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## Visible-light-induced selective defluoroalkylations of polyfluoroarenes with alcohols†

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To provide  $\alpha$ -polyfluoroarylalcohols, a novel protocol for the selective defluoroalkylation of polyfluoroarenes with easily accessible alcohols was reported *via* the cooperation of photoredox and hydrogen atom transfer (HAT) strategies with the assistance of Lewis acids under visible light irradiation. The protocol featured broad scope, excellent regioselectivity for both C–H and C–F bond cleavages, and mild conditions. Mechanistic studies suggested that the reaction occurred through Lewis acid-promoted HAT to provide an alkyl radical and sequential addition to polyfluoroarenes. Impressively, the regioselectivity for C–F cleavage was verified with the Fukui function. The feasibility and application of this protocol on fluoroarene synthesis were well illustrated by gram-scale synthesis under both batch and flow conditions, late-stage decoration of bioactive compounds, and further transformations of the fluoroarylalcohols.

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### Introduction

Fluoroarenes are important motifs exhibiting wide applications in pharmaceuticals,<sup>1–6</sup> agrochemicals,<sup>7,8</sup> and materials.<sup>9</sup> Among the newly released top 200 pharmaceuticals in 2021,<sup>10</sup> over 10% of them contain aryl C–F bonds including eight with polyfluoroarenes. However, the synthetic methods for polyfluoroarenes were still limited to traditional methods, such as direct fluorination with highly reactive fluorine sources, leading to poor selectivity.<sup>11–15</sup> Selective C–F bond activation of readily available poly- or perfluoroarenes to construct novel C–C bonds provided an alternative method for fluoroarene synthesis.<sup>16–21</sup> However, due to the inertness of C–F bonds, the majority of the reports on the transformation of C–F bonds of polyfluoroarenes into C–C bonds occurred with strong nucleophiles such as Grignard, zinc, and copper reagents *via* directed transition metal catalysis to ensure the regioselectivity for C–F bond activations. The preinstalled proximal directing or activating groups and highly reactive reaction partners largely undermined the feasibility of these strategies.

With the significant development of visible-light-induced organic transformations in recent years,<sup>22–32</sup> photocatalytic chemo- and regioselective conversion of C–F bonds in polyfluoroarenes to C–C bonds *via* defluoroalkylation has drawn significant attention.<sup>33,34</sup> Weaver reported a series of C–F functionalizations of polyfluoroarenes *via* photoreduction of polyfluoroarenes and sequential radical addition to unsaturated C–C bonds present in alkenes,<sup>35</sup> alkynes,<sup>36</sup> and arenes.<sup>37</sup> On the other hand, the Hashmi group developed a visible-light-induced defluoroalkylation reaction to achieve the  $\alpha$ -fluoroarylation of *N*-dialkylanilines through a radical–radical coupling pathway.<sup>38</sup> Recently, the Ritter group reported a defluoroalkylation of polyfluoroarenes using aliphatic carboxylic acids as the alkylation reagent *via* photocatalytic decarboxylation for alkyl radical formations.<sup>39</sup> However, the facile and efficient defluoroalkylations of polyfluoroarenes *via* direct coupling of C(sp<sup>3</sup>)–H and C–F bonds are still underdeveloped.

$\alpha$ -Polyfluoroarylalcohols are important skeletons in drugs and bioactive compounds (Fig. 1a).<sup>4</sup> However, the synthetic methods were still limited to the nucleophilic addition of polyfluoroaryl precursors such as Grignard<sup>40,41</sup> and silane reagents<sup>42</sup> to aldehydes or ketones with or without transition metal catalysis (Fig. 1b). Recently, Luo, Radius and Marder reported a transition metal-free, base-promoted additions of polyfluoroarylboronates to aldehydes and ketones,<sup>43</sup> based on their achievements in nickel-catalyzed defluoroborylation of polyfluoroarenes<sup>44,45</sup> and palladium-catalyzed dechloroborylation of chlorine-substituted polyfluoroarenes.<sup>46</sup> The usage of highly reactive or not easily accessible fluoroaryl reagents dramatically restricted the application of these methodologies and the variety of the products. Meanwhile, alcohols were one of the most abundant and accessible starting materials for organic transformations.<sup>47</sup> Using alcohols as

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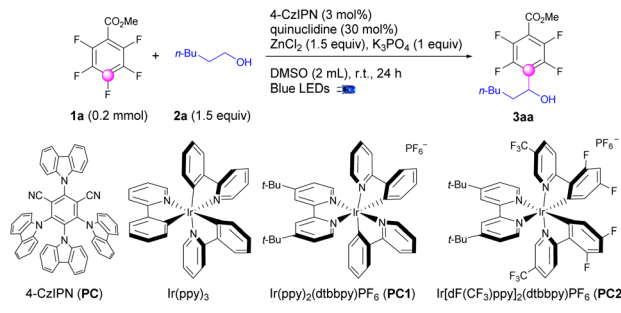


alkylation reagents *via* photocatalytic hydrogen atom transfer (HAT) of their  $\alpha$ -C-H bonds has witnessed significant progress in recent years. Elegant studies from Macmillan's group using alcohol as the alkyl radical precursor provided an efficient methodology to construct C-C bonds *via* radical addition to Michael acceptors<sup>48</sup> or cross-coupling with aryl halides with the cooperation of nickel catalysis.<sup>49</sup> Nevertheless, the defluoroalkylations of polyfluoroarenes using alcohols as the alkyl source *via* HAT were rarely reported and challenging, maybe because of the nucleophilicity of alcohols. Nucleophilic aromatic substitution ( $S_NAr$ ) readily occurred with polyfluoroarenes to provide defluoroetherification products under basic conditions.<sup>50</sup> In 1991, Pahor *et al.* reported a seminal study on the defluoroalkylation of polyfluoroarenes with alcohols using benzophenone as the stoichiometric HAT reagent under neutral conditions and UV irradiation,<sup>51</sup> albeit with poor selectivity, low efficiency, and limited scope for both substrates (Fig. 1c). Since then, no significant progress has been made on this transformation. Considering the development of photocatalytic selective C-F activation of polyfluoroarenes and HAT reactions of alcohols and our continuous interest in fluoroarene synthesis,<sup>52</sup> herein we hypothesized that with the assistance of Lewis acids, the activations of  $\alpha$ -C-H of alcohols could be facilitated *via* the cooperation of photoredox and HAT catalysis to produce an alkyl radical, which would react with polyfluoroarenes to deliver valuable  $\alpha$ -polyfluoroaryl alcohols (Fig. 1d).

## Results and discussion

The optimization of the reaction conditions was initiated using methyl 2,3,4,5,6-pentafluorobenzoate (**1a**) and hexan-1-ol (**2a**) as the reaction partners, and a catalytic system containing photoredox catalysts (PCs), HAT catalysts, Lewis acids, and bases (Table 1). After substantial exploration, we achieved the optimal conditions for defluoroalkylation with a combination of 4-

Table 1 Condition optimization for photocatalytic defluoroalkylation of polyfluoroarenes



Entry	Deviation	Yield <sup>b</sup> (%)
1 <sup>a</sup>	No	87 <sup>c</sup>
2	Ir(ppy) <sub>3</sub> (2 mol%) instead of 4-CzIPN	0
3	PC1 (1 mol%) instead of 4-CzIPN	6
4	PC2 (1 mol%) instead of 4-CzIPN	70
5	MeCN, EtOAc, DMF, or DMA as solvent	<15
6	No light, 4-CzIPN, or quinuclidine	0
7	Without ZnCl <sub>2</sub>	28
8	Without K <sub>3</sub> PO <sub>4</sub>	86
9	ZnCl <sub>2</sub> (50 mol%) and without K <sub>3</sub> PO <sub>4</sub>	70

<sup>a</sup> Reaction conditions: methyl 2,3,4,5,6-pentafluorobenzoate (**1a**, 0.20 mmol), hexan-1-ol (**2a**, 0.30 mmol), 4-CzIPN (3 mol%), quinuclidine (30 mol%), ZnCl<sub>2</sub> (0.30 mmol), DMSO (4 mL), 18 W blue LED irradiation, room temperature, 24 h. <sup>b</sup> Yields of **3aa** were determined by analysis of the crude <sup>1</sup>H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Isolated yields.

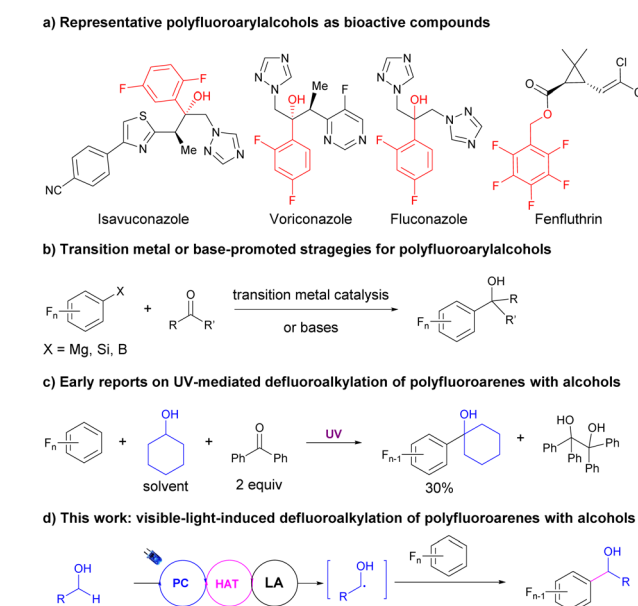


Fig. 1 Applications and synthetic strategies of polyfluoroarylalcohols.

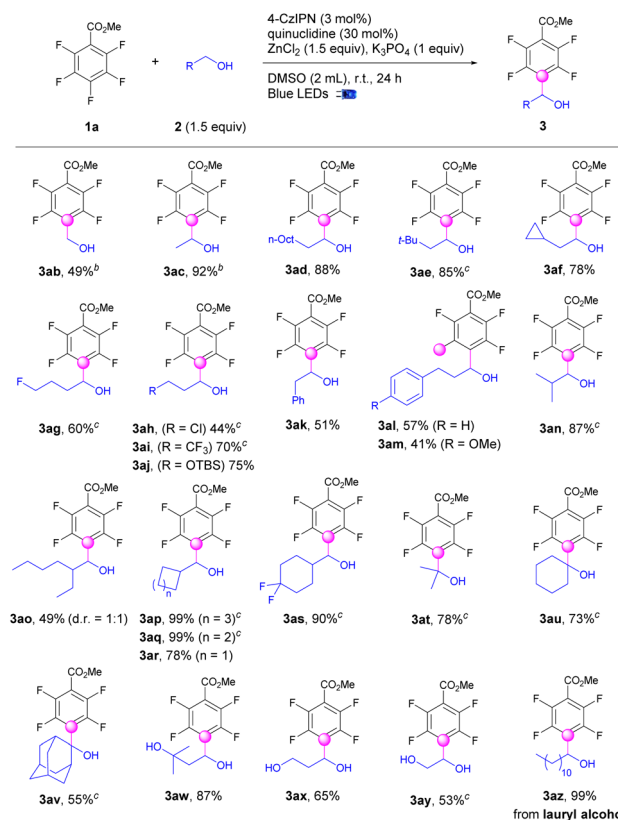
CzIPN (3 mol%), quinuclidine (30 mol%), ZnCl<sub>2</sub> (1.5 equiv.) and K<sub>3</sub>PO<sub>4</sub> (1.0 equiv.) in DMSO under blue LED irradiation to afford polyfluoroarylalcohol products (**3aa**) in 87% isolated yields (Table 1, entry 1). Using precious transition metal complexes such as Ir(ppy)<sub>3</sub>, Ir(ppy)<sub>2</sub>(dtbbpy)PF<sub>6</sub>, and Ir[dF(CF<sub>3</sub>)ppy]<sub>2</sub>(dtbbpy)PF<sub>6</sub> instead of 4-CzIPN as photoredox catalysts, the yields for **3aa** were dramatically decreased (entry 2–4). Other solvents including MeCN, EtOAc, DMF, or DMA led to sluggish reaction mixtures, providing **3aa** only in less than 15% yields (entry 5). Control experiments exhibited the necessity for the presence of light, 4-CzIPN, and quinuclidine (entry 6). Excluding ZnCl<sub>2</sub> sharply lowered the yields to 28% (entry 7). The absence of bases led to comparable yields of **3aa** (entry 8). Notably, without bases, the usage of ZnCl<sub>2</sub> could be decreased to less than the stoichiometric amount (entry 9).

After the establishment of the optimized conditions, we continued to evaluate the scope of polyfluoroarenes (**1**) for defluoroalkylations with hexan-1-ol (**2a**) (Scheme 1). Perfluoroarenes including hexafluorobenzene and pentafluoropyridine worked well to produce the monoalkylation products (**3ba–3ca**) in good to excellent yields with specific regioselectivities. Mono and di-alkylation of perfluoro-1,1'-biphenyl (**3da–3ea**) could be selectively achieved by adjusting the equivalents of alcohols. Defluoroalkylation of pentafluorobenzene occurred smoothly to give the product (**3fa**) in 57% yields. Pentafluoroarenes bearing electron-withdrawing groups *i.e.*, CF<sub>3</sub> were exceptional candidates for this transformation (**3ga**). Quite a few

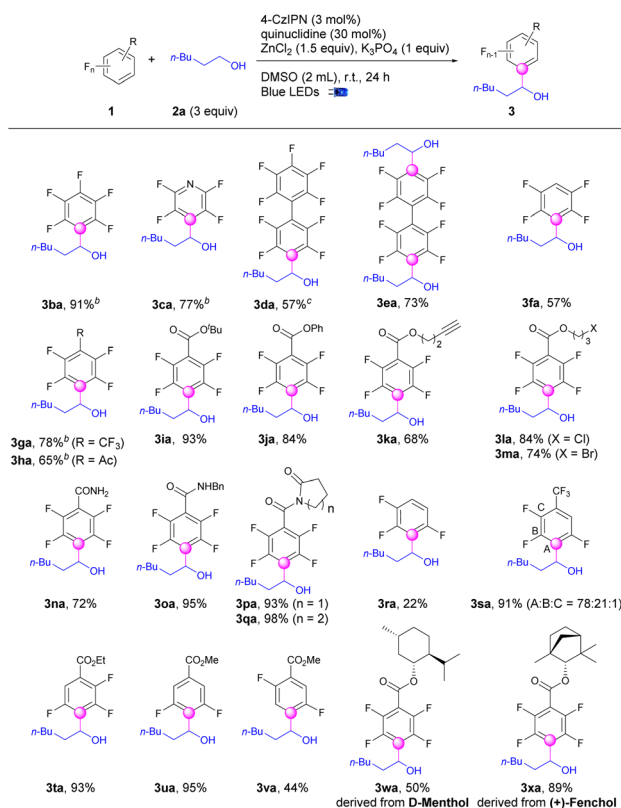


functional groups such as acetyl, ester, alkynyl, chloro, bromo, amide, pyrrolidinone, and piperidinone were well tolerated and produced the corresponding alkyltetrafluorobenzene derivatives (**3ha–3qa**) in good to excellent yields. 1,2,3,4-Tetrafluorobenzene was defluoroalkylated exclusively at the 2-position (**3ra**), albeit in a lower yield. Nevertheless, adding a trifluoromethyl group or an ester group led to much higher yields for the defluoroalkylated products (**3sa–3ta**) of tetrafluoroarenes, albeit with lower regioselectivity for **3sa**. Trifluoroarenes bearing ester groups with different substitution patterns both underwent defluoroalkylation selectively to produce the desired products (**3ua–3va**) in 95% and 44% yields, respectively. Interestingly, the selectivity for C–F cleavage in **1f** and **1r** was different but complementary with transition-metal catalysis.<sup>53,54</sup> In addition, no directing effect of the proximal groups such as ester and amide groups, was exhibited for the C–F bond activations. This protocol was also amendable to natural products such as *D*-menthol and (+)-fenchol derived pentafluoroarenes and gave the tetrafluoroarene products (**3wa–3xa**) in appreciable yields.

The applications of this strategy on C–H fluoroarylation of various alcohols (**2**) with methyl 2,3,4,5,6-pentafluorobenzoate (**1a**) were also explored (Scheme 2). Simple linear alkyl alcohols such as methanol, ethanol, and 1-decanol were fluoroarylated at the  $\alpha$ -position of alcohols (**3ab–3ad**) in 49–92% yields. Sterically hindered  $\beta$ -alkyl substituted alcohols were also applicable for



Scheme 2 Photocatalytic selective fluoroarylations of alcohols. <sup>a</sup>All cited yields are isolated yields. The product was produced as a single isomer unless otherwise noted. <sup>b</sup>**2** (5.0 equiv.) was used. <sup>c</sup>**2** (3.0 equiv.) was used.

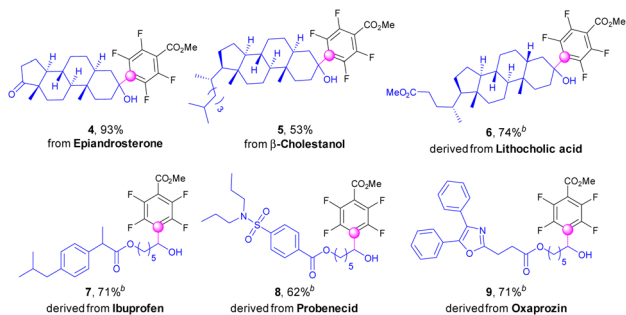


Scheme 1 Photocatalytic selective defluoroalkylation of polyfluoroarenes. <sup>a</sup>All cited yields are isolated yields. The product was produced as a single isomer unless otherwise noted. <sup>b</sup>**2a** (5.0 equiv.) was used. <sup>c</sup>**2a** (1.5 equiv.) was used.

fluoroarylation (**3ae–3af**). Functional groups such as fluoro, chloro, CF<sub>3</sub>, and OTBS were well incorporated to provide the tetrafluoroarylalcohols (**3ag–3aj**) in 44–75% yields. Gratefully, aryl substituted alcohols performed the alkylation exclusively at the  $\alpha$ -position of alcohols instead of benzylic positions to give the fluoroarylated products (**3ak–3am**) in moderate yields. Notably, the alcohols with sterically hindered  $\alpha$ -substituents were workable for fluoroarylation to afford the products (**3an–3ao**) in 41–87% yields.  $\alpha$ -Cycloalkyl methanols including cyclohexyl, cyclopentyl, and cyclobutyl were successful candidates for fluoroarylation to afford products (**3ap–3as**) in good to excellent yields. To our delight, the fluoroarylation of acyclic and cyclic secondary alcohols such as isopropanol, cyclohexanol, and even 2-adamantanol occurred smoothly to deliver the desired products (**3at–3av**) in 55–78% yields. Diols including 3-methylbutane-1,3-diol, ethane-1,2-diol and propane-1,3-diol worked well for selective mono-fluoroarylation to give fluoroarylated diols (**3aw–3ay**) in good yields. The bioactive lauryl alcohol was also a suitable candidate to provide the fluoroarylation products (**3az**) quantitatively.

Impressively, the protocol was further applicable for direct fluoroarylations of complex natural products and pharmaceutical derivatives with alcohol functionalities (Scheme 3). Epiandrosterone, an anabolic steroid, which is the source of testosterone and other sex hormones, could be directly polyfluoroarylated to afford the products (**4**) in excellent yields. The fluoroarylation of





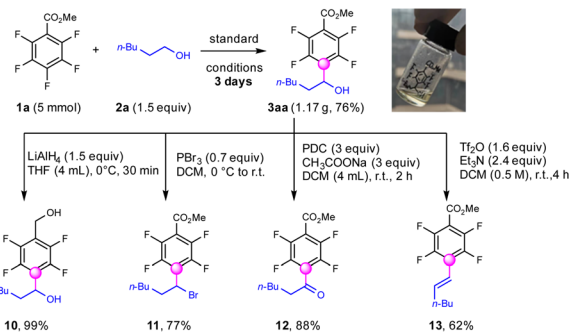
**Scheme 3** Photo-mediated selective fluoroarylation of bioactive alcohols. <sup>a</sup>All cited yields are isolated yields. The product was produced as a single isomer unless otherwise noted. <sup>b</sup>1a (3.0 equiv.) was used.

$\beta$ -cholestanol was also successful to give the derivative (5) in moderate yields. Lithocholic acid known as one of the bile acids was efficiently decorated with a fluoroaryl group after esterification (6). Alcohols linked with pharmaceutical moieties, such as ibuprofen, probenecid, and oxaprozin, could be fluoroarylated successfully to deliver the complex  $\alpha$ -polyfluoroarylalcohols (7–9) in good yields with excess amounts of inexpensive polyfluoroarenes.

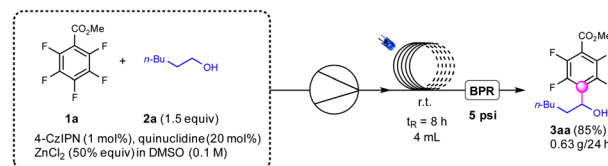
To test the feasibility of this transformation, the gram-scale synthesis of  $\alpha$ -fluoroaryl alcohols was performed which afforded the products (3aa) in 76% yields under standard conditions for 3 days (Scheme 4). This product 3aa was further reduced by  $\text{LiAlH}_4$  to deliver fluoroaryl-diols (10) in 99% yields, which were important precursors for the synthesis of insecticides.<sup>55</sup> The hydroxyl groups in the products could be transformed into bromine (11) using  $\text{PBr}_3$  in 77% yields.<sup>56</sup> The oxidation of the alcohols to ketone products (12) occurred smoothly with PDC in 88% yields.<sup>57</sup> The combination of  $\text{Ti}_2\text{O}$  and  $\text{NEt}_3$  could dehydroxylate the fluoroarylalcohols to afford the *E*-fluoroarylalkenes exclusively in 62% yields (13),<sup>58</sup> which could not be achieved by previous reported photocatalytic defluoroalkenylation strategies.<sup>36</sup> To our delight, the continuous-flow conditions were applicable for a modified protocol utilizing 4CzIPN (1 mol%), quinuclidine (20 mol%) and  $\text{ZnCl}_2$  (50 mol%) under base-free conditions, to produce 3aa with higher efficiency compared with that for batch conditions.

To elucidate the mechanism for defluoroalkylation, we performed a series of experiments (Scheme 5). No desired product was obtained with the addition of TEMPO suggesting a radical mechanism (Scheme 5a). In the presence of benzyl acrylate, the yield of 3aa was decreased to 9% accompanied by the formation of 5-pentylidihydrofuran-2(3*H*)-one, which indicated the presence of an alcohol  $\alpha$ -carbon radical (Scheme 5b).<sup>48</sup> Meanwhile, when adding radical trappers for polyfluoroaryl radicals, such as alkynes<sup>36</sup> and trimethoxybenzene,<sup>37</sup> no radical addition products were observed with no significant influence on the yields of 3aa. Stern–Volmer quenching studies indicate that the quenching effect of quinuclidine was much stronger than that of polyfluoroarenes and alcohols (see the ESI†). In addition, the stronger C–F bonds of pentafluorochlorobenzene (1y) instead of the C–Cl bond were selectively activated to produce the defluoroalkylation products (3ya) under standard conditions with moderate regioselectivity

#### a) Gram scale productions under batch conditions and further product transformations



#### b) Gram scale productions under flow conditions



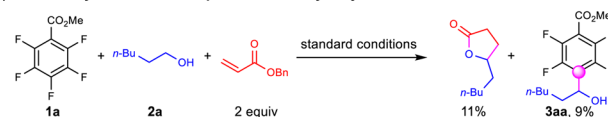
**Scheme 4** Gram scale productions and further product transformations.

(Scheme 5c), indicating that the reaction might not involve the single electron reduction of the polyfluoroarenes.<sup>59</sup> CV testing on the substrates showed that the reductive potential of the polyfluoroarenes ( $E_{\text{red}} = -2.67$  V vs.  $\text{Ag}/\text{AgCl}$  in DMSO) was much lower than  $E_{\text{PC}^{\text{n}}/\text{PC}^{\text{n}-1}} (-1.21$  V vs. SCE in  $\text{CH}_3\text{CN}$ ), while the oxidative potential of quinuclidine ( $E_{\text{ox}} = 1.14$  V vs.  $\text{Ag}/\text{AgCl}$  in DMSO) was slightly lower than  $E_{\text{PC}^{\text{n}}/\text{PC}^{\text{n}-1}} (1.35$  V vs. SCE in  $\text{CH}_3\text{CN}$ ).<sup>60</sup> Above all, the photoredox cycle could be initiated *via*

#### a) Radical inhibition experiments using 2,2,6,6-tetramethyl-1-piperidyl-oxo (TEMPO)



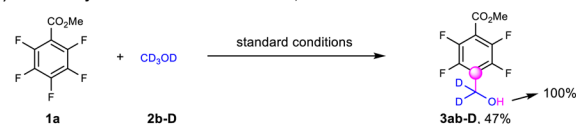
#### b) Defluoroalkylation of 1a in the presence of benzyl acrylate



#### c) Defluoroalkylation of pentafluorochlorobenzene



#### d) Defluoroalkylation with deuterated methanol, 2b-D



#### e) Kinetic isotope effect (KIE) experiments



**Scheme 5** Experiments to elucidate the reaction mechanism.



reductive quenching of the excited photocatalyst with quinuclidine. D4-methanol (**2b-D**) led to tetrafluoroarylated methanol (**3ab-D**) in moderate yields with no H-D exchanges at the  $\alpha$ -position, while the deuterium atom on the hydroxyl group was exclusively exchanged to hydrogen (Scheme 5d), indicating the formation of an alkoxide intermediate. The intermolecular competition reaction of **2b** and **2b-D** with **1a** was conducted to figure out a KIE value of 5.8, suggesting that the C-H activation *via* HAT could be the rate-controlling step.<sup>61</sup> Finally, quantum yields (0.31) were determined to exclude the radical chain mechanism.<sup>62</sup>

Plausible catalytic cycles were proposed based on all the above observations (Scheme 6). As illustrated in Scheme 6, the PC (4-CzIPN) was first photo-excited to PC\* under blue LED irradiation. Reductive quenching occurred for PC\* with quinuclidine to deliver a quinuclidine radical cation and PC<sup>n-1</sup>. This radical cation abstracted the hydrogen atom from the alkoxide zinc intermediate **I**, which is the product of the reaction between alcohol and ZnCl<sub>2</sub>,<sup>49</sup> to give the alkyl radical **II**. Radical addition of **II** then occurred with polyfluoroarenes to deliver the aryl-radical **III**. Followed by the reduction of **III** with PC<sup>n-1</sup>, the polyfluoroaryl anion **IV** was produced along with the recovery of the PC. The resulting intermediate **IV** would extrude the fluoride to afford the final product **3**,<sup>63</sup> followed by the sequential zinc-proton exchange. To illustrate the regioselectivity for C-F bond cleavage in polyfluoroarenes, the orbital-weighted Fukui index (OW<sub>f</sub><sup>+</sup>) was computed for representative polyfluoroarene substrates,<sup>64-67</sup> including **1a**, **1f-1g**, **1r**, and **1t-1v** (Fig. 2). The orbital weighted Fukui function could analyze the contribution of inner orbitals to the reactivity and

predict accurate regioselectivity for C-F cleavage of polyfluoroarenes.<sup>68</sup> The isosurface images of OW<sub>f</sub><sup>+</sup> are shown in Fig. 2. Interestingly, the defluoroalkylation occurred specifically on the carbon atoms (C1) exhibiting the highest OW<sub>f</sub><sup>+</sup> values in these substrates, which was in good accord with the nucleophilic carbon radical addition mechanism and provided a straightforward strategy to predict the regioselectivity for these types of radical addition reactions to polyfluoroarenes.

## Conclusions

In summary, we have established a feasible protocol for the selective defluoroalkylation of polyfluoroarenes with alcohols utilizing a cooperative catalytic system combining photocatalysts, HAT catalysts, and Lewis acids. Varieties of polyfluoroaryl alcohols were successfully constructed *via* selective C-F activation of polyfluoroarenes and C-H activation of alcohols. Notably, the strategy was applicable to direct late-stage decoration of natural products and bioactive alcohols and could also be conducted under continuous flow conditions efficiently to facilitate promising large-scale productions. With the preservation of the hydroxy group, the further transformation led to broad functionalities and will see broad applications in the synthesis of value-added fluoroaryl compounds.

## Data availability

All experimental and characterization data, as well as NMR spectra are available in the ESI.†

## Author contributions

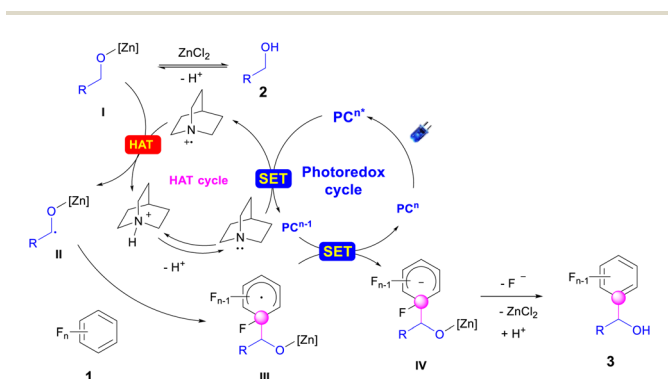
M. W., W. X. and Q. S. designed this project. W. X., Q. S., H. Z., C. X., Q. Z. and Y. X. conducted the experiments, analyzed the data, and prepared the ESI.† Y. L. performed the DFT calculations. M. W. and W. X. analyzed the data and prepared the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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Scheme 6 Proposed mechanism for defluoroalkylation of polyfluoroarenes.

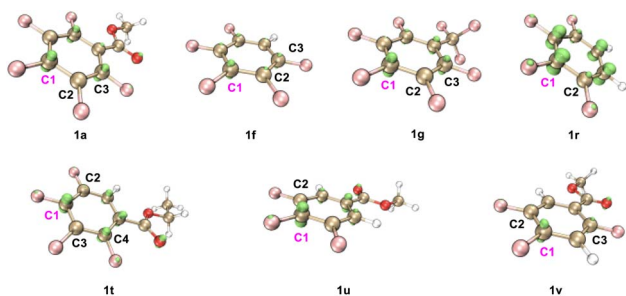


Fig. 2 The orbital-weighted Fukui index (OW<sub>f</sub><sup>+</sup>) of the representative substrates.



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## Notes and references

- 1 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- 2 W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.
- 3 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
- 4 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- 5 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359.
- 6 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- 7 P. Jeschke, *ChemBioChem*, 2004, **5**, 570–589.
- 8 P. Jeschke, *Pest Manage. Sci.*, 2017, **73**, 1053–1066.
- 9 M. L. Tang and Z. Bao, *Chem. Mater.*, 2011, **23**, 446–455.
- 10 <https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%202020%20Pharmaceuticals%202021V2.pdf>, 2022.
- 11 C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2015, **54**, 3216–3221.
- 12 C. N. Neumann and T. Ritter, *Acc. Chem. Res.*, 2017, **50**, 2822–2833.
- 13 Q. Cheng and T. Ritter, *Trends Chem.*, 2019, **1**, 461–470.
- 14 R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2019, **58**, 14824–14848.
- 15 E. Nobile, T. Castanheiro and T. Besset, *Angew. Chem., Int. Ed.*, 2021, **60**, 12170–12191.
- 16 H. Amii and K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119–2183.
- 17 T. Fujita, K. Fuchibe and J. Ichikawa, *Angew. Chem., Int. Ed.*, 2019, **58**, 390–402.
- 18 N. A. LaBerge and J. A. Love, in *Organometallic Fluorine Chemistry*, ed. T. Braun and R. P. Hughes, Springer International Publishing, Cham, 2015, pp. 55–111, DOI: [10.1007/3418\\_2015\\_90](https://doi.org/10.1007/3418_2015_90).
- 19 T. Ahrens, J. Kohlmann, M. Ahrens and T. Braun, *Chem. Rev.*, 2015, **115**, 931–972.
- 20 J. L. Kiplinger, T. G. Richmond and C. E. Osterberg, *Chem. Rev.*, 1994, **94**, 373–431.
- 21 J. Weaver and S. Senaweera, *Tetrahedron*, 2014, **70**, 7413–7428.
- 22 D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77–80.
- 23 M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**, 12886–12887.
- 24 J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113.
- 25 J. Xuan and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828–6838.
- 26 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363.
- 27 K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035–10074.
- 28 D. Ravelli, S. Protti and M. Fagnoni, *Chem. Rev.*, 2016, **116**, 9850–9913.
- 29 N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166.
- 30 L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem., Int. Ed.*, 2018, **57**, 10034–10072.
- 31 R. C. McAtee, E. J. McClain and C. R. J. Stephenson, *Trends Chem.*, 2019, **1**, 111–125.
- 32 R. Cannalire, S. Pelliccia, L. Sancineto, E. Novellino, G. C. Tron and M. Giustiniano, *Chem. Soc. Rev.*, 2021, **50**, 766–897.
- 33 J. Wang, H. Gao, C. Shi, G. Chen, X. Tan, X. Chen, L. Xu, X. Cai, B. Huang and H. Li, *Chem. Commun.*, 2021, **57**, 12203–12217.
- 34 B. Niu, K. Sachidanandan, B. G. Blackburn, M. V. Cooke and S. Laulhé, *Org. Lett.*, 2022, **24**, 916–920.
- 35 A. Singh, J. J. Kubik and J. D. Weaver, *Chem. Sci.*, 2015, **6**, 7206–7212.
- 36 A. Singh, C. J. Fennell and J. D. Weaver, *Chem. Sci.*, 2016, **7**, 6796–6802.
- 37 S. Senaweera and J. D. Weaver, *J. Am. Chem. Soc.*, 2016, **138**, 2520–2523.
- 38 J. Xie, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2017, **56**, 7266–7270.
- 39 X. Sun and T. Ritter, *Angew. Chem., Int. Ed.*, 2021, **60**, 10557–10562.
- 40 M. Abarbri, F. Dehmel and P. Knochel, *Tetrahedron Lett.*, 1999, **40**, 7449–7453.
- 41 X. Jia, J. Wang, X. Ding, J. Yang, N. Li, N. Zhao and Z. Huang, *J. Org. Chem.*, 2015, **80**, 10874–10882.
- 42 G.-F. Du, F. Xing, C.-Z. Gu, B. Dai and L. He, *RSC Adv.*, 2015, **5**, 35513–35517.
- 43 Z. Liu, G. K. Kole, Y. P. Budiman, Y.-M. Tian, A. Friedrich, X. Luo, S. A. Westcott, U. Radius and T. B. Marder, *Angew. Chem., Int. Ed.*, 2021, **60**, 16529–16538.
- 44 J. Zhou, M. W. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder and U. Radius, *J. Am. Chem. Soc.*, 2016, **138**, 5250–5253.
- 45 Y.-M. Tian, X.-N. Guo, M. W. Kuntze-Fechner, I. Krummenacher, H. Braunschweig, U. Radius, A. Steffen and T. B. Marder, *J. Am. Chem. Soc.*, 2018, **140**, 17612–17623.
- 46 Y. P. Budiman, S. Lorenzen, Z. Liu, U. Radius and T. B. Marder, *Chem.–Eur. J.*, 2021, **27**, 3869–3874.
- 47 B. K. Chi, J. K. Widness, M. M. Gilbert, D. C. Salgueiro, K. J. Garcia and D. J. Weix, *ACS Catal.*, 2022, **12**, 580–586.
- 48 J. L. Jeffrey, J. A. Terrett and D. W. C. MacMillan, *Science*, 2015, **349**, 1532–1536.
- 49 J. Twilton, M. Christensen, D. A. DiRocco, R. T. Ruck, I. W. Davies and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2018, **57**, 5369–5373.
- 50 D. Prescher, V. E. Platonov, K. V. Dvornikova, J. Schulze, O. I. Osina and G. G. Yakobson, *J. Fluorine Chem.*, 1985, **29**, 204.



- 51 B. Šket, M. Zupan, N. Zupančič and B. Pahor, *Tetrahedron*, 1991, **47**, 5029–5042.
- 52 W. Xu, Q. Zhang, Q. Shao, C. Xia and M. Wu, *Asian J. Org. Chem.*, 2021, **10**, 2454–2472.
- 53 Y. M. Tian, X. N. Guo, M. W. Kuntze-Fechner, I. Krummenacher, H. Braunschweig, U. Radius, A. Steffen and T. B. Marder, *J. Am. Chem. Soc.*, 2018, **140**, 17612–17623.
- 54 B. Cui, S. Jia, E. Tokunaga and N. Shibata, *Nat. Commun.*, 2018, **9**, 4393.
- 55 Y. Shono, K. Ujihara, T. Iwasaki, M. Sugano, T. Mori, T. Matsunaga and N. Matsuo, *Pestic. Chem.*, 2007, 149–158, DOI: [10.1002/9783527611249.ch16](https://doi.org/10.1002/9783527611249.ch16).
- 56 X.-L. Su, L. Ye, J.-J. Chen, X.-D. Liu, S.-P. Jiang, F.-L. Wang, L. Liu, C.-J. Yang, X.-Y. Chang, Z.-L. Li, Q.-S. Gu and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2021, **60**, 380–384.
- 57 H. Hagiwara, K. Hamano, M. Nozawa, T. Hoshi, T. Suzuki and F. Kido, *J. Org. Chem.*, 2005, **70**, 2250–2255.
- 58 S. Sato, K. Sakata, Y. Hashimoto, H. Takikawa and K. Suzuki, *Angew. Chem., Int. Ed.*, 2017, **56**, 12608–12613.
- 59 S. M. Senaweera, A. Singh and J. D. Weaver, *J. Am. Chem. Soc.*, 2014, **136**, 3002–3005.
- 60 J. Luo and J. Zhang, *ACS Catal.*, 2016, **6**, 873–877.
- 61 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066–3072.
- 62 M. A. Cisnesia and T. P. Yoon, *Chem. Sci.*, 2015, **6**, 5426–5434.
- 63 W. Xu, H. Jiang, J. Leng, H.-W. Ong and J. Wu, *Angew. Chem., Int. Ed.*, 2020, **59**, 4009–4016.
- 64 T. Lu and F. Chen, *J. Comput. Chem.*, 2012, **33**, 580–592.
- 65 Y. Ma, J. Liang, D. Zhao, Y.-L. Chen, J. Shen and B. Xiong, *RSC Adv.*, 2014, **4**, 17262–17264.
- 66 J. Klein, P. Fleurat-Lessard and J. Pilmé, *J. Comput. Chem.*, 2021, **42**, 840–854.
- 67 H. Huang, L. Liu, J. Wang, Y. Zhou, H. Hu, X. Ye, G. Liu, Z. Xu, H. Xu, W. Yang, Y. Wang, Y. Peng, P. Yang, J. Sun, P. Yan, X. Cao and B. Z. Tang, *Chem. Sci.*, 2022, **13**, 3129–3139.
- 68 R. Pino-Rios, O. Yañez, D. Inostroza, L. Ruiz, C. Cardenas, P. Fuentealba and W. Tiznado, *J. Comput. Chem.*, 2017, **38**, 481–488.

