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

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Supporting Information

ABSTRACT: The first direct and straightforward nucleophilic fluoromethylation of organic compounds is reported. The tactic employs a "fleeting" lithium fluorocarbenoid ($LiCH_2F$) generated from commercially available fluoroiodomethane. Precise reaction conditions were developed for the 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 fluoroalcohols, fluoroamines, and fluoromethylated oxygenated heterocycles could be prepared in very good yields through a single synthetic operation. The scalability of the reaction and its application to complex molecular architectures (e.g., steroids) are documented.

The presence of fluorine in an organic framework profoundly influences the physicochemical properties, thus making the resulting compounds unique and highly valuable scaffolds across the chemical sciences. Such behavior is advantageously exploited in drug discovery not only to modulate critical parameters, including pharmacokinetics and pharmacodynamics, but also to design radiopharmaceuticals for positron emission tomography.[1−3] Recent achievements in fluoroalkylation chemistry have 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 or carbenes or, alternatively, by means of other electrophilic reagents.[4,5] Moreover, compared with trifluoro- or difluoromethylation, monofluoromethylation strategies still remain 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.[8,9] Conceptually, a selective nucleophilic monofluoromethylation could be accomplished through two main strategies: (a) direct transfer of a "CH_2F" moiety and (b) transfer of the fluorinated group linked to a suitable auxiliary that must be removed 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, fluoromethylated sulfones, sulfoximines, and bis(phenylsulfonyl) could be advantageously employed as effective agents (Olah, Hu, and Shibata).[10−13]

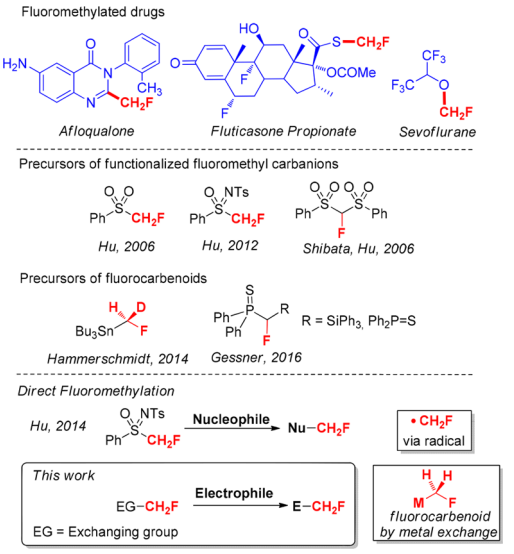

Figure 1. State of the art in monofluoromethylation.

Hu recently succeeded in directly fluoromethylating O, S, N, and 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−CH_2F bond formation strategy.[15] In this context, the availability of a reagent that can introduce the CH_2F group in one direct synthetic operation would be highly desirable. Conceptually, the ideal generation of a putative M−CH_2−F reagent—i.e., a carbenoid (M = metal)—would represent de facto a straightforward synthetic tactic toward the immediate one-pot functionalization of a given electrophile (Figure 1). In this context, very recently

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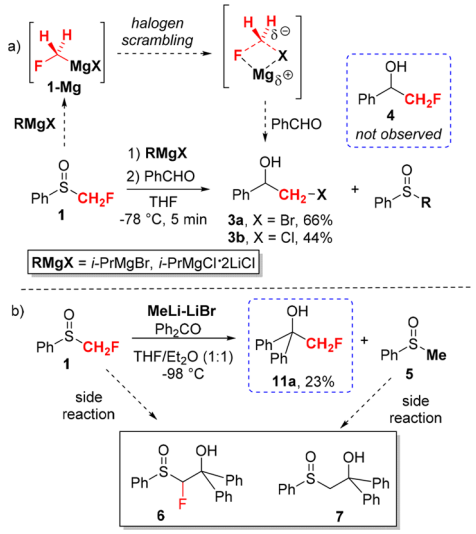
Gessner succeeded in isolating and characterizing Li, Na, and K fluorocarbenoids stabilized by electron-withdrawing groups (Figure 1). In this interesting report,[16] the authors stated that "Li/F systems are still regarded as the 'beast' in carbenoid chemistry. This is due to their extreme sensitivity and reactivity connected with the facile LiF elimination typically at temperatures as low as −78 °C. Hence, applications are extremely limited." Additionally, a seminal contribution by Hammerschmidt[17] demonstrated the high configurational stability of a chiral lithiated, fluorinated deuterocarbenoid (LiCHDF) as well as the dramatic chemical instability of this species even at very low temperature (−95 °C), thus limiting its synthetic potential.

Moved by this challenge and inspired by Hammerschmidt's report, we embarked on a research endeavor aimed at exploiting the reactivity of Mg and Li fluoromethyl carbenoids. The study commenced by considering fluoromethyl sulfoxide **1** and fluoroiodomethane (**2**) as simple potential precursors of fluoromethylating reagents via metalation chemistry. Upon treatment of **1** with a Grignard reagent (*i*-PrMgBr or *i*-PrMgCl·2LiCl) followed by external electrophilic trapping with benzaldehyde, bromohydrine **3a** or chlorohydrine **3b** was s1 obtained as the main reaction product (Scheme 1). Surprisingly,

Scheme 1. Metalation of Fluoromethyl Sulfoxide 1

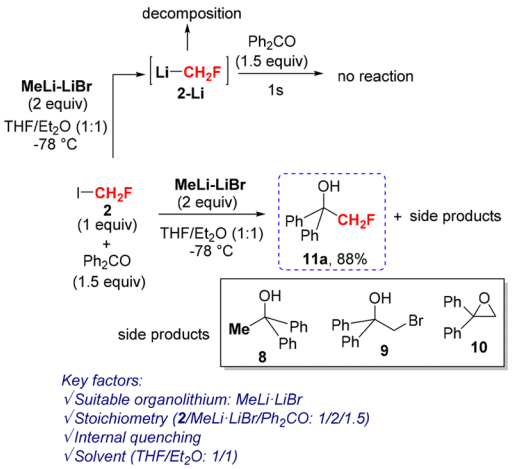


after extensive optimization, the expected fluoromethylated adduct **4** could not be formed.[18] Presumably, adducts **3** were formed as a consequence of halogen scrambling at the level of magnesium fluorocarbenoid **1-Mg** (Scheme 1a).

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 such a possibility unlikely. Analogous F/I halogen scrambling was noticed by Charette with electrophilic zinc fluorocarbenoids.[19]

Switching to a lithium reagent (MeLi·LiBr) was beneficial: pleasingly, with a 1:1 THF/Et_2O mixture at −98 °C, the desired fluoromethylated adduct **11a** could be isolated in 23% yield (Scheme 1b). 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 1b). Taking into consideration the well-established applicability of dihalomethanes as carbenoid precursors,[20] we deemed commercially available **2** to be a convenient source for the MCH_2F reagent.[21] In striking contrast to sulfoxide **1**, both *i*-PrMgCl·2LiCl and *i*-PrMgBr were ineffective in promoting the metalation of **2**, and only attack of the Grignard to the electrophile was observed.[18] After extensive reaction tuning, **2** was identified as the optimal substrate for lithiation,[18] and the desired fluorohydrin **11a** was obtained in an excellent 88% yield (Scheme 2). Crucial factors enabling the success of the reaction s2

Scheme 2. Reactivity of Fluoroiodomethane (2)



under Barbier-type conditions (i.e., internal quenching) were (1) the use of MeLi·LiBr as the lithiating agent at −78 °C, (2) the use of 1:1 (v/v) THF/Et_2O as the medium, and (3) a precise **2**/MeLi·LiBr/electrophile stoichiometry of 1/2/1.5.[18]

During the optimization study, side products **8** and **9** were found in the crude reaction mixture, likely as a consequence of halogen scrambling induced by LiBr or direct insertion of a carbene into the C═O bond of the electrophile. The amounts of **8** and **9** were strictly dependent on the reaction conditions and possibly on the chemical stability of **2-Li**.[22] As expected, lithium fluorocarbenoid **2-Li** was found to be extremely reactive, fully decomposing under external trapping conditions even when the electrophile was added after only 1 s (Scheme 2).[18] Similarly, polar solvents such as THF and higher temperatures enhanced the decomposition of **2-Li**. In fact, when the temperature was increased to −40 °C under internal quenching conditions, epoxide **10** was formed in 10% yield compared with **11a** in 72% yield. The use of toluene or Et_2O as the solvent was 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*-fluoroalcohols **11a−z** s3 were obtained in good to excellent yields with 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-sized cyclic ketone, providing fluoroalcohol **11l** in 94% yield with 90:10 dr. Aromatic and heteroaromatic aldehydes provided fluorohydrins **11o−u** in good yields in almost all cases, with the exception of **11p** (because of 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 to give fluorohydrins **11t−z** without affecting the chemical integrity of the double bond.

Surprisingly, the use of chromanone led to both 1,2- and 1,4-addition products (**11aa** and **12**, respectively). However, **11aa**

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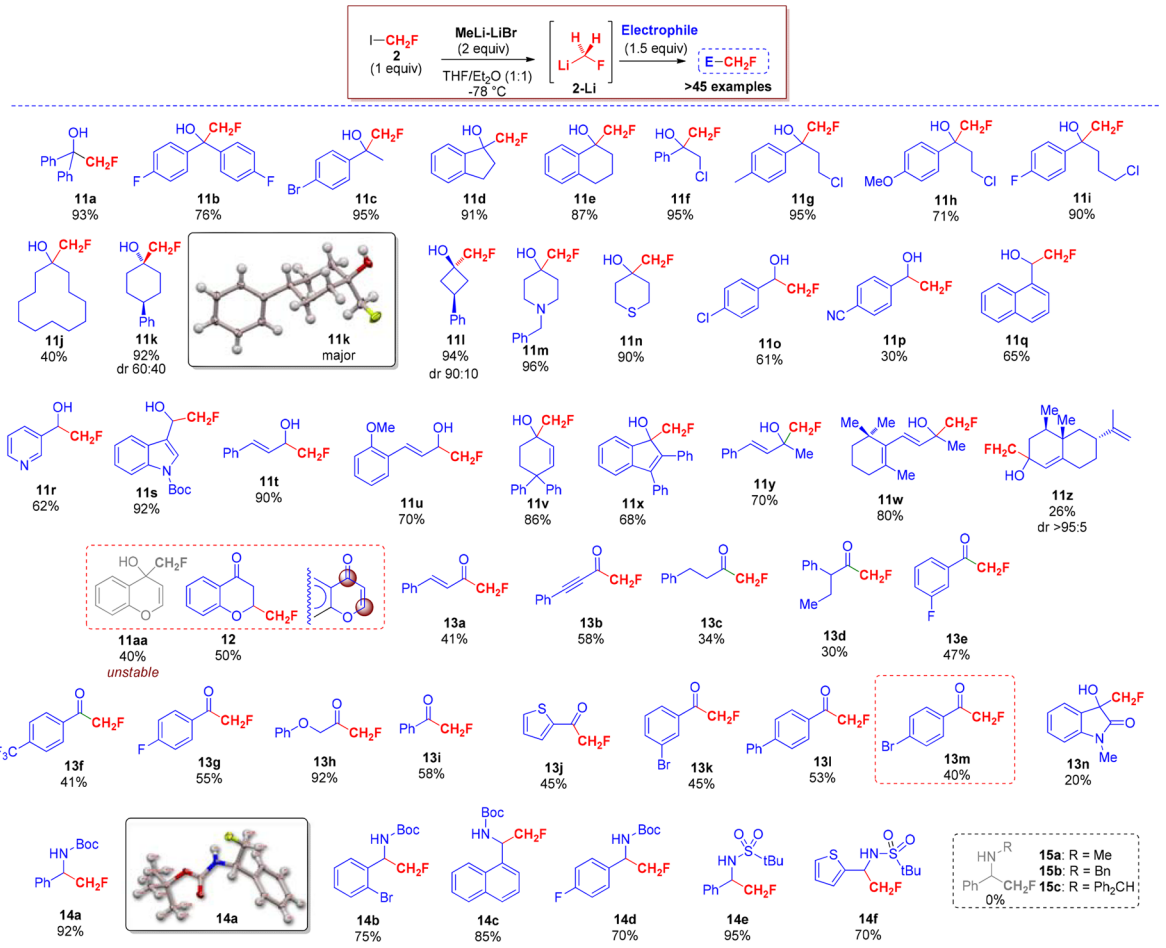
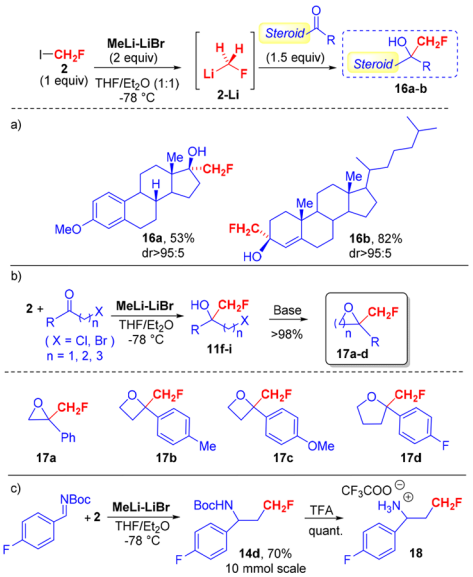
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 3. Scope of the Direct Nucleophilic Fluoromethylation Strategy



was found to be 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 direct access to α-fluorinated ketones **13a–l**. Unsaturated motifs (alkenes and alkynes) were perfectly tolerated in terms of chemocontrol (i.e., **13a** and **13b**), as were heterocycles and halogenated aromatics (i.e., **13j** and **13k**). The special ketone isatin was fluoromethylated to give adduct **13n** in a lower yield of 20% due to its low solubility in the reaction medium. To further benchmark the methodology, aromatic and heteroaromatic imines were employed as electrophiles to obtain highly valuable β-fluoroamines **14a–f**.[25,26] The process requires imines bearing electron-withdrawing N substituents (Boc, *t*-BuSO, *t*-$BuSO_2$), whereas the use of *N*-alkyl- or *N*-benzylimines 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 4a). Remarkably, the reaction of fluorocarbenoid **2-Li** occurred with superb stereoselectivity, furnishing **16a** and **16b** as single stereoisomers. The functional group compatibility was pivotal for the design of an unprecedented two-step access to α-fluoromethylated oxygenated heterocycles such as the challenging epifluorohydrin **17a**, fluoromethylated oxetanes **17b** and **17c**, and tetrahydrofuran **17d** by the chemoselective intramolecular cyclization (Scheme 4b). Next, given the importance of β-fluoroamines, a 10 mmol preparation of **18** was achieved using a two-step sequence involving direct fluoromethylation of *N*-Boc-imine followed by acidic removal of the Boc group (Scheme 4c).

Scheme 4. Further Applications of the Direct Fluoromethylation Strategy



In conclusion, a novel one-pot strategy for direct nucleophilic fluoromethylation has been developed. This method overcomes the drawbacks associated with the use of auxiliary groups requiring proper removal after introduction of the fluorinated fragment. This work demonstrates that the fleeting carbenoid

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fluoromethyllithium can be efficiently exploited for synthetic purposes. Through fine-tuning of the reaction conditions it is possible to avoid decomposition of the intermediates, allowing the reaction to be carried out with various electrophiles, including structurally complex molecules. We believe that this work paves the way for further progress in fluoromethylation strategies and fluorinated organometallics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07891.

Procedures, optimization tables, and spectral data (PDF)
Crystallographic data for **14a** (CIF)
Crystallographic data for **11k** (CIF)

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Notes

The authors declare no competing financial interest.

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

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