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Palladium-Catalyzed Regioselective C-H Functionalization of Arenes Substituted by Two *N*-Heterocycles and Application in Late-Stage Functionalization

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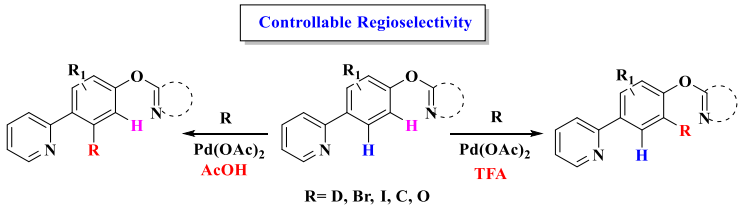


Abstract

Reported herein is a Pd-catalyzed regioselective C-H activation method that is used for C-H deuteration, carbonylation, halogenation, and oxidation of arene substrates substituted by two *N*-heterocycles. When conducted in acetic acid (AcOH) these reactions occur at the five-membered palladacycle sites, whereas they switch to the six-membered palladacycle sites in trifluoroacetic acid (TFA). This controllable regioselective C-H activation is applied for late-stage functionalization (LSF) of bioactive molecules. A mechanism study indicated that the regioselectivity is achieved by Brönsted acid-Lewis base interactions and electronic effects (in TFA) and the different kinetic stabilities of palladacycle intermediates (in AcOH).

Introduction

Site-specifically deuterium-labelled compounds have been widely used in the pharmaceutical industry because of their ability to improve the half-life time and toxicity profiles of small molecules.[1] For instance, replacement of the hydrogen with deuterium at the chiral center of a thalidomide analogue (Fig.1a, **1**) increases the exposure for each enantiomer in vivo without changing their pharmacokinetics.[1c] Another example, deutetrabenazine (Fig.1a, **2**), has recently become the first deuterated drug approved by the US FDA, which has deuterium incorporated at its methoxyl group and exhibits a longer half-life time and lower toxicity than its parent compound.[1d] These and other recent examples have highlighted that deuterium-incorporation is a practical strategy for the development of new drug candidates, often generating new leads from old drugs with improved metabolic stability and efficacy in vivo. e.g. **3** (Fig.1a,).[2]

Transition-metal catalyzed C-H activation has been a versatile method to manipulate inert C-H bonds during the past decade.[3] Many excellent studies have

applied directed C-H activation for the *ortho*-deuteration of relatively simple molecules.[4] However, the application of directed C-H activation for late-stage functionalization (LSF) of *N*-heterocycle-containing bioactive molecules has been limited because of the strongly coordinating ability of Lewis basic heterocycles with metals, which can result in catalyst arrest or the generation of undesired products.[5] To date, several creative methods have been developed to overcome these limitations (Fig.1b).[6] In 2014, Patterson and workers reported that a pyridine group was blocked by a Lewis acid or an *N*-oxide to avoid Pd-catalyst arrest.[6a] Another report by Yu et al. in 2014 demonstrated that a simple *N*-methoxy amide group could serve as both a directing group and an anionic ligand that overrode the conventional positional selectivity patterns.[6b] In 2016, Ackermann and his colleagues developed cobalt-catalyzed C-H amidation that tolerated strongly coordinating nitrogen heterocycles.[6c] Very recently, Yu and co-workers used an oxazoline-based directing group to override the poisoning effect of a wide range of heterocycle substrates in LSF of *N*-heterocycle-containing molecules.[6d] Because the structures of many druggable molecules or other biological probes contain multiple similar *N*-hetrocycles (e.g., pyridine groups),[7] the metal-catalyzed regioselective C-H functionalization of such molecules are still challenging, and the regioselective LSF of molecules with multiple *N*-hetrocycles is even more difficult.

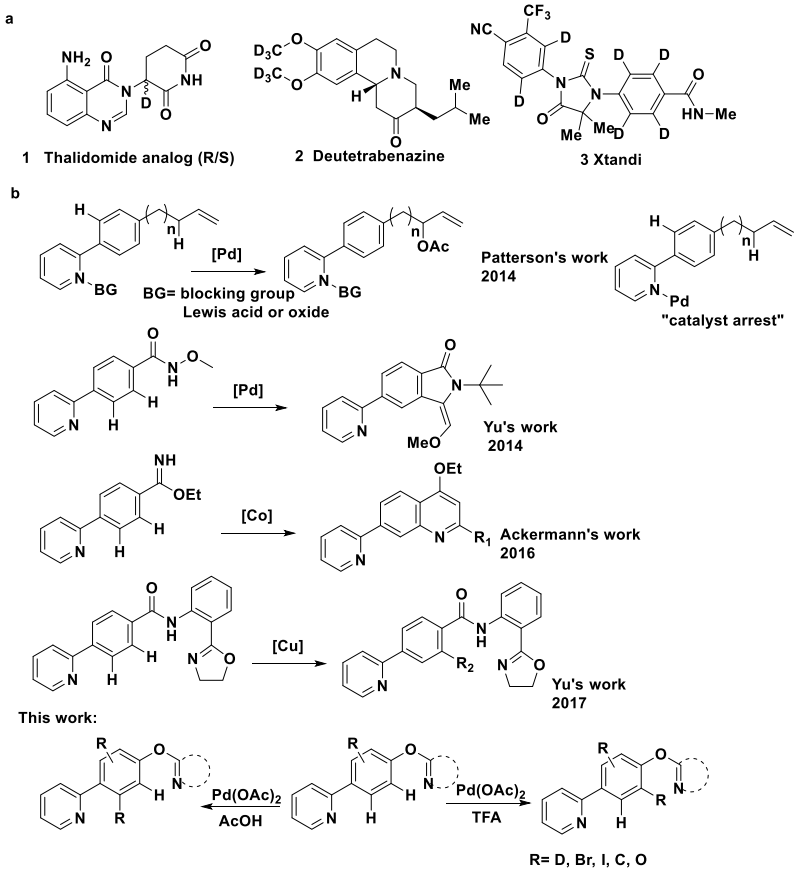


Figure 1. a: D-incorporation in drug molecules; **b:** C-H activations overcoming the limitations of heterocycles.

Generally, *N*-heterocycles act as directing groups in Pd-catalysed *ortho*-C-H

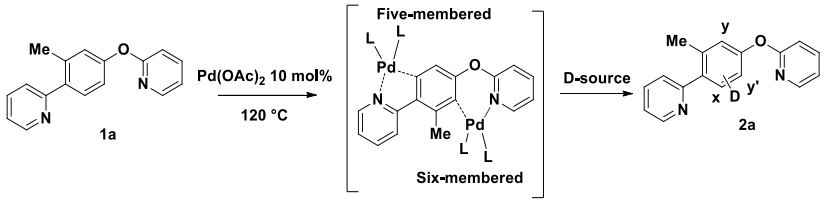
activation through the formation of five-membered or six-membered palladacycles via concerted metalation deprotonation.[8] These two types of intermediate exhibit characteristic differences in their reactivities in subsequent transformation reactions.[9] We envisioned that this differential reactivity could be utilized to achieve regioselective C-H functionalization in substrates that contain multiple *N*-heterocycles, particularly in druggable molecules or natural products. Due to the emerging importance of deuterium at specific positions in drug molecules, we initially intended to explore this speculation in Pd-catalyzed C-H deuteration of arenes. This regioselective reaction was successfully applied for the late stage functionalization of drug candidates and extended to the regioselective Carbon-Carbon, Carbon-halegon and Carbon-Oxygen bond formation reactions.

Results and Discussion

The arene 2-(3-methyl-4-(pyridin-2-yl)phenoxy)pyridine **1a**, with its two pyridine directing groups, was chosen as a model substrate. In this molecule, one pyridine group (PG-6) is connected with the phenyl core via an *O*-atom, which can form a six-membered palladacycle intermediate; the other pyridine group (PG-5) is directly linked to the phenyl core that alternatively gives a five-membered palladacycle intermediate (Table 1). When treating **1a** with 10 mol% $Pd(OAc)_2$ in d_4-AcOH at 120 °C, deuterated product **2a** was obtained with 81% D-incorporation at the five-membered palladacycle site (*x* site) and 11% D-incorporation at the six-membered palladacycle sites (*y* and *y'* sites) after 48 h reaction (Table 1, entry 1). Several base additives were then examined. All the buffer-liked reaction systerms gave lower rate of D-incorporation (Table 1, entry 2, 5-10). Further screening revealed that the amount of base (Table 1, entry 3-4), amount of solvent or reaction time (Table 1, entry 11) couldn't improve the rate of D-incorporation or selectvity in d_4-AcOH. Interestingly, when *d*-TFA was chosen as the deuterium source without additives, C-H deuteration mainly occurred at the *y* and *y'* sites at 120 °C for 24 h (Table 1, entry 12). This observation indicated contrary regioselective C-H activation process controlled by an acid. The addition of D_2O yielded poorer regioselectivity in *d*-TFA indicating that *in situ* generated water by base and acid neutralization in entry 2 (the optimal regioselective condition) did not contribute to the regioselectivity (Table 1, entry 13). Increasing the reaction temperature to 140 °C (Table 1, entry 15, 17) resulted in poorer regioselectivity in both d_4-AcOH and *d*-TFA, however, decreasing the reaction temperature to 100 °C significanty reduced the rate of D-incorporation at either *x* site in d_4-AcOH (Table 1, entry 14) or *y* and *y'* sites in *d*-TFA (Table 1, entry 16).

We further examined a variety of substituents of the phenyl core (Table 2). All of the tested substrates gave excellent regioselectivity at *x* sites in d_4-AcOH. Among them, **1a** (3-methyl) and **1j** (4-methylphenyl) showed the best reactivity, with 81% and 75% D-incorporation (**2a** and **2j**), respectively. Other substrates (**1b**-**1i**, **1k**-**1l**), and especially those with electron-withdrawing groups (**1d**, **1f**, **1i**), showed worse reactivity, with 20%-52% D-incorporation (**2b**-**2i**, **2k**-**2l**). Compared to d_4-AcOH, using *d*-TFA as the deuterium source resulted in moderate to excellent D-incorporatio-

Table 1. Conditions optimization[a]



Entry	Base	solvent	Deuterium incorporation[%][b]		
			x	y	y'
1	**None**	***d*$_4$-AcOH**	**81**	**11**	**11**
2	Na_2CO_3	*d*$_4$-AcOH	70	0	0
3	Na_2CO_3[c]	*d*$_4$-AcOH	83	28	28
4	Na_2CO_3[d]	*d*$_4$-AcOH	82	27	27
5	K_2CO_3	*d*$_4$-AcOH	68	0	0
6	Cs_2CO_3	*d*$_4$-AcOH	43	0	0
7	Li_2CO_3	*d*$_4$-AcOH	50	0	0
8	K_3PO_4	*d*$_4$-AcOH	52	0	0
9	KF	*d*$_4$-AcOH	76	10	10
10	NaOAc	*d*$_4$-AcOH	71	7	7
11	None	*d*$_4$-AcOH[e]	79	10	10
12	**None**	***d*-TFA[f]**	**14**	**90**	**90**
13	None	*d*-TFA[g]	47	91	91
14	None	*d*$_4$-AcOH[h]	45	0	0
15	None	*d*$_4$-AcOH[i]	79	14	14
16	None	*d*-TFA[j]	0	75	75
17	None	*d*-TFA[k]	35	90	90

[a] Reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ 10 mol %, base 2.0 equiv., solvent 1.0 mL, 120 °C, 48 h in sealed tube. [b] Deuterium incorporation was determined by ^{1}H-NMR. [c] Base: 0.5 equiv. [d] Base: 1.0 equiv. [e] Solvent: 3.0 mL, reaction time: 72 h. [f] Reaction time: 24 h in *d*-TFA. [g] 0.1 mmol D_2O was added. [h, j] Reaction temperature: 100 °C. [i, k] Reaction temperature: 140 °C.

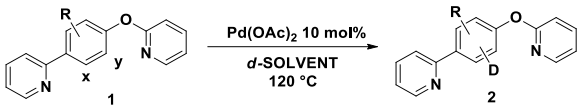
n (40%-95%), and good selectivity at *y* sites. ^{1}H-NMR analysis detected no D-incorporation at the *x* sites of **1c**, **1f**, and **1k** in *d*-TFA giving products of **2c'**, **2f'**, and **2k'** with their lower rate of D-incorporation, probably because of the existence of strong electron-withdrawing groups. As for other substrates, C-H deuteration occurred mainly at *y* sites (from 53% of **2g'** to 97% of **2d'**), with much less D-incorporation at *x* sites.

Substrates with other *N*-heterocycles were also studied (Table 3). Replacing the pyridine group with pyrimidine afforded products with good D-incorporation (**2m**: 72%) and excellent regioselectivity in *d*$_4$-AcOH, or excellent D-incorporation (**2m':** 90%) and good regioselectivity in *d*-TFA. Although substrates substituted by benzoglioxaline (**1n**), benzothiazole (**1o**), thiazole (**1p**), or benzoxazole (**1q**) decomposed in *d*$_4$-AcOH; with *d*-TFA, the corresponding deuterated products (**2n'-q'**) of each of these were obtained, and gave moderate to good D-incorporation (32%-85%) and excellent regioselectivity. We also tested substrates bearing N atom instead of the O atom in **1a**. Unfrotunately, the corresponding substrates did not show the above regioselectivity (data not shown).

Next, we wanted to test whether the regioselectivity of other different C-H

functionalization reactions were controllable in AcOH and TFA. Owing to the prevalence of carbonyl group in organic molecules, we first explored the regioselective C-H carbonylation reaction. To our delight, such acid-controlled regioselectivity could be accomplished successfully for the tested substrates (Scheme 1).

Table 2. Scope of the substrates for C-H deuteration[a]



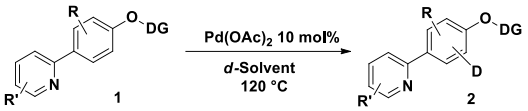
d_4-CH_3COOH	d-CF_3COOH	d_4-CH_3COOH	d-CF_3COOH
[81%][b] D [11%] D D D Me [11%] **2a**	[14%] D [90%] D D D Me [90%] **2a'**	Ph O N D [52%] **2g**	Ph O N D [53%] [16%] **2g'**
[50%] D O N D [50%] **2b**	[10%] D [95%] D O N D [95%] [10%] **2b'**	4-ClC_6H_4 [9%] D O N D [36%] **2h**	4-ClC_6H_4 O N D [82%] [17%] **2h'**
[48%] D O N Me **2c**	D [56%] O N Me **2c'**	4-$NO_2C_6H_4$ O N D [26%] **2i**	4-$NO_2C_6H_4$ O N D [70%] [17%] **2i'**
[28%] D O N F **2d**	[30%] D [97%] D O N F **2d'**	4-MeC_6H_4 O N D [75%] **2j**	4-MeC_6H_4 [26%] D O N D [90%] [35%] **2j'**
[52%] D O N Cl **2e**	D [40%] [10%] D O N Cl [32%] **2e'**	3-MeC_6H_4 O N D [48%] **2k**	3-MeC_6H_4 O N D [54%] **2k'**
[20%] D O N NO_2 **2f**	D [17%] O N NO_2 **2f'**	4-FC_6H_4 O N D [35%] **2l**	4-FC_6H_4 O N D [80%] [13%] **2l'**

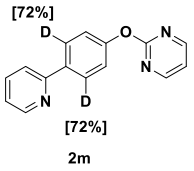
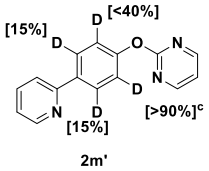
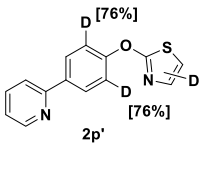
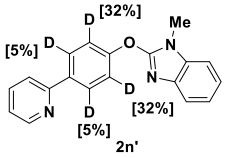
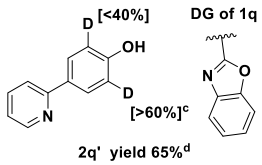
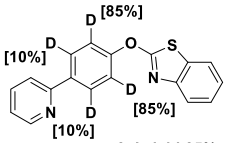
[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ 10 mol %, solvent 1.0 mL, 120 °C, 48 h (d_4-AcOH) or 24 h (d-TFA) in sealed tube, yield > 99%. [b] Deuterium incorporation: Determined by ^{1}H-NMR.

We also applied our acid-controlled strategy to the regioselective C-H iodination, bromination, and oxidation (Scheme 2).

We further explored the possibility for the late-stage functionalization of bioactive molecules using this Pd-catalyzed regioselective C-H activation (Scheme 3). Compound **7a** is an intermediate of a known voltage-gated sodium channel blocker analogue **7**.[7a] **7a** could be regioselectively deuterated by this method (with 95% D-incorporation) following a one-step transformation to the anticipated D-labelled compound ***d*-7**. Another ACC2 inhibitor analogue **8**[7b] was regioselectively deuterated and iodinated in a single step with acceptable yields as well. It is worth to note that this LSF method does not involve the installation or removal of directing groups.[10]

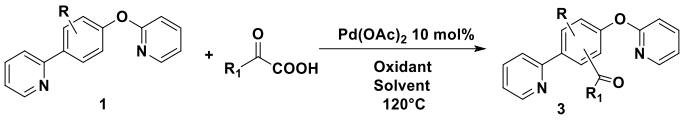
Table 3. Scope of the directing groups for C-H deuteration[a]

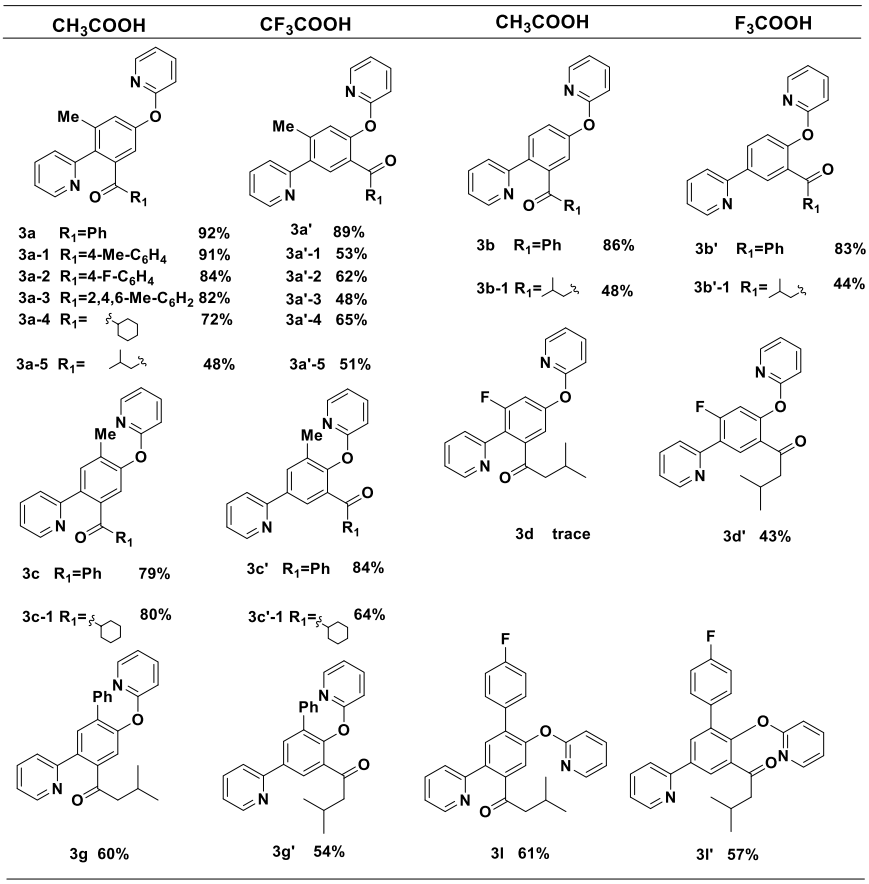


d_4-CH_3COOH	d-CF_3COOH	d-CF_3COOH
		
2m	2m'	2p'
		
2n'	2q' yield 65%[d]	
		
2o' yield 85%		

[a] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ 10 mol %, solvent 1.0 mL, 120 °C, 48 h (d_4-AcOH) or 24 h (d-TFA) in sealed tube. Yield > 99% if not mentioned. [b] Deuterium incorporation: Determined by ^{1}H-NMR. [c] Determined by ES-HRMS. [d] Product without directing group was obtained.

Scheme 1. Regioselective C-H Carbonylation [a]

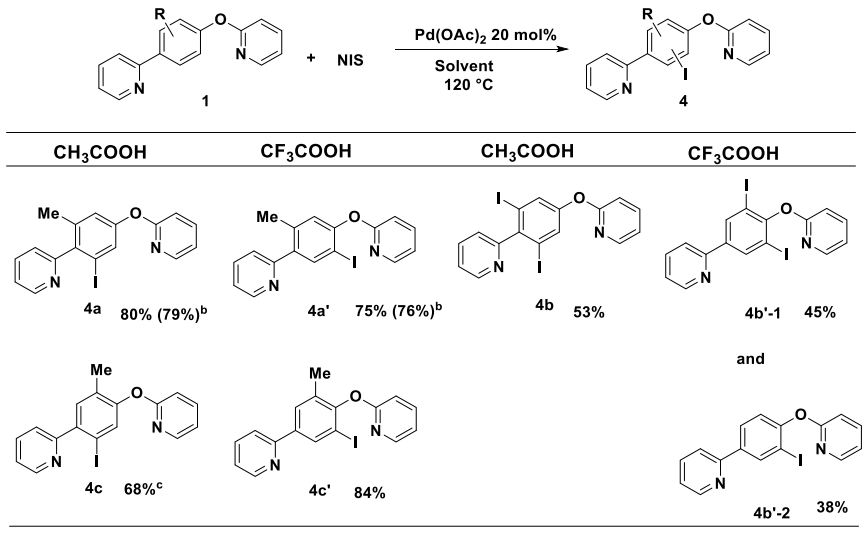




[a] Reaction conditions: With TFA (See SI for the details): **1** (0.1 mmol), $Pd(OAc)_2$ 10 mol %, TFA 0.9 mL/DCE 0.1 mL, Peroxy acid 1.5 equiv., $K_2S_2O_8$ 2.0 equiv, 120 °C, 24 h in sealed tube; With AcOH (reported conditions): **1** (0.1 mmol), $Pd(OAc)_2$ 10 mol %, Dioxane 0.75 mL/AcOH 0.15 mL/DMSO 0.1 mL, Peroxy acid 1.5 equiv., $K_2S_2O_8$ 1.0 equiv, Ag_2CO_3 2.0 equiv, 120 °C, 24 h in sealed tube.

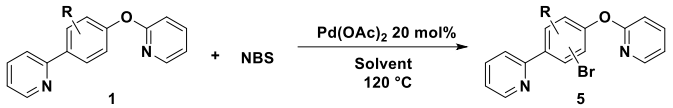
Scheme 2. Different C-H functionalization reactions with controllable regioselectivity.

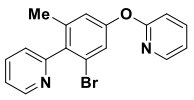
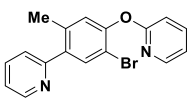
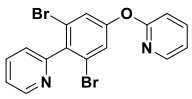
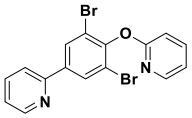
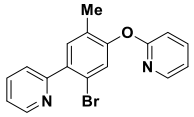
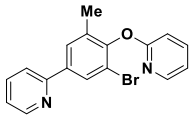
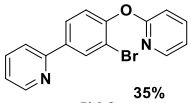
1) Regioselective C-H Iodination[a]



[a] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ 20 mol %, solvent 1.0 mL, NIS 1.5 equiv., 120 °C, 6-8 h in sealed tube. [b] 10 mol% $Pd(OAc)_2$ was used. [c] 2 h at 80 °C.

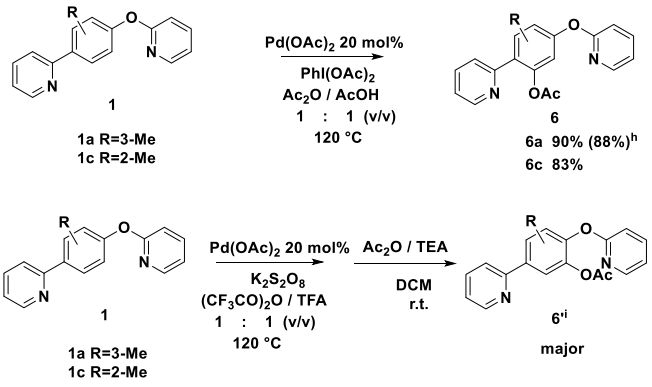
2) Regioselective C-H Bromination[d]



CH_3COOH	F_3COOH	CH_3COOH	CF_3COOH
			
5a major[e]	5a' 90% (86%)[f]	5b 82%	5b'-1 50% and 5b'-2 35%
			
5c 82%	5c' 93%		

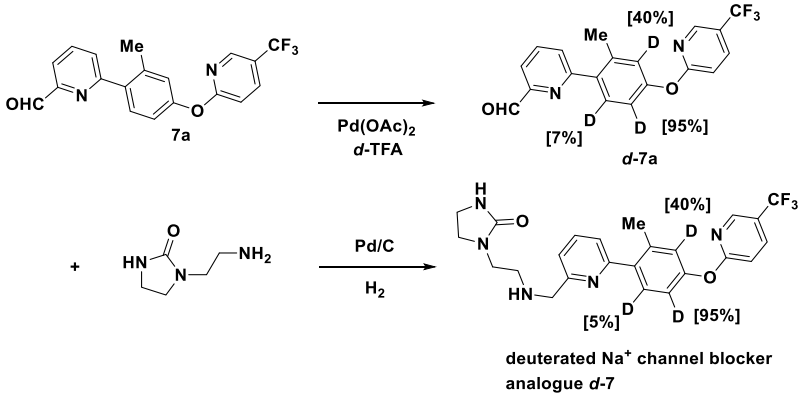
[d] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ 20 mol %, solvent 1.0 mL, NBS 1.5 equiv., 120 °C, 6-8 h in sealed tube. [e] Mixture was obtained, but there was no **5a'** isolated determined by NMR. [f] 10 mol% $Pd(OAc)_2$ was used.

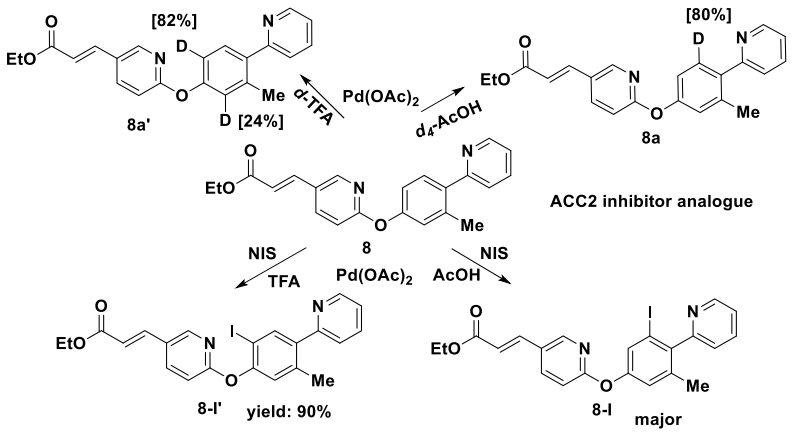
3) Regioselective C-H Oxidation[g]



[g] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ 20 mol %, solvent 1.0 mL, Oxidant 2.0 equiv., 120 °C, 12 h.[h] 10 mol% $Pd(OAc)_2$ was used. [i] Mixture was obtained due to the similar polarities, but there was no 6a or 6c isolated determined by NMR.

Scheme 3. LSF of bioactive molecules' analogues





We finally conducted additional experiments to gain insight into the mechanism for the controllable regioselectivity in this C-H functionalization. The treatment of **1b** with *d*-TFA afforded **1b**·TFA (**9b**) after solvent evaporation (Scheme 4, eq 1). ^{1}H-NMR analysis showed apparent chemical shift variation of the hydrogens on PG-5 (Figure 2, $H_{a'\text{-}d'}$) of **9b** compared to those (Figure 2, $H_{a\text{-}d}$) of **1b**. Subsequent reaction of **9b** with $Pd(OAc)_2$ in d_4-AcOH afforded **2b-1** with poorer regioselectivity and lower rate of D-incorporation. These observations indicated that the nitrogen atom of PG-5 was protonated. Theoretical calculation supported that the protonated PG-5 is with a lower energy. Therefore it is much easier to be protonated that resulted in losing affinity to Pd catalyst (See SI, Scheme S1). We then evaluated the reactivity of 2-(4-hydroxypenyl)-pyridine **1q'** in the deuteration reaction with *d*-TFA. Surprisingly, D-incorporation was only observed at the *ortho*-site of the hydroxyl group (Scheme 4, eq 2). When $Pd(CF_3COO)_2$ was used as the catalyst, C-H deuteration occurred mainly at the *y* and *y'* sites in *d*-TFA (Scheme 4, eq 3). Additionally, upon stoichiometric reaction of **1b** with $Pd(OAc)_2$ in AcOH or TFA, two metal-ligand complexes (**I** and **II**) exhibiting distinct ^{1}H-NMR signals were obtained (See SI). Further protonolysis of complex **I** in *d*-TFA afforded **2b'-1** with more than 90% D-incorporation at the *x, x', y* and *y'* sites (Scheme 4, eq 4). Protonolysis of complex **II** in *d*-TFA afforded **2b'-2** with 99% D-incorporation at the *y* and *y'* sites, but only 30% D-incorporation at the *x* and *x'* sites (Scheme 4, eq 5).

Based on these results, we propose a mechanism for this Pd-catalyzed regioselective C-H activation (Figure 3). In AcOH, complexation of the substrate and $Pd(OAc)_2$ forms complex **I** with kinetically favoured five-membered palladacycle (Figure 3A). In TFA, on the one hand, the directly connected pyridine group is firstly protonated, which blocks the formation of the five-membered palladacycle intermediate. On the other hand, the $Pd(OAc)_2$ precatalyst is converted to the $[Pd(TFA)]^+$ species, which is significantly more electrophilic,[11] it inserts into the electron-rich C-H bond specifically to form complex **II** with the six-membered palladacycle (Figure 3B). Following the formation of complex **I** and **II** in AcOH and TFA, respectively, we speculate that each undergoes a nucleophilic reaction to form the C-D bonds and C-halogen bonds with D^+, Br^+ or I^+ as the electrophile[9a]. Alternatively, complexes **I** and **II** can also undergo oxidative addition/reductive elimination to form C-C or C-O bonds with similar pathway to the literatures.[8e, 12]

Scheme 4. Mechanism experiments

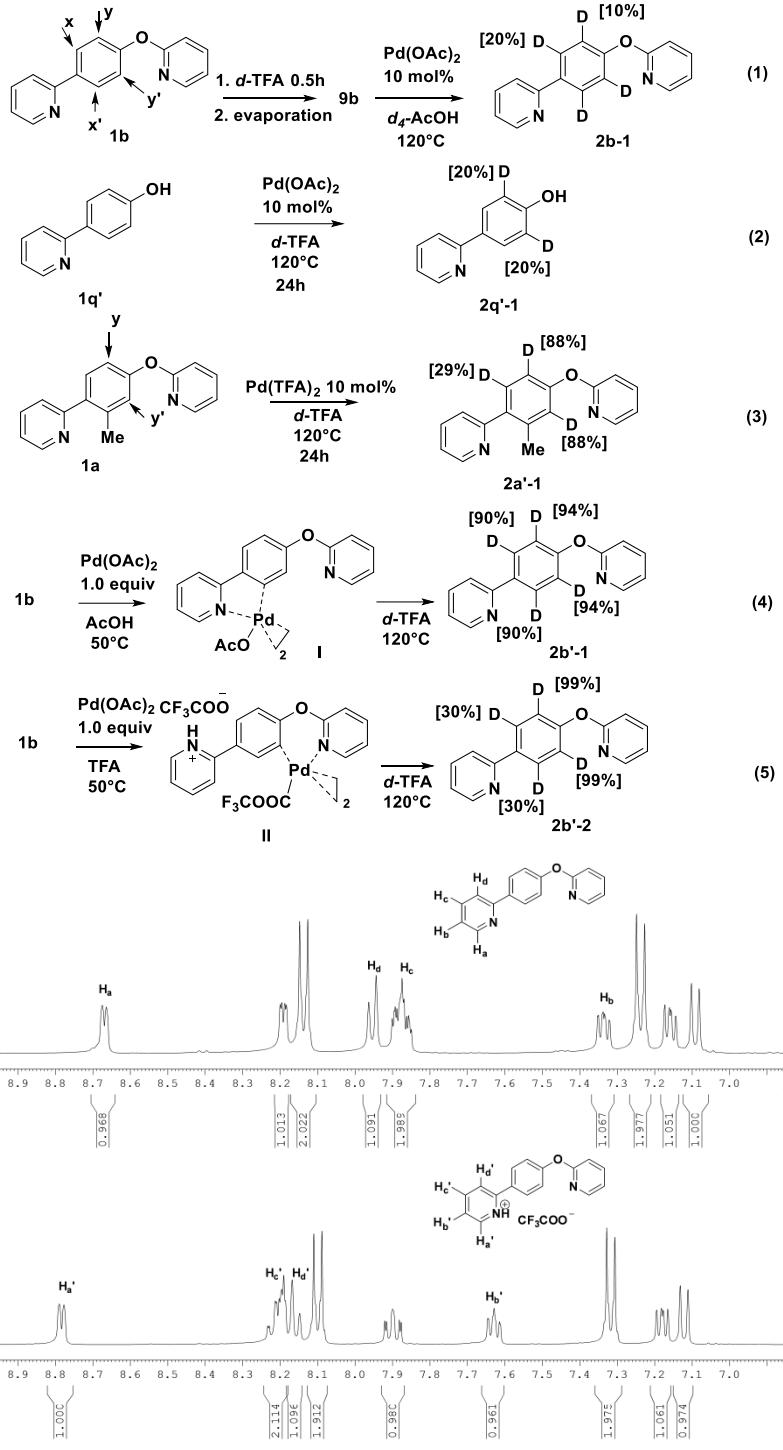


Figure 2. ^{1}H-NMR of **1b** (up) and **9b** (down)

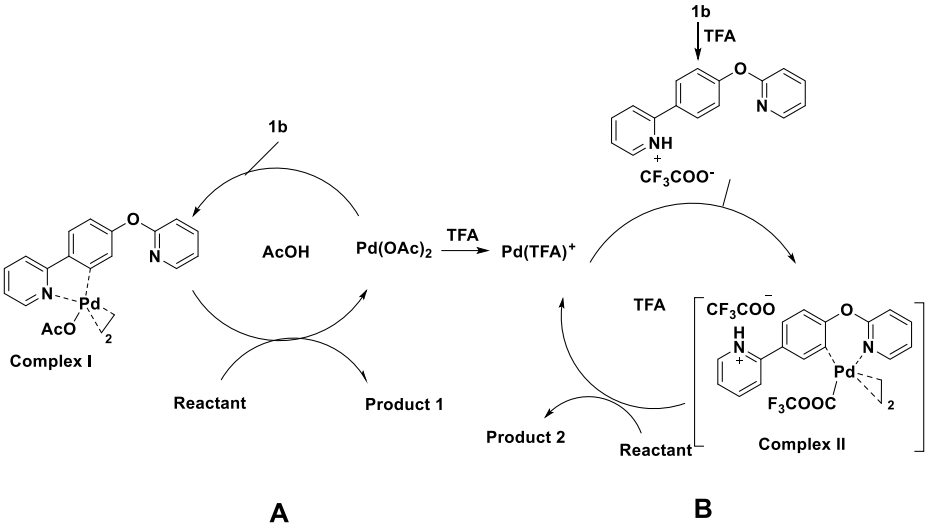


Figure 3. Proposed mechanism

Conclusion

In summary, we have developed a new Brönsted acid-controlled strategy to achieve regioselectivity in Pd-catalyzed C-H deuteration, carbonylation, iodination, bromination and oxidation of substrates containing two pyridine groups in a single molecule. Our mechanism study showed that this regioselectivity is controlled by Brönsted acid-Lewis base interactions and electronic effects (in TFA) and the different kinetic stabilities of palladacycle intermediates (in AcOH). This Brönsted acid-Lewis base interaction can selectively overcome the strongly coordinating ability of Lewis basic heterocycles to metals and achieve the regioselectivity of C-H activation. This method is further applied for the late-stage C-H deuteration and iodination of bioactive molecules.

Experimental Section

General information

Unless otherwise stated, all reagents were purchased from commercial suppliers and were used without further purification. The substrate **1** was synthesized by coupling reactions (See Supporting Information). The reactions were heated on an oil bath. If the rate of D-incorporation was under 40%, the molecular formula given by ES-HRMS will not contain the corresponding deuterium atom. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on Bruker Advance 400, spectrometer. Chemical shifts of ^{1}H NMR spectra are reported as in units of parts per million (ppm). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); m (multiplets), etc. The number of protons (n) for a given resonance is indicated by nH. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as in units of parts per million (ppm). High-resolution LC-MS was carried out by Agilent LC/MSD TOF using a column of Agilent ZORBAX SB-C18 (rapid resolution, 3.5 μm, 2.1 × 30 mm) at a flow of 0.40 mL/min. The solvent was MeOH/water (75:25 (v/v)), containing 5 mmol/L ammonium formate. The ion source is electrospray ionization (ESI).

General procedure for the regioselective C-H deuteration

The substrate **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol) was dissolved in d_4-AcOH or *d*-TFA (1.0 mL), and the tube was sealed with a PTFE stopcock. The mixture was stirred at 120 °C for 48 h (reaction in d_4-AcOH) or 24 h (reaction in *d*-TFA). After cooled to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ aqueous three times. The organic layer was dried by Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by Combiflash column chromatography (PE:EA=1:1) to give the deuterated products.

*2-(3-Methyl-4-(pyridin-2-yl)phenoxy)pyridine (**1a**)* Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, *J* = 4.4 Hz, 1H), 8.19 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.89 (m, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.37 (dd, *J* = 7.2, 5.1 Hz, 1H), 7.15 (dd, *J* = 6.9, 5.2 Hz, 1H), 7.05 (m, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 159.0, 154.1, 149.5, 147.9, 140.6, 137.8, 137.0, 136.9, 131.4, 124.4, 123.4, 122.4, 119.5, 118.9, 112.1, 20.7. ES-HRMS: Calcd for $C_{17}H_{15}ON_2$ $[M+H]^+$, 263.1173, Found 263.1178.

*2-(3-Methyl-4-(pyridin-2-yl)phenoxy-2,5,6-d_3)pyridine (**2a**)* (26.3 mg, >99% yield) D-incorporation was determined against integral at δ 7.55; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, *J* = 4.4 Hz, 1H), 8.19 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.89 (m, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), **7.43 (d, *J* = 8.3 Hz, 0.19H)**, 7.37 (dd, *J* = 7.2, 5.1 Hz, 1H), 7.15 (dd, *J* = 6.9, 5.2 Hz, 1H), **7.05 (m, 2.78H)**, 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 158.9, 154.1, 149.4, 147.9, 140.6, 137.7, 137.0, 136.8, 131.4 (labelled), 124.4, 123.4, 122.4, 119.5, 118.8, 112.1, 20.6. ES-HRMS: Calcd for $C_{17}H_{14}DON_2$ $[M+H]^+$, 264.1226, Found 264.1235.

*2-(3-Methyl-4-(pyridin-2-yl)phenoxy-2,5,6-d_3)pyridine (**2a'**)* (26.3 mg, >99% yield) D-incorporation was determined against integral at δ 7.55; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, *J* = 4.4 Hz, 1H), 8.19 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.89 (m, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), **7.43 (s, 0.86H)**, 7.37 (dd, *J* = 7.2, 5.1 Hz, 1H), 7.15 (dd, *J* = 6.9, 5.2 Hz, 1H), **7.05 (m, 1.20H)**, 2.33 (s, 3H). ES-HRMS: Calcd for $C_{17}H_{13}D_2ON_2$ $[M+H]^+$, 265.1304, Found 265.1295.

*2-(4-(Pyridin-2-yl)phenoxy)pyridine (**1b**)* While solid; m.p. 102-105°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (dd, *J* = 7.0, 6.4 Hz, 1H), 8.19 (dd, *J* = 4.9, 1.5 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.87 (m, 2H), 7.35 (m, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.16 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.3, 155.9, 155.3, 149.9, 147.9, 140.7, 137.6, 135.4, 128.4, 122.8, 121.6, 120.4, 119.7, 112.3. ES-HRMS: Calcd for $C_{16}H_{13}ON_2$ $[M+H]^+$, 249.1018, Found 249.1022.

*2-(4-(Pyridin-2-yl)phenoxy-3,5-d_2)pyridine (**2b**)* (24.9 mg, >99% yield) D-incorporation was determined against integral at δ 7.09; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (dd, *J* = 7.0, 6.4 Hz, 1H), 8.19 (dd, *J* = 4.9, 1.5 Hz, 1H), **8.14 (d, *J* = 8.7 Hz, 1.00H)**, 7.95 (d, *J* = 8.0 Hz, 1H), 7.87 (m, 2H), 7.35 (m, 1H), 7.24 (m, 2H), 7.16 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H). ES-HRMS: Calcd for $C_{16}H_{11}D_2ON_2$ $[M+H]^+$, 251.1147, Found 251.1138.

*2-(4-(Pyridin-2-yl)phenoxy-2,3,5,6-d_4)pyridine (**2b'**)* (25.0 mg, >99% yield) D-incorporation was determined against integral at δ 7.09; ^{1}H NMR (400 MHz, DMSO-

d$_6$): δ 8.68 (dd, *J* = 7.0, 6.4 Hz, 1H), 8.19 (dd, *J* = 4.9, 1.5 Hz, 1H), **8.14 (m, 1.80H)**, 7.95 (d, *J* = 8.0 Hz, 1H), 7.87 (m, 2H), 7.35 (m, 1H), **7.24 (m, 0.10H)**, 7.16 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.2, 155.8, 155.2, 149.8, 147.9, 140.7, 137.9, 135.1, 128.3, 122.8, 121.6 (labelled), 120.5, 119.8, 112.3. ES-HRMS: Calcd for $C_{16}H_{11}D_2ON_2$ $[M+H]^+$, 251.1147, Found 251.1138.

*2-(2-Methyl-4-(pyridin-2-yl)phenoxy)pyridine (**1c**)* Colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.66 (m, 1H), 8.13 (m, 1H), 8.05 (m, 1H), 7.95 (m, 2H), 7.87 (m, 2H), 7.34 (dd, *J* = 6.2, 5.4 Hz, 1H), 7.13 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.3, 156.0, 153.4, 149.9, 147.9, 140.6, 137.6, 135.8, 130.9, 129.8, 125.8, 122.8, 122.6, 120.5, 119.2, 111.4, 16.6. ES-HRMS: Calcd for $C_{17}H_{15}ON_2$ $[M+H]^+$, 263.1173, Found 263.1175.

*2-(2-Methyl-4-(pyridin-2-yl)phenoxy-5-d)pyridine (**2c**)* (26.4 mg, >99% yield) D-incorporation was determined against integral at δ 7.34; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.66 (m, 1H), 8.13 (m, 1H), 8.05 (m, 1H), **7.95 (m, 1.52H)**, 7.87 (m, 2H), 7.34 (dd, *J* = 6.2, 5.4 Hz, 1H), 7.13 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 1H), 2.17 (s, 3H). ES-HRMS: Calcd for $C_{17}H_{14}DON_2$ $[M+H]^+$, 264.1226, Found 264.1230.

*2-(2-Methyl-4-(pyridin-2-yl)phenoxy-6-d)pyridine (**2c'**)* (26.3 mg, >99% yield) D-incorporation was determined against integral at δ 7.34; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.66 (m, 1H), 8.13 (m, 1H), 8.05 (m, 1H), 7.95 (m, 2H), 7.87 (m, 2H), 7.34 (dd, *J* = 6.2, 5.4 Hz, 1H), **7.17 (d, *J* = 8.4 Hz, 0.44H)**, 7.13 (m, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.2, 155.4, 153.6, 148.9, 147.8, 140.7, 138.9, 134.8, 131.0, 130.1, 126.1, 123.2, 122.6, 121.2, 119.3, 111.4, 16.6. ES-HRMS: Calcd for $C_{17}H_{14}DON_2$ $[M+H]^+$, 264.1226, Found 264.1226.

*2-(3-Fluoro-4-(pyridin-2-yl)phenoxy)pyridine (**1d**)* Brown oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.60 (d, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 3.8 Hz, 1H), 7.90 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.81 (m, 1H), 7.73 (m, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 2H), 7.13 (dd, *J* = 9.8, 2.3 Hz, 1H), 7.08 (m, 1H), 7.04 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 162.9, 162.8 (d, $^1J_{C\text{-}F}$ = 245 Hz), 154.2, 152.5 (d, $^3J_{C\text{-}F}$ = 11 Hz), 149.9, 147.8, 140.7, 136.8, 132.9 (d, $^3J_{C\text{-}F}$ = 10 Hz), 129.8 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 124.1, 122.8, 119.7, 112.7 (d, $^2J_{C\text{-}F}$ = 21 Hz), 112.0, 110.8 (d, $^2J_{C\text{-}F}$ = 23 Hz). ES-HRMS: Calcd for $C_{16}H_{12}FON_2$ $[M+H]^+$, 267.0946, Found 267.0951.

*2-(3-Fluoro-4-(pyridin-2-yl)phenoxy-5-d)pyridine (**2d**)* (26.5 mg, >99% yield) D-incorporation was determined against integral at δ 7.66; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.60 (d, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 3.8 Hz, 1H), **7.90 (dd, *J* = 8.4, 7.2 Hz, 0.72H)**, 7.81 (m, 1H), 7.73 (m, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 2H), 7.13 (dd, *J* = 9.8, 2.3 Hz, 1H), 7.08 (m, 1H), 7.04 (d, *J* = 8.3 Hz, 1H). ES-HRMS: Calcd for $C_{16}H_{12}FON_2$ $[M+H]^+$, 267.0946, Found 267.0953.

*2-(3-Fluoro-4-(pyridin-2-yl)phenoxy-5,6-d$_2$)pyridine (**2d'**)* (26.6 mg, >99% yield) D-incorporation was determined against integral at δ 7.66; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.60 (d, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 3.8 Hz, 1H), **7.90 (dd, *J* = 8.4, 7.2 Hz, 0.70H)**, 7.81 (m, 1H), 7.73 (m, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 2H), **7.13 (m, 0.03H)**, 7.08 (m, 1H), 7.04 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 162.9, 162.8 (d, $^1J_{C\text{-}F}$ = 245 Hz), 154.2, 152.5 (d, $^3J_{C\text{-}F}$ = 11 Hz), 149.9, 147.8, 140.7, 136.8, 132.9 (d, $^3J_{C\text{-}F}$ = 10 Hz), 129.8 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 124.1, 122.8, 119.7, 112.7 (d,

$^{2}J_{C\text{-}F}$ = 21 Hz, labelled), 112.0, 110.8 (labelled). ES-HRMS: Calcd for $C_{16}H_{11}DFON_2$ $[M+H]^+$, 268.0996, Found 268.0990.

*2-(3-Chloro-4-(pyridin-2-yl)phenoxy)pyridine (**1e**)* Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (m, 1H), 8.21 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.91 (td, *J* = 7.8, 1.9 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.42 (m, 2H), 7.24 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.19 (dd, *J* = 6.9, 5.3 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.9, 156.1, 154.8, 149.9, 147.9, 140.9, 136.9, 135.6, 132.9, 132.0, 125.0, 123.2, 122.9, 120.7, 120.1, 112.4. ES-HRMS: Calcd for $C_{16}H_{12}ON_2Cl$ $[M+H]^+$, 283.0631 (^{35}Cl), Found 283.0632 (^{35}Cl).

*2-(3-Chloro-4-(pyridin-2-yl)phenoxy-5-d)pyridine (**2e**)* (28.2 mg, >99% yield) D-incorporation was determined against integral at δ 7.69; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (m, 1H), 8.21 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.91 (td, *J* = 7.8, 1.9 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), **7.63 (d, *J* = 8.5 Hz, 0.48H)**, 7.42 (m, 2H), 7.24 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.19 (dd, *J* = 6.9, 5.3 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H). ES-HRMS: Calcd for $C_{16}H_{11}DON_2Cl$ $[M+H]^+$, 284.0695 (^{35}Cl), Found 284.0683 (^{35}Cl).

*2-(3-Chloro-4-(pyridin-2-yl)phenoxy-2,5,6-d$_3$)pyridine (**2e'**)* (28.1 mg, >99% yield) D-incorporation was determined against integral at δ 7.69; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (m, 1H), 8.21 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.91 (td, *J* = 7.8, 1.9 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), **7.63 (d, *J* = 8.5 Hz, 0.90H)**, **7.42 (m, 1.68H)**, **7.24 (dd, *J* = 8.5, 2.3 Hz, 0.60H)**, 7.19 (dd, *J* = 6.9, 5.3 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 162.8, 156.0, 154.8, 149.8, 147.9, 140.9, 136.8, 135.6, 132.9, 132.0, 125.0, 123.2, 122.8, 120.7, 120.1, 112.4. ES-HRMS: Calcd for $C_{16}H_{11}DON_2Cl$ $[M+H]^+$, 284.0695 (^{35}Cl), Found 284.0682 (^{35}Cl).

*2-(3-Nitro-4-(pyridin-2-yl)phenoxy)pyridine (**1f**)* Yellow solid; m.p. 104-106°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (d, *J* = 4.2 Hz, 1H), 8.22 (d, *J* = 4.6 Hz, 1H), 7.96 (q, *J* = 7.7 Hz, 2H), 7.83 (m, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.43 (m, 1H), 7.22 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6, 154.5, 154.4, 150.0, 149.7, 147.8, 141.1, 137.9, 132.6, 130.5, 125.6, 123.6, 123.1, 120.4, 117.8, 112.5. ES-HRMS: Calcd for $C_{16}H_{12}O_3N_3$ $[M+H]^+$, 294.0867, Found 294.0873.

*2-(3-Nitro-4-(pyridin-2-yl)phenoxy-5-d)pyridine (**2f**)* (29.0 mg, >99% yield) D-incorporation was determined against integral at δ 7.43; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (d, *J* = 4.2 Hz, 1H), 8.22 (d, *J* = 4.6 Hz, 1H), 7.96 (q, *J* = 7.7 Hz, 2H), **7.83 (m, 1.80H)**, 7.77 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.43 (m, 1H), 7.22 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.5, 154.5, 154.4, 150.0, 149.7, 147.8, 141.1, 138.0, 132.6, 130.4, 125.6, 123.6, 123.1, 120.4, 117.7, 112.5. ES-HRMS: Calcd for $C_{16}H_{12}O_3N_3$ $[M+H]^+$, 294.0867, Found 294.0868.

*2-(3-Nitro-4-(pyridin-2-yl)phenoxy-6-d)pyridine (**2f'**)* (29.2 mg, >99% yield) D-incorporation was determined against integral at δ 7.43; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (d, *J* = 4.2 Hz, 1H), 8.22 (d, *J* = 4.6 Hz, 1H), 7.96 (q, *J* = 7.7 Hz, 2H), 7.83 (m, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), **7.58 (d, *J* = 8.4 Hz, 0.83H)**, 7.43 (m, 1H), 7.22 (m, 2H). ES-HRMS: Calcd for $C_{16}H_{12}O_3N_3$ $[M+H]^+$, 294.0867, Found 294.0869.

*2-((5-(Pyridin-2-yl)-[1,1'-biphenyl]-2-yl)oxy)pyridine (**1g**)* Yellow solid; m.p. 129-130°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (m, 1H), 8.19 (d, *J* = 2.2 Hz, 1H), 8.12 (m, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.89 (td, *J* = 7.8, 1.8 Hz, 1H), 7.78 (m, 1H), 7.52

(m, 2H), 7.37 (m, 3H), 7.31 (m, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.5, 155.7, 152.0, 150.0, 147.8, 140.5, 137.7, 136.1, 134.6, 129.5, 129.2, 128.7, 127.8, 127.3, 123.7, 123.0, 120.7, 119.3, 111.8. ES-HRMS: Calcd for $C_{22}H_{17}ON_2$ $[M+H]^+$, 325.1330, Found 325.1335.

*2-((5-(Pyridin-2-yl)-[1,1'-biphenyl]-2-yl-4-d)oxy)pyridine (**2g**)* (32.4 mg, >99% yield) D-incorporation was determined against integral at δ 7.89; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.69 (m, 1H), 8.19 (d, *J* = 2.2 Hz, 1H), **8.12 (m, 1.48H)**, 8.06 (d, *J* = 8.0 Hz, 1H), 7.89 (td, *J* = 7.8, 1.8 Hz, 1H), 7.78 (m, 1H), 7.52 (m, 2H), 7.37 (m, 3H), 7.31 (m, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H). ES-HRMS: Calcd for $C_{22}H_{16}DON_2$ $[M+H]^+$, 326.1398, Found 326.1379.

*2-((5-(Pyridin-2-yl)-[1,1'-biphenyl]-2-yl-3,4-d$_2$)oxy)pyridine (**2g'**)* (32.2 mg, >99% yield) D-incorporation was determined against integral at δ 8.06; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.69 (m, 1H), 8.19 (d, *J* = 2.2 Hz, 1H), **8.12 (m, 1.84H)**, 8.06 (d, *J* = 8.0 Hz, 1H), 7.89 (td, *J* = 7.8, 1.8 Hz, 1H), 7.78 (m, 1H), 7.52 (m, 2H), 7.37 (m, 3H), 7.31 (m, 1H), **7.27 (d, *J* = 8.5 Hz, 0.47H)**, 7.06 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.5, 155.7, 152.0, 149.9, 147.8, 140.5, 137.7, 136.1, 134.6, 129.4, 129.2, 128.7, 127.9, 127.3, 123.7, 123.0, 120.7, 119.3, 111.8. ES-HRMS: Calcd for $C_{22}H_{16}DON_2$ $[M+H]^+$, 326.1398, Found 326.1382.

*2-((4'-Chloro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl)oxy)pyridine (**1h**)* White solid; m.p. 105-107°C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (d, *J* = 4.3 Hz, 1H), 8.19 (d, *J* = 1.9 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.09 (d, *J* = 3.5 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.89 (m, 1H), 7.80 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 7.2, 5.0 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 6.7, 5.4 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.4, 155.6, 151.9, 150.0, 147.8, 140.5, 137.7, 136.5, 136.2, 133.4, 132.7, 131.0, 129.3, 128.7, 127.7, 123.7, 123.0, 120.7, 119.4, 111.9. $C_{22}H_{16}ON_2Cl$ $[M+H]^+$, 359.0945 (^{35}Cl), Found 359.0948 (^{35}Cl).

*2-((4'-Chloro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-4,6-d$_2$)oxy)pyridine (**2h**)* (35.6 mg, >99% yield) D-incorporation was determined against integral at δ 7.80; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (d, *J* = 4.3 Hz, 1H), **8.19 (m, 0.91H)**, **8.14 (m, 0.64H)**, 8.09 (d, *J* = 3.5 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.89 (m, 1H), 7.80 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 7.2, 5.0 Hz, 1H), 7.28 (m, 1H), 7.06 (dd, *J* = 6.7, 5.4 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H). ES-HRMS: Calcd for $C_{22}H_{16}ON_2Cl$ $[M+H]^+$, 359.0945 (^{35}Cl), Found 359.0943 (^{35}Cl).

*2-((4'-Chloro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-3,4-d$_2$)oxy)pyridine (**2h'**)* (35.7 mg, >99% yield) D-incorporation was determined against integral at δ 7.80; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (d, *J* = 4.3 Hz, 1H), 8.19 (m, 1H), **8.14 (m, 0.83H)**, 8.09 (d, *J* = 3.5 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.89 (m, 1H), 7.80 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 7.2, 5.0 Hz, 1H), **7.28 (m, 0.18H)**, 7.06 (dd, *J* = 6.7, 5.4 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.3, 155.6, 151.9, 150.0, 147.8, 140.5, 137.7, 136.5, 136.2, 133.4, 132.7, 131.0, 129.3, 128.7, 127.7, 123.7 (labelled), 123.0, 120.7, 119.4, 111.9. ES-HRMS: Calcd for $C_{22}H_{15}DON_2Cl$ $[M+H]^+$, 360.1000 (^{35}Cl), Found 360.1008 (^{35}Cl).

2-((4'-Nitro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl)oxy)pyridine ***(1i)*** Yellow solid; m.p. 105-106°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.0 Hz, 1H), 8.26 (d, J = 2.1 Hz, 1H), 8.21 (m, 3H), 8.09 (m, 2H), 7.90 (td, J = 7.8, 1.6 Hz, 1H), 7.81 (m, 3H), 7.37 (dd, J = 7.2, 4.9 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.08 (dd, J = 6.8, 5.3 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2, 155.4, 152.1, 150.0, 147.8, 147.0, 144.5, 140.7, 137.7, 136.3, 132.5, 130.6, 129.3, 128.7, 123.8, 123.7, 123.1, 120.8, 119.6, 112.1. ES-HRMS: Calcd for $C_{22}H_{16}O_3N_3$ $[M+H]^+$, 370.1182, Found 370.1186.

2-((4'-Nitro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-4-d)oxy)pyridine ***(2i)*** (36.6 mg, >99% yield) D-incorporation was determined against integral at δ 7.08; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.0 Hz, 1H), 8.26 (d, J = 2.1 Hz, 1H), **8.21 (m, 2.74H)**, 8.09 (m, 2H), 7.90 (td, J = 7.8, 1.6 Hz, 1H), 7.81 (m, 3H), 7.37 (m, 1H), 7.32 (m, 1H), 7.08 (dd, J = 6.8, 5.3 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H). ES-HRMS: Calcd for $C_{22}H_{16}O_3N_3$ $[M+H]^+$, 370.1182, Found 370.1186.

2-((4'-Nitro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-3,4-d$_2$)oxy)pyridine ***(2i')*** (36.7 mg, >99% yield) D-incorporation was determined against integral at δ 7.08; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.0 Hz, 1H), 8.26 (d, J = 2.1 Hz, 1H), **8.21 (m, 2.83H)**, 8.09 (m, 2H), 7.90 (td, J = 7.8, 1.6 Hz, 1H), 7.81 (m, 3H), 7.37 (m, 1H), **7.32 (m, 0.30H)**, 7.08 (dd, J = 6.8, 5.3 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 155.3, 152.1, 149.9, 147.8, 147.0, 144.5, 140.7, 137.8, 136.2, 132.5, 130.6, 129.3, 128.7, 123.8, 123.7, 123.2, 120.8, 119.6, 112.0. ES-HRMS: Calcd for $C_{22}H_{15}DO_3N_3$ $[M+H]^+$, 371.1248, Found 371.1232.

2-((4'-Methyl-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl)oxy)pyridine ***(1j)*** Yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, J = 4.1 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.09 (m, 2H), 8.04 (d, J = 7.4 Hz, 1H), 7.88 (td, J = 7.8, 1.6 Hz, 1H), 7.78 (m, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.35 (dd, J = 7.1, 5.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 7.9 Hz, 2H), 7.06 (dd, J = 6.7, 5.2 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 155.8, 151.9, 150.0, 147.8, 140.5, 137.7, 137.1, 136.1, 134.8, 134.6, 129.4, 129.3, 129.0, 127.1, 123.7, 122.9, 120.7, 119.2, 111.8, 21.1. ES-HRMS: Calcd for $C_{23}H_{19}ON_2$ $[M+H]^+$, 339.1485, Found 339.1491.

2-((4'-Methyl-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-4-d)oxy)pyridine ***(2j)*** (33.6 mg, >99% yield) D-incorporation was determined against integral at δ 7.78; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, J = 4.1 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), **8.09 (m, 1.25H)**, 8.04 (d, J = 7.4 Hz, 2H), 7.88 (td, J = 7.8, 1.6 Hz, 1H), 7.78 (m, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.35 (dd, J = 7.1, 5.0 Hz, 1H), 7.25 (m, 1H), 7.17 (d, J = 7.9 Hz, 2H), 7.06 (dd, J = 6.7, 5.2 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 155.7, 151.9, 149.9, 147.7, 140.5, 137.8, 137.2, 136.0, 134.6, 129.4, 129.3, 129.0, 127.1 (labelled), 123.6, 123.0, 120.7, 119.3, 111.7, 21.0. ES-HRMS: Calcd for $C_{23}H_{18}DON_2$ $[M+H]^+$, 340.1554, Found 340.1541.

2-((4'-Methyl-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-3,4,6-d$_3$)oxy)pyridine ***(2j')*** (33.8 mg, >99% yield) D-incorporation was determined against integral at δ 7.78; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, J = 4.1 Hz, 1H), **8.17 (s, 0.74H)**, **8.09 (m, 1.65H)**, 8.04 (d, J = 7.4 Hz, 2H), 7.88 (td, J = 7.8, 1.6 Hz, 1H), 7.78 (m, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.35 (dd, J = 7.1, 5.0 Hz, 1H), **7.25 (m, 0.10H)**, 7.17 (d, J = 7.9 Hz,

2H), 7.06 (dd, *J* = 6.7, 5.2 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 2.28 (s, 3H). ES-HRMS: Calcd for $C_{23}H_{18}DON_2$ $[M+H]^+$, 340.1554, Found 340.1551.

*2-((3'-Methyl-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl)oxy)pyridine (**1k**)* Yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (m, 1H), 8.18 (m, 1H), 8.10 (m, 2H), 8.05 (m, 1H), 7.90 (m, 1H), 7.77 (m, 1H), 7.34 (m, 3H), 7.25 (m, 2H), 7.11 (m, 1H), 7.05 (m, 1H), 6.97 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 155.8, 152.0, 149.9, 147.8, 140.4, 137.8, 137.7, 137.6, 136.1, 134.7, 129.8, 129.4, 128.4, 127.2, 126.3, 123.7, 122.9, 120.7, 119.2, 111.8, 21.4. ES-HRMS: Calcd for $C_{23}H_{19}ON_2$ $[M+H]^+$, 339.1485, Found 339.1489.

*2-((3'-Methyl-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-4-d)oxy)pyridine (**2k**)* (33.6 mg, >99% yield) D-incorporation was determined against integral at δ 7.05; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (m, 1H), 8.18 (m, 1H), **8.10 (m, 1.52H)**, 8.05 (m, 1H), 7.90 (m, 1H), 7.77 (m, 1H), 7.34 (m, 3H), 7.25 (m, 2H), 7.11 (m, 1H), 7.05 (m, 1H), 6.97 (m, 1H), 2.28 (s, 3H). ES-HRMS: Calcd for $C_{23}H_{18}DON_2$ $[M+H]^+$, 340.1554, Found 340.1549.

*2-((3'-Methyl-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-3-d)oxy)pyridine (**2k'**)* (33.6 mg, >99% yield) D-incorporation was determined against integral at δ 7.05; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (m, 1H), 8.18 (m, 1H), 8.10 (m, 2H), 8.05 (m, 1H), 7.90 (m, 1H), 7.77 (m, 1H), 7.34 (m, 3H), **7.25 (m, 1.46H)**, 7.11 (m, 1H), 7.05 (m, 1H), 6.97 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6, 155.7, 152.0, 149.9, 147.8, 140.4, 137.8, 137.7, 137.6, 136.1, 134.7, 129.8, 129.4, 128.5, 127.2, 126.3, 123.7, 122.9, 120.7, 119.2, 111.8, 21.4. ES-HRMS: Calcd for $C_{23}H_{18}DON_2$ $[M+H]^+$, 340.1554, Found 340.1540.

*2-((4'-Fluoro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl)oxy)pyridine (**1l**)* Yellow solid; m.p. 99-100°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, *J* = 3.8 Hz, 1H), 8.17 (s, 1H), 8.11 (m, 2H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.89 (t, *J* = 7.3 Hz, 1H), 7.79 (t, *J* = 7.1 Hz, 1H), 7.56 (dd, *J* = 7.7, 5.9 Hz, 2H), 7.37 (m, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 8.7 Hz, 2H), 7.06 (m, 1H), 6.98 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 162.0 (d, *J* = 243 Hz), 155.7, 152.0, 149.9, 147.8, 140.5, 137.7, 136.2, 134.0 (d, *J* = 3 Hz), 133.6, 131.2 (d, *J* = 8 Hz), 129.4, 127.5, 123.6, 123.0, 120.7, 119.3, 115.5 (d, *J* = 21 Hz), 111.9. ES-HRMS: Calcd for $C_{22}H_{16}FON_2$ $[M+H]^+$, 343.1239, Found 343.1241.

*2-((4'-Fluoro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-4-d)oxy)pyridine (**2l**)* (34.0 mg, >99% yield) D-incorporation was determined against integral at δ 7.37; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, *J* = 3.8 Hz, 1H), 8.17 (s, 1H), **8.11 (m, 1.65H)**, 8.06 (d, *J* = 7.9 Hz, 1H), 7.89 (t, *J* = 7.3 Hz, 1H), 7.79 (t, *J* = 7.1 Hz, 1H), 7.56 (dd, *J* = 7.7, 5.9 Hz, 2H), 7.37 (m, 1H), 7.27 (m, 1H), 7.20 (t, *J* = 8.7 Hz, 2H), 7.06 (m, 1H), 6.98 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 162.0 (d, *J* = 243 Hz), 155.6, 152.0, 149.9, 147.8, 140.5, 137.7, 136.2, 134.0 (d, *J* = 3 Hz), 133.6, 131.2 (d, *J* = 8 Hz), 129.4, 127.5, 123.6, 123.0, 120.7, 119.3, 115.5 (d, *J* = 21 Hz), 111.8. ES-HRMS: Calcd for $C_{22}H_{16}FON_2$ $[M+H]^+$, 343.1239, Found 343.1241.

*2-((4'-Fluoro-5-(pyridin-2-yl)-[1,1'-biphenyl]-2-yl-3,4-d_2)oxy)pyridine (**2l'**)* (34.1 mg, >99% yield) D-incorporation was determined against integral at δ 7.37; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, *J* = 3.8 Hz, 1H), 8.17 (s, 1H), **8.11 (m, 1.87H)**, 8.06

(d, J = 7.9 Hz, 1H), 7.89 (t, J = 7.3 Hz, 1H), 7.79 (t, J = 7.1 Hz, 1H), 7.56 (dd, J = 7.7, 5.9 Hz, 2H), 7.37 (m, 1H), **7.27 (m, 0.20H)**, 7.20 (t, J = 8.7 Hz, 2H), 7.06 (m, 1H), 6.98 (d, J = 8.2 Hz, 1H). ES-HRMS: Calcd for $C_{22}H_{15}DFON_2$ $[M+H]^+$, 344.1301, Found 344.1297.

*2-(4-(Pyridin-2-yl)phenoxy)pyrimidine (**1m**)* While solid; m.p. 114-115°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (m, 3H), 8.16 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 7.9 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.31 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.1, 160.5, 155.8, 154.0, 150.0, 137.7, 136.1, 128.3, 122.9, 122.3, 120.5, 117.5. ES-HRMS: Calcd for $C_{15}H_{12}ON_3$ $[M+H]^+$, 250.0971, Found 250.0974.

*2-(4-(Pyridin-2-yl)phenoxy-3,5-d_2)pyrimidine (**2m**)* (25.0 mg, >99% yield) D-incorporation was determined against integral at δ 7.97; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (m, 3H), **8.16 (m, 0.56H)**, 7.97 (d, J = 7.9 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.31 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.0, 160.5, 155.7, 154.0, 150.0, 137.7, 136.1 (labelled), 128.3 (labelled), 122.9, 122.3, 120.6, 117.5. ES-HRMS: Calcd for $C_{15}H_{10}D_2ON_3$ $[M+H]^+$, 252.1100, Found 252.1085.

*2-(4-(Pyridin-2-yl)phenoxy-2,3,5,6-d_4)pyrimidine (**2m'**)* (25.1 mg, >99% yield) D-incorporation was determined against integral at δ 7.97; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (m, 3H), **8.16 (m, 1.70H)**, 7.97 (d, J = 7.9 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), **7.31 (m, 2.70H)**. ES-HRMS: Calcd for $C_{15}H_{11}DON_3$ $[M+H]^+$, 251.1037, Found 251.1035.

*1-Methyl-2-(4-(pyridin-2-yl)phenoxy)-1H-benzo[d]imidazole (**1n**)* While solid; m.p. 163-165°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.5 Hz, 1H), 8.20 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.90 (td, J = 7.8, 1.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.46 (m, 2H), 7.37 (dd, J = 6.9, 5.1 Hz, 1H), 7.17 (m, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.7, 155.6, 154.7, 150.0, 139.6, 137.7, 136.2, 134.4, 128.4, 123.0, 121.9, 121.7, 120.8, 120.6, 118.1, 109.8, 28.9. Calcd for $C_{19}H_{16}ON_3$ $[M+H]^+$, 302.1282, Found 302.1287.

*1-Methyl-2-(4-(pyridin-2-yl)phenoxy-2,3,5,6-d_4)-1H-benzo[d]imidazole (**2n'**)* (29.9 mg, >99% yield) D-incorporation was determined against integral at δ 8.00; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.5 Hz, 1H), **8.20 (m, 1.90H)**, 8.00 (d, J = 8.0 Hz, 1H), 7.90 (td, J = 7.8, 1.7 Hz, 1H), **7.56 (d, J = 8.7 Hz, 1.36H)**, 7.46 (m, 2H), 7.37 (dd, J = 6.9, 5.1 Hz, 1H), 7.17 (m, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.7, 155.6, 154.7, 150.0, 139.6, 137.7, 136.2, 134.4, 128.4, 123.0, 121.9, 121.7, 120.8, 120.6, 118.1, 109.8, 28.9. ES-HRMS: Calcd for $C_{19}H_{16}ON_3$ $[M+H]^+$, 302.1282, Found 302.1284.

*2-(4-(Pyridin-2-yl)phenoxy)benzo[d]thiazole (**1o**)* While solid; m.p. 105-106°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (d, J = 3.9 Hz, 1H), 8.23 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 7.9 Hz, 1H), 7.93 (m, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.9, 155.4, 155.3, 150.0, 148.9, 137.8, 137.3, 132.3, 128.8, 127.0, 124.7, 123.2, 122.7, 121.7, 121.5, 120.7. $C_{18}H_{13}ON_2S$ $[M+H]^+$, 305.0740, Found 305.0743.

*2-(4-(Pyridin-2-yl)phenoxy-2,3,5,6-d_4)benzo[d]thiazole (**2o'**)* (26.1 mg, 85% yield) D-incorporation was determined against integral at δ 8.01; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (d, J = 3.9 Hz, 1H), **8.23 (m, 1.80H)**, 8.01 (d, J = 7.9 Hz, 1H), 7.93

(m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), **7.58 (m, 0.30H)**, 7.44 (t, *J* = 7.6 Hz, 1H), 7.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 171.9, 155.4, 155.3, 150.0, 148.9, 137.8, 137.3, 132.3, 128.8, 127.0, 124.8, 123.2, 122.7, 121.7, 121.5, 120.7. ES-HRMS: Calcd for $C_{18}H_{11}D_2ON_2S$ $[M+H]^+$, 307.0868, Found 307.0859.

*2-(4-(Pyridin-2-yl)phenoxy)thiazole (**1p**)* While solid; m.p. 104-105°C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (d, *J* = 3.9 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.89 (m, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.35 (m, 2H), 7.28 (m, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 172.9, 156.2, 155.4, 150.0, 138.0, 137.7, 136.7, 128.7, 123.1, 120.6, 120.6, 115.4. ES-HRMS: Calcd for $C_{14}H_{11}ON_2S$ $[M+H]^+$, 255.0582, Found 255.0586.

***d**-2-(4-(Pyridin-2-yl)phenoxy)thiazole (**2p'**)* (25.6 mg, >99% yield) D-incorporation was determined against integral at δ 7.98; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (d, *J* = 3.9 Hz, 1H), 8.19 (m, 2H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.89 (m, 1H), **7.45 (m, 0.48H)**, **7.35 (m, 1.74H)**, 7.28 (m, 0.06H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 172.9, 156.2, 155.4, 150.0, 137.9, 137.7, 136.7, 128.6, 123.1, 120.7, 120.6, 115.4 (labelled). ES-HRMS: Calcd for $C_{14}H_8D_3ON_2S$ $[M+H]^+$, 258.0583, Found 258.0574.

*4-(Pyridin-2-yl)phenol (**1q'**)* White solid; m.p. 145-1149°C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.74 (s, 1H), 8.59 (d, *J* = 4.4 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.82 (m, 2H), 7.23 (t, *J* = 5.2 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 158.9, 156.5, 149.7, 137.3, 130.0, 128.3, 121.8, 119.4, 115.9. ES-HRMS: Calcd for $C_{11}H_{10}ON$ $[M+H]^+$, 172.0754, Found 172.0756.

4-(pyridin-2-yl)phen-2,6-d$_2$*-ol (**2q'**)* (11.2 mg, 65% yield) D-incorporation was determined against integral at δ 7.23; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 9.74 (s, 1H), 8.59 (d, *J* = 4.4 Hz, 1H), 7.94 (m, 2H), 7.82 (m, 2H), 7.23 (t, *J* = 5.2 Hz, 1H), **6.87 (m, 1.00H)**. ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 159.3, 156.0, 148.7, 138.6, 129.0, 128.6, 122.2, 120.2, 116.0. ES-HRMS: Calcd for $C_{11}H_9DON$ $[M+H]^+$, 173.0819, Found 173.0814.

2-(3-Methyl-4-(pyridin-2-yl)phenoxy-2,5,6-d$_3$*)pyridine (**2a'-1**)* (26.3 mg, >99% yield) D-incorporation was determined against integral at δ 7.55; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.67 (d, *J* = 4.4 Hz, 1H), 8.19 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.89 (m, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), **7.43 (s, 0.71H)**, 7.37 (dd, *J* = 7.2, 5.1 Hz, 1H), 7.15 (dd, *J* = 6.9, 5.2 Hz, 1H), **7.05 (m, 1.24H)**, 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.4, 158.9, 154.1, 149.4, 147.9, 140.6, 137.6, 137.0, 136.8, 131.3, 124.4, 123.4, 122.4, 119.5, 118.8 (labelled), 112.1, 20.6.

2-(4-(Pyridin-2-yl)phenoxy-2,3,5,6-d$_4$*)pyridine (**2b-1**)* (20.3 mg, 82% yield) D-incorporation was determined against integral at δ 7.09; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (m, 1H), 8.19 (m, 1H), **8.14 (m, 1.60H)**, 7.95 (m, 1H), 7.87 (m, 2H), 7.35 (m, 1H), **7.24 (m, 1.80H)**, 7.16 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 163.2, 155.9, 155.3, 149.9, 147.9, 140.7, 137.7, 135.3, 128.3, 122.8, 121.6, 120.4, 119.7, 112.2.

2-(4-(Pyridin-2-yl)phenoxy-2,3,5,6-d$_4$*)pyridine (**2b'-1**)* (22.6 mg, 90% yield) D-incorporation was determined against integral at δ 7.35; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (dd, *J* = 7.0, 6.4 Hz, 1H), 8.19 (dd, *J* = 4.9, 1.5 Hz, 1H), **8.14 (0.20H)**, 7.95 (d, *J* = 8.0 Hz, 1H), 7.87 (m, 2H), 7.35 (m, 1H), **7.24 (0.12H)**, 7.16 (m, 1H), 7.09 (d, *J*

= 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2, 155.8, 155.2, 149.9, 147.9, 140.7, 137.7, 135.2, 128.2 (labelled), 122.8, 121.5 (labelled), 120.4, 119.8, 112.2.

2-(4-(Pyridin-2-yl)phenoxy-2,3,5,6-d_4)pyridine ***(2b'-2)*** (25.0 mg, >99% yield) D-incorporation was determined against integral at δ 7.35; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (dd, *J* = 7.0, 6.4 Hz, 1H), 8.19 (dd, *J* = 4.9, 1.5 Hz, 1H), **8.14 (m, 1.40H)**, 7.95 (d, *J* = 8.0 Hz, 1H), 7.87 (m, 2H), 7.35 (m, 1H), **7.24 (0H)**, 7.16 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.3, 155.9, 155.3, 150.0, 147.9, 140.7, 137.8, 135.3, 128.3, 122.8, 121.6 (labelled), 120.4, 119.8, 112.3.

4-(pyridin-2-yl)phen-2,6-d_2-ol ***(2q'-1)*** (17.0 mg, >99% yield) D-incorporation was determined against integral at δ 7.23; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 1H), 8.59 (d, *J* = 4.4 Hz, 1H), 7.94 (m, 2H), 7.82 (m, 2H), 7.23 (t, *J* = 5.2 Hz, 1H), **6.87 (m, 1.60H)**. ^{13}C NMR (100 MHz, DMSO-d_6): 158.9, 156.6, 149.7, 137.4, 130.1, 128.3, 121.8, 119.4, 115.9.

Ethyl (E)-3-(6-(3-methyl-4-(pyridin-2-yl)phenoxy)pyridin-3-yl)acrylate ***(8)*** White solid; m.p. 93-95°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, *J* = 4.2 Hz, 1H), 8.48 (m, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 16.1 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.36 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 14.1 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 164.5, 158.9, 153.5, 149.4, 149.1, 140.9, 139.0, 137.8, 137.3, 137.0, 131.4, 126.0, 124.4, 123.6, 122.4, 119.2, 118.7, 112.1, 60.5, 20.6, 14.6. ES-HRMS: Calcd for $C_{22}H_{21}O_3N_2$ $[M+H]^+$, 361.1543, Found 361.1546.

d*-Ethyl (E)-3-(6-(3-methyl-4-(pyridin-2-yl)phenoxy-5-d)pyridin-3-yl)acrylate* ***(8a)*** (35.9 mg, >99% yield) D-incorporation was determined against integral at δ 8.67; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, *J* = 4.2 Hz, 1H), 8.48 (m, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 16.1 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), **7.44 (d, *J* = 8.2 Hz, 0.20H)**, 7.36 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 2H), 7.08 (m, 1H), 6.68 (d, *J* = 14.1 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 164.5, 158.8, 153.5, 149.4, 149.1, 141.0, 139.0, 137.8, 137.3, 137.1, 131.4 (labelled), 126.0, 124.5, 123.7, 122.4, 119.2, 118.6, 112.1, 60.5, 20.6, 14.6. ES-HRMS: Calcd for $C_{22}H_{20}DO_3N_2$ $[M+H]^+$, 362.1609, Found 362.1597.

d*-Ethyl (E)-3-(6-(3-methyl-4-(pyridin-2-yl)phenoxy-2,6-d_2)pyridin-3-yl)acrylate* ***(8a')*** (36.0 mg, >99% yield) D-incorporation was determined against integral at δ 8.67; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (d, *J* = 4.2 Hz, 1H), 8.48 (m, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 16.1 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.36 (m, 1H), **7.12 (m, 1.76H)**, **7.08 (m, 0.18H)**, 6.68 (d, *J* = 14.1 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 164.5, 158.7, 153.5, 149.4, 149.0, 140.8, 138.9, 137.8, 137.3, 137.1, 131.3, 126.0, 124.4, 123.5, 122.5, 119.1 (labelled), 118.6, 112.2, 60.6, 20.5, 14.5. ES-HRMS: Calcd for $C_{22}H_{20}DO_3N_2$ $[M+H]^+$, 362.1609, Found 362.1595.

General procedure for the C-H carbonylation reaction

1) The substrate **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), peroxy acid (0.15 mmol), $K_2S_2O_8$ (0.2 mmol) was dissolved in TFA (0.9 mL) and DCE (0.1 mL), and the tube

was charged with Ar and sealed with a PTFE stopcock. The mixture was stirred at 120 °C for 24 h. After cooled to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ aqueous three times. The organic layer was dried by Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE:EA=4:1) to give the desired products.

2) The substrate **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), peroxy acid (0.15 mmol), $K_2S_2O_8$ (0.1 mmol), Ag_2CO_3 (0.2mmol) was dissolved in Dioxane (0.75mL), AcOH (0.15 mL) and DMSO (0.1 mL), and the tube was charged with Ar and sealed with a PTFE stopcock. The mixture was stirred at 120 °C for 24 h. After cooled to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ aqueous three times. The organic layer was dried by Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE:EA=4:1) to give the desired products

(3-Methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)(phenyl)methanone ***(3a)*** (33.6 mg, 92% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.39 (m, 1H), 8.22 (d, *J* = 3.1, 1H), 7.89 (m, 1H), 7.67 (m, 1H), 7.55 (d, *J* = 7.6, 2H), 7.50 (t, *J* = 7.4, 1H), 7.36 (m, 4H), 7.16 (m, 3H), 7.06 (d, *J* = 2.0, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 196.8, 163.2, 156.7, 153.3, 149.4, 147.9, 141.5, 140.8, 138.7, 137.3, 136.3, 135.9, 133.3, 129.7, 128.7, 125.8, 125.1, 122.4, 119.9, 119.0, 112.3, 20.4. ES-HRMS: Calcd for $C_{24}H_{19}O_2N_2$ $[M+H]^+$, 367.1441, Found 367.1441.

(4-Methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone ***(3a')*** (32.5 mg, 89% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.69 (m, 1H), 8.00 (m, 1H), 7.90 (td, *J* = 7.7, 1.8, 1H), 7.68 (m, 3H), 7.63 (dt, *J* = 7.9, 1.0, 1H), 7.57 (m, 1H), 7.54 (s, 1H), 7.41 (m, 3H), 7.26 (s, 1H), 7.02 (m, 1H), 6.71 (d, *J* = 8.3, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 194.3, 162.8, 157.9, 151.2, 149.6, 147.2, 141.1, 140.4, 137.5, 137.2, 137.1, 133.5, 131.6, 129.9, 129.7, 128.7, 125.2, 124.5, 122.7, 119.4, 111.5, 20.7. ES-HRMS: Calcd for $C_{24}H_{19}O_2N_2$ $[M+H]^+$, 367.1441, Found 367.1441.

(3-Methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)(p-tolyl)methanone ***(3a-1)*** (34.5 mg, 91% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.40 (d, *J* = 4.3 Hz, 1H), 8.22 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.89 (td, *J* = 8.4, 2.0 Hz, 1H), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 2.1 Hz, 1H), 7.16 (m, 5H), 7.02 (d, *J* = 2.3 Hz, 1H), 2.30 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 196.2, 163.1, 156.8, 153.2, 149.3, 147.9, 143.8, 141.6, 140.8, 138.7, 136.2, 135.8, 134.7, 130.0, 129.2, 125.7, 124.8, 122.4, 119.8, 118.8, 112.2, 21.5, 20.4. ES-HRMS: Calcd for $C_{25}H_{21}O_2N_2$ $[M+H]^+$, 381.1598, Found 381.1591.

(4-Methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)(p-tolyl)methanone ***(3a'-1)*** (20.1 mg, 53% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.01 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.90 (td, *J* = 7.7, 1.5 Hz, 1H), 7.71 (m, 1H), 7.61 (dd, *J* = 11.9, 8.0 Hz, 3H), 7.49 (s, 1H), 7.40 (m, 1H), 7.24 (m, 3H), 7.03 (dd, *J* = 7.0, 5.1 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 2.42 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 193.9, 162.9, 157.9, 151.1, 149.6, 147.3, 144.0, 140.8, 140.4, 137.2, 136.9, 134.8, 131.4, 130.2, 129.9, 129.3, 125.1, 124.5, 122.7, 119.4, 111.6, 21.6, 20.7.

ES-HRMS: Calcd for $C_{25}H_{21}O_2N_2$ $[M+H]^+$, 381.1598, Found 381.1590.

(4-Fluorophenyl)(3-methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)methanone ***(3a-2)*** (32.2 mg, 84% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (d, J = 4.3 Hz, 1H), 8.22 (dd, J = 4.9, 1.3 Hz, 1H), 7.90 (m, 1H), 7.69 (m, 1H), 7.62 (m, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.16 (m, 5H), 7.09 (d, J = 2.3 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.3, 165.0 (d, $^1J_{C\text{-}F}$ = 250 Hz), 163.1, 156.5, 153.4, 149.4, 147.9, 141.3, 140.8, 138.6, 136.3, 135.8, 134.1 (d, $^4J_{C\text{-}F}$ = 3 Hz), 132.6 (d, $^3J_{C\text{-}F}$ = 11 Hz), 125.8, 125.1, 122.5, 119.8, 119.0, 115.7 (d, $^2J_{C\text{-}F}$ = 22 Hz), 112.2, 20.4. ES-HRMS: Calcd for $C_{24}H_{18}O_2N_2F$ $[M+H]^+$, 385.1347, Found 385.1335.

(4-Fluorophenyl)(4-methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)methanone ***(3a'-2)*** (23.8 mg, 62% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.7 Hz, 1H), 8.00 (m, 1H), 7.91 (t, J = 7.6 Hz, 1H), 7.73 (m, 3H), 7.64 (d, J = 7.8 Hz, 1H), 7.55 (s, 1H), 7.41 (m, 1H), 7.24 (m, 3H), 7.03 (m, 1H), 6.74 (d, J = 8.2 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 192.9, 165.3 (d, $^1J_{C\text{-}F}$ = 250 Hz), 162.8, 157.9, 151.1, 149.6, 147.3, 141.3, 140.5, 137.2, 137.1, 134.1 (d, $^4J_{C\text{-}F}$ = 3 Hz), 132.6 (d, $^3J_{C\text{-}F}$ = 10 Hz), 131.5, 129.7, 125.2, 124.6, 122.8, 119.5, 115.8 (d, $^2J_{C\text{-}F}$ = 22 Hz), 111.5, 20.4. ES-HRMS: Calcd for $C_{24}H_{18}O_2N_2F$ $[M+H]^+$, 385.1347, Found 385.1329.

Mesityl(3-methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)methanone ***(3a-3)*** (33.4 mg, 82% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (m, 1H), 8.16 (m, 1H), 7.87 (m, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.25 (m, 1H), 7.15 (m, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.75 (s, 2H), 2.18 (s, 3H), 2.03 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.5, 163.0, 158.1, 153.4, 149.3, 147.7, 140.8, 140.0, 139.5, 138.9, 137.2, 136.9, 136.0, 135.0, 128.8, 127.1, 124.6, 122.2, 120.8, 119.8, 112.1, 21.0, 20.1, 20.1. ES-HRMS: Calcd for $C_{27}H_{25}O_2N_2$ $[M+H]^+$, 409.1911, Found 409.1900.

Mesityl(4-methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)methanone ***(3a'-3)*** (19.5 mg, 48% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.1 Hz, 1H), 7.99 (dd, J = 5.0, 1.6 Hz, 1H), 7.91 (td, J = 7.7, 1.8 Hz, 1H), 7.74 (s, 1H), 7.70 (m, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.41 (m, 1H), 7.22 (s, 1H), 7.02 (dd, J = 6.6, 5.1 Hz, 1H), 6.70 (s, 2H), 6.62 (d, J = 8.3 Hz, 1H), 2.40 (s, 3H), 2.15 (s, 3H), 1.95 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.5, 163.2, 157.7, 152.7, 149.7, 146.8, 143.8, 139.8, 138.6, 138.1, 138.0, 137.3, 133.6, 132.7, 129.1, 128.3, 127.2, 124.5, 122.9, 118.8, 111.2, 21.0, 20.7, 19.4. ES-HRMS: Calcd for $C_{27}H_{25}O_2N_2$ $[M+H]^+$, 409.1911, Found 409.1896.

Cyclohexyl(3-methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)methanone ***(3a-4)*** (26.7 mg, 72% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (m, 1H), 8.20 (m, 1H), 7.90 (m, 2H), 7.43 (m, 2H), 7.24 (m, 1H), 7.13 (m, 3H), 2.18 (m, 4H), 1.55 (m, 4H), 1.03 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 208.0, 163.2, 157.4, 153.5, 149.6, 147.9, 142.8, 140.8, 138.5, 136.7, 135.1, 125.6, 125.0, 122.7, 119.8, 118.1, 112.2, 49.1, 28.8, 25.7, 25.5, 20.3. ES-HRMS: Calcd for $C_{24}H_{25}O_2N_2$ $[M+H]^+$, 373.1911, Found 373.1904.

Cyclohexyl(4-methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)methanone ***(3a'-4)*** (24.1 mg, 65% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (d, J =

4.7 Hz, 1H), 8.15 (d, *J* = 4.2 Hz, 1H), 7.91 (m, 2H), 7.67 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.41 (dd, *J* = 7.2, 5.2 Hz, 1H), 7.16 (m, 3H), 3.07 (m, 1H), 2.36 (s, 3H), 1.61 (m, 4H), 1.13 (m, 6H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 204.1, 163.2, 158.0, 151.5, 149.6, 147.7, 141.5, 140.8, 137.4, 137.2, 131.2, 129.9, 125.7, 124.5, 122.7, 119.6, 111.9, 48.8, 28.9, 25.8, 25.6, 20.6. ES-HRMS: Calcd for $C_{24}H_{25}O_2N_2$ $[M+H]^+$, 373.1911, Found 373.1895.

3-Methyl-1-(3-methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)butan-1-one ***(3a-5)*** (16.6 mg, 48% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.61 (m, 1H), 8.20 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.88 (m, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.38 (m, 1H), 7.24 (m, 1H), 7.19 (m, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 2.28 (d, *J* = 6.6 Hz, 2H), 2.15 (s, 3H), 1.88 (m, 1H), 0.71 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 204.6, 163.3, 157.6, 153.5, 149.6, 147.9, 143.3, 140.8, 138.6, 136.5, 135.2, 125.6, 125.1, 122.7, 119.7, 118.1, 112.1, 50.9, 24.3, 22.6, 20.3. ES-HRMS: Calcd for $C_{22}H_{23}O_2N_2$ $[M+H]^+$, 347.1754, Found 347.1745.

3-Methyl-1-(4-methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)butan-1-one ***(3a'-5)*** (17.6 mg, 51% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.70 (m, 1H), 8.14 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.91 (m, 2H), 7.76 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.41 (m, 1H), 7.15 (m, 3H), 2.72 (d, *J* = 6.8 Hz, 2H), 2.36 (s, 3H), 2.01 (m, 1H), 0.76 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 200.2, 163.3, 158.0, 151.6, 149.6, 147.8, 142.0, 140.8, 137.4, 137.2, 131.2, 130.4, 125.7, 124.5, 122.8, 119.5, 112.0, 51.0, 24.6, 22.6, 20.6. ES-HRMS: Calcd for $C_{22}H_{23}O_2N_2$ $[M+H]^+$, 347.1754, Found 347.1743.

Phenyl(2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)methanone ***(3b)*** (30.3 mg, 86% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.22 (m, 2H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.91 (m, 1H), 7.77 (m, 2H), 7.60 (m, 2H), 7.45 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.15 (m, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 196.3, 162.9, 155.7, 154.6, 148.9, 147.9, 140.9, 140.9, 137.8, 137.5, 135.4, 132.8, 130.5, 129.0, 128.7, 123.0, 122.5, 122.5, 121.5, 120.0, 112.5. ES-HRMS: Calcd for $C_{23}H_{17}O_2N_2$ $[M+H]^+$, 353.1285, Found 353.1270.

Phenyl(5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)methanone ***(3b')*** (29.2 mg, 83% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.68 (d, *J* = 4.6 Hz, 1H), 8.35 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.25 (d, *J* = 2.1 Hz, 1H), 8.03 (m, 2H), 7.91 (t, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 3H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.42 (m, 4H), 7.04 (m, 1H), 6.76 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 194.7, 162.7, 154.9, 152.2, 150.1, 147.3, 140.6, 137.9, 137.1, 135.5, 133.8, 132.6, 130.5, 129.8, 128.8, 128.1, 123.5, 123.3, 120.7, 119.6, 111.7. ES-HRMS: Calcd for $C_{23}H_{17}O_2N_2$ $[M+H]^+$, 353.1285, Found 353.1273.

3-Methyl-1-(2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)butan-1-one ***(3b-1)*** (15.9 mg, 48% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.55 (m, 1H), 8.18 (m, 1H), 7.93 (m, 2H), 7.78 (m, 2H), 7.34 (m, 2H), 7.18 (m, 3H), 2.43 (m, 2H), 2.00 (m, 1H), 0.83 (m, 6H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 204.8, 163.0, 156.6, 154.4, 149.2, 147.9, 143.7, 140.8, 137.8, 134.6, 131.0, 122.8, 122.6, 120.2, 119.9, 115.9, 112.3, 51.2, 24.5, 22.8. ES-HRMS: Calcd for $C_{21}H_{21}O_2N_2$ $[M+H]^+$, 333.1598, Found 333.1583.

3-Methyl-1-(5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)butan-1-one ***(3b'-1)*** (14.6

mg, 44% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (m, 1H), 8.40 (d, J = 2.3 Hz, 1H), 8.28 (dd, J = 8.5, 2.3 Hz, 1H), 8.14 (m, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.91 (m, 2H), 7.40 (m, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.16 (m, 2H), 2.78 (d, J = 6.8 Hz, 2H), 2.05 (m, 1H), 0.79 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 201.3, 163.0, 155.0, 152.5, 150.0, 147.8, 140.8, 137.8, 135.8, 133.3, 131.1, 127.7, 124.0, 123.2, 120.7, 119.7, 112.1, 51.2, 24.6, 22.6. ES-HRMS: Calcd for $C_{21}H_{21}O_2N_2$ $[M+H]^+$, 333.1598, Found 333.1584.

(4-Methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)(phenyl)methanone ***(3c)*** (29.0 mg, 79% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (d, J = 4.7 Hz, 1H), 8.16 (m, 1H), 7.97 (m, 2H), 7.76 (m, 2H), 7.57 (d, J = 7.4 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.13 (m, 4H), 2.26 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.2, 163.1, 156.0, 152.6, 148.9, 147.8, 140.8, 138.4, 138.0, 137.3, 136.1, 133.0, 132.7, 132.0, 129.1, 128.6, 122.7, 122.6, 122.5, 119.5, 111.6, 16.5. ES-HRMS: Calcd for $C_{24}H_{19}O_2N_2$ $[M+H]^+$, 367.1441, Found 367.1437.

(3-Methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)(phenyl)methanone ***(3c')*** (30.7 mg, 84% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (d, J = 4.0, 1H), 8.27 (d, J = 1.7, 1H), 8.05 (m, 2H), 7.94 (dd, J = 4.9, 1.4, 1H), 7.90 (td, J = 7.8, 1.7, 1H), 7.74 (m, 3H), 7.60 (t, J = 7.4, 1H), 7.45 (t, J = 7.7, 2H), 7.37 (dd, J = 7.1, 5.1, 1H), 6.98 (dd, J = 6.8, 5.3, 1H), 6.72 (d, J = 8.3, 1H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 194.9, 162.7, 155.1, 150.1, 150.0, 147.2, 140.4, 137.8, 137.2, 135.7, 133.7, 133.6, 132.9, 131.9, 129.9, 128.8, 125.7, 123.2, 120.7, 119.0, 110.8, 16.9. ES-HRMS: Calcd for $C_{24}H_{19}O_2N_2$ $[M+H]^+$, 367.1441, Found 367.1441.

Cyclohexyl(4-methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl)methanone ***(3c-1)*** (29.7 mg, 80% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (d, J = 4.2 Hz, 1H), 8.13 (dd, J = 4.9, 1.3 Hz, 1H), 7.95 (t, J = 7.3 Hz, 1H), 7.94 (m, 2H), 7.77 (s, 1H), 7.38 (m, 1H), 7.12 (m, 2H), 7.03 (s, 1H), 2.17 (m, 4H), 1.63 (m, 4H), 1.24 (m, 2H), 0.94 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 208.1, 163.1, 156.3, 152.5, 149.3, 147.8, 140.8, 140.2, 137.8, 134.8, 132.6, 132.1, 122.8, 122.4, 121.8, 119.4, 111.5, 50.1, 29.1, 25.9, 25.6, 16.4. ES-HRMS: Calcd for $C_{24}H_{25}O_2N_2$ $[M+H]^+$, 373.1911, Found 373.1895.

Cyclohexyl(3-methyl-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)methanone ***(3c'-1)*** (23.8 mg, 64% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.6 Hz, 1H), 8.19 (d, J = 1.5 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.06 (m, 2H), 7.88 (m, 2H), 7.38 (m, 1H), 7.12 (m, 2H), 3.01 (m, 1H), 2.13 (s, 3H), 1.62 (m, 4H), 1.13 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 205.6, 163.0, 155.2, 150.1, 150.0, 147.6, 140.8, 137.7, 136.1, 134.3, 133.0, 132.1, 125.2, 123.2, 120.8, 119.1, 110.9, 48.9, 28.8, 25.8, 25.5, 16.9. ES-HRMS: Calcd for $C_{24}H_{25}O_2N_2$ $[M+H]^+$, 373.1911, Found 373.1905.

1-(4-Fluoro-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)phenyl)-3-methylbutan-1-one ***(3d')*** (15.0 mg, 43% yield) yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.54 (d, J = 4.2 Hz, 1H), 7.93 (m, 2H), 7.71 (m, 2H), 7.60 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 8.9 Hz, 1H), 7.23 (m, 1H), 6.98 (dd, J = 6.7, 5.1 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 2.65 (d, J = 6.7 Hz, 2H), 1.98 (m, 1H), 0.76 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.6, 162.5, 158.9 (d, $^1J_{C\text{-}F}$ = 248 Hz), 153.8, 149.9, 148.2 (d, $^3J_{C\text{-}F}$ = 7 Hz), 147.3, 140.6, 136.8, 133.7 (d, $^3J_{C\text{-}F}$ = 10 Hz), 131.3 (d, $^4J_{C\text{-}F}$ = 3 Hz), 125.0 (d, $^2J_{C\text{-}F}$ = 20 Hz), 124.1,

123.0, 119.4, 113.8 (d, $^{2}J_{C\text{-}F}$ = 23 Hz), 111.3, 53.0, 24.0, 22.4. ES-HRMS: Calcd for $C_{21}H_{20}O_2N_2F$ $[M+H]^+$, 351.1503, Found 351.1487.

3-Methyl-1-(5-(pyridin-2-yl)-2-(pyridin-2-yloxy)-[1,1'-biphenyl]-4-yl)butan-1-one ***(3g)*** (24.4 mg, 60% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (m, 1H), 8.09 (m, 1H), 7.94 (m, 2H), 7.79 (m, 2H), 7.57 (m, 2H), 7.37 (m, 4H), 7.29 (s, 1H), 7.08 (m, 1H), 7.01 (d, J = 8.3 Hz, 1H), 2.47 (d, J = 6.6 Hz, 2H), 2.03 (m, 1H), 0.85 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 204.5, 163.4, 156.6, 151.1, 149.2, 147.7, 142.5, 140.6, 137.7, 136.8, 135.7, 135.6, 132.1, 129.2, 128.7, 128.2, 123.0, 122.4, 119.4, 111.9, 51.2, 24.6, 22.8. ES-HRMS: Calcd for $C_{27}H_{25}O_2N_2$ $[M+H]^+$, 409.1911, Found 409.1893.

3-Methyl-1-(5-(pyridin-2-yl)-2-(pyridin-2-yloxy)-[1,1'-biphenyl]-3-yl)butan-1-one ***(3g')*** (22.0 mg, 54% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (m, 1H), 8.37 (d, J = 2.3 Hz, 1H), 8.28 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.94 (m, 2H), 7.71 (m, 1H), 7.43 (m, 3H), 7.30 (m, 3H), 6.97 (m, 1H), 6.88 (d, J = 8.3 Hz, 1H), 2.78 (d, J = 6.8 Hz, 2H), 2.01 (m, 1H), 0.75 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 201.7, 163.0, 154.9, 150.1, 148.5, 147.3, 140.4, 137.8, 137.3, 136.8, 136.4, 135.5, 132.0, 129.3, 128.6, 128.0, 126.6, 123.4, 121.0, 118.9, 111.4, 50.9, 24.3, 22.5. ES-HRMS: Calcd for $C_{27}H_{25}O_2N_2$ $[M+H]^+$, 409.1911, Found 409.1897.

1-(4'-Fluoro-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)-[1,1'-biphenyl]-4-yl)-3-methylbutan-1-one ***(3l)*** (25.9 mg, 61% yield) yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56 (m, 1H), 8.09 (dd, J = 4.9, 1.3 Hz, 1H), 7.92 (m, 2H), 7.81 (m, 2H), 7.61 (m, 2H), 7.39 (m, 1H), 7.29 (s, 1H), 7.21 (m, 2H), 7.13 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 2.46 (d, J = 6.6 Hz, 2H), 2.03 (m, 1H), 0.85 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 204.5, 163.2, 162.2 (d, $^{1}J_{C\text{-}F}$ = 244 Hz), 156.5, 151.1, 149.2, 147.7, 142.6, 140.6, 137.7, 135.6, 134.7, 133.1 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 132.1, 131.3 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 123.0, 122.4, 119.5, 115.6 (d, $^{2}J_{C\text{-}F}$ = 21 Hz), 111.9, 51.2, 24.6, 22.8. ES-HRMS: Calcd for $C_{27}H_{24}O_2N_2F$ $[M+H]^+$, 427.1816, Found 427.1796.

1-(4'-Fluoro-5-(pyridin-2-yl)-2-(pyridin-2-yloxy)-[1,1'-biphenyl]-3-yl)-3-methylbutan-1-one ***(3l')*** (24.3 mg, 57% yield) yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (m, 1H), 8.37 (d, J = 2.3 Hz, 1H), 8.27 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.94 (m, 2H), 7.73 (m, 1H), 7.50 (m, 2H), 7.42 (m, 1H), 7.17 (m, 2H), 6.98 (m, 1H), 6.89 (d, J = 8.3 Hz, 1H), 2.78 (d, J = 6.8 Hz, 2H), 2.00 (m, 1H), 0.75 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 201.7, 162.9, 162.0 (d, $^{1}J_{C\text{-}F}$ = 243 Hz), 154.8, 150.0, 148.5, 147.3, 140.5, 137.8, 136.4, 135.8, 135.5, 133.6 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 132.0, 131.4 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 126.7, 123.4, 121.0, 119.0, 115.5 (d, $^{2}J_{C\text{-}F}$ = 21 Hz), 111.4, 51.2, 24.3, 22.5. ES-HRMS: Calcd for $C_{27}H_{24}O_2N_2F$ $[M+H]^+$, 427.1816, Found 427.1805.

General procedure for the C-H Bromination and Iodination reaction

The substrate **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 or 0.02 mmol), NIS or NBS (0.15 mmol) was dissolved in AcOH or TFA (1.0 mL), and the tube was sealed with a PTFE stopcock. The mixture was stirred at 120 °C for 6-8 h. After cooled to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ aqueous three times. The organic layer was dried by

Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE:EA=4:1) to give the desired products.

2-(3-Iodo-5-methyl-4-(pyridin-2-yl)phenoxy)pyridine ***(4a)*** (31.0 mg, 80% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (d, J = 4.2 Hz, 1H), 8.21 (dd, J = 4.9, 1.3 Hz, 1H), 7.91 (m, 2H), 7.54 (d, J = 2.1 Hz, 1H), 7.43 (m, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.17 (m, 2H), 7.11 (d, J = 8.3 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2, 161.0, 153.9, 149.8, 147.9, 141.7, 140.8, 138.8, 137.2, 128.9, 125.1, 123.2, 123.1, 119.8, 112.1, 99.1, 21.4. ES-HRMS: Calcd for $C_{17}H_{14}ON_2I$ $[M+H]^+$, 389.0145, Found 389.0134.

2-(5-Iodo-2-methyl-4-(pyridin-2-yloxy)phenyl)pyridine ***(4a')*** (29.1 mg, 75% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.7 Hz, 1H), 8.14 (d, J = 4.8 Hz, 1H), 7.90 (t, J = 7.7 Hz, 2H), 7.86 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.41 (m, 1H), 7.14 (m, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.9, 157.3, 153.8, 149.6, 147.7, 140.7, 140.2, 139.3, 138.1, 137.1, 125.6, 124.5, 122.8, 119.4, 111.7, 88.5, 20.3. ES-HRMS: Calcd for $C_{17}H_{14}ON_2I$ $[M+H]^+$, 389.0145, Found 389.0138.

2-(3,5-Diiodo-4-(pyridin-2-yl)phenoxy)pyridine ***(4b)*** (26.5 mg, 53% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (m, 1H), 8.22 (dd, J = 4.9, 1.9, 1H), 7.93 (m, 2H), 7.79 (s, 2H), 7.44 (dd, J = 7.4, 4.9, 1H), 7.33 (d, J = 7.8, 1H), 7.21 (dd, J = 7.2, 5.0, 1H), 7.15 (d, J = 8.3, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 162.8, 154.1, 149.5, 147.8, 145.2, 141.0, 137.2, 131.6, 124.6, 123.8, 120.2, 112.3, 97.6. ES-HRMS: Calcd for $C_{16}H_{11}ON_2I_2$ $[M+H]^+$, 500.8955, Found 500.8959.

2-(2,6-Diiodo-4-(pyridin-2-yl)phenoxy)pyridine ***(4b'-1)*** (22.5 mg, 45% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (m, 1H), 8.59 (s, 2H), 8.09 (m, 2H), 7.92 (m, 2H), 7.42 (m, 1H), 7.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7, 154.3, 152.9, 150.1, 147.5, 140.9, 139.4, 137.9, 137.6, 123.7, 121.2, 119.5, 111.7, 93.8. ES-HRMS: Calcd for $C_{16}H_{11}ON_2I_2$ $[M+H]^+$, 500.8955, Found 500.8959.

2-(2-Iodo-4-(pyridin-2-yl)phenoxy)pyridine ***(4b'-2)*** (14.2 mg, 38% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (dd, J = 4.8, 0.8, 1H), 8.61 (d, J = 2.1, 1H), 8.14 (m, 2H), 8.02 (d, J = 8.0, 1H), 7.91 (td, J = 7.8, 1.9, 2H), 7.39 (m, 1H), 7.29 (d, J = 8.5, 1H), 7.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8, 154.8, 154.3, 150.0, 147.7, 140.8, 137.8, 137.6, 137.6, 128.2, 123.7, 123.3, 120.8, 119.6, 111.9, 92.7. ES-HRMS: Calcd for $C_{16}H_{12}ON_2I$ $[M+H]^+$, 374.9988, Found 374.9990

2-(5-Iodo-2-methyl-4-(pyridin-2-yl)phenoxy)pyridine ***(4c)*** (26.4 mg, 68% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (m, 1H), 8.15 (dd, J = 4.9, 1.8, 1H), 7.90 (m, 2H), 7.63 (s, 1H), 7.58 (d, J = 7.8, 1H), 7.42 (m, 2H), 7.13 (m, 2H), 2.08 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0, 160.1, 152.5, 149.4, 147.8, 141.9, 140.8, 136.7, 132.9, 132.7, 131.1, 124.6, 123.1, 119.4, 111.5, 93.5, 16.1. ES-HRMS: Calcd for $C_{17}H_{14}ON_2I$ $[M+H]^+$, 389.0145, Found 389.0145.

2-(3-Iodo-5-methyl-4-(pyridin-2-yloxy)phenyl)pyridine ***(4c')*** (32.6 mg, 84% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, J = 4.7, 1H), 8.42 (d, J = 1.8, 1H), 8.08 (dd, J = 5.4, 1.6, 1H), 8.04 (d, J = 1.3, 1H), 8.01 (d, J = 8.0, 1H), 7.90 (td, J = 8.0, 1.5, 2H), 7.38 (dd, J = 7.4, 4.8, 1H), 7.12 (m, 2H), 2.16 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 154.5, 152.9, 150.0, 147.6, 140.8, 137.8, 137.8, 135.2, 133.2, 129.7, 123.3, 120.8, 119.2, 111.2, 94.0, 17.7. ES-HRMS: Calcd for $C_{17}H_{14}ON_2I$

$[M+H]^+$, 389.0145, Found 389.0145.

*2-(5-Bromo-2-methyl-4-(pyridin-2-yloxy)phenyl)pyridine (**5a'**)* (30.6 mg, 90% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.2 Hz, 1H), 8.14 (m, 1H), 7.88 (m, 2H), 7.70 (s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.41 (m, 1H), 7.25 (s, 1H), 7.15 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.9, 157.4, 150.6, 149.6, 147.7, 140.8, 139.1, 137.4, 137.2, 134.3, 126.5, 124.5, 122.9, 119.5, 113.3, 111.5, 20.2. ES-HRMS: Calcd for $C_{17}H_{14}ON_2Br$ $[M+H]^+$, 341.0284 (^{79}Br), Found 341.0280 (^{79}Br).

*2-(3,5-Dibromo-4-(pyridin-2-yl)phenoxy)pyridine (**5b**)* (33.2 mg, 82% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (d, J = 3.0, 1H), 8.23 (d, J = 2.7, 1H), 7.94 (m, 2H), 7.64 (m, 2H), 7.45 (m, 2H), 7.24 (m, 1H), 7.18 (d, J = 8.2, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.7, 158.2, 154.6, 149.8, 147.8, 141.0, 138.4, 137.3, 125.3, 125.1, 123.8, 123.5, 120.3, 112.4. ES-HRMS: Calcd for $C_{16}H_{11}ON_2Br_2$ $[M+H]^+$, 404.9232 (^{79}Br) Found 404.9234, 406.9212, 408.9189.

*2-(2,6-Dibromo-4-(pyridin-2-yl)phenoxy)pyridine (**5b'-1**)* (20.2 mg, 50% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (d, J = 4.1, 1H), 8.44 (m, 2H), 8.13 (d, J = 8.0, 1H), 8.10 (m, 1H), 7.94 (t, J = 7.8, 2H), 7.44 (dd, J = 7.3, 4.9, 1H), 7.23 (d, J = 8.3, 1H), 7.17 (dd, J = 6.7, 5.4, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7, 153.0, 150.1, 148.7, 147.5, 141.1, 139.0, 138.0, 130.8, 124.0, 121.3, 119.8, 119.2, 111.1. ES-HRMS: Calcd for $C_{16}H_{11}ON_2Br_2$ $[M+H]^+$, 404.9232 (^{79}Br) Found 404.9234, 406.9212, 408.9189.

*2-(2-Bromo-4-(pyridin-2-yl)phenoxy)pyridine (**5b'-2**)* (11.4 mg, 35% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (d, J = 4.6, 1H), 8.43 (m, 1H), 8.14 (m, 2H), 8.05 (d, J = 7.9, 1H), 7.93 (m, 2H), 7.39 (m, 2H), 7.17 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.7, 154.3, 151.7, 150.1, 147.7, 140.9, 137.9, 137.6, 131.5, 127.5, 124.8, 123.4, 120.8, 119.7, 116.9, 111.6. ES-HRMS: Calcd for $C_{16}H_{12}ON_2Br$ $[M+H]^+$, 327.0127 (^{79}Br) Found 327.0129 (^{79}Br).

*2-(5-Bromo-2-methyl-4-(pyridin-2-yl)phenoxy)pyridine (**5c**)* (27.8 mg, 82% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (m, 1H), 8.16 (dd, J = 4.6, 1.5, 1H), 7.90 (m, 2H), 7.65 (d, J = 7.8, 1H), 7.50 (s, 1H), 7.43 (m, 2H), 7.5 (m, 2H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0, 157.6, 152.8, 149.6, 147.8, 140.8, 138.0, 136.7, 134.1, 130.7, 126.6, 124.9, 123.2, 119.5, 118.3, 111.5, 16.0. ES-HRMS: Calcd for $C_{17}H_{14}ON_2Br$ $[M+H]^+$, 341.0284 (^{79}Br), Found 341.0280 (^{79}Br).

*2-(3-Bromo-5-methyl-4-(pyridin-2-yloxy)phenyl)pyridine (**5c'**)* (31.6 mg, 93% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.67 (m, 1H), 8.23 (d, J = 2.0, 1H), 8.08 (dd, J = 4.9, 1.4, 1H), 8.06 (d, J = 1.6, 1H), 8.03 (d, J = 8.0,1H), 7.91 (m, 2H), 7.38 (m, 1H), 7.13 (m, 2H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 154.5, 150.0, 149.9, 147.6, 140.8, 137.8, 137.5, 134.2, 129.0, 128.9, 123.4, 120.8, 119.3, 117.9, 110.9, 17.3. ES-HRMS: Calcd for $C_{17}H_{14}ON_2Br$ $[M+H]^+$, 341.0284 (^{79}Br), Found 341.0280 (^{79}Br).

*Ethyl (E)-3-(6-(2-iodo-5-methyl-4-(pyridin-2-yl)phenoxy)pyridin-3-yl)acrylate (**8-I'**)* (43.8 mg, 90% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, J = 4.4 Hz, 1H), 8.46 (d, J = 1.9 Hz, 1H), 8.32 (dd, J = 8.6, 2.1 Hz, 1H), 7.89 (m, 2H), 7.64 (dd, J = 20.4, 12.0 Hz, 2H), 7.40 (dd, J = 7.0, 5.3 Hz, 1H), 7.19 (m, 2H), 6.69 (d,

J = 16.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.30 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.5, 163.9, 157.3, 153.5, 149.6, 148.9, 140.9, 140.2, 139.7, 139.2, 138.2, 137.1, 126.1, 125.7, 124.5, 122.8, 118.7, 112.0, 88.4, 60.5, 20.3, 14.6. ES-HRMS: Calcd for $C_{22}H_{20}O_3N_2I$ $[M+H]^+$, 487.0513, Found 487.0498.

General procedure for the C-H oxidation reaction

a) The substrate **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 or 0.02 mmol), $PhI(OAc)_2$ (0.2 mmol) was dissolved in AcOH (0.5 mL) and Ac_2O (0.5 mL), and the tube was sealed with a PTFE stopcock. The mixture was stirred at 120 °C for 12 h. After cooled to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ aqueous three times. The organic layer was dried by Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE:EA=2:1) to give the desired products.

b) The substrate **1** (0.1 mmol), $Pd(OAc)_2$ (0.01 or 0.02 mmol), $K_2S_2O_8$ (0.2 mmol) was dissolved in TFA (0.9 mL) and $(CF_3CO)_2O$ (0.1 mL), and the tube was sealed with a PTFE stopcock. The mixture was stirred at 120 °C for 12 h. After cooled to room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ aqueous three times. The organic layer was dried by Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Ac_2O (0.02 mL) and triethylamine (0.02 mL) were added to the solution. The mixture was stirred at room temperature for 2 h. The solvent was evaporated *in vacuo*. The residue was dissolved in DCM (20 mL) and washed with saturated $NaHCO_3$ aqueous three times. The organic layer was dried by Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (PE:EA=2:1) to give the mixed products.

*3-Methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl acetate (**6a**)* (28.9 mg, 90% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (d, *J* = 4.8, 1H), 8.21 (dd, *J* = 4.9, 1.3, 1H), 7.90 (m, 2H), 7.41 (dd, *J* = 7.0, 5.4, 1H), 7.34 (d, *J* = 7.8, 1H), 7.18 (dd, *J* = 6.8, 5.4, 1H), 7.11 (d, *J* = 8.3, 1H), 7.03 (d, *J* = 1.8, 1H), 6.90 (d, *J* = 2.0, 1H), 2.11 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.0, 163.0, 154.8, 154.0, 149.6, 149.3, 148.0, 140.8, 139.2, 137.1, 130.1, 125.4, 123.0, 120.6, 119.9, 113.7, 112.2, 20.7, 20.1. ES-HRMS: Calcd for $C_{19}H_{16}O_3N_2$ $[M+H]^+$, 321.1233, Found 321.1230.

*4-Methyl-2-(pyridin-2-yl)-5-(pyridin-2-yloxy)phenyl acetate (**6c**)* (26.6 mg, 83% yield) colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (m, 1H), 8.16 (m, 1H), 7.88 (m, 2H), 7.71 (s, 1H), 7.65 (d, *J* = 7.9, 1H), 7.36 (m, 1H), 7.13 (m, 3H), 6.98 (s, 1H), 2.14 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 163.0, 154.8, 152.9, 149.9, 147.9, 146.8, 140.8, 137.2, 132.9, 129.6, 128.6, 123.6, 122.8, 119.5, 117.4, 111.5, 21.1, 16.0. ES-HRMS: Calcd for $C_{19}H_{16}O_3N_2$ $[M+H]^+$, 321.1233, Found 321.1230.

Procedure for the reductive amination

To the solution of compound ***d*-7a** (0.1 mmol) in methanol (3 mL) was added the corresponding amine (0.15 mmol). The mixture was stirred at room temperature for 1h. Then Pd/C (5%, 35 mg) was added and the solution was stirred under hydrogen (1atm) for another 3 h. The Pd/C was removed by filtration and the filtrated was purified by Combiflash C18 column to give the desired product ***d*-7**.

1-(2-(((6-(2-Methyl-4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyridin-2-yl)methyl)amino)ethyl)imidazolidin-2-one (7) Colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H), 7.85 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 1H), 7.16 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.26 (s, 1H), 3.87 (s , 2H), 3.33 (t, J = 7.7 Hz, 2H), 3.17 (dd, J = 13.2, 6.9 Hz, 4H), 2.67 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 162.8, 160.1, 158.0, 153.0, 145.8 (q, $^{4}J_{C\text{-}F}$ = 4.4 Hz), 138.0, 137.8, 137.4, 131.5, 124.3 (q, $^{1}J_{C\text{-}F}$ = 270 Hz), 123.8, 122.3, 121.0, 120.7, 120.4, 119.4, 112.2, 54.7, 47.2, 45.3, 43.5, 37.9, 20.7. ES-HRMS: Calcd for $C_{24}H_{25}O_2N_5F_3$ $[M+H]^+$, 472.1939, Found 472.1954.

d-*1-(2-(((6-(2-Methyl-4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl-3,5,6-d_3)pyridin-2-yl)methyl)amino)ethyl)imidazolidin-2-one (**d-7**)* (30.8 mg, 65% yield) D-incorporation was determined against integral at δ 8.25; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H), 7.85 (t, J = 7.7 Hz, 1H), **7.47 (s, 0.95H)**, 7.41 (t, J = 7.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 1H), **7.16 (s, 0.60H)**, **7.12 (m, 0.05H)**, 6.26 (s, 1H), 3.87 (s, 2H), 3.33 (t, J = 7.7 Hz, 2H), 3.17 (dd, J = 13.2, 6.9 Hz, 4H), 2.67 (t, J = 6.3 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 162.8, 159.8, 158.0, 153.0, 145.8 (q, $^{4}J_{C\text{-}F}$ = 4.4 Hz), 138.0, 137.8, 137.4, 131.4, 124.3 (d, $^{1}J_{C\text{-}F}$ = 270 Hz), 123.8, 122.4, 121.0, 120.7, 120.5, 119.4 (labelled), 112.2, 54.5, 47.1, 45.3, 43.4, 37.9, 20.6 ES-HRMS: Calcd for $C_{24}H_{23}D_2O_2N_5F_3$ $[M+H]^+$, 474.2069, Found 474.2065.

Procedure for the synthesis of complex I and II

1b (0.5 mmol), $Pd(OAc)_2$ (0.5 mmol) was dissolved in AcOH or TFA (5 mL). The mixture was stirred at 50 °C for 10 h. The solvent was removed *in vacuo.* The residue was washed with MeOH or ethyl acetate to give the complex **I** or **II.**

Complex **I** ^{1}H NMR (400 MHz, DMSO-d_6): δ1H NMR (400 MHz, DMSO) δ 8.31 (m, 1H), 7.89 (m, 2H), 7.66 (m, 1H), 7.46 (m, 1H), 7.18 (m, 3H), 6.82 (m, 1H), 6.64 (m, 1H), 6.32 (m, 1H), 1.86 (s, 3H).

Complex **II** ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.82 (dd, J = 6.0, 1.5 Hz, 1H), 8.36 (dd, J = 5.6, 1.2 Hz, 1H), 8.00 (m, 2H), 7.42 (m, 1H), 7.13 (m, 3H), 6.87 (td, J = 7.8, 1.6 Hz, 1H), 6.72 (*d*, J = 7.3 Hz, 1H), 4.86 (m, 1H).

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Supporting informationt

The synthesis of substrate **1** and copies of ^{1}H and ^{13}C NMR spectra of substrate **1** and the products or intermediates

Reference

(1) a) Katsnelson, A. *Nature Med.* **2013**, *19*, 656. b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529-2591. c) Jacques, V.; Czarnik, A. W.; Judge, T. M.; Van der Ploeg, L. H. T.; DeWitt, S. H. *Proc. Natl. Acad. Sci.* **2015**, *112*, E1471-1479. d) Elmore, C. S. *Annu. Rep. Med. Chem.* **2009**, *44*, 515-534.

(2) a) Chen, Y. *PCT Int. Appl*. **2013**, WO 2013087004. b) *Faming Zhuanli Shenqing*,

2013, CN 103159680.
(3) For selected reviews on C-H activation, see: a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094-5115. b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740-4761. c) Sun, C.-L.; Li B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293-1314. d) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067-2096. e) Conejero, S.; Paneque, M.; Poveda, M. L.; Santos, L. L.; Carmona, E. *Acc. Chem. Res.* **2010**, *43*, 572-580. f) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704-724. g) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281-295.
(4) For selected examples, see: a) Kerr, W. J.; Lindsay, D. M.; Reid, M.; Atzrodt, J.; Derdau, V. P.; Weck, R. *Chem. Commun.* **2016**, *52*, 6669-6672. b) Rojahn, L. P.; Salas, F.; Mnzini, S.; Nolan, S. P. *Org. Biomol. Chem.* **2014**, *12*, 8683-8688. c) Bresó-Femenia, E.; Godard, C.; Claver, C.; Chaudret, B.; Castillón, S. *Chem. Commun.* **2015**, *51*, 16342-16345. d) Hickman, A. J.; Cismesia, M. A.; Sanford, M. S. *Organometallics*, **2012**, *31*, 1761-1766.
(5) For selected examples, see: a) Cho, J.-Y.; Iverso, C. N.; Smith III, M. R. *J. Am. Chem. Soc*. **2000**, *122*, 12868-12869. b) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546-576. c) Wencel-Delord, J.; Glorius, F. *Nature Chem.* **2013**, *5*, 369-375. d) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275-1277. e) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326-10329.
(6) a) Malik, H. A.; Taylor, B. L. H.; Kerrigan, J. R.; Grob, J. E.; Houk, K. N.; Du Bois, J.; Hamann, L. G.; Patterson, A. W. *Chem. Sci.* **2014**, *5*, 2352-2361. b) Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Nature*, **2014**, *515*, 389-393. c) Wang, H.; Lorion, M. M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 10386-10390. d) Shang, M.; Wang, M.-M.; Saint-Denis, T. G.; Li, M.-H.; Dai, H.-X. ; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 5317-5321.
(7) For selected examples, see: a) Ni, C.; Shao, B.; Tafesse, L.; Yao, J.; Yu, J.; Zhou, X. *PCT Int. Appl.* **2012**, WO 2012035421. b) Akira, M.; Naotake, K.; Yuji, N.; Sachie, T.; Shiro, K.; Kana, W.; Mitsuhiro, Y. *PCT Int. Appl.* **2013**, WO 2013035827. c) Yao, J.; Tafesse, L. *PCT Int. Appl.* **2014**, WO 2014151393. d) Yamagishi, T.; Okumura, Y.; Nukui, S.; Nakao, K. *PCT Int. Appl.* **2005**, WO 2005021508.
(8) For selected examples, see: a) Xu, J.-W.; Zhang, Z.-Z.; Rao, W.-H.; Shi, B.-F. *J. Am. Chem. Soc.* **2016**, *138*, 10750-10753. b) Das, P.; Saha, D.; Guin, J. *ACS Catal.* **2016**, *6*, 6050-6054. c) Liang, Y.-F.; Wang, X.; Tang, C.; Shen, T.; Liu, J.; Jiao, N. *Chem. Commun.* **2016**, *52*, 1416-1419.
(9) a) Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 734-737. b) Yang, Y.-F.; Chen, G.; Hong, X.; Yu, J.-Q.; Houk, K. N. *J. Am. Chem. Soc.* **2017**, *139,* 8514-8521.
(10) a) Dai, H. X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y. H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222-7228. b) Liu, X.-H.; Park, H.; Hu, J.-H.; Hu, Y.; Zhang, Q.-L.; Wang, B.-L.; Sun, B.; Yeung, K.-S.; Zhang F.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 888-896.
(11) a) Lu, W.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Takaki K.; Fujiwara, Y. *J.*

Organomet. Chem. **1999**, *580*, 290-294. b) Taniguchi, Y.; Yamaoka, Y.; Nakata, K.; Takaki K.; Fujiwara, Y. *Chem. Lett.* **1995**, *24*, 345-346.
(12) a) Lee, P.-Y.; Liang, P.; Yu, W.-Y. *Org. Lett.* **2017**, *19*, 2082-2085. b) Zhang, Q.; Wang, Y.; Yan, T.; Li, L.; Li, D. *Tetrahydron Lett.* **2016**, *57*, 90-94.