Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2025, **16**, 8478

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

Received 20th February 2025
Accepted 7th April 2025

DOI: 10.1039/d5sc01367d

rsc.li/chemical-science

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 physiochemical 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 physiochemical 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.[1–4] 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".[5,6] On a different note, fluoromethyl groups, while similar in size to methyl substituents, exert different and unique effects on drug candidate properties.[7–10] The presence of fluorine atoms is reported to improve stability by replacing metabolically labile hydrogen atom(s),[11–13] to modulate conformation,[14–16] or to influence membrane permeability *via* lipophilicity modulation.[17] 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.[18–20] 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.[21–24] 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).[25] 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,[26–28] 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.[29] 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.[30,31] More recently,

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d5sc01367d

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.[32]

Various synthetic methods have been developed to incorporate C_1-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.[33–39] Thus, strategies allowing for *ortho*-methylations[40–43] and trifluoromethylation[44–47] 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_1-alkylation across all analogues continues to be challenging. *Meta*-methylation has been elegantly accomplished by Yu.[48–50] 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_1 aliphatic substituents to efficiently diversify the parent compound, thereby avoiding the need for lengthy *de novo* syntheses.

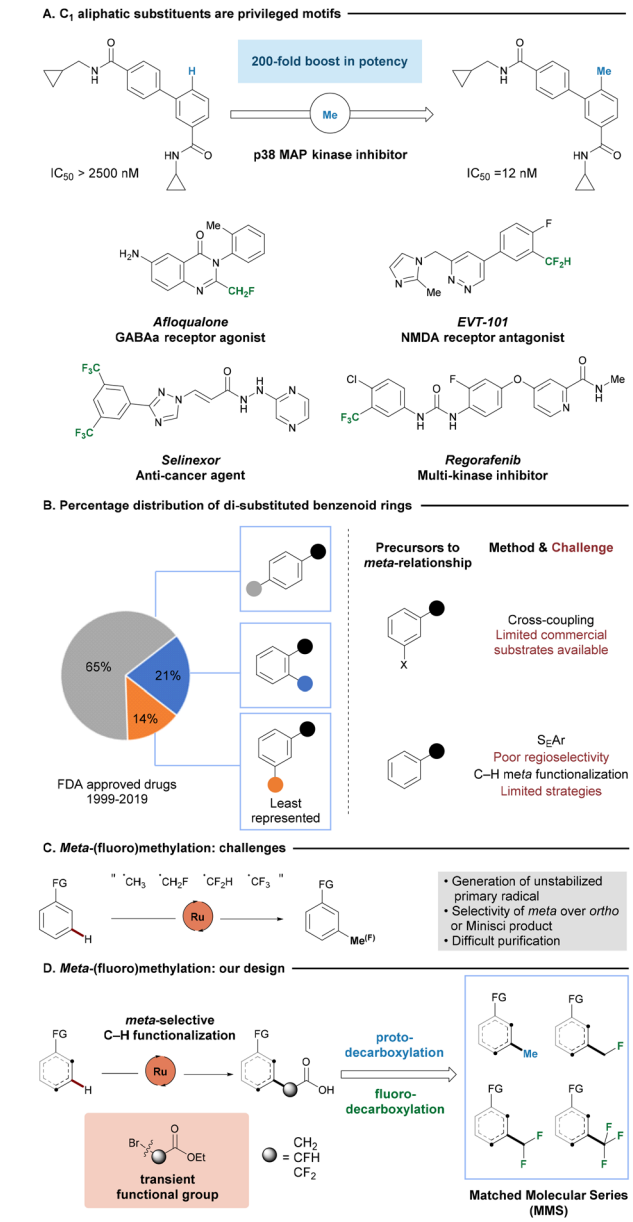


Fig. 1 Access to di-substituted arenes.

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.[51–60] The initial project design relied on generating small aliphatic radicals directly through a single electron transfer (SET/XAT) process from a ruthenium intermediate.[61–63] 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.[64] 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.[65–67] Our approach proved compatible with a range of different coordinating groups bearing an *N*(sp2) 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,[68,69] 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.[70,71] The restriction prompts scientists to develop alternative routes to synthesize the API without relying on precursors falling into the category of PFAS.[72] 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.

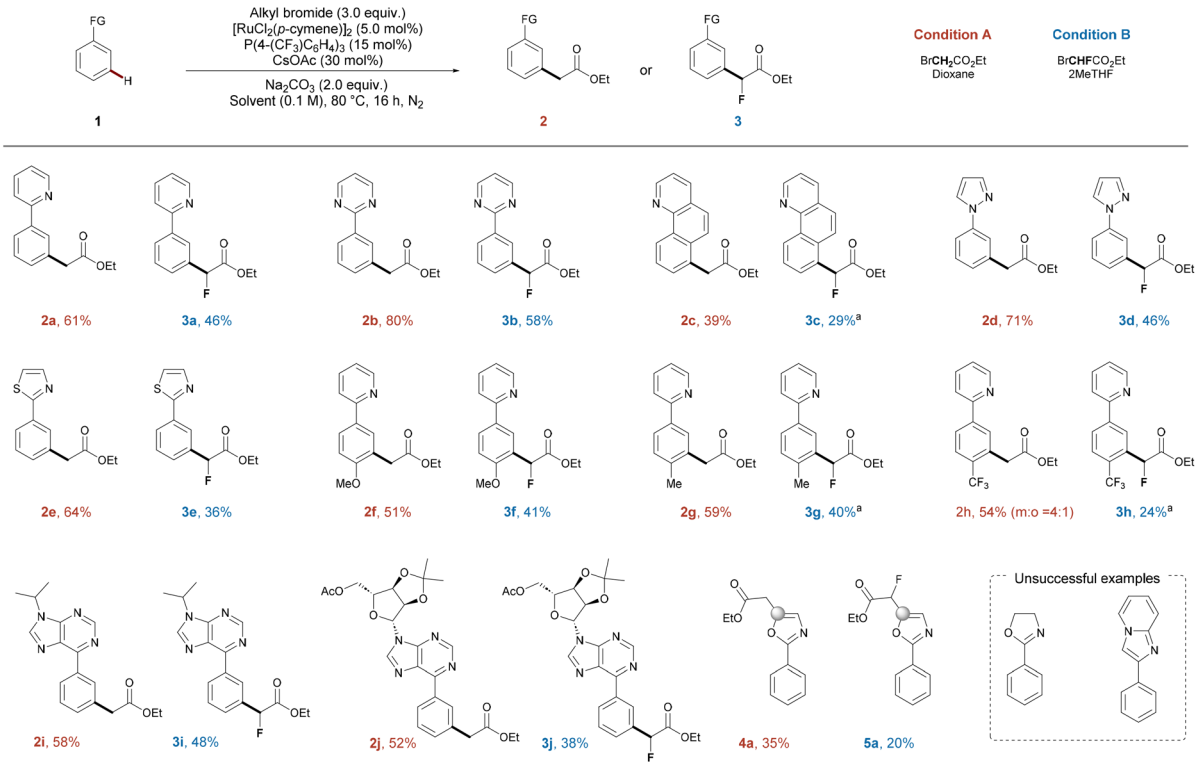
Results and discussion

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_3K methyl halides were shown to be ineffective in Ru-catalyzed alkylation while $BrCH_2TMS$

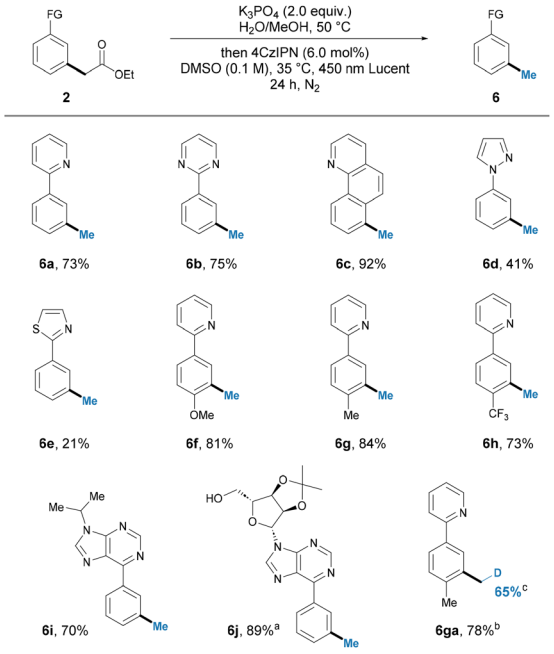
produced the desired *meta* product in 9% NMR yield. However, further optimization did not improve the yield and switching to ICH_2TMS altered the selectivity to, in this case, the *ortho*-position. After careful consideration, substrates bearing an ester stabilizing group were chosen to be the ideal candidates. First, the ester group offers excellent site-selectivity to the desired *meta* position. Second, all the non-, mono- and di-fluorinated substates 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-medi ated 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.[73,74] Disappointingly, dihydrooxazole and imidazopyridine did not furnish any desired products, with only unreacted substrate observed.

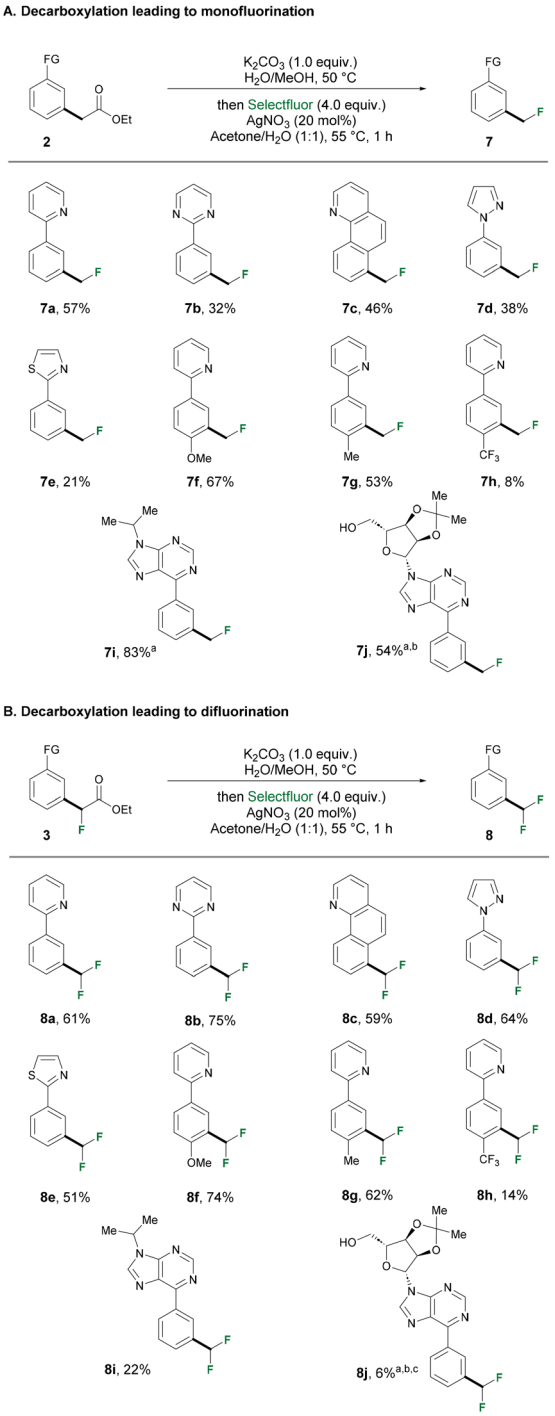
We then turned our attention to investigate the one pot saponification-protodecarboxylation, which would lead to our final *meta*-methylation goal. Conventionally, decarboxylation is performed under harsh reaction conditions, typically requiring heating to over 200 °C, which would pose a challenge to molecules bearing sensitive functional groups. Inspired by a photochemical $^{12}CO_2$ to $^{13/14}CO_2$ isotope exchange strategy reported by the Audisio group, we tested our ester substrates under 450 nm blue LED irradiation.[75] The generation of alpha fluoro-radicals through photo-decarboxylation was also reported.[76,77] 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. [a]Reactions were carried out using $[RuCl_2(p\text{-cymene})]_2$ (10 mol%) and $P(4\text{-}(CF_3)C_6H_4)_3$ (30 mol%).

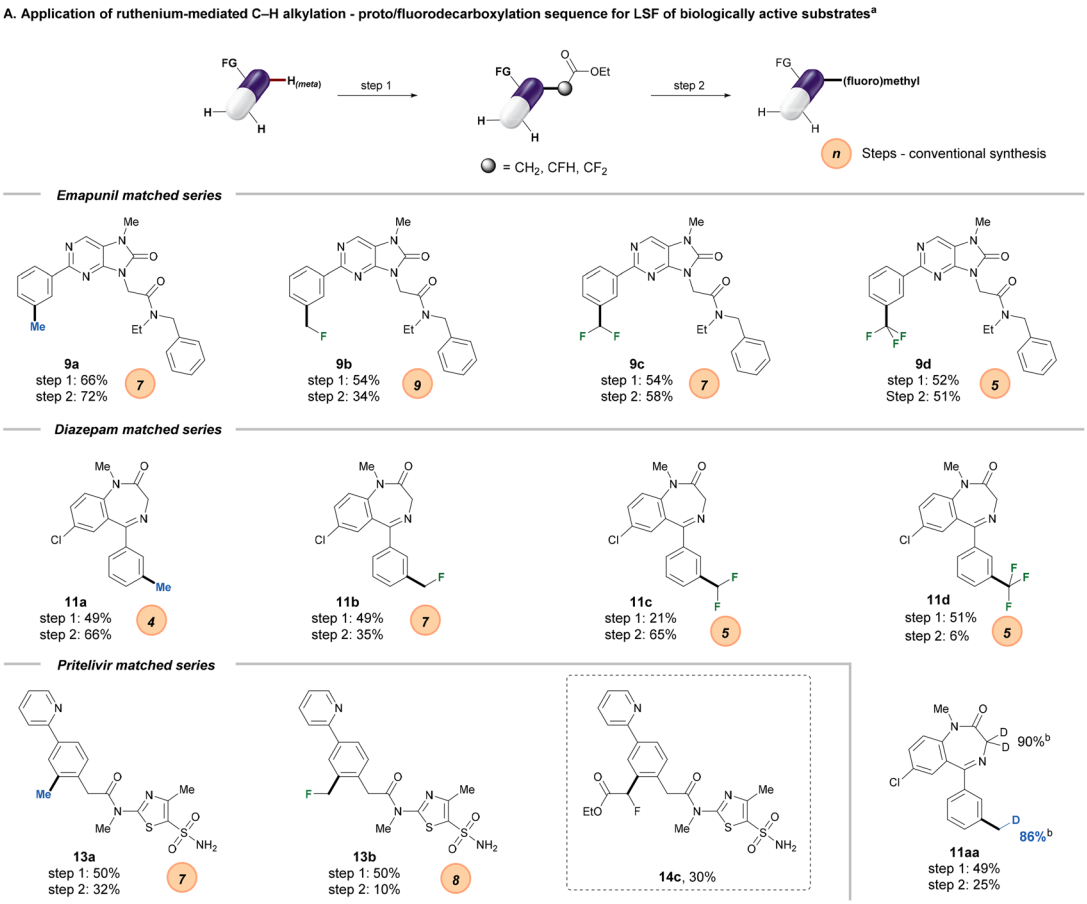


Scheme 2 One pot saponification-protodecarboxylation sequence. [a]Traceless removal of acetyl group during saponification. [b]10 equiv. D_2O were added along with 4CzIPN. [c]Percentage deuterium incorporation.



Scheme 3 One pot saponification-fluorodecarboxylation sequence. [a]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 $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (6.0 mol%) in DMF (0.1 M) for 24 h at 35 °C. [b]Traceless removal of acetyl group during saponification. [c]Conversion determined by LC-MS.

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.[78] 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 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



B. Modulation of pharmaceutically relevant properties

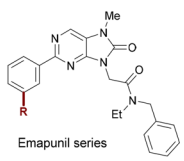
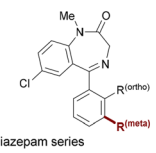
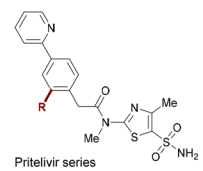
Parent compound (R = H)	Compound	Solubility (μM, pH 7.4)	LogD (octanol, pH 7.4)	Prot. Bind. (% free)
 Emapunil series	R = H, 9	3.1	3.2	0.9
	R = Me, 9a	0.1	3.9	0.8
	R = CH_2F, 9b	0.3	3.5	1.3
	R = CF_2H, 9c	0.3	3.9	0.8
	R = CF_3, 9d	0.1	4.8	0.2
 Diazepam series	R = H, 11	175	2.7	2.0
	R = $Me^{(ortho)}$, 11a'[d]	85	2.9	8.5
	R = $Me^{(meta)}$, 11a	478	3.3	2.1
	R = CH_2F, 11b	787	2.7	6.5
	R = CF_2H, 11c	421	3.1	3.3
	R = CF_3, 11d	292	3.5	2.1
 Pritelivir series	R = H, 13	4.5	2.2	-[c]
	R = Me, 13a	13	2.4	-[c]
	R = CH_2F, 13b	168	2.3	-[c]

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

the versatility of the two-step protocol. Of note, all the respective mono- and difluromethylated 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,[79] 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_1 unit at the *meta* position could be synthesized. In addition, 86% deuterium incorporation was achieved when 10 equivalents of D_2O 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_2F and CF_2H compared to CH_3), agreeing with previous studies.[80–82] 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.[83] Monofluoromethylated and difluoromethylated compounds are in general less lipophilic than the corresponding methylated and trifluoromethylated analogues due to the present of larger dipole moments.[84] As the parent compound became more lipophilic (Emapunil > Diazepam > Pritelivir), the boost in log *D* from $-CH_3$ to $-CF_3$ also became more prominent.[85] It is also interesting to note that installation of CH_2F 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.[42] *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_1-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_2 footprint by significantly reducing the number of step counts compared to *de novo* synthesis. Lastly, the remote incorporation of C_1 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.

Acknowledgements

The authors thank European Union's Horizon 2020 research and innovation program (Marie Skłodowska-Curie Grant Agreement No. 860762) for financial support, Martina Apell for

HRMS analysis, Ileana Guzzetti and Richard Lewis for NMR analysis, Lucas Guillemard for project discussion, Robert Sheppard for helpful comments, Martin Hayes and Rong Zhao for proof-reading and Malin Lemurell for project support. M. J. J. like to thank the Swedish Foundation for Strategic Environmental Research (Mistra SafeChem, project number 2018/11).

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