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Controlled chemoselective defluorination and non-defluorination for [5 + 1] aromatic annulation via Meisenheimer-type nitrogen anion and radical intermediates†

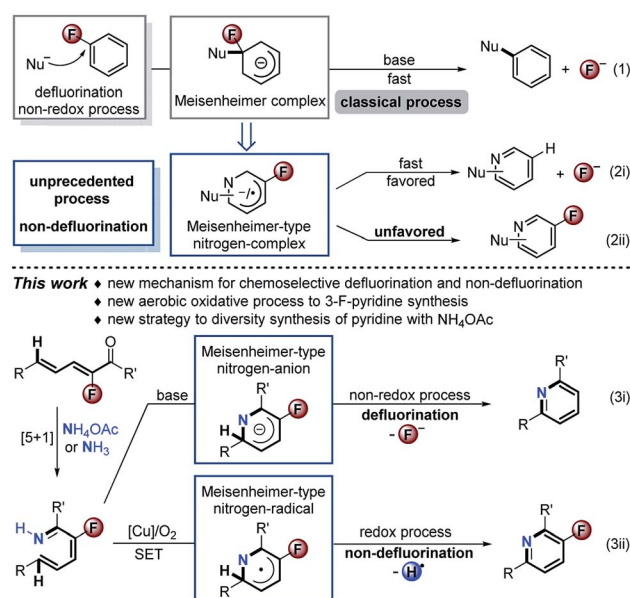
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Reported is a unique chemoselectivity approach to base-promoted defluorinative and Cu(I)-catalyzed aerobic oxidative non-defluorinative [5 + 1] condensation aromatizations of simple unsaturated ketones with ammonium salts via Meisenheimer-type nitrogen anion and radical intermediates. The CuBr/O₂ catalysis provides a straightforward approach to diverse 3-fluoropyridines in high yields. The synthetic utility of the strategy is highlighted by the concise synthesis of several F-modified bioactive compounds.

Organofluorine chemistry has played a privileged role in all aspects of pure and applied chemistry.¹ It is well known that introduction of a fluorine atom into a molecule could significantly modify its biological properties.² Exploitation of highly chemoselective synthetic strategies to obtain easily accessible organofluorine compounds of biological importance is an attractive method. Theoretically, effective control of intermediate conversion is one of the origins of chemoselective synthesis. Nucleophilic aromatic substitution (S_NAr) of fluorinated arenes is a versatile synthetic tactic. Nevertheless, the exhaustive defluorination is rather inevitable via Meisenheimer intermediates (Scheme 1, eqn (1)).³ 3-Fluoro-2H-pyridin-1-ide should be more reactive due to the electronegativity of the nitrogen atom and fluorine substitution. Such a Meisenheimer-type nitrogen complex might follow two reaction pathways: defluorination (Scheme 1, eqn (2i)) and non-defluorination (eqn (2ii)), the latter has not been realized so far. Herein, we report a unique chemoselectivity approach to base-promoted defluorinative and Cu-catalyzed aerobic oxidative non-defluorinative [5 + 1] condensation aromatizations of simple unsaturated ketones with ammonium salts (eqn (3)). The strategy features a formal C_{sp}²-H activation, good atom-/step-economy, and wide substrate scope, providing a new practical approach to diverse pyridines. The usefulness of this method is highlighted in the concise total synthesis of a blood lipid regulator, its fluorine-modified analogues and fluorine-modified AMPK receptor inhibitor. Preliminary mechanism investigation reveals that the

[Cu]/O₂ oxidative catalysis involves a single electron transfer (SET) process and unprecedentedly interrupts the traditional preponderant defluorination of Meisenheimer-type intermediates.

The pyridine skeleton is a fundamental moiety in bio-, chemical-, and pharmaceutical molecules.⁴ Among these, 3-fluoropyridine as a core fragment is widespread in the design of pharmaceuticals.⁵ Currently available methods toward 3-fluoropyridines involve the Balz–Schiemann reaction, electrophilic/nucleophilic fluorination, deoxofluorination, and Rh-catalyzed [4 + 2] cyclization, which always suffer from narrow scope,



Scheme 1 Traditional S_NAr defluorination and current chemoselective defluorination/non-defluorination via [5 + 1] aromatic annulation.

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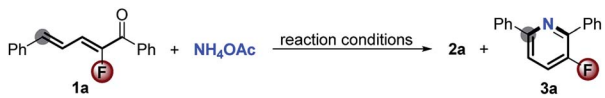


poor chemoselectivity, and requirement of expensive raw materials.⁵ In this regard, development of a new practical access is still in great demand. In principle, the straightforward [5 + 1] cyclization of 2-fluoro-2,4-dien-1-ones with simple ammonium salts or free ammonia represents the state-of-the-art tactic from the standpoint of atom and step economy,⁶ but still is undisclosed reasonably because of the overwhelmingly competitive defluorination. By an oxidative SET/radical strategy, we anticipate that efficiently non-defluorinative aromatization of the aforementioned Meisenheimer-type nitrogen intermediate could be a potential solution to the issue.

Initially, in order to verify the feasibility of the designed [5 + 1] aromatic annulation, we treated a wide range of 2-fluoro-2,4-dien-1-ones **1** with a simple ammonium salt, NH₄OAc (5.0 equiv.) under basic conditions (Cs₂CO₃) in DMSO at 120 °C for 12 h. As shown in Scheme 2, the reactions (Scheme 1, eqn (3i)) took place smoothly and gave a series of pyridines **2a–r** in excellent yields *via* complete defluorination regardless of the steric hindrance and electronic properties of substituents (for optimization of the reaction conditions, see the ESI†).

Encouraged by the above results and the recent surge of interest to develop copper-catalyzed aerobic oxidation reactions of amines,⁷ we anticipate that Cu/O₂-catalysis might have the potential to interdict fluoride displacement of Meisenheimer-type intermediates to realize the first access to 3-fluoropyridines through a straightforward [5 + 1] cyclization with simple ammonium salts and free ammonia as the sole nitrogen source. As shown in Table 1, the reaction of 2-fluoro-1,5-diphenylpenta-2,4-dien-1-one **1a** with NH₄OAc (5.0 equiv.) in the presence of CuBr (10 mol%) in a mixed solvent (DMSO/toluene, 5% v/v) at 140 °C in a sealed O₂ atmosphere for 12 h afforded **3a** in 17% yield. Surprisingly, as a sharp contrast to the defluorinative aromatic annulation (Scheme 2), only a trace of the

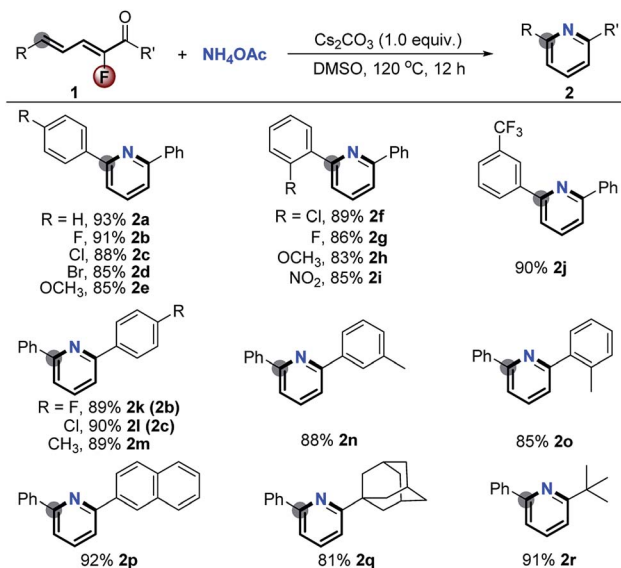
Table 1 Optimization of the reaction conditions^a

		
Entry	Reaction conditions (mol%)	Yield (%)
1	CuBr (10), O ₂	2a/3a , trace/17
2	CuBr (10), TFA (10), O ₂	2a/3a , 2/89 (80) ^b
3	CuBr (5.0), TFA (10), O ₂	3a , 59
4	CuCl (10), TFA (10), O ₂	2a/3a , 17/61
5	CuI (10), TFA (10), O ₂	2a/3a , 15/52
6	Cu(MeCN) ₄ PF ₆ (10), TFA (10), O ₂	2a/3a , 21/30
7	CuBr ₂ (10), TFA (10), O ₂	2a/3a , 30/10
8	FeBr ₂ (10), TFA (10), O ₂	2a/3a , 28/60
9	MnBr ₂ (10), TFA (10), O ₂	2a/3a , 10/80
10	CuBr (10), HOTf (10), O ₂	3a , 6
11	CuBr (10), HOAc (10), O ₂	3a , 18
12 ^c	CuBr (10), TFA (10), O ₂	2a/3a , 3/61
13 ^d	CuBr (10), TFA (10), O ₂	2a/3a , 5/80
14	CuBr (10), TFA (10), air	2a/3a , 68/20
15	CuBr (10), TFA (10), Ar	2a , 85
16	TFA (10), O ₂	2a , 10

^a **1a** (0.1 mmol), NH₄OAc (5.0 equiv.), O₂ (1 atm, closed), 12 h, at 140 °C, 5% (v/v) DMSO/toluene (1.0 mL), yields given by GC-MS using *n*-dodecane as an internal standard. ^b Yield of isolated **3a** was given in the parentheses. ^c Using NH₄Cl instead of NH₄OAc. ^d Using NH₃ (in MeOH) instead of NH₄OAc.

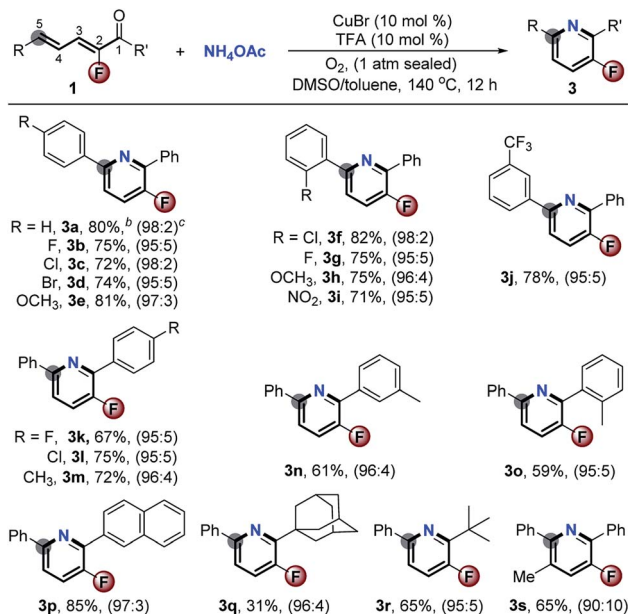
defluorinated product **2a** was detected in the Cu-catalyzed aerobic oxidation process (entry 1). Stimulated by the excellent ratio of the non-defluorinative and defluorinative product (chemoselectivity) and promising yield, further optimization of the reaction conditions was carried out to improve the yield. To our delight, just addition of 10 mol% trifluoroacetic acid (TFA) dramatically increased the yield from 17% up to 89% with only 2% loss of fluorine in the product (entry 2), reasonably due to the facilitative formation of imine which is the real intermediate in this Cu-catalyzed aerobic oxidation reaction. Lowering the loading of CuBr to 5.0 mol% decreased the yield to 59% (entry 3). Other catalysts including CuCl, CuI, Cu(MeCN)₄PF₆, CuBr₂, FeBr₂ and MnBr₂ had adverse effects on the reaction (entries 4–9). Other acids such as HOTf and HOAc had a detrimental effect on the yield but still without release of fluorine (entries 10 and 11). NH₄Cl and free NH₃ (in MeOH) as nitrogen donors also showed acceptable performance (entries 12 and 13). The competitive dehalogenative aromatization was dominant if the reaction took place in air (entry 14). As expected, only dehalogenative aromatization occurred in the absence of O₂ or CuBr catalyst (entries 15 and 16).

As illustrated in Scheme 3, the CuBr/TFA oxidative catalysis effectively converted a series of 2-fluoro-2,4-dien-1-ones with NH₄OAc into diverse polysubstituted 3-fluoropyridine derivatives in good yields with excellent chemoselectivity. Different groups including halide, methoxyl and nitro in the 5-aromatic ring were well tolerated, giving the corresponding products **3a–j** in good yields (71–82%) and excellent chemoselectivity of more



Scheme 2 Results to verify the feasibility of [5 + 1] aromatic annulation under basic conditions *via* defluorination.^a **1** (0.1 mmol), NH₄OAc (5.0 equiv.), Cs₂CO₃ (1.0 equiv.), 12 h, at 120 °C, DMSO (1.0 mL). Yields of isolated products are given.

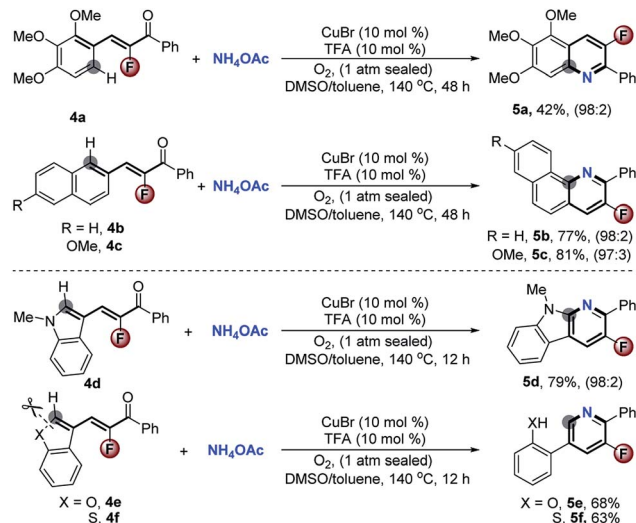




Scheme 3 Scope of 2-fluoro-2,4-dien-1-ones for CuBr-catalyzed aerobic oxidative non-dehydrofluorinative [5 + 1] condensation aromatizations. ^a1a–s (0.1 mmol), NH₄OAc (5.0 equiv.), O₂ (1 atm, closed), 12 h, at 140 °C, 5% (v/v) DMSO/toluene (1.0 mL). ^bYield of isolated products are given. ^cThe ratio of non-defluorinative and defluorinative products in the parentheses was determined by GC–MS using *n*-dodecane as an internal standard.

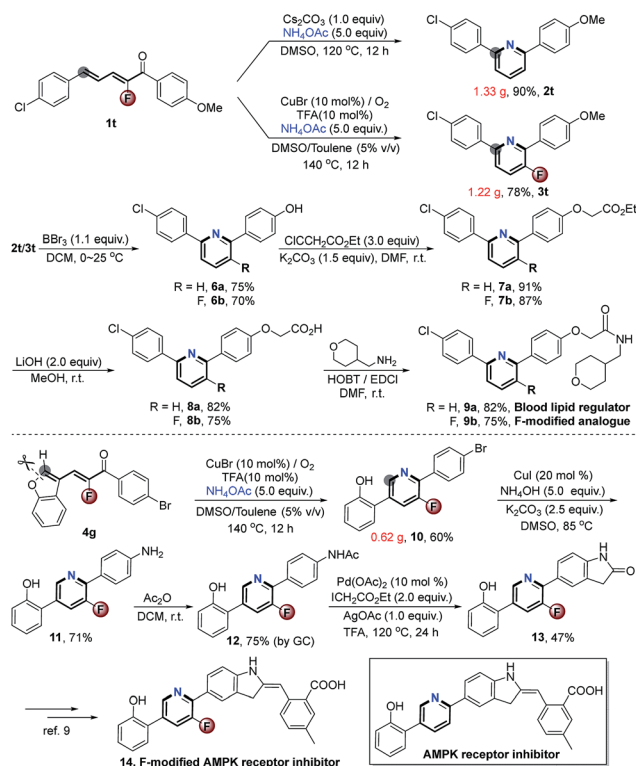
than 95 : 5. Substrates with F, Cl and methyl at the carbonyl aromatic ring were also applicable, delivering the products **3k–o** in 59–75% yields without negative effects on fluorine retention. Reasonably, steric hindrance had a strong effect on the reactivity. Surprisingly, the more bulky substrate **1p**, especially adamantyl (**1q**) and *tert*-butyl 2-fluoro-2,4-dien-1-one (**1r**) were also compatible with the direct [5 + 1] aromatic annulation without any defluorination although the yields of the desired adducts **3p–r** were decreased from 85% to 31% on account of the increase of steric hindrance. The 4-methyl substituted starting material **1s** was readily converted into the multifunctional 3-fluoropyridine **3s** with moderate result.

Stimulated by the satisfactory performance and to further evaluate the generality of the valuable approach, we next extended the scope of substrates to diverse types of α -fluoro- α,β -unsaturated inert aromatic ketones. As demonstrated in Scheme 4, several hetero-polycyclic fused 3-fluoropyridines **5a–d** were easily obtained in good yields with >97 : 3 chemoselectivity *via* a formal C_{sp}²–H activation. This reaction provides a practical access to such useful kinds of compounds which are generally difficult to synthesize by traditional methods.⁵ Significantly, with (*Z*)-3-(benzofuran-3-yl)-2-fluoro-1-phenylprop-2-en-1-one **4e** and (*Z*)-3-(benzo[*b*]thiophen-3-yl)-2-fluoro-1-phenylprop-2-en-1-one **4f** as the reactants, the concomitant cleavage of C–O and C–S bonds happened during the aromatic cyclization to exclusively furnish the corresponding 2-(5-fluoro-6-phenylpyridin-3-yl)phenol **5e** and 2-(5-fluoro-6-phenylpyridin-3-yl)benzenethiol **5f** in 68% and 63% yields, respectively.



Scheme 4 Scope of typical α -fluoro- α,β -unsaturated ketones for the CuBr-catalyzed aerobic oxidative reaction.

Finally, the synthetic utility of this [5 + 1] aromatic annulation was highlighted by the concise synthesis of several bioactive compounds (Scheme 5). Accordingly, treatment of **1t** under basic (Scheme 2) and Cu-catalyzed aerobic oxidation conditions (Scheme 3) could exclusively afford **2t** and its F-substituted derivative **3t** in 90% and 78% yields, respectively. Demethylation of **2t/3t** by BBr₃ gave **6a/b** in good yields. After etherification with ClCCH₂CO₂Et and hydrolysis, acids **8a/b** could be isolated in good yields. Blood lipid regulator **9a**⁸ and its F-modified



Scheme 5 Concise synthesis of F-modified bioactive compounds.



analogue **9b** were easily obtained *via* direct amidation with (tetrahydro-2H-pyran-4-yl)methanamine. Valuably, this method avoided the use of noble transition-metal catalysts which are indispensable in conventional approaches. Another interesting utilization is to prepare the key intermediate **13** of the F-modified AMPK receptor inhibitor **14**.⁹ *Via* [5 + 1] aromatic cyclization and concomitant ring-opening of furan, the Cu-catalyzed aerobic oxidation could facilitate the synthesis of 2-(6-(4-bromophenyl)-5-fluoropyridin-3-yl)phenol **10** with high step-economy by employing **4g** as the starting substrate. Upon CuI-catalyzed amination with NH₄OH followed by acetylation, **10** was smoothly converted into **12** in acceptable GC-yield. Compound **13** was formed in 47% yield by reacting **12** with ICH₂CO₂Et in the presence of a Pd catalyst. The 4-step reaction provided **13** in total 15% yield. Otherwise, the traditional process for the preparation of its defluorinated complex requires 8 steps in about 10% yield. Obviously, the current approach offers great advantages in terms of efficiency and low cost.

To gain insight into the mechanism, a series of deuterium labeled control reactions were executed (Scheme 6). Under the basic reaction conditions (Scheme 2), the treatment of NH₄OAc-D₇ instead of NH₄OAc with **1a** gave **2a** and **2a-D** in 91% yield with a ratio of 4 : 1 (eqn (1)). No deuterium labeled product was detected when **1a-D** reacted with NH₄OAc under the same reaction conditions (eqn (2)). Using D₂O/DMSO (5%, v/v) as the solvent, the yield of **2a** and **2a-D** was 87% with a ratio of 7 : 3 (eqn (3)), which reveals the hydrogen exchange between the substrates and H₂O during the reaction process. In dramatic contrast, the CuBr/O₂ catalytic system provided **3a** in about 80% yield exclusively for both the above deuterium labeled reactions (eqn (4) and (5)). The addition of butylated hydroxytoluene (BHT) in the CuBr-catalyzed aerobic reaction strictly exacerbated the defluorination process (eqn (6)), which suggests that this reaction might involve radical intermediates. In order to

verify the radical-mediated pathway, we next detected the presence of radicals by means of electron paramagnetic resonance (EPR) with the addition of 5,5-dimethyl-1-pyrroline N-oxide (DMPO) for the reaction **2a** and NH₄OAc under CuBr-catalyzed aerobic conditions. Fortunately, the sextet signal for [•]O₂– was captured, while no signal was observed during the Cs₂CO₃-promoted reaction (see the ESI†). All of the results reasonably confirmed our initial hypothesis (Scheme 1, eqn (3)). The 3-fluoro-2H-pyridin-1-ide Meisenheimer-type anion intermediate underwent a non-redox defluorination process under basic conditions, and the CuBr catalytic aerobic conditions promoted it to an unfavored non-defluorination *via* a SET/radical pathway.⁷

Conclusions

In summary, we developed a versatile strategy towards chemo-selective synthesis of diverse pyridines *via* the straightforward [5 + 1] aromatic cyclization of 2-fluoro-2,4-dien-1-ones with ammonium salts. By controlling the oriented conversion of Meisenheimer-type nitrogen anion and radical intermediates under basic and CuBr-catalyzed aerobic reaction conditions, unique chemoselectivity in defluorination and non-defluorination was realized. The synthetic utility of this strategy was highlighted by the concise synthesis of several F-modified bioactive compounds.

Conflicts of interest

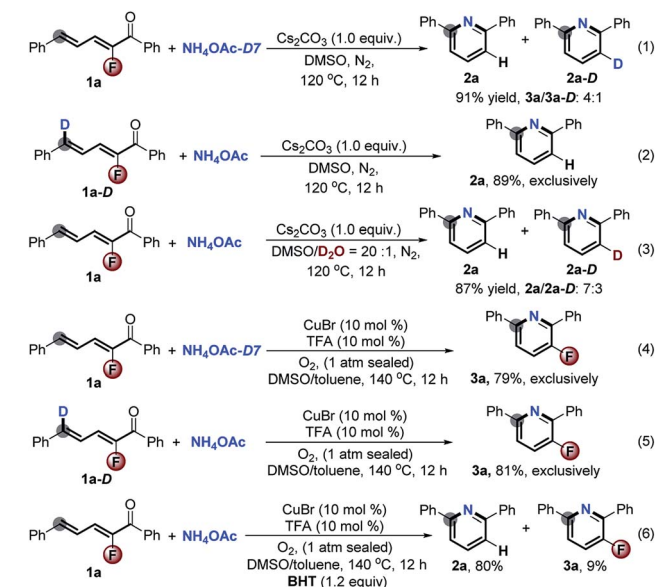
There are no conflicts to declare.

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Scheme 6 Controlled reactions for mechanism investigation.



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