

Fluoroiodomethane: A versatile CH₂F Source

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Vittorio Pace received his Ph.D. in Chemical Sciences from the Complutense University of Madrid in 2010. After post-doctoral training at Vienna, Manchester, and Stockholm, he obtained a tenure track position at the University of Vienna. In 2016 he received the Habilitation in Pharmaceutical Chemistry from the University of Vienna and in 2017 the Habilitation for Full Professor of Organic Chemistry.

Background

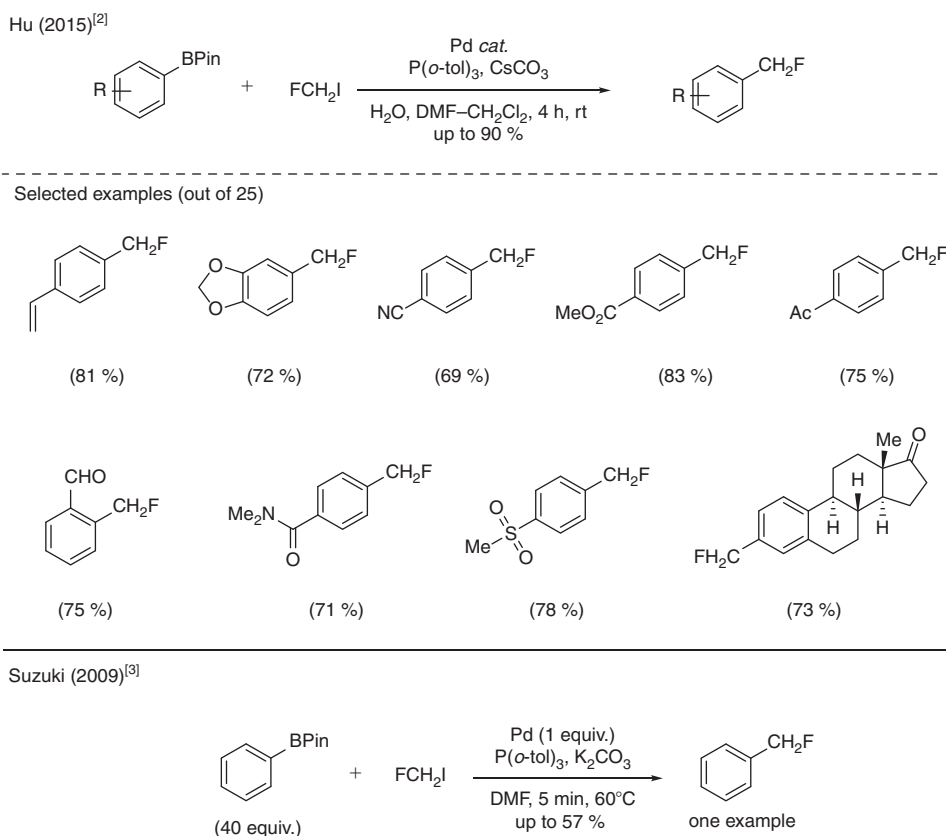
Fluoroiodomethane (FCH₂I, CAS 373-53-5) is a liquid (bp 53.4°C) that is easy to manipulate and useful as a precursor of the fluoromethyl (CH₂F) unit. This C1 building block features different reactivity for the two carbon halogen bonds: accordingly, the

CH₂-I linkage can be conveniently used for accomplishing nucleophilic substitution,^[1] iodine-metal exchange, or transition-metal catalysed processes, leaving the fluoromethyl motif intact.

Fluoromethylation of Aromatic Rings

In 2015, Hu reported the first example of a straightforward palladium-catalysed direct monofluoromethylation of aryl boronic esters having ICH₂F as the fluoromethyl donor unit (Scheme 1).^[2] The protocol is particularly attractive because of the mild reaction

conditions and the very good functional group tolerance. In this sense, Hu's procedure improved previous work by Suzuki, which involved the preparation of benzyl fluoride using pinacolboronate (40 equiv.) and stoichiometric palladium.^[3]

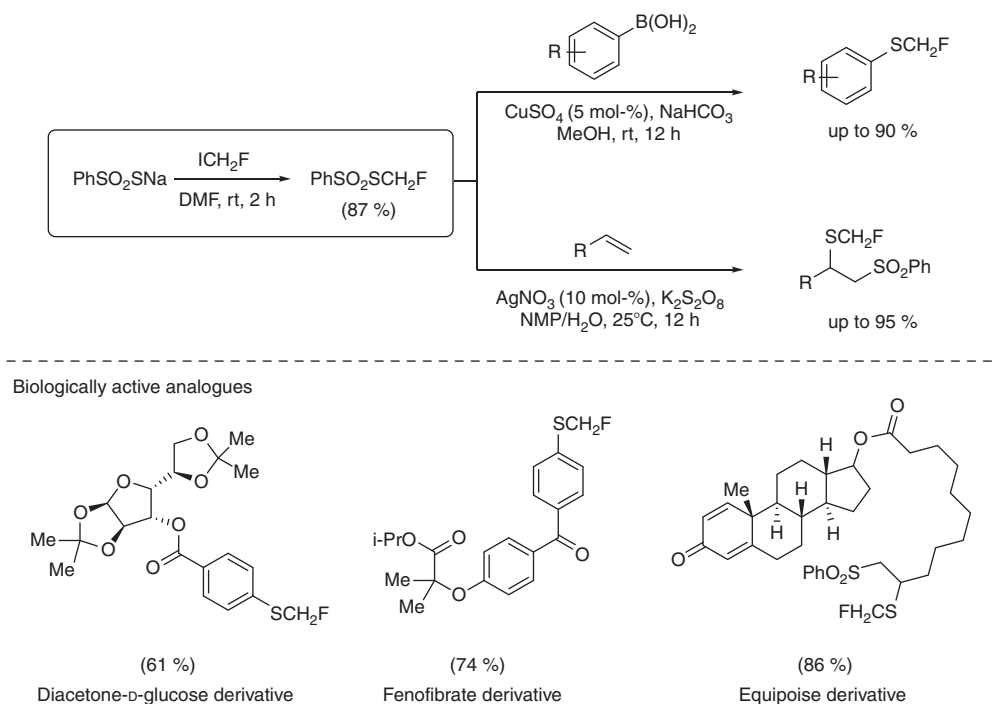


Scheme 1. Hu's and Suzuki's monofluoromethylation of arylboronate esters.

Preparation of a Fluoromethylthiolating Agent

Lu and Shen reported the preparation of a powerful electrophilic monofluoromethylthiolating reagent, *S*-(fluoromethyl)benzenesulfonothioate, by treating PhSO₂SNa with ICH₂F. The product provided better results than FCH₂Cl and was effective under mild conditions (Scheme 2).^[4] Subsequently, they investigated the

reactivity of various aryl boronic acids in the presence of a copper catalyst and olefins in the presence of a combination of a silver salt and an oxidant to give the corresponding monofluoromethylthioethers in high yields. This strategy, constituting an excellent tool for forming both C(sp²)- and C(sp³)-SCH₂F linkages, has a broad scope and can be conveniently adopted for preparing important drug derivatives.

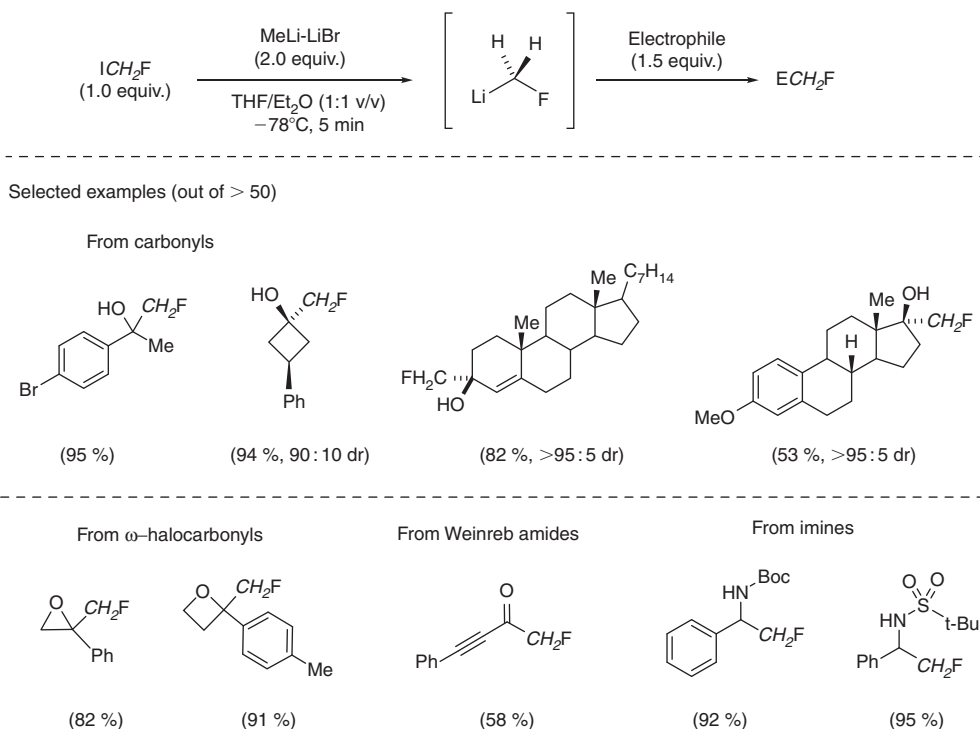


Scheme 2. Direct electrophilic monofluoromethylthiolation.

Use as Precursor of Fluoromethylolithium

In 2017, Pace, Luisi, and co-workers documented an unprecedented direct strategy enabling the nucleophilic fluoromethylation of carbon electrophiles (Scheme 3).^[5] The success of the transformation relies on the formation of the labile fluoromethylolithium via a fast iodine–lithium exchange carried out on ICH₂F with MeLi–LiBr in a 1 : 1 mixture of THF/Et₂O at –78 °C. Such a homologation tactic features a robust scope, thus allowing the straightforward formal insertion of a CH₂F fragment into a plethora of

electrophiles including carbonyls (aldehydes and ketones for accessing fluorinated alcohols), ω-halocarbonyls (which upon ring closure afford oxygenated cycles), Weinreb amides (as precursors of α-fluoroketones), and imines (for forming β-fluoroamines). Some additional points merit mention: 1) Despite the carbenoid nature of fluoromethylolithium,^[6] full chemoselectivity was observed with substrates bearing sensitive functionalities. 2) Good stereocontrol can be achieved during the addition. 3) The wide scope of the method means that complex structures are tolerated.

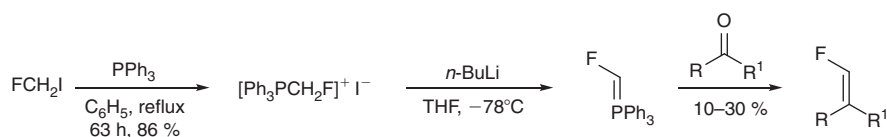


Scheme 3. Direct nucleophilic fluoromethylation.

Use in Wittig-Type Olefinations

Upon nucleophilic substitution with triphenylphosphine on ICH₂F, followed by deprotonation with *n*-butyllithium, Burton showed the formation of the corresponding Wittig-type ylide which reacted with carbonyl compounds giving fluoroolefins

(Scheme 4).^[7] However, the fact that only modest yields were obtained (~10–30%), and the requirement for an additional base to trigger the collapse of the intermediate betaine, limits the practical applicability of this methodology.



Scheme 4. Use of ICH₂F as a precursor of Wittig-type ylides.

Conclusions

Fluoroiodomethane is a convenient reagent with which to introduce the CH₂F fragment into organic or organometallic arrays. This is a particularly challenging task in synthetic chemistry as documented by the difficulties found in developing suitable monofluoromethylation strategies.^[8] The limited stability of CH₂F-containing

carbanions for a long time represented an important challenge for routine use in synthesis. In fact, classical approaches relied on stabilising the putative carbanion through the introduction of a strong electron withdrawing group (e.g. sulfone) whose removal, after accomplishing the desired insertion, was not trivial as this required harsh conditions, e.g. Na(Hg).

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgements

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