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Exploiting a "Beast" in Carbenoid Chemistry: Development of a Straightforward Direct Nucleophilic Fluoromethylation Strategy

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Supporting Information Placeholder

ABSTRACT: The first direct and straightforward nucleophilic fluoromethylation of organic compounds is reported. The tactic employs a "fleeting" lithium fluorocarbenoid ($LiCH_2F$) generated from the commercially available fluoroiodomethane. Precise reaction conditions were developed for generation and synthetic exploitation of such a labile species. The versatility of the strategy is showcased in *ca.* 50 examples involving a plethora of electrophiles. Highly valuable chemicals such as fluoro alcohols, fluoro amines and fluoromethylated oxygenated heterocycles could be prepared in very good yields through a single synthetic operation. The scalability of the reaction and the application to complex molecular architectures (*e.g.* steroids) is documented.

The presence of fluorine in an organic framework profoundly influences the physico-chemical properties, thus making the resulting compounds unique and highly valuable scaffolds across the chemical sciences. Such a behavior is advantageously exploited in drug discovery not only for modulating critical parameters including pharmacokinetics and pharmacodynamics but, also for designing radiopharmaceuticals for positron emission tomography (PET).[1,2,3] Recent achievements in fluoroalkylation chemistry culminated nowadays in established and robust methodologies for installing trifluoromethyl (CF_3) or difluoromethyl (CF_2) units mainly *via* the generation of the corresponding radicals, carbenes or, alternatively, by means of other electrophilic reagents.[4,5] Moreover, compared to trifluoro- or difluoromethylation, monofluoromethylation strategies remain still a formidable challenge. The direct introduction of a fluoromethyl unit holds great importance because of the isosteric correspondence of the CH_2F group to a CH_3 group[6] as showcased in some fluoromethylated drugs reported in Figure 1. As for nucleophilic fluoroalkylations, that is the transfer of fluoroalkyl groups to an electrophile by a fluorinated carbanion equivalent, important aspects concerning the thermal and chemical stability of the intermediates were recently disclosed.[7] Hu reported the so-called "*negative fluorine effect*" (NFE) to highlight the influence of fluorine on the thermal stability and nucleophilic fluoroalkylation reactivity of fluorinated carbanions.[8] Conceptually, a selective nucleophilic monofluoromethylation could be accomplished through two main strategies: a) the direct transfer of a "*CH_2F*" moiety; b) the transfer of the fluorinated group linked to a suitable auxiliary requiring removal at the end of the sequence.[9] To date, the limited chemical stability of fluoromethyl carbanions has been efficiently overcome through the stabilizing effect displayed by strong electron-withdrawing functionalities (Figure 1). Accordingly, fluoromethyl- sulfones, sulfoximines and bis-(phenylsulfonyl) could be advantageously employed as effective agents (Olah, Hu and Shibata).[10-13]

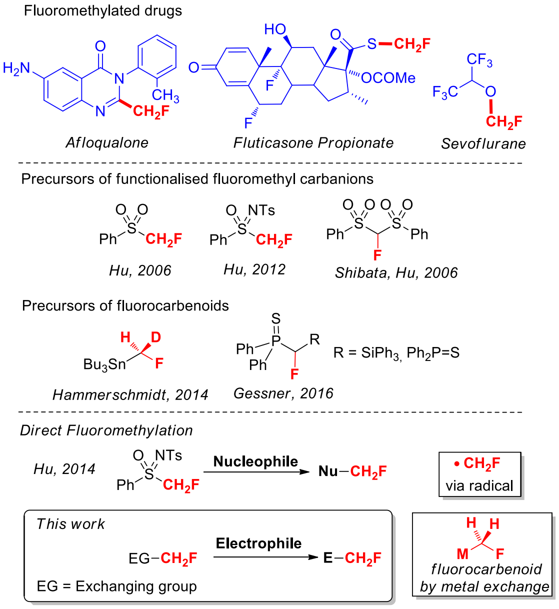
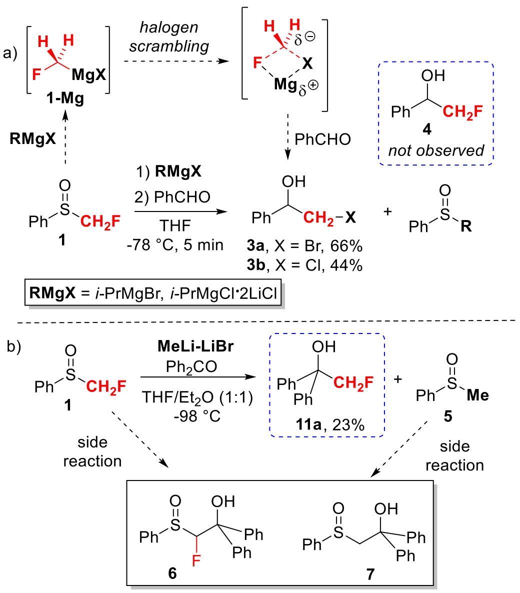


Figure 1. State-of-the-Art of monofluoromethylations.

Recently, Hu succeeded in directly fluoromethylating *O*-, *S*-, *N*-, *P*-nucleophiles through CH_2F radical species generated from fluoromethylated sulfoximines (Figure 1).[14] Unfortunately, such methodology was not suitable for *C*-nucleophiles thus, leaving undisclosed the development of a direct $C\text{-}CH_2F$ bond formation strategy.[15] In this context, the availability of a reagent able to introduce - in one direct synthetic operation - the CH_2F group is highly desirable. Conceptually, the ideal generation of a putative $M\text{-}CH_2\text{-}F$ reagent – *i.e.* carbenoid – (M = metal) would represent *de facto* a straightforward synthetic tactic towards the immediate one-pot functionalization of a given electrophile (Figure 1). In this context, very recently Gessner succeeded in isolating and characterizing Li, Na and K fluorocarbenoids stabilized by electron-withdrawing groups (Figure 1). In such an interesting report, the author textually stated: ".. *Li/F systems are still regarded as the* *"beast" in carbenoid chemistry. This is due to their extreme sensitivity and reactivity connected with the facile LiF elimination typically at temperatures as low as –78 °C. Hence, applications are extremely limited".*[16] Additionally, seminal contributions by Hammerschmidt demonstrated the high configurational stability of a chiral lithiated fluorinated deutero carbenoid (LiCHDF), as well as the dramatic chemical instability of this species even at very low temperature (-95 °C) thus, limiting its synthetic potential.[17]

Moved by this challenge, and inspired by Hammerschmidt's report, we embarked in a research endeavor aimed at exploiting the reactivity of Mg, and Li fluoromethyl carbenoids. The study commenced considering fluoromethyl sulfoxide **1** and fluoroiodomethane **2**, as simple potential precursors of fluoromethylating reagents *via* metalation chemistry. Upon treatment of fluoromethylsulfoxide **1** with a Grignard reagent (*i*-PrMgBr or *i*-PrMgCl·2LiCl), followed by the external electrophilic trapping with benzaldehyde, bromohydrine **3a** or chlorohydrine **3b** were obtained as the main reaction products (Scheme 1). Surprisingly, after extensive optimization, the expected fluoromethylated adduct **4**, could not be formed.[18] Presumably, adducts **3a**,**b** were formed as a consequence of a halogen scrambling at the magnesium fluorocarbenoid **1-Mg** level (Scheme 1, a).

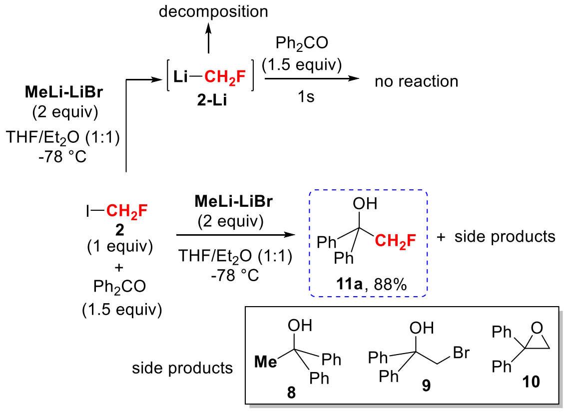
Scheme 1. Metalation of fluoromethylsulfoxide 1.



Effectively, the attempted nucleophilic displacement of **1** with MgX_2, and LiX (X = Br, Cl) in a THF solution, resulted in full recovery of starting material **1**, thus making unlikely such a possibility. Analogous F/I halogen scrambling has been noticed by Charette and co-workers with electrophilic zinc fluorocarbenoids.[19]

The switching to a lithium reagent (MeLi·LiBr) was beneficial: pleasingly, using a 1:1 mixture of THF/Et_2O at -98 °C, the desired fluoromethylated adduct **11a** could be isolated in 23% yield (Scheme 1, b). Further attempts to improve the reaction performance were elusive, since collateral products (**6** and **7**) resulting from the reaction between **1** and **5** were detected (Scheme 1, b). Taking into consideration the well-established applicability of dihalomethanes as carbenoid precursors,[20] we deemed the commercially available fluoroiodomethane **2** a convenient source for the MCH_2F reagent.[21] In striking contrast to sulfoxide **1**, both *i*-PrMgCl·2LiCl and *i*-PrMgBr were ineffective to promote the metalation of **2** and, only the attack of the Grignard to the electrophile was observed.[18] After extensive reaction tuning, fluoroiodomethane **2** was identified as the optimal substrate for lithiation:[18] the desired fluorohydrin **11a** was obtained in an excellent 88% yield (Scheme 2). Crucial factors for enabling the success of the reaction under Barbier-type conditions (*i.e.* internal quenching) were: 1) the use of MeLi·LiBr as lithiating agent at -78 °C; 2) a 1:1 *v/v* mixture of THF/Et_2O as the medium; 3) a precise 1/2/1.5 stoichiometry between **2**/MeLi-LiBr/electrophile respectively.[18]

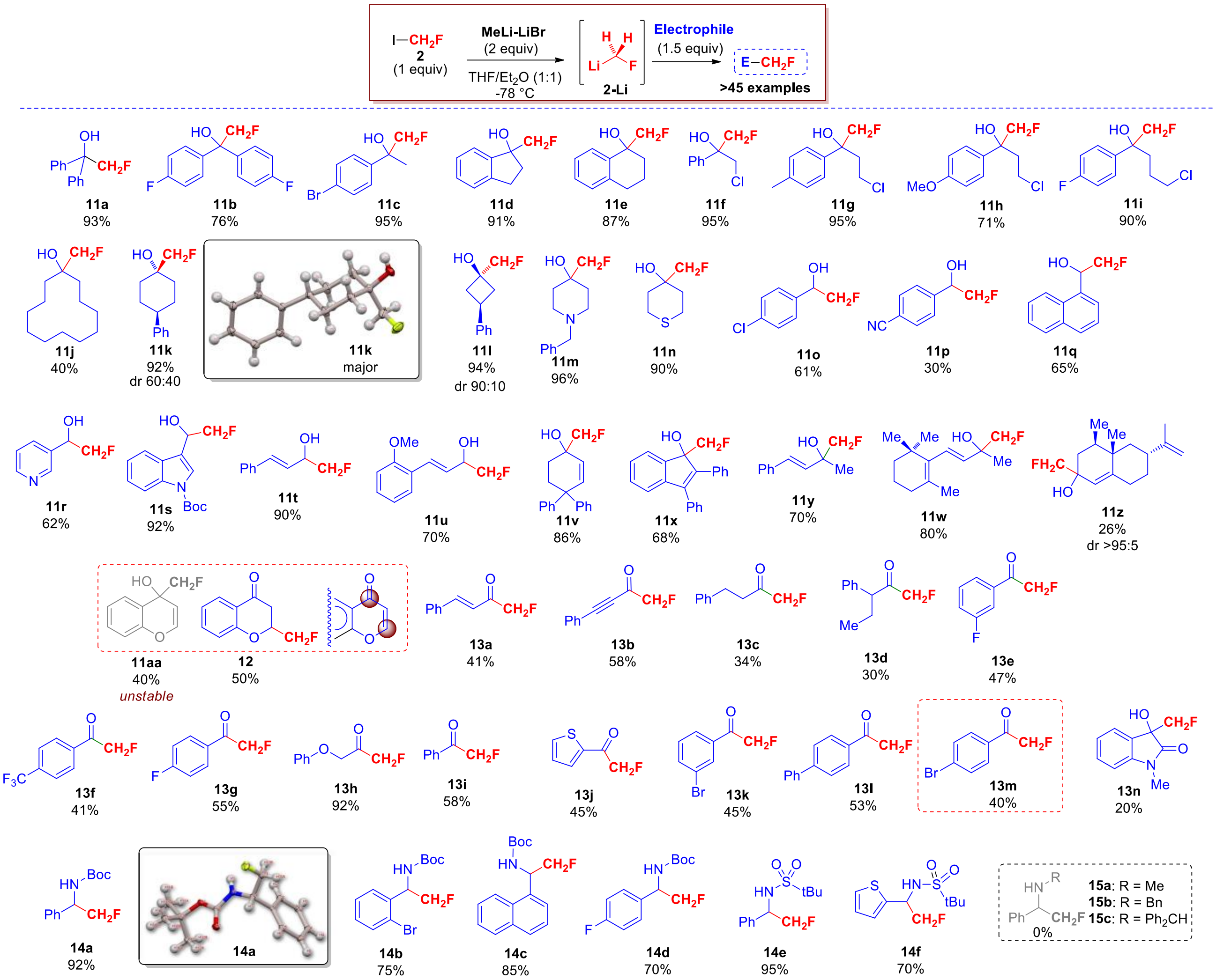
Scheme 2. Reactivity of fluoroiodomethane 2.



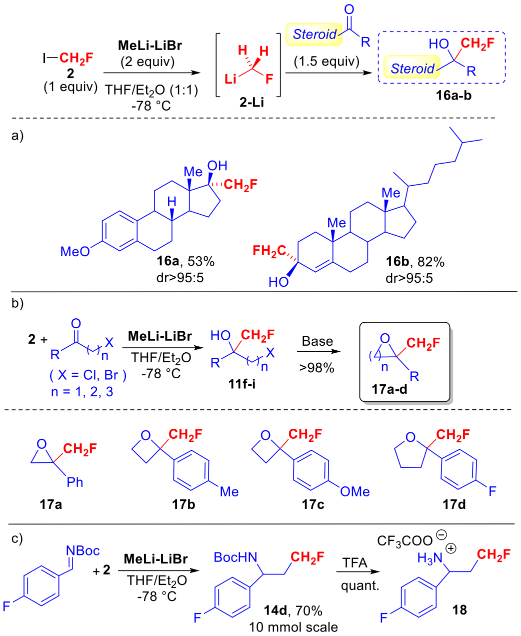
Key factors:
√Suitable organolithium: MeLi·LiBr
*√Stoichiometry (**2**/MeLi·LiBr/Ph_2CO: 1/2/1.5)*
√Internal quenching
√Solvent (THF/Et_2O: 1/1)

During the optimization study, side products **9** and **10** were found in the crude reaction mixture, likely as consequence of a halogen scrambling induced by LiBr, or the direct insertion of a carbene into the C=O of the electrophile. The amounts of **8** and **9** were strictly dependent on the reaction conditions, and possibly on to the chemical stability of **2-Li.**[22] As expected, lithium fluorocarbenoid **2-Li** was found extremely reactive, fully decomposing under external trapping conditions, even when the electrophile was added after only 1 second (Scheme 2).[18] Similarly, polar solvents such as THF, and higher temperatures exalted the decomposition of **2-Li**. In fact, increasing temperature up to -40 °C - under internal quenching conditions - epoxide **10** was formed in 10% yield, whereas **11a** in 72% yield. The use of toluene or Et_2O as reaction solvent proved to be ineffective.[18] Remarkably, our protocol could be conveniently applied to a wide range of electrophiles including carbonyls, imines, and Weinreb amides (Scheme 3). Useful β-fluoro alcohols **11a-z** were obtained in good to excellent yields and high chemocontrol, as showcased by adducts **11c, 11o** and **11f-i** featuring additional potentially exchangeable halogens.[23] Carbocyclic and heterocyclic enolizable ketones furnished the corresponding fluoromethylated products **11j-n** in very good yields.[26] The reaction proceeded with stereocontrol in the case of a small-size cyclic ketone, providing fluoro alcohol **11l** in 94% yield and 90:10 *dr*. Aromatic and heteroaromatic aldehydes provided fluorohydrins **11o-u** in good yields in almost all cases, with exception of **11p** (due to its volatility) where chemocontrol in the presence of a nitrile electrophilic functionality was fully preserved. α,β-Unsaturated carbonyls reacted chemoselectively in 1,2-fashion giving fluorohydrins **11t-z** without affecting the chemical integrity of the double bond. β-Ionone smoothly provided adduct **11z**, a formal isostere of an important intermediate for the synthesis of vitamin D, as a single stereoisomer. ***NB intermedio di vitD è 11w TOGLIAMO TUTTO.***

Scheme 3. Scope of the direct nucleophilic fluoromethylation strategy.



Surprisingly, the use of chromanone, led to both 1,2- and 1,4-addition products **11aa** and **12**. However, **11aa** was found highly unstable and only adduct **12** was isolated in 50% yield (Scheme 3).[24] Less electrophilic Weinreb amides were excellent acylating agents for $LiCH_2F$, thus enabling the direct access to α-fluorinated ketones **13a-l**. Unsaturated motifs (alkene and alkynes) were perfectly tolerated in terms of chemocontrol (*i.e.* **13a,b**), as well as heterocycles and halogenated aromatics (*i.e.* **13j,k**). A special ketone, such as isatine, was fluoromethylated giving adduct **13n** in lower yield 20% yield due to its low solubility in the reaction medium. To further benchmark the methodology, aromatic and heteroaromatic imines were employed as electrophiles, obtaining highly valuable β-fluoroamines 1**4a-f.**[25,26] The process requires imines bearing *N*-electron-withdrawing groups (Boc, *t*-BuSO, *t*-$BuSO_2$), whereas the use of *N*-alkyl or *N*-benzyl imines was unsuccessful (*i.e* **15a-c**, Scheme 3). Biologically relevant and complex scaffolds such as 3-*O*-methylestrone and 4-colesten-3-one efficiently underwent the transformation (Scheme 4, a). Remarkably, the reaction of the fluorocarbenoid **2-Li** occurred with superb stereoselectivity, furnishing **16a,b** as single stereoisomers. The functional groups compatibility, was pivotal to design an unprecedented two-steps access to α-fluoromethylated oxygenated heterocycles such as the challenging epifluorohydrin **17a**, fluoromethylated oxetanes **17b-c** and tetrahydrofuran **17d** by the chemoselective intramolecular cyclization (Scheme 3, b). Next, given the importance of β-fluoro amines, a 10 mmol preparation of **18** was achieved using a two-step sequence based on the direct fluoromethylation of *N*-Boc imine, followed by acidic removal of the Boc group (Scheme 4, c).



Scheme 4. Further application of the direct fluoromethylation strategy.

In conclusion, a novel one-pot strategy for the direct nucleophilic fluoromethylation has been developed. This method overcomes the drawbacks associated with the use of auxiliary groups requiring proper removal after introducing the fluorinated fragment. This work demonstrated that the fleeting carbenoid fluoromethyllithium, could be efficiently exploited for synthetic purposes. Through the fine tuning of the reaction conditions, it is possible to avoid decomposition of the intermediates, allowing the reaction with various electrophiles, including structurally complex molecules. We believe that this work paves the way for further progresses in fluoromethylation strategies and fluorinated organometallics.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

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26) CCDC 1564590-1564591 contain the X-ray crystal structure of **11k** and **14a** respectively.

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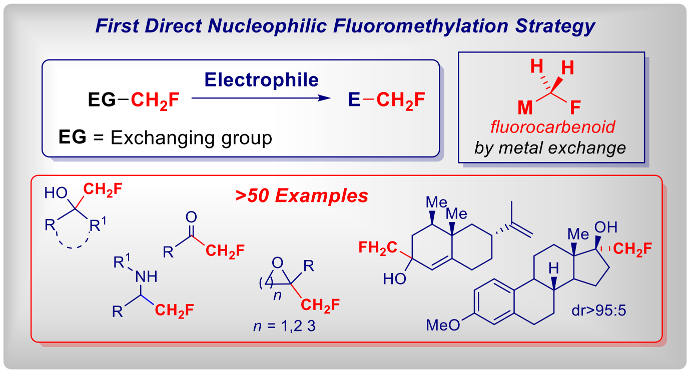
First Direct Nucleophilic Fluoromethylation Strategy
EG−CH$_2$F
Electrophile
E−CH$_2$F
EG = Exchanging group
H H
M F
fluorocarbenoid
by metal exchange
>50 Examples
HO CH$_2$F
R R^1
O
R CH$_2$F
R^1 NH
R CH$_2$F
O R
( )$_n$
CH$_2$F
n = 1,2 3
Me Me
FH$_2$C
HO
Me OH
CH$_2$F
H
MeO
dr>95:5