_3$, 1,4-dioxane, 150 °C, 12 h			[127]
$BrCF_2CO_2Et$	*hν*	*fac*-[Ir(ppy)$_3$], Na_2CO_3, DCM-EtOH, 60 °C			[128]
$BrCF_2CO_2Et$	Δ	K_2CO_3, CuCl, 1,10-Phen, MeCN, 80 °C, 5 h			[116]
ICF_2CO_2Et	Δ	$Pd(PPh_3)_4$, dppf, KOAc (or CsOAc) 1,4-dioxane, 20 h, 80 ° C			[19]
ICF_2CO_2Et	Δ	CuCl, 1,10-Phen,Cs_2CO_3, DCE, Ar, 60 °C			[90]
$TMSCF_3$	Δ	PPh_3, LiI, DMF/dioxane, 120 °C, 24 h			[120]
$TMSCF_3$	Δ	NaI,THF, r.t.			[121]
	Δ	Ir(dF(CF_3)ppy)$_2$(dtbpy)BF_4, BlOMe, NMP, r.t.			[129]
$BrCF_2P(O)(OEt)_2$	*hν*	$[Au_2(\mu\text{-dppm})_2](OTf)_2$ 2,6-lutidine MeCN, r.t., solar light			[113]

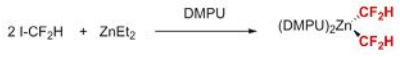
Table 2. (Continued)

Reagent	Conditions 1	Conditions 2	Group modification	Target class of compounds	Ref.
$BrCF_2P(O)(OEt)_2$	*hν*	*fac*-[Ir(ppy)$_3$], KOAc 1,4-dioxane, H_2O			[22] [83]
$TMSCF_2CO_2Et$	Δ	$AgOT_f$, KF, DCE, reflux, 16 h			[63]
$TMSCF_2CO_2Et$	Δ	$AgNO_3$, NaOAc $PhI(OAc)_2$, NMP, 48 h, r.t.			[80]
$BrCF_2C(O)NR^2R^3$	Δ	$Pd(OAc)_2$, Dppe, K_2CO_3 dioxane,120 °C			[87]
$PhSO_2CF_2H$	Δ	*t*-BuONa, Cs_2CO_3, $PhI(OAc)_2$, I_2, Ar, DMF, 50 °C			[84]
$PhSO_2CF_2H$	Δ	1) $N(TMS)_3$, Me_4NF, DMF 2) Bu_4NF, r.t.			[130]
$FSO_2CF_2CO_2Me$	*hν*	*fac*-[Ir(ppy)$_3$], NMP, r.t., 20 h			[131]



3, X = I, R = H, 82%
4, X = I, R = 4-Ph, 80%
5, X = I, R = 4-F, 61%
6, X = I, R = 4-CHO, 81%
7, X = Br, R = 4-Ph, 85%
8, X = Br, R = 4-F, 78%
9, X = Br, R = 2-COPh, 71%
10, X = OT_f, R = H, 58%
11, X = OT_f, R = 4-COMe, 85%

Scheme 1. Scope of the direct difluoromethylation reaction of ArX.



Scheme 2. Synthesis of $(DMPU)_2Zn(CF_2H)_2$.

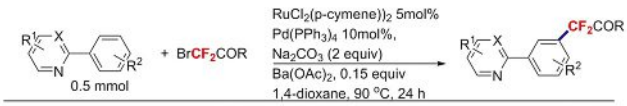
ylating reagent.[57] Hu and colleagues have also accomplished a copper-mediated aerobic (phenylsulfonyl)difluoromethylation of arylboronic acids[16] with $BrCF_2SO_2Ph$.[21]

In a more recent report, Shen and colleagues[55a] identified a Pd-catalyzed reaction of heteroaryl chlorides, bromides and iodides with [(SIPr)Ag(CF_2H)] (SIPr = 1,3-bis(2,6- diisopropyl phenyl)imidazolin-2-ylidene), a nucleophilic[55b] difluoromethylating reagent, $Pd(dba)_2$, DPEPhos (bis-[2-(diphenylphosphino)phenyl]ether) as ligand in toluene as solvent to yield difluoromethylated heteroaryl compounds in high yields.

The difluoromethylating reagents used by Vicic[53] and Mikami[56] necessitate volatile starting materials such as HCF_2I. Furthermore, all the above methods require the presence of a leaving group on the arene ring. C_{Ar}–H substitutions by a CF_2Y group[58] would render greater synthetic advantages because no leaving groups on the aromatic moiety would be necessary.

Wang and collaborators[59] introduced in 2017 a ruthenium-catalyzed *meta*-selective C_{Ar}–H difluoromethylation of arenes using an *ortho*-metalation strategy to afford a variety of novel *meta*-mono- and difluoromethylated 2-phenylpyridines, 2-phenylpyrimidines, and 1-phenylpyrazoles in moderate to good yields. This novel transformation has a broad substrate scope, good functional group tolerance and is high-yielding. The new dual catalytic system using compatible Ru^{II} and Pd^0 complexes enables key processes of C_{Ar}–H activation/difluoromethyl radical formation to take place and achieves a *meta*-selective functionalization under mild reaction conditions. The scope of the transformation is illustrated in Scheme 3.

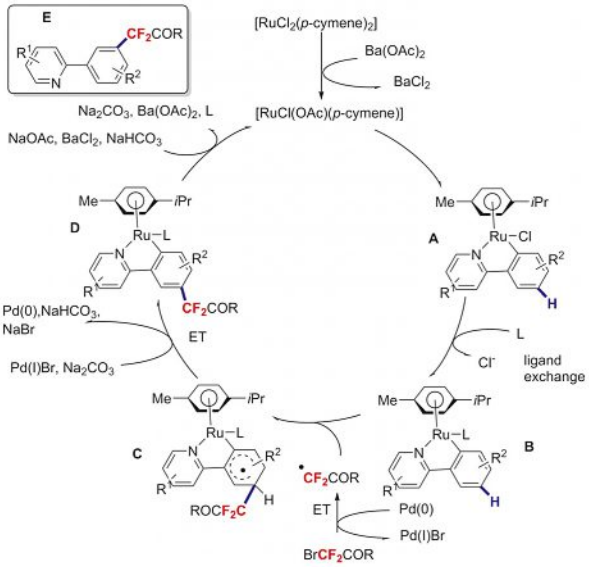
2-Phenylpyridines afford good substitution yields of CF_2Y *meta*-substituted biphenyl products (products **12**–**14**). 2-Phe-



12, X = C, R^1 = R^2 = H, 74%
13, X = C, R^1 = H , R^2 = 4-MeO, 79%
14, X = C, R^1 = 6-MeO, R^2 = H, 54%
15, X = N, R^1 = H, R^2 = H, 68%
16, X = N, R^1 = H, R^2 = 4-MeO, 79%
17, X = N, R^1 = H, R^2 = 4-F, 70%
18, X = N, R^1 = 4-F, R^2 = H, 55%
19, X = N, R^1 = 4-Me, R^2 = H, 67%

Scheme 3. Scope of the Ru-catalyzed *meta*-selective C–H difluoromethylation of Ar–H.

nylpyrimidines do also afford good yields of CF_2Y-*meta*-substituted 2-phenylpyrimidines (products **15**–**19**). Removal of the ester moiety can be achieved to provide access to CF_2H-substituted compounds.[40,41] The proposed reaction mechanism is illustrated in Scheme 4. Firstly, a five-membered cyclometalated



Scheme 4. Proposed reaction mechanism for the Ru-catalyzed *meta*-selective C_{Ar}–H difluoromethylation.

complex **A** is formed through a reversible *ortho*-ruthenation of 2-phenylpyridines with RuCl(OAc)(*p*-cymene) generated in situ from $[RuCl_2(p\text{-cymene})]_2$ and $Ba(OAc)_2$. Subsequently, an active catalyst species **B** might be formed from **A** by further ligand exchange and/or C–H activation with a second molecule of 2-phenylpyridine, which then reacts with CF_2COR radical produced from $BrCF_2COR$ by reduction with Pd^0 through an electron transfer (ET) process to provide intermediate **C**. It is known that the strong directing-group effect of the Ru–C(sp^2) σ-bond can lead to a functionalization at the *para*- or *ortho*-position of the Ru–C(sp^2) bond.[60] It is worth noting that *ortho*-functionalization of the Ru–C(sp^2) bond in the present case is inhibited by a steric hindrance effect, similar to the Ru-catalyzed *meta*-selective sulfonation, alkylation, bromination, and nitration of 2- phenylpyridines.[61] Next, intermediate **D** is produced from **C** with aid of Na_2CO_3 and a Pd^I species, accompanied by simultaneous release of a Pd^0. Finally, the desired product **E** is rendered through proto-demetalation with a concurrent regeneration of a Ru^{II} to complete the catalytic cycle. However, an alternative possibility involving a Pd^0/Pd^{II} catalytic cycle might also operate for the ET processes. These results indicate that $Ba(OAc)_2$ is an important additive to generate complex **A**.

Ackermann and colleagues[61] have very recently introduced a Ru^{II}-catalyzed metal C_{Ar}–H difluoromethylation of arenes by phosphine/α-congested carboxylate cooperation. The authors employ halo-difluoroacetates, a Ni co-catalyst, that is, $Ni(PPh_3)_2Cl_2$, Na_2CO_3 as a base, and 1,4-dioxane as solvent. Phosphine ligands, such as $P(Ar)_3$, are crucial in affording a *meta*-selectivity. In fact the best catalytic ligand was found to be the electron-deficient $P(4\text{-}CF_3\text{-}C_6H_4)_3$. The Ru catalyst **20** employed is shown in Figure 3. Under these reaction conditions, a range of pyridyl-substituted pyrimidines, indazoles, and pyrazoles afford products with exclusive *meta*-selectivity. Also, purine nucleobases, of considerable importance for the synthesis of bioactive compounds, are obtained under this protocol, depicted in Scheme 5.

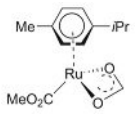
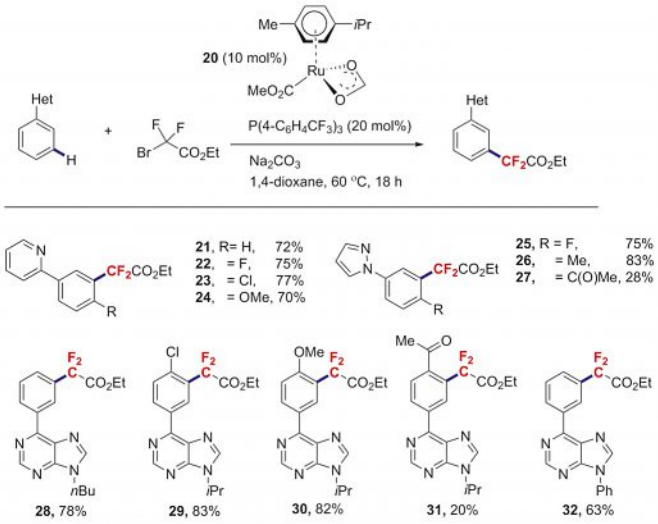


Figure 3. Ruthenium-biscarboxylate catalyst **20**.



Scheme 5. Scope of the difluoromethylation reaction employing photocatalyst **20**.

The pyridyl-guided substrates give excellent yields of CF_2CO_2Et-substituted compounds. Substrates bearing halogen atoms such as F and Cl, afford substituted products **22**, **23** in 75 and 77% yields, respectively. Pyrazoles bearing F, Me, and C(O)Me substituents also afford good product yields with *meta*-selectivity (products **25**, **26**, and **27**, respectively). The direct difluoromethylation of purine nucleobases afford CF_2-substituted products **28**–**32** in 78, 83, 82, 20, and 63% yields, respectively (Scheme 5). It is observed that C–H difluoromethylation did not occur at the kinetically more acidic C-8 positions of the purine motif.

The authors[61] also found by competition experiments that electron-rich substrates are more reactive than electron-poor counterparts. The reactions conducted in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a well-known radical scavenger, lead to complete inhibition of the catalytic activity. The authors[61] could also disclose the nature of the active catalyst species, in which a participation of the carboxylate functionality is observed (Figure 4) in a pyridyl-complexed carboxylate Ru^{II} catalyst **33**. All of these directing group-assisted C_{Ar}–H transformations exclusively lead to proximity-induced *ortho*- or *meta*-functionalizations.[62]

A limitation of the methods developed by Wang[59] and Ackermann[61] for C_{Ar}–H CF_2-substitution is the use of complex Ru catalysts and elevated reaction temperatures. Hao and collabo-

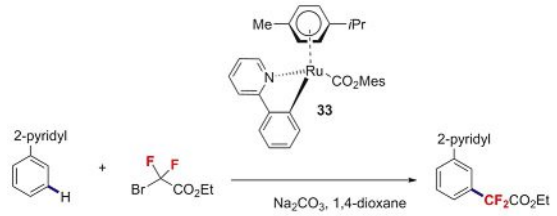
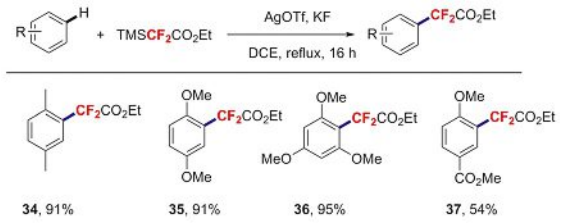


Figure 4. Catalyst **33** as active species for difluoromethylation.

rators[63] have recently accomplished a Ag-mediated C_{Ar}–H difluoromethylation of arenes. They employ $AgOT_f$, KF, and $TMSCF_2CO_2Et$ in a 4:4:1 ratio, in DCE as solvent at 85 °C. The scope of the transformation is depicted in Scheme 6.

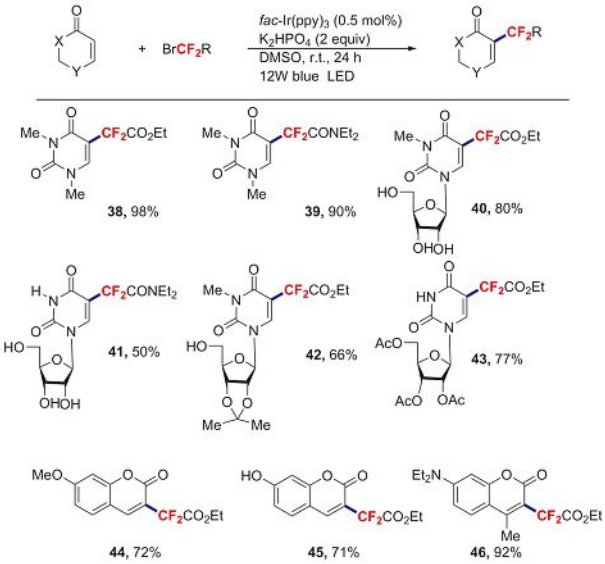


Scheme 6. Scope of the Csp^2–H difluoromethylation reaction.

Several probe experiments, such as the employment of TEMPO, 1,4-dinitrobenzene, and hydroquinone, determined that the reaction proceeds through radical intermediates, as the CF_2CO_2Et product yields are found to be drastically reduced in the presence of probes. On the basis of the former experiments and others,[63] the authors propose initial formation of $AgCF_2CO_2Et$, which promptly decomposes to CF_2CO_2Et radical that reacts with an arene ring to yield a cyclohexadienyl-type radical intermediate, which in turn is oxidized to a carbocation intermediate undergoing re-aromatization by proton loss affording a Ar–CF_2 substituted product.

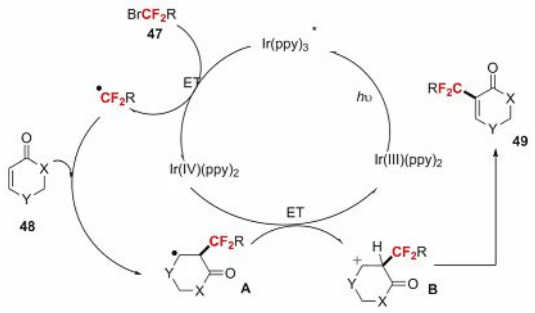
In recent years, radical fluoroalkylation reactions by visible-light photoredox catalysis have attracted considerable attention due to mild reaction conditions and broad functional group tolerance, and many radical difluoroalkylation reagents including $PhSO_2CF_2I$,[58] $BrCF_2COOEt$,[30,28] and fluoroalkanesulfonyl halides HCF_2SO_2Cl,[64,65] have been used for this purpose. Chung-Ya He and colleagues have very recently introduced a method for the difluoromethylation of uracils, pyrimidinones and coumarins employing $BrCF_2CO_2Et$ and $BrCF_2CONEt_2$ as difluoromethylating agents under photocatalysis.[66] The photocatalyst employed is *fac*-Ir(ppy)$_3$, K_2HPO_4 as a base, in DMSO as solvent; irradiation source is a blue LED. The scope of the reaction is illustrated in Scheme 7.

The reaction of 1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione employing reaction conditions from Scheme 7 affords 98% yield of **38**. As observed from Scheme 7, pyrimidine bases derived from uridines afford good yields of CF_2-substituted products **40**–**43**, in yields ranging from 50–80%. 7-OMe, 7-OH, and 4-Me-7-N(Et)$_2$ coumarin derivatives afford CF_2-substituted products **44**–**46** in 72, 71, and 92% yields, respectively.



Scheme 7. Scope of the difluoromethylation of pyrimidinones and coumarins.

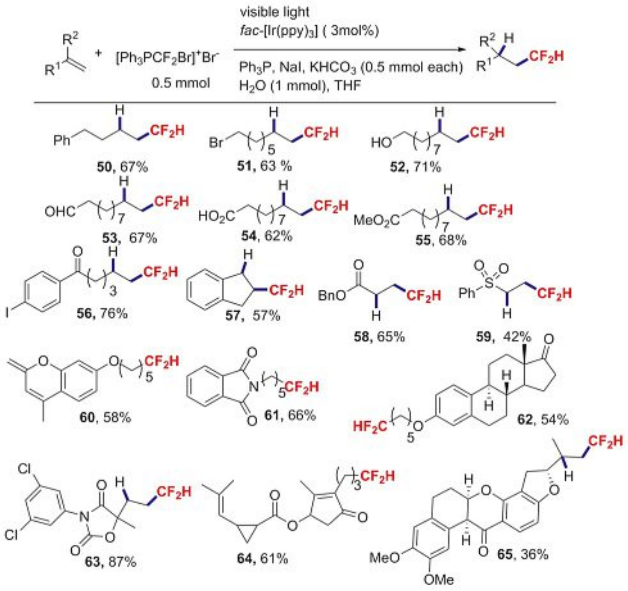
The authors[66] supply a plausible reaction mechanism shown in Scheme 8. Irradiation with visible light excites Ir(ppy)$_3$ converting it into a strong reductive species [i.e., *Ir(ppy)$_3$, ($E_{1/2} = -2.14$ V vs. $FeCp_2$)] that suffers an ET process to generate $^{\bullet}CF_2R$ from $BrCF_2R$ (**47**). Subsequent regioselective addition of $^{\bullet}CF_2R$ to uracils (**48**) leads to intermediate **A**, which is further oxidized to cation species **B** through another ET process with strong oxidant $Ir^{IV}(ppy)_3$. Finally, deprotonation of **B** with base could afford the corresponding product **49**.



Scheme 8. Proposed reaction mechanism for difluoromethylation of uracil derivatives.

Difluoromethylation of C–C double bonds

Qing and colleagues[67] have recently disclosed a visible light-induced hydrodifluoromethylation of alkenes with $[Ph_3PCF_2Br]^+Br^-$,[24] for a direct and efficient synthesis of difluoromethylated alkanes, which are usually obtained by several steps. Importantly, this work represents an unprecedented and practical method of CF_2H radical generation from fluorinated phosphonium salts. The methodology entails the use of $[Ph_3PCF_2Br]^+Br^-$,[45] photocatalyst *fac*-[Ir(ppy)$_3$], NaI, $KHCO_3$, PPh_3, H_2O in THF as solvent (Scheme 9).



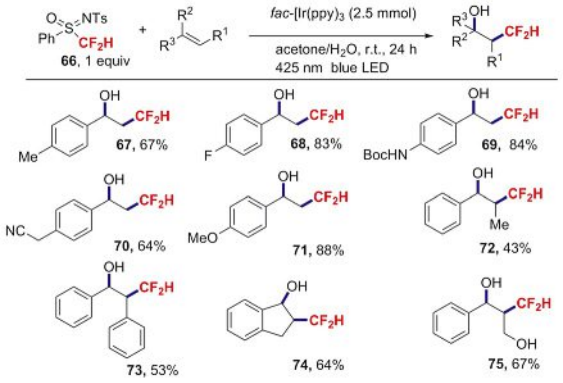
Scheme 9. Scope of the difuoromethylation reaction employing $[Ph_3PCF_2Br]^+Br$.

When the reaction is performed in D_2O, a group CF_2D is appended to the alkene and a hydro(H)difluoromethyldeuteride product is observed, confirming that H_2O serves as a hydrogen source of the difluoromethyl group. When the reaction is performed in [D_8]THF, a product containing a D at the β-carbon atom of the functionality CF_2H is observed, purporting that one of the hydrogen atoms of THF is transferred to the alkene.[67]

On the basis of these experiments, the authors[67] propose a mechanism in which the reaction of $[Ph_3PCF_2Br]^+Br^-$ with H_2O, a difluorocarbene is formed,[68,69] which is then converted into HCF_2I and HCF_2Br. Both of these compounds react with PPh_3 to give the corresponding $[PPh_3CF_2H]^+X^-$. Alternatively, CF_2 carbene might be captured by PPh_3 to give difluoromethylene ylide,[68b] which then reacts with either H_2O or HBr to produce $[PPh_3CF_2H]^+X^-$. Upon visible-light irradiation of *fac*-$[Ir^{III}(ppy)_3]$, excited *fac*-$[Ir^{III}(ppy)_3]$* catalyst is formed, which acts as a strong reductant to $[PPh_3CF_2H]^+X^-$, affording a CF_2H radical (and $PPh_{3+}X^-$), which subsequently adds to the alkene to form radical intermediate that abstracts a hydrogen atom from THF to give a hydrodifluoromethylated product and another radical intermediate that may be oxidized by *fac*-$[Ir^{IV}(ppy)_3]$.

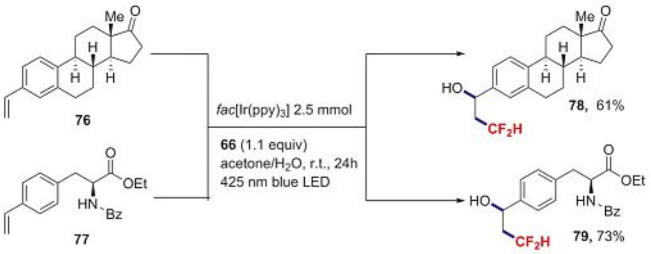
Koike, Akita and colleagues[14] have recently come up with a visible-light photocatalytic protocol to introduce a CF_2H functionality into alkenes. The methodology introduces both an OH and CF_2H groups through the employment of *fac*-[Ir(ppy)$_3$] photocatalyst, a blue LED (λ_{max} = 425 nm), in acetone/H_2O and the Hu's reagent *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine **66** (1 equiv) as a CF_2H source. The scope of the photocatalytic hydroxydifluoromethylation reaction of alkenes is depicted in Scheme 10.

Styrenes with various functional groups (4-Me, 4-F, 4-NHBoc, 4-$CNCH_2$, and 4-MeO) smoothly afford the CF_2H-containing alcohols in yields ranging from 64–88% (products **67**–**71**). β-



Scheme 10. Scope of the photocatalytic reaction of alkenes with Hu's reagent **66**.

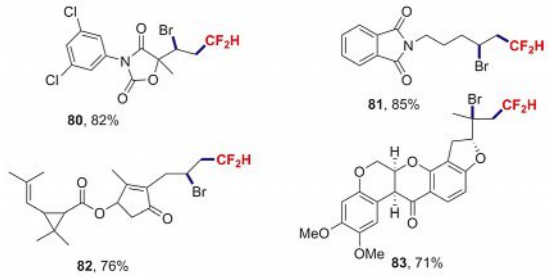
Methyl styrene and β-phenyl styrene afford products **72** and **73** in 43 and 53% yields, respectively. Indene, and *trans*-cinnamic alcohol afford products **74** and **75** in 64 and 67% yields, respectively (Scheme 10). It should be noted that this photocatalytic method with Hu's reagent **66** is compatible with a wide variety of functionalities, including hydroxyl (not shown), *N*-protected amino, halogens, nitriles, esters (not shown), etc. Furthermore, the addition of CF_2H and OH functions is regioselective, regardless of terminal or internal alkenes. The authors[13] also investigated biological relevant substrates such as vinyl estrone **76** and vinyl-*N*-benzoyl-L-tyrosine ethyl ester **77**, affording products **78** and **79** in 61 and 73% yields, respectively, as shown in Scheme 11. The authors postulate a plausible reaction mechanism,[14] which is similar to that shown in Scheme 8, in which case, a one-electron reduction of **66** leads to CF_2H radicals and sulfonamide (after protonation).



Scheme 11. Hydroxydifluoromethylation of estrone **76** and tyrosine derivative **77** with Hu's reagent **66**.

Qing and co-workers[70] have introduced a variation of the above protocol for the hydroxydifluoromethylation and alcoxydifluoromethylation of styrene derivatives, employing $[PPh_3CF_2]^+Br^-$ as a difluoromethylating reagent. Their hydroxyl and alcoxy-difluoromethylated product yields are comparable or slightly higher than those reported by Koike, Akita and colleagues.[14] Essentially, the reaction entails the same photocatalyst *fac*-Ir[ppy]$_3$ (3 mol%), visible light, $[PPh_3CF_2]^+Br^-$ (0.75 mmol) as difluoromethylating source, in acetone/H_2O or alcohol. The reaction mechanism suggested for this transformation is analogous to that shown in Scheme 8.

In another report, Qing and collaborators[71] have extended the protocol towards an Ir-photocatalyzed bromodifluoromethylation of alkenes with $[Ph_3PCF_2H]^+Br^-$ in the presence of CuBr in DMF as solvent. Some examples of bromodifluoromethylation of bioactive compounds are shown in Scheme 12.



Scheme 12. Bromodifluoromethylation of bioactive compounds.

Bromodifluoromethylation of fungicide Vinclozolin®, affords product **80** in 82% yield. Insecticides Allethrin® and Rotenone®, afford products **82** and **83** in 76 and 71% yields, respectively. The current protocol is also applied to the preparation of CF_2H-containing alkenes through a one-pot addition/elimination process using DBU, in which reduction of Br is attained. The reaction mechanism is similar to that of Scheme 8, except that radical adduct (Scheme 8) is oxidized by Ir^{IV} to a carbocation that readily reacts with bromide ion. The iodo-difluoromethylation of olefins had previously been accomplished by Hu and colleagues.[72]

Benzoxazines and oxazolines are common structural units present in many naturally occurring heterocyclic products and pharmaceutically active molecules. They have extensive applications as *anti*-inflammatory agents, anticonvulsants, antibiotics, and *anti*-fungals or progesterone receptor agonists in medicinal chemistry, or as useful synthetic intermediates in organic synthesis.[73] However, very scarce reports on the construction of CF_2H-containing benzoxazines and oxazolines through a reaction of olefinic amides with a difluoromethylation reagent are known.

An oxydifluoromethylation reaction of olefinic amides has recently been accomplished by Fu and collaborators.[74] The reaction entails the use of an olefin amide, 2-[(difluoromethyl)sulfonyl]benzo[d]thiazole **84** (Figure 5) as difluoromethylating reagent, together with photocatalyst *fac*-[Ir(ppy)$_3$], Na_2CO_3 as base in MeCN as solvent. The light source is a 5 W blue LED. The scope of the transformation is illustrated in Scheme 13.

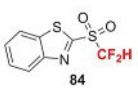
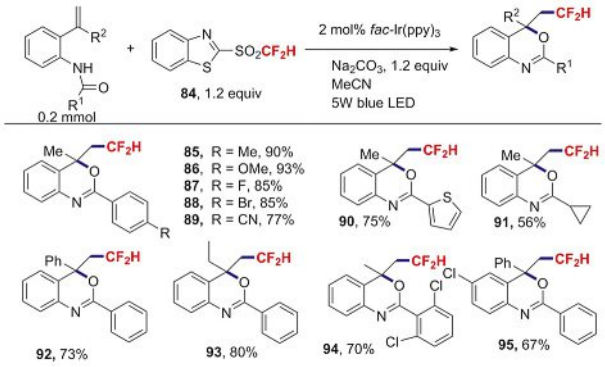


Figure 5. 2-((Difluoromethyl)sulfonyl)benzo[d]thiazole **84** as difluoromethylating reagent.

Using benzamide derivatives containing electron-neutral, electron-donating and electron-withdrawing groups as substrates, the reactions proceed smoothly to give CF_2H-containing benzoxazines in good to excellent yields (77–93%). A variety of important functional groups, including halide (products **87**, **88** in 85% yields), ether (product **86**, yield 93%), and cyano (product **89**, 77% yield), are well



Scheme 13. Scope of the photocatalytic oxydifluoromethylation reaction of olefinic amides.

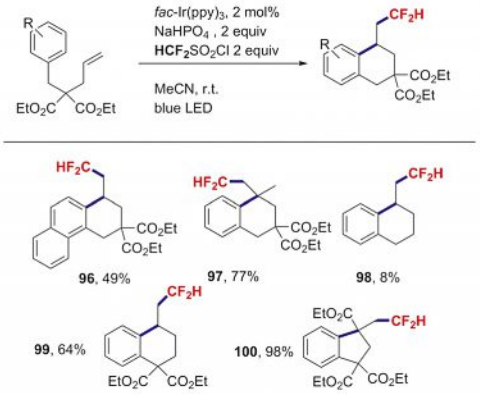
tolerated under the mild reaction conditions. In addition, the hindrance effect of this reaction is also not obvious, as a 2,6-dichloro-substituted substrate affords product **60** in 70% yield. Heteroarylamide containing a thiophene unit affords product **90** in 75% yield. The olefinic amides bearing a C_2H_5 or Ar group at an α-position of the styryl system are also successful in this transformation, rendering good to excellent yields of benzoxazines (products **92**, **93**, and **95**, in yields 73, 80, and 67%, respectively).

The authors probe the reaction mechanism in the presence of TEMPO, a well-known radical scavenger. The oxydifluoromethylation reaction is suppressed and a TEMPO-CF_2H adduct is formed in 63% yield, as estimated by ^{19}F NMR spectroscopy analysis, which indicated that a free radical pathway might be involved in the present reaction.

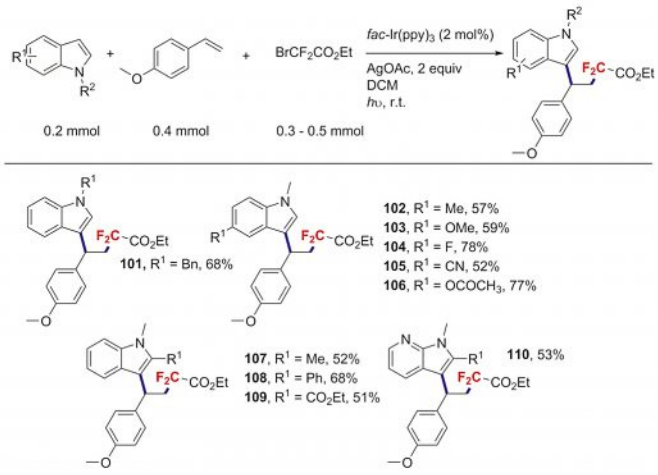
The authors propose a plausible mechanism, which is similar to that shown in Scheme 8. The excited photocatalyst (i.e., [*fac*-$Ir^{III}(ppy)_3$*]) formed under visible-light irradiation is a potent reductant capable of reducing **84** (which has a first reduction potential of -1.17 V vs. saturated calomel electrode (SCE), notably high, and enough to be reduced to a radical anion by Ir^{III}[75]), to generate a [*fac*-$Ir^{IV}(ppy)_3$]$^+$ complex and a $CF_2H^\bullet$ radical species **A**, which adds to the double bond.

Dolbier and collaborators[76] introduced in 2017 a photoredox-catalyzed difluoromethylation of unactivated alkenes followed by C–C bond formation to an aryl ring (homolytic aromatic substitution). The reactions are conducted under mild conditions and afford tetralin derivatives with CF_2H groups in good yields. In addition, the study indicates that *6-exo* radical cyclization of an alkyl radical to a phenyl ring is faster than the respective *5-exo* radical cyclization. The authors employ HCF_2SO_2Cl as difluoromethylating species, *fac*-Ir(ppy)$_3$ as photocatalyst, Na_2HPO_4 as base, in MeCN as solvent irradiated with a blue LED for 18 h. The applications of the methodology are depicted with representative examples in Scheme 14.

Diethyl 2-allyl-2-(naphthalen-1-ylmethyl)malonate, affords product **96** in 49% yield, according to the reaction conditions protocol. Diethyl 2-benzyl-2-(2-methylallyl)malonate renders product **97** in 77% yield, whereas unactivated pent-4-en-1-yl-benzene affords very poor yields of product (i.e., **98**, 8%). Diethyl 2-(but-3-en-1-yl)-2-phenylmalonate and diethyl 2-allyl-2-



Scheme 14. Photoredox-catalyzed difluoromethylation of unactivated alkenes followed by C–C bond formation to an aryl ring.



Scheme 16. Scope of the visible light-induced three-component 1,2-difluoroalkylarylation of styrenes.

phenylmalonate give products **99** and **100** in 64 and 98% yields, respectively.

Based on earlier mechanistic probes,[77,65] the authors[76] propose a reaction mechanism in which an excited photocatalyst reduces HCF_2SO_2Cl to HCF_2 radicals (and chloride anion and SO_2), which adds to the double bond, Scheme 15).

The authors[76] argue that *6-exo*-cyclization to an *ortho* position of an aryl ring must be faster than the analogous *5-exo* cyclization, as supported by other reports.[78] Nonetheless, they perform a series of computational studies at the M06-2X/6–311 + G(2df,p)// M06-L/6-31G(d) level of theory, which confirm that the transition state free energy for the *5-exo* cyclization of a 3-phenylpropyl radical is much higher than that for a *6-exo* cyclization of the 4- phenylbutyl radical.

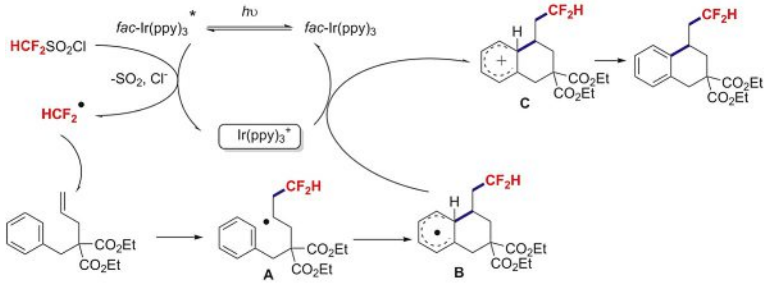
Zhu and collaborators[79] have recently introduced a visible-light-induced three-component 1,2-difluoroalkylarylation of styrenes with α-carbonyl difluoroalkyl bromides and indoles. The reaction entails the use of *fac*-[Ir(ppy)$_3$] as photocatalyst, indole derivative, styrene derivative, AgOAc as base, $BrCF_2CO_2Et$ as difluoromethylating reagent, and solvent (DCM). The scope of the transformation is represented in Scheme 16 below. Indoles substituted at the *6*-position with Me (**102**, 57% yield), OMe (**103**, 59% yield), F (**104**, 78% yield), CN (**105**, 52% yield) and OCOMe groups (**106**, 77% yield) afford a three-component tandem difluoromethylation reaction.

To gain insight into the mechanism of this transformation, a radical-trapping experiment was carried out. Notably, the reaction is completely suppressed by the radical inhibitor TEMPO, thus implying that this current reaction involves a free radical process. Irradiation of photocatalyst *fac*-[Ir(ppy)$_3$] with visible light will produce a long-lived excited state (−1.73 V vs. SCE in MeCN), which can undergo an ET process in the presence of $BrCF_2CO_2Et$ to generate a CF_2 radical and Ir^{4+} (+0.77 V vs. SCE in MeCN). Then, addition of $^{\bullet}CF_2$ to alkene gives a more stable benzyl radical intermediate, which is subsequently oxidized into a cation intermediate by Ir^{4+} (**C**). Finally, a β-difluoroalkylated carbocation intermediate is attacked by nucleophilic indoles to afford cation intermediate, followed by base-mediated deprotonation to give the final selective difluoroalkylated product.

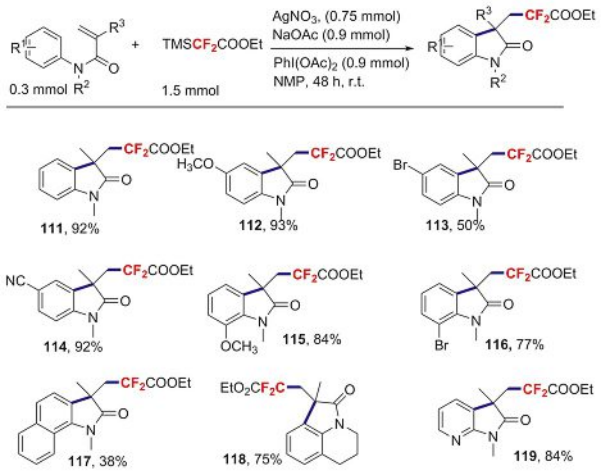
In summary, the use of photocatalyst *fac*-[Ir(ppy)$_3$] enables photoreduction of $BrCF_2CO_2Et$, $BrCF_2NEt_2$,[66] $Ph_3PCF_2Br^+Br^-$,[67] *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine,[14] 2-((difluoromethyl)sulfonyl)benzo[*d*]thiazole,[74] and HCF_2SO_2Cl[76] to CF_2Y radicals that could add to double bonds.

Wang, Hao and colleagues[80] have recently reported on a thermal Ag-promoted cascade reaction for the difluoromethylation of activated alkenes towards the synthesis of oxindoles. They employ $TMSCF_2CO_2Et$ as difluoromethylating agent, $AgNO_3$, NaOAc as base, $PhI(OAc)_2$ as oxidant in *N*-methylpyrrolidone (NMP) as solvent. The scope of the transformation is depicted in Scheme 17.

Electron-neutral *N*-phenylacrylamides and those bearing electron-donating groups afford good yields of oxindoles



Scheme 15. Proposed reaction mechanism for the difluoromethylation of unactivated alkenes.

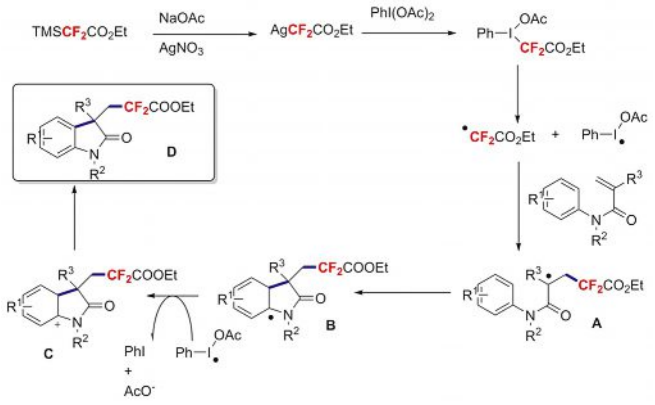


Scheme 17. Scope of the Ag-promoted cascade reaction for the difluoromethylation of activated alkenes.

(products **111**, **112**, and **115**, in 92, 93, and 84% yields, respectively). Electron-deficient *N*-phenylacrylamides also afford very good yields of oxindoles (products **113**, **114**, and **116**, in 50, 92, and 77% yields, respectively). *N*-(naphthalen-1-yl)acrylamide affords 38% yield of product **117**, whereas 1-(3,4-dihydroquinolin-1(2*H*)-yl)-2-methylprop-2-en-1-one affords product **118** in 75% yield. *N*-(pyridin-2-yl)acrylamide affords product **119** in 84% yield.

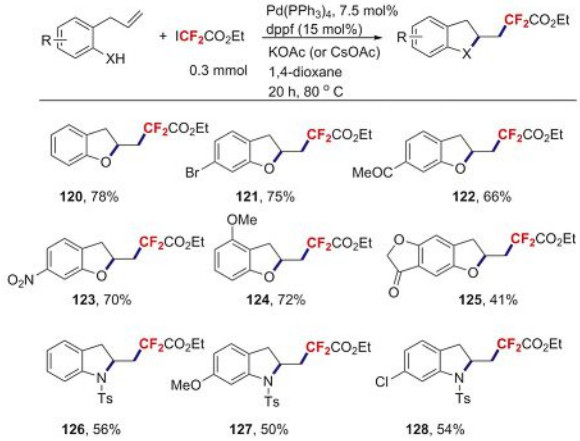
In the presence of radical scavengers such as TEMPO, the formation of difluoromethylated oxindole is inhibited, and a TEMPO-CF_2COOEt adduct is detected quantitatively. These results[80] suggest that addition of a generated CF_2COOEt radical to an alkene initiates the cascade sequence. The authors propose a reaction mechanism such as that shown in Scheme 18.

First, a CF_2COOEt radical intermediate is generated and further stabilized by the combination of AgI and $PhI(OAc)_2$. The subsequent addition of the CF_2COOEt radical intermediate to an activated C=C bond of the *N*-arylacrylamide affords radical intermediate **A**, which undergoes an intramolecular radical cyclization to generate intermediate **B**. The oxidation of **B** produces the corresponding carbocation **C**, and loss of H^+ and rearomatization affords the desired difluoromethylated oxindole **D**.[80]



Scheme 18. Proposed reaction mechanism for the Ag-promoted cascade reaction for the difluoromethylation of activated alkenes.

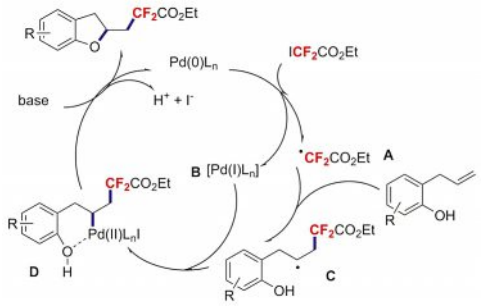
Jian and colleagues[19] have informed in 2017 a difluoromethylation reaction of olefins towards the synthesis of difluoromethylated 2,3-dihydrofurans and indolines. They employ ICF_2CO_2Et as difluoromethylating reagent, $Pd(PPh_3)_4$ as catalyst, DPPF as ligand, in 1,4-dioxane as solvent for 20 h at 80 °C. The scope of the transformation is illustrated in Scheme 19.



Scheme 19. Synthesis of 2,3-dihydrofurans and indolins.

It can be observed from Scheme 19 that 2-allylphenols and 2-allylamines afford good yields of 2,3-dihydrofuran and 2,3-dihydroindole derivatives. Substrates with electron-rich substituents afford also good yields of product (i.e., **124**). 6-Allyl-5-hydroxybenzofuran-3(2*H*)-one affords product **125** in 41% yield. Electron-neutral *N*-(2-allylphenyl)-4-methylbenzenesulfonamides and benzosulfonamides bearing electron-rich and electron-withdrawing substituents afford products **126**–**128** in 56, 50, and 54% yields, respectively. The authors[19] proposed a reaction mechanism as illustrated in Scheme 20.

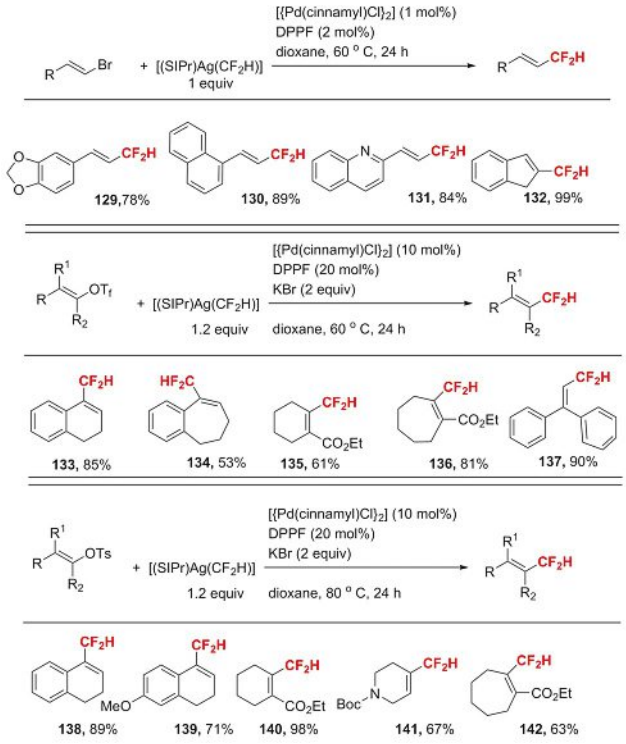
Based on radical trapping experiments, formation of an electrophilic fluoroalkyl radical **A** through a radical/ET pathway from a Pd^0 complex to ICF_2CO_2Et with concomitant generation of Pd^I complex **B** is proposed. Subsequent electrophilic radical addition of **A** across the double C–C bond of olefins is a key step that leads to the formation of a carbon-free radical **C**. Fur-



Scheme 20. Proposed reaction mechanism for the Pd-catalyzed difluoromethylation of olefins.

ther oxidation of a radical complex **C** with Pd^{I} leads to a Pd^{II} complex **D**. Finally, reductive elimination of **D** from an α-OH group affords the coupling product and recycled the active Pd^{0} catalytic species. The authors, however,[19] propose an alternative pathway with Pd^{0} as a radical initiator followed by an intramolecular S_N2 substitution as feasible. 2-Allylaniline substrates would undergo a similar mechanism.

Shen and colleagues have introduced in 2015[44b] a difluoromethylation reaction of vinyl bromides, vinyl triflates, and vinyl tosylates employing [(SIPr)Ag(CF_2H)] (SIPr = 1,3-bis(2,6- diisopropyl phenyl)imidazolin-2-ylidene), a nucleophilic difluoromethylating reagent, [{Pd(cinnamyl)Cl}$_2$] as Pd catalyst, DPPF as ligand, in dioxane at 60 °C for 24 h. The scope of the transformations is illustrated in Scheme 21.

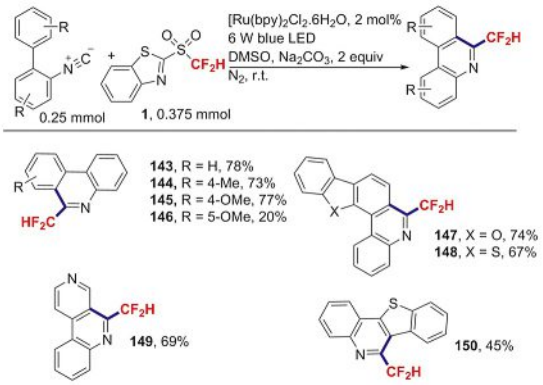


Scheme 21. Scope of the difluoromethylation reaction of vinyl bromides, vinyl triflates, and vinyl tosylates with [(SIPr)Ag(CF_2H)] and [{Pd(cinnamyl)Cl}$_2$] as Pd catalyst, DPPF as ligand.

The reactions of vinyl bromides proceed in high yields as observed in the first row of products, Scheme 21. Vinyl triflates (second row of products, Scheme 21) and vinyl tosylates (third row of products) also afford good substitution yields of difluoromethylated products.

Difluoromethylation of isocyanides

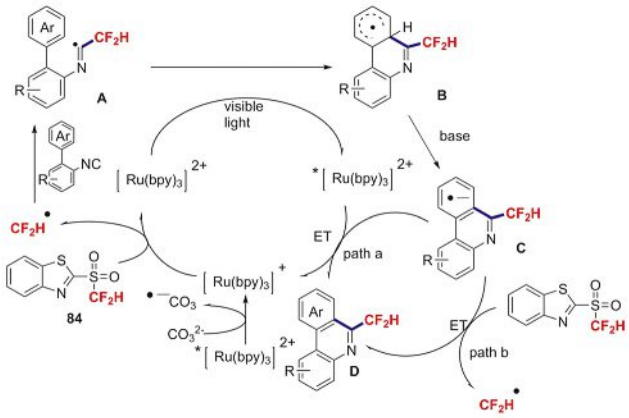
Hu and colleagues[75] have recently accomplished a difluoromethylation of isocyanides[17] towards the synthesis of phenanthridine derivatives employing [Ru(bpy)$_3$]Cl$_2$·6H$_2$O as photocatalyst, Na_2CO_3 as base, 2-((difluoromethyl)sulfonyl)benzo[*d*]-thiazole **84** as difluoromethylating reagent (Figure 5), a 6 W blue LED in DMSO as solvent under N_2 atmosphere. The scope of the difluoromethylation reaction towards the synthesis of CF_2H-phenanthridines is illustrated in Scheme 22.



Scheme 22. Scope of the difluoromethylation reaction of isocyanides.

2-Isocyano-1,1′-biphenyl reacts with **84** to afford product **143** in 78% yield (Scheme 22). 2-Isocyano-4-methyl-1,1′-biphenyl affords product **144** in 73% yield. The 4-methoxy and 5-methoxy-2-isocyano-1,1′-biphenyl derivatives afford products **145** and **146** in 77, and 20% yields, respectively. Fused heteroaryl rings containing either O or S atoms, afford products **147** and **148** in 74 and 67% yields, respectively. 4-(2-Isocyanophenyl)pyridine affords product **149** in 69% yield (Scheme 22). 2-(2-isocyanophenyl)benzo[*b*]thiophene gives product **150** in 45% yield.

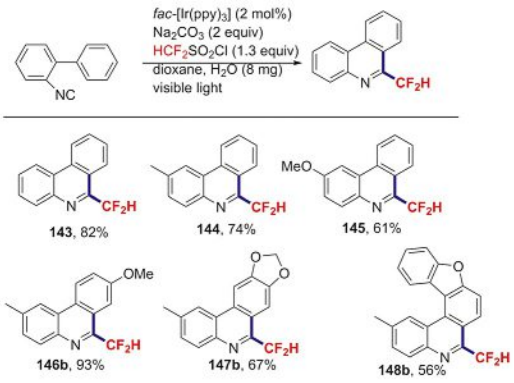
Difluoromethyl(sulfonyl)benzo[*d*]thiazole **84** has a first reduction potential of −1.17 V vs. SCE, notably high, and enough to be reduced to a radical anion by regular metal photocatalysts.[75] The fluoroalkylation reaction involves a reductive quenching cycle of the photocatalyst, [Ru(bpy)$_3$]Cl$_2$·6H$_2$O [$E_{1/2}$ $_{(Ru2+/Ru+)}$ = −1.33 V vs. SCE] (Scheme 23).[81] In the reaction system, a carbonate ion (CO_3^{2-}) probably serves as an initial electron donor[82] to reduce $*[Ru]^{2+}$ to $[Ru]^{+}$ and then $[Ru]^{+}$ reduces the fluoroalkyl sulfone **84** to start the catalytic cycle. On the basis of all of these results, a photoredox catalytic cycle is proposed by the authors[75] in Scheme 23. The CF_2H radical



Scheme 23. Proposed mechanism for the difluoroalkylation of isocyanides.

adds to isocyanide to yield imidoyl radical **A**, which undergoes intramolecular radical cyclization to form intermediate **B**. Deprotonation of **B** by a base provides radical anion **C**, which is oxidized by $*[Ru]^{2+}$ to generate product **D** and photocatalyst $[Ru]^{+}$ (path a). It is also possible that **C** reacts with fluoroalkyl sulfone **84** through a ET process to generate product **D** and CF_2H radical (path b).

Dolbier and collaborators[77,65] have also achieved the synthesis of 6-substituted CF_2H-phenanthridines from 2-isocyano-1,1′-biphenyl derivatives. In this case, the difluoromethylating reagent is CF_2HSO_2Cl, the photocatalyst is fac-$[Ir(ppy)_3]$, Na_2CO_3 as base, in 1,4-dioxane as solvent with traces of water under visible light illumination. Interestingly, the authors[77] could also accomplish a direct (late-stage) synthesis of 6-substituted CF_2H-phenanthridines from 2-isocyano-1,1′-biphenyl derivatives employing $PhCF_2Br$ as a difluoromethylating reagent, provided that the solvent (1,4-dioxane) contained traces of water. The scope of the transformation is illustrated in Scheme 24.



Scheme 24. Scope of the difluoromethylation reaction of isocyanides with HCF_2SO_2Cl.

It can be observed that the yields are comparative to those reported by Hu and collaborators,[75] as reflected in substrates **143**–**145** from Scheme 22 and Scheme 24. In the latter case (i.e., with use of HCF_2SO_2Cl), the authors[77,65] proposed a reaction mechanism as shown in Scheme 25.

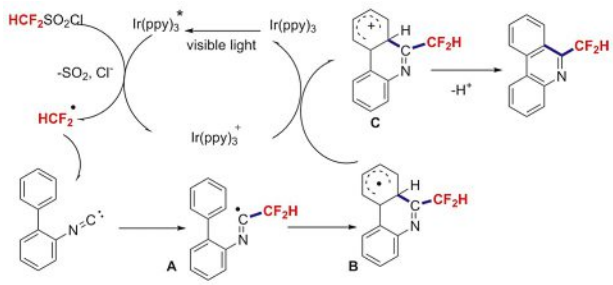
First, an excited Ir catalyst reduces the sulfonyl chloride to form a difluoromethyl radical and in turn the catalyst is oxidized to a strong oxidant species (Scheme 25). The CF_2H radical then adds to 2-isocyano-1,1′-biphenyl to generate an imidoyl radical **A**, which cyclizes on the arene to render a cyclohexadienyl radical intermediate **B**. Then **B** is oxidized by a high-valent catalyst to form cationic intermediate **C** with regeneration of catalyst. Finally, intermediate **C** is deprotonated to form the product. Another application of this reagent (i.e., HCF_2SO_2Cl) has been provided by the same authors[65] for the photoredox-catalyzed intramolecular difluoromethylation of *N*-benzylacrylamides coupled with a dearomatizing spirocyclization towards the access to CF_2H-containing 2-azaspiro[4.5]deca-6,9-diene-3,8-diones.[65]

A notorious difference is observed between the mechanisms proposed by Hu[75] and that by Dolbier[77,65] for the synthesis of phenanthridine derivatives. Although Hu's mechanism allows for the presence of a radical anion intermediate, Dolbier proposes a Wheland intermediate for the re-aromatization process.

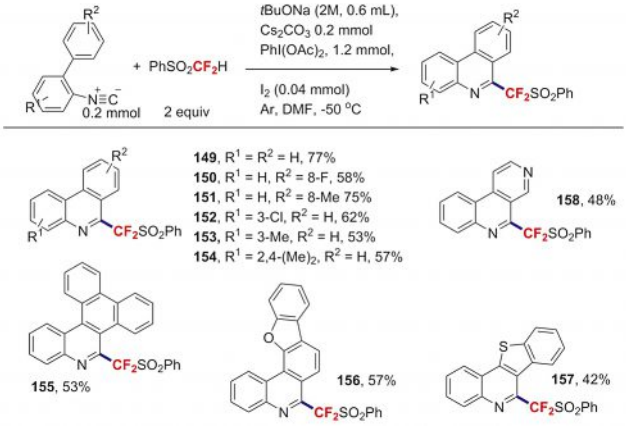
Liu and collaborators[22] have introduced a photocatalytic process for the difluoromethylphosphonylation of isocyanides towards the synthesis of 6-difluoromethylphosphonated phenanthridines.[83] The protocol employs $BrCF_2P(O)(OEt)_2$ as difluoromethylating reagent (2 equiv), KOAc (1.2 equiv) as base, photocatalyst *fac*-$[Ir(ppy)_3]$ (1 mol%), a 3 W blue LED lamp, in toluene as solvent. Essentially, the reaction is similar to that presented by Hu and collaborators[75] for the CF_2H incorporation into isocyanides[17] towards the synthesis of 6-CF_2H substituted phenanthridines except that the difluoromethylating reagent is **84**, and the photocatalyst in the Hu's paper is $[Ru(bpy)_3]Cl_2.6H_2O$.

Hu and collaborators[84] have also accomplished a thermal synthesis of difluoromethylated phenanthridine derivatives through the use of $PhSO_2CF_2H$ reagent. The reaction involves $PhSO_2CF_2H$ as the CF_2 source, $PhI(OAc)_2$ as oxidant, *t*BuOK/DMF, Cs_2CO_3 as base, and I_2 in DMF as solvent at $-50\,^{\circ}C$ (Scheme 26).

The substrate scope is varied in the sense that diverse functional groups can be tolerated on the biphenyl-2-isocyanide moiety, such as X groups, alkyl groups, etc. 4-(2-isocyanophenyl)pyridine affords product **158** in 48% yield. 9-(2-isocyanophenyl)phenanthrene, affords product **155** in 53% yield. 4-(2-isocyanophenyl)dibenzo[*b*,*d*]furan affords product **156** in 57%



Scheme 25. Synthesis of 6-CF_2H-substituted phenanthridines.

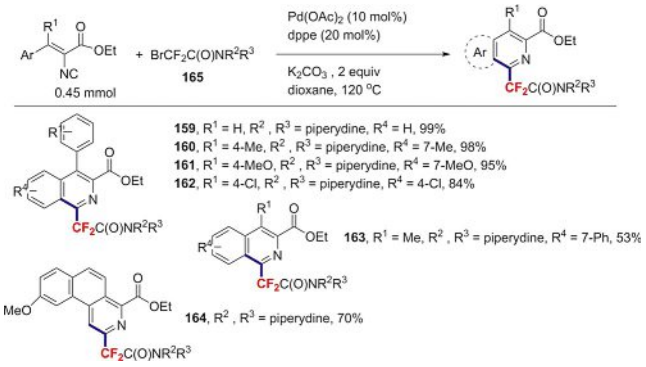


Scheme 26. Scope of the synthesis of difluoromethylated phenanthridines.

yield, and 2-(2-isocyanophenyl)benzo[*b*]thiophene affords product **157** in 42% yield. Removal of the ester moiety is achieved to provide access to CF_2H-substituted compounds according to reported protocols.[40,41]

The authors propose a reaction mechanism that is similar to that shown in Scheme 15,[85] except that the addition of radical $PhSO_2CF_2$ adds to the isocyanide in a fashion analogous to that presented in Scheme 23, proposed by Hu and colleagues.[86]

Liu and co-workers[87] presented in 2017 a difluoromethylation reaction towards the synthesis of difluoroalkylated isoquinolines via palladium-catalyzed radical cascade/cyclization of vinyl isocyanides with bromodifluoroacetic acid derivatives. The reaction[87] entails the use of $Pd(OAc)_2$ as catalyst, 1,2-bis(diphenylphosphino)ethane (dppe) as ligand, K_2CO_3 as base, in 1,4-dioxane as solvent. The scope of the transformation is illustrated in Scheme 27.



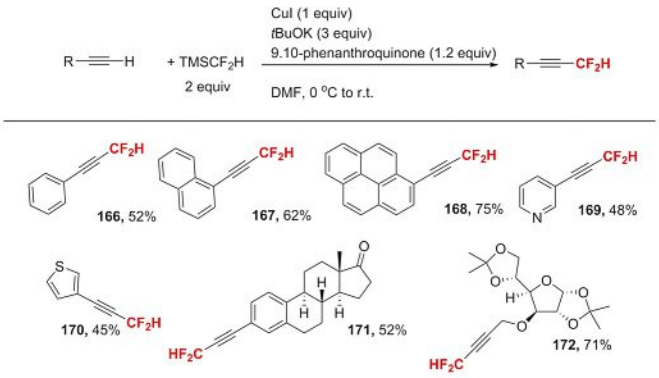
Scheme 27. Scope of difluoroalkylated isoquinolines via palladium-catalyzed radical cascade/cyclization of vinyl isocyanides.

The reaction has a broad substrate scope regarding vinyl isocyanides. 2-bromo-2,2-difluoro-1-(piperidin-1-yl)ethanone **165** reacts well with vinyl isocyanides, which are derived from diaryl ketones, alkyl aryl ketones, or aryl aldehydes and give the corresponding 1-difluoroalkyl-substituted isoquinolines (**159**–**162**) in good yields.

The authors[87] proceeded to studying the reaction mechanism. When TEMPO is added under standard reaction conditions, the desired transformation is completely inhibited and a 99% yield of an adduct between TEMPO and radical $CF_2C(O)NR^2R^3$ is found. The reaction mechanism is essentially similar to that shown by Jian and colleagues[19] for the synthesis of difluoromethylated dihydrofurans and indolines (Scheme 19, vide supra). In the present case,[87] the CF_2CO_2Et radical produced through Pd^0 reduction, adds to the isocyanide to generate an imidoyl radical that effects homolytic aromatic cyclization as in Scheme 20.

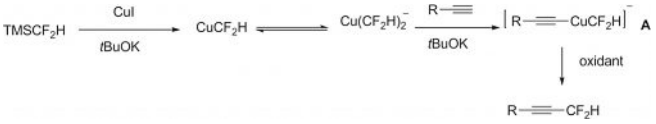
Difluoromethylation of C–C triple bonds[10]

Qing and colleagues[21b] have developed a difluoromethylation reaction of terminal alkynes employing $TMSCF_2H$ as difluoromethylating species, CuI-9.10-phenanthroquinone as ligand, *t*BuOK as oxidant, in DMF as solvent. The scope of the transformation is depicted in Scheme 28.



Scheme 28. Scope of the difluoromethylation of terminal alkynes with $TMSCF_2H$.

The difluoromethylation of phenylacetylene, 1-naphthylacetylene, 1-ethynylpyrene, and 3-ethynylpyridine afford products **166**–**169** in 52, 62, 75, and 48% yields, respectively. The difluoromethylation of 3-ethynylthiophene afford product **170** in 45% yield. This direct difluoromethylation protocol could also be applied for complex molecules, such as estrone and glucofuranose derivatives, affording the corresponding difluoromethylated alkynes **171** and **172** isolated in moderate to good yields. These results showed that this protocol can be applicable to "late-stage difluoromethylation" of medicinally relevant compounds. The authors propose the following reaction mechanism, illustrated in Scheme 29.

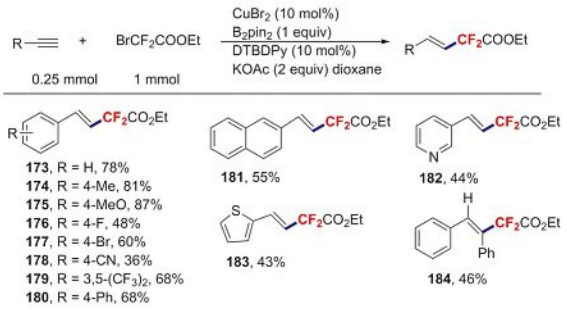


Scheme 29. Proposed reaction mechanism for difluoromethylation of terminal alkynes.

The generation of both $CuCF_2H$ ($\delta = -110.8$ ppm, d, $J = 45.3$ Hz) and $Cu(CF_2H)_2^-$ ($\delta = -116.9$ ppm, d, $J = 44.2$ Hz) is observed by ^{19}F NMR spectroscopy. After the alkyne is added, a new fluorine-containing intermediate is formed ($\delta = -115.9$ ppm, d, $J = 42.7$ Hz). Finally, the desired difluoromethylated product is detected after addition of oxidant. The difluoromethyl-copper species are firstly generated and then reacted with alkyne to give intermediate **A**. Subsequently, intermediate **A** is oxidized to high-valent copper complexes, which finally undergoes a reductive elimination to afford product.[21b]

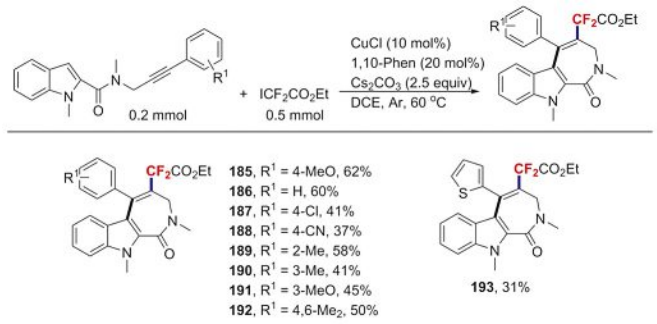
Song and collaborators[89] have come up with a difluoromethylation reaction of alkynes using $BrCF_2CO_2Et$, $CuBr_2$, bis(pinacolato)diboron (Bin_2pin_2) as additive, 4,4′-di-*tert*-butyl-2,2′-dipyridyl (DTBDPy) as ligand, KOAc as base in 1,4-dioxane as solvent. The scope of the reaction is depicted in Scheme 30.

Liang and co-workers have[90] have reported a Cu-catalyzed difluoromethylation of propargylamides-substituted indoles towards the synthesis of mono- and bis-difluoromethylated indo-



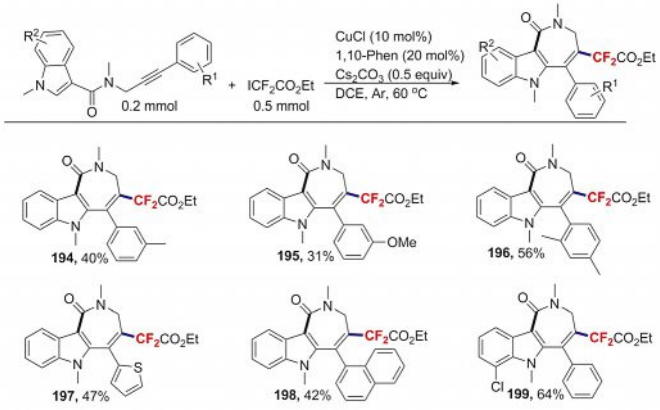
Scheme 30. Scope of the difluoromethylation reaction employing $BrCF_2CO_2Et$.

loazepinone derivatives. The reaction involves 3-propargylamide-substituted indole or 2-propargylamide-substituted indole, ICF_2CO_2Et as the difluoromethylating agent, CuCl, 1.10-phennanthroline as ligand, Cs_2CO_3 as base in dry DCE at 60 °C. The scope of the transformation is illustrated in Scheme 31 for



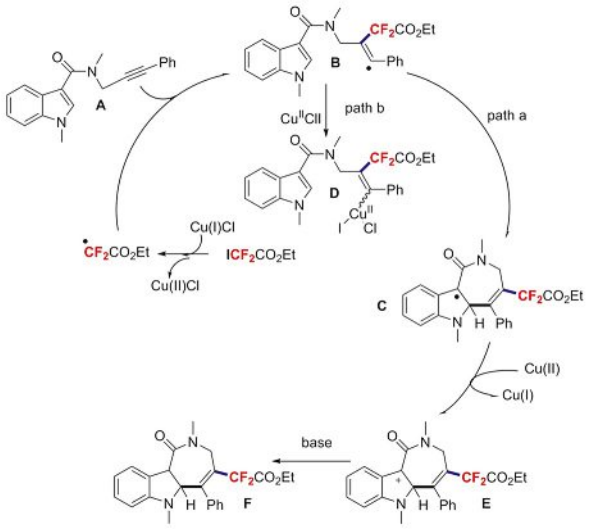
Scheme 31. Scope of difluoromethylation of propargylamides substituted indoles.

2-propargylamide-substituted indole substrates. As for 3-propargylamides-substituted indoles, the scope of the transformation is illustrated in Scheme 32. It can be observed from Schemes 31 and 32 that cyclized products are obtained in reasonable good yields.



Scheme 32. Scope of difluoromethylation of propargylamides-substituted indoles.

Through a series of experiments,[90] it was noticed that the reaction is inhibited by the presence of radical scavengers, purporting that the mechanism involves participation of radical species. The authors[90] propose a mechanism for the above reaction, as shown in Scheme 33. The CF_2CO_2Et radical is gener-



Scheme 33. Proposed reaction mechanism for the Cu^{I} catalyzed difluoromethylation.

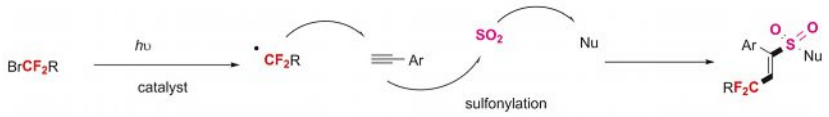
ated from ICF_2CO_2Et in the presence of CuCl. The difluoromethyl radical then adds to the alkyne moiety of **A** to form vinyl radical intermediate **B**. Intermediate **B** then undergoes intramolecular cyclization to form a new intermediate **C** (path a). Besides, a side product **D** is also obtained from **B** via a reductive elimination process (path b). Through an ET pathway, intermediate **E** is generated from intermediate **C**, which undergoes deprotonation to give the end product **F**.

The photocatalyzed addition of CF_2Y radicals to triple bonds followed by ulterior cyclization has also been studied. Liang and colleagues have recently reported on the difluoroalkylation-cyclization cascade of 1,8-enynes with $BrCF_2CO_2Et$.[90b] On the other hand, Rastogi and colleagues have proposed an intramolecular photocatalyzed difluoromethylation-cyclization of 1,3-diarylpropynones towards the synthesis of difluoromethylated indenones.[90c]

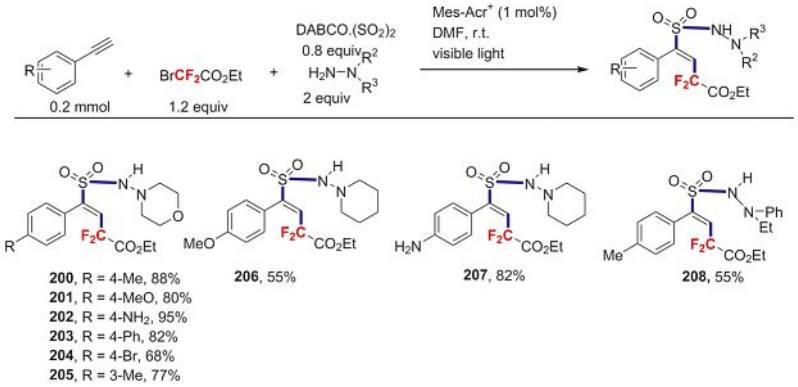
Wu and collaborators[91] introduced in 2017 a photocatalytic difluoromethylation four-component multistep reaction with excellent atom economy. The reaction involves a vicinal difluoroalkylation and aminosulfonylation of alkynes. The tandem radical process is depicted in Scheme 34.

The sulfonylation is carried out with $DABCO(SO_2)_2$ (DABCO = 1,4-diazabicyclo[2.2.2]octane) reagent. This bench-stable sulfur dioxide surrogate could be further applied in a radical reaction of aryldiazonium salts with aryl propiolates, leading to formation of 3-sulfonated coumarins.[92] The scope of the transformation is illustrated in Scheme 35.

Aryl alkynes with substitution groups at a *4*-position afford products in good-to-excellent substitution yields (products **200**–**204**) when a morpholine base is employed. When *N*-pi-



Scheme 34. Proposed radical tandem process for the vicinal difluoroalkylation and aminosulfonylation of alkynes.



Scheme 35. Scope of the photocatalytic difluoromethylation-four-component multistep reaction.

peridine hydrazine is used instead of morpholine hydrazine, good yields are also obtained from the tandem four-component reaction (products **206**, **207**).

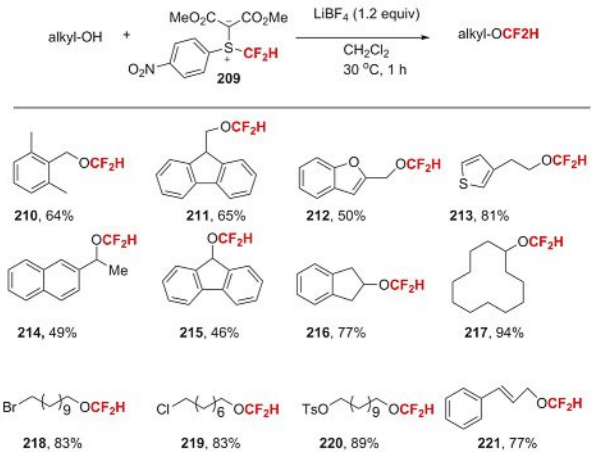
The authors[91] studied the mechanism of this multicomponent reaction of alkynes, and $DABCO(SO_2)_2$ with hydrazines, adding TEMPO. As expected, the reaction is terminated in the presence of 2.0 equiv of TEMPO. The authors propose that $DABCO(SO_2)_2$ combines with $BrCF_2CO_2Et$ to generate a halogen-bonding (XB) adduct[33] that is reduced by excited Mes-Acr^+ to give a CF_2CO_2Et radical in the presence of visible light. The ulterior reaction sequence is that shown in Scheme 34.

Difluoromethylation of OH functionality

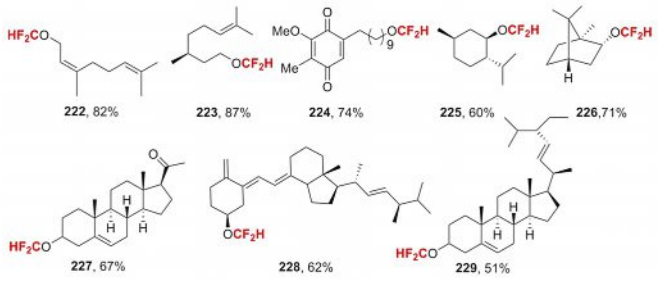
Among the many fluorinated groups, fluoroalkoxy groups such as OCF_3, OCF_2H, OCH_2F, and OCH_2CF_3 are increasingly being used in an array of applications.[93] In particular, the difluoromethoxy group (OCF_2H) is of great interest; being the bulkier analogue of OCF_3, OCF_2H is as well a strong electron-withdrawing group which could decrease the electron density of the potential drug and is also capable of hydrogen donation, which could improve the binding selectivity of a molecule.[94] The difluoromethylation of phenols has been accomplished employing 2-chloro-2,2-difluoroacetophenone,[95a] $[PPh_3{}^+CF_2CO_2]^-$,[95b] or HCF_2OTf[95c] as difluoromethylating reagents.

Zhu and colleagues[96] have more recently accomplished a difluoromethylation of 2′-hydroxychalcones for the divergent synthesis of 2′-difluoromethoxychalcones and 2,2-difluoro-3-styryl-2,3-dihydrobenzofuran-3-ols. Shen and co-workers[97] have come up with a difluoromethylating reagent for alcohols to render difluoromethyl alkyl ethers in excellent yields. The reagent used is difluoromethyl-(4-nitrophenyl)-bis(carbomethoxy)methylide sulfonium ylide **209**, which in the presence of a Lewis acid $LiBF_4$, in CH_2Cl_2 as solvent at 30 °C affords good yields of difluoromethyl ethers from alkyl alcohols.

The authors[97] explored the applicability of reagent **209** towards a series of alcohols, as shown in Scheme 36. Thus, a series of primary and secondary alcohols affords good yields of difluoromethyl ethers **210**–**213** and **214**–**217**, respectively. Noticeably, alcohols bearing functional groups such as Cl, Br, or TsO, which are sensitive to basic conditions that are commonly used to generate the difluorocarbene,[95] could be efficiently converted into the corresponding difluoromethyl ethers in high yields (products **218**–**220**), according to Scheme 36. Furthermore, alcohols containing an alkene group reacted efficiently with **209** to give difluoromethylethers in good yields (product 110, 77% yield). The authors[97] further explored the scope of the transformation through the application of the



Scheme 36. Difluoromethylation of primary, secondary and functionalized alcohols with reagent **209**.



Scheme 37. Difluoromethylated ethers of biological relevant substrates.

protocol on natural products and products with biological activity, as shown in Scheme 37.

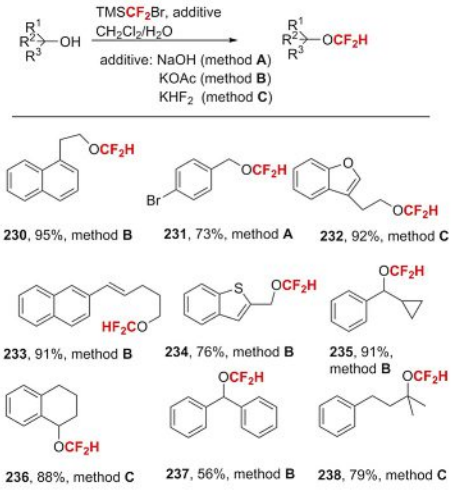
Biologically active molecules such as nerol, affords product **222** in 82% yield. (−)-Citronellol, idebenone (a drug used for treatment of Alzheimer's disease[86]), and L-mentol, afford products **223**–**225**, in 87, 64, and 60% yields, respectively. (−)-Borneol affords product **226** in 71% yield. Pregnenolone, vitamin D3, and stigmasterol, afford products **227**–**229**, in 67, 62, and 51% yields, respectively.

Notably, the synthesis of difluoromethylated derivative of idebenone (**224**), can be scaled up to 10 mmol scale affording a 74% yield of **224**. These results demonstrate the utility of the Lewis acid-mediated difluoromethylation of alcohols to access compounds that are not easily obtained by other common methods.

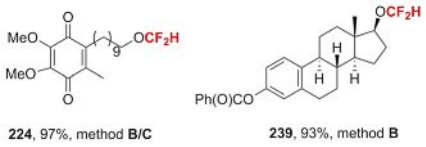
Hu and collaborators[98] have reported in 2017 a convenient difluoromethylation reaction of alcohols employing $TMSCF_2Br$, KHF_2 as additive (or NaOH, or KAOc), in CH_2Cl_2/H_2O as solvent, at room temperature. The reaction mainly proceeds through direct interaction between a neutral alcohol and difluorocarbene, which is different from the difluoromethylation of phenols. Moreover, alcohols containing other moieties that are also reactive toward difluorocarbene can be transformed divergently by using $TMSCF_2Br$. The protocol can be applied to primary, secondary and even tertiary alcohols. The applications of this transformation are illustrated in Scheme 38.

The difluoromethylation of primary alcohols affords products **230**–**234** in very good yields (73–95%). Secondary alcohols afford products **235**, **236**, and **237** in 91, 88, and 56% yields, respectively. Tertiary alcohols, for instance, afford product **238** in 79% yield (Scheme 38).

The authors[98] have also accomplished the difluoromethylation reaction of bioactive compounds, such as idebenone and estradiol benzoate, affording products **224**, and **239**, in 97 and 93% yields, respectively (Scheme 39). The yields of difluoromethylated ethers obtained from alcohols are comparable or even better than those reported by Shen and colleagues,[97] from Scheme 36 and Scheme 37. For instance, in the case of idebenone, Hu and co-workers[98] have obtained an almost quantitative yield of product **224** (cf. Schemes 37 and Scheme 39). Another difference found in the methodology of Hu and co-workers[98] is that the protocol can be applied to tertiary alcohols and substrates with olefinic moieties (i.e., product **233**).

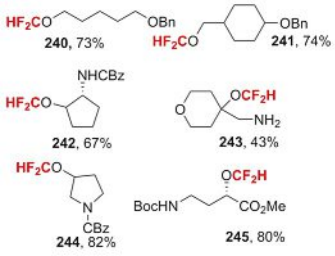


Scheme 38. Scope of the difluoromethylation reaction of alcohols with commercially available $TMSCF_2Br$.



Scheme 39. Difluoromethylation of idebenone and estradiol benzoate with commercially available $TMSCF_2Br$.

Iaroshenko and Mykhailiuk[99] have recently reported a CuI-mediated difluoromethylation reaction of aliphatic alcohols. The protocol involves the use of $FSO_2CF_2CO_2H$ (1.5 equiv), as difluoromethylating species, catalyst CuI (0.2 equiv) in MeCN as solvent at 50 °C. Some of these examples are illustrated in Scheme 40.



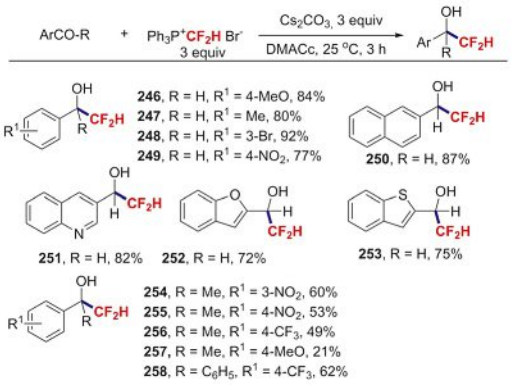
Scheme 40. Difluoromethylation of aliphatic alcohols.

Difluoromethylation of carbonyl compounds

Direct difluoromethylation of carbonyl compounds[20] remains a significant challenge. $PhMe_2SiCF_2H$,[100] $TMSCF_2H$,[101,102] $PPh_3{}^+CF_2HBr^-$,[85] $PhSONRCF_2H$,[103] and Me_3SiCF_2Br[85b,104] have been reported to be nucleophilic difluoromethylation reagents in the presence of a suitable Lewis base. However, the scope of these reagents has been limited by the use of harsh reaction conditions or the high volatility of $TMSCF_2H$. Furthermore, $PhMe_2SiCF_2H$ is a poor nucleophile for the conversion of ketones, and strongly basic conditions and low reaction tempera-

tures are usually required for nucleophilic addition of R_3SiCF_2H to ketones. Difluoromethylation of aromatic aldehydes has been accomplished using reagent $PPh_3^+CF_2CO_2^-$ in the presence of TMSCl/ KF or more recently employing $Zn(CF_2SO_2Ph)_2$ or $Cd(CF_2SO_2Ph)_2$.[105,12]

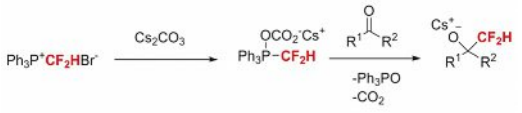
Xiao and co-workers[104] have recently performed the nucleophilic difluoromethylation of aromatic compounds towards the synthesis of difluoromethylated alcohols, employing $Ph_3P^+CF_2HBr^-$ (DFPB) as difluoromethylating species, in the presence of Cs_2CO_3 as base, in dimethylacetamide (DMAc), as solvent at room temperature. The applicability of the transformation is depicted in Scheme 41.



Scheme 41. Difluoromethylation of aromatic carbonyl compounds employing $Ph_3P^+CF_2HBr^-$.

Aromatic aldehydes with either electron donating or electron withdrawing groups react with $Ph_3P^+CF_2HBr^-$ to afford good product yields (products **246**–**249**). 2-Naphthaldehyde reacts under the same reaction conditions to afford product **250** in 87% yield. Quinoline-3-carbaldehyde, benzofuran-2-carbaldehyde, and benzothiophene-2-carbaldehyde afford products **251**–**253** in 82, 72, and 75% yields, respectively. Aryl methyl ketones with electron-withdrawing groups on the aryl moiety, afford good yields of difluoromethylated alcohols (products **254**–**256**). However, aryl rings with electron-rich substituents, afford lower yields of difluoromethylated alcohols (i.e., product **257**), probably through deactivation of the carbonyl group through resonance effect.

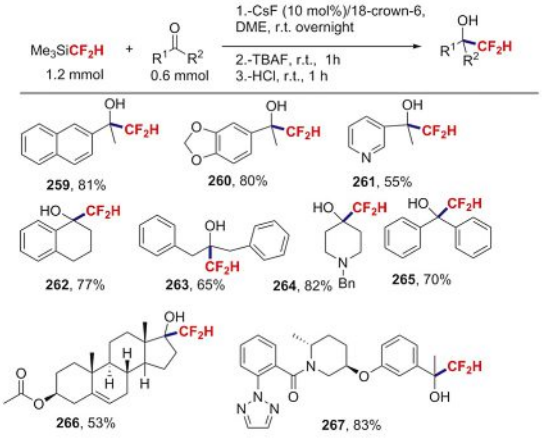
It is noteworthy that the Wittig difluoroolefination is almost completely suppressed in all of these reactions. The reaction cannot be accomplished when aliphatic carbonyl compounds[20] are used as substrates. The authors[104] explored the reaction mechanism through a series of mechanistic probes, such as TEMPO and 1,4-dintrobenzene, and observed that product yields are not varied significantly when these radical scavengers are used. Therefore, the authors excluded an ET pathway. They[104] propose that the reaction may proceed through direct transfer of the "CF_2H" group (Scheme 42). On the basis of the strong affinity between phosphorus and oxygen and previous observations that Cs_2CO_3 can attack at the positive phosphorus in tetra-arylphosphonium salts to produce nucleophilic aryl species,[106] it is suggested that direct



Scheme 42. Proposed reaction mechanism for the difluoromethylation of aromatic carbonyl compounds.

attack of the carbonate anion at the positive phosphonium to give the five-coordinate phosphorus species **D** may be possible.[107] The subsequent decarboxylation of intermediate **D** would result in the formation of Ph_3PO and cleavage of the nucleophilic CF_2H group. The nucleophilic attack at the carbonyl carbon would afford intermediate **E**, which upon protonation furnishes the final product. Apparently, Cs_2CO_3 acts as a nucleophile instead of a base in this transformation.

Hu and collaborators[108a] have come up with a nucleophilic difluoromethylation reaction of enolizable ketones with $TMSCF_2H$ by using a combination of CsF and 18-crown-6 as initiation system. Mechanistic investigations demonstrate that $[(18\text{-crown-6})Cs]^+[Me_3Si(CF_2H)_2]^-$ is a key intermediate in this catalytic reaction. The scope of the transformation is depicted in Scheme 43.



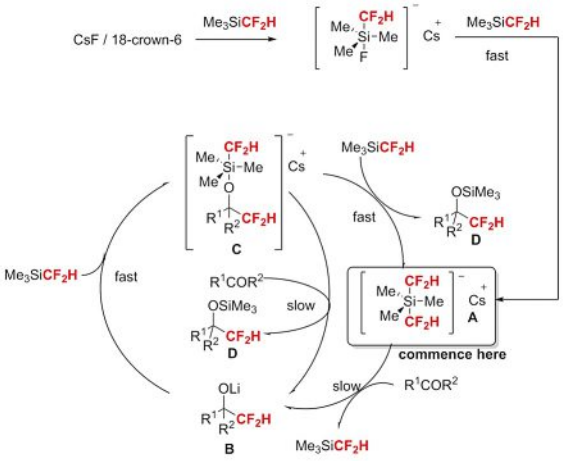
Scheme 43. Scope of the difluoromethylation reaction of enolizable carbonyl compounds with $TMSCF_2H$.

Reaction of 1-(naphthalen-2-yl)ethanone, 1-(benzo[*d*][1,3]dioxol-5-yl)ethanone, and 1-(pyridin-3-yl)ethanone afford products **259**–**261** in 81, 80, and 55% yields, respectively (Scheme 43). 3,4-Dihydronaphthalen-1(*2H*)-one, 1,3-diphenylpropan-2-one, and 1-benzylpiperidin-4-one afford products **262**–**264** in 77, 85, and 62% yields, respectively. Benzophenone affords product **265** in 70% yield.

The authors[108a] also applied the protocol to biologically active compounds, for instance, difluoromethylation of a stigmasterol acetate derivative, which affords product **266** in 53% yield. Compound **267** (Scheme 43) has found applications as a potential antagonist of the orexin receptor.[108b] It was previously prepared using a two-step method: nucleophilic (phosphoryl) difluoromethylation of the corresponding ketone followed

by removal of the phosphonate group.[109] Using the present methodology,[108a] product **267** is obtained in 83% yield.

The presence of the complex $[(18\text{-crown-6})Cs]^+[Me_3Si(CF_2H)_2]^-$ as key intermediate was confirmed by a series of variable temperature VT ^{19}F NMR experiments.[109] The authors[109] therefore postulate a mechanism involving complex $[(18\text{-crown-6})Cs]^+[Me_3Si(CF_2H)_2]^-$ as key intermediate, as proposed in Scheme 44.



Scheme 44. Proposed reaction mechanism for the difluoromethylation of carbonyl compounds.

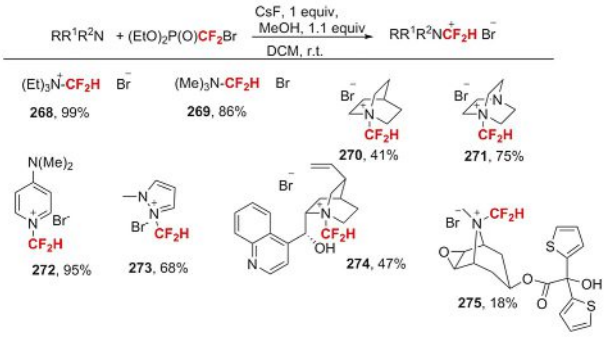
The process commences with initial generation of $[Me_3Si(CF_2H)_2]^-$ from a catalytic amount CsF/18-crown-6 and Me_3SiCF_2H. The complexation of 18-crown-6 with Cs^+ inhibits formation of the strongly basic, free difluoromethanide anion CF_2H^-, thus stabilizing $[Me_3Si(CF_2H)_2]^-$ and favoring carbonyl addition rather than enolization. The following step between **A** and a carbonyl substrate leads to formation of alcoxyde **B**, which further attacks the silicon atom of Me_3SiCF_2H to produce a new pentacoordinate silicon species **C**. This step is followed by transfer of a CF_2H^- anion to Me_3SiCF_2H to release the target product and to regenerate **A**.

Another recent nucleophilic difluoromethylation of carbonyl compounds is that reported by Zhou and colleagues,[110] who employ $P(O)(OEt_2)_2CF_2TMS$ as difluoromethylating species.

Difluoromethylation of tertiary amines[111]

Zafrani, Gershonov and colleagues[112] have recently reported a transition metal-fee difluoromethylation strategy of functionalized tertiary amines. The reaction employs $(OEt)_2P(O)CF_2Br$ as difluoromethylating reagent, CsF, MeOH as H source, in DCM as solvent. The scope of the transformation is illustrated in Scheme 45.

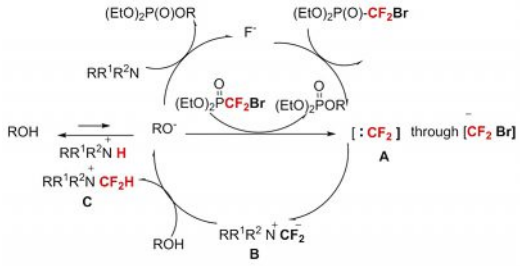
It is observed that alkyl-substituted tertiary amines such as triethyl and trimethyl amines, render products **268** and **269** in 99 and 86% yields, respectively. Quinuclidine and 1,4-diazabicyclo[2.2.2]octane, render products **270** and **271** in 41 and 75% yields, respectively. 4-*N*,*N*′-dimethylamino-pyridine, and 1-methylimidazoline afford products **272** and **273** in 95 and 68%



Scheme 45. Scope of the difluoromethylation of tertiary amines.

yields, respectively. Cinchonidine ((*R*)-quinolin-4-yl((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methanol) affords product **274** in 47% yield. This latter is a notable example of both chemoselectivity and the mildness of the difluoromethylation procedure within a multifunctional compound such as cinchonidine.

The product **275** revealed again that difluoromethylation took place exclusively on the nitrogen atom even with a multifunctional amine containing thiophene, hydroxyl, ester, and epoxide groups are present. The authors[112] propose a reaction mechanism such as that shown in Scheme 46.



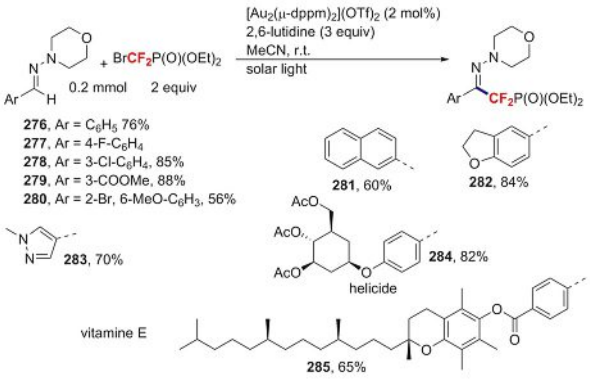
Scheme 46. Proposed reaction mechanism for difluoromethylation of tertiary amines.

The catalytic cycle, starting with P–C bond cleavage, can be initiated by either F^- from a source such as CsF or R_3N/ MeOH, which directly attacks the phosphonate to obtain difluorocarbene intermediate **A**. The nucleophilic attack of the amine free base on difluorocarbene **A** followed by protonation at the CF_2 carbanion ensues (**B**–**C**), generating an alkoxide, which can induce cleavage of the phosphonate.[112]

Difluoromethylation of hydrazones and diazonium salts

Hashmi and colleagues[113] have recently accomplished a gold-catalyzed highly selective photoredox difluoromethylation of hydrazones. The reaction involves the use of $BrCF_2PO(OEt)_2$ as CF_2 source, $[Au_2(\mu\text{-dppm})_2](OT_f)_2$ as catalyst, 2,6-lutidine as base in MeCN as solvent, at room temperature. The irradiation source is solar light (or UV-A light). The scope of the transformation is depicted in Scheme 47.

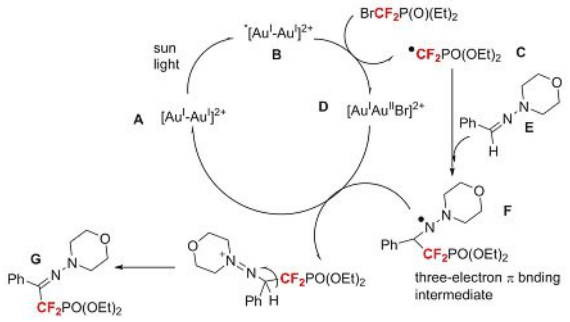
The C=N double bonds of the products could be selectively reduced with BH_3-THF under very mild reaction conditions,



Scheme 47. Scope of the gold-catalyzed difluoromethylation of hydrazones.

leading to *gem*-difluoromethylated β-amino phosphonic acids and β-amino acid derivatives. Furthermore, difluoromethylated hydrazones can be hydrolyzed to the corresponding difluoromethyl ketones by simple acid treatment. Direct heating of the difluoromethylated products in methanol at 70 °C enabled substitution of two C–F bonds by methanol, producing dimethoxy ketal. The addition of radical trapping reagents (TEMPO) or an ET scavenger (1,4-dinitrobenzene) significantly inhibits this transformation, indicating that a ET radical process is operating.

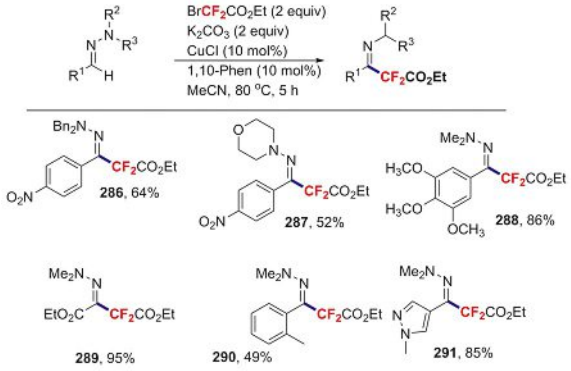
The authors[113] postulate a plausible mechanism, as shown in Scheme 48. First, irradiation of $[Au_2(\mu\text{-dppm})_2](OT_f)_2$ **A** generates a high energy, long-lived photoexcited state, $^*[Au_2(\mu\text{-dppm})_2]^{2+}$ **B**, which is a strong one-electron donor ($E^0_{([Au2]^{3+}/^*[Au2]^{2+})} = -1.5$–$1.7$ V).[114] Next, an ET from gold species **B** to



Scheme 48. Au-photocatalyzed difluoroalkylation of hydrazones.

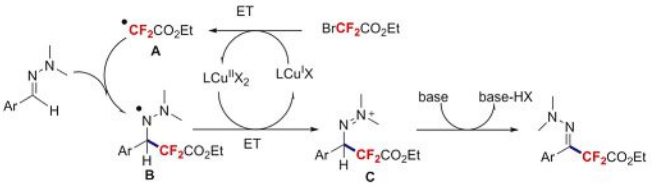
$BrCF_2P(O)(OEt)_2$ delivers $CF_2P(O)(OEt)_2$ radical **C** and Au intermediate **D**. The electrophilic radical **C** then attacks hydrazone **E** to produce the three-electron π-bonding aminyl radical intermediate **F**. Owing to the lone pair on the adjacent nitrogen atom, **F** is much more stable than other aminyl radicals produced from imines and oximes.[115] Finally, oxidation of aminyl radical **F** by gold species **D** followed by deprotonation affords the desired difluoromethylated product G. The authors[113] also showed by DFT calculations that products with the C=N bond in *E* configuration are lower in energy than those with *Z* configuration, and that isomerization activation energy usually amounts to more than 20 kcal mol^{-1}. The Au photocatalyst favors formation of the thermodynamic *E*-configured product.

Boyssi, Monteiro and collaborators[116] have recently reported on the C–H difluoroalkylation of aldehyde hydrazones with $BrCF_2CO_2Et$ under Cu catalysis. The protocol employs CuCl, 1,10-phenanthroline as ligand, K_2CO_3 as base in MeCN as solvent at 80 °C. The scope of the transformation is depicted in Scheme 49.



Scheme 49. Scope of the difluoromethylation reaction of aldehyde hydrazones.

Hydrazones derived from 4-nitrobenzaldehyde afford products **286** and **287** in 64 and 52% yields, respectively. The hydrazone of 3,4,5-trimethoxybenzaldehyde affords product **288** in 86% yield. 4-Carbaldehyde-*N*-methylimidazoline hydrazone affords product **291** in 85% yield. The proposed reaction mechanism is depicted in Scheme 50.

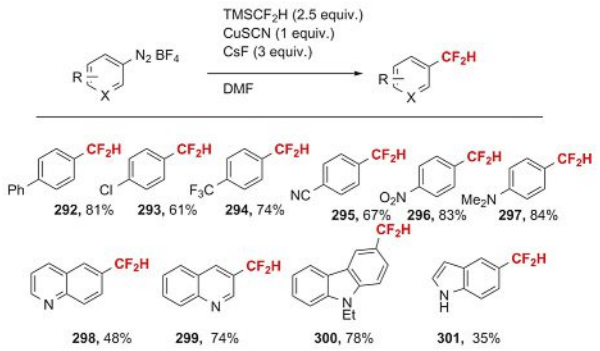


Scheme 50. Proposed mechanism for the difluoromethylation of hydrazones derived from aldehydes.

The mechanism involves formation of an electrophilic fluoroalkyl radical **A** from $BrCF_2CO_2Et$ via bromide abstraction by the Cu^I complex with concomitant generation of Cu^{II}. The radical **A** would then be trapped by the hydrazone to generate a difluoroalkylated aminyl radical intermediate **B**. Oxidation of this intermediate with Cu^{II} would lead to cationic species **C**, which would then undergo proton abstraction, thereby restoring the hydrazone functional group and recycling copper(I). Such Cu^I/Cu^{II} redox mechanism contrasts with radical-free Cu^I/Cu^{III} catalytic cycles previously proposed for the difluoroalkylation of electron-rich alkenes and arenes proceeding via difluoroalkylcopper intermediates.[117]

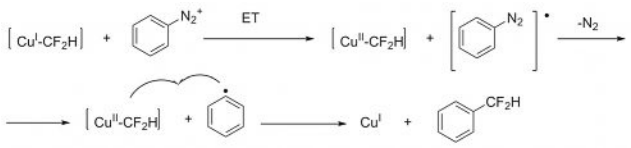
Goossen and collaborators[118a,b] accomplished in 2014 a difluoromethylation of (hetero)arenediazonium salts.[118c] The au-

thors[118a] employed $TMSCF_2H$ as source of difluoromethyl group, CuSCN, CsF in DMF as solvent. The scope of the transformation is illustrated in Scheme 51.



Scheme 51. Difluoromethylation of (hetero)arenediazonium salts.

Both (hetero)arenediazonium compounds with electron-donating and -withdrawing groups afford good yields of difluoromethylated products. Quinolone, carbazole and indole diazonium salts afford good yields of the, respectively difluoromethylated products. When 4-methoxyaniline was diazotized in situ with *tert*-butyl nitrite and the resulting solution added to the preformed Cu-CF_2H species, the desired product was obtained in 45% yield based on the aniline, purporting that one-pot reactions are also possible. The reaction mechanism was investigated by addition of radical inhibitors and a radical trapping experiment. When radical quenchers such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or *p*-benzoquinone are present, the reaction is completely suppressed. Moreover, in the difluoromethylation of 2-(allyloxy)diazonium tetrafluoroborate, the cyclized product was obtained. These results, which confirm that the reaction proceeds through a radical mechanism, are in good agreement with related studies for other Sandmeyer-type reactions and support the mechanistic outline given in Scheme 52 below.[118]

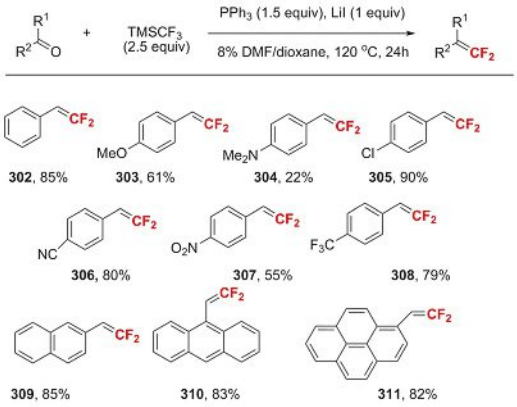


Scheme 52. Proposed Sandmeyer mechanism for difluoromethylation of aryldiazonium salts.

In another report, Lu, Cai and co-workers[39] have reported the visible-light-initiated of arene diazonium tetrafluoroborates. The reaction entails the radical addition of α-aryl-β,β-difluoroenol silyl with arene diazonium tetrafluoroborates at room temperature, which involves an innate radical long chain cycle. A variety of α-aryl-α,α-difluoroketones were formed in moderate to high yields, and can be easily further transformed into various difluoromethylarenes under basic conditions.

Synthesis of dilfuoromethylenated compounds

The synthesis of *gem*-difluoroalkenes has recently been reviewed by Cao and colleagues.[119] Here we present new examples reported in the literature. Prakash and colleagues[120] have accomplished the nucleophilic difluoromethylenation[95] of carbonyl compounds using $TMSCF_3$, PPh_3, LiI in 8% DMF/dioxane at 120 °C, 24 hrs. The applicability of the transformation is illustrated in Scheme 53.



Scheme 53. Scope of substrates for the difluoromethylenation reaction.

It can be observed from Scheme 53 that electron neutral and electron donating *para*-substituted benzaldehydes afford good yields of difluoromethylenated products (products **302**–**304**). Good to excellent yields of difluoromethylenated products can be obtained from electron-poor *para*-substituted benzaldehydes (compounds **306**–**308**). 2-Naphthaldehyde, 9-anthracene carbaldehyde and pyrene-1-carbaldehyde do also afford good yields of products (**309**–**311**). Generally, better difluoromethylenated product yields are obtained from electron-poor aromatic aldehydes than electron-rich compounds.

The authors[120] have attempted the difluoromethylenation[95] reaction of some carbonyl compounds derived from biological active compounds, such as 5α-cholestan-3-one and a polyene-containing retinal, under slightly different reaction conditions, this time employing $TMSCF_3$ (2.5 equiv), PPh_3 (3 equiv), LiI (2 equiv) in 30% DMF/toluene, at 45 °C, 40 h. Under these latter reaction conditions, the authors[120] obtained products **312** and **313** in 43 and 53% yields, respectively (Figure 6). Based on control experiments, the authors[120] propose a reaction mechanism such as that shown in Scheme 54.

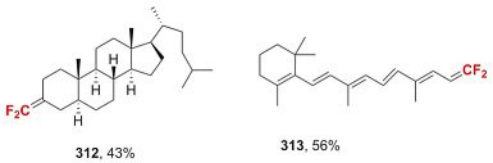
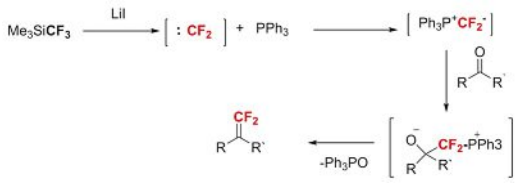
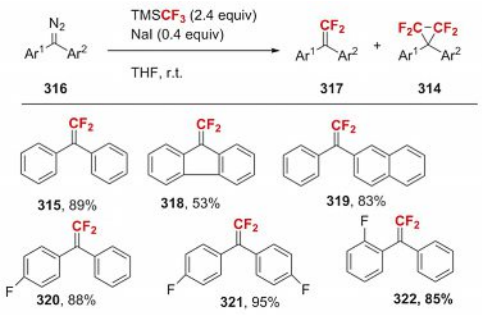


Figure 6. Difluoromethylenation reaction of some biological active compounds carbonyl.



Scheme 54. Proposed reaction mechanism for the difluoromethylenation.

Hu and co-workers[121] have accomplished the difluoromethylenation of diazo compounds with $TMSCF_3$ and $TMSCF_2Br$ through a transition-metal-free cross-coupling of two carbine precursors. The authors[121] have investigated the reaction of diaryl diazomethanes (Scheme 54). The reaction of these substrates with $TMSCF_2Br$ at high temperatures (80 °C to 110 °C) affords only moderate yields of diaryldifluoroolefins due to their low thermal stability, being the products (i.e.: diaryldifluoroolefins) more reactive towards difluorocarbene and affording tetrafluorocyclopropanation side products **314**. When $TMSCF_3$ is used instead of $TMSCF_2Br$, a control of the release of difluorocarbene by using a sub-stoichiometric amount of NaI and conducting the reaction at room temperature converts a variety of diaryl diazomethanes **316** into diaryldifluoroolefins **317** in good to excellent yields, with minimized amounts of side products **314** (Scheme 55).



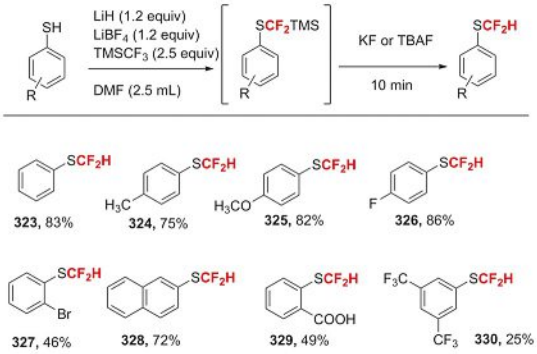
Scheme 55. Representative examples of dilfuoromethylenation of diaryldiazo compounds.

The authors[121] have also accomplished a difluoromethylenation of aziridines, obtaining the *gem*-difluoroolefination products in excellent yields. The reactions also proceed by a carbene pathways.

Difluoromethylation of SH functionality

In 2008, Hu and colleagues[122] had accomplished a phenysulfonyl difluoromethylation of sulfides with a hypervalent iodine(III)-CF_2SO_2Ph reagent. In 2009, the same leading author[123] accomplished a difluoromethylation of thiolates with *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine. In 2012, Baran and collaborators[11] have accomplished the difluoromethylation CF_2H of thiols employing $Zn(SO_2CF_2H)_2$[12] as difluoromethylating reagent. Greany and colleagues reported in 2013 a difluoromethylation of thiols using sodium dichloroacetate.[124]

Prakash and colleagues attained in 2015 a direct S-difluoromethylation of thiols using the Ruppert Prakash reagent.[125] The reaction entails the use of $TMSCF_3$ as difluoromethylating reagent, LiH and $LiBF_4$ in DMF as solvent. The scope of the transformation is illustrated in Scheme 56. The authors proposed a reaction mechanism such as that illustrated in Scheme 57.

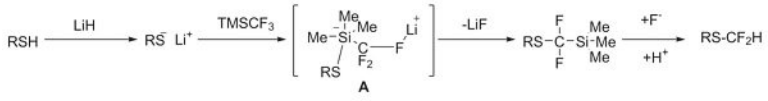


Scheme 56. Scope of the S-difluoromethylation reaction with the Ruppert–Prakash reagent.

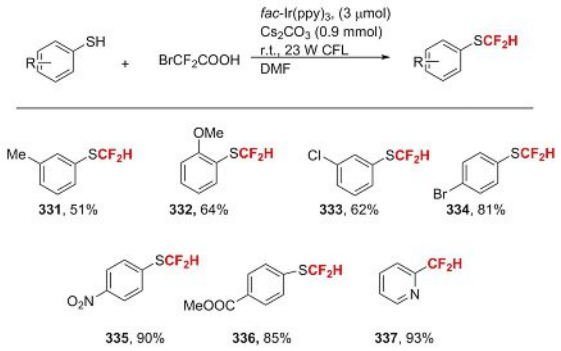
Lithium thiolate is generated in the presence of LiH, which attacks silicon to produce a pentavalent intermediate **A**; the pentavalent intermediate eliminates a fluoride with help of Lewis acidic Li^+ to give the product. Additionally, use of NaH as a base instead of LiH, led to decomposition of $TMSCF_3$ into several unidentified products along with CF_3H and TMSF, and no expected product was formed. Moreover, no tetrafluoroethylene and related products were observed under the reaction conditions, clearly ruling out the involvement of free singlet difluoromethylene.[125a] In 2016, Besset and collaborators[125b] published a review article describing the synthesis of molecules containing the SCF_2H and SCF_2FG functionality.

In 2017, Fu and colleagues[125b] accomplished the visible-light photoredox difluoromethylation of thiophenols with commercially available $BrCF_2CO_2H$. The photocatalyst used is fac-$Ir(ppy)_3$, Cs_2CO_3, in DMF under visible light irradiation. The scope of the transformation is illustrated in Scheme 58.

The difluoromethylation of thiophenols with electron-donating groups render fairly good yields of difluoromethylated products (products **331**, **332** in 51 and 64% yields, respectively). Thiophenols with electron-withdrawing groups afford excellent yields of difluoromethylated thiols, products **333**–**336**,



Scheme 57. Proposed reaction mechanism for the difluoromethylation of thiols with Ruppert–Prakash reagent.



Scheme 58. Scope of the difluoromethylation reaction of phenols.

in yields ranging from 62–90%. Pyridine-2-thiol, affords product **337** in 93% yield.

Summary and Outlook

Distinct synthetic approaches have been presented to accomplish the late-stage introduction of CF_2H/CF_2Y groups into diverse families of organic substrates: metal-mediated photocatalytic and thermal processes, and transition-metal-free difluoromethylations of organic substrates.

Further work is needed in the areas of photocatalysis, especially in transition-metal-free strategies involving organic dyes and other metal-free organic compounds aimed at producing the CF_2 radical species. This is of particular concern in the pharmaceutical industry to avoid the use of transition metals. In this particular area, photocataltytic difluoromethylation reactions of non-activated arenes are unexplored. This is probably challenging because re-aromatization of an initially formed cyclohexadienyl-type radical intermediate would involve oxidizing conditions not easily met.

Another area which deserves particular attention, in terms of difluoromethylating strategies, is the application of flow systems to achieve CF_2H substitutions in high yields and minimal reaction times. This area, that is, flow systems, has received particular attention for trifluoromethylation, perfluoroalkylation and fluorination reactions, however, no report of a difluoromethylation flow system has been presented.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: bioactive compounds · difluoromethylation reactions · photocatalysis · transition metals

[1] Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, *60*, 797–804.
[2] N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.
[3] a) W. F. Goure, K. L. Leschinsky, S. J. Wratten, J. P. Chupp, *J. Agric. Food Chem.* **1991**, *39*, 981–986; b) S. Kaneko, T. Yamazaki, T. Kitazume, *J. Org. Chem.* **1993**, *58*, 2302–2312.
[4] S. Boland, J. Alen, A. Bourin, K. Castermans, N. Boumans, L. Panitti, J. Vanormelingen, D. Leysen, O. Defert, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4594–4597.
[5] A. Koperniku, H. Liu, P. B. Hurley, *Eur. J. Org. Chem.* **2016**, 871–886.
[6] a) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, **2006**; b) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, **2004**; c) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, 2nd Ed., Wiley-VCH, Weinheim, **2013**.
[7] P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2015**, *54*, 6558–6561; *Angew. Chem.* **2015**, *127*, 6658–6661.
[8] C. S. Thomoson, L. Wang, W. R. Dolbier, *J. Fluorine Chem.* **2014**, *168*, 34–39.
[9] a) K. Aikawa, K. Maruyama, K. Honda, K. Mikami, *Org. Lett.* **2015**, *17*, 4882–4885; b) K. Aikawa, K. Maruyama, J. Nitta, R. Hashimoto, K. Mikami, *Org. Lett.* **2016**, *18*, 3354–3357.
[10] a) S. Okusu, E. Tokunaga, N. Shibata, *Org. Lett.* **2015**, *17*, 3802–3805; b) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786.
[11] Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494–1497.
[12] M. V. Ivanova, A. Bayle, T. Besset, T. Poisson, X. Pannecoucke, *Angew. Chem. Int. Ed.* **2015**, *54*, 13406–13410; *Angew. Chem.* **2015**, *127*, 13604–13608.
[13] M.-C. Belhomme, T. Poisson, X. Pannecoucke, *J. Org. Chem.* **2014**, *79*, 7205–7211.
[14] Y. Arai, R. Tomita, G. Ando, T. Koike, M. Akita, *Chem. Eur. J.* **2016**, *22*, 1262–1265.
[15] J. Rong, C. Ni, J. Hu, *Asian J. Org. Chem.* **2017**, *6*, 139–152.
[16] Y.-L. Xiao, Q.-Q. Min, C. Xu, R.-W. Wang, X. Zhang, *Angew. Chem. Int. Ed.* **2016**, *55*, 5837–5841; *Angew. Chem.* **2016**, *128*, 5931–5935.
[17] J.-W. Gu, X. Zhang, *Org. Lett.* **2015**, *17*, 5384–5387.
[18] F. Zhang, Q.-Q. Min, X. Zhang, *Synthesis* **2015**, *47*, 2912–2923.
[19] J. Liao, L. Fan, W. Guo, Z. Zhang, J. Li, C. Zhu, Y. Ren, W. Wu, H, Jiang, *Org. Lett.* **2017**, *19*, 1008–1011.
[20] W. Miao, C. Ni, Y. Zhao, J. Hu, *Org. Lett.* **2016**, *18*, 2766–2769.
[21] a) X. Li, J. Zhao, M. Hu, D. Chen, C. Ni, L. Wang, J. Hu, *Chem. Commun.* **2016**, *52*, 3657–3660; b) S.-Q. Zhu, X.-H. Xu, F.-L. Qing, *Org. Chem. Front.* **2015**, *2*, 1022–1025.
[22] S. Wang, W.-L. Jia, L. Wang, Q. Liu, *Eur. J. Org. Chem.* **2015**, 6817–6821.
[23] T. Besset, T. Poisson, X. Pannecoucke, *J. Fluorine Chem.* **2015**, *178*, 225.
[24] Z. Feng, Y.-L. Xiao, X. Zhang, *Org. Chem. Front.* **2016**, *3*, 466–469.
[25] S. Ge, W. Chaladaj, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4149–4152.
[26] K. Fujikawa, A. Kobayashi, H. Amii, *Synthesis* **2012**, *44*, 3015–3018.
[27] K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560–5563.
[28] X. Sun, S. Yu, *Org. Lett.* **2014**, *16*, 2938–2941.
[29] J. Jung, E. Kim, Y. You, E. J. Cho, *Adv. Synth. Catal.* **2014**, *356*, 2741–2748.
[30] C. Yu, N. Iqbal, S. Park, E. J. Cho, *Chem. Commun.* **2014**, *50*, 12884–12887.
[31] P. K. Mykhailiuk, S. Afonin, G. V. Palamarchuk, O. V. Shishkin, A. S. Ulrich, I. V. Komarov, *Angew. Chem. Int. Ed.* **2008**, *47*, 5765–5767; *Angew. Chem.* **2008**, *120*, 5849–5851.
[32] J. Zhu, F. Wang, W. Huang, Y. Zhao, W. Ye, J. Hu, *Synlett* **2011**, *7*, 899–902.
[33] N. Surapanich, C. Kuhaharn, M, Pohmakotr, V. Reutrakul, *Eur. J. Org. Chem.* **2012**, 5943–5952.
[34] J.-Y. Wang, Y.-M. Su, F. Yin, Y. Bao, X. Zhang, Y.-M. Xu, X.-S. Wang, *Chem. Commun.* **2014**, *50*, 4108–4111.

[35] J.-Y. Wang, X. Zhang, Y. Bao, Y.-M. Xu, X.-F. Cheng, X.-S. Wang, *Org. Biomol. Chem.* **2014**, *12*, 5582 – 5585.
[36] G. Li, Y.-X. Cao, C.-G. Luo, Y.-M. Su, Y. Li, Q. Lan, X.-S. Wang, *Org. Lett.* **2016**, *18*, 4806 – 4809.
[37] Z. He, M. Hu, T. Luo, L. Li, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11545 – 11547; *Angew. Chem.* **2012**, *124*, 11713 – 11715.
[38] V. V. Levin, A. A. Zemtsov, M. I. Struchkova, A. D. Dilman, *Org. Lett.* **2013**, *15*, 917 – 919.
[39] Y. Wu, G. Lu, B. Zhou, M. Bu, L. Wan, C. Cai, *Chem. Commun.* **2016**, *52*, 5965 – 5968.
[40] a) X. Li, S. Li, S. Sun, F. Yang, W. Zhu, Y. Zhu, Y. Wu, Y. Wu, *Adv. Synth. Catal.* **2016**, *358*, 1699 – 1704; b) M. Ke, Q. Song, *J. Org. Chem.* **2016**, *81*, 3654 – 3664.
[41] X. Zeng, X. Wei, J. J. Song, M. Sarvestani, D. R. Fandrick, B. Qu, S. Rodriguez, J. D. Sieber, J.-N. Desrosiers, N. K. Yee, F. Roschangar, C. H. Senanayake, *Asian J. Org. Chem.* **2015**, *4*, 1262 – 1264.
[42] C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao, Y.-C. Gu, *Coord. Chem. Rev.* **2014**, *261*, 28 – 72.
[43] Y. Lu, C. Liu, Q.-Y. Chen, *Curr. Org. Chem.* **2015**, *19*, 1638 – 1650.
[44] a) M. V. Ivanova, A. Bayle, T. Besset, X. Pannecoucke, T. Poisson, *Chem. Eur. J.* **2016**, *22*, 10284 – 10293; .b) D. Chang, Y. Gu, Q. Shen, *Chem. Eur. J.* **2015**, *21*, 6074 – 6078.
[45] C. Zhang, *Adv. Synth. Catal.* **2017**, *359*, 372 – 383.
[46] C. Ni, L. Zhu, J. Hu, *Acta Chim. Sinica* **2015**, *73*, 90 – 115.
[47] B. Chen, D. A. Vicic in *Transition-Metal-Catalyzed Difluoromethylation, Difluoromethylenation, and Polydifluoromethylenation Reactions, Chapter Organometallic Fluorine Chemistry, Volume 52 of the series Topics in Organometallic Chemistry*, pp. 113 – 141.
[48] J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465 – 7478.
[49] C. Ni, J. Hu, *Chem. Soc. Rev.* **2016**, *45*, 5441 – 5454.
[50] T. Koike, M. Akita, *Acc. Chem. Res.* **2016**, *49*, 1937 – 1945.
[51] a) T. Chatterjee, N. Iqbal, Y. You, E. J. Cho, *Acc. Chem. Res.* **2016**, *49*, 2284 – 2294; b) B. L. Tóth, O. Tischler, Z. Novák, *Tetrahedron Lett.* **2016**, *57*, 4505 – 4513.
[52] X. Pan, H. Xia, J. Wu, *Org. Chem. Front.* **2016**, *3*, 1163 – 1185.
[53] a) L. Xu, D. A. Vicic, *J. Am. Chem. Soc.* **2016**, *138*, 2536 – 2539; b) H. Serizawa, K. Ishii, K. Aikawa, K. Mikami, *Org. Lett.* **2016**, *18*, 3686 – 3689.
[54] P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524 – 5527.
[55] a) Y. Gu, X. Leng, Q. Shen, *Nat. Commun.* **2014**, *5*, 5405 – 5411; b) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683 – 730.
[56] K. Aikawa, H. Serizawa, K. Ishii, K. Mikami, *Org. Lett.* **2016**, *18*, 3690 – 3693.
[57] Z. Feng, Q.-Q. Min, X. Zhang, *Org. Lett.* **2016**, *18*, 44 – 47.
[58] Y.-M. Su, Y. Hou, F. Yin, Y.-M. Xu, Y. Li, Z. Zheng, X.-S. Wang, *Org. Lett.* **2014**, *16*, 2958 – 2961.
[59] Z.-Y. Li, L. Li, Q.-L. Li, K. Jing, H. Xu, G.-W. Wang, *Chem. Eur. J.* **2017**, *23*, 3285 – 3290.
[60] M. Gagliardo, D. J. M. Snelders, P. A. Chase, R. J. M. K. Gebbink, G. P. M. van Klink, G. van Koten, *Angew. Chem. Int. Ed.* **2007**, *46*, 8558 – 8573; *Angew. Chem.* **2007**, *119*, 8710 – 8726.
[61] a) Z. Ruan, S.-K. Zhang, C. Zhu, P. N. Ruth, D. Stalke, L. Ackermann, *Angew. Chem.* **2017**, *129*, 2077 – 2081; b) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011**, *133*, 19298 – 19301.
[62] M.-C. Belhomme, T. Besset, T. Poisson, X. Pannecoucke, *Chem. Eur. J.* **2015**, *21*, 12836 – 12865.
[63] J. Li, W. Wan, G. Ma, Y. Chen, Q. Hu, K. Kang, H. Jiang, J. Hao, *Eur. J. Org. Chem.* **2016**, 4916 – 4921.
[64] a) Z. Gu, H. Zhang, P. Xu, Y. Cheng, C. Zhu, *Adv. Synth. Catal.* **2015**, *357*, 3057 – 3063.
[65] Z. Zhang, X.-J. Tang, W. R. Dolbier Jr., *Org. Lett.* **2016**, *18*, 1048 – 1051.
[66] C.-Y. He, J. Kong, X. Li, X. Li, Q. Yao, F.-M. Yuan, *J. Org. Chem.* **2017**, *82*, 910 – 917.
[67] Q.-Y. Lin, X.-H. Xu, K. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2016**, *55*, 1479 – 1483; *Angew. Chem.* **2016**, *128*, 1501 – 1505.
[68] a) R. M. Flynn, R. G. Manning, R. M. Kessler, D. J. Burton, S. W. Hansen, *J. Fluorine Chem.* **1981**, *18*, 525 – 531; b) D. J. Burton, Z.-Y. Yang, W. Qiu, *Chem. Rev.* **1996**, *96*, 1641 – 1716.
[69] C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842 – 863.
[70] Y. Ran, Q.-Y. Lin, X.-H. Xu, F.-L. Qing, *J. Org. Chem.* **2016**, *81*, 7001 – 7007.
[71] Q.-Y. Lin, Y. Ran, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2016**, *18*, 2419 – 2422.
[72] Y. Li, J. Liu, L. Zhang, L. Zhu, J. Hu, *J. Org. Chem.* **2007**, *72*, 5824 – 5827.
[73] a) P. Zhang, E. A. Terefenko, A. Fensome, J. Wrobel, R. Winneker, S. Lundeen, K. B. Marschke, Z. Zhang, *J. Med. Chem.* **2002**, *45*, 4379 – 4382; b) P. D. Morse, D. A. Nicewicz, *Chem. Sci.* **2015**, *6*, 270 – 274; c) M. C. Pirrung, L. N. Tumey, A. L. McClerren, C. R. H. Raetz, *J. Am. Chem. Soc.* **2003**, *125*, 1575 – 1586; d) H. B. Bode, H. Irschik, S. C. Wenzel, H. Reichenbach, R. Muller, G. Hofle, *J. Nat. Prod.* **2003**, *66*, 1203 – 1206.
[74] W. Fu, X. Han, M. Zhu, C. Xu, Z. Wang, B. Ji, X.-Q. Hao, M.-P. Song, *Chem. Commun.* **2016**, *52*, 13413 – 13416.
[75] J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu, J. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2743 – 2747; *Angew. Chem.* **2016**, *128*, 2793 – 2797.
[76] Z. Zhang, H. Martinez, W. R. Dolbier Jr., *J. Org. Chem.* **2017**, *82*, 2589 – 2598.
[77] Z. Zhang, X. Tang, W. R. Dolbier Jr., *Org. Lett.* **2015**, *17*, 4401 – 4403.
[78] H. Egami, R. Shimizu, S. Kawamura, M. Sodeoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4000 – 4003; *Angew. Chem.* **2013**, *125*, 4092 – 4095.
[79] Y. Duan, W. Li, P. Xu, M. Zhang, Y. Cheng, C. Zhu, *Org. Chem. Front.* **2016**, *3*, 1443 – 1446.
[80] X. Wang, W. Wan, Y. Chen, J. Li, H. Jiang, Y. Wang, H. Deng, J. Hao, *Eur. J. Org. Chem.* **2016**, 3773 – 3779.
[81] D. P. Rillema, G. Allen, T. J. Meyer, D. Conrad, *Inorg. Chem.* **1983**, *22*, 1617 – 1622.
[82] a) M. Bühl, P. DaBell, D. W. Manley, R. P. McCaughan, J. C. Walton, *J. Am. Chem. Soc.* **2015**, *137*, 16153 – 16162; for the application of Cs_2CO_3 as a radical initiator, see: b) T. Xu, W. Cheung, X. Hu, *Angew. Chem. Int. Ed.* **2014**, *53*, 4910 – 4914; *Angew. Chem.* **2014**, *126*, 5010 – 5014; c) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 3990 – 3993.
[83] M. Zhu, W. Fu, G. Zou, C. Xu, Z. Wang, *J. Fluorine Chem.* **2015**, *180*, 1 – 6.
[84] P. Xiao, J. Rong, C. Ni, J. Guo, X. Li, D. Chen, J. Hu, *Org. Lett.* **2016**, *18*, 5912 – 5915.
[85] a) V. V. Levin, V. O. Smirnov, M. I. Struchkova, A. D. Dilman, *J. Org. Chem.* **2015**, *80*, 9349 – 9353; b) A. L. Trifonov, A. A. Zemtsov, V. V. Levin, M. I. Struchkova, A. D. Dilman, *Org. Lett.* **2016**, *18*, 3458 – 3461.
[86] K. Schaffler, D. Hadler, M. Stark, *Arzneim.-Forsch.* **1998**, *48*, 720.
[87] Y. Liu, K. Zhang, W. Jiang, Y. Yang, Y. Jiang, X. Liu, Y. Xie, J. Wu, J. Cai, X.-H. Xu, *Asian J. Org. Chem.* **2017**, *12*, 568 – 576.
[88] Q.-Y. Chen, Z.-Y. Yang, C.-X. Zhao, Z.-M. Qiu, *J. Chem. Soc. Perkin Trans. 1* **1988**, 563 – 567.
[89] M. Ke, Q. Feng, K. Yang, Q. Song, *Org. Chem. Front.* **2016**, *3*, 150 – 155.
[90] a) H.-L. Hua, B.-S. Zhang, Y.-T. He, Y.-F. Qiu, J.-Y. Hu, Y.-C. Yang, Y.-M. Liang, *Chem. Commun.* **2016**, *52*, 10396 – 10399; b) H. Huang, Y. Li, *J. Org. Chem.* **2017**, *82*, 4449 – 4457; c) S. B. Nagode, A. K. Chaturvedi, N. Rastogi, *Asian J. Org. Chem.* **2017**, *6*, 453 – 457.
[91] Y. Xiang, Y. Li, Y. Kuang, J. Wu, *Chem. Eur. J.* **2017**, *23*, 1032 – 1035.
[92] K. Zhou, H. Xia, J. Wu, *Org. Chem. Front.* **2016**, *3*, 865 – 869.
[93] G. Sachs, J. Shin, R. Hunt, *Current Gastroenterology Reports* **2010**, *12*, 437 – 447.
[94] J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626 – 1631.
[95] a) L. Zhang, J. Zheng, J. Hu, *J. Org. Chem.* **2006**, *71*, 9845 – 9848; b) J. Zheng, J.-H. Lin, J. Cai, J. C. Xiao, *Chem. Eur. J.* **2013**, *19*, 15261 – 15266; c) P. S. Fier, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 2092 – 2095; *Angew. Chem.* **2013**, *125*, 2146 – 2149.
[96] M.-Q. Hua, W. Wang, W.-H. Liu, T. Wang, Q. Zhang, Y. Huang, W.-H. Zhu, *J. Fluorine Chem.* **2016**, *181*, 22 – 29.
[97] J. Zhu, Y. Liu, Q. Shen, *Angew. Chem. Int. Ed.* **2016**, *55*, 9050 – 9054; *Angew. Chem.* **2016**, *128*, 9196 – 9200.
[98] Q. Xie, C. Ni, R. Zhang, L. Li, J. Rong, J. Hu, *Angew. Chem. Int. Ed.* **2017**, *56*, 3206 – 3210; *Angew. Chem.* **2017**, *129*, 3254 – 3258.
[99] K. Levchenko, O. P. Datsenko, O. Serhiichuk, A. Tolmachev, V. O. Iaroshenko, P. K. Mykhailiuk, *J. Org. Chem.* **2016**, *81*, 5803 – 5813.
[100] T. Hagiwara, T. Fuchikami, *Synlett* **1995**, *7*, 717 – 718.
[101] O. M. Michurin, D. S. Radchenko, I. V. Komarov, *Tetrahedron* **2016**, *72*, 1351 – 1356.
[102] Y. Zhao, W. Huang, J. Zheng, J. Hu, *Org. Lett.* **2011**, *13*, 5342 – 5345.
[103] X. Shen, W. Zhang, C. Ni, Y. Gu, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 16999 – 17002.
[104] Z. Deng, J.-H. Lin, J. Cai, J.-C. Xiao, *Org. Lett.* **2016**, *18*, 3206 – 3209.
[105] F. Jiang, C. Ni, J. Hu, *J. Fluorine Chem.* **2017**, *198*, 67 – 75.

[106] Z. Deng, J.-H. Lin, J.-C. Xiao, *Nat. Commun.* **2016**, *7*, 10337 – 10344.
[107] P. A. Byrne, Y. Ortin, D. G. Gilheany, *Chem. Commun.* **2015**, *51*, 1147 – 1150.
[108] a) D. Chen, C. Ni, Y. Zhao, X. Cai, X. Li, P. Xiao, *Angew. Chem. Int. Ed.* **2016**, *55*, 12632 – 12636; *Angew. Chem.* **2016**, *128*, 12822 – 12826; b) R. Spinazzi, PG. Andreis, GP. Rossi, GG. Nussdorfer, *Pharmacol. Rev.* **2006**, *58*, 46 – 57.
[109] D. Chen, C. Ni, Y. Zhao, X. Cai, X. Li, P. Xiao, J. Hu, *Synfacts* **2016**, *12*, 1256.
[110] Y.-H. Wang, Z.-Y. Cao, J. Zhou, *J. Org. Chem.* **2016**, *81*, 7807 – 7816.
[111] L. Chu, X. Zhang, F.-L. Qing, *Org. Lett.* **2009**, *11*, 2197 – 2200.
[112] Y. Zafrani, D. Amir, L. Yehezkel, M. Madmon, S. Saphier, N. Karton-Lifshin, E. Gershonov, *J. Org. Chem.* **2016**, *81*, 9180 – 9187.
[113] J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph, A. Stephen, K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 2934 – 2938; *Angew. Chem.* **2016**, *128*, 2987 – 2991.
[114] a) D. Li, C.-M. Che, H.-L. Kwong, V. W.-W. Yam, *J. Chem. Soc. Dalton Trans.* **1992**, 3325 – 3329; b) C.-M. Che, H.-L. Kwong, C.-K. Poon, V. W.-W. Yam, *J. Chem. Soc. Dalton Trans.* **1990**, 3215 – 3219.
[115] D. Hager, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 16986 – 16989.
[116] A. Prieto, R. Melot, D. Bouyssi, N. Monteiro, *ACS Catal.* **2016**, *6*, 1093 – 1096.
[117] a) G. Caillot, J. Dufour, M.-C. Belhomme, T. Poisson, L. Grimaud, X. Pannecoucke, I. Gillaizeau, *Chem. Commun.* **2014**, *50*, 5887 – 5890; b) M.-C. Belhomme, D. Dru, H.-Y. Xiong, D. Cahard, T. Besset, T. Poisson, X. Pannecoucke, *Synthesis* **2014**, *46*, 1859 – 1870; c) M.-C. Belhomme, A. Bayle, T. Poisson, X. Pannecoucke, *Eur. J. Org. Chem.* **2015**, 1719 – 1726.
[118] a) C. Matheis, J. Jouvin, L. J. Goossen, *Org.Lett.* **2014**, *16*, 5984 – 5987; b) B. Bayarmagnai, C. Matheis, K. Jouvin, L. K. Goossen, *Angew. Chem. Int. Ed.* **2015**, *54*, 5753 – 5756; *Angew. Chem.* **2015**, *127*, 5845 – 5848; c) J. Li, X.-L. Yu, J. Cossy, S.-Y. Lv, H.-L. Zhang, F. Su, L. Hai, P. K. Mykhailiuk, Y. Wu, *Eur. J. Org. Chem.* **2017**, 266 – 270.
[119] X. Zhang, S. Cao, *Tetrahedron Lett.* **2017**, *58*, 375 – 392.
[120] S. Krishnamoorthy, J. Kothandaraman, J. Saldana, G. K. Surya Prakash, *Eur. J. Org. Chem.* **2016**, 4965 – 4969.
[121] a) M. Hu, C. Ni, L. Li, Y. Han, J. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 14496 – 14501; b) S. R. Ovalles, J. H. Hansen, H. M. Davies, *Org. Lett.* **2011**, *13*, 4284 – 4287.
[122] W. Zhang, J. Zhu, J. Hu, *Tetrahedron Lett.* **2008**, *49*, 5006 – 5008.
[123] W. Zhang, F. Wang, J. Hu, *Org.Lett.* **2009**, *11*, 2109 – 2111.
[124] V. P. Mehta, M. F. Greaney, *Org. Lett.* **2013**, *15*, 5036 – 5039.
[125] a) G. K. Surya Prakash, S. Krishnamoorthy, S. Kar, G. A. Olah, *J. Fluorine Chem.* **2015**, *180*, 186 – 191; b) H.-Y. Xiong, X. Pannecoucke, T. Besset, *Chem. Eur. J.* **2016**, *22*, 16734 – 16749; c) J. Yang, M. Jiang, Y. Jin, H. yang, H. Fu, Org. Lett. 2017, https://doi.org/10.1002/acsorglett.7b01118.
[126] H. Xiang, Q. Zhao, Z. Tang, J. Xiao, P. Xia, C. Wang, C. Yang, X. Chen, H. Yang, *Org. Lett.* **2017**, *19*, 146 – 149.
[127] H. Chen, P. Li, M. Wang, L. Wang, *Org. Lett.* **2016**, *18*, 4794 – 4797.
[128] L.-C. Yu, J.-W. Gu, S. Zhang, X. Zhang, *J. Org. Chem.* **2017**, *82*, 3943 – 3949.
[129] B. Yang, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2016**, *18*, 5956 – 5959.
[130] M. Hu, B. Gao, C. Ni, L. Zhang, J. Hu, *J. Fluorine Chem.* **2013**, *155*, 52 – 58.
[131] W. Yu, X.-H. Xu, F.-L. Qing, *Org. Lett.* **2016**, *18*, 5130 – 5133.

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