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Mn-Mediated Direct Regioselective C−H Trifluoromethylation of Imidazopyridines and Quinoxalines

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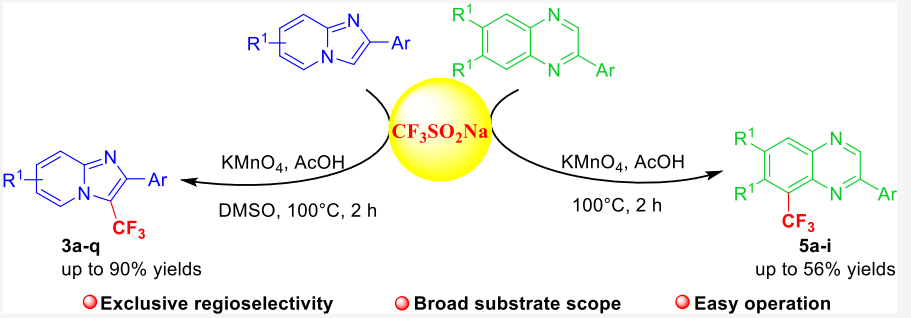

ABSTRACT: A simple and highly efficient strategy has been developed for direct C−H trifluoromethylation at C-3 of imidazopyridines and C-8 of quinoxalines with readily available Langlois reagent through $KMnO_4$/AcOH system. This protocol showed broad substrate scope and afforded moderate-to-excellent yields of both products. It is the first report that the functionalization of quinoxalines occurred regioselectively at the C-8 position of quinoxalines. Mechanistic studies revealed that reaction proceeded via radical pathway.

INTRODUCTION

Trifluoromethyled compounds have received a significant amount of attention in medicinal chemistry due to the incorporation of a CF_3 group into organic molecules that can significantly enhance their physical, chemical, and biological properties such as membrane permeability, favorable protein−ligand interactions, lipophilicity, bioavailability, and metabolic stability in comparison with their nonfluorinated analogs (Figure 1).[1] Over the past decades, various protocols for the preparation of trifluoromethylated organic compounds utilizing numerous trifluoromethylating agents including CF_3I, $TMSCF_3$, CF_3SO_2Na, CF_3SO_2Cl, Baran's reagent, Umemoto's reagent, Togni's reagent, etc., have been developed.[2] In particular, sodium trifluoromethanesulfinate ($NaSO_2CF_3$) was reported by Langlois et al. in 1980 and represents one of the cheapest and most a readily available reagents for trifluoromethylation of organic compounds through radical reaction.[3] Among the reported strategies, the direct trifluoromethylation of organic compounds via C−H functionalization reaction is of high interest, due to its high atom economy and no require to prefunctionalization.[4]

On the other hand, imidazopyridines and quinoxalines are recognized as important class of nitrogen-containing heterocycles and found in a wide variety of natural products and pharmaceuticals and materials science. These scaffolds exhibit varied biological activities, such as antitumor, anti-inflammatory, antiparasitic, antipyretic, cytotoxic, antiviral, antiulcer,

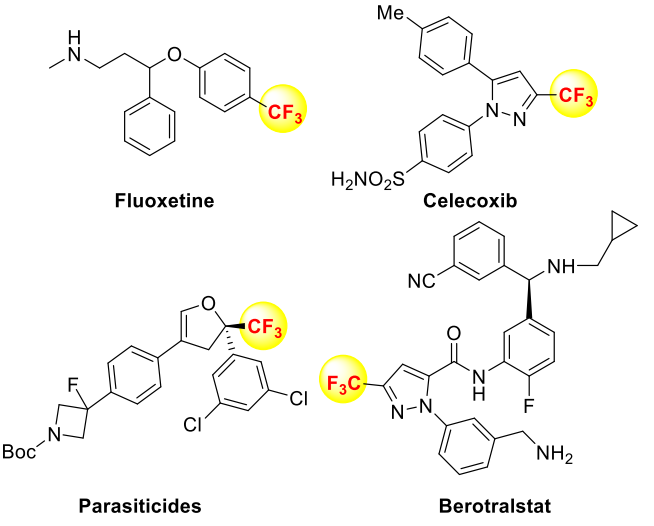

Figure 1. The trifluoromethyl-containing pharmaceuticals.

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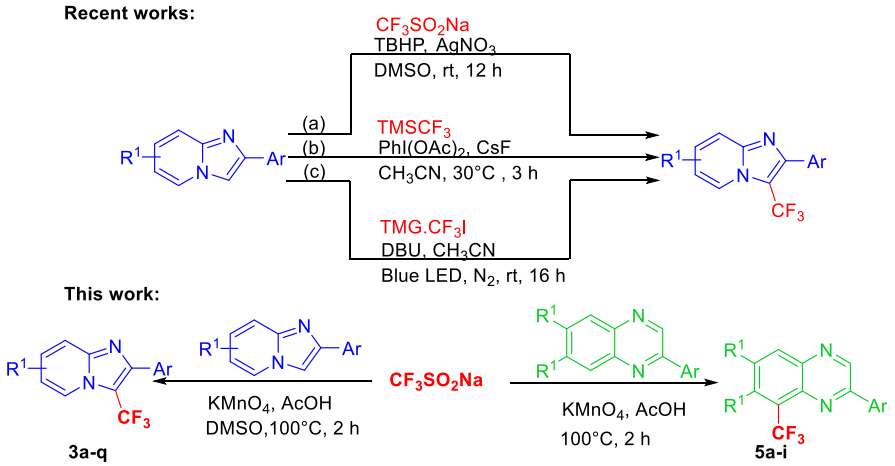
Scheme 1. Strategies to Regioselective Trifluoromethylation of Nitrogen-Containing Heterocycles

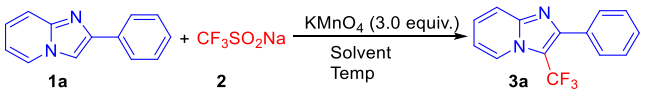


antifungal, anti-rhinoviral and anticancer.[5] Therefore, synthesis and functionalization of these scaffolds have been paid much attention from the synthetic community.[6] Various methods have been developed for the C−H bond functionalization of the C-3 position of the imidazopyridine structures using different substituents such as aryl, alkyl, halogen, thiol, and trifluoromethyl.[7] Among these reported methods, direct trifluoromethylation of imidazo[1,2-*a*]pyridines via trifluoromethyl radicals have received considerable attention. In 2015, Hajra and co-workers were the first group to report the successful synthesis of 3-trifluoromethylimidazo[1,2-*a*]-pyridines using Langlois' reagent ($NaSO_2CF_3$) as CF_3 radical source in the presence of TBHP and $AgNO_3$ at room temperature (Scheme 1a).[8] The direct C3-trifluoromethylation of imidazo[1,2-*a*]pyridine derivatives with Ruppert-Prakash reagent ($TMSCF_3$) in the presence of $PhI(OAc)_2$ and CsF in CH_3CN was described by Wu et al. in 2019 (Scheme 1b).[9] Very recently, Deng and co-workers disclosed a visible-light-promoted C3-trifluoromethylation of imidazopyridine derivatives using tetramethylguanidine trifluoromethyl iodide complex ($TMG{\cdot}CF_3I$) as CF_3 radical source in the presence of DBU as base (Scheme 1c).[10] Despite such advances, there still remains need for novel and simple synthetic strategies that are facile and effective. In addition, the strategy C−H functionalization of quinoxaline derivatives have remained largely unexplored, and this area of research is still in its infancy. To the best of our knowledge, no examples involving trifluoromethylation of quinoxaline derivatives have been reported to date. Therefore, the development of new synthetic methods to the functionalization these compounds remains a high-value achievement. Inspired by these studies and our continuing interest in the radical reactions, herein we report regioselective C3-trifluoromethylation of imidazo[1,2-*a*]pyridines and C8-trifluoromethylation of quinoxalines using Langlois' reagent ($NaSO_2CF_3$) as CF_3 radical source in the presence of Mn^{III} species, which is generated in situ by the $KMnO_4$/AcOH system.

RESULTS AND DISCUSSION

To verify the feasibility of our hypothesis, reaction of 2-phenylimidazo[1,2-*a*]pyridine **1a** with Langlois' reagent ($NaSO_2CF_3$) **2** was selected as the model substrates to optimize the reaction conditions (Table 1). Initially, the reaction of **1a** with CF_3SO_2Na **2** was studied in the presence

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	yield %
1	AcOH	80	45
2	AcOH/DMSO (1:1)	80	68
3	AcOH/PhCl (1:1)	80	35
4	AcOH/$PhCH_3$ (1:1)	80	20
5	AcOH/DCE (1:1)	80	43
6	AcOH/acetone (1:1)	80	10
7	AcOH/DMF (1:1)	80	20
8	AcOH/CH_3CN (1:1)	80	55
9	AcOH/EtOAc (1:1)	80	61
10	**AcOH/DMSO** (1:1)	**100**	72
11	AcOH/DMSO (1:2)	100	65
12	AcOH/DMSO (1:4)	100	52
13[b]	AcOH/DMSO (1:1)	100	59
14[c]	AcOH/DMSO (1:1)	100	47
15[d]	AcOH/DMSO (1:1)	100	72

[a]Reaction conditions: 1a (0.2 mmol), 2 (0.6 mmol), solvent (1.0 mL), $KMnO_4$ (3.0 equiv), at 100 °C for 2 h. [b]$KMnO_4$ (4.0 equiv). [c]Reaction time 4 h. [d]N_2 atmosphere.

3.0 equiv of $KMnO_4$ as oxidant in AcOH as solvent, at the temperature of 80 °C for 2h. To our delight, desired product **3a** was obtained in 45% yield (entry 1). Encouraged by this initial result, we examined the effect of various common solvents. Screening of several solvent systems including (DMSO, PhCl, $PhCH_3$, DCE, DMF, CH_3CN, EtOAc, and acetone)/AcOH revealed that AcOH/DMSO gives the best result for this reaction (entries 2−9). When the reaction temperature was raised to 100 °C, the desired product **3a** was formed in 72% yields (entry 10). In addition, the effect of different AcOH/DMSO ratios on the reaction yield was tested (entries 11 and 12), unfortunately, no results were obtained on the improvement of the product yield. Increasing the usage of $KMnO_4$ to 4.0 equiv led to form product **3a** in 59% yield (entry 13). No further improvement of the yield was observed with the increasing reaction time to 4 h (entry 14). As a note, when the model reaction was conducted under N_2 atmosphere, the yield of the desired product was not changed (entry 15). The above optimization results suggested that the maximum

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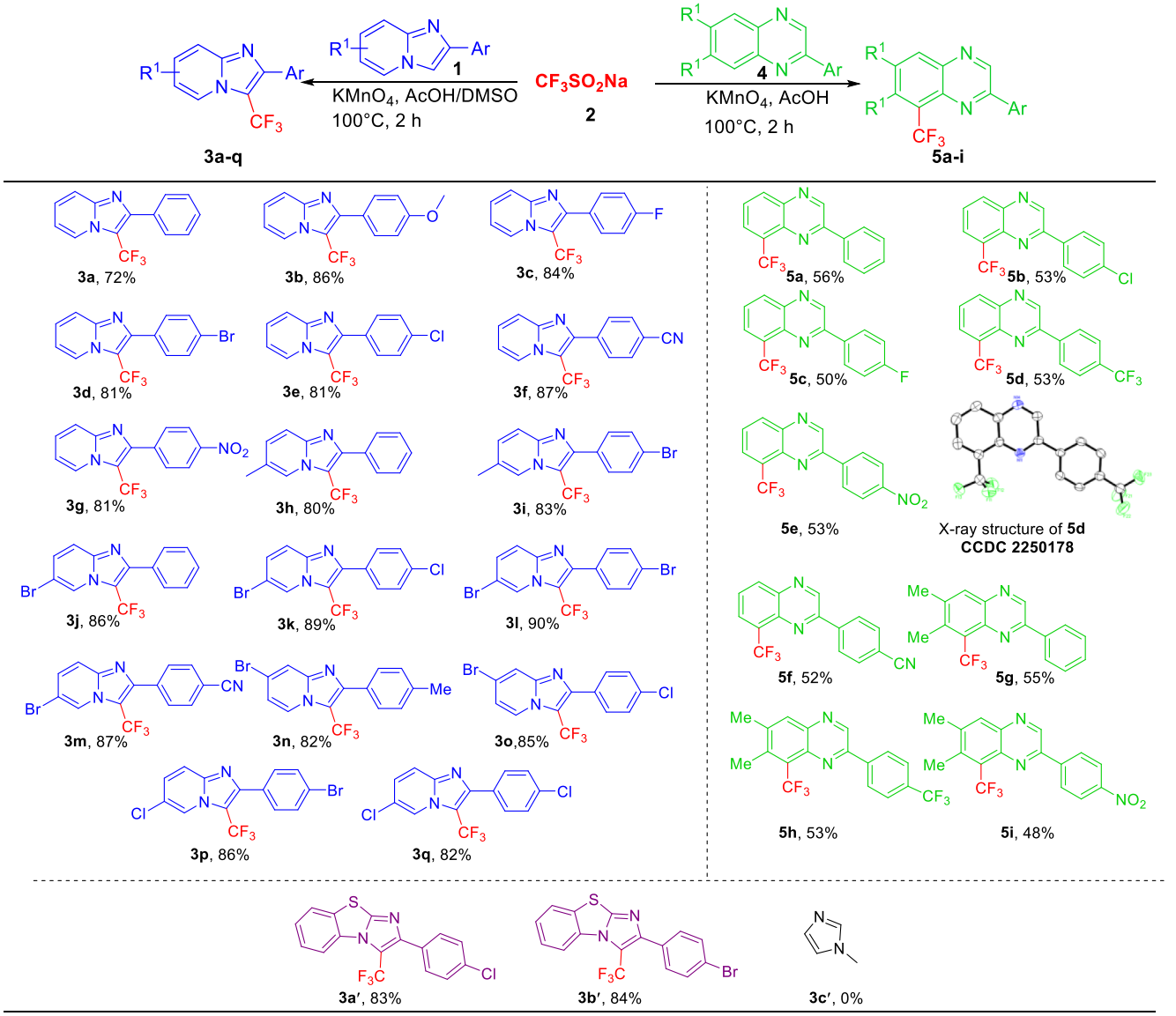
Table 2. Substrate Scope of the Trifluoromethylation of Imidazo[1,2-*a*]pyridines and Quinoxalines[a]



[a]Reaction conditions: 1 (0.2 mmol), 2/4 (0.6 mmol), solvent (1.0 mL), $KMnO_4$ (3.0 equiv), at 100 °C for 2 h.

yield of the desired product **3a** (72%) can be obtained under condition of using 3.0 equiv of $KMnO_4$ as the oxidant in AcOH/DMSO as solvent at 100 °C for 2 h.

With the optimized reaction conditions in hand, the generality of this method using Langlois' reagent ($NaSO_2CF_3$) **2** and variously substituted imidazo[1,2-*a*]pyridines **1** was investigated and the results are summarized in Table 2. Imidazo[1,2-*a*]pyridines with electron-donating (OMe), halogen (F, Cl, Br), as well as some other electron-withdrawing (CN, NO_2) groups on the benzene ring participated in the reaction well to deliver the desired products **3a**−**3g** in 72−87% yields. Subsequently, imidazopyridines bearing substituents on the pyridine rings were also explored. 6-Methyl-2-arylimidazo-[1,2-*a*]pyridine **2h** and **2i** react with trifluoromethylating agent to afford the desired products **3h** and **3i** in 80 and 83% yields, respectively. When Br and Cl were substituted on the C-6 or C-7 position of imidazo[1,2-*a*]pyridines, the reaction performed well and gave the corresponding products **3j**−**3q**, in 82−90% yields. In addition, we investigated the trifluoromethylation of 1-methyl-1H-imidazole and 2-arylbenzo[*d*]-imidazo[2,1-*b*]thiazoles under standard reaction conditions. Fortunately, trifluoromethylation of benzo[*d*]imidazo[2,1-*b*]-thiazoles were led to form desired products **3a′** and **3b′** in 83 and 84% yields, respectively. But, 1-methyl-1H-imidazole was not compatible with this transformation, and the corresponding products **3c′** were not detected after 6 h. It is noteworthy to mention, to show the diversity of the reaction, we also employed quinoxalines **4** as a coupling partner and studied it to the same reaction conditions. Surprisingly, we observed desired product **5a** in 48% yield. Hence, to increase the product yield, we explored different solvent and temperature. A better yield was obtained in AcOH as solvent (please see the optimization table included in the Supporting Information). As depicted in Table 2, a variety of quinoxalines bearing electron-donating, -withdrawing and neutral groups on the phenyl ring were tolerated, allowing the construction of C8-trifluoromethylated quinoxalines **5a**−**5i** in moderate yields. The structure of **5d** also was unambiguously confirmed by X-ray analysis, the

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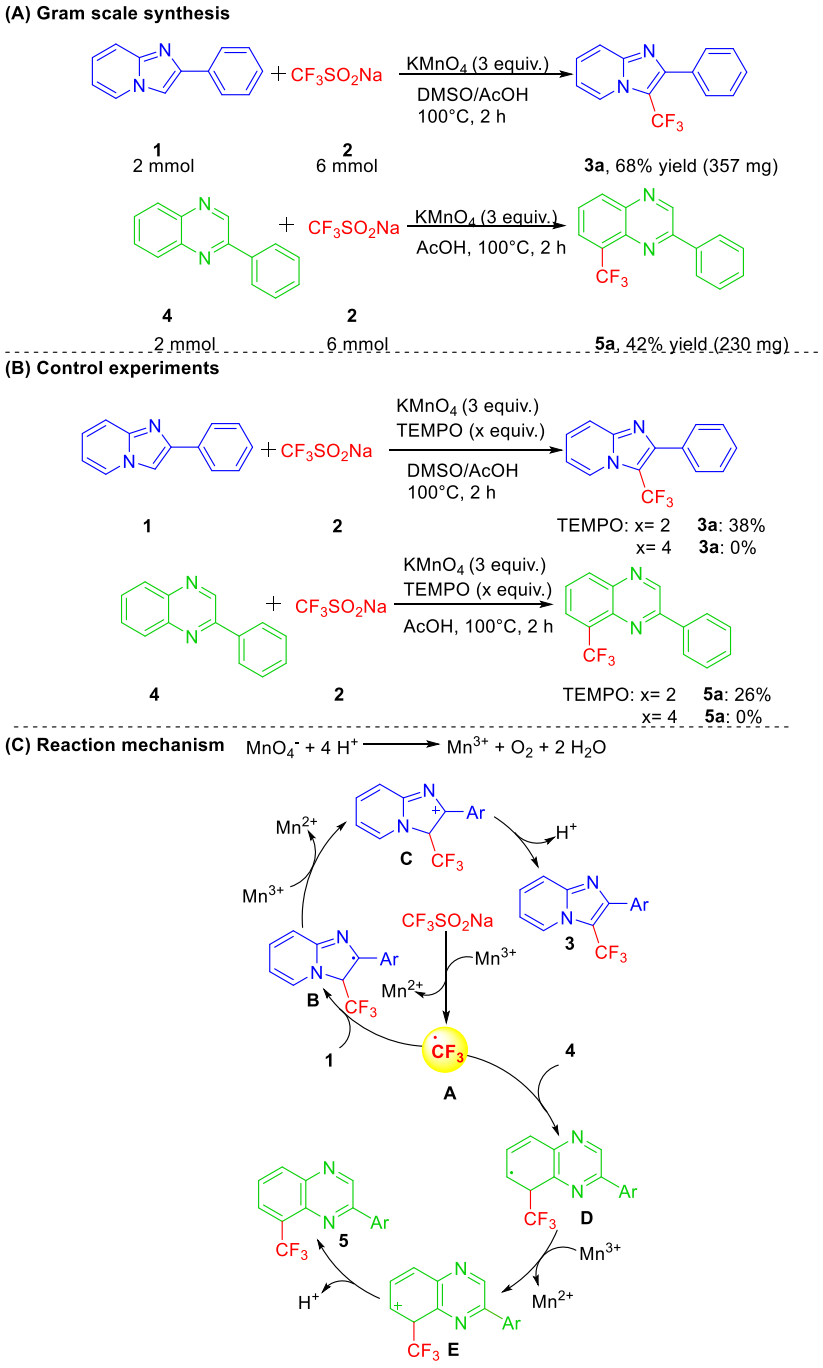
Scheme 2. Mechanistic Study and Proposed Reaction Mechanism



ellipsoid probability level is 50%. Additionally, 6,7-dimethyl-2-arylquinoxalines performed smoothly to deliver the desired product **5g**−**5i** in 48−55% yields. To demonstrate the practicability of this approach, we next carried out the gram-scale synthesis of **3a** and **5a** under the standard conditions and the desired products **3a** and **5a** were obtained in 68% (357 mg) and 42% (230 mg) yields, respectively (Scheme 2A).

To gain insight to the reaction mechanism, a radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction mixture in varying quantities, and yields of the desired products **3a** and **5a** were sharply decreased (Scheme 2B). These results suggested that this reaction might involve a radical pathway. On the basis of experimental results above and previous reports,[3,11] a plausible reaction mechanism is depicted in Scheme 2C. First, Mn^{III} species are generated from the reaction $KMnO_4$ and AcOH under the thermal condition, which then reacts with the Langlois' reagent ($NaSO_2CF_3$) **2** to deliver trifluoromethyl radical **A**. Subsequently, the trifluoromethyl radical is added selectively to C3 of imidazo[1,2-*a*]pyridine/C8 of quinoxalines to give radical intermediate **B**/**D**. Then, a single-electron transfer (SET) from intermediate **B**/**D** to Mn^{III} leads to release the cation intermediate **C**/**E** and simultaneously Mn^{III} reduces into Mn^{II}. Probably, both the intermediates **B**/**D** and **C**/**E** can be stabilized through conjugation with adjacent aryl group. Finally, deprotonation of intermediate **C**/**E** affords the desired product **3**/**5**.

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In summary, we have developed an operationally simple and efficient approach for regioselective trifluoromethylation of imidazopyridines and quinoxalines using Langloi's reagent as CF_3 radical source by $KMnO_4$/AcOH system. The Mn^{III} species is generated in situ from $KMnO_4$/RCOOH system for the formation of trifluoromethyl radicals. A variety of trifluoromethyled imidazo[1,2-*a*]pyridines and quinoxalines with high functional group tolerance were obtained in moderate-to-excellent yields. To the best of our knowledge, this is the first report for the direct C8-trifluoromethylation of quinoxalines. The attractive features of this protocol are the use of inexpensive and readily available materials, short time, and regioselectivity. Further investigations on the detailed mechanism and applications of this method on the other heteroaromatic compounds are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All chemicals and solvents used in this study were purchased from chemical suppliers (Merck, Sigma-Aldrich, Fluka, and Alpha-Aesar), and used without further purification. The reaction process was monitored by thin-layer chromatography (TLC) using aluminum-coated plates of silica gel (MERCK, 60F254), via detection under UV fluorescence (wavelength of 254 nm). Chromatographic separations of products were carried out by flash column chromatography on MACHEREY-NAGEL silica gel 60 (230−400 mesh). Melting points (m.p.) were determined with an Electrothermal 9100 digital melting point apparatus and are uncorrected. Nuclear Magnetic Resonance (NMR) spectra (^{1}H and ^{13}C NMR) were recorded on a Bruker AVANCE 300, 400 and 500 MHz (DRX) spectrometer. Chemical shifts (δ) are quoted in ppm and the coupling constants (J) in Hz. Multiplets were indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet, complex pattern), dd (doublet of doublet), ddd (doublet of doublet of doublet), td (triplet of doublet), tt (triplet of triplet), and bs (broad singlet). High-resolution mass spectrum (HRMS) (ESI-TOF) was recorded using Waters LCT Premier XE mass spectrometer. X-ray crystal data were measured on a Bruker APEX-II Quazar area detector.

General Experimental Procedures. *General Procedure for Preparation of Imidazo[1,2-a]pyridines **2a−b′**.*[12] A mixture of 2-aminopyridine (5.0 mmol), α-bromo ketone (5.5 mmol), and $NaHCO_3$ (6.0 mmol) in EtOH (10.0 mL) was heated at 70 °C in an oil bath for 1−2 h. The completion of reaction as was indicated by TLC monitoring, then the solvent was removed under the reduced pressure. The product was extracted with ethyl acetate (2 × 10.0 mL). The combined organic phase was dried over Na_2SO_4. The solvent was removed under the reduced pressure. The solid product was recrystallized by ethanol affording desired imidazo[1,2-*a*]pyridines.

*General Procedure for Trifluoromethylation of 2-Arylimidazo-[1,2-a]pyridine **3a−b′**.* First, the solution of potassium permanganate (0.6 mmol, 0.094 g, 3.0 equiv)/acetic acid (0.5 mL) was heated at 100 °C in an oil bath for 15 min. When the reaction mixture completely changed color from purple to brown, time was given for the mixture to reach ambient temperature. Then, dimethyl sulfoxide (0.5 mL) was added to the reaction vessel and 2-arylimidazo[1,2-*a*]pyridine **1** (0.2 mmol, 0.038 g, 1.0 equiv) and sodium trifluoromethanesulfinate **2** (0.6 mmol, 0.096 g, 3.0 equiv) were added to it. Then, the reaction mixture was heated at 100 °C in an oil bath for 2 h. After completion of the reaction as was indicated by TLC monitoring, the reaction mixture was cooled to ambient temperature. A saturated solution of $NaHCO_3$ (3.0 mL) was added and the product was extracted with ethyl acetate (3 × 4.0 mL). The combined organic phase was dried over Na_2SO_4. The solvent was removed under the reduced pressure. The residue was purified by column chromatography using *n*-hexane/EtOAc (8:1) as eluent to afford pure products **3a−b′**.

*General Procedure for the Preparation of Compound **3a** in a Scale of 2.0 mmol.* The solution of potassium permanganate (6.0 mmol, 0.948 g, 3.0 equiv)/acetic acid (2.0 mL) was heated at 100 °C in an oil bath for 15 min. When the reaction mixture completely changed color from purple to brown, time was given for the mixture to reach ambient temperature. Then, dimethyl sulfoxide (2.0 mL) was added to the reaction vessel and 2-phenyimidazo[1,2-*a*]pyridine **1** (2.0 mmol, 0.388 g, 1.0 equiv) and sodium trifluoromethanesulfinate **2** (6.0 mmol, 0.936 g, 3.0 equiv) were added to it. Then, the reaction mixture was heated at 100 °C in an oil bath for 2 h. After completion of the reaction as was indicated by TLC monitoring, the reaction mixture was cooled to ambient temperature. A saturated solution of $NaHCO_3$ (9.0 mL) was added and the product was extracted with ethyl acetate (3 × 6.0 mL). The combined organic phase was dried over Na_2SO_4. The solvent was removed under the reduced pressure. The residue was purified by column chromatography using *n*-hexane/EtOAc (8:1) as eluent to afford pure product **3a** in **68**% (357 mg) yield.

*General Procedure for Preparation of Quinoxalines **4a−i**.*[13] *o*-Phenylenediamine (5.0 mmol) was added to the solution of arylglyoxal (5.0 mmol) in acetic acid as a solvent (10.0 mL) and the reaction mixture was heated at 80 °C in an oil bath for 1 h and the progress of the reaction was monitored by thin TLC. The reaction mixture was cooled to ambient temperature. A saturated solution of $NaHCO_3$ (40.0 mL) was added and the product was extracted with ethyl acetate (3 × 20.0 mL). The combined organic phase was dried over Na_2SO_4. The solvent was removed under the reduced pressure. The solid product was recrystallized by ethyl acetate affording desired quinoxalines **4a−i**.

*General Procedure for Trifluoromethylation of 2-Arylquinoxaline **5a−i**.* First, the solution of potassium permanganate (0.6 mmol, 0.094, 3.0 equiv)/acetic acid (0.5 mL) was heated at 100 °C in an oil bath for 15 min. When the reaction mixture completely changed color from purple to brown, time was given for the mixture to reach ambient temperature. Then, 2-arylquinoxaline **4** (0.2 mmol, 0.041, 1.0 equiv) and sodium trifluoromethanesulfinate **2** (0.6 mmol, 0.096, 3.0 equiv) were added to the reaction vessel and the reaction mixture was heated at 100 °C in an oil bath for 2 h. After completion of the reaction as was indicated by TLC monitoring, the reaction mixture was cooled to ambient temperature. A saturated solution of $NaHCO_3$ (3.0 mL) was added and the product was extracted with ethyl acetate (3 × 4.0 mL). The combined organic phase was dried over Na_2SO_4. The solvent was removed under the reduced pressure. The residue was purified by column chromatography using *n*-hexane/EtOAc (8:1) as eluent to afford pure products **5a−i**.

*General Procedure for the Preparation of Compound **5a** in a Scale of 2 mmol.* The solution of permanganate (6.0 mmol, 0.948 g, 3.0 equiv)/acetic acid (2.0 mL) was heated at 100 °C in an oil bath for 15 min. When the reaction mixture completely changed color from purple to brown, time was given for the mixture to reach ambient temperature. Then, 2-phenylquinoxaline **4** (2.0 mmol, 0.412 g 1.0 equiv) and sodium trifluoromethanesulfinate **2** (6.0 mmol, 0.936 g, 3.0 equiv) were added to the reaction vessel and the reaction mixture was heated at 100 °C in an oil bath for 2 h. After completion of the reaction as was indicated by TLC monitoring, the reaction mixture was cooled to ambient temperature. A saturated solution of $NaHCO_3$ (9.0 mL) was added and the product was extracted with ethyl acetate (3 × 5.0 mL). The combined organic phase was dried over Na_2SO_4. The solvent was removed under the reduced pressure. The residue was purified by column chromatography using *n*-hexane/EtOAc (8:1) as eluent to afford pure product **5a** in **42**% (230 mg) yield.

*6-Methyl-2-phenylimidazo[1,2-a]pyridine **(2h)**.* Yield: 958 mg, 92%; yellow solid; mp 164−167 °C [lit.[12d] mp 176−177 °C]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J = 8.4, 1.4 Hz, 2H), 7.80 (br s, 1H), 7.70 (s, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.32 (tt, J = 7.3, 1.5 Hz, 1H), 6.99 (dd, J = 9.3, 1.7 Hz, 1H), 2.26 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.1, 144.6, 133.7, 128.7, 128.1, 127.9, 125.9, 123.4, 122.2, 116.6, 108.0, 18.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_2$, 209.1079; found, 209.1075.

*7-Bromo-2-(p-tolyl)imidazo[1,2-a]pyridine **(2n)**.* Yield: 1364 mg, 95%; yellow solid; mp 177−180 °C [lit.[12e] mp 280 °C]. ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 8.04 (dd, J = 7.1, 1.0 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H) 7.86 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 6.93 (dd, J = 7.1, 1.9 Hz, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 146.3, 145.5, 138.4, 130.0, 129.6, 126.0, 125.8, 119.4, 118.5, 116.5, 108.0, 21.4. HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{14}H_{12}BrN_2$, 287.0184; found, 287.0176.

2-Phenyl-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3a)***. Yield: 38 mg, 72%; yellow oil; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, J = 7.0 Hz, 1H), 7.69−7.76 (m, 3H), 7.43−7.51 (m, 3H), 7.39 (t, J = 7.9 Hz, 1H), 6.99 (t, J = 6.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 148.0 (q, J = 1.3 Hz), 146.1, 132.9, 129.6 (q, J = 1.1 Hz), 128.9, 128.2, 127.0, 125.5 (q, J = 3.8 Hz), 121.9 (q, J = 265.6 Hz), 118.1, 113.9, 109.8 (q, J = 39.2 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{10}F_3N_2$, 263.0796; found, 263.0790.

2-(4-Methoxyphenyl)-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3b)***. Yield: 50 mg, 86%; light yellow solid; mp 78−80 °C [lit.[9] mp 81−83 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 9.1 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.42 (dt, J = 8.0, 0.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.01 (t, J = 7.3 Hz, 1H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.4, 147.6, 145.8, 130.9, 127.2, 125.5 (q, J = 3.1 Hz), 124.8, 122.0 (q, J = 265.6 Hz), 117.8, 114.0, 113.7, 109.1 (q, J = 40.5 Hz), 55.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{12}F_3N_2O$, 293.0902; found, 293.0895.

2-(4-Fluorophenyl)-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3c)***. Yield: 47 mg, 84%; light yellow solid; mp 78−80 °C [lit.[9] mp 55−57 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, J = 7.0 Hz, 1H), 7.66−7.75 (m, 3H), 7.37−7.43 (m, 1H), 7.13−7.19 (m, 2H), 7.00 (td, J = 7.5, 1.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 163.3 (d, J = 247.1 Hz), 147.0 (q, J = 1.8 Hz), 146.1, 131.4 (dq, J = 8.7, 1.3 Hz), 129.0 (d, J = 3.3 Hz), 127.1, 125.5 (q, J = 3.8 Hz), 121.8 (q, J = 265.6 Hz), 118.1, 115.2 (d, J = 21.3 Hz), 114.0, 109.5 (q, J = 39.2 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_9F_4N_2$, 281.0702; found, 281.0694.

2-(4-Bromophenyl)-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3d)***. Yield: 55 mg, 81%; light yellow solid; mp 76−78 °C [lit.[9] mp 94−96 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, J = 7.0 Hz, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.55−7.61 (m, 4H), 7.39 (t, J = 8.0 Hz, 1H), 6.99 (t, J = 7.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 146.8 (q, J = 1.8 Hz), 146.1, 131.8, 131.5, 131.1 (q, J = 1.3 Hz), 127.2, 125.5 (q, J = 3.1 Hz), 123.5, 121.8 (q, J = 265.6 Hz), 118.2, 114.2, 109.6 (q, J = 39.5 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_9BrF_3N_2$, 340.9901; found, 340.9896.

2-(4-Chlorophenyl)-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3e)***. Yield: 48 mg, 81%; light yellow solid; mp 93−95 °C [lit.[9] mp 84−86 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 7.0 Hz, 1H), 7.73 (d, J = 9.1 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.4 Hz, 1H), 7.02 (t, J = 6.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 146.8, 146.1, 135.2, 131.3, 130.9, 128.5, 127.2, 125.5 (q, J = 4.0 Hz), 121.8 (q, J = 265.9 Hz), 118.1, 114.1, 109.6 (q, J = 39.7 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_9ClF_3N_2$, 297.0406; found, 297.0405.

4-(3-(Trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)benzonitrile ***(3f)***. Yield: 50 mg, 87%; light yellow solid; mp 163−165 °C [lit.[9] mp 147−148 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, J = 7.0 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.06 (t, J = 6.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 146.3, 145.8 (q, J = 1.6 Hz), 137.5, 132.1, 130.4, 127.5, 125.6 (q, J = 3.2 Hz), 121.6 (q, J = 266.2 Hz), 118.6, 118.4, 114.7, 112.7, 110.2 (q, J = 39.8 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9F_3N_3$, 288.0749; found, 288.0742.

2-(4-Nitrophenyl)-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3g)***. Yield: 50 mg, 81%; light yellow solid; mp 145−147 °C [lit.[9] mp 139−140 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, J = 6.8 Hz, 1H), 8.32 (d, J = 8.9 Hz, 2H), 7.89 (d, J = 8.9 Hz, 2H), 7.77 (d, J = 9.1 Hz, 1H), 7.43−7.49 (m, 1H), 7.07 (dt, J = 7.0, 1.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 148.1, 146.3, 145.4 (q, J = 2.2 Hz), 139.2, 130.7 (q, J = 1.5 Hz), 127.7, 125.6 (q, J = 3.8 Hz), 123.4, 121.5 (q, J = 268.1 Hz), 118.4, 114.7, 110.5 (q, J = 39.5 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_9F_3N_3O_2$, 308.0647; found, 308.0642.

6-Methyl-2-phenyl-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3h)***. Yield: 44 mg, 80%; light yellow solid; mp 73−75 °C [lit.[14] mp 97−98 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.69 (d, J = 7.6 Hz, 2H), 7.64 (d, J = 9.3 Hz, 1H), 7.44−7.50 (m, 3H), 7.24 (d, J = 9.1 Hz, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 147.7 (q, J = 1.5 Hz), 145.1, 133.0, 130.1, 129.6 (q, J = 1.2 Hz), 128.8, 128.1, 123.8, 123.1 (q, J = 3.4 Hz), 121.9 (q, J = 265.7 Hz), 117.4, 109.2 (q, J = 38.6 Hz), 18.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{12}F_3N_2$, 277.0953; found, 277.0947.

2-(4-Bromophenyl)-6-methyl-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3i)***. Yield: 59 mg, 83%; white solid; mp 130−132 °C; [silica gel (8:1 hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.53−7.58 (m, 3H), 7.25 (d, J = 9.1 Hz, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 146.5 (q, J = 1.8 Hz), 145.2, 132.0, 131.8, 131.4 (q, J = 2.2 Hz), 131.2, 130.3, 124.1, 123.3, 121.8 (q, J = 265.9 Hz), 117.4, 109.5 (q, J = 38.0 Hz), 18.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{11}BrF_3N_2$, 355.0058; found, 355.0051.

6-Bromo-2-phenyl-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3j)***. Yield: 59 mg, 86%; white solid; mp 110−112 °C [lit.[14] mp 104−106 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.67−7.71 (m, 2H), 7.64 (d, J = 9.5 Hz, 1H), 7.44−7.50 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 148.6 (q, J = 1.9 Hz), 144.5, 132.3, 130.5, 129.6 (q, J = 1.6 Hz), 129.4, 128.2, 125.6 (q, J = 4.2 Hz), 121.6 (q, J = 266.2 Hz), 118.7, 109.9 (q, J = 39.9 Hz), 108.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_9BrF_3N_2$, 340.9901; found, 340.9893.

6-Bromo-2-(4-chlorophenyl)-3-(trifluoromethyl) imidazo[1,2-a]pyridine ***(3k)***. Yield: 67 mg, 89%; white solid; mp 150−152 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.64 (d, J = 9.2 Hz, 3H), 7.45−7.51 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.4 (q, J = 1.5 Hz), 144.6, 135.5, 130.8 (q, J = 1.3 Hz), 129.1, 128.6, 127.5, 125.6 (q, J = 3.9 Hz), 122.8 (q, J = 266.5 Hz), 118.6, 110.0 (q, J = 39.4 Hz), 109.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_8BrClF_3N_2$, 374.9511; found, 374.9501.

6-Bromo-2-(4-bromophenyl)-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3l)***. Yield: 76 mg, 90%; white solid; mp 159−161 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.61−7.66 (m, 3H), 7.57 (d, J = 8.6 Hz, 2H), 7.49 (dd, J = 9.5, 2.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.3 (q, J = 1.3 Hz), 144.6, 131.6, 131.3, 131.1 (q, J = 1.3 Hz), 130.9, 125.6 (q, J = 3.7 Hz), 123.8, 121.5 (q, J = 266.5 Hz), 118.7, 109.9 (q, J = 39.4 Hz), 109.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_8Br_2F_3N_2$, 418.9006; found, 418.9007.

4-(6-Bromo-3-(trifluoromethyl) imidazo[1,2-a]pyridin-2-yl)benzonitrile ***(3m)***. Yield: 64 mg, 87%; white solid; mp 179−172 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 9.6 Hz, 1H), 7.53 (dd, J = 9.5, 1.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 146.3 (q, J = 1.4 Hz), 144.7, 136.9, 132.1, 131.3, 130.2 (q, J = 1.2 Hz), 125.6 (q, J = 3.6 Hz), 121.6 (q, J = 266.2 Hz), 118,8, 118.5, 113.0, 110.4 (q, J = 40.2 Hz), 109.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_8BrF_3N_3$, 365.9854; found, 365.9846.

7-Bromo-2-(p-tolyl)-3-(trifluoromethyl)imidazo[1,2-a]pyridine ***(3n)***. Yield: 58 mg, 82%; white solid; mp 118−120 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 7.1 Hz, 1H), 7.96−7.98 (d, J = 1.0 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.14 (dd, J = 7.3 Hz, 1.9 Hz, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.4, 145.9, 139.5, 129.5, 129.1, 129.0, 125.7 (q, J = 3.2 Hz), 121.6 (q, J = 263.3 Hz), 121.5, 120.1, 118.1, 109.7 (q, J = 39.2 Hz), 21.4. ^{19}F NMR (376 MHz,

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$CDCl_3$): δ −57.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{11}BrF_3N_2$, 355.0058; found, 355.0053.

7-Bromo-2-(4-chlorophenyl)-3-(trifluoromethyl)imidazo[1,2-a]-pyridine ***(3o)***. Yield: 64 mg, 85%; white solid; mp 158−160 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 7.4 Hz, 1H), 7.97 (d, *J* = 1.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.17 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.1, 146.0, 135.7, 130.9, 130.4, 128.7, 125.7 (q, *J* = 3.1 Hz), 121.5 (q, *J* = 265.4 Hz), 121.9, 120.2, 118.4, 110.0 (q, *J* = 39.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −50.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_8BrClF_3N_2$, 374.9511; found, 374.9509.

2-(4-Bromophenyl)-6-chloro-3-(trifluoromethyl)imidazo[1,2-a]-pyridine ***(3p)***. Yield: 65 mg, 86%; white solid; mp 141−142 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.68 (d, *J* = 9.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.38 (dd, *J* = 9.5, 1.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.4 (q, *J* = 2.8 Hz), 144.4, 132.2, 131.53, 131.52, 131.0 (q, *J* = 1.9 Hz), 128.8, 123.6 (q, *J* = 270.7 Hz), 123.5 (q, *J* = 3.8 Hz), 122.7, 118.3, 110.1 (q, *J* = 44.1 Hz).^{19}F NMR (470 MHz, $CDCl_3$): δ −57.7. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_8BrClF_3N_2$, 374.9511; found, 374.9505.

6-Chloro-2-(4-chlorophenyl)-3-(trifluoromethyl)imidazo[1,2-a]-pyridine ***(3q)***. Yield: 54 mg, 82%; white solid; mp 90−92 °C [lit.[14] mp 83−85 °C]; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.69 (d, *J* = 9.5 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 9.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 147.4 (q, *J* = 2.4 Hz), 144.4, 135.5, 130.8 (q, *J* = 1.5 Hz), 130.7, 128.8, 128.6, 123.6 (q, *J* = 266.0 Hz), 123.4 (q, *J* = 3.9 Hz), 122.6, 118.3, 110.2 (q, *J* = 40.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ −57.7. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_8Cl_2F_3N_2$, 331.0017; found, 331.0011.

2-(4-Chlorophenyl)-3-(trifluoromethyl)benzo[d]imidazo[2,1-b]-thiazole ***(3a′)***. Yield: 59 mg, 83%; white solid; mp 174−176 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.40−7.44 (m, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.0, 148.7 (q, *J* = 2.5 Hz), 135.1, 132.0, 131.2, 130.8 (q, *J* = 1.5 Hz), 130.1, 128.4, 126.9, 125.7, 124.3, 121.3 (q, *J* = 266.3 Hz), 114.8 (q, *J* = 4.6 Hz), 112.6 (q, *J* = 40.8 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ −55.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_9ClF_3N_2S$, 353.0127; found, 353.0129.

2-(4-Bromophenyl)-3-(trifluoromethyl)benzo[d]imidazo[2,1-b]-thiazole ***(3b′)***. Yield: 67 mg, 84%; white solid; mp 191−193 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.51−7.54 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.0, 148.7 (q, *J* = 1.2 Hz), 132.0, 131.6, 131.4, 131.1, 130.1 (q, *J* = 2.7 Hz), 126.9, 125.8, 124.4, 123.4, 121.3 (q, *J* = 263.5 Hz), 114.8, 112.6 (q, *J* = 38.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ −55.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_9BrF_3N_2S$, 396.9622; found, 396.9619.

2-(4-Chlorophenyl)quinoxaline ***(4b)***. Yield: 1119 mg, 93%; yellow solid; mp 130−132 °C [lit.[13d] mp 135−137 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.25−8.31 (m, 2H), 8.22 (d, *J* = 8.5 Hz, 2H), 7.84−7.93 (m, 2H), 7.60 (d, *J* = 8.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.8, 142.4, 141.9, 140.4, 137.0, 134.7, 131.0, 130.9, 130.4, 129.6, 128.9, 128.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{10}ClN_2$, 241.0533; found, 241.0529.

2-(4-Fluorophenyl)quinoxaline ***(4c)***. Yield: 1017 mg, 91%; yellow solid; mp 119−120 °C [lit.[13d] mp 119−121 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 8.25 (d, *J* = 9.0 Hz, 1H), 8.24 (d, *J* = 9.0 Hz, 1H), 8.14−8.19 (m, 2H), 7.76−7.86 (m, 2H), 7.29 (t, *J* = 8.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.3 (d, *J* = 249.1 Hz), 150.8, 142.9, 142.3, 141.4, 132.9, 130.5, 129.7, 129.6, 129.5 (d, *J* = 8.7 Hz), 129.1, 116.3 (d, *J* = 21.7 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{10}FN_2$, 225.0828; found, 225.0826.

2-(4-(Trifluoromethyl)phenyl)quinoxaline ***(4d)***. Yield: 1289 mg, 94%; yellow solid; mp 147−148 °C [lit.[13d] mp 143−144 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H), 8.34 (d, *J* = 8.1 Hz, 2H), 8.18 (t, *J* = 8.0 Hz, 2H), 7.79−7.86 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.3, 142.7, 142.3, 141.7, 140.0, 132.0 (q, *J* = 32.5 Hz), 130.8, 130.4, 129.8, 129.1, 127.8, 126.1, 124.0 (q, *J* = 270.8 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{10}F_3N_2$, 275.0796; found, 275.0798.

6,7-Dimethyl-2-phenylquinoxaline ***(4g)***. Yield: 1043 mg, 89%; yellow solid; mp 125−127 °C [lit.[13d] mp 130−131 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.25 (s, 1H), 8.18−8.22 (m, 2H), 7.96 (s, 1H), 7.91 (s, 1H), 7.53−7.62 (m, 3H), 2.55 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.1, 141.5, 141.4, 141.3, 140.9, 139.4, 136.7, 130.2, 129.2, 128.6, 127.4, 20.5, 20.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{15}N_2$, 235.1235; found, 235.1226.

6,7-Dimethyl-2-(4-(trifluoromethyl)phenyl)quinoxaline ***(4h)***. Yield: 1390 mg, 92%; yellow solid; mp 120−123 °C [lit.[13e] mp 109−111 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.30 (d, *J* = 8.1 Hz, 2H), 7.91 (d, *J* = 5.0 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 2.54 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.4, 141.6, 141.5, 141.3, 141.2, 140.1, 131.6 (q, *J* = 32.5 Hz), 128.7, 127.7, 127.6, 126.0, 123.9 (q, *J* = 269.7 Hz), 20.5, 20.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{14}F_3N_2$, 303.1109; found, 303.1107.

6,7-Dimethyl-2-(4-nitrophenyl)quinoxaline ***(4i)***. Yield: 1271 mg, 91%; yellow solid; mp 135−137 °C [lit.[13f] mp 197−200 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 2H), 8.00−8.03 (m, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 2.57 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.6, 142.0, 141.9, 141.5, 140.7, 140.0, 139.4, 128.7, 127.7, 127.3, 126.1, 20.52, 20.51. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{14}N_3O_2$, 280.1086; found, 280.1087.

2-Phenyl-8-(trifluoromethyl)quinoxaline ***(5a)***. Yield: 31 mg, 56%; white solid; mp 120−122 °C; [silica gel (8:1 hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 9.46 (s, 1H), 8.29−8.35 (m, 3H), 8.14 (d, *J* = 7.4 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.55−7.63 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 151.6, 143.6, 141.4, 139.3, 135.9, 133.5, 130.8 (q, *J* = 4.2 Hz), 129.3, 128.8, 128.5, 127.8 (q, *J* = 29.9 Hz), 127.7, 123.7 (q, *J* = 266.6 Hz). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{10}F_3N_2$, 275.0796; found, 275.0790.

2-(4-Chlorophenyl)-8-(trifluoromethyl)quinoxaline ***(5b)***. Yield: 33 mg, 53%; yellow solid; mp 150−153 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 9.43 (s, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 2H), 8.15 (d, *J* = 7.2 Hz, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.5, 143.2, 141.5, 139.1, 137.3, 134.3, 133.5, 129.5, 128.9, 128.7 (q, *J* = 3.9 Hz), 128.2, 128.0 (q, *J* = 29.9 Hz), 123.6 (q, *J* = 263.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −59.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9ClF_3N_2$, 309.0406; found, 309.0401.

2-(4-Fluorophenyl)-8-(trifluoromethyl)quinoxaline ***(5c)***. Yield: 29 mg, 50%; yellow solid; mp 181−183 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.30−8.38 (m, 3H), 8.17 (d, *J* = 7.3 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 7.6, 5.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.7 (d, *J* = 250.2 Hz), 150.6, 143.2, 141.2, 133.4, 132.1 (d, *J* = 1.8 Hz), 129.8 (d, *J* = 8.6 Hz), 128.7 (q, *J* = 5.2 Hz), 128.2, 128.2 (q, *J* = 29.2 Hz), 128.1, 122.3 (q, *J* = 271.0 Hz), 116.4 (d, *J* = 21.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −59.6, δ −109.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9F_4N_2$, 293.0702; found, 293.0692.

8-(Trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)quinoxaline ***(5d)***. Yield: 36 mg, 53%; white solid; mp 159−161 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.43 (d, *J* = 8.1 Hz, 2H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 7.2 Hz, 1H), 7.84−7.88 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.1, 143.4, 141.8, 139.2, 139.1, 133.6, 132.5 (q, *J* = 32.5 Hz), 128.9 (q, *J* = 5.4 Hz), 128.7, 128.3 (q, *J* = 30.1 Hz), 128.0, 126.2 (q, *J* = 3.5 Hz), 123.9 (q, *J* = 271.8 Hz), 122.2 (q, *J* = 272.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −59.7, −62.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_9F_6N_2$, 343.0670; found, 343.0661. Single crystal was obtained using EtOAc/*n*-hexane (5:1).

2-(4-Nitrophenyl)-8-(trifluoromethyl)quinoxaline ***(5e)***. Yield: 34 mg, 53%; yellow solid; mp 218−220 °C; [silica gel (8:1 hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 8.52 (d, *J* = 9.2 Hz, 2H), 8.47 (d, *J* = 9.0 Hz, 2H), 8.39 (dd, *J* = 8.5, 0.8 Hz, 1H),

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8.23 (d, J = 7.3 Hz, 1H), 7.91 (t, J = 7.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.2, 143.3, 141.9, 141.6, 139.0, 133.6, 129.3, 129.1(q, J = 4.7 Hz), 128.6, 128.5 (q, J = 30.0 Hz), 128.4, 124.4, 123.5 (q, J = 272.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −59.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_9F_3N_3O_2$, 320.0647; found, 320.0645.

4-(8-(Trifluoromethyl)quinoxalin-2-yl)benzonitrile ***(5f)***. Yield: 31 mg, 52%; white solid; mp 250−252 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.51 (s, 1H), 8.46 (td, J = 8.4, 1.7 Hz, 2H), 8.38 (dd, J = 8.4, 0.6 Hz, 1H), 8.22 (d, J = 7.2 Hz, 1H), 7.92 (d, J = 7.8 Hz, 2H), 7.90 (t, J = 8.5 Hz, 1H).^{19}F NMR (376 MHz, $CDCl_3$): δ −59.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_9F_3N_3$, 300.0749; found, 300.0748.

6,7-Dimethyl-2-phenyl-8-(trifluoromethyl)quinoxaline ***(5g)***. Yield: 33 mg, 55%; white solid; mp 149−151 °C; [silica gel (8:1 hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.29−8.33 (m, 2H), 8.06 (s, 1H), 7.54−7.62 (m, 3H), 2.68 (q, J = 2.9 Hz, 3H), 2.60 (s, 3H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.2, 142.2, 141.5, 140.4, 139.2 (q, J = 4.3 Hz), 136.4, 132.1, 130.5,129.4, 129.2, 127.5, 125.5 (q, J = 27.6 Hz), 125.2 (q, J = 276.0 Hz), 21.8, 17.5 (q, J = 4.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −50.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}F_3N_2$, 303.1109; found, 303.1104.

6,7-Dimethyl-8-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyl)-quinoxaline ***(5h)***. Yield: 39 mg, 53%; white solid; mp 142−145 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.43 (d, J = 8.1 Hz, 2H), 8.12 (s, 1H), 7.86 (d, J = 8.1 Hz, 2H), 2.71 (q, J = 3.0 Hz, 3H), 2.64 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.6, 142.0, 141.9, 141.2, 139.7, 139.6, 132.2, 131.9, 127.7, 126.0 (q, J = 3.6 Hz), 125.8 (q, J = 32.4 Hz), 125.6 (q, J = 28.2 Hz), 124.0 (q, J = 276.0 Hz), 123.9 (q, J = 271.0 Hz), 21.8 (q, J = 2.8 Hz), 17.4 (q, J = 4.5 Hz).^{19}F NMR (376 MHz, $CDCl_3$): δ −50.8, −62.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{13}F_6N_2$, 371.0983; found, 371.0977.

6,7-Dimethyl-2-(4-nitrophenyl)-8-(trifluoromethyl)quinoxaline ***(5i)***. Yield: 33 mg, 48%; yellow solid; mp 219−221 °C; [silica gel (8:1 *n*-hexane/EtOAc)]. ^1H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 8.50 (d, J = 9.1 Hz, 2H), 8.45 (d, J = 9.1 Hz, 2H), 8.13 (s, 1H), 2.27 (q, J = 2.9 Hz, 3H), 2.65 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.9, 142.2, 141.9, 141.8, 140.0, 139.9, 132.2, 128.3 (q, J = 31.0 Hz), 128.2, 124.9 (q, J = 3.1 Hz), 124.3, 123.3 (q, J = 267.5 Hz), 120.5, 21.9, 17.5 (q, J = 3.7 Hz).^{19}F NMR (376 MHz, $CDCl_3$): δ −50.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}F_3N_3O_2$, 348.0960; found, 348.0945.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c00621.

^1H, ^{19}F, and $^{13}C\{^1H\}$ NMR spectra, and HRMS for compounds **3a−q**, **3a′−b′**, **5a−i** as well as X-ray crystallography data for compound **5d** (PDF)

Accession Codes

CCDC 2250178 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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