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Selective *meta*-C-H trifluoromethylation of pyridines *via* 1,4-dihydropyridinephosphonate

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ABSTRACT

The *meta*-selective trifluoromethylation of pyridines has remained a significant challenge due to the inherent electronic constraints of the aromatic system. This study developed a novel dearomatization-rearomatization strategy based on 1,4-dihydropyridinephosphonate intermediates, which underwent copper-catalyzed regioselective C–CF_3 bond formation with Togni II reagent followed by DABCO-promoted rearomatization, achieving highly regioselective *meta*-C-H trifluoromethylation of pyridine derivatives. This approach accommodated mostly *meta*-substituted pyridine substrates and enabled late-stage *meta*-C-H trifluoromethylation of pharmaceutical molecules containing pyridine motifs.

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Over the past decade, the strategic development of introducing fluorine-containing groups into organic molecules has emerged as a prominent field of research [1–9]. Trifluoromethyl (CF_3), for instance, exhibits a strong electron-withdrawing effect and can significantly enhance key molecular properties, including lipophilicity, metabolic stability, and bioavailability [10–12]. Pyridines and their derivatives are prevalent nitrogen-containing heterocycles in pharmaceuticals, materials, and agrochemicals [13–18], and also serve as prominent ligands [19]. Due to the beneficial effects conferred by CF_3 group introduction, CF_3-containing pyridine cores feature in numerous drugs and agrochemicals (Fig. 1A) [20–24]. A prominent example is Tipranavir, a non-peptidic *anti*-HIV drug featuring a trifluoromethylated pyridine scaffold, which exhibits approximately 10–fold higher antiviral activity than its phenyl-based counterpart [25]. Traditional methods for pyridine functionalization rely on prefunctionalized substrates [26–35]. However, the step economy and ready availability of C–H bonds as substrates make direct trifluoromethylation of pyridine C–H bonds a highly attractive strategy [36–38]. This approach is particularly valuable for the late-stage functionalization of existing bioactive molecules, a capability crucial for accelerating drug candidate screening.

The nitrogen atom in pyridine possesses a lone pair of electrons, enabling protonation or coordination with Lewis acids, which significantly reduces the electron density of the heteroaromatic ring, particularly at the *ortho*- and *para*-positions [39]. Consequently, current C-H functionalization of pyridines, including C-H trifluoromethylation, predominantly targets at the *ortho*- and *para*-positions [40–49]. However, the direct *meta*-C-H functionalization of pyridines remains highly challenging. In recent years, a number of ingenious strategies have been developed for the *meta*-C-H functionalization of pyridines, including the use of directing groups [50–52], non-directed metalation [53–57], temporary dearomatization strategies [38,58–77] and ring-opening, functionalization, then ring-closing strategies [78–82]. Nevertheless, to the best of our knowledge, most of the direct C-H-trifluoromethylation methods have substrate dependence as well as low yields and poor selectivity, Studer and his co-workers conducted a dedicated study on *meta*-C-H trifluoromethylation of pyridines [37]. In 2022, Studer group employed a dearomatized oxazino-pyridine intermediate, which was produced by 1,4-Huisgen cycloaddition with pyridines [70], for regioselective trifluoromethylation under light conditions, followed by acid-promoted rearomatization to obtain *meta*-trifluoromethylated pyridines with high selectivity (Fig. 1B).

Herein, based on temporary dearomatization strategy, we disclose a method to create a 1,4-dihydropyridinephosphonate that undergoes regioselective trifluoromethylation, followed by base-promoted rearomatization to afford *meta*-trifluoromethylated pyridines in one-pot process (Fig. 1C). This method tolerates a variety of functional groups and is applicable for late-stage *meta*-C-H trifluoromethylation of pharmaceutical molecules containing pyridine motifs, while at the same time, it offers a complementary scope to the Studer approach.

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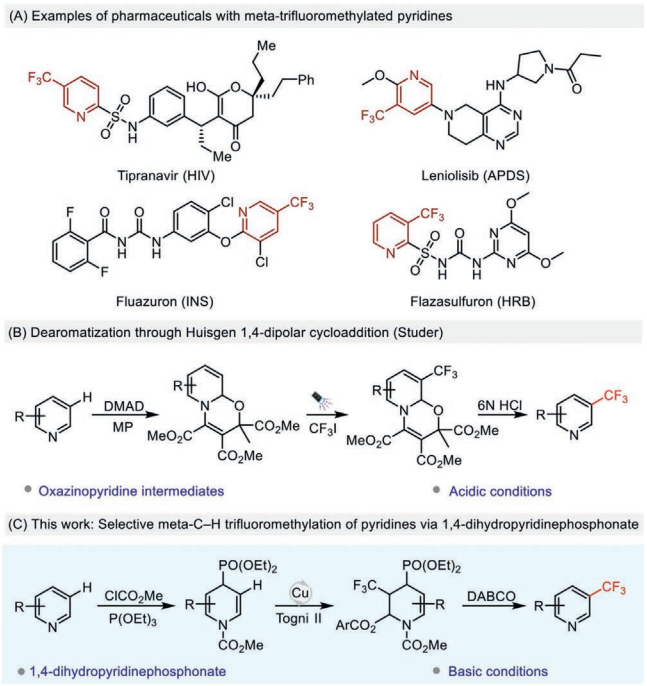
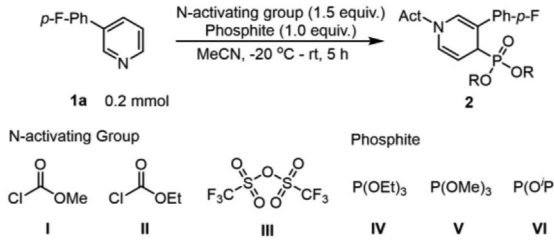


Fig. 1. *meta*-C-H trifluoromethylation of pyridines. (A) Examples of pharmaceuticals with *meta*-trifluoromethylated pyridines. (B) Dearomatization through Huisgen 1,4-dipolar cycloaddition for *meta*-trifluoromethylation of pyridines. (C) This work: Selective *meta*-C-H trifluoromethylation of pyridines *via* 1,4-dihydropyridinephosphonate.

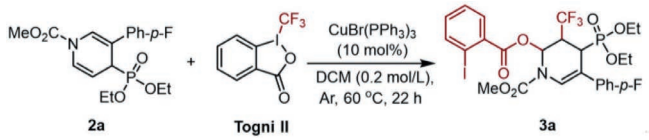
Table 1
Optimization for pyridine dearomatization.



Entry	*N*-Activating reagents	Phosphites	Yield (%)[a]
1	**I**	**IV**	96
2	**I**	**V**	70
3	**I**	**VI**	93
4	**II**	**IV**	91
5	**II**	**V**	63
6	**II**	**VI**	91
7	**III**	**IV**	N.D.
8	**III**	**V**	N.D.
9	**III**	**VI**	N.D.
10[b]	**I**	**IV**	83
11[c]	**I**	**IV**	23
12[d]	**I**	**IV**	N.D.

[a] Yields were determined by crude ^{1}H NMR spectra using 1,3,5-trimethylbenzene as internal standard.
[b] Using DCM as solvent.
[c] Activation at 0 °C.
[d] Activation at room temperature.

Table 2
Optimization for trifluoromethylation of pyridine dearomatization intermediates.[a]



Entry	Deviation from standard conditions	**3a** Yield (%)[b]
1	None	71
2	CuI instead of $CuBr(PPh_3)_3$	46
3	$Cu(MeCN)_4PF_6$ instead of $CuBr(PPh_3)_3$	55
4	w/o Cu catalyst	N.D.
5	DCE instead of DCM	69
6	ACN instead of DCM	60
7	DMSO instead of DCM	23

[a] Reaction conditions: **2a** (0.1 mmol, 1.0 equiv.), Togni II (1.2 equiv.), $CuBr(PPh_3)_3$ (10 mol%), DCM (0.2 mol/L), 60 °C, 22 h, Ar.
[b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard.

The choice of pyridine *N*-activating groups and nucleophiles is crucial for the process and directly impacts the selectivity and yield of dearomatization, the efficiency of trifluoromethylation and the ease of rearomatization. Based on Akiba's method [83] for the synthesis of 1,4-dihydropyridinephosphonates, we implemented several optimizations to the procedure. We began our investigation with 3-(4-fluorophenyl)pyridine (**1a**) as the model substrate with three electrophiles potentially suited as *N*-activating reagents (**I–III**, Table 1) and three phosphites as nucleophiles (**IV–VI**, Table 1). It indicated that $P(OEt)_3$ was superior to $P(OMe)_3$ and $P(O^iPr)_3$ in forming 1,4-dihydropyridinylphonate from **1a** when methyl chloroformate served as *N*-activating reagent (entries 1–3). Comparable yields were obtained with ethyl chloroformate as the *N*-activating reagent and $P(OEt)_3$ or $P(O^iPr)_3$ as the nucleophiles, both of which performed better than $P(OMe)_3$ (entries 4–6). Notably, N-Tf-dihydropyridinylphosphonate remained inaccessible through this strategy using $P(OEt)_3$, $P(OMe)_3$, or $P(O^iPr)_3$ (entries 7–9). The reaction performed in DCM provided lower yields (entry 10). Only 23 % yield of the reaction was observed at 0°C with methyl chloroformate, leaving substantial unreacted starting material (entry 11), while room-temperature conditions failed to initiate effective pyridine activation (entry 12).

Based on the results in Table 1, methyl chloroformate was selected as the *N*-activating reagent, and the 1,4-dihydropyridinephosphonate **2a** derived from triethyl phosphite served as the model substrate for subsequent regioselective CF_3 introduction under copper catalysis, using 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni II) as the CF_3 source. Through systematic experimentation, we achieved a 71 % yield of the trifluoromethylation product **3a** using catalytic $CuBr(PPh_3)_3$ (10 mol%) and 1.2 equiv. Togni II (entry 1, Table 2). Togni II was found to be essential for activating substrate **2a** to afford **3a**. When alternative trifluoromethylation reagents (such as Togni I and Umemoto reagents) were employed, no significant associated trifluoromethylated products were detected (see Supporting information for further details). Given the critical role of copper salts play in enamine trifluoromethylation, systematic screening of copper catalysts was conducted, identifying $CuBr(PPh_3)_3$ as the optimal catalyst due to its superior efficacy (entries 2 and 3, Table 2). Notably, no product formation was observed in the absence of copper catalyst (entry 4, Table 2). In the testing of other solvents including 1,2-dichloroethane (DCE), acetonitrile (ACN), and dimethyl sulfoxide (DMSO), significantly decreased the conversion of **2a** (entries 5–7, Table 2). Subsequently, the rearomatization of **3a** was optimized (Table 3). In the presence of base, **3a** was converted to product **4a**, with 1,4-diazabicyclo[2.2.2]octane (DABCO) proving more efficient than *t*-BuONa or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entries 2 and 3, Table 3). The reaction proceeds optimally in DMSO (entries 4 and 5, Table 3). Additionally, a one-pot, two-step procedure was attempted, affording **4a** in 60 % yield from **2a** (entry 6, Table 3). This yield proved comparable to that achieved

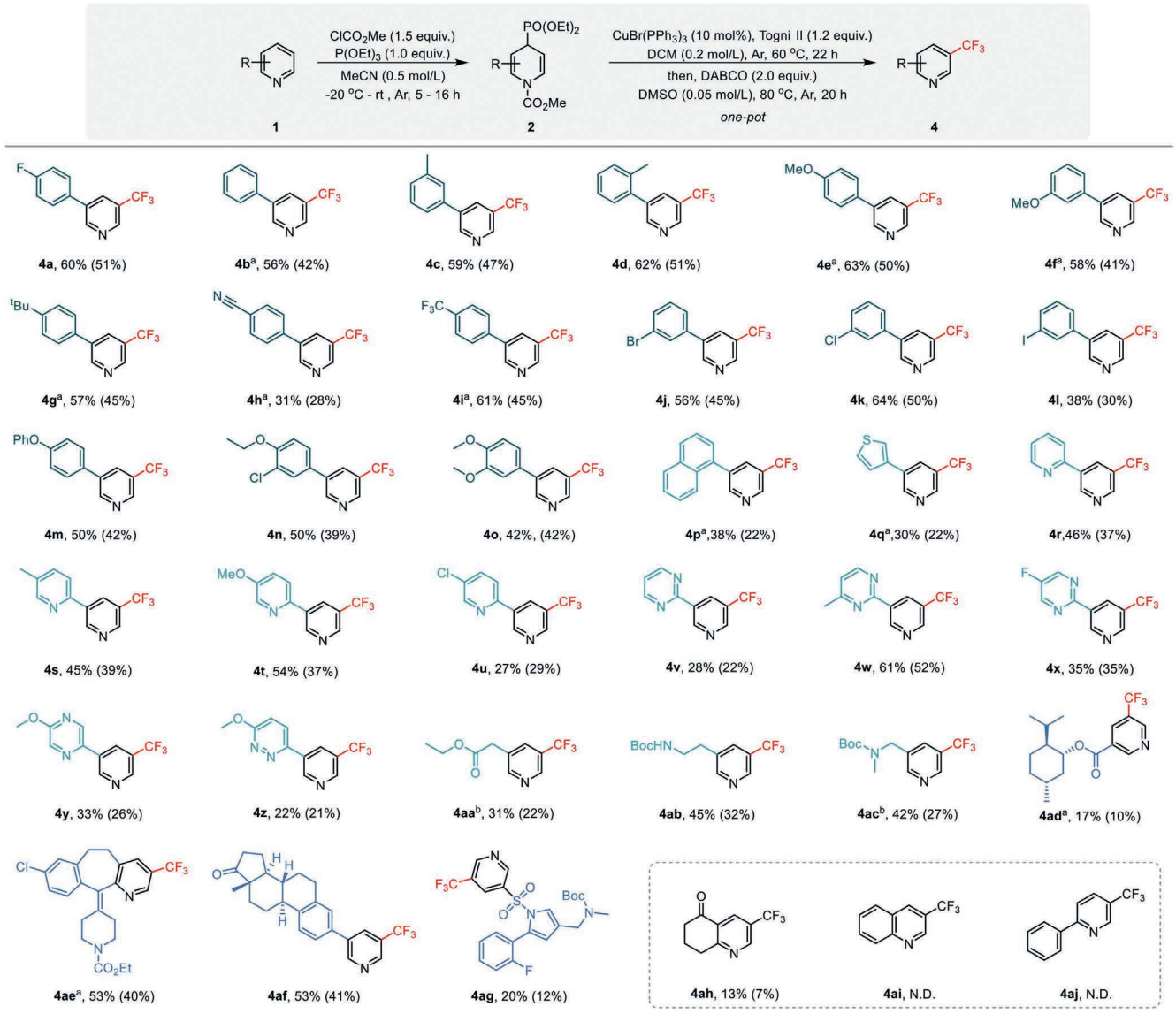
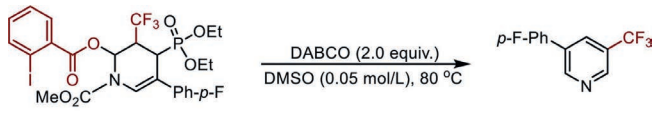


Fig. 2. Substrate scope of *meta*-C-H trifluoromethylation of pyridines. Reaction conditions: **2a** (1.0 equiv.), Togni II (1.2 equiv.), $CuBr(PPh_3)_3$ (10 mol%), DCM (0.2 mol/L), 60 °C, Ar, 22 h, then remove the solvent under vacuum, DABCO (2.0 equiv.), DMSO (0.05 mol/L), 80 °C, Ar, 20 h. The yields based on dearomatized intermediate **2** were determined *via* ^{19}F NMR with $PhOCF_3$ as internal standard, the yields in parentheses were isolated yields. [a] DABCO (4.0 equiv.). [b] The intermediate **3aa** was isolated prior to rearomatization.

Table 3
Optimization for rearomatization.[a]



3a **4a**

Entry	Deviation from standard conditions	**4a** Yield (%)[b]
1	None	88
2	*t*-BuONa instead of DABCO	69
3	DBU instead of DABCO	11
4	DCE instead of DMSO	N.D.
5	DCM instead of DMSO	N.D.
6[c]	One-pot procedure from **2a**	60

[a] Reaction conditions: **3a** (0.05 mmol, 1.0 equiv.), DABCO (2.0 equiv.), DMSO (0.05 mol/L), 80 °C. DABCO: 1,4-diazabicyclo[2.2.2]octane; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.
[b] Determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as internal standard.
[c] One-pot procedure, yield based on dearomatized intermediate **2a**.

through sequential reactions, while significantly streamlining the synthetic process.

Under the optimized conditions, the scope of the trifluoromethylation reaction was evaluated with various substrates (Fig. 2). The method proved applicable to a range of functionalized pyridine derivatives. Replacement of the fluorine substituent on the aromatic ring with electron-donating groups (*e.g.*, methyl, methoxy, *tert*-butyl) in mono- and disubstituted derivatives also provided the trifluoromethylated products **4c**–**4g** and **4m**–**4p** in moderate yields. Electron-withdrawing groups such as cyano and trifluoromethyl were also compatible, providing products **4h**–**4i**. Furthermore, carbon–halogen bonds remained intact under the reaction conditions, delivering products **4j**–**4l** with preserved halogen atoms in moderate yields. These halogenated derivatives serve as versatile synthetic building blocks for further coupling transformations. Notably, when an electron-rich thiophene ring occupied the *meta*-position of pyridine, the reaction exclusively delivered *meta*-selective trifluoromethylation on the pyridine ring (**4q**). Our approach was also successful in achieving *meta*-selective

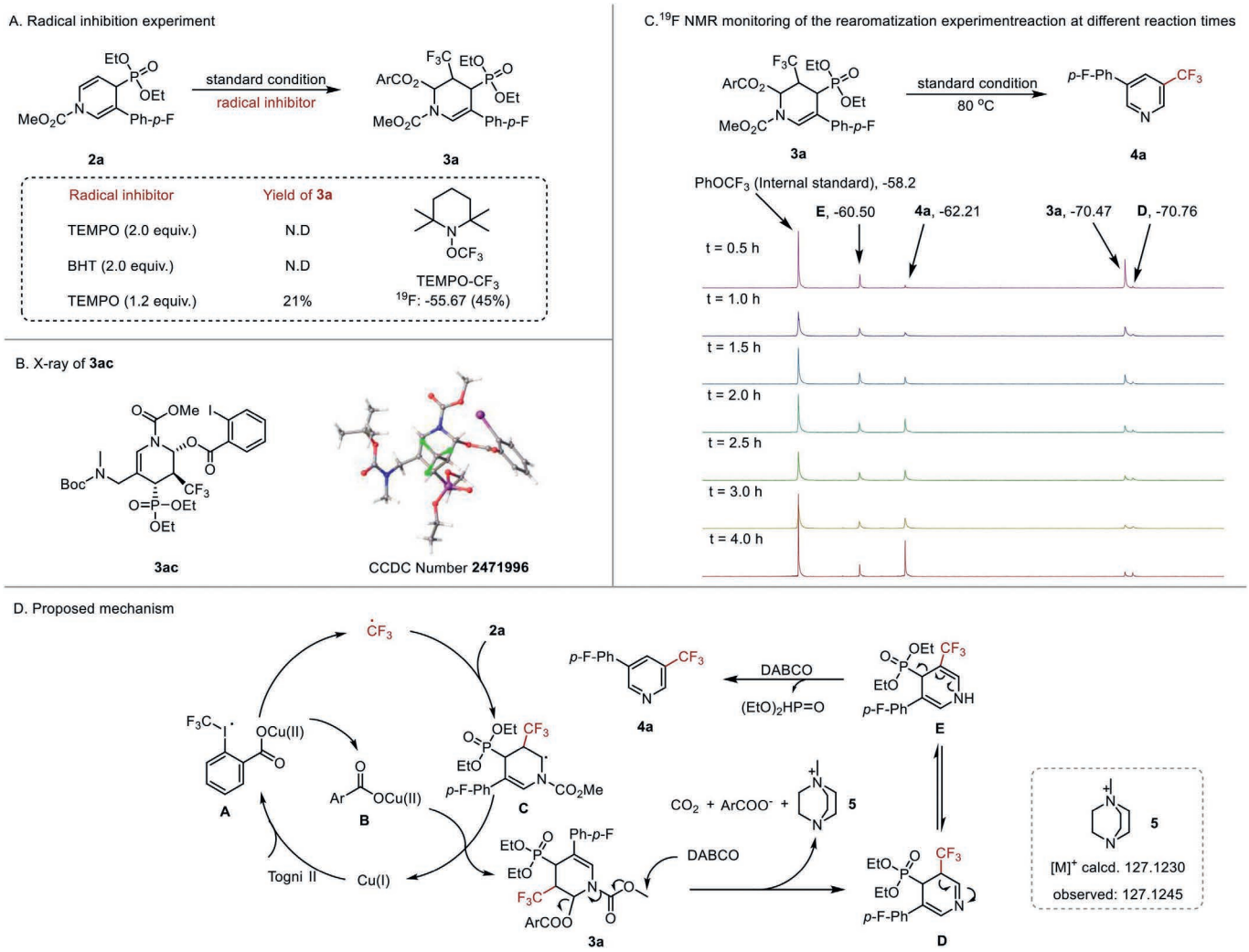


Fig. 3. Mechanistic studies. (A) Radical inhibition experiments. (B) X-ray of **3ac**. (C) ^{19}F NMR monitoring of the rearomatization experiment reaction at different reaction times. (D) Proposed mechanism.

trifluoromethylation of pyridine derivatives containing heteroaromatic substituents (**4s**–**4z**), such as pyrimidine, pyrazine, and pyridazine, despite the significant electron deficiency caused by these heterocycles. Additionally, the protocol also tolerated functional groups such as esters and amides (**4aa**–**4ac**). Given the multifaceted roles of pyridines in drug development, the late-stage functionalization of pyridines could rapidly optimize a candidate's pharmacokinetic and pharmacodynamic (PK/PD) properties and facilitate the discovery of new drugs. This method was extended to bioactive molecule-derived substrates (**4ad**–**4ag**), including L-menthol, loratadine, estrone, and vonoprazan, underscoring its utility in medicinal chemistry. Unfortunately, this approach is restricted mostly to *meta*-substituted pyridines, the yield of 2,3-disubstituted pyridine derivatives was relatively low (**4ah**), sometimes with no product formed (**4ai**). For the *ortho*-aryl-substituted pyridines, significant steric hindrance prevented dearomatization (**4aj**). Finally, a gram-scale reaction of **2b** afforded compound **4b** in 42 % yield.

To gain a deeper understanding of the mechanism, some preliminary studies were conducted. The addition of 2.0 equiv. 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2.0 equiv. butylated hydroxytoluene (BHT) as radical inhibitors completely inhibited the reaction. When TEMPO was reduced to 1.2 equiv., the yield of **3a** decreased to 21 %, while the TEMPO-CF_3 adduct was detected with a yield of 45 % by ^{19}F NMR (Fig. 3A). Moreover, the structure of intermediate **3ac** derived from **2ac** was confirmed by single-crystal X-ray diffraction (SC-XRD) analysis (Fig. 3B). Furthermore, monitoring the rearomatization process by ^{19}F NMR spectroscopy revealed that the concentrations of two intermediates (δ -70.76 and -60.50) changed as the reaction proceeded (Fig. 3C). By comparing them with the signals of the starting material **3a** (δ -70.47) and the product **4a** (δ -62.42), in combination with the molecular weights of **5** monitored by HRMS, we surmised that the two intermediates were **D** (δ -70.76) and **E** (δ -60.50), respectively. According to the above experimental results and related literature studies [84–94], a plausible reaction mechanism is proposed (Fig. 3D): (i) The Togni II reagent undergoes copper-catalyzed single-electron transfer (SET) to generate a trifluoromethyl radical and a Cu(II) specie **B**; (ii) This radical adds to the 1,4-dihydropyridinephosphonate **2a** to give the radical intermediate **C**; (iii) Intermediate **C** reacts with **B** to yield intermediate **3a** while regenerating the Cu(I) catalyst; (iv) Finally, **3a** undergoes DABCO-mediated aromatization *via* intermediates **D** and **E** to afford the *meta*-trifluoromethylated pyridine product **4a**.

In summary, we developed a novel dearomatization-rearomatization strategy based on 1,4-dihydropyridinephosphonate intermediates, which undergo copper-catalyzed regioselective C–CF_3 bond formation with Togni II reagent followed by DABCO-promoted rearomatization, achieving *meta*-C-H trifluoromethy-

lation of pyridine derivatives. A variety of pyridines bearing either electron-donating or electron-withdrawing (hetero)aryl substituents were converted to their corresponding trifluoromethylated products. The reaction proceeded with high regioselectivity, and *meta*-trifluoromethylated products were obtained as the sole regioisomer. Carbon-halogen bonds, esters, aryl ethers, and amides were tolerated under the reaction conditions. This activation paradigm overcomes the inherent site-selectivity constraints of traditional aromatic systems, demonstrating broad applicability to various pyridine-containing heterocyclic substrates and successful implementation in late-stage trifluoromethylation of pharmaceutical molecules. We anticipate this work will contribute to the development of robust methods for *meta*-selective transformations of pyridines.

CRediT authorship contribution statement

Wanqiu Zhao: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Aijia Zhang:** Formal analysis, Data curation. **Qingyun Huang:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Conceptualization. **Pingping Tang:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2025.112133.

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