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Convenient and efficient access to tri- and tetra-substituted 4-fluoropyridines *via* a [3 + 2]/[2 + 1] cyclization reaction

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ABSTRACT

A [3 + 2]/[2 + 1] cycloaddition reaction of *gem*–difluorocyclopropenes is presented, offering a mild and efficient approach to accessing tri- and tetra-substituted 4-fluoropyridines in moderate to good yields with excellent regioselectivity. Multiple synthetic applications, including process-scale reactions, modification of bioactive molecules, derivatization reactions and synthesis of the analogue of the PKM2 modulator, are subsequently described.

Pyridine is one of the most prevalent heterocyclic skeletons in bioactive molecules. The fluorine atom embodies high electronegativity and a small atomic radius [1,2], and its incorporation into pyridine drastically improves the lipophilicity, bioavailability, metabolic stability and, in some cases, the potency of known biologically active molecules (Fig. 1). Despite their increasing importance in pharmaceuticals and agrochemicals [3–8], developing a simple and practical method to prepare fluoropyridines, especially 4-fluoropyridines, still encounters great challenges.

The classical approach for the formation of 4-fluoropyridines is the Balz-Schiemann reaction (Scheme 1a) [9]. Acidic conditions, toxicity of the reagents, and potential for explosions impede their synthetic applications. Nucleophilic substitution [10–20] of 4-halo or nitropyridines by inorganic or organic fluoride salts [21–31] offers an alternative route for accessing 4-fluoropyridines (Scheme 1b). However, the poor solubility of inorganic fluoride salts, stoichiometric usage of cost and toxic organic fluoride salts, make the reaction proceed under harsh conditions, leading to inferior conversion and functional group tolerance.

gem–Difluorocyclopropene is an intriguing framework, as it contains three important structural motifs: electrophilic difluoromethylene, alkene and the smallest carbocycle, thus possessing unusual electric and steric properties. Taking advantage of the *gem*–difluorocyclopropene as a valuable two-carbon donor, Waser and coworkers reported a [3 + 2] annulation of cyclopropenes with cyclopropylanilines to access to 6,6-difluorobicycle[3.1.0]hexanes [32]. Furthermore, Cossy realized a concise, and efficient synthesis of 5-fluoropyridazines by a [3 + 3] cycloaddition reaction [33] using the *gem*–difluorocyclopropene as a three-carbon donor [34,35]. Considering the importance of 4-fluoropyridines in pharmaceuticals and agrochemicals, we herein report that a convenient and effective [3 + 2]/[2 + 1] annulation reaction between *gem*–difluorocyclopropenes [36–49] and isocyanides **2** [50–55] or aldimine esters **3** [56–59] to produce highly functionalized 4-fluoropyridines in moderate to good yields (Scheme 1c). Specifically, the whole transformation is characterized by the following points: i) Unlike the direct fluorination reactions of pyridines, this novel cycloaddition reaction originates from readily available substrates, and the construction of the pyridine ring and the introduction of a fluorine atom at specific position are completed simultaneously, thus providing a new pathway for the synthesis of 4-fluoropyridines; ii) In the cyclization reactions, the carbon-carbon π bond of *gem*–difluorocyclopropene is broken, while two carbon-carbon single bonds are formed; iii) The reactions are conducted under mild and air conditions, by which both tri- and tetra-substituted 4-fluoropyridines are obtained in moderate to good

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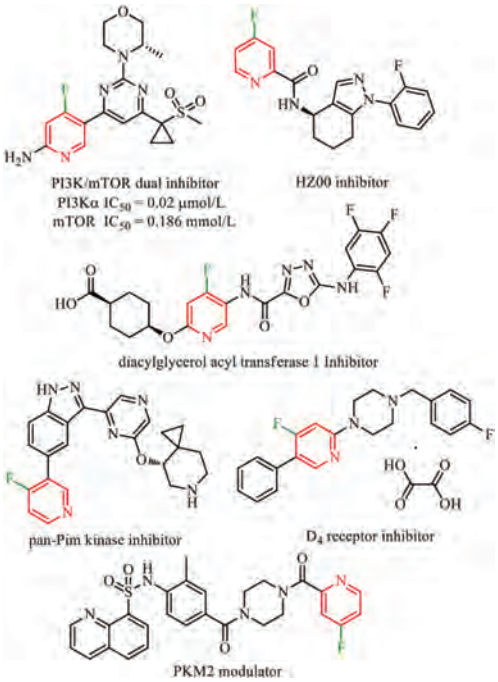
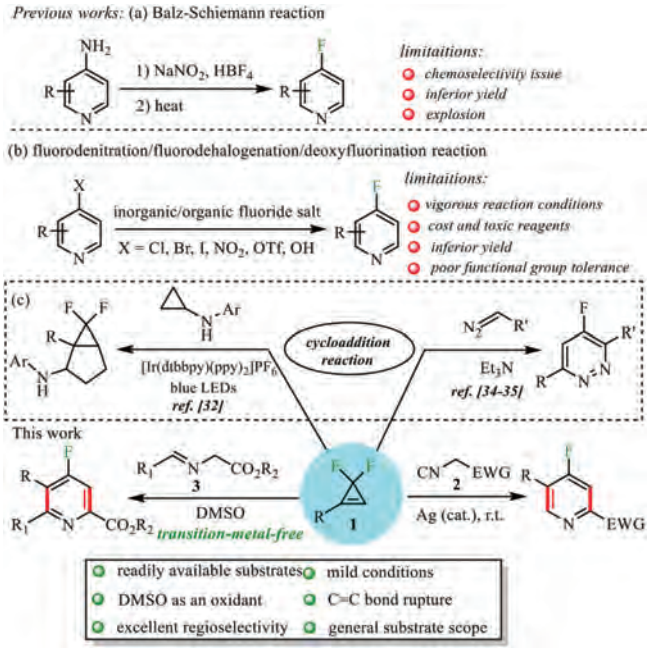


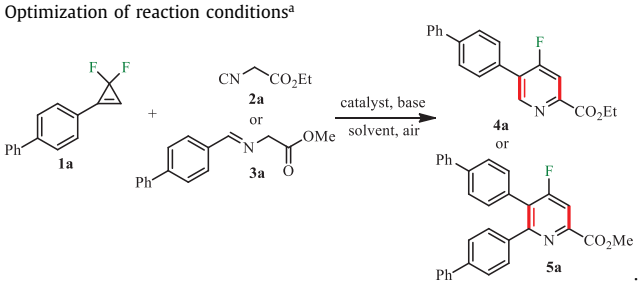
Fig. 1. Selected biologically active 4-fluoropyridines.



Scheme 1. Tactics for the construction of 4-fluoropyridines.

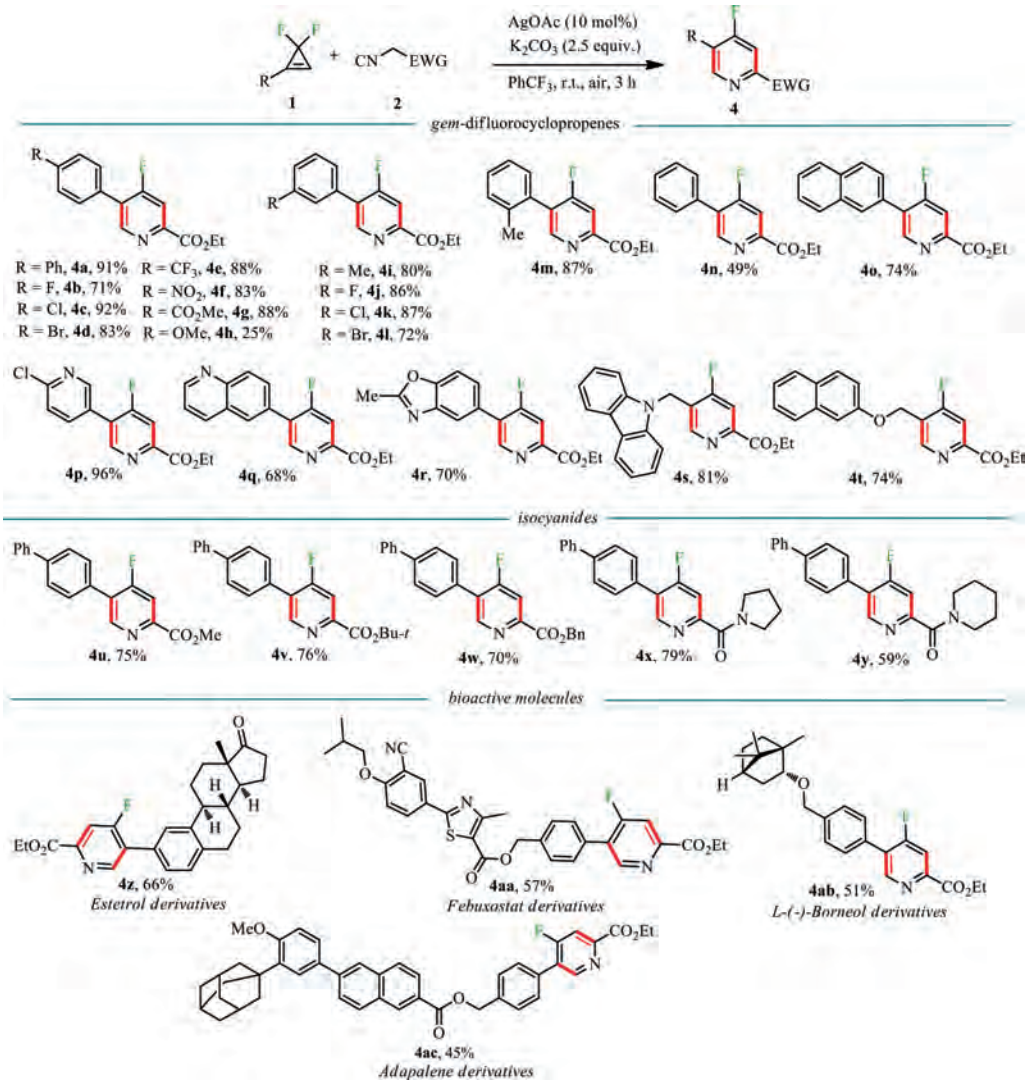
yields with wide substrate applicability and pure regioselectivity; iv) In the synthesis of tetra-substituted 4-fluoropyridines, the reac-

Table 1
Optimization of reaction conditions[a]



Entry	Catalyst	Base	Solvent	Yield (%)[b]	
				4a	**5a**
1	AgOAc	K_2CO_3	$PhCF_3$	91	n.d.
2	Ag_2CO_3	K_2CO_3	$PhCF_3$	81	n.d.
3	Ag_2O	K_2CO_3	$PhCF_3$	75	n.d.
4	$AgBF_4$	K_2CO_3	$PhCF_3$	36	n.d.
5	$Cu(OAc)_2$	K_2CO_3	$PhCF_3$	74	n.d.
6[c]	–	K_2CO_3	$PhCF_3$	trace	n.d.
7	AgOAc	Na_2CO_3	$PhCF_3$	77	n.d.
8	AgOAc	Li_2CO_3	$PhCF_3$	66	n.d.
9	AgOAc	K_3PO_4	$PhCF_3$	76	n.d.
10	AgOAc	K_2CO_3	DCE	45	n.d.
11	AgOAc	K_2CO_3	THF	54	n.d.
12	AgOAc	K_2CO_3	DMF	34	n.d.
13[d]	AgOAc	K_2CO_3	$PhCF_3$	n.d.	22
14[d]	AgOAc	K_3PO_4	$PhCF_3$	n.d.	41
15[c]	–	K_3PO_4	$PhCF_3$	n.d.	54
16[e]	–	K_3PO_4	DMSO	n.d.	65
17[f]	–	K_3PO_4	DMSO	n.d.	68
18[g]	–	K_3PO_4	DMSO	n.d.	64

n.d. = not detected.
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2 equiv.), catalyst (10 mol%), base (2.5 equiv.), solvent (1 mL), r.t., in air, 3 h.
[b] Isolated yields.
[c] Without the catalyst.
[d] **1a** (0.2 mmol), **3a** (1.5 equiv.), catalyst (10 mol%), base (1.5 equiv.), DDQ (2 equiv.), solvent (1 mL), 70 °C, in air, 4 h.
[e] DMSO as the solvent.
[f] Without DDQ.
[g] In argon atmosphere.

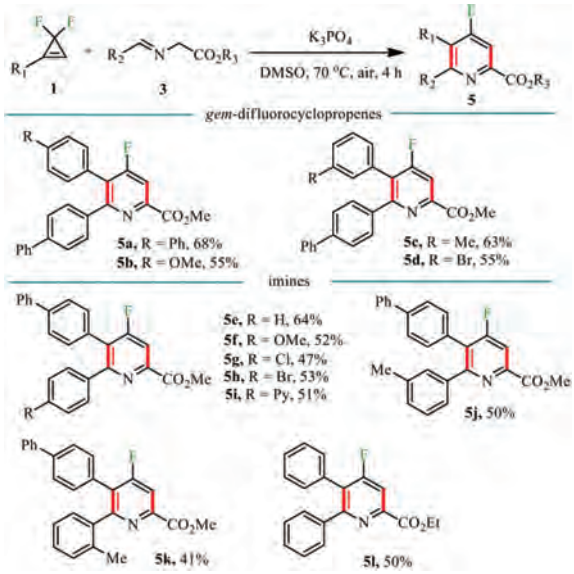


Scheme 2. Substrate scope for trisubstituted 4-fluoropyridines. Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv.), AgOAc (10 mol%), K_2CO_3 (2.5 equiv.), $PhCF_3$ (1 mL) at room temperature for 3 h in air, isolated yield.

tion proceeds without transition metals, and DMSO is utilized as both a solvent and an oxidant.

The reaction was initially investigated using *gem*–difluorocyclopropene **1a** and ethyl isocyanoacetate **2a** as model substrates, AgOAc as the catalyst and K_2CO_3 as the base in $PhCF_3$ at room temperature; to our delight, the desired product **4a** was obtained in 91% yield (Table 1, entry 1). Other catalysts such as Ag_2CO_3, Ag_2O, $AgBF_4$ and $Cu(OAc)_2$ prevented the substrate **1a** from being completely converted, and the reaction did not proceed without the catalyst (Table 1, entries 2–6). Replacing K_2CO_3 with other bases made the reaction worse (Table 1, entries 7–9). Subsequent solvent screening revealed that $PhCF_3$ made better conversion (Table 1, entries 10–12). Then the reaction between *gem*–difluorocyclopropene **1a** and aldimine ester **3a** in the conditions of AgOAc as the catalyst, K_2CO_3 as the base, DDQ as an oxidant, and $PhCF_3$ as the solvent was detected. When the temperature was elevated to 70 °C, tetra-substituted 4-fluoropyridine **5a** was produced in 22% yield (Table 1, entry 13). Substituting K_2CO_3 with K_3PO_4 increased the yield to 41% (Table 1, entry 14). The reaction still conducted smoothly without the catalyst and gave the product **5a** in 54% yield (Table 1, entry 15). When the solvent was changed to DMSO, the yield of **5a** was further promoted to 65% (Table 1, entry 16). Interestingly, the reaction was almost impervious even if no DDQ was added (Table 1, entries 17 and 18). Consequently, the optimal reaction conditions for the preparation of **4a** were determined to be **1a** (0.2 mmol) in the presence of **2a** (2.0 equiv.), AgOAc (10 mol%), K_2CO_3 (2.5 equiv.) and, $PhCF_3$ (1 mL) at room temperature for 3 h, while **5a** was obtained in the presence of **1a** (0.2 mmol), **3a** (1.5 equiv.), K_3PO_4 (1.5 equiv.) and DMSO (1 mL) at 70 °C for 4 h.

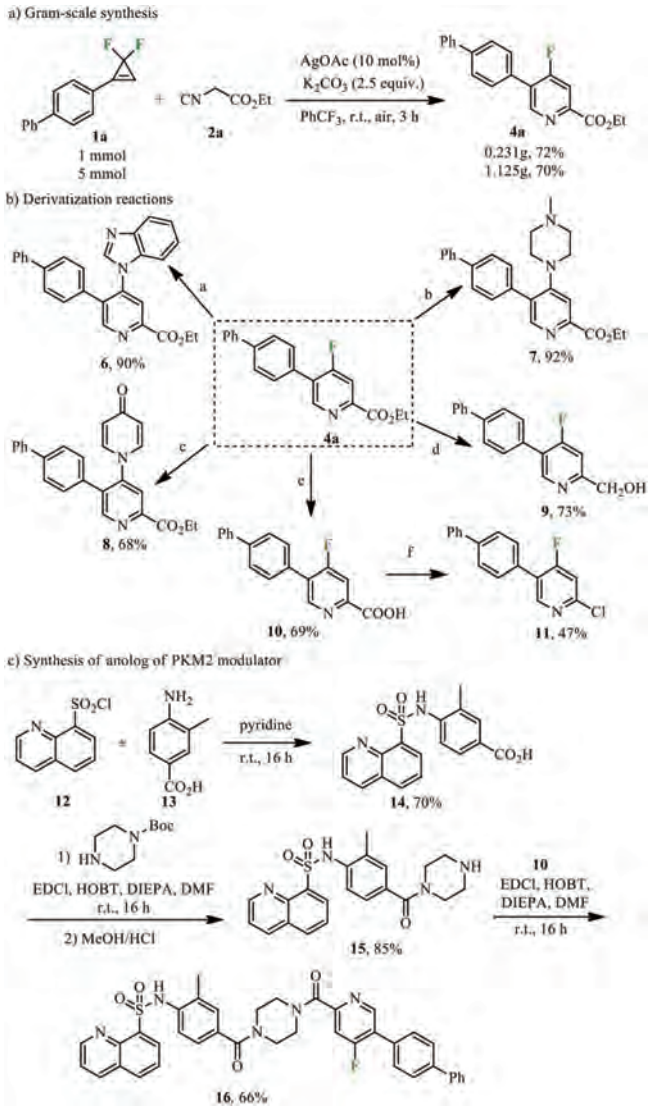
With optimized conditions in hand, the reactions between *gem*–difluorocyclopropenes **1** and isocyanides **2** were tested first. As shown in Scheme 2, the *gem*–difluorocyclopropene substrates bearing electron-donating substituents such as Me, Ph and electron-withdrawing substituents such as F, Cl, Br, CF_3, NO_2, CO_2Me in the *para*- or *meta*-positions of the phenyl moiety worked smoothly under standard conditions, and gave the products **4a**-**4k** in good yields. However, when the *para* position of the phenyl moiety in the *gem*–difluorocyclopropene substrate embedded strong electron-donating methoxy group, the yield of the product **4h** was significantly reduced. Specifically, a 2-methyl-substituted substrate did not retard the process and gave product **4m** in 87% yield. The substrates with aromatic heterocycles, for example, pyridine, quinolone and benzoxazole were also tolerant, producing the products **4p**-**4r** in 68%–96% yields. Alkyl-substituted difluorocyclopropenes were also compatible with the reaction system. Methy-



Scheme 3. Substrate scope for tetra-substituted 4-fluoropyridines. Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv.), K_3PO_4 (1.5 equiv.), DMSO (1 mL) at 70 °C for 4 h in air. Isolated yields.

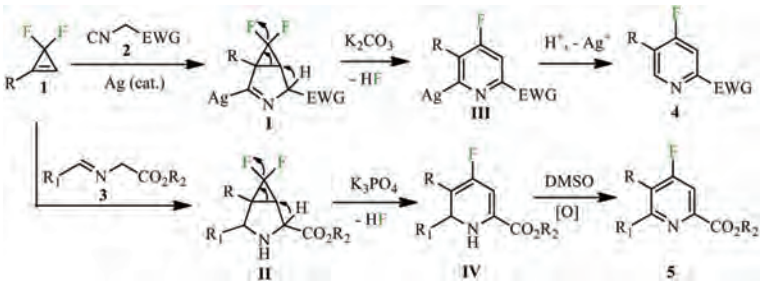
lene groups with nitrogen-centred linkages such as carbazole gave the product **4s** in 81% yield, while oxygen-centred linkages such as naphthol afforded product **4t** in 74% yield. The reaction still proceeded effectively with other esters such as methyl ester, *tert*–butyl ester, and benzyl ester, even amides in isonitriles (**4u**-**4y**), although the yields were slightly reduced. To further highlight the synthetic versatility of our method, several complex natural products and drugs, were subjected to the reaction conditions. Estetrol (**1z**) and L-(-)-borneol (**1ab**) derivatives gave the corresponding 4-fluoropyridines **4z** and **4ab** in 66% and 51% yield, respectively. Febuxostat **1aa** and Adapalene **1ac** also were converted to 4-fluoropyridine derivatives (**4aa**, 57% and **4ac**, 45%).

The substrate scope for tetra-substituted 4-fluoropyridines was then screened (Scheme 3). The *gem*–difluorocyclopropene substrates with both electron-donating substituents such as Me, Ph, OMe and electron-withdrawing substituents such as Br in the *para*- or *meta*-positions of the phenyl moiety were utilized under standard conditions, and generated the products **5a**-**5d** in moderate to good yields. Subsequent screening of the aldimine esters [60] revealed that electrical properties of the substituted groups in the *para*- or *meta*-positions of the benzene ring had little effect on the reaction (**5f**-**5j**). Other esters such as ethyl ester were also compatible with the reaction, producing the product **5l** in 50% yield. Out of our expectation, aldimine esters with alkyl groups such as benzyl, *n*-pentyl, *n*–butyl, *n*-propyl, and even alkenyl and ester groups showed no reactivity in the protocol.



Scheme 4. Synthetic applications. Reaction conditions: (a) **4a** (0.2 mmol), benzimidazole (0.4 mmol), MeCN (1 mL), 80 °C, 4 h, Ar; (b) **4a** (0.2 mmol), 1-methylpiperazine (0.4 mmol), MeCN (1 mL), r.t., 4 h, Ar; (c) **4a** (0.2 mmol), 4-hydroxypyridine (0.4 mmol), K_2CO_3 (0.4 mmol), NMP (1 mL), at 140 °C for 3 h; (d) **4a** (0.2 mmol), $NaBH_4$ (0.6 mmol), ethanol (1 mL), 0–25 °C, 2 h; (e) **4a** (0.2 mmol), KOH (0.4 mmol), methanol (1 mL), 35 °C, 2 h; (f) **4a** (0.2 mmol), $NaHCO_3$ (0.2 mmol), *t*-BuCl (0.3 mmol), CH_2Cl_2 (1 mL), 60 °C. Isolated yield.

To demonstrate the scalability of this methodology, the reaction of **1a** with **2a** was performed on 1.0 mmol and 5.0 mmol scales, affording 72% and 70% yields of the product **4a**, respectively (Scheme 4a). The nucleophilic substitutions of 4-fluoropyridine **4a** with benzimidazole, 1-methylpiperazine and 4-hydroxypyridine re-



Scheme 5. Possible catalytic cycle.

leased the corresponding products **6**, **7** and **8** in 90%, 92% and 68% yield, respectively (Scheme 4b, paths a-c). $NaBH_4$ reduction of the carbonyl group in **4a** afforded alcohol **9** in 73% yield (path d). Hydrolysis of the ester groups in **4a** produced **10** in 69% yield (path e), which further conducted a chlorinated decarboxylation reaction to obtain the product **11** in 47% yield (path f). Next, total syntheses of the anolog of PKM2 modulator was investigated (Scheme 4c). The product **15** was formed after a two-step reaction sequence of the sulfamidation and condensation, which further condensed with **10** to finally obtain the anolog of PKM2 modulator **16**.

On the basis of related literature reports [61,62] and our preliminary studies, a plausible mechanism is proposed in Scheme 5. A [3 + 2] cycloaddition reaction of *gem*–difluorocyclopropenes **1** with isocyanides **2** or imines **3** to produce intermediates **I** and **II**. The synergy of the electron-pushing effect of α-carbon of the ester group and the electron-pulling effect of *gem*–difluoride stimulates the ring-opening defluorination reaction of intermediates **I** and **II**, releasing intermediates **III** and **IV**. Finally, the intermediate **IV** was oxidized by DMSO to generate tetrasubstituted-4-fluoropyridines **5**.

In summary, we report a novel [3 + 2]/[2 + 1] cycloaddition reaction of *gem*–difluorocyclopropenes with isocyanides or imines, providing a modular, concise and efficient approach for accessing tri- and tetra-substituted 4-fluoropyridines in moderate to good yields with high regioselectivity. This reaction starts from simple and readily available substrates, proceeding under mild and air conditions, and its substrate scope is general. In the synthesis of tetra-substituted 4-fluoropyridines, the reaction proceeds without transition metals, and DMSO is utilized as both a solvent and an oxidant.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.02.031.

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