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ARTICLE

A Unified Strategy for Remote C–H Fluorination of Phenylacetic Acids and Their Homologues at *meta*-Position

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Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

The site-selective C–H bond fluorination of substituted aromatics at the electronic and geometric disfavored *meta*-position is of great interest and importance in medical chemistry and organic chemistry, yet has remained unexplored to date. By employing a newly developed U-shaped template, we herein report for the first time the Pd-catalysed *meta*-selective C–H bond fluorination of phenylacetic acids and their homologues. The reaction features high site-selectivity and is compatible with diverse homologues of phenylacetic acids, constituting a unified strategy for the remote aromatic C–H bond fluorination of carboxylic acids.

Introduction

Aryl fluoride compounds are among the fastest-growing classes of organic molecules, playing a vital role in pharmaceuticals, agrochemicals, and functional materials due to the magic fluorine effect.^{1–2} Notably, the substitution patterns of fluorine atom on the aromatics could significantly influence the physical properties (*e.g.* permeability, metabolic stability, and potency) of these compounds. To this end, the fluorine scan of a lead compound, which involves the systematic replacement of hydrogen with fluorine, has emerged as a powerful and common strategy for the drug discovery (Scheme 1a).³ Despite the success, given the challenging C–F bond formation, parallel *de novo* synthetic routes were often required to bring fluorine atom onto the specific position of the non-fluorinated lead molecules, which would significantly attenuate the efficiency of fluorine scan in drug discovery.⁴

In this context, the direct and selective replacement of the aromatic C–H bond with C–F bond, known as C–H fluorination, has emerged as an attractive alternative pathway to assemble fluorine-containing molecules.⁵ Many groups,⁶ including our group,⁷ have developed a variety of strategies for the selective and late-stage C–H fluorination of aromatics. Generally, the non-directed electrophilic or radical C–H fluorination of aromatics is only suitable with those possessing electron-donating groups, and therefore the dominant *ortho*- and / or *para*-selective fluorination are often observed due to the intrinsic electronic effect.⁸ To better control the *ortho*- / *para*-selectivity, the chelation assisted C–H fluorination has been

developed and the geometric favoured *ortho*-selectivity could be achieved (Scheme 1b). Despite the recent advances, the selective C–H fluorination at the *meta*-position of substituted aromatics has remained unexplored due to significant electronic and geometric challenges.

On the other hand, phenylacetic acids are ubiquitous in many bioactive molecules. More interestingly, changing the chain length of a phenylacetic acid lead compound towards their homologues might significantly modulate the bioactivity.⁹ Given the importance of *meta*-fluorinated phenylacetic acid derivatives in pharmaceuticals, a unified *meta*-selective C–H fluorination of phenylacetic acids and their homologues is of great interest and importance both in organic chemistry and medical chemistry, yet has remained unknown to date. It has been previously reported by the groups of Yu, Maiti, Li, and many others that the well-designed U-shaped templates could facilitate the remote C–H functionalization (*e.g.* arylation, alkenylation, halogenation, hydroxylation) of arenes.¹⁰ However, the analogues *meta*-selective remote C–H bond fluorination of aromatics has yet not been reported, probably due to the challenging C–F bond formation. Herein, in light of these literatures and our previous finding on the selective C–H fluorination, we report for the first time the Pd-catalysed C–H fluorination of phenylacetic acid derivatives at the remote *meta*-position by using a pyridine-containing directing group. In addition, diverse homologues of phenylacetic acid (up to 4 “CH₂” units) could also be compatible in this protocol, constituting a unified strategy for the remote aromatic C–H fluorination of carboxylic acids.

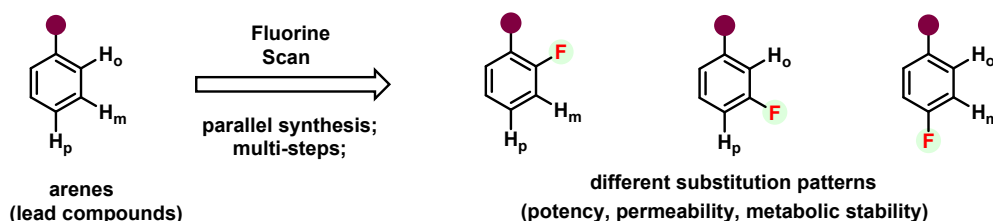
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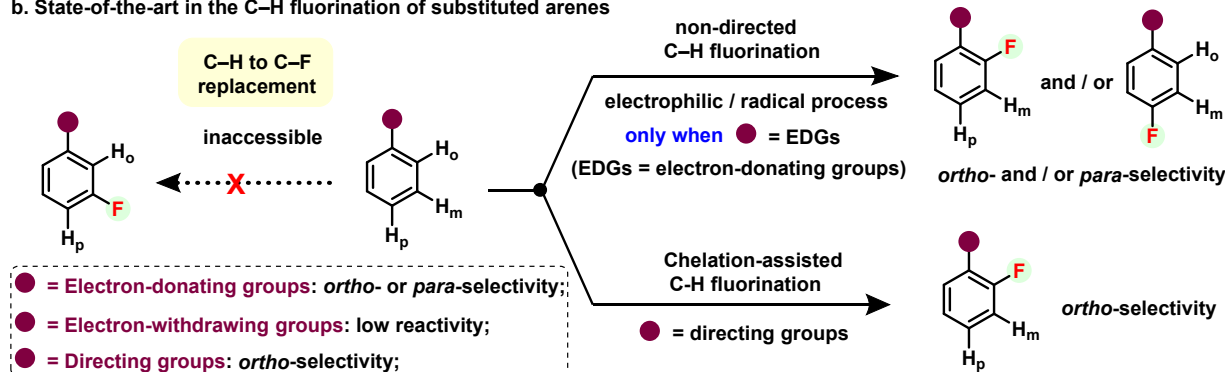
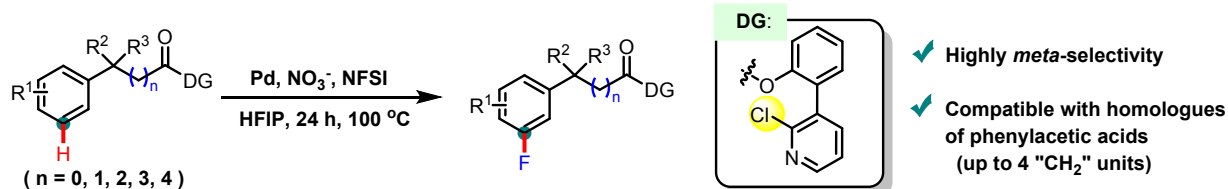


ARTICLE

a. Fluorine scan strategy in drug discovery due to the "magic fluorine effect"



b. State-of-the-art in the C–H fluorination of substituted arenes

c. A unified strategy for the *meta*-selective C–H fluorination of phenylacetic acids and their homologues (This work):

Scheme 1: Remote *meta*-selective C–H fluorination of substituted aromatics: a. Fluorine scan strategy in drug discovery; b. State-of-the-art in the C–H fluorination of substituted aromatics; c. A unified strategy for the remote *meta*-selective C–H fluorination of phenylacetic acids and their homologues (this work).

Results and discussion

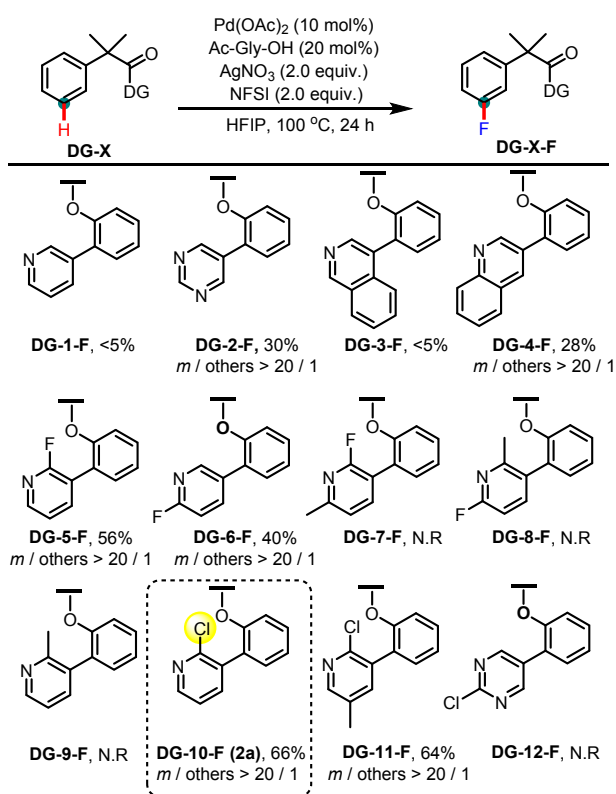
Inspired by the previously reported U-shaped templates for the remote C–H bond functionalization,¹¹ we prepared diverse N-heterocycle-based biaryl directing groups (DGs) to test the remote C–H fluorination of phenylacetic acids (Table 1). On the basis of our previous nitrate promoted C–H fluorination and the general reaction conditions for remote C–H functionalization,^{7b} phenylacetic acid derivatives with different DGs were treated with Pd(OAc)₂, AgNO₃, amino acid ligand, and N-fluorobenzenesulfonimide (NFSI) using hexafluoro-2-propanol (HFIP) as solvent. In our preliminary attempts, the influence of coordinating N-heterocycles was investigated. It was found that the non-substituted 3-pyridyl directing group was inefficient in this reaction (**DG-1-F**). Changing the pyridyl moiety to 4-pyrimidyl group could provide the desired fluorinated product

in a promising 30% yield with excellent *meta*-selectivity (**DG-2-F**). 4-isoquinolinyl (**DG-3-F**) and 3-quinolinyl (**DG-4-F**) groups were also tested and a comparable result was obtained in the case of **DG-3-F**. These results indicated that the substitution pattern of N-heterocycles could significantly influence the coordinating ability of nitrogen centre and therefore manipulating the reactivity. With this consideration in mind, more directing groups possessing different substituted N-heterocycle were prepared. Indeed, directing group bearing a 2-fluoro-3-pyridyl moiety could dramatically improve the yield of fluorination product to 56% with high *meta*-selectivity (**DG-5-F**). Switching the fluorine atom to C6-position diminished the yield (**DG-6-F**). Introducing a methyl group to the C2-position of pyridine moiety would shut down the reaction, probably due to increased steric impulsion (**DG-7-F**, **DG-8-F**, **DG-9-F**). Interestingly, replacing the C2-fluoro group with C2-chloro group could further improve the reaction yield (**DG-10-F**,



66%).¹² Installing an extra methyl group at the *para*-position of chloro substituent did not improve the yield (**DG-11-F**) and the chloro-substituted 4-pyrimidyl group was inefficient in this reaction (**DG-12-F**).

Table 1 Screening the DGs



Reaction conditions: **DG-X** (0.2 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), NFSI (2.0 equiv.), AgNO₃ (2.0 equiv.), HFIP (2.0 mL), 24 h, 100 °C; Yield is determined by GC using dodecane as an internal standard.

Having established the optimised directing group, we proceeded to further screen the reaction conditions using **DG-10 (1a)** as the substrate. Firstly, Pd(OAc)₂ still outperformed other Pd catalysts, such as PdCl₂ and Pd(PPh₃)₄ (Table 2, entries 1-4). The absence of amino acid ligand did not significantly influence the reaction outcome even with a slightly increased yield (entry 5). However, the removal of silver nitrate resulted in a sharp decrease in the yield of **2a**, which is consistent with our previous finding in the selective C–H fluorination (entry 6). Replacing AgNO₃ with AgSbF₆ gave a slightly lower yield, while other nitrate, *e.g.* KNO₃, was much less effective in this reaction (entries 7-8). It was speculated that the SbF₆⁻ ion might also play a similar role as nitrate anion to generate the cationic Pd species, which would promote the C–H activation and C–F bond reductive elimination. Adding more AgNO₃ would further enhance the production of **2a** (entry 10, 77%). Either lowering or elevating the reaction temperature diminished the yield (entries 11-12). Among the different solvents tested in this work (see Table S2 in SI for details), HFIP still outperformed others, *e.g.* trifluoroacetic acid, CH₃NO₂, and 1,2-dichloroethane. This is in agreement with the previous reported unique solvent effect of HFIP in the palladium-catalysed C–H functionalization

reactions, in particularly those for remote aromatic C–H functionalization.^{11n, 13} Finally, a better yield of 86% was obtained when running the reaction for 48 h (entry 13, 72% isolated yield). The re-evaluation of different U-shaped directing groups under the optimised ligand-free conditions was also conducted and **DG-10-F** still outperformed others (see Fig S3 in SI for details). The highly *meta*-selective C–H fluorination of phenylacetic acid derivative is remarkable, constituting the first successful example of remote C–H fluorination of aromatics.

Table 2. Screening of the conditions^a

Entry	Cat. (10 mol%)	Add. (2.0 or 3.0 eqv.)	Ligand (0 or 20%)	Yield of 2a (%)
1	Pd(OAc) ₂	AgNO ₃ (2.0 eqv.)	Ac-Gly-OH	66
2	PdCl ₂	AgNO ₃ (2.0 eqv.)	Ac-Gly-OH	45
3	Pd(PPh ₃) ₄	AgNO ₃ (2.0 eqv.)	Ac-Gly-OH	65
4	/	AgNO ₃ (2.0 eqv.)	Ac-Gly-OH	n.r.
5	Pd(OAc) ₂	AgNO ₃ (2.0 eqv.)	/	70
6	Pd(OAc) ₂	/	/	29
7	Pd(OAc) ₂	AgSbF ₆ (2.0 eqv.)	/	65
8	Pd(OAc) ₂	KNO ₃ (2.0 eqv.)	/	31
9	Pd(OAc) ₂	AgNO ₃ (1.0 eqv.)	/	55
10	Pd(OAc) ₂	AgNO ₃ (3.0 eqv.)	/	77
11 ^b	Pd(OAc) ₂	AgNO ₃ (3.0 eqv.)	/	55
12 ^c	Pd(OAc) ₂	AgNO ₃ (3.0 eqv.)	/	65
13 ^d	Pd(OAc) ₂	AgNO ₃ (3.0 eqv.)	/	86 (72) ^e

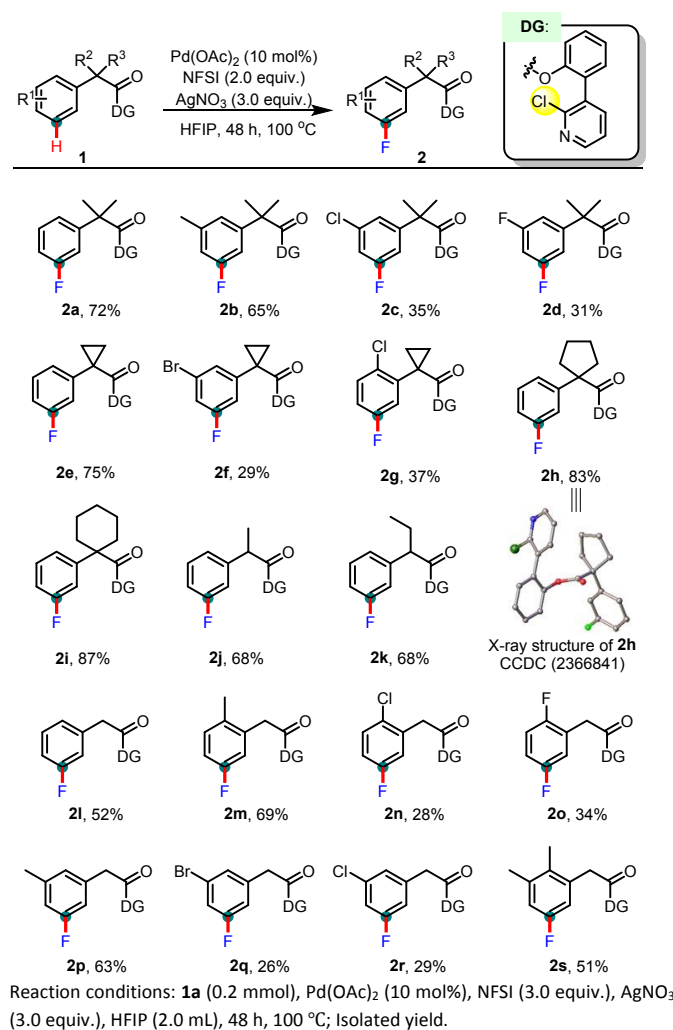
Reaction conditions unless otherwise noted: ^a **1a** (0.2 mmol), Pd(OAc)₂ (10 mol%), NFSI (2.0 equiv.), AgNO₃ (2.0 or 3.0 equiv.), HFIP (2.0 mL), 24 h, 100 °C. Yield was determined by GC using dodecane as an internal standard, n.r. = no reaction. ^b 80 °C; ^c 120 °C; ^d 48 h; ^e Isolated yield.

Having optimized the reaction conditions, we proceeded to evaluate the substrate scope of this protocol. As summarized in Table 3, various phenylacetic acids bearing different α -substituents were examined. The substrates featuring a gem-dimethyl group at the α -position (**2a-2d**) showed enhanced reactivity compared to those without this substitution, probably due to the Thorpe-Ingold effect.¹⁴ Besides, α,α -Disubstituted cyclic alkyl moieties, *e.g.* strained cyclopropyl (**2e, 2f, 2g**) and unstrained cyclopentyl (**2h**), and cyclohexyl (**2i**) groups, could also survive the reaction conditions. Moreover, the solid structure of the *meta*-fluorinated product **2h** was unambiguously determined by single crystal X-ray diffraction analysis. We further explored other α -substituted phenylacetic acid derivatives. As expected, the reaction of compounds that possessing a single methyl (**2j**) or ethyl group (**2k**) at the α -position also afforded the desired products in good yields. In



addition, the more flexible α -free phenylacetic acid derivatives were also tested and comparable yields were obtained (**2i-2s**).

Table 3 The scope of *meta*-C–H fluorination of phenylacetate derivatives

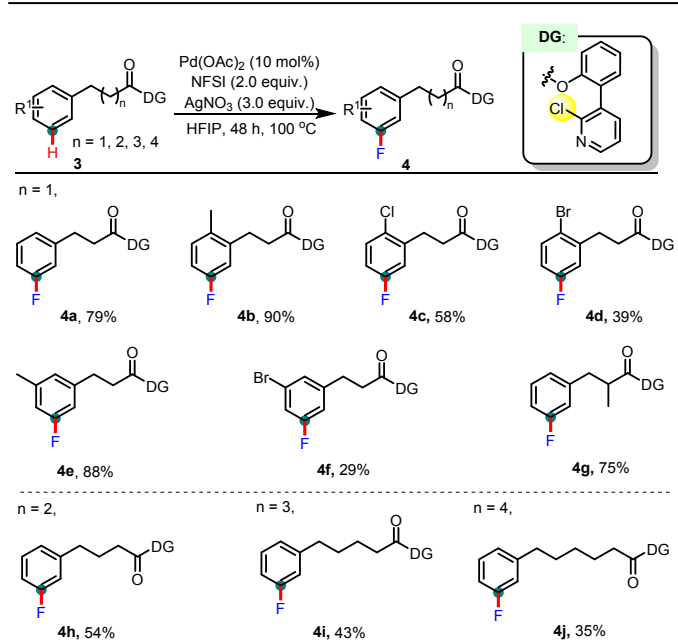


Notably, the type and position of substituents on the aromatic ring could significantly influence the reactivity. In general, the substrates bearing electron-donating groups were more reactive than those with electron-withdrawing groups, suggesting that the electrophilic C–H palladation might be involved in the C–H cleavage step. Substituents tethered at the *ortho* or *meta* positions of the directing group were well tolerated, while the sterically demanding *para*-substituted substrates failed to give the desired *meta*-fluorinated products (see page S37 in SI for details).

Given the importance of phenylacetic acid homologues in pharmaceuticals, a general and unified strategy that enables the remote C–H fluorination of these compounds are great interest to the fields of both organic chemistry and drug discovery. With this consideration in mind, we next attempted to extend the study to other phenyl substituted aliphatic acid derivatives with longer carbon chain linkers. As summarized in Table 4, the reaction tolerated substrates with various chain lengths (*n* up to 4). Phenylpropionic acids reacted successfully

to afford the desired *meta*-fluorinated products (**4a-4g**). For instance, electron-donating groups such as alkyl substituents (**4b, 4e**)

Table 4 The scope of *meta*-C–H fluorination of arene aliphatic acid of long chains



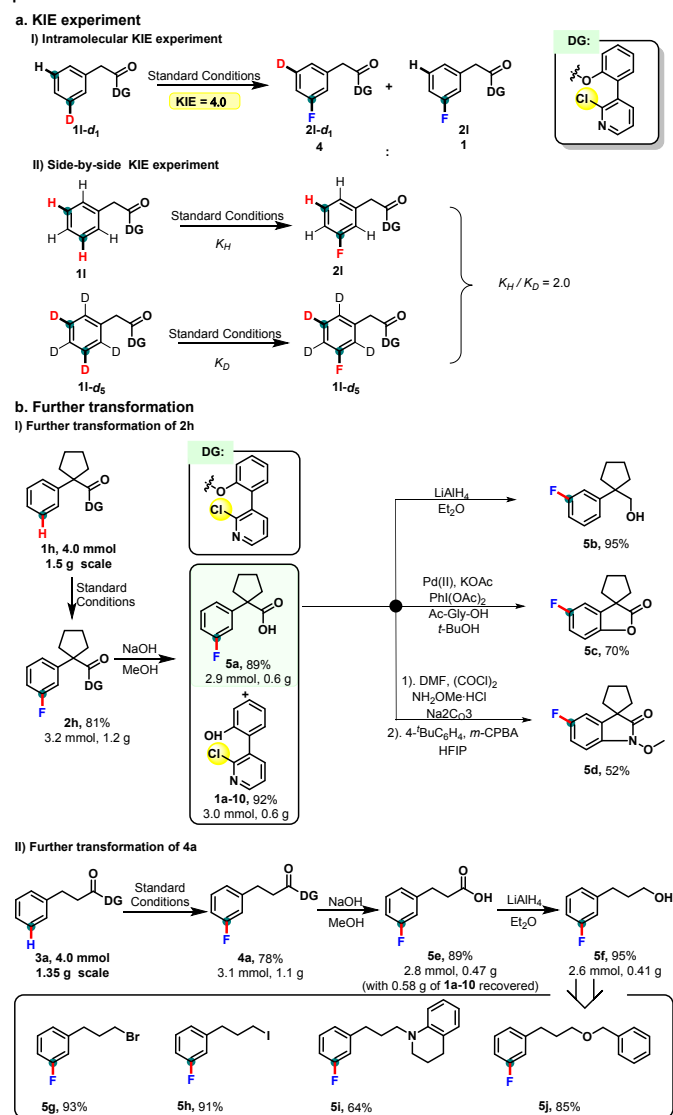
proceeded smoothly. Halogen groups (**4c, 4d, 4f**) and an α -methyl substituent (**4g**) were also compatible with this transformation. Additionally, carboxylic acids with even longer-chain, e.g. phenylbutyric acid (**4h**), phenylvaleric acid (**4i**), and phenylhexanoic acid (**4j**), proved to be viable substrates as well.

The results aligned with our expectations, consistently demonstrating good *meta*-selectivity and acceptable yields. Notably, a gradual decrease in yield was observed with further prolonged chain length. We presume that the enhanced flexibility of the molecular skeleton in longer-chain acids reduces the effective interaction probability between the directing group and the aromatic ring, thereby compromising reaction efficiency.¹⁵

To gain mechanistic insight into this remote C–H fluorination process, kinetic isotope effect (KIE) experiments were conducted. The intramolecular competition experiment between the deuterated substrate **11-d₁** and **11** afforded a primary KIE value of 4.0. Moreover, the KIE measured from two parallel reactions that using **11-d₅** and **11** respectively was 2.0. These results indicate that C–H bond cleavage is probably involved in the rate-determining steps (Scheme 2a).¹⁶ To further demonstrate the synthetic practicality of this *meta*-C–H fluorination protocol, a gram-scale reaction of phenylacetate was performed, delivering the desired product **2h** in without a significant loss in yield (81%, Scheme 2b(I)). Under mild conditions, the pyridine-based directing group could readily be removed, furnishing both fluorinated phenylacetic acid **5a** and the biaryl directing auxiliary (**1a-10**) in good yields. Owing to the



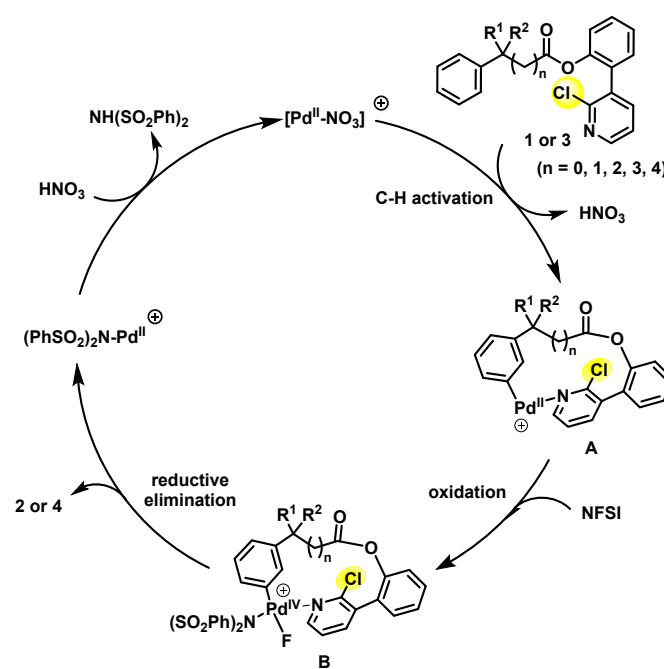
transformation ability of carboxylic acid moiety, the obtained **5a** could easily be transformed to other compounds, such as the reductive product alcohol **5b** and cyclization products **5c** and **5d**. Next, a gram-scale fluorination of phenylpropionic acid also proceeded smoothly to give **4a** in 78% yield (81%, Scheme 2b(II)). Subsequent removal of the directing group provided phenylpropionic acid **5e** along with the corresponding biphenyl auxiliary. The utility of this fluorinated product was further demonstrated by the following transformations: the hydrogenation of **5e** yielded 3-fluorophenylpropanol (**5f**), a versatile synthon that was efficiently converted to other derivatives, e.g. halides (**5g**, **5h**), amine (**5i**), and ether (**5j**) products.



Scheme 2: a. KIE experiment b. Further transformation: I) Further transformation of **2h**; II) Further transformation of **3a**.

Based on our previous reports and other literatures, a possible mechanism for the *meta*-selective aromatic C–H fluorination is proposed and depicted in Scheme 3.^{7a-e, 17} The catalytic cycle is initiated by the *in situ* generation of a highly electrophilic cationic $[\text{Pd}(\text{NO}_3)]^+$ species, which interacts and coordinates with substrate **1** or **3**. Owing to the unique steric

hindrance and positioning effect of the U-shaped long-chain directing group, the coordinated $[\text{Pd}^{\text{II}}]$ species selectively activates the *meta*-C–H bond on the benzene ring through electrophilic palladation, affording a macro-palladacycle intermediate **A**. Subsequently, the divalent palladium species **A** is oxidized by NFSI to form the tetravalent palladium species **B**. Reductive elimination from **B** affords the fluorinated product **2** or **4**, concurrently reducing the palladium center to form the $[(\text{PhSO}_2)_2\text{N-Pd}^{\text{II}}]^+$ species. Finally, anion exchange of this resulting $[\text{Pd}^{\text{II}}]$ intermediate with HNO_3 regenerates the reactive palladium nitrate species and closes the catalytic cycle. However, alternative mechanism involving the possible oxidation of substrate-binding Pd^{II} species to Pd^{IV} prior to the C–H bond palladation could not be excluded. In this case, the C–H activation at Pd^{IV} center would take place.^{17a}



Scheme 3. Proposed mechanism

Conclusions

In summary, through the design of a novel directing group, we have achieved for the first time the *meta*-selective aromatic C–H fluorination of phenylacetic acid derivatives. Notably, this protocol was also feasible for the analogous C–H fluorination of other homologues of phenylacetic acid, constituting a unified strategy for the precision H / F exchange at remote position of the phenyl substituted carboxylic acids. This work not only opens a new avenue for the aromatic C–H fluorination but also enriches the reaction types for the remote aromatic C–H functionalization.

Author contributions

S.-J. Lou and D.-Q. Xu conceived and directed the project. K. Zhou X. Chen, Y. Wang, X. Yang, K. Liu, Q. Pan and D.-L. Pan, performed the experiments and analysed the data. S.-J. Lou, Y.-



J. Mao and K. Zhou wrote the manuscript with input from all the authors. All authors have read and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Experimental procedures, single crystal X-ray diffraction data, characterisation data, and NMR spectra for new compounds can be found in the ESI.

Acknowledgements

This work was supported in part by the National Natural Science Foundation of China (No.22301275), the Central Government Guided Local Science and Technology Development Fund Project (No. 2025ZY01113), the "Jianbing" and "Lingyan" Research and Development Program of Zhejiang province (2023C02059), the Beidou Scientific Research Project of Zhejiang University of Technology and Zhejiang Key Laboratory of Green Pesticides and Cleaner Production Technology, Zhejiang Provincial Natural Science Foundation of China under Grant No. LMS25B020004, and the Research Foundation for Advanced Talents from ZJUT (No. 2021101016929).

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View Article Online
DOI: 10.1039/D6SC01331G

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The data supporting the findings of this study are available as follows: Crystallographic data for [2h] have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number [2366841] and can be obtained from <https://www.ccdc.cam.ac.uk/structures/>. Additional experimental data, including characterisation data and NMR spectra for new compounds, are provided in the Electronic Supplementary Information (ESI).

