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# A unified approach to *meta*-selective methylation, mono-, di- and trifluoromethylation of arenes†

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Matched molecular series (MMS) are series of molecules that differ only by a single modification at a specific site. The synthesis of MMS is a desirable strategy in drug discovery campaigns. Small aliphatic motifs, notably methyl, mono-, di- and trifluoromethyl substituents ( $C_1$  units), are known to have profound effects on the physicochemical properties and/or potency of drug candidates. In this context, we herein report a unique strategy for achieving direct *meta*-selective methylation, mono-, di-, and trifluoromethylation from the same parent compound. This approach takes advantage of a highly *meta*-selective ruthenium(II)-catalyzed alkylation, followed by a subsequent photocatalyzed protodecarboxylation or silver-mediated fluorodecarboxylation to reveal the (fluoro)methyl moiety. This method enables the late-stage access to MMS in small molecules bearing a variety of orienting groups as well as bio-relevant molecules containing complex functionalities, bypassing the need for *de novo* synthesis to access individual compounds in a series. Moreover, key physicochemical properties of drug candidates were successfully modulated, highlighting opportunities to accelerate medicinal chemistry programs in a sustainable fashion.

## Introduction

In medicinal chemistry, incorporating small  $C_1$  aliphatic substituents, including methyl, monofluoromethyl, difluoromethyl and trifluoromethyl groups, has proven to be a valuable strategy for enhancing the pharmacokinetic or pharmacodynamic properties of parent compounds (Fig. 1A). These derivatives are referred to as matched molecular series (MMS) as an extension of the concept of matched molecular pairs (MMP), where a series of compounds share a common scaffold but structurally differ from one another at a single site.<sup>1–4</sup> The addition of a methyl group to a target molecule has the potential to enhance the potency or efficacy of a compound, widely recognized as the “magic methyl effect”.<sup>5,6</sup> On a different note, fluoromethyl groups, while similar in size to methyl substituents, exert different and unique effects on drug candidate properties.<sup>7–10</sup> The presence of fluorine atoms is reported to improve stability by replacing metabolically labile hydrogen atom(s),<sup>11–13</sup> to modulate conformation,<sup>14–16</sup> or to influence membrane permeability *via* lipophilicity modulation.<sup>17</sup> In

addition, mono- and difluoromethyl groups may serve as bioisosteres of hydroxyl and thiol functional groups due to their ability to behave as hydrogen bond donors.<sup>18–20</sup> As a result, methyl, mono-, di- and trifluoromethyl analogues of drug candidates can bring immense value in the drug development process, as important biological properties can be positively influenced while leaving core structures intact.

Benzenoid rings are by far the most privileged ring system present in small molecule drugs.<sup>21–24</sup> Considering substitution patterns of arenes, *para*-substituted phenyl rings significantly outnumber analogues bearing *ortho*- or *meta*-substitution patterns, with the latter being the least represented scaffold (Fig. 1B).<sup>25</sup> The scarcity of the *meta*-substitution pattern underscores a considerable unmet need for efficient synthetic methodologies. To access a di-substituted benzenoid without the need for reconstructing the ring, chemists typically either perform functional group interconversions on one of the existing substituents of a di-functionalized ring or introduce a new group to a mono-functionalized ring. The former strategy, typically employed in C–C cross-coupling reactions,<sup>26–28</sup> is heavily dependent on the availability of the starting material. However, *meta*-substituted aryl halides, the most widely used precursors for such transformations, have the poorest commercial availability.<sup>29</sup> Alternatively, electrophilic aromatic substitution ( $S_EAr$ ) is one of the most conventional reactions to introduce a new substituent on a phenyl ring. However, the success of  $S_EAr$  relies on the electronic and steric nature of the existing substituents on the phenyl ring. Electron withdrawing substituents can direct  $S_EAr$  to *meta*-functionalization, but often suffer from sluggish reaction rates.<sup>30,31</sup> More recently,

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researchers achieved direct remote C–H functionalization with carefully designed template systems. However, the installation and removal of templates added additional synthetic steps and challenges.<sup>32</sup>

Various synthetic methods have been developed to incorporate C<sub>1</sub>-alkyl moieties onto an arene through direct C–H bond functionalization, with the aim of minimizing the number of synthetic steps to the synthesis of desired analogues.<sup>33–39</sup> Thus, strategies allowing for *ortho*-methylations<sup>40–43</sup> and trifluoromethylation<sup>44–47</sup> have been developed. In sharp contrast, direct C–H *ortho*-mono- or difluoromethylation, to the best of our knowledge, has not yet been reported. Furthermore, *meta*-C<sub>1</sub>-alkylation across all analogues continues to be challenging. *Meta*-methylation has been elegantly accomplished by Yu.<sup>48–50</sup> Yet, di-functionalization remains a largely unsolved

issue. Hence, there is a continued strong demand to develop a unified protocol that allows access to all four possible C<sub>1</sub> aliphatic substituents to efficiently diversify the parent compound, thereby avoiding the need for lengthy *de novo* syntheses.

Ruthenium(II/III) catalysis in combination with a carboxylate ligand was reported to be able to direct XAT-substrates towards overall *meta*-functionalization of an arene bearing an intrinsic Lewis-basic motif.<sup>51–60</sup> The initial project design relied on generating small aliphatic radicals directly through a single electron transfer (SET/XAT) process from a ruthenium intermediate.<sup>61–63</sup> However, screening a variety of radical precursors proved the transformation to be challenging, mainly due to the instability and short lifetime of the primary radical (Fig. 1C). In addition, the similarity in structure and lipophilicity between the desired product, substrate and side products often resulted in difficult purification.<sup>64</sup> Therefore, we considered the (fluoro)methylation, through initial C–H functionalization of an alkylating agent, along with a C–C cleavage would lead to our desired products.

Here in, we report an expedient method to achieve methylation, mono-, di-, and trifluoromethylation from the same parent compound through a common intermediate (Fig. 1D). Our strategy explores the excellent remote selectivity of ruthenium catalysis, in combination with a photocatalyzed protodecarboxylation or silver-mediated fluorodecarboxylation to furnish the desired protonated or fluorinated product.<sup>65–67</sup> Our approach proved compatible with a range of different coordinating groups bearing an N(sp<sup>2</sup>) Lewis-basic motif, which is omnipresent in active pharmaceutical ingredients (API) and related drug-like compounds. This generally applicable protocol also allows for the expedient access of MMS *via* the late-stage functionalization (LSF) of complex bioactive structures,<sup>68,69</sup> and provides opportunities for investigating structure–activity relationships (SAR) of potential drug candidates without lengthy *de novo* syntheses of individual compound of interest. In addition, a new restriction proposal from the European Union legislation attempts to address the issue of pollution from undegradable per- and polyfluoroalkyl substances (PFAS) by banning the manufacture, supply and use of such substances, with the exception of API.<sup>70,71</sup> The restriction prompts scientists to develop alternative routes to synthesize the API without relying on precursors falling into the category of PFAS.<sup>72</sup> Our method offers opportunities to address the problem by decorating the target compound with trifluoromethyl group in the final step of synthesis. Finally, our strategy offers complementarity in site-selectivity to small aliphatic substituent incorporation at either proximal *ortho*-C–H or remote *para*-C–H bonds on arenes, to expand the accessibility of largely unexplored chemical space.

## Results and discussion

We commenced our studies by exploring a range of alkyl halides bearing a transient radical stabilizing group (Scheme S1 in ESI†). BPin, nitrile and BF<sub>3</sub>K methyl halides were shown to be ineffective in Ru-catalyzed alkylation while BrCH<sub>2</sub>TMS

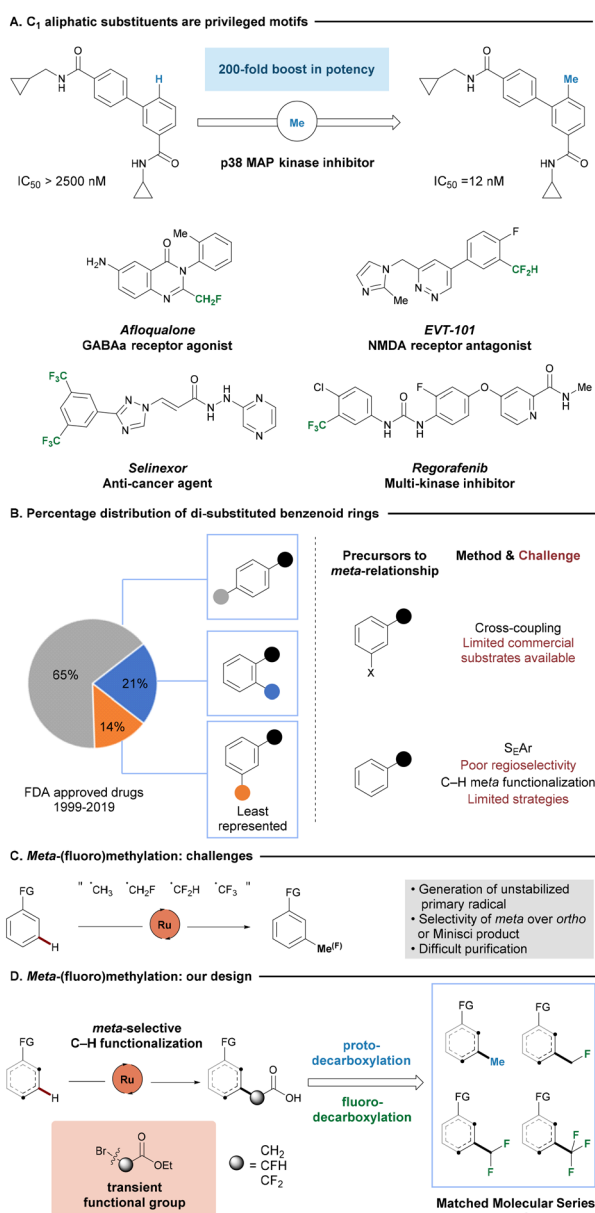


Fig. 1 Access to di-substituted arenes.

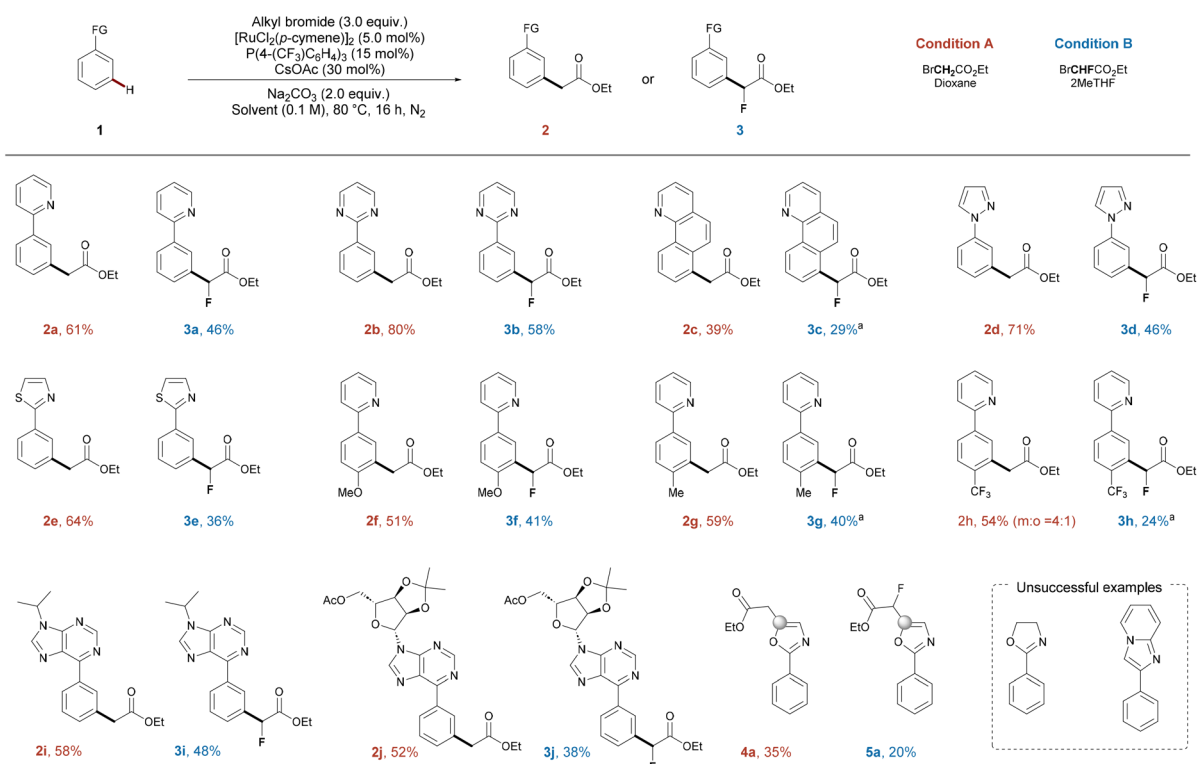


produced the desired *meta* product in 9% NMR yield. However, further optimization did not improve the yield and switching to  $\text{ICH}_2\text{TMS}$  altered the selectivity to, in this case, the *ortho*-position. After careful consideration, substrates bearing an ester stabilizing group were chosen to be the ideal candidates. First, the ester group offers excellent site-selectivity to the desired *meta* position. Second, all the non-, mono- and di-fluorinated substrates are commercially available, which could greatly reduce the cost of an industrial application. Third, an acid functional group can be revealed easily from the ester protection group through saponification, which could then be utilized in a subsequent decarboxylative protonation or fluorination step.

Next, we explored the scope and limitations of the ruthenium-mediated alkylation (Scheme 1). We were pleased to observe that the protocol can be applied to a range of different medicinally relevant heteroarenes including pyridine (**1a**), pyrimidine (**1b**), quinoline (**1c**), pyrazole (**1d**) and thiazole (**1e**). To our delight, bioactive moieties such as purine nucleobase derivative (**1i**, **1j**), including those bearing sensitive protecting groups, were well-tolerated under the optimized conditions. In addition, *para*-substituents bearing different electronic properties, including methoxy (**1f**), methyl (**1g**) and trifluoromethyl (**1h**) groups, proved feasible. Surprisingly, when switching from 2-phenylthiazole to 2-phenyloxazole, the mechanism was completely overturned from *meta*-C–H functionalisation to conventional Friedel Crafts-type reaction.<sup>73,74</sup> Disappointingly,

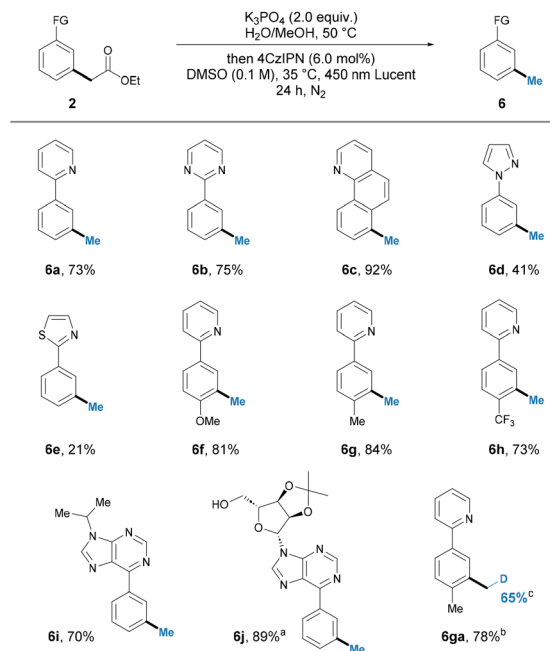
dihydrooxazole and imidazopyridine did not furnish any desired products, with only unreacted substrate observed.

We then turned our attention to investigate the one pot saponification-protodecarboxylation, which would lead to our final *meta*-methylation goal. Conventionally, decarboxylation is performed under harsh reaction conditions, typically requiring heating to over 200 °C, which would pose a challenge to molecules bearing sensitive functional groups. Inspired by a photochemical  $^{12}\text{CO}_2$  to  $^{13/14}\text{CO}_2$  isotope exchange strategy reported by the Audisio group, we tested our ester substrates under 450 nm blue LED irradiation.<sup>75</sup> The generation of alpha fluoro-radicals through photo-decarboxylation was also reported.<sup>76,77</sup> A high-throughput experimentation (HTE) optimization campaign was conducted with three different esters bearing zero, one or two fluorine atoms as substrates (ESI, Scheme S2†). The substrates were subjected to three different bases for the saponification step. Then, solvents were removed under vacuum followed by addition of photocatalyst and a new set of solvents. Photocatalyzed decarboxylation was shown to suffer from increasing difficulty going from esters intermediates bearing zero, one, to two fluorine atoms. The presence of more electron-withdrawing fluorine atoms could potentially make the electropotential of the carboxylate ion more positive, thus more difficult to oxidize, hindering the radical decarboxylation. Therefore, we decided to adopt this strategy only to access the privileged methyl substituent. Of note, it is surprising that all three solvents gave satisfying conversion. DMSO was eventually selected for carrying out the scope exploration since it is



**Scheme 1** Ruthenium-catalyzed *meta*-selective alkylation of arenes. <sup>a</sup>Reactions were carried out using [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (10 mol%) and P(4-(CF<sub>3</sub>)C<sub>6</sub>H<sub>4</sub>)<sub>3</sub> (30 mol%).



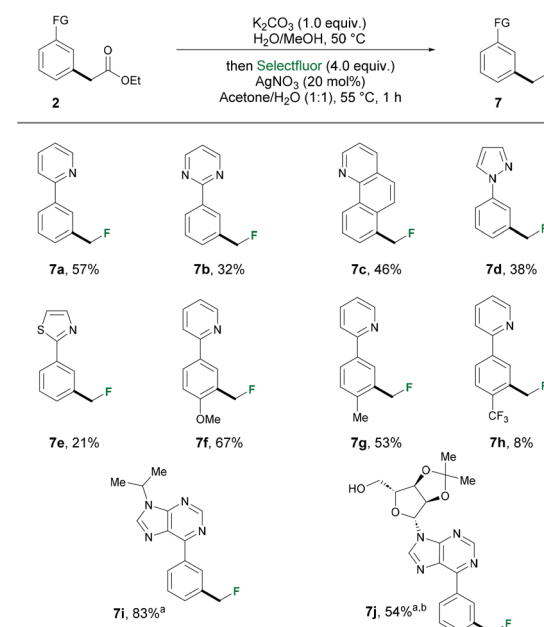


Scheme 2 One pot saponification-protodecarboxylation sequence.

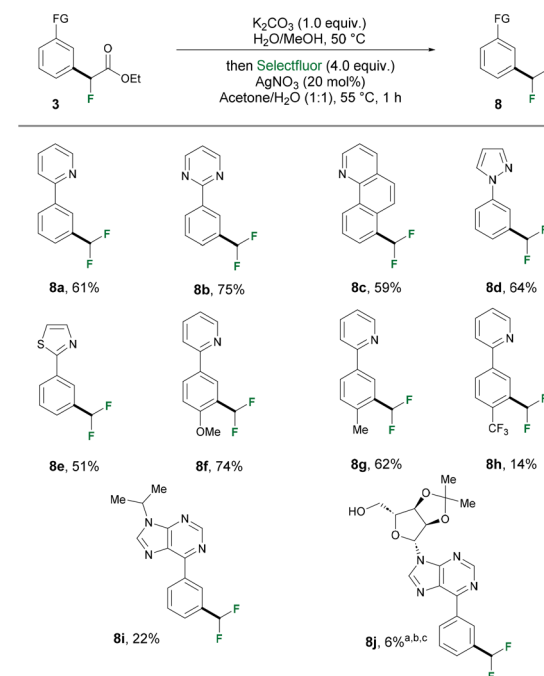
<sup>a</sup>Traceless removal of acetyl group during saponification. <sup>b</sup>10 equiv.  $D_2O$  were added along with 4CzIPN. <sup>c</sup>Percentage deuterium incorporation.

classified as a greener solvent compared to DMF or DMA. With optimized conditions in hand, we explored the versatility of photodecarboxylation (Scheme 2). All the ester intermediates obtained from the ruthenium(II/III)-catalyzed alkylation step successfully furnished the desired methylation product in satisfactory yields. Deacetylation occurred when acetate intermediate **2j** was subjected to saponification, but to our delight, the presence of free hydroxyl group was well tolerated in the subsequent protodecarboxylation. When 10 equivalents of  $D_2O$  were added in the photocatalyzed reaction, a final  $CH_2D$  group was successfully formed to yield **6ga**, offering opportunities for the late-stage selective deuterium labelling of drug molecules. The success of deuteration opens the door for potential tritiation of compounds of interest.<sup>78</sup> In order to obtain mono- and difluoromethylated compounds, a silver-catalyzed fluorodecarboxylation methodology was applied. This strategy also offers a unique opportunity to access trifluoromethylated products, which were inaccessible *via* protodecarboxylation, and was exemplified in the LSF of bioactive molecules. The non-fluorinated and monofluorinated intermediates that were obtained from either conditions **A** or conditions **B** (Scheme 1) were subjected to the same set of conditions for fluorodecarboxylation (Scheme 3). The ester intermediates (**2&3**) were first hydrolyzed by  $K_2CO_3$  to furnish the acetates, then a solvent switch in the same reaction vial was performed, followed by the subsequent silver-mediated fluorodecarboxylation. The intermediates from Scheme 1 successfully underwent the saponification-fluorodecarboxylation sequence to furnish the corresponding mono- or difluoromethylated product with the exception of purine derivatives (**2i**, **2j**, **3j**). These set of

#### A. Decarboxylation leading to monofluorination



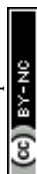
#### B. Decarboxylation leading to difluorination

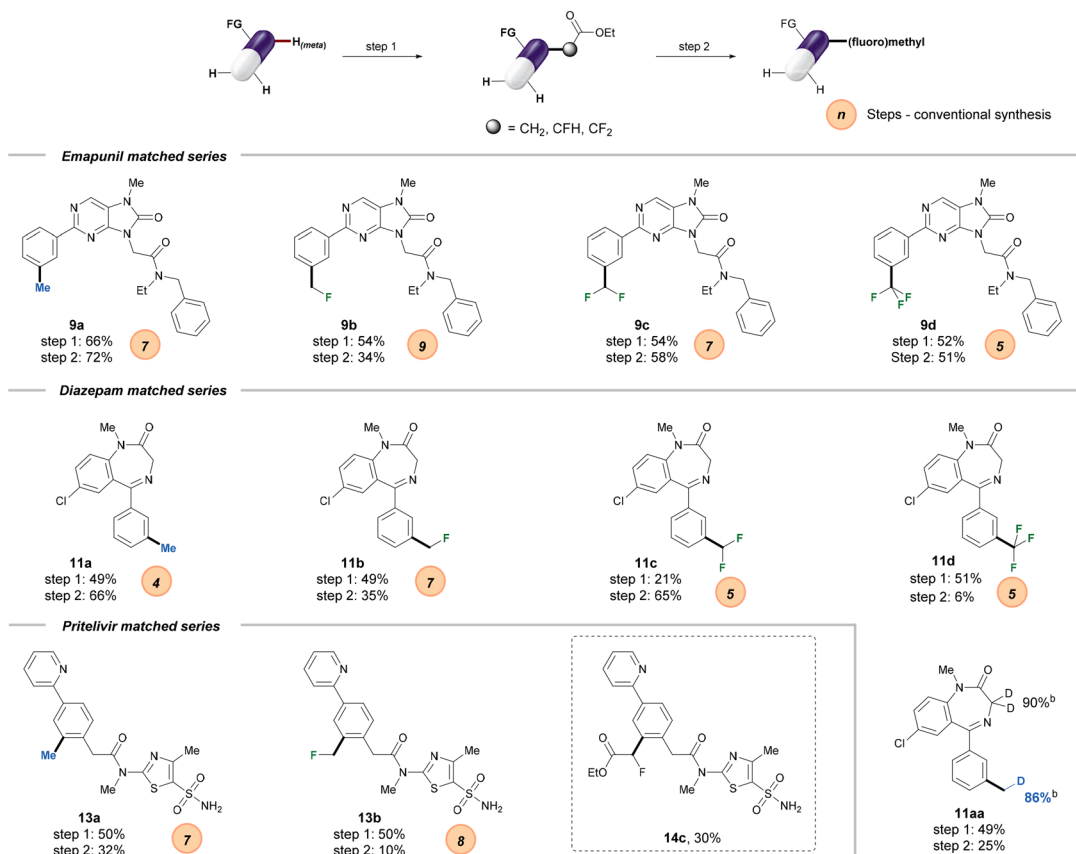


Scheme 3 One pot saponification-fluorodecarboxylation sequence.

<sup>a</sup>Reaction was carried out with the corresponding ethyl acetate and  $K_2CO_3$  (2.0 equiv.) in  $MeOH/MeOH$  for saponification, followed by irradiation under 450 nm blue light with  $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$  (6.0 mol%) in DMF (0.1 M) for 24 h at 35 °C. <sup>b</sup>Traceless removal of acetyl group during saponification. <sup>c</sup>Conversion determined by LC-MS.

compounds proved to be challenging in the fluorodecarboxylation step. Instead, we opted for protodecarboxylation strategy described in Scheme 2, yet still managed to furnish moderate to good yield of the desired products (**7i**, **7j**, **8j**), which highlighted



A. Application of ruthenium-mediated C–H alkylation - proto/fluorodecarboxylation sequence for LSF of biologically active substrates<sup>a</sup>

## B. Modulation of pharmaceutically relevant properties

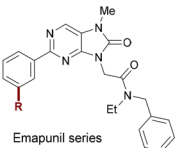
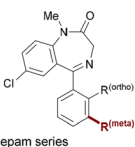
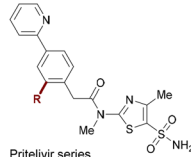
Parent compound (R = H)	Compound	Solubility ( $\mu\text{M}$ , pH 7.4)	LogD (octanol, pH 7.4)	Prot. Bind. (% free)
 Emapunil series	R = H, <b>9</b>	3.1	3.2	0.9
	R = Me, <b>9a</b>	0.1	3.9	0.8
	R = CH <sub>2</sub> F, <b>9b</b>	0.3	3.5	1.3
	R = CF <sub>2</sub> H, <b>9c</b>	0.3	3.9	0.8
	R = CF <sub>3</sub> , <b>9d</b>	0.1	4.8	0.2
 Diazepam series	R = H, <b>11</b>	175	2.7	2.0
	R = Me <sup>(ortho)</sup> , <b>11a<sup>d</sup></b>	85	2.9	8.5
	R = Me <sup>(meta)</sup> , <b>11a</b>	478	3.3	2.1
	R = CH <sub>2</sub> F, <b>11b</b>	787	2.7	6.5
	R = CF <sub>2</sub> H, <b>11c</b>	421	3.1	3.3
	R = CF <sub>3</sub> , <b>11d</b>	292	3.5	2.1
 Pritelivir series	R = H, <b>13</b>	4.5	2.2	– <sup>c</sup>
	R = Me, <b>13a</b>	13	2.4	– <sup>c</sup>
	R = CH <sub>2</sub> F, <b>13b</b>	168	2.3	– <sup>c</sup>

Fig. 2 Late-stage functionalization of bioactive molecules and physiochemical properties modulation. <sup>a</sup>Detailed reaction conditions are provided in ESI.† <sup>b</sup>Percentage deuterium incorporation. <sup>c</sup>Unstable in plasma. <sup>d</sup>Reported in literature.<sup>42</sup>

the versatility of the two-step protocol. Of note, all the respective mono- and difluoromethylated products were obtained in moderate to good yields. Interestingly, fluorodecarboxylation of

the monofluorinated intermediate (**8a–8i**) generally resulted in higher yields compared to the non-fluorinated counterpart (**7a–7i**). Li's group reported a detailed study of such transformation,





indicating that the reactivity of carboxylic acids drops in the order tertiary > secondary > primary,<sup>79</sup> which serves in part to explain the discrepancy in yields we observed from the two sets of intermediates.

Our newly developed (fluoro)methylation strategy was then applied to more complex bioactive molecules bearing multiple sites for potential functionalization. We were pleased to find that the ruthenium(II/III)-catalyzed alkylation successfully incorporated a masked (fluoro)methyl radical into the desired site of functionalization with traces amount (less than 5% by LC-MS) of *ortho*-product observed when ethyl bromoacetate was used as the radical precursor (Fig. 2A). In all cases, bis-functionalization was not observed. The targeted *meta*-product and undesired *ortho*-product were easily separated owing to their differences in lipophilicity brought about by the transient ester functional group, highlighting an important advantage of the indirect (fluoro)methylation. With emapunil and diazepam as starting material, all four homologues bearing one extra C<sub>1</sub> unit at the *meta* position could be synthesized. In addition, 86% deuterium incorporation was achieved when 10 equivalents of D<sub>2</sub>O was added during the protodecarboxylation of diazepam-ethyl acetate intermediate to furnish **11aa** in 12% yield over 2 steps. Ruthenium-catalyzed alkylation was shown to be compatible with pritelivir to yield the unfluorinated and monofluorinated ester intermediate. Yet, fluorodecarboxylation did not yield the desired product with the latter. Nonetheless, an overall *meta*-methylation and monofluoromethylation was still achieved producing two analogues of the parent compound. Of note, trimethyltin hydroxide was used to selectively hydrolyze the transient ester functional group since saponification would also hydrolyze the tertiary amide present in the core structure. In any medicinal chemistry campaign, time is one of the most important factors. As a result, LSF is evolving to be one of the most appealing strategies for accessing synthetically challenging target compounds. We compared the preparation of derivatives of pharmaceuticals (**9a–9d**, **11a–11d**, **13a–13b**) with traditional *de novo* synthesis to produce identical compounds. In this context, expedient access to these unique sets of MMS brings significant value to the study of physiochemical properties and potency of drug candidates, thus speeding up the DMTA cycle in drug discovery.

Access to MMS of marketed pharmaceuticals enabled the generation of key DMPK data including solubility, log *D* and protein binding (Fig. 2B). A general increase in log *D* was observed when a methyl group was installed. Further replacing the hydrogen atoms by fluorine atoms reduced lipophilicity, resulting in a drop in log *D* (CH<sub>2</sub>F and CF<sub>2</sub>H compared to CH<sub>3</sub>), agreeing with previous studies.<sup>80–82</sup> The trifluoromethylated analogue presented a noticeable increase in lipophilicity compared to the methylated compound, which was consistent with previous report that trifluoromethyl group increased the hydrophilicity when there is no solubilizing group in close proximity.<sup>83</sup> Monofluoromethylated and difluoromethylated compounds are in general less lipophilic than the corresponding methylated and trifluoromethylated analogues due to the present of larger dipole moments.<sup>84</sup> As the parent compound became more lipophilic (Emapunil > Diazepam > Pritelivir), the

boost in log *D* from –CH<sub>3</sub> to –CF<sub>3</sub> also became more prominent.<sup>85</sup> It is also interesting to note that installation of CH<sub>2</sub>F group may have a dramatic impact on the solubility of the target compound. Finally, the site of functionalization can modulate the properties of the parent compound differently. The difference in the medicinal chemistry relevant data of methylation occurring at *ortho* vs. *meta* position of diazepam could be explained by the perturbation of the conformation of the phenyl ring.<sup>42</sup> *Ortho*-methylation has a higher probability of twisting the phenyl ring out of plane from the 7-membered ring due to higher steric congestion.

## Conclusion

In summary, we have devised a strategy allowing direct access to a *meta*-selective C–H methylation and mono-, di-, and trifluoromethylation protocol of arene to quickly access a range of C<sub>1</sub>-substituted compounds from the same parent molecule. The site-selectivity was tuned by exploiting the unique reactivity of ruthenium catalysis, and the molecular diversity was achieved by either photocatalyzed protodecarboxylation or silver-mediated fluorodecarboxylation. Moreover, this approach was successfully applied to marketed pharmaceuticals to produce MMS of the parent drug. Specifically, trifluoromethylation was achieved in the last step of synthesizing a potential API, thereby bypassing the generation of intermediate that could be classified as PFAS. An array of pharmaceutically relevant analogues was generated quickly, thus could speed up substantially the drug development campaign. In the meantime, the sustainable strategy reduces the CO<sub>2</sub> footprint by significantly reducing the number of step counts compared to *de novo* synthesis. Lastly, the remote incorporation of C<sub>1</sub> unit provided opportunities to modulate physiochemical properties of bioactive molecules, presenting the potential of this methodology to accelerate optimization towards suitable drug candidates.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Author contributions

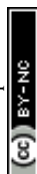
Conceptualization: E. Y. L., M. J. J. and L. A.; methodology: E. Y. L.; writing – original draft: E. Y. L.; writing – review & editing: E. Y. L., M. J. J. and L. A.; funding acquisition: M. J. J. and L. A.; supervision: M. J. J. and L. A.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- 1 M. Awale, S. Riniker and C. Kramer, Matched Molecular Series Analysis for ADME Property Prediction, *J. Chem. Inf. Model.*, 2020, **60**, 2903–2914.
- 2 C. E. Keefer and G. Chang, The use of matched molecular series networks for cross target structure activity relationship translation and potency prediction, *MedChemComm*, 2017, **8**, 2067–2078.
- 3 C. Tyrchan and E. Evertsson, Matched Molecular Pair Analysis in Short: Algorithms, Applications and Limitations, *Comput. Struct. Biotechnol. J.*, 2017, **15**, 86–90.
- 4 M. Wawer and J. Bajorath, Local Structural Changes, Global Data Views: Graphical Substructure–Activity Relationship Trailing, *J. Med. Chem.*, 2011, **54**, 2944–2951.
- 5 D. Aynedinova, M. C. Callens, H. B. Hicks, C. Y. X. Poh, B. D. A. Shennan, A. M. Boyd, Z. H. Lim, J. A. Leitch and D. J. Dixon, Installing the “magic methyl” –C–H methylation in synthesis, *Chem. Soc. Rev.*, 2021, **50**, 5517–5563.
- 6 H. Schönherr and T. Cernak, Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256–12267.
- 7 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, Applications of Fluorine in Medicinal Chemistry, *J. Med. Chem.*, 2015, **58**, 8315–8359.
- 8 W. K. Hagmann, The Many Roles for Fluorine in Medicinal Chemistry, *J. Med. Chem.*, 2008, **51**, 4359–4369.
- 9 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Fluorine in medicinal chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- 10 H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, Fluorine in Medicinal Chemistry, *ChemBioChem*, 2004, **5**, 637–643.
- 11 G. Rong, C. Wang, L. Chen, Y. Yan and Y. Cheng, Fluoroalkylation promotes cytosolic peptide delivery, *Sci. Adv.*, 2020, **6**, eaaz1774.
- 12 B. M. Johnson, Y.-Z. Shu, X. Zhuo and N. A. Meanwell, Metabolic and Pharmaceutical Aspects of Fluorinated Compounds, *J. Med. Chem.*, 2020, **63**, 6315–6386.
- 13 B. K. Park and N. R. Kitteringham, Effects of Fluorine Substitution on Drug Metabolism: Pharmacological and Toxicological Implications, *Drug Metab. Rev.*, 1994, **26**, 605–643.
- 14 L. E. Zimmer, C. Sparr and R. Gilmour, Fluorine Conformational Effects in Organocatalysis: An Emerging Strategy for Molecular Design, *Angew. Chem., Int. Ed.*, 2011, **50**, 11860–11871.
- 15 L. Hunter, The C–F bond as a conformational tool in organic and biological chemistry, *Beilstein J. Org. Chem.*, 2010, **6**, 38.
- 16 D. Y. Buissonneaud, T. van Mourik and D. O'Hagan, A DFT study on the origin of the fluorine gauche effect in substituted fluoroethanes, *Tetrahedron*, 2010, **66**, 2196–2202.
- 17 Z. Wang, H. R. Felstead, R. I. Troup, B. Linclau and P. T. F. Williamson, Lipophilicity Modulations by Fluorination Correlate with Membrane Partitioning, *Angew. Chem., Int. Ed.*, 2023, **62**, e202301077.
- 18 J. Yang, S. Ponra, X. Li, B. B. C. Peters, L. Massaro, T. Zhou and P. G. Andersson, Catalytic enantioselective synthesis of fluoromethylated stereocenters by asymmetric hydrogenation, *Chem. Sci.*, 2022, **13**, 8590–8596.
- 19 Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, Difluoromethyl Bioisostere: Examining the “Lipophilic Hydrogen Bond Donor” Concept, *J. Med. Chem.*, 2017, **60**, 797–804.
- 20 J. A. Erickson and J. I. McLoughlin, Hydrogen Bond Donor Properties of the Difluoromethyl Group, *J. Org. Chem.*, 1995, **60**, 1626–1631.
- 21 R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in Drugs, *J. Med. Chem.*, 2014, **57**, 5845–5859.
- 22 J. Wang and T. Hou, Drug and Drug Candidate Building Block Analysis, *J. Chem. Inf. Model.*, 2010, **50**, 55–67.
- 23 P. Ertl, S. Jelfs, J. Mühlbacher, A. Schuffenhauer and P. Selzer, Quest for the Rings. *In Silico* Exploration of Ring Universe To Identify Novel Bioactive Heteroaromatic Scaffolds, *J. Med. Chem.*, 2006, **49**, 4568–4573.
- 24 X. Q. Lewell, A. C. Jones, C. L. Bruce, G. Harper, M. M. Jones, I. M. McLay and J. Bradshaw, Drug Rings Database with Web Interface. A Tool for Identifying Alternative Chemical Rings in Lead Discovery Programs, *J. Med. Chem.*, 2003, **46**, 3257–3274.
- 25 A. Nilova, L.-C. Campeau, E. C. Sherer and D. R. Stuart, Analysis of Benzenoid Substitution Patterns in Small Molecule Active Pharmaceutical Ingredients, *J. Med. Chem.*, 2020, **63**, 13389–13396.
- 26 A. Biffis, P. Centomo, A. Del Zotto and M. Zecca, Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review, *Chem. Rev.*, 2018, **118**, 2249–2295.
- 27 P. Ruiz-Castillo and S. L. Buchwald, Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions, *Chem. Rev.*, 2016, **116**, 12564–12649.
- 28 C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062–5085.
- 29 For the purposes of this manuscript, commercial availability for each aryl halides bearing a halide (X) and a R group with either *ortho*-, *meta*-, or *para*-substitution pattern was assessed using the Reaxys database. The reported counts represent compounds with molecular weight of 408 or less. Using these criteria, searches *via* Reaxys produces the following number of commercial compounds for each substitution pattern: *ortho*-aryl halide: 67 346; *meta*-aryl halide: 65 605; *para*-aryl halide, **198**, 131, Reaxys, Elsevier, n.d., <https://www.reaxys.com/#/search/quick>, accessed 2024-10-22.



- 30 A. D. Nguyen, R. J. Zanolini and J. L. Gustafson, in *Handbook of CH- Functionalization*, 2022, pp. 1–26, DOI: [10.1002/9783527834242.chf0184](https://doi.org/10.1002/9783527834242.chf0184).
- 31 G. A. Olah, Aromatic substitution. XXVIII. Mechanism of electrophilic aromatic substitutions, *Acc. Chem. Res.*, 1971, **4**, 240–248.
- 32 G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin and J.-Q. Yu, Achieving Site-Selectivity for C–H Activation Processes Based on Distance and Geometry: A Carpenter's Approach, *J. Am. Chem. Soc.*, 2020, **142**, 10571–10591.
- 33 T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson and L. Ackermann, C–H activation, *Nat. Rev. Methods Primers*, 2021, **1**, 43.
- 34 C. Sambiasi, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, A comprehensive overview of directing groups applied in metal-catalysed C–H functionalisation chemistry, *Chem. Soc. Rev.*, 2018, **47**, 6603–6743.
- 35 C.-S. Wang, P. H. Dixneuf and J.-F. Soulé, Photoredox Catalysis for Building C–C Bonds from C(sp<sup>2</sup>)–H Bonds, *Chem. Rev.*, 2018, **118**, 7532–7585.
- 36 Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, Transition metal-catalyzed C–H bond functionalizations by the use of diverse directing groups, *Org. Chem. Front.*, 2015, **2**, 1107–1295.
- 37 T. W. Lyons and M. S. Sanford, Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions, *Chem. Rev.*, 2010, **110**, 1147–1169.
- 38 J. F. Hartwig, Evolution of C–H Bond Functionalization from Methane to Methodology, *J. Am. Chem. Soc.*, 2016, **138**, 2–24.
- 39 J. F. Hartwig and M. A. Larsen, Undirected, Homogeneous C–H Bond Functionalization: Challenges and Opportunities, *ACS Cent. Sci.*, 2016, **2**, 281–292.
- 40 E. Weis, M. A. Hayes, M. J. Johansson and B. Martín-Matute, Iridium-catalyzed C–H methylation and d3-methylation of benzoic acids with application to late-stage functionalizations, *iScience*, 2021, **24**, 102467.
- 41 S. Ni, M. Hribersek, S. K. Baddigam, F. J. L. Ingner, A. Orthaber, P. J. Gates and L. T. Pilarski, Mechanochemical Solvent-Free Catalytic C–H Methylation, *Angew. Chem., Int. Ed.*, 2021, **60**, 6660–6666.
- 42 S. D. Friis, M. J. Johansson and L. Ackermann, Cobalt-catalysed C–H methylation for late-stage drug diversification, *Nat. Chem.*, 2020, **12**, 511–519.
- 43 X.-Y. Chen and E. J. Sorensen, Pd-Catalyzed, ortho C–H Methylation and Fluorination of Benzaldehydes Using Orthoanilic Acids as Transient Directing Groups, *J. Am. Chem. Soc.*, 2018, **140**, 2789–2792.
- 44 L. Hu, X. Chen, Q. Gui, Z. Tan and G. Zhu, Highly mono-selective ortho-trifluoromethylation of benzamides via 8-aminoquinoline assisted Cu-promoted C–H activations, *Chem. Commun.*, 2016, **52**, 6845–6848.
- 45 M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai and J.-Q. Yu, Exceedingly Fast Copper(II)-Promoted ortho C–H Trifluoromethylation of Arenes using TMSCF<sub>3</sub>, *Angew. Chem., Int. Ed.*, 2014, **53**, 10439–10442.
- 46 L.-S. Zhang, K. Chen, G. Chen, B.-J. Li, S. Luo, Q.-Y. Guo, J.-B. Wei and Z.-J. Shi, Palladium-Catalyzed Trifluoromethylation of Aromatic C–H Bond Directed by an Acetamino Group, *Org. Lett.*, 2013, **15**, 10–13.
- 47 X.-G. Zhang, H.-X. Dai, M. Wasa and J.-Q. Yu, Pd(II)-Catalyzed Ortho Trifluoromethylation of Arenes and Insights into the Coordination Mode of Acidic Amide Directing Groups, *J. Am. Chem. Soc.*, 2012, **134**, 11948–11951.
- 48 H. Shi, A. N. Herron, Y. Shao, Q. Shao and J.-Q. Yu, Enantioselective remote meta-C–H arylation and alkylation via a chiral transient mediator, *Nature*, 2018, **558**, 581–585.
- 49 G. Cheng, P. Wang and J.-Q. Yu, meta-C–H Arylation and Alkylation of Benzylsulfonamide Enabled by a Palladium(II)/Isoquinoline Catalyst, *Angew. Chem., Int. Ed.*, 2017, **56**, 8183–8186.
- 50 X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, Ligand-enabled meta-C–H activation using a transient mediator, *Nature*, 2015, **519**, 334–338.
- 51 L. Guillemard, L. Ackermann and M. J. Johansson, Late-stage meta-C–H alkylation of pharmaceuticals to modulate biological properties and expedite molecular optimisation in a single step, *Nat. Commun.*, 2024, **15**, 3349.
- 52 G. Li, C. Jia, X. Cai, L. Zhong, L. Zou and X. Cui, Ruthenium-catalyzed meta-C–H bond alkylation of aryl 2-pyridyl ketones, *Chem. Commun.*, 2020, **56**, 293–296.
- 53 X.-G. Wang, Y. Li, H.-C. Liu, B.-S. Zhang, X.-Y. Gou, Q. Wang, J.-W. Ma and Y.-M. Liang, Three-Component Ruthenium-Catalyzed Direct Meta-Selective C–H Activation of Arenes: A New Approach to the Alkylarylation of Alkenes, *J. Am. Chem. Soc.*, 2019, **141**, 13914–13922.
- 54 J. Li, K. Korvorapun, S. De Sarkar, T. Rogge, D. J. Burns, S. Warratz and L. Ackermann, Ruthenium(II)-catalysed remote C–H alkylations as a versatile platform to meta-decorated arenes, *Nat. Commun.*, 2017, **8**, 15430.
- 55 P. Gandeepan, J. Koeller, K. Korvorapun, J. Mohr and L. Ackermann, Visible-Light-Enabled Ruthenium-Catalyzed meta-C–H Alkylation at Room Temperature, *Angew. Chem., Int. Ed.*, 2019, **58**, 9820–9825.
- 56 A. Sagadevan and M. F. Greaney, meta-Selective C–H Activation of Arenes at Room Temperature Using Visible Light: Dual-Function Ruthenium Catalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 9826–9830.
- 57 J. A. Leitch and C. G. Frost, Ruthenium-catalysed  $\sigma$ -activation for remote meta-selective C–H functionalisation, *Chem. Soc. Rev.*, 2017, **46**, 7145–7153.
- 58 A. J. Paterson, C. J. Heron, C. L. McMullin, M. F. Mahon, N. J. Press and C. G. Frost,  $\alpha$ -Halo carbonyls enable meta selective primary, secondary and tertiary C–H alkylations by ruthenium catalysis, *Org. Biomol. Chem.*, 2017, **15**, 5993–6000.
- 59 J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa and L. Ackermann, N-Acyl Amino Acid Ligands for Ruthenium(II)-Catalyzed meta-C–H tert-Alkylation with





- Removable Auxiliaries, *J. Am. Chem. Soc.*, 2015, **137**, 13894–13901.
- 60 N. Hofmann and L. Ackermann, meta-Selective C–H Bond Alkylation with Secondary Alkyl Halides, *J. Am. Chem. Soc.*, 2013, **135**, 5877–5884.
- 61 P. J. Deneny, R. Kumar and M. J. Gaunt, Visible light-mediated radical fluoromethylation *via* halogen atom transfer activation of fluoriodomethane, *Chem. Sci.*, 2021, **12**, 12812–12818.
- 62 S. M. Hell, C. F. Meyer, S. Ortalli, J. B. I. Sap, X. Chen and V. Gouverneur, Hydrofluoromethylation of alkenes with fluoriodomethane and beyond, *Chem. Sci.*, 2021, **12**, 12149–12155.
- 63 K. Korvorapun, M. Moselage, J. Struwe, T. Rogge, A. M. Messinis and L. Ackermann, Regiodivergent C–H and Decarboxylative C–C Alkylation by Ruthenium Catalysis: ortho *versus* meta Position-Selectivity, *Angew. Chem., Int. Ed.*, 2020, **59**, 18795–18803.
- 64 Y. Chen, Advances in the Synthesis of Methylated Products through Indirect Approaches, *Adv. Synth. Catal.*, 2020, **362**, 998–1014.
- 65 K. Korvorapun, N. Kaplaneris, T. Rogge, S. Warratz, A. C. Stückl and L. Ackermann, Sequential meta-/ortho-C–H Functionalizations by One-Pot Ruthenium(II/III) Catalysis, *ACS Catal.*, 2018, **8**, 886–892.
- 66 Z. Ruan, S.-K. Zhang, C. Zhu, P. N. Ruth, D. Stalke and L. Ackermann, Ruthenium(II)-Catalyzed meta C–H Mono- and Difluoromethylations by Phosphine/Carboxylate Cooperation, *Angew. Chem., Int. Ed.*, 2017, **56**, 2045–2049.
- 67 C. C. Yuan, X. L. Chen, J. Y. Zhang and Y. S. Zhao, meta-Selective C–H difluoromethylation of various arenes with a versatile ruthenium catalyst, *Org. Chem. Front.*, 2017, **4**, 1867–1871.
- 68 L. Zhang and T. Ritter, A Perspective on Late-Stage Aromatic C–H Bond Functionalization, *J. Am. Chem. Soc.*, 2022, **144**, 2399–2414.
- 69 L. Guillemand, N. Kaplaneris, L. Ackermann and M. J. Johansson, Late-stage C–H functionalization offers new opportunities in drug discovery, *Nat. Rev. Chem.*, 2021, **5**, 522–545.
- 70 E. C. A. (ECHA), Per- and polyfluoroalkyl substances (PFAS), <https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas>, accessed 2024-10-02, 2024.
- 71 N. D. Tyrrell, A Proposal That Would Ban Manufacture, Supply, and Use of All Fluoropolymers and Most Fluorinated Reagents within the Entire EU, *Org. Process Res. Dev.*, 2023, **27**, 1422–1426.
- 72 M. Spennacchio, M. Bernús, J. Stanić, D. Mazzarella, M. Colella, J. J. Douglas, O. Boutureira and T. Noël, A unified flow strategy for the preparation and use of trifluoromethyl-heteroatom anions, *Science*, 2024, **385**, 991–996.
- 73 A. E. Obukhov and L. I. Belen'kii, Reactivity and electronic structure of the ground and excited states of oxazole, 2-phenyloxazole, and 2-phenylthiazole, *Chem. Heterocycl. Compd.*, 1999, **35**, 832–854.
- 74 L. I. Belen'kii, Effect of the acid-base properties of heteroaromatic compounds on their electrophilic substitution reactions (review), *Chem. Heterocycl. Compd.*, 1986, **22**, 587–608.
- 75 V. Babin, A. Talbot, A. Labiche, G. Destro, A. Del Vecchio, C. S. Elmore, F. Taran, A. Sallustrau and D. Audisio, Photochemical Strategy for Carbon Isotope Exchange with CO<sub>2</sub>, *ACS Catal.*, 2021, **11**, 2968–2976.
- 76 F. Pasca, Y. Gelato, M. Andresini, D. Serbetci, P. Natho, G. Romanazzi, L. Degennaro, M. Colella and R. Luisi, Continuous Flow Decarboxylative Monofluoroalkylation Enabled by Photoredox Catalysis, *JACS Au*, 2025, **5**, 684–692.
- 77 Á. Gutiérrez-Bonet and W. Liu, Synthesis of Alkyl Fluorides and Fluorinated Unnatural Amino Acids *via* Photochemical Decarboxylation of  $\alpha$ -Fluorinated Carboxylic Acids, *Org. Lett.*, 2023, **25**, 483–487.
- 78 S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge and M. Beller, Recent Developments for the Deuterium and Tritium Labeling of Organic Molecules, *Chem. Rev.*, 2022, **122**, 6634–6718.
- 79 F. Yin, Z. Wang, Z. Li and C. Li, Silver-Catalyzed Decarboxylative Fluorination of Aliphatic Carboxylic Acids in Aqueous Solution, *J. Am. Chem. Soc.*, 2012, **134**, 10401–10404.
- 80 B. Jeffries, Z. Wang, R. I. Troup, A. Goupille, J. Y. Le Questel, C. Fallan, J. S. Scott, E. Chiarparin, J. Graton and B. Linclau, Lipophilicity trends upon fluorination of isopropyl, cyclopropyl and 3-oxetanyl groups, *Beilstein J. Org. Chem.*, 2020, **16**, 2141–2150.
- 81 A. P. Truong, G. Tôth, G. D. Probst, J. M. Sealy, S. Bowers, D. W. G. Wone, D. Dressen, R. K. Hom, A. W. Konradi, H. L. Sham, J. Wu, B. T. Peterson, L. Ruslim, M. P. Bova, D. Kholodenko, R. N. Motter, F. Bard, P. Santiago, H. Ni, D. Chian, F. Soriano, T. Cole, E. F. Brigham, K. Wong, W. Zmolek, E. Goldbach, B. Samant, L. Chen, H. Zhang, D. F. Nakamura, K. P. Quinn, T. A. Yednock and J.-M. Sauer, Design of an orally efficacious hydroxyethylamine (HEA) BACE-1 inhibitor in a preclinical animal model, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6231–6236.
- 82 C. G. Wermuth, P. Ciapetti, B. Giethlen and P. Bazzini, in *Comprehensive Medicinal Chemistry II*, ed. J. B. Taylor and D. J. Triggle, Elsevier, Oxford, 2007, vol. 2, pp. 649–711.
- 83 N. Muller, When Is a Trifluoromethyl Group More Lipophilic than a Methyl Group? Partition Coefficients and Selected Chemical Shifts of Aliphatic Alcohols and Trifluoroalcohols, *J. Pharm. Sci.*, 1986, **75**, 987–991.
- 84 Q. A. Huchet, B. Kuhn, B. Wagner, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira and K. Müller, On the polarity of partially fluorinated methyl groups, *J. Fluorine Chem.*, 2013, **152**, 119–128.
- 85 B. Jeffries, Z. Wang, H. R. Felstead, J.-Y. Le Questel, J. S. Scott, E. Chiarparin, J. Graton and B. Linclau, Systematic Investigation of Lipophilicity Modulation by Aliphatic Fluorination Motifs, *J. Med. Chem.*, 2020, **63**, 1002–1031.

