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Regioselective C–H chlorination: towards the sequential difunctionalization of phenol derivatives and late-stage chlorination of bioactive compounds†

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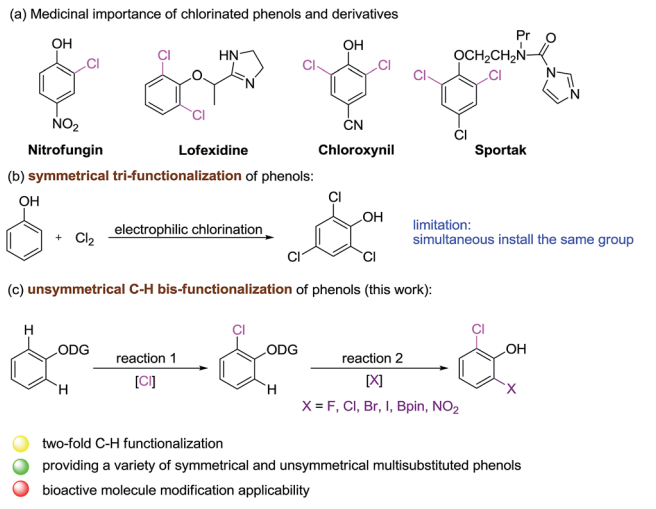
We have developed a protocol for the auxillary directed C–H chlorination of phenol derivatives using catalytic amounts of palladium acetate that is amenable to the late-stage chlorination of diflufenican and estrone. The 2-pyridine group allows for a highly efficient palladium-catalyzed chlorination and sequential *ortho* C–H functionalization reaction of phenol derivatives to produce a variety of symmetrical and unsymmetrical 2,4,6-trisubstituted phenols.

Introduction

Catalytic C–H activation/chlorination is one of the most efficient pathways to prepare aryl chlorides.[1,2] The resulting aryl chlorides serve as synthetic handles that participate in transition metal catalyzed cross-coupling reactions,[3] and they also function as precursors of organometallic reagents utilized for nucleophilic addition and substitution reactions.[4] Currently, their use in the development of site-selective chlorination of phenol is highly attractive as these compounds are prevalent in numerous pharmaceuticals and agrochemicals, such as Nitrofungin,[5a] Lofexidine,[5b] Chloroxynil[5c] and Sportak[5d] (Scheme 1a).

Currently, electrophilic aromatic substitution represents the leading strategy to obtain chlorinated phenols (Scheme 1b), yet producing a mixture of *ortho* and *para* substituted products. In addition, many efforts have been devoted toward the development of new routes to *ortho*-chlorinated phenols, including dehalogenation,[6] arene oxidation,[7] or *O*-methoxymethyl directed lithiation.[8] However, these methods suffer from limitations, such as requirement of harsh reaction condition and limited substrate scope. Recently, efficient methods have been developed. Snider demonstrated that bulky amine catalyzed *ortho*-chlorination of phenols by sulfuryl chloride.[9] Gustafson reported the preparation of *ortho*-chlorinated phenols by employing Nagasawa's bis-thiourea catalyst.[10] However, the former was only effective for electron-deficient phenols, whereas, the later often gave the undesired *para*-substituted phenols. Moreover, palladium-catalyzed C–H chlorination of phenyl carbamate was also reported.[2j] Up to now, the metal-catalyzed double C–H functionalization of phenol and their derivatives has not been explored and remains a great challenge. Therefore, an efficient and general methodology for the synthesis of densely functionalized phenol and derivatives is highly desired.

2-Aryloxypyridines are ubiquitous motif found in numerous biologically active molecules and pesticide.[11] During the past few years, palladium-catalyzed *ortho* mono-arylation,[12] -nitration,[13] -alkenylation,[14] -acylation,[15] -fluorination,[16]



Scheme 1 Synthesis and application of chloro-containing multi-functionalization phenols.

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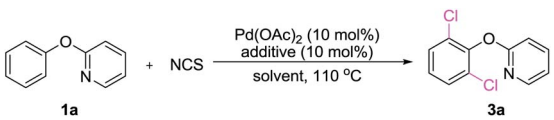
-acetoxylation[17] -alkoxylation,[18] and sulfonylation[19] of 2-aryloxypyridines have been developed. However, to the best of our knowledge, selective chlorination, bromination, iodination and borylation of 2-aryloxypyridines have not been reported. Herein, we report a new protocol for double symmetrical and unsymmetrical C–H functionalization of phenols, directed by a removable 2-pyridine group, enabling the introduction of two Cl or different functional groups (Cl/F, Br, I, NO_2 and Bpin) into *ortho* positions of phenols (Scheme 1c).

Results and discussion

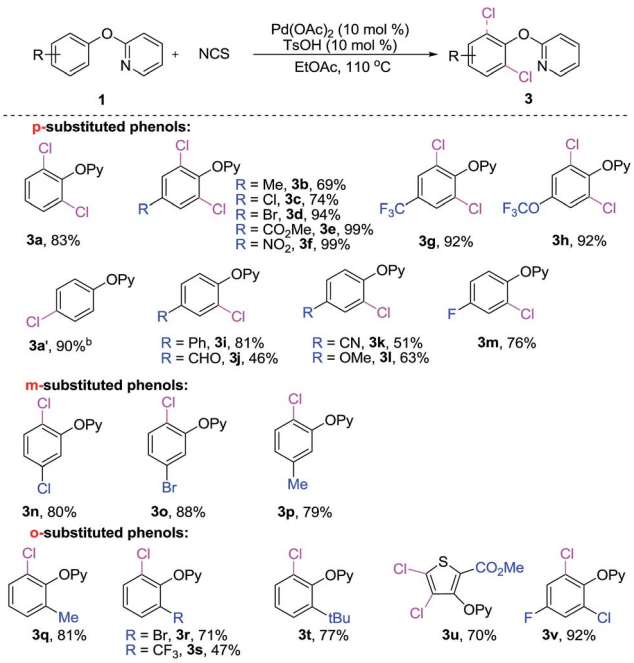
At the onset of this project, we selected 2-phenoxypyridine (**1a**) and NCS as a model substrates to examine the feasibility of palladium-catalyzed C–H chlorination reaction. As shown in Table 1, we observed that the choice of additive had a considerable impact on the chlorination reactions. Further exploration confirmed that TsOH was the most efficient promoter. However, no significant results could be achieved when $K_2S_2O_8$ or $Na_2S_2O_8$ used as the additive.[2h] It is worth noting that when the reaction was conducted in a coordinating solvent, such as DMF and dioxane, the desired product was not observed, and the starting material was recoveried. Lowering the amount of NCS decrease the yield of **3a** to 58%, and 10% of the monochlorinated product was isolated. Finally, the optimal yield of dichlorinated product **3a** was obtained when 2-phenoxypyridine and NCS (molar ration 1.0 : 3.0) were stirred in EtOAc in the presence of $Pd(OAc)_2$ (10 mol%) and TsOH (10 mol%) at 100 °C for 6 h. The practical utilization of current method was demonstrated by scaling up the reaction: when **1a** was subjected to dichlorination on 10 mmol scale, **3a** was obtained in 69% yield (entry 1). Interestingly, we found that when 2.0 equiv. of NCS in DMF, only *para*-chlorination product (**3a′**) was obtained (Scheme 2) in 90% yield without any trace of isomers.

Table 1 Optimization of double-chlorination reaction[a]



Entry	Additive	Equiv. of NCS	Solvent	Yield[b]%
1	TsOH	3.0	EtOAc	83 (69)[c]
2	AcOH	3.0	EtOAc	22
3	$K_2S_2O_8$	3.0	EtOAc	0
4	$Na_2S_2O_8$	3.0	EtOAc	0
5	AgOAc	3.0	EtOAc	0
6	TsOH	3.0	DMF	Trace
7	TsOH	3.0	Dioxane	Trace
8	TsOH	3.0	Toluene	62
9	TsOH	1.5	EtOAc	58

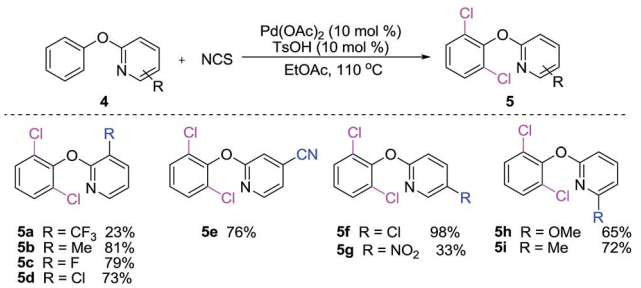
[a] Conditions: **1** (0.2 mmol), NCS (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), additive (10 mol%), solvent (2.0 mL), 110 °C, under N_2, 6 h. [b] Isolated yields. [c] 10 mmol gram-scalable reaction.



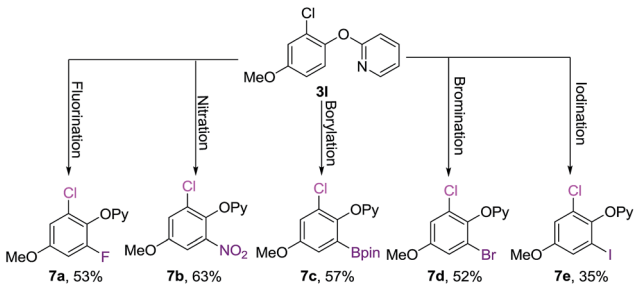
Scheme 2 C–H chlorination of 2-aryloxylpyridine. [a]Conditions: **1** (0.2 mmol), NCS (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), TsOH (10 mol%), EtOAc (2.0 mL), 110 °C, under N_2, 6 h, isolated yields. [b]NCS (2.0 equiv.), DMF (2.0 mL), 100 °C, under open air, 2 h, isolated yields.

With the optimal conditions in hand, we next examined the scope of 2-aryloxypyridines. As shown in Scheme 2, both electron-donating and -withdrawing groups at *ortho*-, *meta*-, or *para*-position of phenyl groups were well tolerated and afforded the corresponding chlorinated products in good to excellent yields. It is worth mentioning that the degree of chlorination is dependent on the substitutent on phenyl ring of 2-phenoxypyridine derivatives. When *para*-positions of 2-phenoxypyridine were substituted by a methyl (**3b**), chloride (**3c**), bromide (**3d**), ester (**3e**), nitro (**3f**), trifluoromethyl (**3g**) and trifluoromethoxy (**3h**), the corresponding dichlorination products were yields. In contrast, when 2-aryloxypyridine bearing a phenyl (**3i**), aldehyde (**3j**), nitrile (**3k**), methoxy (**3l**) and fluoro (**3m**) in *para*-position, affording the monochlorination products. Notably, the chlorination reaction was highly steric sensitive, in the cases of **1n–p**, the less congested C–H bonds of the *meta*-position of 2-phenoxypyridines (**3n–p**) were regioselectively chlorinated. Furthermore, the *ortho*-substituted 2-aryloxypyridines (**3q–v**) are also viable substrates in the current reaction, giving the corresponding products in good yields.

The diversity of 2-phenoxypyridines for dichlorination was examined. As shown in Scheme 3, we found that the dichlorination of 2-phenoxypyridine derivatives bearing electron-rich substitutents on pyridine rings reacted smoothly providing the corresponding dichlorinated products in fair to excellent yields (**5a–i**). The reactions of electron-deficient substrates, gave lower yields of products (**5a**, **5g**). Probably containing the electron-withdrawing substituents 2-phenoxypyridines weakens their coordinating abilities and lowers their activities of phenol's C–H bonds.



Scheme 3 C–H chlorination of 2-phenoxypyridine derivatives.



Scheme 5 Sequential C–H functionalization of 2-phenoxypyridine. [a]Reaction conditions: (a) **3l** (0.2 mmol), NFSI (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), EtOAc (2.0 mL), 110 °C, under N_2, 6 h, isolated yields. (b) **3l** (0.2 mmol), $AgNO_2$ (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv.), DCE (2.0 mL), 110 °C, under N_2, 48 h, isolated yields. (c) **3l** (0.2 mmol), B_2pin_2 (2.0 equiv.), $[RhCp^*Cl_2]_2$ (5 mol%), PCy_3 (30 mol%), EtOAc (2.0 mL), 100 °C, under N_2, 24 h, isolated yields. (d) **3l** (0.2 mmol), NBS (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), TsOH (10 mol%), EtOAc (2.0 mL), 110 °C, under N_2, 6 h, isolated yields. (e) **3l** (0.2 mmol), NIS (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), TsOH (10 mol%), EtOAc (2.0 mL), 110 °C, under N_2, 6 h, isolated yields.

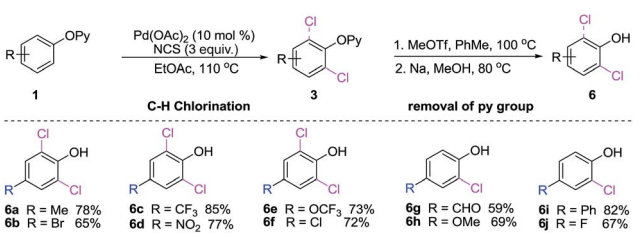
The advantage of 2-pyridyl directing group lies in the possibility of their removal to provide the structurally diversified 2,6-dichlorinated and 2-chlorinated phenols (Scheme 4).[12a] Significantly, the current reaction offer opportunities to synthesis *ortho*-chlorination phenols with electron-withdrawing groups (**6b–f**, **6j**) and electron-donating groups (**6a**, **6g–i**), which nicely complements the aforementioned approaches (Scheme 5).

With the palladium-catalyzed C–H chlorination protocol in hand, we tried to achieve sequential C–H functionalization access to a variety of polysubstituted phenols. We began using our current monoselective C–H chlorination, which is compatible with various substitutents (**3i–m**). Three grams of monochlorinated **3l** could be prepared in one pot *via* coupling of **1l** with NCS, further functionalizations of **3l** were explored. Subsequential C–H fluorination (**7a**),[17] nitration (**7b**),[14] bromination (**7d**) and iodination (**7e**) were quite successful, and the highly polysubstituted phenols **7a–e** were obtained in good yields. We also developed the Cp*Rh(III)-catalyzed C–H bond borylation of **3l** in the presence of PCy_3 at 100 °C in EtOAc within 12 h, and **7c** was afforded in 57% yield.

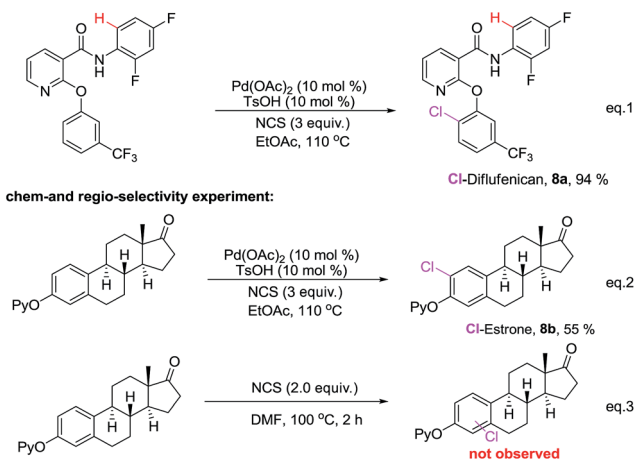
Next, we evaluated the utility of this work in the context of late-stage functionalization of known bioactive molecular (Scheme 6). Selective C–H functionalization of a phenyl ring is always a ticklish problem. Diflufenican acts as residual and foliar herbicide, contains two potential directing groups, a phenoxy pyridine and amide functionality. To our delight, its chlorination under the optimized conditions selectively occurred at the *para* position of aryloxy group gave the monochlorinated product **8a** in 94% yield. Meanwhile, to illustrate the chemoselectivity, the current palladium-catalyzed chlorination reaction and direct chlorination in DMF of estrone were comparatively studied (Scheme 6 eqn (2) and eqn (3)), in the presence of the palladium catalyst, the desired chlorinated product **8b** was isolated in 55% yield, in contrast, utilizing the aforementioned DMF reaction condition, we didn't observe appreciable chlorination.

A few control experiments were conducted to shed light on the mechanism of dichlorination reaction. Kinetic isotope effect (KIE) studies, between 2-phenoxypyridine and five-deuterated 2-phenoxypyridine showed a KIE of 1.8 (Scheme 7, eqn (1)). It suggested that the C–H dichlorination of phenols might proceeds the concerted metalation and deprotonation mechanism.[20] When complex **A**[12a] was used as the catalyst, 2-phenoxypyridine could be smoothly converted to **3a** with NCS (Scheme 7, eqn (2)), which suggesting that complex **A** is probably the catalytically active species.

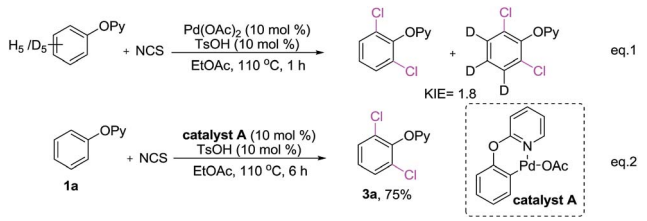
On the basis of these results and previous literatures, a plausible reaction mechanism was proposed in Scheme 8. The reaction begins with the pyridine-assisted *ortho* C–H activation of 2-aryloxypyridine to form cyclopalladate complex **A**, subsequently oxidative addition with NCS generated Pd(IV)



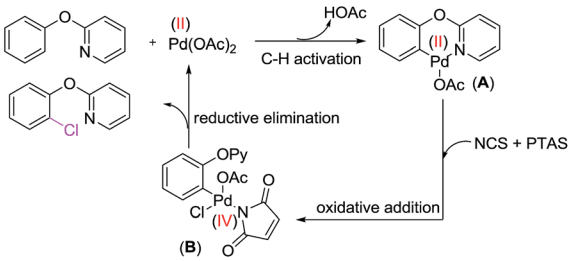
Scheme 4 Removal of pyridyl group.



Scheme 6 Late-stage C–H chlorination of diflufenican and estrone.



Scheme 7 Mechanistic studies.



Scheme 8 Proposed reaction mechanism.

intermediate **B**. Finally, reductive elimination of **B** afforded the chlorinated product and regenerates the catalyst. PTSA[2f] is probably to play dual roles in the activation N–Cl bond by protonating a carbonyl group of the NCS, and increasing the electrophilicity of the Pd(II) center by replacement of AcO^- with TsO^-.

Conclusions

In this work, we have described a convenient and straightforward strategy for C–H chlorination/sequential C–H functionalization of phenols, employing 2-pyridyl as the removable group. A variety of 2,4,6-trisubstituted phenols could be readily accessed through this step-by-step difunctionalization of both *ortho* C–H bonds of phenols. The present protocol could be applied to the late-stage of diflufenican and estrone, to facilitate drug development, especially for new herbicide agent.

General information

^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) and ^{19}F NMR (470 MHz) spectra were recorded in $CDCl_3$ solutions using a 500 MHz spectrometer. Alternatively, ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (377 MHz) spectra were recorded in $CDCl_3$ solutions using a 400 MHz spectrometer. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. All reactions were conducted using standard Schlenk techniques. Column chromatography was performed using EM silica gel 60 (300–400 mesh). ^{1}H NMR and ^{13}C NMR spectra are provided as ESI.† 2-phenoxy pyridine derivatives[21] were prepared according to the reported procedures. ^{1}H and ^{13}C spectra of known compounds were in accordance with those described in the literature.

General procedure of palladium-catalyzed C–H chlorination of 2-aryloxylpyridine

A 25 mL Schlenk tube equipped with a stir bar was charged with 2-aryloxylpyridine (0.2 mmol), NCS (0.6 mmol), $Pd(OAc)_2$ (10 mol%), TsOH (10 mol%). The tube was fitted with a rubber septum, and then it was evacuated and refilled with nitrogen three times. Under nitrogen, EtOAc (2 mL) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced by a Teflon screw cap under nitrogen flow. The reaction mixture was stirred at 100 °C for 6 h. After cooling down, the reaction mixture was diluted with 10 mL of ethyl ether, filtered through a pad of silica gel, concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to provide the corresponding product.

General procedure of DMF promoted C–H chlorination of 2-aryloxylpyridine to afford the *para*-chlorination product

A 25 mL Schlenk tube equipped with a stir bar was charged with 2-aryloxylpyridine NCS (2.0 equiv.), DMF (2 mL) were added in the Schlenk under open air, then obturated with Teflon screw-cap. The reaction mixture was stirred at 100 °C for 2 h. After it was cooled, the reaction mixture was diluted with 10 mL of ethyl ether, and filtered through a pad of silica gel, followed by washing the pad of silica gel with the same solvent (20 mL). The filtrate was washed with water (3 × 15 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to provide the corresponding product.

General procedure of removal of pyridyl group

To a solution of 2-(2,6-dichloro-4-methylphenoxy)pyridine (**3b**) (101 mg, 0.4 mmol) in dry toluene (10 mL), MeOTf (144 mg, 0.88 mmol) was added. The solution was stirred at 100 °C under N_2 atmosphere for 2 h. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under vacuum. The crude product was dissolved in dry methanol (2.0 mL) and then added to a solution of Na (276 mg, 12 mmol) in dry methanol (10 mL) under N_2 atmosphere. The reaction mixture was heated to reflux for 30 min, cooled to room temperature. After evaporating the solvent under vacuum, water (30 mL) was added, and the aqueous solution was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4. The solution was concentrated by vacuum and the residue was purified by column chromatography on silica gel (hexane/EtOAc: 10/1) to give the corresponding product **6a**.

2-(2,6-Dichlorophenoxy)pyridine (3a). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (40 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 3.5 Hz, 1H), 7.33 (t, J = 7.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.14 (t, J = 8.5 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.00 (t, J = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 147.4, 146.4, 139.6, 129.8, 128.8, 126.4, 118.7, 110.6; HRMS (TIC): calcd for $C_{11}H_8Cl_2NO$ $[M + H]^+$ 239.9978, found 239.9976.

2-(4-Chlorophenoxy)pyridine (3a′). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (37 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16–8.15 (m, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 6.97 (t, J = 5.6 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4, 152.7, 147.6, 139.6, 129.8, 129.6, 122.6, 118.8, 111.7; HRMS (TIC): calcd for $C_{11}H_8ClNO$ $[M + H]^+$ 206.0367, found 206.0365.

2-(2,6-Dichloro-4-methylphenoxy)pyridine (3b). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (35.1 mg, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 4.5 Hz, 1H), 7.65 (t, J = 7.0 Hz, 1H), 7.13 (s, 2H), 6.97–6.91 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 146.4, 142.9, 138.5, 135.7, 128.3, 128.1, 117.6, 109.6, 19.7; HRMS (TIC): calcd for $C_{12}H_{10}Cl_2NO$ $[M + H]^+$ 254.0134, found 254.0131.

2-(2,4,6-Trichlorophenoxy)pyridine (3c). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (35.1 mg, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, J = 4.5 Hz, 1H), 7.74 (t, J = 6.5 Hz, 1H), 7.40 (s, 2H), 7.08–7.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 147.3, 145.4, 139.8, 131.0, 130.4, 128.7, 128.1, 121.7, 118.9, 110.7; HRMS (TIC): calcd for $C_{11}H_7Cl_3NO$ $[M + H]^+$ 273.9588 found 273.9591.

2-(4-Bromo-2,6-dichlorophenoxy)pyridine (3d). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (59.6 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 4.5 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.55 (s, 2H), 7.07 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 147.4, 146.4, 139.6, 129.8, 128.8, 128.1, 16.4, 121.7, 118.7, 110.6; HRMS (TIC): calcd for $C_{11}H_7BrCl_2NO$ $[M + H]^+$ 317.9083, found 317.9085.

Methyl 3,5-dichloro-4-(pyridin-2-yloxy)benzoate (3e). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (59.1 mg, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 3H), 7.76 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 5.0 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 161.7, 150.2, 147.3, 139.9, 130.1, 130.0, 128.6, 119.1, 110.8, 52.7; HRMS (TIC): calcd for $C_{13}H_{10}Cl_2NO_3$ $[M + H]^+$ 298.0032, found 298.0030.

2-(2,6-Dichloro-4-nitrophenoxy)pyridine (3f). Following the general procedure, using 5 : 1 petroleum ether–EtOAc as the eluant afforded a white liquid (56.2 mg, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 2H), 8.04 (d, J = 6.0 Hz, 1H), 7.80 (t, J = 8.5 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 152.1, 147.2, 144.8, 140.1, 131.1, 124.2, 119.5, 110.8; HRMS (TIC): calcd for $C_{11}H_7Cl_2N_2O_3$ $[M + H]^+$ 284.9828, found 284.9825.

2-(2,6-Dichloro-4-(trifluoromethyl)phenoxy)pyridine (3g). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (56.2 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 5.0 Hz, 1H), 7.77 (t, J = 6.5 Hz, 1H), 7.67 (s, 2H), 7.11 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 149.5, 147.3, 140.0, 130.8, 128.9 (q, J_F = 33.8 Hz), 126.0 (q, J_F = 3.8 Hz), 122.7 (q, J_F = 271.2 Hz), 119.2, 110.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ −62.6 (s, 1F); HRMS (TIC): calcd for $C_{12}H_7Cl_2F_3NO$ $[M + H]^+$ 307.9852, found 307.9850.

2-(2,6-Dichloro-4-(trifluoromethoxy)phenoxy)pyridine (3h). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (59.3 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 6.5 Hz, 1H), 7.75 (t, J = 7.0 Hz, 1H), 7.30 (s, 2H), 7.08 (d, J = 8.5 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 147.3, 145.7 (q, J_F = 1.2 Hz), 145.5, 139.8, 130.6, 121.6, 120.3 (q, J_F = 256.2 Hz), 119.1, 110.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ −58.1 (s, 3F); HRMS (TIC): calcd for $C_{12}H_7Cl_2F_3NO_2$ $[M + H]^+$ 323.9801, found 323.9800.

2-((3-Chloro-[1,1′-biphenyl]-4-yl)oxy)pyridine (3i). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (45.6 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 6.0 Hz, 1H), 7.75 (t, J = 8.5 Hz, 1H), 7.60–7.54 (m, 4H), 7.46–7.37 (m, 4H), 7.10–7.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 162.1, 147.4, 145.5, 140.0, 137.7, 138.3, 129.9, 129.0, 128.2, 127.4, 127.0, 121.5, 118.8, 110.7; HRMS (TIC): calcd for $C_{17}H_{13}ClNO$ $[M + H]^+$ 282.0680, found 282.0684.

3-Chloro-4-(pyridin-2-yloxy)benzaldehyde (3j). Following the general procedure, using 4 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (21.3 mg, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.16 (d, J = 3.0 Hz, 1H), 8.01 (s, 1H), 7.84–7.76 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.09–7.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.8, 162.2, 154.9, 147.1, 140.4, 133.6, 131.4, 129.2, 128.3, 123.7, 119.5, 111.8; HRMS (TIC): calcd for $C_{12}H_9ClNO_2$ $[M + H]^+$ 234.0317, found 234.0315.

3-Chloro-4-(pyridin-2-yloxy)benzonitrile (3k). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded white liquid (23.3 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 3.5 Hz, 1H), 7.79–7.76 (m, 2H), 7.61–7.59 (m, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.09–7.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 154.0, 147.4, 140.0, 134.3, 131.7, 128.3, 124.2, 119.6, 117.4, 111.8, 109.6; HRMS (TIC): calcd for $C_{12}H_8ClN_2O$ $[M + H]^+$ 231.0320, found 231.0321.

2-(2-Chloro-4-methoxyphenoxy)pyridine (3l). Following the general procedure, using 5 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (29.4 mg, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 5.5 Hz, 1H), 7.71–7.66 (m, 1H), 7.31–7.20 (m, 1H), 7.03–6.91 (m, 4H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 156.8, 147.4, 140.0, 139.5, 129.8, 118.6, 114.5, 110.7, 110.5, 102.0, 55.9; HRMS (TIC): calcd for $C_{12}H_{11}ClNO_2$ $[M + H]^+$ 236.0473, found 236.0470.

2-(2-Chloro-4-fluorophenoxy)pyridine (3m). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (51.4 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18–8.12 (m, 1H), 7.72–7.66 (m, 1H), 7.23–7.17 (m, 1H), 7.10–6.97 (m, 3H), 6.90 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3 (d, J_F = 98.8 Hz), 160.4 (d, J_F = 22.5 Hz), 158.5 (d, J_F = 26.2 Hz), 147.5 (d, J_F = 26.2 Hz), 139.5 (d, J_F = 15.0 Hz), 124.7 (d, J_F = 10.0 Hz), 122.7 (d, J_F = 8.8 Hz), 118.6 (d, J_F = 20.0 Hz), 117.6 (d, J_F = 26.2 Hz), 116.2 (d, J_F = 22.5 Hz), 111.2 (d, J_F = 46.2 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −118.5 (s, 1F); HRMS (TIC): calcd for $C_{11}H_8ClFNO$ $[M + H]^+$ 224.0273, found 224.0275.

2-(2,5-Dichlorophenoxy)pyridine (3n). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (38.1 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26–8.21 (m, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.54–7.26 (m, 3H), 7.04–6.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 150.4, 147.5, 139.8, 133.0, 131.1, 128.3, 126.2, 124.2, 119.0, 111.3; HRMS (TIC): calcd for $C_{11}H_8Cl_2NO$ $[M + H]^+$ 239.9978, found 239.9976.

2-(5-Bromo-2-chlorophenoxy)pyridine (3o). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (49.7 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.77 (t, J = 7.2 Hz, 1H), 7.42 (s, 1H), 7.39–7.34 (m, 2H), 7.06–7.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 150.3, 147.5, 139.8, 131.5, 129.1, 127.0, 126.6, 120.4, 119.1, 111.5; HRMS (TIC): calcd for $C_{11}H_8BrClNO$ $[M + H]^+$ 283.9473, found 283.9474.

2-(2-Chloro-5-methylphenoxy)pyridine (3p). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (34.8 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27–8.22 (m, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.41–7.32 (m, 1H), 7.09–7.02 (m, 3H), 6.95 (d, J = 8.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 148.4, 146.5, 138.4, 137.2, 129.1, 125.9, 123.3, 123.1, 117.4, 110.0, 20.0; HRMS (TIC): calcd for $C_{12}H_{11}ClNO$ $[M + H]^+$ 220.0524, found 220.0523.

2-(2-Chloro-6-methylphenoxy)pyridine (3q). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (35.5 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 7.16–7.12 (m, 1H), 7.01–6.99 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 147.0, 146.5, 138.5, 132.7, 128.4, 126.9, 126.8, 124.9, 117.2, 109.2, 15.8; HRMS (TIC): calcd for $C_{12}H_{11}ClNO$ $[M + H]^+$ 220.0524, found 220.0523.

2-(2-Bromo-6-chlorophenoxy)pyridine (3r). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (40.1 mg, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 4.5 Hz, 1H), 7.74 (t, J = 7.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.09–6.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.9, 147.5, 147.3, 139.6, 131.8, 129.7, 129.5, 126.9, 118.9, 118.7, 110.7; HRMS (TIC): calcd for $C_{11}H_8BrClNO$ $[M + H]^+$ 283.9473, found 283.9474.

2-(2-Chloro-6-(trifluoromethyl)phenoxy)pyridine (3s). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded yellow liquid (25.7 mg, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.70 (t, J = 8.4 Hz, 2H), 7.38–7.32 (m, 2H), 7.12 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 151.8, 147.5, 139.6, 138.4, 132.9, 127.1 (q, J_F = 5.0 Hz), 124.5, 123.6, 123.0 (q, J_F = 151.2 Hz), 119.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ −61.8 (s, 3F); HRMS (TIC): calcd for $C_{12}H_8ClF_3NO$ $[M + H]^+$ 274.0241, found 274.0240.

2-(2-(*tert*-Butyl)-6-chlorophenoxy)pyridine (3t). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a brown liquid (40.1 mg, 77% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.17 (d, J = 4.5 Hz, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.15–7.10 (m, 2H), 7.01–6.91 (m, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 147.1, 146.6, 143.7, 138.3, 128.0, 127.4, 124.9, 124.6, 116.9, 109.7, 34.3, 29.5, 28.2, 17.4; HRMS (TIC): calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$ 262.0993, found 262.0990.

Methyl-4,5-dichloro-3-(pyridin-2-yloxy)thiophene-2-carboxylate (3u). Following the general procedure, using 8 : 1 petroleum ether–EtOAc as the eluant afforded a brown liquid (42.3.3 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 5.0 Hz, 1H), 7.66 (t, J = 6.5 Hz, 1H), 7.33 (s, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.93 (t, J = 7.0 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 159.4, 148.7, 146.2, 138.6, 123.5, 121.4, 118.6, 117.8, 109.8, 51.1; HRMS (TIC): calcd for $C_{11}H_8Cl_2NO_3S$ $[M + H]^+$ 303.9597, found 303.9595.

2-(2,6-Dichloro-4-fluorophenoxy)pyridine (3v). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (48.4 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 4.0 Hz, 1H), 7.66 (t, J = 7.0 Hz, 1H), 7.08 (t, J = 8.0 Hz, 2H), 6.99–6.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 158.7, 156.7, 146.2, 142.1, 138.7, 129.3 (d, J_F = 12.5 Hz), 117.9, 115.2 (d, J_F = 25.0 Hz), 109.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −113.9 (s, 1F); HRMS (TIC): calcd for $C_{11}H_7Cl_2FNO$ $[M + H]^+$ 257.9883, found 257.9885.

2-(2,6-Dichlorophenoxy)-3-(trifluoromethyl)pyridine (5a). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (14.1 mg, 23% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.0 Hz, 1H), 7.42–7.33 (m, 1H), 7.25–7.22 (m, 1H), 7.11–7.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 150.7, 149.0, 137.1 (q, J_F = 5.0 Hz), 130.6, 128.1 (q, J_F = 108.8 Hz), 127.9, 126.7, 120.0 (q, J_F = 271.2 Hz), 117.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ −63.4 (s, 3F); HRMS (TIC): calcd for $C_{12}H_7Cl_2F_3NO$ $[M + H]^+$ 307.9852, found 307.9850.

2-(2,6-Dichlorophenoxy)-3-methylpyridine (5b). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (41.1 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J = 5.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.04 (t, J = 8.0 Hz, 1H), 6.84–6.82 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 145.9, 143.4, 138.7, 128.7, 127.6, 125.1, 119.8, 117.8, 14.8; HRMS (TIC): calcd for $C_{12}H_{10}Cl_2NO$ $[M + H]^+$ 254.0134, found 254.0131.

2-(2,6-Dichlorophenoxy)-3-fluoropyridine (5c). Following the general procedure, using 10 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (40.8 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.26–7.18 (m, 1H), 7.11 (t, J = 8.5 Hz, 3H), 7.00 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7 (d, J_F = 6.2 Hz), 150.6 (d, J_F = 200.0 Hz), 144.0 (d, J_F = 75 Hz), 143.1, 129.9 (d, J_F = 45 Hz), 126.8 (d, J_F = 81.2 Hz), 124.4 (d, J_F = 8.8 Hz), 123.4 (d, J_F = 31.2 Hz), 118.8 (d, J_F = 18.8 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −137.7 (s, 1F); HRMS (TIC): calcd for $C_{11}H_7Cl_2FNO$ $[M + H]^+$ 257.9883, found 257.9885.

3-Chloro-2-(2,6-dichlorophenoxy)pyridine (5d). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (40.1 mg, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 3.5 Hz, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 8.0 Hz, 1H), 7.01–6.98 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 146.3, 144.9, 139.5, 129.6, 128.8, 126.7, 119.8, 118.3; HRMS (TIC): calcd for $C_{11}H_7Cl_3NO$ $[M + H]^+$ 273.9588, found 273.9591.

6-(2,6-Dichlorophenoxy)nicotinonitrile (5e). Following the general procedure, using 5 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (40.4 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 6.5 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.22–7.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 151.9, 142.6, 129.4, 128.9, 127.2, 122.0, 120.9, 116.5, 111.5; HRMS (TIC): calcd for $C_{12}H_7Cl_2N_2O$ $[M + H]^+$ 264.9930, found 264.9927.

5-Chloro-2-(2,6-dichlorophenoxy)pyridine (5f). Following the general procedure, using 15 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (53.3 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 2.0 Hz, 1H), 7.71–7.68 (m, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 146.1, 145.7, 139.6, 129.7, 128.8, 126.7, 126.3, 111.7; HRMS (TIC): calcd for $C_{11}H_7Cl_3NO$ $[M + H]^+$ 273.9588, found 273.9591.

2-(2,6-Dichlorophenoxy)-5-nitropyridine (5g). Following the general procedure, using 5 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (18.7 mg, 33% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (d, J = 2.5 Hz, 1H), 8.55 (d, J = 6.0 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.24–7.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 145.6, 144.8, 141.0, 135.3, 129.3, 128.9, 127.3, 111.0; HRMS (TIC): calcd for $C_{11}H_7Cl_2N_2O_3$ $[M + H]^+$ 284.9828, found 284.9825.

2-(2,6-Dichlorophenoxy)-6-methoxypyridine (5h). Following the general procedure, using 2 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (35.0 mg, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 3.5 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.93 (d, J = 3.0 Hz, 2H), 6.90–6.76 (m, 2H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 154.9, 153.6, 140.7, 129.2, 124.8, 121.1, 110.6, 109.2, 54.6; HRMS (TIC): calcd for $C_{12}H_{10}Cl_2NO_2$ $[M + H]^+$ 270.0083, found 270.0084.

2-(2,6-Dichlorophenoxy)-6-methylpyridine (5i). Following the general procedure, using 5 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (36.6 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 6.4 Hz, 2H), 7.22–7.15 (m, 3H), 6.90 (d, J = 6.8 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 154.4, 139.7, 129.7, 124.9, 124.6, 122.1, 120.2, 109.4, 22.4; HRMS (TIC): calcd for $C_{12}H_{10}Cl_2NO$ $[M + H]^+$ 254.0134, found 254.0131.

2-(2-Chloro-6-fluoro-4-methoxyphenoxy)pyridine (7a). A 25 mL Schlenk tube equipped with a stir bar was charged with **3l** (0.2 mmol), NFSI (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), EtOAc (2.0 mL), 110 °C, under N_2, 6 h, using 10 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (26.7 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J = 4.5 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.05–7.00 (m, 2H), 6.95 (s, 1H), 6.82–6.68 (m, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 155.8, 146.3 (d, J_F = 3.8 Hz), 138.6 (d, J_F = 7.5 Hz), 134.5, 128.7 (d, J_F = 23.8 Hz), 127.4, 117.7 (d, J_F = 15.0 Hz), 113.5, 109.6 (d, J_F = 27.5 Hz), 101.0 (d, J_F = 22.5 Hz), 54.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ −123.4 (s, 1F); HRMS (TIC): calcd for $C_{12}H_{10}ClFNO_2$ $[M + H]^+$ 254.0379, found 254.0382.

2-(2-Chloro-4-methoxy-6-nitrophenoxy)pyridine (7b). A 25 mL Schlenk tube equipped with a stir bar was charged with **3l** (0.2 mmol), $AgNO_2$ (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv.), DCE (2.0 mL), 110 °C, under N_2, 48 h, using 5 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (35.3 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 4.5 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.93–6.87 (m, 2H), 6.78–6.76 (m, 1H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 155.8, 146.4, 138.9, 138.5, 128.8, 124.4, 117.6, 113.5, 112.5, 109.5, 54.9; HRMS (TIC): calcd for $C_{12}H_{10}ClN_2O_4$ $[M + H]^+$ 281.0324, found 281.0323.

2-(2-Chloro-4-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pyridine (7c). A 25 mL Schlenk tube equipped with a stir bar was charged with **3l** (0.2 mmol), B_2pin_2 (2.0 equiv.), $[RhCp^*Cl_2]_2$ (5 mol%), PCy_3 (30 mol%), EtOAc (2.0 mL), 100 °C, under N_2, 24 h, using 10 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (41.1 mg, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 4.5 Hz, 1H), 7.66 (t, J = 8.5 Hz, 1H), 6.96–6.92 (m, 2H), 6.88 (s, 2H), 3.74 (s, 3H), 1.51 (s, 6H), 1.18 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 156.8, 147.5, 140.0, 139.5, 129.8, 126.1, 125.4, 118.6, 114.5, 113.6, 110.6, 83.5, 65.6, 56.7, 55.9, 25.0, 24.6; HRMS (TIC): calcd for $C_{18}H_{22}BClNO_4$ $[M + H]^+$ 362.1325, found 362.1323.

2-(2-Bromo-6-chloro-4-methoxyphenoxy)pyridine (7d). A 25 mL Schlenk tube equipped with a stir bar was charged with **3l** (0.2 mmol), NBS (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), TsOH (10 mol%), EtOAc (2.0 mL), 110 °C, under N_2, 6 h using 10 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (32.3 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.04–6.98 (m, 2H), 6.94 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 156.8, 147.4, 139.9, 139.5, 129.8, 125.4, 118.6, 114.5, 111.0, 110.6, 55.9; HRMS (TIC): calcd for $C_{12}H_{10}BrClNO_2$ $[M + H]^+$ 313.9578, found 313.9580.

2-(2-Chloro-6-iodo-4-methoxyphenoxy)pyridine (7e). A 25 mL Schlenk tube equipped with a stir bar was charged with **3l** (0.2 mmol), NIS (3.0 equiv.), $Pd(OAc)_2$ (10 mol%), TsOH (10 mol%), EtOAc (2.0 mL), 110 °C, under N_2, 6 h, using 10 : 1 petroleum ether–EtOAc as the eluant afforded a light yellow liquid (25.3 mg, 35% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 5.0 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 6.97–6.93 (m, 2H), 6.88 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4, 157.2, 147.5, 143.3, 139.4, 127.8, 124.4, 118.3, 115.6, 113.7, 110.8, 55.8; HRMS (TIC): calcd for $C_{12}H_{11}ClINO_2$ $[M + H]^+$ 361.9439, found 361.9437.

2-(2-Chloro-5-(trifluoromethyl)phenoxy)-*N*-(2,4-difluorophenyl)-nicotinamide (8a). Following the general procedure, using 8 : 1 petroleum ether–EtOAc as the eluant afforded a light brown liquid (80.7 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.71–8.69 (m, 1H), 8.52–8.47 (m, 1H), 8.24–8.22 (m, 1H), 7.68–7.55 (m, 3H), 7.29–7.26 (m, 1H), 6.95–6.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 158.8 (dd, J_F = 245.0, 11.2 Hz), 158.6, 152.9 (dd, J_F = 246.2, 11.2 Hz), 150.4, 148.5, 142.9, 131.4, 131.2, 130.6 (q, J_F = 33.8 Hz), 124.2, 123.9 (q, J_F = 3.8 Hz), 123.1 (d, J_F = 7.5 Hz), 122.8 (dd, J_F = 10.0, 3.8 Hz), 122.0 (q, J_F = 3.8 Hz), 120.4, 116.6, 111.3 (dd, J_F = 21.2, 3.8 Hz), 103.6 (dd, J_F = 26.2, 23.8 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −125.3 (s, 1F), −114.5 (s, 1F), −62.5 (s, 3F). HRMS (TIC): calcd for $C_{19}H_{11}ClF_5N_2O_2$ $[M + H]^+$ 429.0424, found 429.0423.

(8*R*,9*S*,13*S*,14*S*)-2-Chloro-8,9,13,14-tetramethyl-3-(pyridin-2-yloxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta

[*a*]phenanthren-17-one (8b). Following the general procedure, using 10 : 1 petroleum ether–EtOAc as the eluant afforded a yellow liquid (46.5 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.77 (t, J = 6.8 Hz, 1H), 7.39 (s, 1H), 7.05–7.01 (m, 3H), 3.06–3.03 (m, 1H), 2.93 (s, 2H), 2.59–2.52 (m, 1H), 2.46–2.41 (m, 2H), 2.19–2.09 (m, 2H), 1.94–1.90 (m, 2H), 1.74–1.52 (m, 4H), 1.30 (s, 1H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6, 162.9, 147.4, 147.2, 139.9, 137.4, 136.3, 127.4, 124.3, 123.8, 118.5, 111.2, 82.9, 47.3, 45.8, 45.7, 43.8, 36.5, 32.3, 28.7, 26.2, 25.2, 15.8; HRMS (TIC): calcd for $C_{26}H_{31}ClNO_2$ $[M + H]^+$ 424.2038, found 424.2039.

Conflicts of interest

The authors declare no competing financial interest.

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