Recent Advances for the Direct Introduction of the CF2Me Moiety
Elodie Carbonnel, Thomas Poisson, Philippe Jubault, Xavier Pannecoucke, Tatiana Besset

To cite this version:
Elodie Carbonnel, Thomas Poisson, Philippe Jubault, Xavier Pannecoucke, Tatiana Besset. Recent Advances for the Direct Introduction of the CF2Me Moiety. Frontiers in Chemistry, Frontiers, 2019, 7, pp.111. 10.3389/fchem.2019.00111. hal-02121212

HAL Id: hal-02121212
https://hal-normandie-univ.archives-ouvertes.fr/hal-02121212
Submitted on 16 May 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Recent Advances for the Direct Introduction of the CF$_2$Me Moiety

Elodie Carbonnel, Thomas Poisson, Philippe Jubault, Xavier Pannecoucke and Tatiana Besset

Normandie Univ, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), Rouen, France

Institut Universitaire de France, Paris, France

Organofluorine chemistry, synthetic methodology, emergent fluorinated groups, CF$_2$Me-containing reagent, C-CF$_2$Me bond formation

INTRODUCTION

The design of tools and unprecedented synthetic pathways in organofluorine chemistry is of prime importance to extend the current tool box (Landelle et al., 2013; Liang et al., 2013; Besset et al., 2014, 2016; Egami and Sodeoka, 2014; Merino and Nevado, 2014; Belhomme et al., 2015; Champagne et al., 2015; Ni and Hu, 2016; Lemos et al., 2018; Song et al., 2018). With more than 40% of agrochemicals and 25% of pharmaceuticals having at least one fluorine atom, this research field is very active and has witnessed a strong interest from academic and industry laboratories (Purser et al., 2008; Fujiwara and O’Hagan, 2014; Ilardi et al., 2014; Wang et al., 2014; Gillis et al., 2015; Ni et al., 2015; Meanwell, 2018). Taking benefit from the unique features of the fluorine atom and fluorinated groups, the biological and physical properties of a molecule might be modulated at will (O’Hagan, 2008). Therefore, it appeared as crucial to further develop efficient transformations for the introduction of fluorinated moieties onto complex molecules and to design and study new fluorine-containing moieties. Among these emergent fluorinated groups, a special attention was paid to the 1,1-difluoroethyl group. Present in various compounds of interest, the CF$_2$Me residue appears as a fluorinated bioisostere of the alkoxy ethers. Indeed, the replacement of the oxygen atom by a CF$_2$ residue makes the molecules more metabolically stable and the presence of a CF$_3$Me moiety impacts the spatial geometry (difference of conformational preference of an OMe vs. CF$_2$Me group) although keeping similar electronic and steric properties (Zhou et al., 2013). In addition, the metabolic stability of the molecules might be modulated by replacing a benzylidene methylene residue.
by a CF₂ one as it was the case for a urea transporter B (UTB) inhibitor (II), used for edema (Anderson et al., 2012). In addition, these compounds bearing this fluorinated moiety already demonstrated interesting properties, like in the case of edema and malaria treatment, for instance (Coteron et al., 2011; Anderson et al., 2012). Consequently, over the last years, the landscape of this research field has been impacted by key contributions from several research groups, who have pioneered the synthesis and application of original reagents to construct C-CF₂Me bonds. The synthesis of CF₂Me-containing molecules mainly relied on the fluorination of (1) carbonyl derivatives (or analogs i.e., thiocarbonyl compounds), (2) benzylic positions, (3) alkynes, or (4) alkenes and was well-documented (for selected examples: Markovskij et al., 1973; Middleton, 1975; York et al., 1996; Lal et al., 1999; Reddy et al., 2005; Yamauchi et al., 2008; Umemoto and Singh, 2012; Xia et al., 2013; Ilchenko et al., 2014; Xu et al., 2014; Ma et al., 2015; Koperniku et al., 2016; Hua et al., 2017; Li et al., 2017; Zhao et al., 2017; Iacono et al., 2018; Tomita et al., 2018). In sharp contrast, the design of new reagents or methodologies for the direct incorporation of this fluorinated moiety onto molecules is still underdeveloped. Recently Li, Dong et al. reviewed the synthesis of (1,1-difluoroethyl)arenes based on the construction of the CF₂Me motif and few examples describing its direct incorporation onto arenes were reported (Li et al., 2018).

The aim of this mini-review is to showcase and discuss the recent advances made on novel synthetic strategies for the direct introduction of the emergent CF₂Me group onto various classes of molecules (arenes, aliphatic, and carbonyl compounds). Therefore, in this review, we will highlight the new technological solutions based on the design of original reagents and methodologies to build up C-CF₂Me bonds. Note that the approaches employed to construct the CF₂Me group will not be discussed. Taking these considerations in mind, a first strategy to access to CF₂Me-containing molecules relies on the introduction of the CF₂Me group by using nucleophilic reagents, whereas a second approach deals with the construction of a C-CF₂Me bond according to a radical pathway.

1,1-DIFLUROETHYLATION OF MOLECULES USING A NUCLEOPHILIC CF₂ME-CONTAINING REAGENT

Transition Metal-Free Reactions to Access CF₂Me-Containing Molecules

In this section, key advances for the direct 1,1-difluoroethylation of carbonyl derivatives via a transition metal-free process will be depicted.

TESCF₂Me and TMSCF₂Me as CF₂Me Sources

In their quest for new fluorine-containing reagents, Prakash et al. (Mogi et al., 2007) reported the synthesis of a 1,1-difluoroethylated reagent, the TESCF₂Me (Scheme 1). The latter resulted from the reaction between TESCl and (1,1-difluoroethyl)phenylsulfone 1 in the presence of magnesium metal in 35% yield on a gram scale. The precursor 1 was itself prepared in three steps from thiophenol (Langlois, 1988; Mogi et al., 2007). Note that the nature of the solvents (THF/HMPA, 1:1) was crucial to ensure the full conversion of the sulfone 1 into the desired TESCF₂Me reagent. When this reagent was reacted with aromatic aldehydes 2, the corresponding 1,1-difluoroethylated secondary alcohols 3 were obtained in moderate to good ¹⁹F NMR yields (50–77%). The reaction was tolerant to electron-donating groups (3b,c) and halogen (3d). The reaction was also sensitive to steric hindrance since when the reaction was conducted with a sterically hindered aldehyde or ketone, only traces of products were obtained. Finally, an enolizable aldehyde and ketone and an α,β-unsaturated...
aldehyde were not suitable substrates in that transformation and constituted the main limitations.

In the course of their studies regarding the difluoromethylation of aldehydes, ketones, and N-tert-butylsulfinimines using the nucleophilic TMSCF₂Me source, Hu and co-workers (Zhao et al., 2011) reported the 1,1-difluoroethylation of carbonyl derivatives 4, 6, and 8 (three examples, up to 92% yield) with the corresponding (1,1-difluoroethyl)trimethylsilane (TMSCF₂Me) under basic conditions (Scheme 2).

### Use of a CF₂Me-Substituted Phosphonium Salt

About 10 years later, Xiao and co-workers reported a new methodology to access CF₂Me-containing molecules by means of a nucleophilic source (Deng et al., 2016). As an alternative to the powerful TESCF₂Me reagent, which has a low boiling point and which required a tedious multi-step synthesis [four steps from thiophenol (Mogi et al., 2007)], Lin and Xiao designed a nucleophilic reagent based on a phosphonium salt. The shelf-stable 1,1-difluoroethyl phosphonium salt was prepared in three-steps from the commercially available and inexpensive PPh₃ and EtBr, in a 29% overall yield (Scheme 3). After the formation of the ethyl phosphonium salt, a subsequent two-step fluorination sequence with NFSI, allowed the formation of the desired reagent on a gram-scale.

This reagent was then successfully applied for the 1,1-difluoroethylation of (het)aromatic aldehydes and the 4-phenyl acetophenone 10. Electron-rich aryl aldehydes were smoothly converted into the desired secondary alcohols in moderate to high yields, as illustrated with the para-phenyl derivative 11a and the para-methoxy derivative 11b. A slight decrease of yield was observed when the reaction was performed from the sterically hindered electron-rich aldehyde 10c. Aryl aldehydes bearing an electron-withdrawing substituent (i.e., CF₃, CN, halogens) were also suitable substrates 10d-h for the reaction. In addition, the substitution pattern had no impact on the reaction outcome since the para-, meta-, and ortho-CF₃ substituted aryl alcohols 11d,e,h were obtained in good yields (68, 73, and 81%, respectively). Note that the 3-quinolinecarboxaldehyde 10i was functionalized in a good yield. However, only traces of the desired 1,1-difluoroethylated product were detected when starting from an aliphatic aldehyde and a lower ¹⁹F NMR yield (21%) was observed when the reaction was carried out with 4-phenyl acetophenone. To further demonstrate the potential of the methodology, the authors applied their methodology to the functionalization of the N-tosyl imines 12a-f and the corresponding products 13 were obtained in moderate to good yields (39–66%). It is worth mentioning that due to the lower reactivity of N-tosyl imines 12 compared to aldehydes 10, 1,1-difluoroethylated amines 13 were obtained in lower yields than 1,1-difluoroethylated alcohols 11. A plausible mechanism was suggested by the authors. After reaction of the Cs₂CO₃ promoter with the 1,1-difluoroethyl phosphonium salt, the intermediate I would be formed. This latter might then undergo a decarboxylation reaction to afford Ph₃PO and release a nucleophilic CF₂Me residue from the cleavage of the P-CF₂Me bond. Then, this species might react with 10 or 12 to afford the desired 1,1-difluoroethylated compound 11 or 13.

### Transition Metal-Promoted Reactions to Access CF₂Me-Containing Derivatives

As a complementary strategy, the development of transition metal promoted 1,1-difluoroethylation of molecules offered an efficient synthetic pathway to build up C-CF₂Me bonds.
SCHEME 3 | Application of the 1,1-difluoroethyl phosphonium salt for the 1,1-difluoroethylation reaction of carbonyl derivatives.

SCHEME 4 | Access to the CF₂Me-containing molecule 14 via a two-step process. 1,10-Phen. = 1,10-Phenanthroline.
Access to 1,1-Difluoroethylated Derivatives From Organozinc Reagents

The group of Dilman (Zemtsov et al., 2014) depicted a two-step process for the synthesis of 1,1-difluoroethylated derivatives, thanks to the in situ formation of the MeCF$_2$ZnX species. The reaction of the difluorocarbene with MeZnI formed the desired organozinc reagent. The latter was engaged in a copper-catalyzed allylation reaction and allowed the synthesis of the corresponding CF$_2$-containing molecules. With this methodology, a single example of a CF$_2$Me-containing molecule 14 was prepared in 66% yield (Scheme 4).

Copper-Mediated 1,1-Difluoroethylation Reaction Using TMSCF$_2$Me as a Fluorinated Source

In 2016, Hu and co-workers (Li et al., 2016) described the copper-mediated 1,1-difluoroethylation reaction of diaryliodonium triflates 15 using CuCF$_2$Me (Scheme 5). The CuCF$_2$Me reagent was in situ generated from the reaction of CuCl with TMSCF$_2$Me (Mogi et al., 2007) in the presence of iBuOK. Then, the synthesis of (1,1-difluoroethyl)arenes 16 was carried out. In presence of 1.5 equivalents of the in-situ generated CuCF$_2$Me and 0.5 equivalents of Et$_3$N·3HF, as a crucial additive, a panel of electron-rich diaryliodonium salts were smoothly converted into the desired CF$_2$Me-containing arenes 16a,b,g in good yields. The reaction conditions were also tolerant toward diaryliodonium salts bearing an electron-withdrawing group such as halogen, ketone, ester, aldehyde, and nitro groups to furnish the 1,1-difluoroethylated arenes 16c-f,h in moderate to high yields. Sterically hindered diaryliodonium salts 15i and 15j were also suitable substrates under these reaction conditions and furnished the desired products 16i-j in good yields. The potential of this strategy was further demonstrated by the 1,1-difluoroethylation of analogs of relevant compounds such as estrone 15k and the anti-inflammatory drug naproxen 15l. Concerning the mechanism, the authors ruled out a radical pathway and proposed the following mechanism pathway: formation of the intermediate Cu(III) species I, which would result from the oxidative addition of the CuCF$_2$Me species with the diaryliodonium salt 15, followed by a final reductive elimination step to furnish the expected product 16.
Cobalt-Catalyzed 1,1-Difluoroethylation Reaction of Aryl Grignard Reagent Using BrCF₂Me

A complementary synthetic route toward the synthesis of 1,1-difluoroethylated arenes was reported by Yamakawa and Ohtsuka (Ohtsuka and Yamakawa, 2016). The cobalt-catalyzed 1,1-difluoroethylation of aryl Grignard derivatives 17a-g was developed (Scheme 6). Various aryl Grignard derivatives were functionalized using two sets of reaction conditions. Note that the nature of the ligand and the solvent played an important role in each catalytic system. Aryl Grignard reagents bearing electron-donating and electron-withdrawing groups at the para position were functionalized leading to the corresponding products 18 in low to good yields. It turned out that the substitution pattern had an impact on the reaction outcome since the derivative 18g bearing a methoxy group at the ortho-position was obtained in a lower yield compared to the compound 18b and 18f with both reaction conditions (A and B). Note that, except for product 18c, the isolated yields were rather lower than the ones determined by ¹⁹F NMR, presumably due to volatility issue of the fluorinated products.

DIRECT INTRODUCTION OF THE CF₂Me MOIETY VIA A RADICAL PROCESS

In this section, the recent breakthroughs for the direct and selective incorporation of the CF₂Me residue onto molecules via a radical process will be discussed. Note that this strategy was mainly used to access 1,1-difluoroethyl-containing heteroarenes.

DFES-Na as the 1,1-Difluoroethyl Source

In 2013, a pioneer work was reported by the group of Baran (Zhou et al., 2013). They designed the synthesis of the sodium difluoroethylsulfinate (DFES-Na) and investigated its application to the functionalization of various heterocycles. The DFES-Na reagent was obtained in two steps from the Hu’s reagent and was prepared on a large scale (>100 g). Under oxidative and robust conditions (TBHP, water as co-solvent under air), various classes of heteroarenes were functionalized (21 examples) in the presence of ZnCl₂ and H₂O. The transformation turned out to be functional group tolerant and moderate to good selectivity was observed. In addition, the authors demonstrated the possible direct radical functionalization of Michael acceptors 21 and thiol derivatives 22 (Scheme 7).

This reagent was then used by the group of Vincent (Ryzhakov et al., 2017) for the direct introduction of the CF₂Me residue on protected indoles 25. The reaction led to the corresponding fluorinated spirocyclic indolines 26 under oxidative conditions (2 examples, Scheme 8).
SCHEME 7 | 1,1-Difluoroethylation of heteroarenes and extension to other classes of compounds with the DFES-Na reagent. [a] After 10 h using DFES-Na (2 equiv) and ZnCl₂ (1 equiv).

SCHEME 8 | Access to 1,1-difluoroethylated spirocyclic indolines with the DFES-Na reagent.
**CF₂Me-Containing Sulfones as the 1,1-Difluoroethyl Source**

In 2015, the group of Dolbier (Zhang et al., 2015) reported the synthesis of fluorinated phenanthridines 28 under visible light photoredox catalysis. Starting from biphenyl isocyanides 27, the 1,1-difluoroalkylation occurred using an Ir photocatalyst via a tandem addition/cyclization/oxidation sequence. Although the study mainly focused on the difluoromethylation reaction, the introduction of the 1,1-difluoroethyl radical was readily performed using the MeCF₂SO₂Cl reagent as precursor of the CF₂Me radical (Scheme 9). Using this reaction manifold, four CF₂Me-containing phenanthridines were synthesized in good yields (up to 83%). The following mechanism was proposed by the authors: first, the generation of the radical CF₂Me from the reduction of the MeCF₂SO₂Cl reagent with the excited Ir catalyst followed by its addition on the isocyanides 27. Then a cyclization would lead to the corresponding radical A, which would be oxidized into the species B, regenerating the Ir-catalyst. A final deprotonation of B would yield to the expected products 28.

A complementary approach was reported by Hu and co-workers in 2016 (Rong et al., 2016). They developed a new class of fluoroalkylation reagents, which enabled the formation...
of \( R_f \) radical using visible light photoredox catalysis. Using fluoroalkylated heteroaryl sulfones, various isocyanides were functionalized with several fluorinated motifs (\( R_f = \text{CH}_2\text{F}, \text{CF}_2\text{H}, \text{CF}_2\text{Me}, \text{CF}_2\text{Ph}, \text{CF}_3, \) and \( \text{CF}_2\text{COPh} \)). Among them, the Ru-catalyzed 1,1-difluoroethylation of two biphenyl isocyanides 30 using the reagent 29 was reported (Scheme 10).

In 2017, the group of Dolbier (Zhang et al., 2017) developed a radical fluoroalkylation of unactivated alkenes under photo redox catalysis to build up fluorinated tetralin derivatives. In that context, a single example of the direct introduction of the \( \text{CF}_2\text{Me} \) group to build up the corresponding carbocyclic compound under Ir catalysis was depicted. The expected product 33 was obtained in 64% yield using the \( \text{MeCF}_2\text{SO}_2\text{Cl} \) reagent (Scheme 11).

**SUMMARY AND OUTLOOK**

In this Mini-review, we discussed the recent advances made for the direct and selective introduction of the valuable \( \text{CF}_2\text{Me} \) group. As alternative to the traditional synthetic routes, these direct approaches represented efficient and new retrosynthetic pathways. In this context, technological solutions based on the design of new tools (original strategies and reagents) for the 1,1-difluoroethylation of several classes of compounds were designed. Two strategies were employed based either on the use of nucleophilic reagents or precursors of \( \text{CF}_2\text{Me} \) radical sources. In the former case, transition metal free approaches as well as transition metal-mediated or -catalyzed transformations were depicted. The complementary synthetic pathway relied on the use of a radical process to access \( \text{CF}_2\text{Me} \)-containing molecules using carefully designed reagents. Beyond these impressive achievements, further developments for the direct introduction of the \( \text{CF}_2\text{Me} \) residue, especially for the late-stage functionalization of complex (bioactive) molecules will be of prime importance to enlarge the existing toolbox. Thanks to the pivotal importance of the organofluorine chemistry in various research fields, we strongly believe that this Mini-review will offer
new perspectives to further study and apply this original fluorinated moiety.

**AUTHOR CONTRIBUTIONS**

EC and TB collected the literature data related to this review article. EC, TP, PJ, and XP wrote sections of the manuscript. TB wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript and approved the submitted version.

**REFERENCES**

Anderson, M. O., Zhang, J., Liu, Y., Yao, C., Phuan, P.-W., and Verkman, A. S. (2012). Nanomolar Potency and Metabolically Stable Inhibitors of Kidney Urea Transporter UT-B1. *J. Med. Chem.* 55, 5942–5950. doi: 10.1021/jm300491y
Belhomme, M.-C., Besset, T., Poisson, T., and Pannecoque, X. (2015). Recent progress toward the introduction of functionalized difluoromethylated building blocks onto C(sp2) and C(sp3) centers. *Chem. Eur. J.* 21, 12836–12865. doi: 10.1002/chem.201501475
Besset, T., Jubbaut, P., Pannecoque, X., and Poisson, T. (2016). New entries toward the synthesis of CF3-containing molecules. *Org. Chem. Front.* 3, 1004–1010. doi: 10.1039/C6QO00164E
Besset, T., Poisson, T., and Pannecoque, X. (2014). Recent progress in direct introduction of fluorinated groups on alkenes and alkynes by means of C-H bond functionalization. *Chem. Eur. J.* 20, 16830–16845. doi: 10.1002/chem.20140537
Champagne, P. A., Desroches, J., Hamel, J.-D., Vandamme, M., and Paquin, J.-F. (2015). Monofluorination of organic compounds: 10 years of innovation. *Chem. Rev.* 115, 9073–9174. doi: 10.1021/cr500706a
Coteron, J. M., Marco, M., Esquivias, J., Deng, X., White, K. L., White, J., et al. (2011). Structure-Guided Lead Optimization of Triazolopyrimidine-Ring Substituents Identifies Potent Plasmidium falciparum Dhodhoroionate Dehydrogenase Inhibitors with Clinical Candidate Potential. *J. Med. Chem.* 54, 5540–5561. doi: 10.1021/jm200592f
Deng, Z., Liu, C., Zeng, X.-L., Lin, J.-H., and Xiao, J.-C. (2016). Nucleophilic 1,1-Difluoroethylation with Fluorinated Phosphonium Salt. *J. Org. Chem.* 81, 12084–12090. doi: 10.1021/acs.joc.6b02723
Egami, H., and Sodeoka, M. (2014). Trifluoromethylation of alkenes with concomitant introduction of additional functional groups. *Angew. Chem. Int. Ed.* 53, 8294–8308. doi: 10.1002/anie.201309260
Fujitani, T., and O’Hagan, D. (2014). Successful fluorine-containing herbicide agrochemicals. *J. Fluorine Chem.* 167, 16–29. doi: 10.1016/j.jfluchem.2014.06.014
Gillis, E. P., Eastman, K. J., Hill, M. D., Donnelly, D. J., and Meanwell, N. A. (2015). Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* 58, 8315–8359. doi: 10.1021/acs.jmedchem.5b00258
Hua, A. M., Mai, D. N., Martinez, R., and Baxter, R. D. (2017). Radical C–H fluorination using unprotected amino acids as radical precursors. *Org. Lett.* 19, 2949–2952. doi: 10.1021/acs.orglett.7b01188
Iacono, C. E., Stephens, T. C., Rajan, T. S., and Pattison, G. (2018). A coupling approach for the generation of α,ω-bis(olate) equivalents: regioselective synthesis of gem-difunctionalized ketones. *J. Am. Chem. Soc.* 140, 2036–2040. doi: 10.1021/jacs.7b12941
Ilardi, E. A., Vitak, E., and Njardarson, J. T. (2014). Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals To Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* 57, 2832–2842. doi: 10.1021/mi401375q
Ilchenko, N. O., Tasch, B. O. A., and Szabó, K. J. (2014). Mild silver-mediated gemailial difluorination of styrenes using an air and moisture-stable fluoriodiane reagent. *Angew. Chem., Int. Ed.* 53, 12897–12901. doi: 10.1002/anie.201408812

**FUNDING**

This work was partially supported by INSA Rouen, Rouen University, CNRS, EFRD, LabexSynOrg (ANR-11-LABX-0029), Région Normandie (Crunch Network) and the IUF (Institut Universitaire de France). EC thanks the LabexSynOrg (ANR-11-LABX-0029) for a doctoral fellowship. TP thanks the IUF for support. TB thanks the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement no. 758710).
O'Hagan, D. (2008). Understanding organofluorine chemistry. An introduction to the C–F bond. Chem. Soc. Rev. 37, 308–319. doi: 10.1039/B711844A

Ohtsuka, Y., and Yamakawa, T. (2016). Cobalt/diamine-catalyzed 1,1-difluoroethylolation and 2,2,2-trifluoroethylation of aryl Grignard reagents with corresponding fluoroalkyl halides. J. Fluorine Chem. 185, 96–102. doi: 10.1016/j.jfluchem.2016.03.007

Okoromoba, O. E., Han, J., Hammond, G. B., and Xu, B. (2014). Designer HF-based fluorination reagent: highly regioselective synthesis of fluoroalkenes and gem-difluoroethylene compounds from alkynes. J. Am. Chem. Soc. 136, 14381–14384. doi: 10.1021/ja508369z

Pursuer, S., Moore, P. R., Swallow, S., and Gouverneur, V. (2008). Fluorine in medicinal chemistry. Chem. Soc. Rev., 2008, 37, 320–330. doi: 10.1039/B610213C

Reddy, V. P., Alleti, R., Perambuduru, M. K., Welz-Biermann, U., Buchholz, H., and Prakash, G. K. S. (2005). gem-Difluorination of 2,2-diaryl-1,3-dithiolanes by Selectfluor® and pyridinium polyhydrogen fluoride. Chem. Commun. 654–656. doi: 10.1039/B414254C

Rong, J., Deng, L., Tan, P., Ni, C., Gu, Y., and Hu, J. (2016). Radical fluoralkylation of isocyanides with fluorinated sulfones by visible-light photoredox catalysis. Angew. Chem. Int. Ed. 55, 2743–2747. doi: 10.1002/anie.201510533

Ryzhakov, D., Jarret, M., Guillot, R., Kouklovsky, C., and Vincent, G. (2017). Radical-mediated deacetylation of indoles with sulfinate reagents for the synthesis of fluorinated spirocyclic indolines. Org. Lett. 19, 6336–6339. doi: 10.1021/acs.orglett.7b03155

Song, H.-X., Han, Q.-Y., Zhao, C.-L., and Zhang, C.-P. (2018). Fluoralkylation reactions in aqueous media: a review. Green Chem. 20, 1662–1731. doi: 10.1039/C8GC00078F

Tomita, R., Al-Maharik, N., Rodil, A., Buhl, M., and O’Hagan, D. (2018). Synthesis of aryl α,α-difluoroethyl thioethers a novel structure motif in organic chemistry, and extending to aryl α,α-difluoro oxoethers. Org. Biomol. Chem. 16, 1113–1117. doi: 10.1039/C7OB029877

Umamoto, T., and Singh, R. P. (2012). Arylsulfur chlorotetrafluorides as useful fluorinating agents: Deoxy- and dethioxy-fluorinations. J. Fluorine Chem. 140, 17–27. doi: 10.1016/j.jfluchem.2012.03.008

Wang, J., Sánchez-Roselló, M., Aceña, J. I., del Pozo, C., Sorochinsky, A. E., Fustero, S., et al. (2014). Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). Chem. Rev. 114, 2432–2506. doi: 10.1021/cr4002879

Xia, J.-B., Zhu, C., and Chen, C. (2013). Visible Light-Promoted Metal-Free C–H Activation: Diarylketone-Catalyzed Selective Benzylic Mono- and Difluorination. J. Am. Chem. Soc. 135, 17494–17500. doi: 10.1021/ja410815u

Xu, P., Guo, S., Wang, L., and Tang, P. (2014). Silver-Catalyzed Oxidative Activation of Benzylic C-H Bonds for the Synthesis of Difluoromethylated Arenes. Angew. Chem., Int. Ed. 53, 5955–5958. doi: 10.1002/anie.201402225

Yamauchi, Y., Fukuhara, T., Hara, S., and Senkobu, H. (2008). Electrochemical carboxylation of α,α-difluorotoluene derivatives and its application to the synthesis of α-fluorinated nonsteroidal anti-inflammatory drugs. Synlett 438–442. doi: 10.1055/s-2008-1032069

York, C., Surya Prakash, G. K., and Olah, G. A. (1996). Desulfurative fluorination using nitrosonium tetrafluoroborate and pyridinium poly(hydrogen fluoride). Tetrahedron 52, 9–14. doi: 10.1016/0040-4209(95)00864-5

Zemtsov, A. A., Kondratyev, N. S., Levin, V. V., Struchkova, M. I., and Dilman, A. D. (2014). Copper-Catalyzed Alkylation of α,α-Difluoro-Substituted Organozinc Reagents. J. Org. Chem. 79, 818–822. doi: 10.1021/jo4024705

Zhang, Z., Martinez, H., and Dolbier, W. R. (2017). Photoredox catalyzed intramolecular fluoroalkylation of unactivated alkenes. J. Org. Chem. 82, 2589–2598. doi: 10.1021/acs.joc.6b03012

Zhang, Z., Tang, X., and Dolbier, W. R. (2015). Photoredox-catalyzed tandem insertion/cyclization reactions of difluoromethyl and 1,1-difluoroalkyl radicals with biphenyl isocyanides. Org. Lett. 17, 4401–4403. doi: 10.1021/acs.orglett.5b02061

Zhao, Y., Huang, W., Zheng, J., and Hu, J. (2011). Efficient and direct nucleophilic difluoromethylation of carbonyl compounds and imines with MeSiCF2H at ambient or low temperature. Org. Lett. 13, 5342–5345. doi: 10.1021/ol202208b

Zhao, Z., Racicot, L., and Murphy, G. K. (2017). Fluorinative rearrangements of substituted phenyllenes mediated by (difluoroiodo)toluene: synthesis of α-(difluoromethyl)styrenes. Angew. Chem., Int. Ed. 56, 11620–11623. doi: 10.1002/anie.201706798

Zhou, Q., Ruffoni, A., Gianatassio, R., Fujiwara, Y., Sella, E., Shabat, D., et al. (2013). Direct synthesis of fluorinated heteroarylether biososoters. Angew. Chem. Int. Ed. 52, 3949–3952. doi: 10.1002/anie.201300763

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Carbonnel, Poisson, Jubault, Pannecoucke and Besset. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.