

Direct and Chemoselective Electrophilic Monofluoromethylation of Heteroatoms (O-, S-, N-, P-, Se-) with Fluoroiodomethane

Raffaele Senatore, Monika Malik, Markus Spreitzer, Wolfgang Holzer, and Vittorio Pace*



Cite This: <https://dx.doi.org/10.1021/acs.orglett.9b04654>



Read Online

ACCESS |



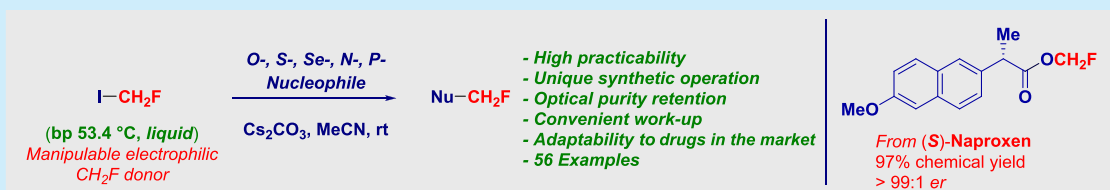
Metrics & More



Article Recommendations



Supporting Information



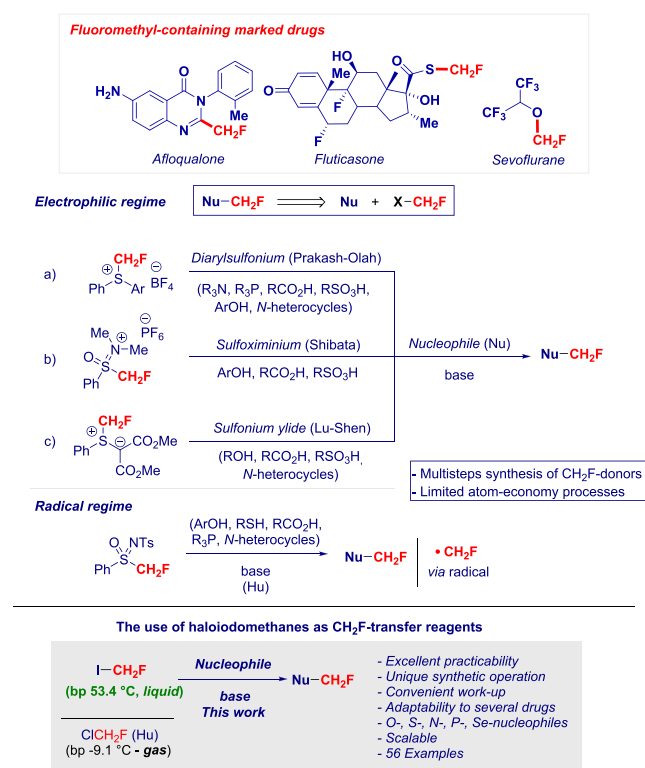
ABSTRACT: The commercially available fluoroiodomethane represents a valuable and effective electrophilic source for transferring the CH_2F unit to a series of heteroatom-centered nucleophiles under mild basic conditions. The excellent manipulability offered by its liquid physical state (bp 53.4 °C) enables practical and straightforward one-step nucleophilic substitutions to retain the chiral information embodied, thus allowing it to overcome *de facto* the requirement for fluoromethylating agents with no immediate access. The high-yielding methodology was successfully applied to a variety of nucleophiles including a series of drugs currently in the market.

Modulating critical physicochemical parameters of organic arrays through the introduction of fluorine-containing motifs represents an established tool in modern chemistry.¹ Accordingly, significant fine-tuning of metabolic stability and lipophilicity within the drug optimization process, *inter alia*, is achieved by exploiting some of the unique properties offered by embodying fluorine such as its small van der Waals radius (1.47 Å)² and its high electronegativity.³ Evidently, depending on the desired degree of fluorination of a given carbon skeleton, a multitude of synthetic techniques can be devised.⁴ Although a plethora of methodologies have emerged for introducing polyfluorinated methyl fragments ($-\text{CF}_3$ and $-\text{CHF}_2$ groups),^{4a,5} protocols for formally transferring the monofluoromethyl (CH_2F) analogue—an isostere for CH_3 or CH_2OH groups—onto a valuable heteroatom remain still underdeveloped.⁶ This aspect is particularly elusive when compared to the widespread relevance of this motif in pharmaceuticals as illustrated in the cases of afloqualone, fluticasone, or sevoflurane *inter alia* (Scheme 1).^{3,7} From a retrosynthetic perspective, the delivery of the formal electrophilic CH_2F unit to the recipient nucleophile represents the conceptually simplest disconnection to achieve the goal.⁸ Indeed, recent advancements indicate the versatility of hypervalent sulfur species as valuable transfer agents working under an electrophilic regime. A breakthrough in the field was documented in 2008 by Prakash and Olah through the development of shelf-stable electrophilic fluoromethylated diarylsulfonium salts capable of releasing the CH_2F motif to various nucleophiles encompassing O-, S-, N-, and P- species (Scheme 1, path a),⁹ subsequently extended to the transfer of $-\text{CHFMe}$ systems by Besset et al.¹⁰ Furthermore, Shibata

introduced in 2011 sulfoximinium salts for accessing fluoromethylated aromatic alcohols and carboxylic and sulfonic acids (among other nucleophiles, i.e., enolates) (Scheme 1, path b).¹¹ Additionally, Lu and Shen designed more versatile analogues (sulfonium ylides) manifesting broader substrate scope, thus allowing the use also of aliphatic alcohols as competent nucleophiles (Scheme 1, path c).¹² Stemming from a radical pathway, Hu and co-workers demonstrated that *N*-tosyl sulfoximines could transfer the CH_2F group to O-, S-, N-, and P-nucleophiles;¹³ importantly, they documented the accelerating effect displayed by the α -fluorine substituent toward nucleophilic substitutions.¹⁴ However, the multistep preparation of these fluoromethyl donor agents jointly with the nonoptimal atom economy associated with their employment tends to circumscribe the applicability to model systems of academic interest, thus making somehow difficult the routine access to fluoromethyl analogues of potential medicinal relevance. Remarkably, Hu proposed the gaseous reagent ClCH_2F —Freon 31 (bp -9.1 °C)—as an effective solution for installing the motif on a variety of heteroatom nucleophiles.¹⁵ Unfortunately, its physical state—gas—poses severe limitations for the experimental execution (e.g., impractical handling process and imprecise measurements of small quantities), which ultimately lead to the eclipse of the innate synthetic potential of such an approach. In this context, the simple

Received: December 27, 2019

Scheme 1. Heteroatom-Based Monofluoromethylation: State-of-the-Art



replacement of the leaving chlorine atom with the heavier iodine confers a dramatic enhancement of the manipulability of the resulting fluoroiodomethane (FIM, bp 53.4 °C).¹⁶ Aware of this practical advantage, our group conducted on it selective iodine/lithium or hydrogen/lithium exchanges en route to unprecedented nucleophilic fluoro-containing carbenoids for preparation, through a single synthetic operation, of α -fluoromethyl skeletons¹⁷ or three-membered fluorinated rings (epoxides and aziridines).¹⁸ Furthermore, recently the reagent is finding significant application in different areas of synthesis as showcased in transition-metal-catalyzed cross-couplings with boronic acids,¹⁹ in Cu-catalyzed borylfluoromethylation of olefins,²⁰ in fluorocyclopropanations,²¹ and in C-selective monofluoromethylation of β -ketoesters²² and fluoromethylphosphonium ylides.²³

Herein, we disclose a convenient direct and simple transfer of the fluoromethyl fragment from the commercially available FIM to a series of heteroatom-based nucleophiles [aromatic (thio and seleno)alcohols, (thio)carboxylic acids, heteroaromatic nitrogen, phosphorus] by means of an intuitive nucleophilic substitution (Scheme 1, bottom). We anticipate the complete adaptability of the methodology for transformations realized on currently employed drugs, thus enabling rapid molecular modifications for preparing pharmaceutical relevant fluoro-analogues.

Because of our interest toward chiral drugs²⁴ and cognizant of the different bioactivity displayed by the enantiomers of the nonsteroidal anti-inflammatory agent Naproxene (**1**), we selected the most active enantiomer—(*S*)-**1** (>99:1 er)—as the model substrate for evaluating both the CH₂F transfer efficiency from FIM and the preservation of the stereochemical information. As indicated in Table 1, the use of a base was critical for accomplishing the transformation (entry 1). Polar

Table 1. Model Reaction: Optimization^a

entry	solvent	base	reaction time (h)	yield of (<i>S</i>)- 2 (%) ^b	er of (<i>S</i>)- 2
1	DMF	-	24	traces	-
2	DMF	NaH	6	71	95:5
3	THF	NaH	6	64	94:6
4	DMF	CsF	6	86	97:3
5	DMF	Cs ₂ CO ₃	6	90	97:3
6	DMF	KF-Celite	12	72	96:4
7	MeCN	CsF	6	91	98:2
8	MeCN	KF-Celite	8	78	97:3
9	MeCN	Cs ₂ CO ₃	6	97	>99:1
10 ^c	MeCN	Cs ₂ CO ₃	4	98	>99:1
11 ^d	MeCN	Cs ₂ CO ₃	6	95	>99:1
12	MeCN	DIPEA	12	61	98:2

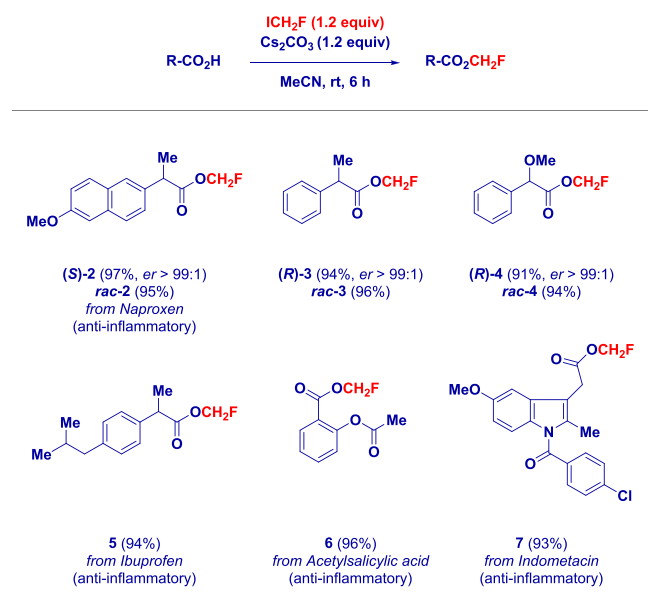
^aUnless otherwise stated, a ratio of (*S*)-**1**:ICH₂F:base = 1:1.2:1.2 was employed. ^bIsolated yield. ^cICH₂F (2.4 equiv), Cs₂CO₃ (2.4 equiv). ^dReaction run at 10 mmol scale.

aprotic solvents performed reasonably well under basic conditions, evidencing a noticeable role of the base in triggering epimerization. Accordingly, running reactions in the presence of NaH resulted in incomplete conversion and perceptible racemization regardless of the solvent used (DMF or THF, entries 2–3). Switching to cesium bases was beneficial in terms of yield and er (entries 4 and 5), while substantial reaction slowing was evidenced with the supported base KF-Celite²⁵ [entry 6 and entry 8 (in MeCN)]. Pleasingly, the combination of acetonitrile and cesium carbonate resulted in the ideal combination for optimizing the process, thus allowing it to reach completion within 6 h without any erosion of the optical purity (entry 9). Some additional points merit mention: (1) analytically pure compounds were recovered after simple extraction of the water phase with diethyl ether, thus advantageously allowing us to skip chromatographic purifications; (2) only a small excess of ICH₂F and Cs₂CO₃ was needed for completing the reaction, higher loading being unfavorable for cost effectiveness/reaction time ratio (entry 10); (3) performing the reaction in 10 mmol scale was possible without affecting both the yield and the er (entry 11); and (4) changing to an organic base such as DIPEA (*N,N*-di-*i*-propyl-*N*-ethylamine) was detrimental, thus confirming the gainful outcome with the cesium salt (entry 12).

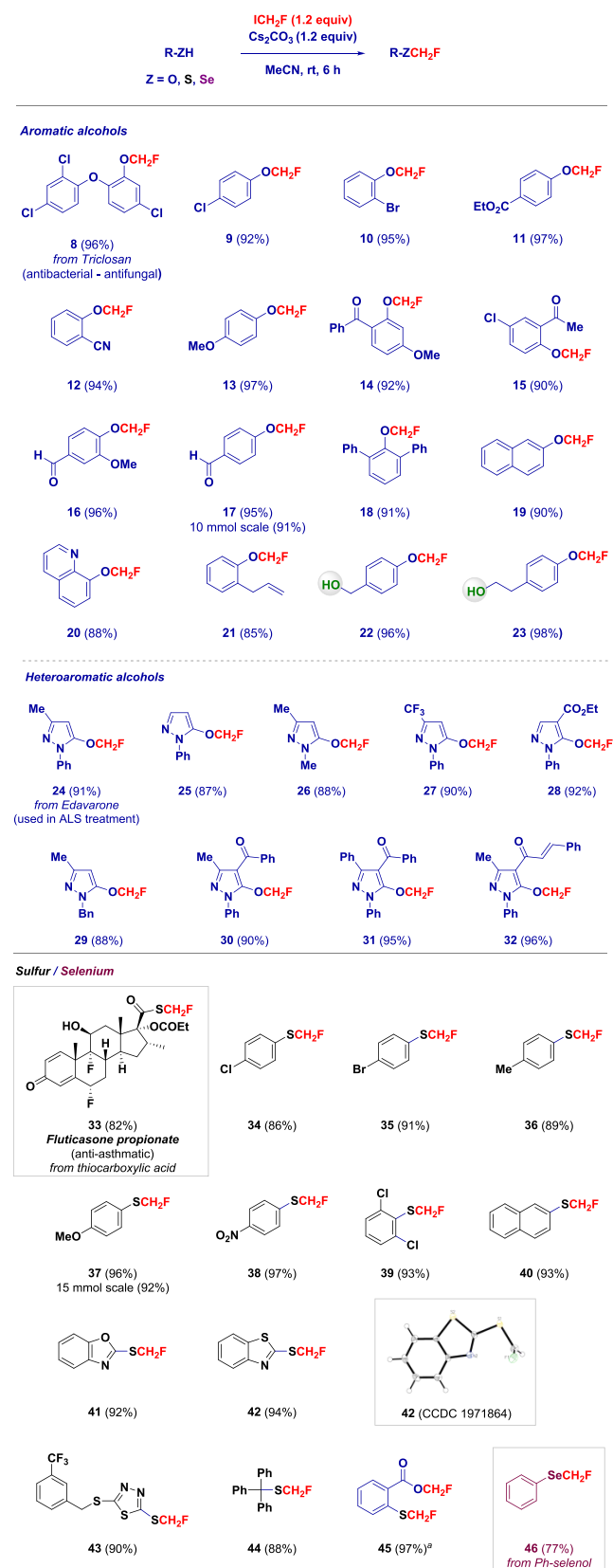
With the optimized conditions in hand, we then studied the scope of the fluoromethylation on additional carboxylic acids (Scheme 2). The full preservation of the optical purity was confirmed in the cases of α -substituted phenylacetic acid derivatives (3 and 4), and other common anti-inflammatory agents underwent the transformation very efficiently: ibuprofen (5), acetylsalicylic acid (aspirin, 6) and indomethacin (7). Remarkably, this approach compared favorably with reported protocols requiring sulfur-based CH₂F donors, nondirectly assembled.¹¹

Pleasingly, the technique could be applied to chemo-selectively fluoromethylate aromatic alcohols²⁶ in the presence of various decorating elements such as halogens (8–10), ester (11), nitrile (12), ethers 13, ketones (14–15), and aldehydes (16–17) (Scheme 3). Notably, sterically hindered (18) and

Scheme 2. Fluoromethylation of Carboxylic Acids



(hetero)polyaromatic systems (19–20) acted as competent partners for the reaction, as well as an allyl-presenting phenol (21). It is worth noting that the established conditions allow us to perfectly discriminate the reactivity of aromatic vs aliphatic alcohols which remained untouched (plausibly because of their inherent lower acidity) during the transformation (22–23). Unfortunately, attempts to realize the double fluoromethylation on both alcohol functionalities in the presence of harder bases (KH or NaH in DMF or THF) resulted in complex mixtures. Furthermore, 2-pyrazolin-5-ones—known to manifest complex prototropic tautomerization phenomena²⁷—could be similarly employed to exclusively afford the corresponding fluoromethyl ethers, including the analogue (24) derived from the anti-amyotrophic lateral sclerosis (ALS) agent edavarone. Substitution across the pyrazole nucleus was uniformly permitted (25–32), the ester- (28), ketone- (30–31), and cinnamoyl- (32) bearing systems being representative examples. Full flexibility of the reaction conditions was evidenced for sulfur-centered nucleophiles,²⁸ including a smooth access to the steroidal agent fluticasone (33) prepared starting from the parent thiocarboxylic acid. In analogy to the aromatic alcohols discussed above, various thiophenol derivatives (34–37) reacted with comparable efficiency, thus providing versatility to the protocol, as for example observed for nitro (38), 2,6-disubstituted phenyl (39), and heteroaromatic mercaptanes (41–43). It should be highlighted that this monofluoromethylthiolation process overcomes *de facto* the initial generation of thioate-type shuttles from the same FIM introduced by Lu and Shen [*S*-(fluoromethyl)-benzenesulfonothioate]²⁸ and Jiang and Yi [Bunte salt FCH_2SSO_3Na].²⁹ The higher acidity of a thiophenol (compared to an aliphatic alcohol) rendered feasible the transformation for the trityl derivative (44), whereas an excess of FIM and Cs_2CO_3 enabled the double functionalization on both oxygen and sulfur sites of thiosalicylic acid (45). The method proved to be modular as indicated by the synthesis of a selenium derivative (46), previously prepared through a complex sequence involving aniline diazotization—conversion into organoselenocyanate—formation of a diselenide, and finally transfer of a RSe^- anion to FIM.³⁰

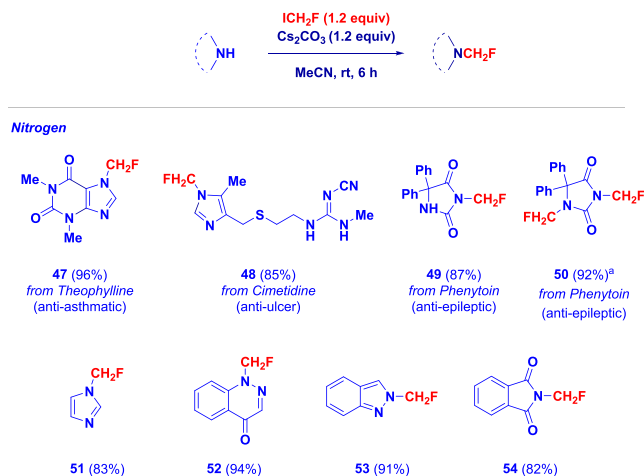
Scheme 3. Fluoromethylation of O-, S-, and Se-Nucleophiles^a

^a ICH_2F (2.4 equiv), Cs_2CO_3 (2.4 equiv).

To cover the range of nucleophilic groups amenable for the proposed functionalization, we then demonstrated the validity

of the technique for medicinally important nitrogenated heterocycles (Scheme 4). The purinic base stimulant drug

Scheme 4. Fluoromethylation of *N*- and *P*-Nucleophiles

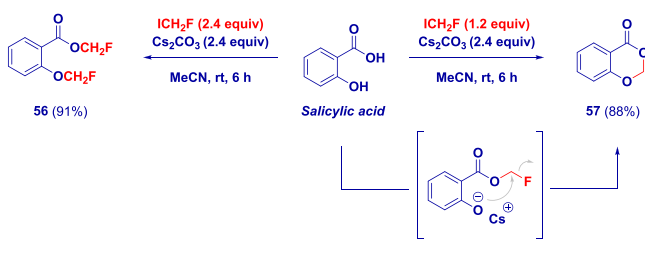


theophylline (47) or the prototypal histaminic-H₂ antagonist cimetidine was selectively fluoromethylated at positions 7 and 1 (the guanidine portion remaining unaffected), respectively. The anticonvulsant and class IB antiarrhythmic agent phenytoin underwent mono- (49) or bis-monofluoromethylation (50) on the hydantoinic nucleus depending on the reaction stoichiometry. Moreover, the nitrogen atoms of imidazole, 4(1*H*)-cinnolinone, indazole, and phthalimide represented excellent linchpins for introducing the CH₂F fragment (51–54). Much to our delight, also di-*n*-butylphosphine oxide was fluoromethylated upon deprotonation in very good yield (55), thus further expanding the scope of substrates suitable for this simple and convenient operation.

The fine-tuning of the stoichiometry of the process was crucial for synthesizing elaborated motifs by taking advantage of the aforementioned inherent reactivity of CH₂F groups toward nucleophilic displacements.¹⁴ Indeed, an excess of ICH₂F and Cs₂CO₃ allowed the bis-derivatization of salicylic acid, yielding 56 (in analogy to the thio compound 45 discussed above), thus formally constituting a homologation process. However, by employing only 1.2 equiv of ICH₂F and an excess of base, the bicyclic lactone 57 was obtained as the unique reaction product (Scheme 5). Presumably, the fluoromethylation occurs (almost) preferentially at the more nucleophilic carboxylate site, giving a reactive (not isolable) fluoromethyl ester which undergoes the internal substitution carried out by the cesium phenoxide.

In summary, we have reported a conceptually highly intuitive and convenient transfer of the fluoromethyl fragment to recipient heteroatom-centered nucleophiles starting from the commercially available and easy to manipulate fluoriodomethane under mild basic conditions. This operationally simple and (often) chromatographic-free protocol is suitable for derivatizing a plethora of common chemical functionalities

Scheme 5. Stoichiometry-Controlled Fluorinative Homologation of Salicylic Acid



including marked and routinely used drugs. Significantly attractive features of this uniformly high-yielding and general methodology can be recapitulated as follows: (1) robust tolerance of sensitive groups (including challenging carbonyls, ester, guanidine, amide, nitro, nitrile groups, *inter alia*) and (2) complete retention of the stereochemical information contained in optically active drugs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.9b04654>.

Experimental procedures, NMR spectra, HPLC traces, and analytical data for all the compounds (PDF)

Accession Codes

CCDC 1971864 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Vittorio Pace – University of Vienna, Department of Pharmaceutical Chemistry 14–1090 Vienna, Austria; orcid.org/0000-0003-3037-5930; Email: vittorio.pace@univie.ac.at; <https://drugsynthesis.univie.ac.at/>

Authors

Raffaele Senatore – University of Vienna, Department of Pharmaceutical Chemistry 14–1090 Vienna, Austria
 Monika Malik – University of Vienna, Department of Pharmaceutical Chemistry 14–1090 Vienna, Austria
 Markus Spreitzer – University of Vienna, Department of Pharmaceutical Chemistry 14–1090 Vienna, Austria
 Wolfgang Holzer – University of Vienna, Department of Pharmaceutical Chemistry 14–1090 Vienna, Austria

Complete contact information is available at: <https://pubs.acs.org/10.1021/acs.orglett.9b04654>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

In memoriam of Professor Gottfried Heinisch. The authors thank the University of Vienna for financial support and ABCR Germany for generous supply of fluoriodomethane. A. Roller

and N. Gajic are kindly acknowledged for X-ray analysis. We are grateful to D. Dobusch for HRMS measurements.

REFERENCES

- (1) For excellent reviews, see: (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, 37, 308–319. (b) Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2015**, 54, 3216–3221. (c) Campbell, M. G.; Ritter, T. *Chem. Rev.* **2015**, 115, 612–633. (d) Orsi, D. L.; Altman, R. A. *Chem. Commun.* **2017**, 53, 7168–7181. (e) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2019**, 58, 14824–14848.
- (2) Bondi, A. J. *Phys. Chem.* **1964**, 68, 441–451.
- (3) For an excellent overview, see: Meanwell, N. A. *J. Med. Chem.* **2018**, 61, 5822–5880.
- (4) For a complete discussion on the topic, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, 52, 8214–8264. (b) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. *Chem. - Eur. J.* **2017**, 23, 14676–14701.
- (5) For recent outstanding contributions, see: (a) Meyer, C. F.; Hell, S. M.; Misale, A.; Trabanco, A. A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2019**, 58, 8829–8833. (b) Scheidt, F.; Schäfer, M.; Sarie, J. C.; Daniliuc, C. G.; Molloy, J. J.; Gilmour, R. *Angew. Chem., Int. Ed.* **2018**, 57, 16431–16435. (c) Ferguson, D. M.; Malapit, C. A.; Bour, J. R.; Sanford, M. S. *J. Org. Chem.* **2019**, 84, 3735–3740.
- (6) For excellent perspectives, see: (a) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465–7478. (b) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, 115, 9073–9174. (c) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, 40, 921–930.
- (7) For selected reviews, see: (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320–330. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, 114, 2432–2506. (c) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, 116, 422–518. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881–1886. (e) Hagmann, W. K. *J. Med. Chem.* **2008**, 51, 4359–4369.
- (8) Monofluoromethylations of alcohols have also been carried out by employing fluorocarbon nucleophiles under Mitsunobu conditions. For an illustrative example, see: Prakash, G. K. S.; Chacko, S.; Alconcel, S.; Stewart, T.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2007**, 46, 4933–4936.
- (9) (a) Prakash, G. K. S.; Ledneczki, I.; Chacko, S.; Olah, G. A. *Org. Lett.* **2008**, 10, 557–560. The same reagent has also been used for preparing fluorocyclopropanes and fluorooxepoxides, see: (b) Melngaile, R.; Sperga, A.; Baldrige, K. K.; Veliks, J. *Org. Lett.* **2019**, 21, 7174–7178. (c) Veliks, J.; Kazia, A. *Chem. - Eur. J.* **2019**, 25, 3786–3789. (d) Kazia, A.; Melngaile, R.; Mishnev, A.; Veliks, J. *Org. Biomol. Chem.* **2020**, DOI: 10.1039/C9OB02712B.
- (10) Carbonnel, E.; Pannecoucke, X.; Besset, T.; Jubault, P.; Poisson, T. *Chem. Commun.* **2018**, 54, 2491–2493.
- (11) Nomura, Y.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, 50, 1885–1889.
- (12) (a) Liu, Y.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2017**, 56, 9930–9934. See also: (b) Ascenso, O. S.; Leitão, E. P. T.; Heggie, W.; Ventura, M. R.; Maycock, C. D. *Tetrahedron* **2017**, 73, 1165–1169.
- (13) (a) Shen, X.; Zhou, M.; Ni, C.; Zhang, W.; Hu, J. *Chem. Sci.* **2014**, 5, 117–122. The same reagent PhS(ONt₃)CH₂F has been used for the radical monofluoromethylation of alkenes under photoredox catalysis, see: (b) Noto, N.; Koike, T.; Akita, M. *ACS Catal.* **2019**, 9, 4382–4387. (c) Koike, T.; Akita, M. *Org. Biomol. Chem.* **2019**, 17, 5413–5419. Radical CH₂F generated in the presence of zinc sulfinate salts has been also used for the fluoromethylation of heterocycles, see: (d) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, 492, 95–99.
- (14) For an authoritative overview, see: Ni, C.; Hu, J. *Chem. Soc. Rev.* **2016**, 45, 5441–5454.
- (15) (a) Zhang, W.; Zhu, L.; Hu, J. *Tetrahedron* **2007**, 63, 10569–10575. See also: (b) Wang, L.; Wei, J.; Wu, R.; Cheng, G.; Li, X.; Hu, J.; Hu, Y.; Sheng, R. *Org. Chem. Front.* **2017**, 4, 214–223.
- (16) (a) Monticelli, S.; Pace, V. *Aust. J. Chem.* **2018**, 71, 473–475. Scattered applications of labeled [¹⁸F]-FIM in heteroatom derivatization for preparing radioligands can be found. See for example: (b) Zhang, M.-R.; Maeda, J.; Ogawa, M.; Noguchi, J.; Ito, T.; Yoshida, Y.; Okauchi, T.; Obayashi, S.; Sahara, T.; Suzuki, K. *J. Med. Chem.* **2004**, 47, 2228–2235. Notably, previously reported uses of labeled FIM were found of limited reproducibility, presumably as a consequence of the instability of the products. See: (c) Zhang, M.-R.; Ogawa, M.; Furutsuka, K.; Yoshida, Y.; Suzuki, K. *J. Fluorine Chem.* **2004**, 125, 1879–1886. While this manuscript was under review, a paper on the fluoromethomethylation of nitrogen heterocyclic compounds with FIM has been published, see: (d) Wang, R.; Ding, T.; Jiang, L.; He, W.; Yi, W. *J. Org. Chem.* **2020**, DOI: 10.1021/acs.joc.9b03193.
- (17) (a) Parisi, G.; Colella, M.; Monticelli, S.; Romanazzi, G.; Holzer, W.; Langer, T.; Degennaro, L.; Pace, V.; Luisi, R. *J. Am. Chem. Soc.* **2017**, 139, 13648–13651. (b) Castoldi, L.; Monticelli, S.; Senatore, R.; Ielo, L.; Pace, V. *Chem. Commun.* **2018**, 54, 6692–6704. Recently, our group applied CHF₂-type carbanions in difluoromethylative homologations, see: (c) Miele, M.; D'Orsi, R.; Sridharan, V.; Holzer, W.; Pace, V. *Chem. Commun.* **2019**, 55, 12960–12963. (d) Miele, M.; Citarella, A.; Micale, N.; Holzer, W.; Pace, V. *Org. Lett.* **2019**, 21, 8261–8265.
- (18) (a) Monticelli, S.; Colella, M.; Pillari, V.; Tota, A.; Langer, T.; Holzer, W.; Degennaro, L.; Luisi, R.; Pace, V. *Org. Lett.* **2019**, 21, 584–588. (b) Ielo, L.; Touqueer, S.; Roller, A.; Langer, T.; Holzer, W.; Pace, V. *Angew. Chem., Int. Ed.* **2019**, 58, 2479–2484.
- (19) (a) Doi, H.; Ban, I.; Nonoyama, A.; Sumi, K.; Kuang, C.; Hosoya, T.; Tsukada, H.; Suzuki, M. *Chem. - Eur. J.* **2009**, 15, 4165–4171. (b) Hu, J.; Gao, B.; Li, L.; Ni, C.; Hu, J. *Org. Lett.* **2015**, 17, 3086–3089. Also the ozone-depleting agent BrCH₂F (bp 19 °C) has been employed, see: (c) An, L.; Xiao, Y.-L.; Min, Q.-Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2015**, 54, 9079–9083.
- (20) Wu, N.-Y.; Xu, X.-H.; Qing, F.-L. *ACS Catal.* **2019**, 9, 5726–5731.
- (21) Colella, M.; Tota, A.; Großjohann, A.; Carlucci, C.; Aramini, A.; Sheikh, N. S.; Degennaro, L.; Luisi, R. *Chem. Commun.* **2019**, 55, 8430–8433.
- (22) Ding, T.; Jiang, L.; Yang, J.; Xu, Y.; Wang, G.; Yi, W. *Org. Lett.* **2019**, 21, 6025–6028.
- (23) Reichel, M.; Martens, J.; Wöllner, E.; Huber, L.; Kornath, A.; Karaghiosoff, K. *Eur. J. Inorg. Chem.* **2019**, 2019, 2530–2534.
- (24) Stadler, M.; Monticelli, S.; Seidel, T.; Luger, D.; Salzer, I.; Boehm, S.; Holzer, W.; Schwarzer, C.; Urban, E.; Khom, S.; Langer, T.; Pace, V.; Hering, S. *J. Med. Chem.* **2019**, 62, 317–341.
- (25) Pace, V.; Martínez, F.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. *Org. Lett.* **2007**, 9, 2661–2664.
- (26) For additional methodologies for preparing fluoromethylethers, see: (a) Park, C.; Lee, B. S.; Chi, D. Y. *Org. Lett.* **2013**, 15, 4346–4349. (b) Geng, Y.; Liang, A.; Gao, X.; Niu, C.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *J. Org. Chem.* **2017**, 82, 8604–8610.
- (27) Holzer, W.; Mereiter, K.; Plagens, B. *Heterocycles* **1999**, 50, 799–818.
- (28) Zhao, Q.; Lu, L.; Shen, Q. *Angew. Chem., Int. Ed.* **2017**, 56, 11575–11578.
- (29) Liu, F.; Jiang, L.; Qiu, H.; Yi, W. *Org. Lett.* **2018**, 20, 6270–6273.
- (30) Cao, Y.; Jiang, L.; Yi, W. *Adv. Synth. Catal.* **2019**, 361, 4360–4368.