

Cite this: *Chem. Sci.*, 2021, 12, 12149

All publication charges for this article have been paid for by the Royal Society of Chemistry

Hydrofluoromethylation of alkenes with fluoroiodomethane and beyond†

Sandrine M. Hell,  ‡ Claudio F. Meyer,  ‡ Sebastiano Ortalli, ‡ Jeroen B. I. Sap, 
Xuanxiao Chen and Véronique Gouverneur  *

A process for the direct hydrofluoromethylation of alkenes is reported for the first time. This straightforward silyl radical-mediated reaction utilises CH_2FI as a non-ozone depleting reagent, traditionally used in electrophilic, nucleophilic and carbene-type chemistry, but not as a CH_2F radical source. By circumventing the challenges associated with the high reduction potential of CH_2FI being closer to CH_3I than CF_3I , and harnessing instead the favourable bond dissociation energy of the C–I bond, we demonstrate that feedstock electron-deficient alkenes are converted into products resulting from net hydrofluoromethylation with the intervention of $(\text{Me}_3\text{Si})_3\text{SiH}$ under blue LED activation. This deceptively simple yet powerful methodology was extended to a range of (halo)methyl radical precursors including ICH_2I , ICH_2Br , ICH_2Cl , and CHBr_2F , as well as CH_3I itself; this latter reagent therefore enables direct hydromethylation. This versatile chemistry was applied to ^{18}F -, ^{13}C -, and D-labelled reagents as well as complex biologically relevant alkenes, providing facile access to more than fifty products for applications in medicinal chemistry and positron emission tomography.

Received 23rd June 2021
Accepted 7th August 2021

DOI: 10.1039/d1sc03421a

rsc.li/chemical-science

Introduction

The introduction of fluoroalkyl groups has garnered significant interest in medicinal chemistry, enabling the modulation of biological and physicochemical properties of lead candidates for drug discovery.^{1–3} Whilst the fields of radical trifluoromethylation and difluoromethylation have been extensively explored,^{4–10} the fluoromethyl radical has received far less attention.^{11–13} This is unexpected as the fluoromethyl group features frequently in pharmaceutical drugs, more often to improve metabolic stability by serving as a bioisosteric replacement of functional groups responsible for poor performance.^{14,15} In recent years, several reagents for the generation of the CH_2F radical have been developed.^{16–20} Often, efficient activation of these reagents requires harsh reaction conditions, such as elevated temperatures, strong oxidants, or strong reductants. Furthermore, many of these reagents are either expensive, highly toxic or non-commercial, requiring multistep syntheses for their preparation. As part of our growing interest in developing “minimalistic” procedures for the late-stage hydrofluoroalkylation of alkene-containing biologically active molecules,^{21–23} we sought to develop an operationally simple method for the direct hydrofluoromethylation of alkenes, as an

attractive strategy for the introduction of this motif to $\text{C}(\text{sp}^3)$ -enriched backbones (Scheme 1).

In 2020, an indirect method for the hydrofluoromethylation of alkenes was developed by Aggarwal and co-workers;¹³ this elegant multi-step procedure starts with the conversion of alkenes into boronic esters, subsequent treatment at low temperature (-78°C) with *in situ* formed fluoroiodomethyl lithium to generate fluoroboronic esters, and a final protodeboronation. Our aim was to develop a one-step method that avoids operational complexity and over-engineering, ideally using fluoroiodomethane which is a non-ozone depleting, easy to handle and inexpensive commercial CH_2F radical precursor. We noted that fluoroiodomethane has found applications as an electrophilic or nucleophilic fluoromethylation reagent as well as in cross-coupling reactions,^{24–27} but has not been explored in the context of radical chemistry.

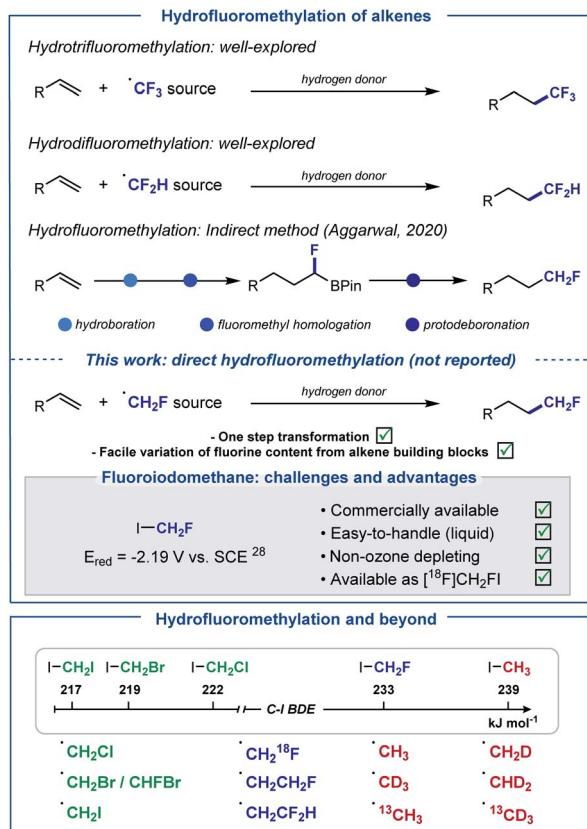
The high reduction potential of CH_2FI ($E_{\text{red}} = -2.19$ V vs. saturated calomel electrode (SCE) in MeCN),²⁸ much closer to MeI ($E_{\text{red}} = -2.39$ V vs. SCE in MeCN)²⁸ than CF_3I ($E_{\text{red}} = -1.22$ V vs. SCE in MeCN),²⁹ encouraged the implementation of an activation pathway exploiting instead the favourable bond dissociation energy (BDE) of C–I (BDE ($\text{FH}_2\text{C}-\text{I}$) = 233 kJ mol⁻¹) versus C–F (BDE ($\text{IH}_2\text{C}-\text{F}$) = 460 kJ mol⁻¹).³⁰ Since the pioneering work of Chatgililoglu,³¹ tris(trimethylsilyl)silane (TTMSS) has found ample applications as a powerful tool for mild radical generation *via* the activation of alkyl halides.^{32–36} In addition, TTMSS has valuably complemented Giese-type reactions, a commonly exploited platform for late-stage functionalisation, by providing a suitable alternative to traditional toxic

University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: veronique.gouverneur@chem.ox.ac.uk

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc03421a

‡ These authors contributed equally to this work.





Scheme 1 Hydro(per)fluoromethylation of alkenes. This work: direct silyl radical-mediated hydrofluoromethylation of electron-deficient alkenes and extension to numerous hydro(halo)methylation reactions.

tin-based reagents.³⁷ Consequently, we envisioned that the supersilyl radical $(TMS)_3Si^\cdot$ would be well suited to release $\cdot CH_2F$ from CH_2FI . Subsequent Giese-type addition of $\cdot CH_2F$ to the electron-deficient alkene would generate a carbon-centered radical intermediate. Hydrogen-atom transfer (HAT) between this electrophilic species and hydridic $(TMS)_3SiH$ would afford the desired hydrofluoromethylated product, and $(TMS)_3Si^\cdot$ entering chain propagation. Initiation for this process would be triggered by photolytic C-I cleavage of FH_2C-I .³⁸ This method offers the prospect of being applicable to a range of other halo-containing alkyl radicals, provided that competitive hydrogen atom abstraction with $(TMS)_3SiH$ does not occur prior to Giese addition. Herein, we report the realisation of this strategy with a wide range of haloiodomethanes for the direct hydrohalomethylation of electron-deficient alkenes including biologically relevant molecules. The method was extended to ¹⁸F-hydrofluoromethylation and hydromethylation with iodo-methane along with five of its D and ¹³C isotopomers.

Results and discussion

Preliminary experiments were conducted with *N*-phenyl acrylamide (**1a**) (Table 1).³⁹ Various combinations of silanes and solvents revealed that the desired hydrofluoromethylated product (**2a**) was obtained in 71% with $(TMS)_3SiH$ in MeCN at

Table 1 Hydrofluoromethylation of *N*-phenyl acrylamide **1a**^a



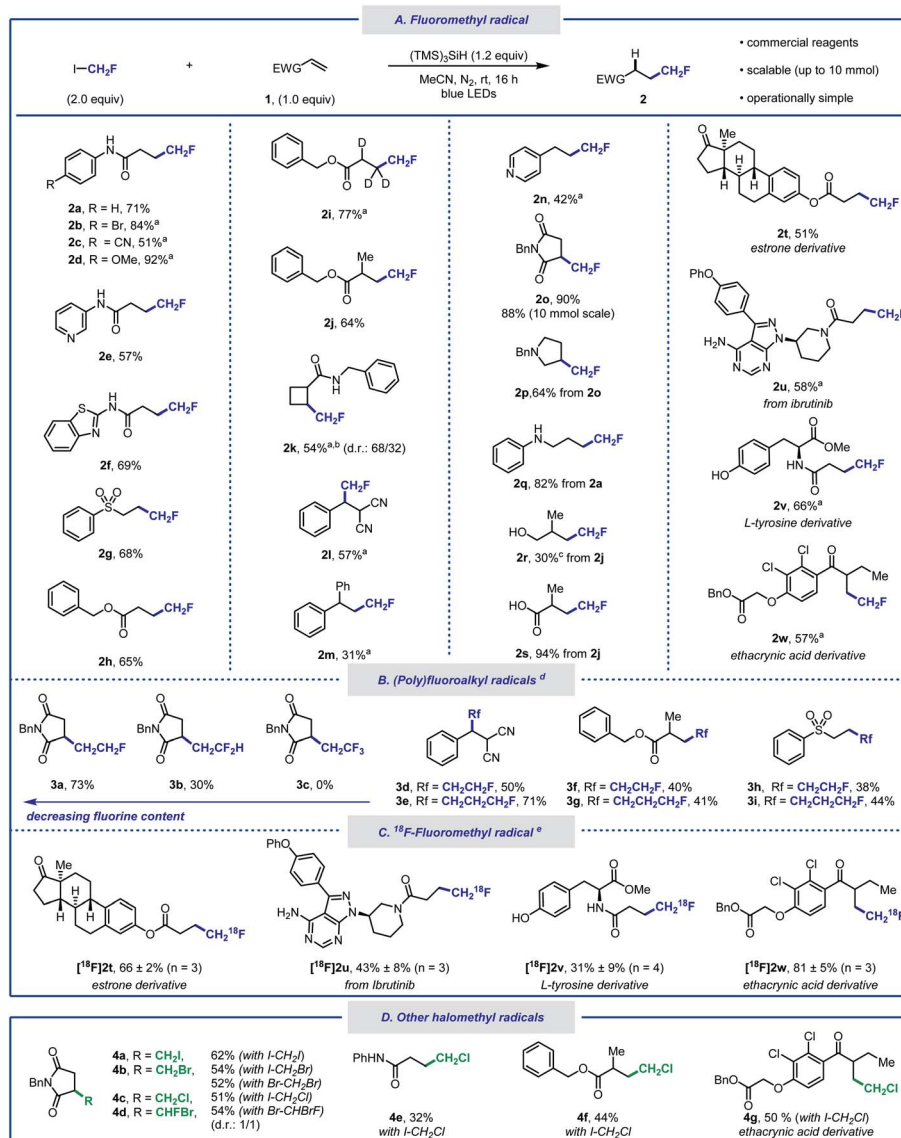
Entry	Deviations from standard conditions	Yield (%)
1	None	71
2	With <i>fac</i> -Ir(ppy) ₃ (0.5 mol%)	75
3	No light	Traces
4	No silane	0
5	With TEMPO (4.0 equiv.) ^b	0

^a Reaction conditions: CH_2FI (0.2 mmol), **1a** (0.1 mmol), $(TMS)_3SiH$ (0.12 mmol), solvent (0.6 mL) under blue light ($\lambda_{max} = 450 \text{ nm}$) irradiation for 16 h. Yields of isolated products. ^b Addition of 4.0 equiv. of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxy). TEMPO- CH_2F was observed in quantitative ¹⁹F NMR analysis of the crude reaction mixture using α,α,α -trifluorotoluene as an internal standard. *fac*-Ir(ppy)₃ = tris[2-phenylpyridinato-C2,N]iridium(III).

room temperature under blue light irradiation for 16 h (entry 1).⁴⁰ The addition of *fac*-Ir(ppy)₃ (0.5 mol%) did not lead to significant improvement (entry 2). The simpler protocol was therefore retained for further investigations. Control experiments indicate that the reaction was not effective in absence of light (entry 3), and unsuccessful in absence of silane or in presence of the radical scavenger TEMPO (entries 4 and 5). No deuterium incorporation was observed in the product when the reaction was performed in CD_3CN .⁴⁰ These data corroborate our proposed radical chain propagation mechanism, initiated by blue-light homolysis of the CH_2F-I bond.³⁸ Giese addition of the fluoromethyl radical to an electron-deficient alkene furnishes an electrophilic carbon-centered radical intermediate, capable of undergoing HAT with $(TMS)_3SiH$. The resulting silyl radical enables chain propagation by abstracting iodine from CH_2FI to afford $(TMS)_3SiI$ along with $\cdot CH_2F$.⁴⁰

With the optimised reaction conditions in hand, we sought to explore the scope of this hydrofluoromethylation protocol (Scheme 2A). Various functional groups, such as methoxy, nitrile, halide, ketone, ether, amide, ester, aniline, and sulfone were tolerated. The addition of *fac*-Ir(ppy)₃ (0.5 mol%) led to higher yields for selected substrates.⁴⁰ *N*-Aryl acrylamides bearing electron-withdrawing and electron-donating groups afforded the desired products in moderate to excellent yields (**2a-d**). The hydrofluoromethylation of *N*-heteroaryl acrylamides, such as pyridyl and benzothiazyl was also successful (**2e, 2f**). Alkenes substituted with sulfones and esters were competent substrates generating **2g** and **2h** in moderate yield. As deuteration can improve metabolic stability,⁴¹ we investigated the hydrofluoromethylation of a deuterated alkene (**1i**) that was successfully converted into $[D_3]2i$. The *gem*-disubstituted alkene **1j** provided **2j** in 64% yield. Pleasingly, the internal alkene **1k** was reactive under our reaction conditions and afforded fluoromethylcyclobutane **2k** in moderate yield. This result is significant as 1,2-disubstituted fluoroalkyl cyclobutanes currently require multiple steps for their preparation.⁴² A non-





Scheme 2 Substrate scope of the hydro(halo)methylation of electron-deficient alkenes. Reaction conditions: alkene (0.5 mmol), (TMS)₃SiH (0.6 mmol), radical precursor (1.0 mmol), MeCN (3.0 mL), N₂ atmosphere, blue light (λ_{max} = 450 nm) irradiation for 16 h, room temperature. (a) Reaction performed with *fac*-Ir(ppy)₃ (0.5 mol%). (b) Product isolated as a mixture of diastereomers. (c) Yield determined by quantitative ¹H NMR using triphenylmethane as an internal standard. (d) Reaction performed using (poly)fluoroalkyl iodide. (e) ¹⁸F-Hydrofluoromethylation performed with [¹⁸F]CH₂FI. Reaction conditions: [¹⁸F]CH₂FI (10 MBq), alkene (0.1 mmol), (TMS)₃SiH (0.12 mmol), *fac*-Ir(ppy)₃ (0.5 mol%), DMF (0.6 mL), blue light (λ_{max} = 450 nm) irradiation for 20 min, room temperature.

cyclic trisubstituted alkene afforded the product in 57% yield (**2l**). Styrene derivatives such as **1m** and **1n** afforded the desired products in synthetically useful yields (**2m**, **2n**). Our protocol is amenable to scale-up as demonstrated by the 10 mmol scale hydrofluoromethylation of *N*-benzylmaleimide affording **2o** in 88% yield. The synthesis of fluorinated pyrrolidine **2p**, amine **2q**, alcohol **2r** and carboxylic acid **2s** was performed in two steps, offering a pathway to diversify the range of products within reach from CH₂FI. The late-stage hydrofluoromethylation of complex biologically active molecules was considered next. The anti-cancer drug ibrutinib as well as estrone, tyrosine and ethacrynic acid derivatives afforded the desired hydrofluoromethylated products in good yields (**2t–w**).

The tolerance of functional groups was investigated with a robustness screening.⁴⁰ These experimental data provide an overview of the many heteroarenes (e.g. pyridazine, 1,3,5-triazine, indole, benzothiazole or oxazole) that are tolerated under the optimised reaction conditions.

Whilst additives containing nucleophilic functional groups such as alcohols and anilines were tolerated, side reactivity arising from nucleophilic substitution was observed.⁴⁰ Competitive alkylation was suppressed when using 1.0 equivalent of CH₂FI, albeit at the expense of reduced yield for the hydrofluoromethylated product. Aliphatic amines were tolerated but yields did not exceed 30%.⁴⁰ The hydrofluoromethylation of alkenes not bearing electron-withdrawing

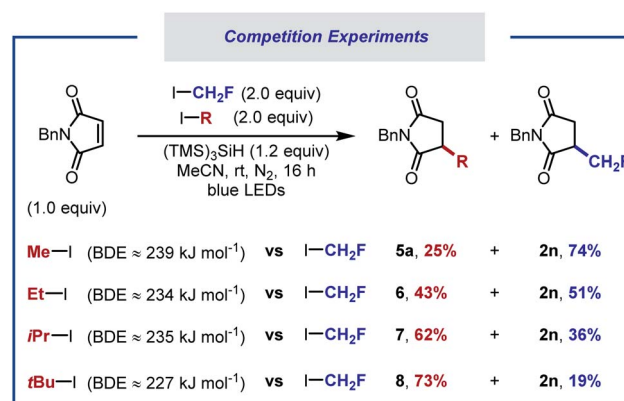


groups was possible albeit significantly less efficient.⁴⁰ With a protocol relying on the favourable C–I bond dissociation energy and considering the importance of homologation in medicinal chemistry,⁴³ we considered the generation of products from a series of homologated fluoroiodoalkanes (Scheme 2B).^{44,45} Hydrofluoroalkylation of alkenes **1g**, **1j** and **1l** provided effortlessly the homologous series of products **3d–i**. Specifically, the fluoroethyl radical was efficiently generated applying similar silyl radical activation, and **3a** was isolated in good yield. The introduction of the fluoroethyl radical was successfully performed on linear terminal, *gem*-disubstituted, and trisubstituted alkenes (**3d**, **3f**, **3h**). The method was further extended to fluoroiodopropane as shown with the synthesis of **3e**, **3g**, and **3i**. Precursors featuring additional fluorine atoms were less suitable with the difluoroethylated product **3b** isolated in 30%, and no product observed when attempting to prepare the hydrotrifluoroethylated product **3c**. Increased fluorine content enhances radical electrophilicity, thereby encouraging undesired H-atom abstraction from (TMS)₃SiH.⁴⁰

Given the success of our protocol, we further investigated the applicability of our method for the generation of [¹⁸F]CH₂F radical from [¹⁸F]CH₂FI (Scheme 2C).^{46–48} Compounds labelled with the radioisotope F-18 are important for applications in Positron Emission Tomography (PET).^{49–53} The synthesis of [¹⁸F]CH₂FI in high molar activity (*A_m*) is well-established and has been automated.^{54–57} To date, this labelled reagent is mainly employed for the electrophilic ¹⁸F-fluoromethylation of phenols.^{58,59} We now demonstrate that [¹⁸F]CH₂FI is well suited for [¹⁸F]CH₂F radical chemistry. Specifically, Ibrutinib, an estrone, a tyrosine, and an ethacrynic acid derivative underwent ¹⁸F-hydrofluoromethylation in radiochemical yields up to 81% ([¹⁸F]**2t–w**). This reaction was best performed for 20 minutes at ambient temperature in the presence of *fac*-Ir(ppy)₃ under blue-light irradiation. This method offers an alternative to nucleophilic ¹⁸F-fluorination with [¹⁸F]fluoride for precursors that are either unstable, require complex multiple steps synthesis, or lead predominantly to elimination products. Haliodomethanes other than fluoroiodomethane were also considered as they would allow for the one-step introduction of reactive halomethyl groups to alkenes (Scheme 2D). Controlled activation of reagents such as ICH₂X (X = Cl, Br, I) would enable their use for example as [•]CH₂⁺ synthon. To date, only few examples for the generation and use of halomethyl radicals have been reported.^{60–64} When diiodomethane was employed under the standard reaction conditions, *N*-benzylmaleimide underwent hydroiodomethylation in 62% yield (**4a**). Similarly, hydrobromomethylation (from dibromomethane or bromiodomethane), hydrochloromethylation (from chloriodomethane), and hydrobromofluoromethylation (from dibromofluoromethane) provided the corresponding halomethyl alkanes in moderate yields (**4b–4d**).^{23,65} Other alkenes afforded the hydrochloromethylated products in moderate yields (**4e–4g**). Although full conversion of starting material was observed for these reactions, purification *via* silica gel chromatography led to elimination, which is reflected in the lower yield for these compounds upon isolation.

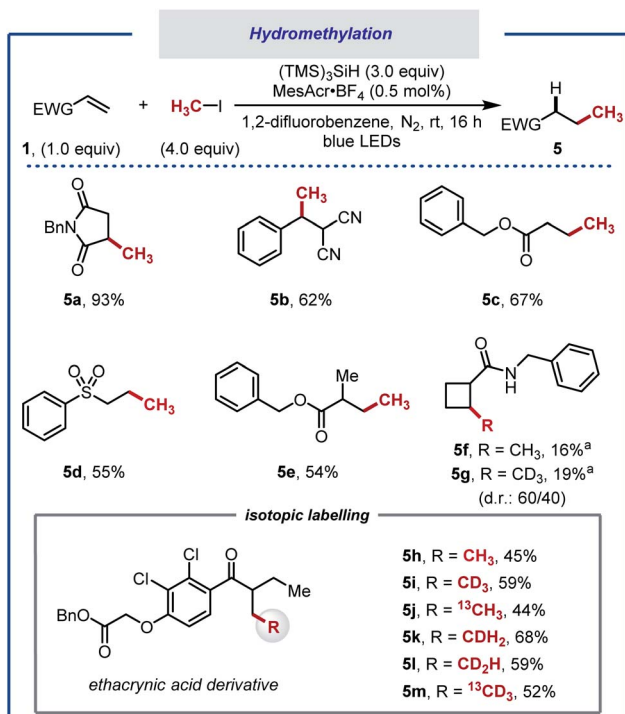
Competition experiments were performed to calibrate the reactivity of fluoroiodomethane *versus* other alkyl iodides (Scheme 3). When equimolar amounts of iodomethane and fluoroiodomethane were subjected to the standard reaction conditions, product resulting from fluoromethyl radical addition was obtained in 74% yield (**2n**), along with 25% of the hydromethylated product **5a**. When the reaction was carried out with equimolar amounts of iodoethane, products **2n** and **6** were formed in close to 1 : 1 ratio. Additional competition experiments showed that the *iso*-propyl and *tert*-butyl adducts (**7**, **8**) were formed preferentially over the hydrofluoromethylated product. The reactivity of these alkyl iodides therefore decreases in the following order: *t*BuI > *i*PrI > CH₂FI ~ EtI > MeI.

A notable outcome of this study was the observation that net methane addition across the double bond took place with iodomethane. Currently, protocols for the generation of the methyl radical from iodomethane (BDE_{CH₃-I} = 239 kJ mol⁻¹, *E_{red}* = -2.39 V *vs.* SCE in MeCN) remain underdeveloped.^{34,66} In recent years, the methyl radical has been generated from numerous precursors.^{67–71} The formation of the methyl radical often requires harsh reaction conditions, limiting the applicability of these protocols. Furthermore, the use of the methyl radical towards application to isotopic labelling is far from trivial. Iodomethane, on the other hand, can provide effortless access to a variety of useful isotopologues that would otherwise be beyond reach. The straightforwardness of our protocol prompted us to optimise the hydromethylation of alkenes using iodomethane as methyl radical precursor (Scheme 4). We noted significant gas release when applying our reaction conditions, attributed to methane resulting from competitive HAT between the methyl radical and MeCN (BDE_{NCCH₂-H} = 389 kJ mol; BDE_{CH₃-H} = 439 kJ mol⁻¹).⁶⁹ A screen of solvents, reactants stoichiometry and photocatalysts allowed for hydromethylation to occur in up to 93% yield (**5a**).⁴⁰ Under the optimised reaction conditions consisting of 4.0 equivalents of MeI, 3.0 equivalents of (TMS)₃SiH and 1,2-difluorobenzene as solvent, in combination with photocatalyst MesAcrBF₄ (0.5 mol%), the hydromethylation of various alkenes took place in good to excellent yield (**5b–f**). Considering that bioactive compounds containing



Scheme 3 Competition experiments with equimolar amounts of different alkyl iodides.





Scheme 4 Hydromethylation of electron-deficient alkenes. Reaction conditions: alkene (0.5 mmol), $(\text{TMS})_3\text{SiH}$ (1.5 mmol), iodomethane (2.0 mmol), 1,2-difluorobenzene (3.0 mL), N_2 atmosphere, blue light ($\lambda_{\text{max}} = 450 \text{ nm}$) irradiation for 16 h, room temperature. (a) Product isolated as a mixture of diastereomers.

stable heavy isotopes are useful for example as mass spectroscopy standards,^{41,72} the hydromethylation of an ethacrynic acid derivative was performed with CH_3I , CH_2DI , CHD_2I , CD_3I , $^{13}\text{CH}_3\text{I}$, and $^{13}\text{CD}_3\text{I}$. All six isotopologues (**5h–5m**) were obtained in moderate yield.^{73–75}

Conclusions

In conclusion, the first direct hydrofluoromethylation of a broad range of electron-deficient alkenes has been developed using fluoriodomethane. Mechanistically, the process harnesses known principles; so its core value is rooted in its immediate synthetic power. With the current global necessity “to do more with less”, this minimalistic and mild chemical method stands out as it is operationally simple with the supersilyl radical precursor $(\text{TMS})_3\text{SiH}$ being the only chemical required in addition to the reaction partners. The mild reaction conditions are compatible with complex biologically active molecules such as Ibrutinib. The methodology was successfully adapted for the ^{18}F -labelling of complex alkenes, and offers a new $\text{C}-\text{CH}_2-^{18}\text{F}$ disconnection strategy for radiotracer development. The method was extended to additional fluoroalkanes enabling facile product homologation, as well as multiple (halo)methyl radicals including the methyl radical itself and five of its D and ^{13}C isotopomers.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

S. M. H., C. F. M., S. O. and J. B. I. S. performed the experiments and analysed the results. C. F. M. and X. C. performed the cyclic voltammetry experiments. S. M. H., C. F. M., S. O., J. B. I. S. and V. G. designed the project and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge Prof. Benjamin Davis and Prof. Jason J. Davis for insightful comments on the manuscript, and useful discussions. This project has received funding from the European Union’s Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 721902 (S. M. H. and C. F. M.). J. B. I. S. acknowledges financial support from an EPSRC Doctoral Prize (EP/T517811/1).

Notes and references

- 1 Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797–804.
- 2 N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880.
- 3 M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633–10640.
- 4 D. A. Nagib and D. W. C. Macmillan, *Nature*, 2011, **480**, 224–228.
- 5 A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950–8958.
- 6 T. Koike and M. Akita, *Top. Catal.*, 2014, **57**, 967–974.
- 7 C. Le, T. Q. Chen, T. Liang, P. Zhang and D. W. C. Macmillan, *Science*, 2018, **360**, 1010–1014.
- 8 T. Koike and M. Akita, *Org. Biomol. Chem.*, 2019, **17**, 5413–5419.
- 9 J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. am Ende, A. A. Trabanco and V. Gouverneur, *Chem. Soc. Rev.*, 2021, **50**, 8214–8247.
- 10 X. J. Tang, Z. Zhang and W. R. Dolbier, *Chem.–Eur. J.*, 2015, **21**, 18961–18965.
- 11 Y. Li, C. Ni, J. Liu, L. Zhang, J. Zheng, L. Zhu and J. Hu, *Org. Lett.*, 2006, **8**, 1693–1696.
- 12 G. K. S. Prakash, S. Chacko, S. Alconcel, T. Stewart, T. Mathew and G. A. Olah, *Angew. Chem., Int. Ed.*, 2007, **46**, 4933–4936.
- 13 V. Fasano, N. Winter, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2020, **59**, 8502–8506.
- 14 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.



- 15 B. M. Johnson, Y. Z. Shu, X. Zhuo and N. A. Meanwell, *J. Med. Chem.*, 2020, **63**, 6315–6386.
- 16 Y. Fujiwara, J. A. Dixon, F. O'hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95–99.
- 17 X. J. Tang and W. R. Dolbier, *Angew. Chem., Int. Ed.*, 2015, **54**, 4246–4249.
- 18 L. An, Y. L. Xiao, Q. Q. Min and X. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 9079–9083.
- 19 N. Noto, T. Koike and M. Akita, *ACS Catal.*, 2019, **9**, 4382–4387.
- 20 J. Sheng, H.-Q. Ni, S.-X. Ni, Y. He, R. Cui, G.-X. Liao, K.-J. Bian, B.-B. Wu and X.-S. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 15020–15027.
- 21 S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Médebielle and V. Gouverneur, *J. Am. Chem. Soc.*, 2013, **135**, 2505–2508.
- 22 C. F. Meyer, S. M. Hell, A. Misale, A. A. Trabanco and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2019, **58**, 8829–8833.
- 23 C. F. Meyer, S. M. Hell, J. B. I. Sap, A. Misale, A. Peschiulli, D. Oehlich, A. A. Trabanco and V. Gouverneur, *Tetrahedron*, 2019, **75**, 130679.
- 24 J. Hu, B. Gao, L. Li, C. Ni and J. Hu, *Org. Lett.*, 2015, **17**, 3086–3089.
- 25 G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace and R. Luisi, *J. Am. Chem. Soc.*, 2017, **139**, 13648–13651.
- 26 N. Y. Wu, X. H. Xu and F. L. Qing, *ACS Catal.*, 2019, **9**, 5726–5731.
- 27 R. Senatore, M. Malik, M. Spreitzer, W. Holzer and V. Pace, *Org. Lett.*, 2020, **22**, 1345–1349.
- 28 Cyclic voltammetry experiments of CH₂FI and CH₃I are described in the ESI.†
- 29 S. M. Bonesi and R. Erra-Balsells, *J. Chem. Soc., Perkin Trans. 2*, 2000, **2**, 1583–1595.
- 30 Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, 2002.
- 31 C. Chatgialloglu, C. Ferreri, Y. Landais and V. I. Timokhin, *Chem. Rev.*, 2018, **118**, 6516–6572.
- 32 J. J. Devery, J. D. Nguyen, C. Dai and C. R. J. Stephenson, *ACS Catal.*, 2016, **6**, 5962–5967.
- 33 P. Zhang, C. Le and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2016, **138**, 8084–8087.
- 34 R. Kumar, N. J. Flodén, W. G. Whitehurst and M. J. Gaunt, *Nature*, 2020, **581**, 415–420.
- 35 S. M. Hell, C. F. Meyer, A. Misale, J. B. I. Sap, K. E. Christensen, M. C. Willis, A. A. Trabanco and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2020, **59**, 11620–11626.
- 36 S. M. Hell, C. F. Meyer, G. Laudadio, A. Misale, M. C. Willis, T. Noël, A. A. Trabanco and V. Gouverneur, *J. Am. Chem. Soc.*, 2020, **142**, 720–725.
- 37 C. Chatgialloglu and J. Lalevée, *Molecules*, 2012, **17**, 527–555.
- 38 Initiation leading to alkyl radical from alkyl iodide *via* light mediated C–I bond homolyses is documented. For a recent example, see: Y. Cheng, C. Mück-Lichtenfeld and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 16832–16836.
- 39 Current methods available to access γ -fluoro carbonyl derivatives such as **2a** are multistep sequences starting with γ -hydroxybutyric acid (or equivalent), a controlled substance with neurotoxic properties.
- 40 For further details, see ESI.†
- 41 S. Kaur and S. Gupta, *Global Journal of Pharmacy & Pharmaceutical Science*, 2017, **1**, 555566.
- 42 A. Skreminskiy, D. M. Volochnyuk and O. Oleksandr, *Eur. J. Org. Chem.*, 2021, **2021**, 87–95.
- 43 L. M. Lima, M. A. Alves and D. N. Do Amaral, *Curr. Top. Med. Chem.*, 2019, **19**, 1734–1750.
- 44 L. M. Kreis, S. Krautwald, N. Pfeiffer, R. E. Martin and E. M. Carreira, *Org. Lett.*, 2013, **15**, 1634–1637.
- 45 B. He, Q. Pan, Y. Guo, Q. Y. Chen and C. Liu, *Org. Lett.*, 2020, **22**, 6552–6556.
- 46 L. Trump, A. Lemos, B. Lallemand, P. Pasau, J. Mercier, C. Lemaire, A. Luxen and C. Genicot, *Angew. Chem., Int. Ed.*, 2019, **58**, 13149–13154.
- 47 C. W. Kee, O. Tack, F. Guibbal, T. C. Wilson, P. G. Isenegger, M. Imiołek, S. Verhoog, M. Tilby, G. Boscutti, S. Ashworth, J. Chupin, R. Kashani, A. W. J. Poh, J. K. Sosabowski, S. Macholl, C. Plisson, B. Cornelissen, M. C. Willis, J. Passchier, B. G. Davis and V. Gouverneur, *J. Am. Chem. Soc.*, 2020, **142**, 1180–1185.
- 48 H. Doi, M. Goto and M. Suzuki, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 1233–1238.
- 49 P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem., Int. Ed.*, 2008, **47**, 8998–9033.
- 50 S. L. Pimlott and A. Sutherland, *Chem. Soc. Rev.*, 2011, **40**, 149–162; G. C. Van de Bittner, E. L. Ricq and J. M. A. Hooker, *Acc. Chem. Res.*, 2014, **47**, 3127–3134.
- 51 M. S. Placzek, W. Zhao, H. Y. Wey, T. M. Morin and J. M. Hooker, *Semin. Nucl. Med.*, 2016, **46**, 20–27.
- 52 M. G. Campbell, J. Mercier, C. Genicot, V. Gouverneur, J. M. Hooker and T. Ritter, *Nat. Chem.*, 2017, **9**, 1–3.
- 53 D. Van der Born, A. Pees, A. J. Poot, R. V. A. Orru, A. D. Windhorst and D. J. Vugts, *Chem. Soc. Rev.*, 2017, **46**, 4709–4773.
- 54 L. Zheng and M. S. Berridge, *Appl. Radiat. Isot.*, 2000, **52**, 55–61.
- 55 J. Bergman, O. Eskola, P. Lehtikoinen and O. Solin, *Appl. Radiat. Isot.*, 2001, **54**, 927–933; M. R. Zhang, M. Ogawa, K. Furutsuka, Y. Yoshida and K. Suzuki, *J. Fluorine Chem.*, 2004, **125**, 1879–1886.
- 56 M. R. Zhang, J. Maeda, M. Ogawa, J. Noguchi, T. Ito, Y. Yoshida, T. Okauchi, S. Obayashi, T. Suhara and K. Suzuki, *J. Med. Chem.*, 2004, **47**, 2228–2235.
- 57 F. T. Chin, C. L. Morse, H. U. Shetty and V. W. Pike, *J. Labelled Compd. Radiopharm.*, 2006, **49**, 17–31.
- 58 M. R. Zhang, J. Maeda, K. Furutsuka, Y. Yoshida, M. Ogawa, T. Suhara and K. Suzuki, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 201–204.
- 59 J. Zessin, O. Eskola, P. Brust, J. Bergman, J. Steinbach, P. Lehtikoinen, O. Solin and B. Johannsen, *Nucl. Med. Biol.*, 2001, **28**, 857–863.



- 60 S. Bailleux, P. Dréan, Z. Zelinger, S. Civiš, H. Ozeki and S. Saito, *J. Chem. Phys.*, 2005, **122**, 134302–134306.
- 61 A. M. Del Hoyo and M. G. Suero, *Eur. J. Org. Chem.*, 2017, **15**, 2122–2125.
- 62 A. M. Del Hoyo, A. G. Herraiz and M. G. Suero, *Angew. Chem., Int. Ed.*, 2017, **56**, 1610–1613.
- 63 J. Dong, X. Wang, Z. Wang, H. Song, Y. Liu and Q. Wang, *Chem. Commun.*, 2019, **55**, 11707–11710.
- 64 Q. Zhu and D. G. Nocera, *J. Am. Chem. Soc.*, 2020, **142**, 17913–17918.
- 65 F. Chen, X. H. Xu and F. L. Qing, *Org. Lett.*, 2021, **23**, 2364–2369.
- 66 L. Hu, X. Liu and X. Liao, *Angew. Chem., Int. Ed.*, 2016, **55**, 9743–9747.
- 67 X. Bao, T. Yokoe, T. M. Ha, Q. Wang and J. Zhu, *Nat. Commun.*, 2018, **9**, 1–8.
- 68 A. Hu, J. J. Guo, H. Pan and Z. Zuo, *Science*, 2018, **361**, 668–672.
- 69 G. Laudadio, Y. Deng, K. Wal, W. Van Der, D. Ravelli, M. Nunō, M. Fagnoni, D. Guthrie, Y. Sun and T. Noël, *Science*, 2020, **369**, 92–96.
- 70 S. K. Kariofillis, B. J. Shields, M. A. Tekle-Smith, M. J. Zacuto and A. G. Doyle, *J. Am. Chem. Soc.*, 2020, **142**, 7683–7689.
- 71 R. W. Pipal, K. T. Stout, P. Z. Musacchio, S. Ren, T. J. A. Graham, S. Verhoog, L. Gantert, T. G. Lohith, A. Schmitz, H. S. Lee, D. Hesk, E. D. Hostetler, I. W. Davies and D. W. C. MacMillan, *Nature*, 2021, **589**, 542–554.
- 72 J. Atzrodt, V. Derdau, T. Fey and J. Zimmermann, *Angew. Chem., Int. Ed.*, 2007, **46**, 7744–7765.
- 73 K. Kloiber, R. Spitzer, M. Tollinger, R. Konrat and C. Kreutz, *Nucleic Acids Res.*, 2011, **39**, 4340–4351.
- 74 G. Nestor, T. Anderson, S. Oscarson and A. M. Gronenborn, *J. Am. Chem. Soc.*, 2017, **139**, 6210–6216.
- 75 F. A. Gallagher, R. Woitek, M. A. McLean, A. B. Gill, R. M. Garcia, E. Provenzano, F. Riemer, J. Kaggie, A. Chhabra, S. Ursprung, J. T. Grist, C. J. Daniels, F. Zaccagna, M. C. Laurent, M. Locke, S. Hilborne, A. Frary, T. Torheim, C. Bournnell, A. Schiller, I. Patterson, R. Slough, B. Carmo, J. Kane, H. Biggs, E. Harrison, S. S. Deen, A. Patterson, T. Lanz, Z. Kingsbury, M. Ross, B. Basu, R. Baird, D. J. Lomas, E. Sala, J. Wason, O. M. Rueda, S. F. Chin, I. B. Wilkinson, M. J. Graves, J. E. Abraham, F. J. Gilbert, C. Caldas and K. M. Brindle, *Proc. Natl. Acad. Sci. U. S. A.*, 2020, **117**, 2092–2098.

