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Pd(II)-Catalyzed Pyridine *N*-Oxides Directed Arylation of Unactivated C_{sp^3}–H Bonds

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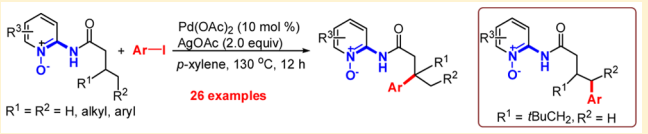
Supporting Information

ABSTRACT: A novel Pd(II)-catalyzed pyridine *N*-oxide directed remote arylation of unactivated C_{sp^3}–H bonds in aliphatic amides with aryl iodides has been developed. This protocol allows installing various aryl groups at the β- or γ-C_{sp^3} atom of alkyl carboxylic acid amides. The key palladabicyclic intermediate of this transformation has been identified by HR-MS and ^{1}H NMR method.

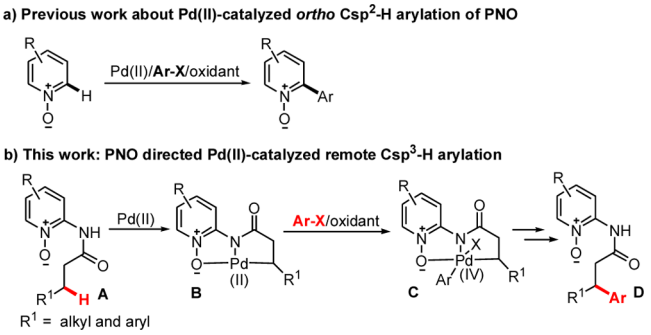


INTRODUCTION

Heteroatom directed transition-metal-catalyzed C–H functionalization provides a concise access to the site-selectively constructing carbon–carbon bonds. In the past decade, remarkable progress in this field has been achieved based on C(sp^2)–H bond activation, which can occur due to that coordination–chelating interaction of metal catalysts with the π-electron system from arenes or alkenes easily enable the C_{sp^2}–H functionalization.[1] In comparison, transition-metal-catalyzed unactivated C_{sp^3}–H functionalization is quite difficult because of the possible β-H elimination from the metalated alkyl intermediates.[2] Nevertheless, Yu recently developed a novel monodentate amide directed Pd(II)-catalyzed C_{sp^3}–H bond arylation and alkylation in which the β-carbon of amide was limited to tertiary or quaternary carbon atom.[3] To surmount this limitation, and considering that the high oxidation state of cyclometalated species could be possibly formed between the heteroatom-containing bidentate group and unbranched-chain-alkyl carbon atom in the absence of the Thorpe–Ingold effect, and the corresponding bidentate coordination would also further inhibit the β-H elimination by saturating the coordination sites on the metal atom, Daugulis, Chen, and Shi et al. therefore explored the effect of various bidentate directing groups on the unactivated C_{sp^3}–H bond functionalization and found 8-aminoquinoline,[4] picolinamide,[5] 2-alkylthioaniline,[6] and 2-(pyridine-2yl)isopropylamine[7] could efficiently enhance the unactivated C_{sp^3}–H bond arylation, alkylation, and acetoxylation. However, albeit significant progress has been achieved in this regard, developing novel bidentate directing groups is still important for exploring the potential novel C–H bond functionalization reactions.

Recently, the pyridine moiety has been widely employed as a directing group to enhance metal-catalyzed C–H bond activation,[8] but the pyridine *N*-oxides (PNO) directed remote C_{sp^3}–H functionalization was rarely reported. Nevertheless, the Chang, Wu, and Fu, Hartwig groups and Fagnou et al. recently realized Pd(II)-catalyzed the *ortho* C–H bond alkylation,[9] alkenylation,[10] and arylation (Scheme 1a)[11] of PNO, respectively. More recently, Song and co-workers reported copper salts could efficiently promote the PNO-directed C_{sp^2}–H bond aryloxylation and alkoxylation.[12] The above-mentioned works implied that PNO could be possibly used as an attractive platform for remote C_{sp^3}–H functionalization. Encouraged by these works, we expect that a suitable pyridine *N*-oxide-containing alkyl amide (**A**) not only may be employed as a bidetante functional group to form a palladabicyclic intermediate (**B**) but also may easily enable the Pd(II) → Pd(IV) process to occur due to the fact that PNO (X-type ligand) can increase the electron density at the Pd(II) center, and finally lead to the remote C_{sp^3}–H functionalization (Scheme 1b).

Scheme 1. PNO-Directed C_{sp^2}–H and C_{sp^3}–H Functionalization



RESULTS AND DISCUSSION

To prove this hypothesis, we initially designed and generated the *N*-(1-oxy-pyridin-2-yl)-propionamide **1a** and investigated the halide substituting effect of phenyl halides (**2a**–**2c**) on the

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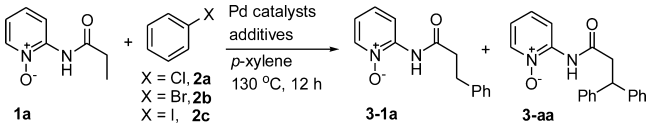
remote C_{sp^3}–H bond arylation in the presence of $PdCl_2$ (10 mol %) and Ag_2CO_3 (2.0 equiv), using *p*-xylene as solvent at 130 °C for 12 h (Table 1, entries 1–3). To our delight, we

Table 1. Optimization of the Reaction Parameters[a]



entry	Pd catalysts	Ar–X, 2	additives	yield (%)
1	$PdCl_2$	**2a**	Ag_2CO_3	8[b]
2	$PdCl_2$	**2b**	Ag_2CO_3	10[b]
3	$PdCl_2$	**2c**	Ag_2CO_3	50[b]
4	$Pd(TFA)_2$	**2c**	Ag_2CO_3	45[b]
5	$Pd(PPh_3)_4$	**2c**	Ag_2CO_3	30[b]/10[c]
6	$PdCl_2(PhCN)_2$	**2c**	Ag_2CO_3	30[b]/12[c]
7	$PdCl_2(CH_3CN)_2$	**2c**	Ag_2CO_3	31[b]/12[c]
8	$Pd(OAc)_2$	**2c**	Ag_2CO_3	78[b]
9	$Pd(OAc)_2$	**2c**	CuOAc	20[b]
10	$Pd(OAc)_2$	**2c**	$Cu(OAc)_2$	trace[b]
11	$Pd(OAc)_2$	**2c**	K_2CO_3	trace
12	$Pd(OAc)_2$	**2c**	$CuCl_2$	35[b]
13	$Pd(OAc)_2$	**2c**	CuCl	Trace
14	$Pd(OAc)_2$	**2c**	NaOAc	30[b]
15	$Pd(OAc)_2$	**2c**	AgOAc	90[b]
16	$Pd(OAc)_2$	**2c**	AgOAc	82[b,d]
17	$Pd(OAc)_2$	**2c**	AgOAc	7[b,e]
18	$Pd(OAc)_2$	**2c**	AgOAc	12[b,f]
19	$Pd(OAc)_2$	**2c**	AgOAc	75[b,g]

[a]Unless otherwise noted, the reactions were carried out using pyridine *N*-oxide (**1a**) (0.10 mmol) and aryl halide (**2**) (0.15 mmol, 1.5 equiv) with palladium catalyst (10 mol %) in the presence of additives (2.0 equiv) in *p*-xylene (2.0 mL) at 130 °C under Ar for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield for **3-1a**. [c]Isolated yield for **3-aa**. [d]Toluene was used as solvent. [e]DMF was used as solvent. [f]DMSO was used as solvent. [g]120 °C of reaction temperature.

quickly found iodobenzene **2c**[13] could furnish 50% yield of the desired monoarylation product **3-1a**, in which the phenyl group was incorporated into the *β*-position of alkyl carboxylic acid amide **1a**. Then, we employed **1a** and iodobenzene **2c** as model substrates and continued to screen various palladium catalysts to further improve the C_{sp^3}–H bond arylation yield. Among the tested palladium catalysts (entries 3–8), $Pd(OAc)_2$ could significantly increase the reaction yield from 50% to 78% (compare entries 3–7 with 8). In contrast, other palladium catalysts such as $Pd(PPh_3)_4$, $PdCl_2(PhCN)_2$, etc. provided a poorer yield, and these palladium catalysts also simultaneously led to the formation in 10–12% yield of the bisarylation product **3-aa** (entries 5–7). Subsequently, we investigated the effect of various additives on this transformation (entries 8–14) and found that silver salts, especially for AgOAc, could effectively enhance the remote C_{sp^3}–H bond arylation, providing a 90% yield of **3-1a** (compare entry 8 with 15); other additives including K_2CO_3, NaOAc, $Cu(OAc)_2$, etc. resulted in worse conversions (entries 9–14). Notably, employing a polar aprotic solvent such as DMF and DMSO drastically decreased the reaction yields (compare entries 17–18 with 15–16); decreasing the reaction temperature also led to poorer conversion to some degree (compare entry 19 with 15). Finally, the best yield of **3-1a** (90%) could be achieved using the $Pd(OAc)_2$/AgOAc/*p*-xylene reaction system at 130 °C for 12 h (entry 15).

With an optimized catalytic system in hand, we next investigated the scope of the current procedure by testing various iodobezene derivatives. As shown in Figure 1, aryl

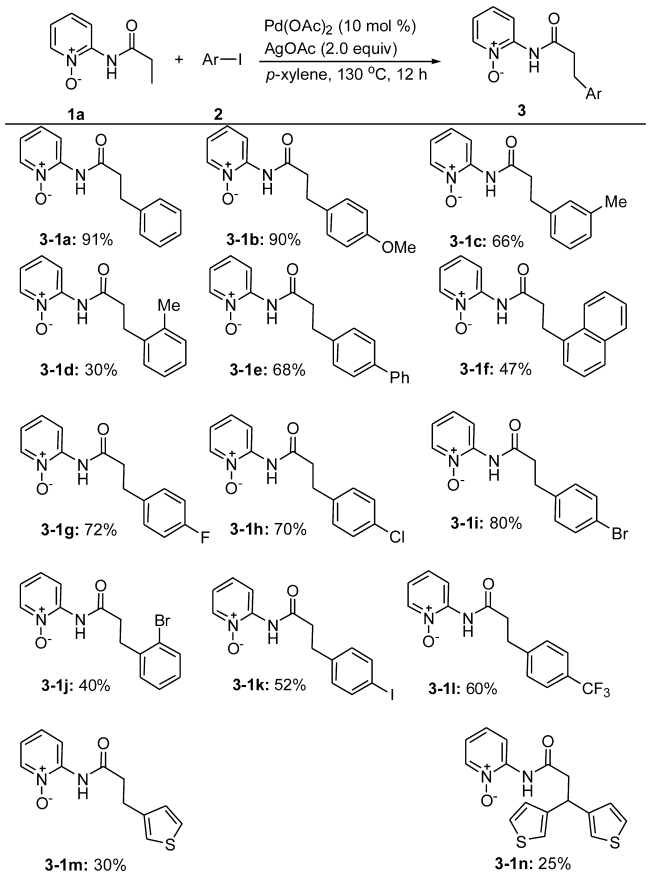


Figure 1. Scope of aryl iodines. Unless otherwise noted, the reactions were carried out using pyridine-*N*-oxide (**1a**) (0.10 mmol) and aryl iodides (**2**) (0.15 mmol, 1.5 equiv) with $Pd(OAc)_2$ (10 mol %) in the presence of AgOAc (2.0 equiv) in *p*-xylene (2.0 mL) at 130 °C under Ar for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. Isolated yields are provided.

iodide substrates exhibited different reactivity which strongly depends on the electronic effect of substituted groups from aryl iodides. For example, the substrates with an electron-donating group and halide at the 3- or 4-position of the benzene ring provided a moderate to excellent yield of arylation products (**3-1a** ≈ **3-1c**, **3-1e** ≈ **3-1k**). In contrast, the electron-deficient 4-trifluoromethyl-phenyl iodide underwent an obviously worse conversion and provided a lower yield of the C_{sp^3}–H bond arylation products (**3-1l**, 60% yield). Moreover, in comparison with *para*-substituted iodobezenes, *ortho*- or *meta*-substituted substrates also obviously inhibited the transformation due to steric hindrance effect of substitutents (**3-1c** vs **3-1d**; **3-1i** vs **3-1j**). Gratifyingly, the C_{sp^3}–H bond arylation between 3-iodothiophene and *N*-(1-oxy-pyridin-2-yl)-propionamide **1a** could also afford the corresponding mono- and bis-thiophenylation products **3-1m** and **3-1n** in an overall yield of 55% yield.

The scope of the procedure with regard to pyridine *N*-oxide-containing alkyl carboxylic acid amides was then explored with iodobenzene **2c** as an arylating agent. The results from Figure 2

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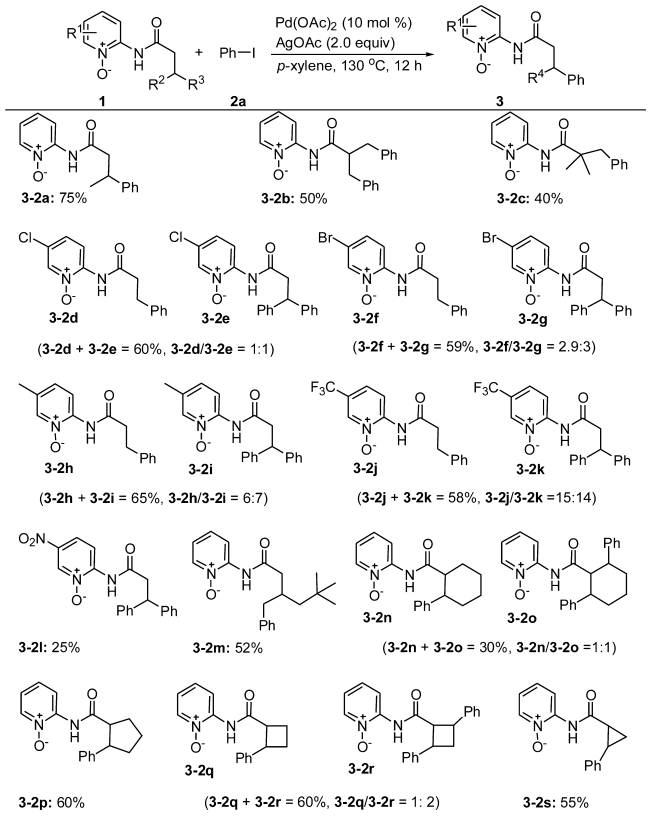


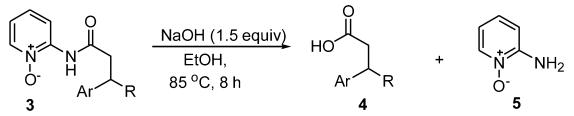
Figure 2. Scope of pyridine *N*-oxides. All reactions were carried out using pyridine-*N*-oxide (**1**) (0.10 mmol) and aryl iodine (**2a**) (0.15 mmol, 1.5 equiv) with $Pd(OAc)_2$ (10 mol %) in the presence of AgOAc (2.0 equiv) in *p*-xylene (2.0 mL) at 130 °C under Ar for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. Isolated yields are provided.

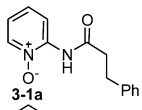
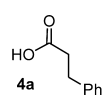
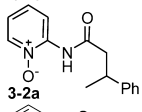
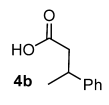
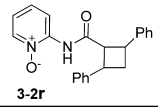
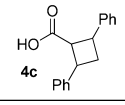
demonstrated that most of the alkyl carboxylic acid amides could be installed with one or two phenyl groups at the β-C_{sp^3} position; also, no significant electronic effect of the 5-substituted pyridine *N*-oxides was found (**3-2a**, **3-2d** ≈ **3-2k**). For example, the electron-rich 5-methyl-pyridine *N*-oxide gave the corresponding mono- and bis-arylation product **3-2h** and **3-2i** in an overall yield of 65% yield. Similarly, electron-poor 5-trifluoromethyl-pyridine *N*-oxide also furnished the mono- and bis-arylation pyridine *N*-oxide derivative **3-2j** (30% yield) and **3-2k** (28% yield) in moderate overall yield. Unfortunately, 5-nitro-pyridine *N*-oxide just afforded 25% yield of **3-2l**. It is worth noting that the β-2,2-dimethyl-propyl group substituted aliphatic amide could also be converted smoothly to a more remote C_{sp^3}–H bond arylation and provided the corresponding γ-phenyl substituted product (**3-2m**) in 52% yield. Moreover, various kinds of six-, five-, four-, and three-membered cycloalkyl substituted amides also allowed for this transformation and afforded the corresponding mono- or bis-arylation products (**3-2n** ≈ **3-2s**) in moderate overall yields. Among them, the structure of **3-2q** was already unambiguously assigned by its single crystal X-ray analysis [see Supporting Information (SI) for more details].

Finally, the pyridine *N*-oxide directing group could be easily removed under base conditions to provide the corresponding β-aryl substituted carboxylic acids which could be used for further synthetic transformations; three examples are shown in Table 2.

To further investigate the primary reaction mechanism, several controlled experiments were carried out (Scheme 2). First, we prepared *N*-pyridin-2-yl-propionamide (**1n**) and tried the C_{sp^3}–H bond arylation of **1n** with iodobenzene (**2c**) under our standard reaction conditions, and no desired product **3-2t** was observed [eq 1]. Moreover, *N*-methyl-*N*-(1-oxy-pyridin-2-yl)-propionamide (**1o**) also could not furnish the corresponding arylation product (**3-2u**) possibly due to the fact that the amide N–H was blocked by the methyl group and could not form palladabicyclic species [eq 2]. The above-mentioned results clearly indicated that pyridine *N*-oxide and the amide N–H group played a significant chelation-assisted directing role to form β-arylation products. Second, when the H/D exchange of *N*-(1-oxy-pyridin-2-yl)-propionamide (**1a**) was conducted in the Pd(II)/AcOD system at 130 °C for 24 h in the absence of iodobenzene **2a**, 85% deuterium incorporation was observed at the β-carbon atom of *D*-**1a** [eq 3] (see SI for more details); this experiment suggested that the C_{sp^3}–H insertion step was involved in the transformation under the standard reaction system. Finally, the intermolecular isotope effect (K_H/K_D = 2.0)

Table 2. Removal of the PNO Directing Group[a]



entry	PNO-containing amides **3**	β-aryl carboxylic acids **4**	yield (%)[b]
1	 **3-1a**	 **4a**	80
2	 **3-2a**	 **4b**	75
3	 **3-2r**	 **4c**	78

[a]All reactions were carried out using PNO-containing amides (**3**) (0.10 mmol) and NaOH (0.15 mmol, 1.5 equiv) in EtOH (2.0 mL) at 85 °C for 8 h, followed by flash chromatography on SiO_2. [b]Isolated yield.

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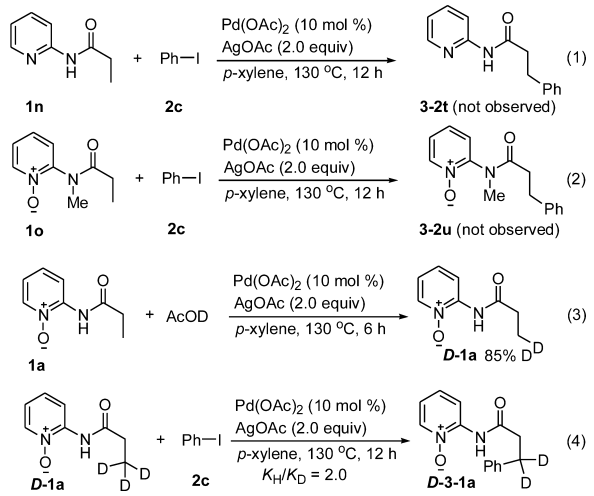
Scheme 2. Preliminary Mechanistic Studies



suggested C_{sp^3}–H bond cleavage occurred in the rate-limiting step [eq 4] (see SI for more details).

From the above-mentioned experimental results, we proposed a possible mechanism that involved a Pd(II)/Pd(IV) redox process (Figure 3). At first, the pyridine N–O^- and

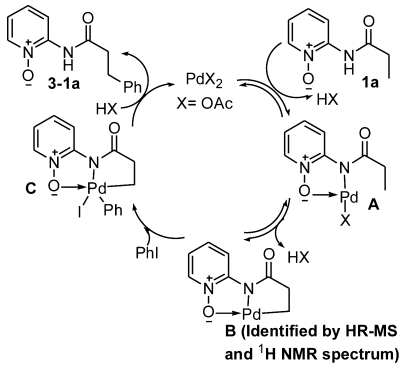


Figure 3. Proposed reaction mechanism.

amide N–H group from substrate **3-1a** coordinated to Pd(II) by abstracting a proton, followed by the cleavage of the β-C_{sp^3}–H bond via a concerted metalation–deprotonation (CMD) mechanism to form palladabicyclic intermediate **B**, which was already identified by HR-MS and ^{1}H NMR spectra.[14] Subsequently, oxidation addition of the reactive palladium intermediate **B** to aryl iodine produced Pd(IV) intermediate **C**. Finally, Pd(IV) intermediate **C** could further reductively eliminate to afford the corresponding β-C_{sp^3}–H bond arylation product **3-1a**, followed by iodide exchange for acetate by Ag^+ completing the catalytic cycle.[15]

In summary, we have developed a novel pyridine *N*-oxides directed, palladium-catalyzed arylation of unactivated C_{sp^3}–H bonds with aryl iodides. This protocol allows installing various aryl groups at the β- or γ-C_{sp^3} atom of alkyl carboxylic acid amides in which the pyridine N–O^- and amide N–H groups were found to play a key chelation-assisted role in activating the C_{sp^3}–H bond. A general reaction mechanism has been proposed involving formation of the palladabicyclic intermediate, which has been identified by the HR-MS and ^{1}H NMR method. Further studies to explore other pyridine *N*-oxide directed, transition-metal-catalyzed novel reactions are now in progress

EXPERIMENTAL SECTION

General Information. All reactions were carried out in flame-dried sealed tubes with magnetic stirring. Unless otherwise noted, all experiments were performed under an argon atmosphere. Solvents were treated with 4 Å molecular sieves or sodium and distilled prior to use. Flash chromatography was performed on silica gel (40–63 mm) by a standard technique. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Splitting patterns are designated as singlet (s), doublet (d), triplet (t), and quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiple (m). Low resolution mass spectra were recorded using an HPLC mass spectrometer. High resolution exact mass measurements (HR-MS) were performed on a TOF spectrometer. Infrared spectra (IR) were reported as wavelength numbers (cm^{-1}). Infrared spectra were recorded by preparing a KBr pellet containing the title compound. Crystal data were obtained by employing graphite monochromated Mo Kα radiation (λ = 0.710 73 Å) at 293(2) K and operating in the φ–ω scan mode. The structure was solved by direct methods using SHELXS-97.

General Procedure for the Synthesis of *N*-(1-Oxy-pyridin-2-yl)-alkylamide Substrates (1a–1n′).[16] General Procedure. A mixture of $SOCl_2$ (1.2 mmol, 1.2 equiv), triethylamine (1.0 mmol, 1 equiv), and the corresponding acid (1 mmol, 1 equiv) in $CHCl_3$ (20 mL) was vigorously refluxed at 70 °C for 2 h. The mixture was concentrated *in vacuo*, and the crude product was submitted to the next reaction without purification. The solution of the above-mentioned crude product was added in the mixture of triethylamine (1.0 mmol, 1 equiv) and 2-aminopyridine (1 mmol, 1 equiv) in $CHCl_3$ (20 mL) at 0 °C and continued to be stirred for 8 h. Then the mixture was evaporated under reduced pressure, and the resulting mixture was dissolved in the $CHCl_3$ (15 mL) and treated with the *m*-CPBA (1.3 mmol, 1.3 equiv) at room temperature for 3 h. Then the reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with saturated Na_2CO_3 aqueous solution (3 × 40 mL) and saturated NaCl aqueous solution (3 × 50 mL), respectively. The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuum*, the crude product was purified through flash chromatography on silica gel with dichloromethane and MeOH (v/v = 20:1 to 10:1) as the eluent to afford the desired pyridine *N*-oxides (**1a–1n′**).

*2-Propionamidopyridine 1-Oxide (**1a**).* Pale yellow solid; 141 mg, 85% yield; mp: 95.0–96.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 6.5 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.99 (t, J = 7.0 Hz, 1H), 2.56 (q, J = 7.4 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 144.2, 137.0, 128.1, 118.4, 114.7, 30.9, 9.1; HR-MS (ESI) calcd for $[M + 1]^+$: $C_8H_{11}N_2O_2$: 167.0815, found: 167.0817; IR (KBr): 2979, 1702, 1568, 1507, 1426, 1210, 756 cm^{-1}.

*2-Butyramidopyridine 1-Oxide (**1b**).* Pale yellow solid; 140 mg, 78% yield; mp: 115.0–116.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 6.5 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.98 (t, J = 7.0 Hz, 1H), 2.50 (t, J = 7.4 Hz, 2H), 1.84–1.74 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 144.2, 137.0, 128.2, 118.4, 114.7, 39.7, 18.6, 13.6; HR-MS (ESI) calcd for $[M + 1]^+$: $C_9H_{13}N_2O_2$: 181.0972, found: 181.0973; IR (KBr): 2965, 1704, 1569, 1508, 1427, 1148, 761 cm $^{-1}$.

*2-Isobutyramidopyridine 1-Oxide (**1c**).* Pale yellow solid; 135 mg, 75% yield; mp: 82.0–83.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 6.4 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.00 (t, J = 6.9 Hz, 1H), 2.79–2.69 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 144.3, 137.0, 128.2, 118.4, 114.7, 36.8, 19.3; HR-MS (ESI) calcd for $[M + 1]^+$: $C_9H_{13}N_2O_2$: 181.0972, found: 181.0971; IR (KBr): 2969, 1703, 1569, 1509, 1428, 1205, 759 cm $^{-1}$.

*2-Pivalamidopyridine 1-Oxide (**1d**).* Pale yellow solid; 155 mg, 80% yield; mp: 90.8–92.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41

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(s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.25 (d, J = 6.5 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.98 (t, J = 7.0 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 144.5, 136.9, 128.1, 118.3, 114.6, 40.5, 27.4; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{10}H_{15}N_2O_2$: 195.0866, found: 195.0864; IR (KBr): 2965, 1568, 1508, 1427, 1203, 761 cm $^{-1}$.

*5-Chloro-2-propionamidopyridine 1-Oxide (**1e**).* White solid; 150 mg, 75% yield; mp: 154.2−155.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.35 (d, J = 9.1 Hz, 1H), 8.21 (s, 1H), 7.24 (d, J = 9.1 Hz, 1H), 2.50 (q, J = 7.4 Hz, 2H), 1.18 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 143.1, 136.1, 128.1, 124.8, 114.4, 30.8, 9.0; HR-MS (ESI) calcd for $[M + 1]^+$: $C_8H_{10}ClN_2O_2$: 201.0425, found: 201.0425; IR (KBr): 2978, 1699, 1583, 1506, 1428, 1214, 848 cm $^{-1}$.

*5-Bromo-2-propionamidopyridine 1-Oxide (**1f**).* White solid; 171 mg, 70% yield; mp: 170.0−172.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (d, J = 44.8 Hz, 1H), 8.36 (d, J = 7.7 Hz, 2H), 7.43 (d, J = 9.1 Hz, 1H), 2.55 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 143.4, 138.1, 130.8, 114.7, 111.3, 77.4, 77.1, 76.8, 31.0, 9.1; HR-MS (ESI) calcd for $[M + 1]^+$: $C_8H_{10}BrN_2O_2$: 244.9920, found: 244.9921; IR (KBr): 2975, 1698, 1564, 1503, 1469, 1248, 891 cm $^{-1}$.

*5-Methyl-2-propionamidopyridine 1-Oxide (**1g**).* Pale yellow solid; 144 mg, 80% yield; mp: 113.0−114.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.10 (s, 1H), 7.17 (d, J = 8.6 Hz, 1H), 2.56 (q, J = 7.5 Hz, 2H), 2.29 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 141.8, 136.6, 129.4, 128.7, 114.2, 30.8, 17.8, 9.1; HR-MS (ESI) calcd for $[M + 1]^+$: $C_9H_{13}N_2O_2$: 181.0972, found: 181.0973; IR (KBr): 2921, 1702, 1532, 1508, 1450, 1278, 951 cm $^{-1}$.

*5-Nitro-2-propionamidopyridine 1-Oxide (**1h**).* Yellow solid; 84 mg, 40% yield; mp: 123.5−125.0 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 9.19 (s, 1H), 8.49 (d, J = 9.4 Hz, 1H), 8.23 (d, J = 9.4 Hz, 1H), 2.69 (q, J = 7.3 Hz, 2H), 1.09 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 174.0, 166.5, 148.4, 139.4, 133.8, 122.4, 112.8, 29.79, 8.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_8H_{10}N_3O_4$: 212.0666, found: 212.0668; IR (KBr): 2965, 1704, 1574, 1520, 1427, 1209, 803 cm $^{-1}$.

*2-Propionamido-5-(trifluoromethyl)pyridine 1-Oxide (**1i**).* White solid; 125 mg, 50% yield; mp: 127.0−128.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.68−8.47 (m, 2H), 7.54 (d, J = 8.8 Hz, 1H), 2.61 (q, J = 7.4 Hz, 2H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 146.4, 134.7, 124.4, 124.4, 123.4 (d, J = 271 Hz), 122.5 (q, J = 35.4 Hz), 122.1, 120.7, 114.2, 31.1, 8.9; HR-MS (ESI) calcd for $[M + Na]^+$: $C_9H_9F_3N_2O_2Na$: 257.0506, found: 257.0502; IR (KBr): 2969, 1708, 1560, 1520, 1431, 1211, 790 cm^{-1}.

*2-(3,5,5-Trimethylhexanamido)pyridine 1-Oxide (**1j**).* White solid; 175 mg, 70% yield; mp: 120.0−122.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 6.4 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 6.99 (t, J = 6.9 Hz, 1H), 2.53 (dd, J = 14.6, 5.9 Hz, 1H), 2.34 (dd, J = 14.5, 8.2 Hz, 1H), 2.25−2.15 (m, 1H), 1.32 (dd, J = 14.0, 3.2 Hz, 1H), 1.18 (dd, J = 14.0, 6.4 Hz, 1H), 1.05 (d, J = 6.5 Hz, 3H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 144.2, 137.1, 128.3, 118.4, 114.7, 50.5, 47.5, 31.0, 29.9, 27.3, 22.6; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{23}N_2O_2$: 251.1754, found: 251.1755; IR (KBr): 2960, 1704, 1569, 1508, 1427, 1148, 761 cm $^{-1}$.

*2-(Cyclohexanecarboxamido)pyridine 1-Oxide (**1k**).* White solid; 167 mg, 76% yield; mp: 150.1−151.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 6.4 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 2.43 (t, J = 11.5 Hz, 1H), 2.02 (d, J = 12.8 Hz, 2H), 1.85 (d, J = 12.4 Hz, 2H), 1.72 (d, J = 10.8 Hz, 1H), 1.56 (q, J = 12.1 Hz, 2H), 1.41−1.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 144.4, 137.0, 128.1, 118.3, 114.7, 77.1, 76.7, 46.5, 29.4, 25.6, 25.5; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{12}H_{17}N_2O_2$: 221.1285, found: 221.1283; IR (KBr): 3060, 2935, 2854, 1707, 1519, 1504, 1429, 1156, 761 cm $^{-1}$.

*2-(Cyclopentanecarboxamido)pyridine 1-Oxide (**1l**).* White solid; 167 mg, 81% yield; mp: 141.1−142.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 6.3 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.98 (t, J = 6.9 Hz, 1H), 2.91 (q, J = 7.9 Hz, 1H), 2.00 (m, J = 11.4, 7.0 Hz, 2H), 1.95−1.86 (m, 2H), 1.78 (m, J = 6.0 Hz, 2H), 1.71−1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 144.3, 137.0, 128.3, 118.3, 114.7, 77.4, 77.1, 76.8, 47.1, 30.4, 25.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{11}H_{15}N_2O_2$: 207.1128, found: 207.1130; IR (KBr): 2953, 1693, 1568, 1504, 1424, 1210, 726 cm $^{-1}$.

*2-(Cyclobutanecarboxamido)pyridine 1-Oxide (**1m**).* Pale yellow solid; 153 mg, 80% yield; mp: 155.3−156.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.39 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 6.4 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 6.90 (t, J = 7.0 Hz, 1H), 3.27 (p, J = 8.4 Hz, 1H), 2.38−2.27 (m, 2H), 2.21 (m, J = 8.7 Hz, 2H), 2.02−1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 144.2, 137.0, 128.1, 118.3, 114.6, 40.9, 25.1, 18.0; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{10}H_{13}N_2O_2$: 193.0972, found: 193.0970; IR (KBr): 2987, 1695, 1568, 1510, 1427, 1207, 762 cm $^{-1}$.

*2-(Cyclopropanecarboxamido)pyridine 1-Oxide (**1n′**).* White solid; 124 mg, 70% yield; mp: 153.3−155.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.42 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 6.4 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 1.76 (m, J = 10.2, 5.9 Hz, 1H), 1.14 (d, J = 2.4 Hz,2H), 0.97 (d, J = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 144.2, 137.0, 128.1, 118.3, 114.7, 16.3, 9.1; HR-MS (ESI) calcd for $[M + 1]^+$: $C_9H_{11}N_2O_2$: 179.0815, found: 179.0814; IR (KBr): 2922, 1691, 1565, 1511, 1429, 1161, 755 cm $^{-1}$.

General Procedure for Pd(II)-Catalyzed C(sp^3)−H Bond Arylation. To an oven-dried Schlenk tube, *N*-(1-oxy-pyridin-2-yl)-alkylamide substrate (**1**) (0.2 mmol, 33.2 mg), aryl iodide (**2**) (0.3 mmol, 61.2 mg), Pd $(OAc)_2$ (0.02 mmol, 4.5 mg), AgOAc (0.4 mmol, 66.4 mg), and *p*-xylene (2 mL) were added under an Ar atmosphere. The mixture was stirred at 130 °C for 12 h. After cooling down to ambient temperature, the reaction mixture was then filtered through a short plug of silica sand and further concentrated *in vacuo*. The crude products were purified through flash chromatography on silica gel with ethyl acetate and petroleum (v/v = 1:1 to 4:1) as the eluent to afford the desired C_{sp^3}−H bond arylation products.

*2-(3-Phenylpropanamido)pyridine 1-Oxide (**3-1a**).* White solid; 44 mg, 91% yield; mp: 104.1−105.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 6.4 Hz, 1H), 7.36−7.28 (m, 3H), 7.24−7.19 (m, 3H), 6.98 (t, J = 6.9 Hz, 1H), 3.08 (t, J = 7.6 Hz, 2H), 2.85 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 144.1, 140.0, 137.1, 128.7, 128.3, 128.1, 126.5, 118.6, 114.8, 39.3, 30.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{15}N_2O_2$: 243.1128, found: 243.1126; IR (KBr): 2923, 1703, 1568, 1506, 1426, 1207, 756 cm^{-1}.

*2-(3,3-Diphenylpropanamido)pyridine 1-oxide (**3-aa**).* White solid; mp: 110.1−112.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.35 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 6.3 Hz, 1H), 7.32−7.14 (m, 11H), 6.89 (t, J = 6.8 Hz, 1H), 4.69 (t, J = 7.7 Hz, 1H), 3.29 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 144.0, 143.2, 137.0, 128.8, 128.1, 127.7, 126.7, 118.6, 114.9, 46.8, 43.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{20}H_{19}N_2O_2$: 319.1441, found: 319.1438; IR (KBr): 2938, 1700, 1567, 1506, 1426, 1207, 760 cm $^{-1}$.

*2-(3-(4-Methoxyphenyl)propanamido)pyridine 1-Oxide (**3-1b**).* Pale yellow solid; 54 mg, 90% yield; mp: 108.1−109.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.00−6.94 (t, 1H), 6.84 (d, J = 7.9 Hz, 2H), 3.78 (s, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.81 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.1, 158.2, 144.1, 137.1, 132.0, 129.3, 128.5, 128.2, 118.6, 114.8, 114.1, 55.3, 39.7, 30.1; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{15}H_{17}N_2O_3$: 273.1234, found: 273.1236; IR (KBr): 2958, 1700, 1567, 1507, 1461, 1133, 758 cm $^{-1}$.

*2-(3-(m-Tolyl)propanamido)pyridine 1-Oxide (**3-1c**).* Pale yellow solid; 33 mg, 66% yield; mp: 102.1−103.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.48 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 6.4 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.07 (m, 3H), 6.99 (t, J = 7.0 Hz, 1H), 3.05 (t, J = 7.7 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 144.1, 140.0, 138.2, 137.1, 129.1, 128.5, 128.2, 127.2, 125.3, 118.6, 114.8, 39.4, 30.8, 21.4; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{15}H_{17}N_2O_2$:

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257.1285, found: 257.1285; IR (KBr): 2925, 1701, 1568, 1508, 1426, 1207, 759 cm $^{-1}$.

*2-(3-(o-Tolyl)propanamido)pyridine 1-Oxide (**3-1d**).* Pale yellow solid; 16 mg, 30% yield; mp: 106.1−106.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.14 (dd, J = 9.9, 5.8 Hz, 4H), 6.98 (t, J = 7.0 Hz, 1H), 3.09−3.04 (m, 2H), 2.83−2.78 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 144.1, 138.2, 137.1, 136.0, 130.4, 128.5, 128.2, 126.6, 126.3, 118.6, 114.8, 38.0, 28.2, 19.3. HR-MS (ESI) calcd for $[M + 1]^+$: $C_{15}H_{17}N_2O_2$: 257.1285, found: 257.1287; IR (KBr): 2923, 1702, 1568, 1507, 1426, 1207, 757 cm $^{-1}$.

*2-(3-([1,1′-Biphenyl]-4-yl)propanamido)pyridine 1-Oxide (**3-1e**).* Pale yellow solid; 42 mg, 68% yield; mp: 120.2−121.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 7.55 (dd, J = 15.8, 7.7 Hz, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 8.0 Hz, 4H), 6.97 (t, J = 6.9 Hz, 1H), 3.11 (t, J = 7.6 Hz, 2H), 2.89 (t, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 140.9, 139.4, 139.1, 137.1, 128.8, 128.2, 127.4, 127.2, 127.0, 118.6, 114.8, 39.2, 30.5; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{20}H_{19}N_2O_2$: 319.1441, found: 319.1447; IR (KBr): 2934, 1705, 1572, 1507, 1434, 1212, 759 cm $^{-1}$.

*2-(3-(Naphthalen-1-yl)propanamido)pyridine 1-Oxide (**3-1f**).* Pale yellow solid; 27 mg, 47% yield; mp: 122.2−123.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 6.4 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 6.4 Hz, 1H), 7.44 (dt, J = 14.7, 7.1 Hz, 2H), 7.31 (s, 2H), 7.25 (t, J = 8.1 Hz, 1H), 6.87 (t, J = 7.0 Hz, 1H), 3.46 (t, J = 7.9 Hz, 2H), 2.90 (t, J = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 144.1, 137.1, 136.1, 134.0, 131.5, 129.0, 128.36, 127.3, 126.2, 126.1, 125.7, 125.6, 123.3, 118.6, 114.9, 38.54, 28.0; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{18}H_{17}N_2O_2$: 293.1285, found: 293.1287; IR (KBr): 2924, 1702, 1568, 1508, 1426, 1207, 757 cm $^{-1}$.

*2-(3-(4-Fluorophenyl)propanamido)pyridine 1-Oxide (**3-1g**).* Pale yellow solid; 38 mg, 72% yield; mp: 120.2−121.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 6.2 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 6.2 Hz, 2H), 6.98 (t, J = 8.0 Hz, 3H), 3.04 (t, J = 7.5 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 162.8 (d, J = 236.7 Hz), 129.8 (d, J = 7.9 Hz), 129.7, 128.2, 118.6, 115.5 (d, J =21.3 Hz), 115.3, 114.8, 39.3, 30.0; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{14}FN_2O_2$: 261.1034, found: 261.1034; IR (KBr): 2921, 1702, 1568, 1508, 1426, 1214, 759 cm $^{-1}$.

*2-(3-(4-Chlorophenyl)propanamido)pyridine 1-Oxide (**3-1h**).* Pale yellow solid; 38 mg, 70% yield; mp: 119.2−120.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.44 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 6.98 (t, J = 7.0 Hz, 1H), 3.05 (t, J = 7.5 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 144.0, 138.5, 137.1, 132.2, 129.7, 128.7, 128.2, 118.7, 114.8, 39.0, 30.1; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{14}ClN_2O_2$: 277.0738, found: 277.0737; IR (KBr): 2965, 1691, 1555, 1509, 1430, 1079, 714 cm $^{-1}$.

*2-(3-(4-Bromophenyl)propanamido)pyridine 1-Oxide (**3-1i**).* Pale yellow solid; 51 mg, 80% yield; mp: 94.2−95.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.43 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 6.5 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 7.8 Hz, 2H), 6.98 (t, J = 7.0 Hz, 1H), 3.02 (t, J = 7.5 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 144.0, 139.1, 137.1, 131.7, 130.1, 128.2, 120.2, 118.7, 114.8, 38.9, 30.2; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{14}BrN_2O_2$: 321.0233, found: 321.0232; IR (KBr): 2922, 1700, 1567, 1508, 1425, 1206, 758 cm $^{-1}$.

*2-(3-(2-Bromophenyl)propanamido)pyridine 1-Oxide (**3-1j**).* Pale yellow solid; 25 mg, 40% yield; mp: 93.2−94.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.37−7.21 (m, 3H), 7.09 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 6.9 Hz, 1H), 3.18 (t, J = 7.7 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 144.1, 139.3, 137.1, 133.0, 130.6, 128.3, 128.2, 127.7, 124.4, 118.6, 114.8, 77.4, 77.1, 76.7, 37.5, 31.4; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{14}BrN_2O_2$: 321.0233, found: 321.0232; IR (KBr): 2922, 1702, 1568, 1507, 1426, 1206, 755 cm^{-1}.

*2-(3-(4-Iodophenyl)propanamido)pyridine 1-Oxide (**3-1k**).* Pale yellow solid; 38 mg, 52% yield; mp: 101.1−102.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.44 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 6.1 Hz, 1H), 7.61 (d, J = 7.9 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 7.7 Hz, 3H), 3.01 (t, J = 7.4 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 144.0, 139.7, 137.7, 137.1, 130.4, 128.4, 118.7, 114.8, 91.6, 38.9, 30.3; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{14}IN_2O_2$: 369.0095, found: 369.0094; IR (KBr): 2922, 1701, 1568, 1508, 1425, 1206, 760 cm^{-1}.

*2-(3-(4-(Trifluoromethyl)phenyl)propanamido)pyridine 1-Oxide (**3-1l**).* Pale yellow solid; 37 mg, 60% yield; mp: 96.2−96.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.45 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.35 (m, J = 13.8, 7.8 Hz, 3H), 6.99 (t, J = 7.0 Hz, 1H), 3.14 (t, J = 7.5 Hz, 2H), 2.89 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 144.2, 144.0, 137.1, 128.7, 128.3, 125.6, 125.5 (d, J = 24.4 Hz), 118.7, 114.8, 38.6, 30.5; HR-MS(ESI) calcd for $[M + 1]^+$: $C_{15}H_{14}F_3N_2O_2$: 311.1002, found: 311.1004; IR(KBr): 3230, 2923, 1706, 1570, 1513, 1424, 1107, 755 cm^{-1}.

*2-(3-(Thiophen-3-yl)propanamido)pyridine 1-Oxide (**3-1m**).* Pale yellow solid; 15 mg, 30% yield; mp: 100.2−101.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.45 (d, J = 8.3 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.26 (s, 1H), 7.04 (s, 1H), 6.98 (d, J = 3.5 Hz, 2H), 3.10 (t, J = 7.5 Hz, 2H), 2.85 (t, J = 7.5 Hz, 32H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 144.1, 140.2, 137.1, 128.2, 127.9, 126.0, 121.0, 118.6, 114.8, 38.6, 25.4; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{12}H_{13}N_2O_2S$: 249.0692, found: 249.0694; IR (KBr): 2920, 1701, 1568, 1507, 1426, 1207, 758 cm $^{-1}$.

*2-(3,3-Di(thiophen-3-yl)propanamido)pyridine 1-Oxide (**3-1n**).* Pale yellow solid; 17 mg, 25% yield; mp: 112.2−113.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 6.4 Hz, 1H), 7.29 (t, J = 6.0 Hz, 1H), 7.26 (t, J = 3.6 Hz, 2H), 7.05 (s, 2H), 6.95 (t, J = 7.5 Hz, 3H), 4.84 (t, J = 7.5 Hz, 1H), 3.20 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 144.0, 143.6, 137.02, 128.1, 127.2, 126.2, 121.0, 118.7, 114.8, 44.7, 38.3; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{16}H_{15}N_2O_2S_2$: 331.0569, found: 331.0572; IR (KBr): 3223, 2923, 1702, 1569, 1507, 1427, 1262, 749 cm^{-1}.

*2-(3-Phenylbutanamido)pyridine 1-Oxide (**3-2a**).* Pale yellow solid; 38 mg, 75% yield, mp: 110.2−111.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.43 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 9.6 Hz, 1H), 7.35−7.25 (m, 5H), 7.21 (t, J = 6.9 Hz, 1H), 6.95 (t, J = 7.0 Hz, 1H), 3.42 (h, J = 7.1 Hz, 1H), 2.86 (dd, J = 15.0, 6.9 Hz, 1H), 2.76 (dd, J = 15.0, 8.0 Hz, 1H), 1.37 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 145.3, 144.1, 137.0, 128.7, 128.2, 126.7, 126.6, 118.5, 114.8, 46.3, 36.6, 21.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{15}H_{17}N_2O_2$: 257.1285, found: 257.1285; IR (KBr): 3231, 2963, 1701, 1568, 1506, 1425, 1208, 760 cm $^{-1}$.

*2-(2-Benzyl-3-phenylpropanamido)pyridine 1-Oxide (**3-2b**).* Pale yellow solid; 33 mg, 50% yield; mp: 123.4−124.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 6.4 Hz, 1H), 7.18 (dd, J = 12.6, 7.2 Hz, 5H), 7.10 (d, J = 7.1 Hz, 6H), 6.83 (t, J = 7.0 Hz, 1H), 3.05−2.92 (m, 3H), 2.81 (dd, J = 12.7, 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 143.8, 138.6, 137.0, 128.8, 128.6, 128.0, 126.7, 118.5, 114.7, 53.0, 38.5; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{21}H_{21}N_2O_2$: 333.1598, found: 333.1598; IR (KBr): 3224, 2960, 1704, 1566, 1504, 1427, 1206, 757 cm $^{-1}$.

*2-(2,2-Dimethyl-3-phenylpropanamido)pyridine 1-Oxide (**3-2c**).* Pale yellow solid; 22 mg, 40% yield; mp: 104.6−104.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 6.3 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 7.9 Hz, 3H), 7.13 (d, J = 6.8 Hz, 2H), 6.97 (t, J = 6.9 Hz, 1H), 2.97 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 137.0, 130.2, 128.1, 126.7, 118.5, 114.6, 46.5, 45.2, 24.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{16}H_{19}N_2O_2$: 271.1141, found: 271.1143; IR (KBr): 3257, 2963, 1691, 1566, 1506, 1424, 1203, 762 cm^{-1}.

*5-Chloro-2-(3-phenylpropanamido)pyridine 1-Oxide (**3-2d**).* Pale yellow solid; 17 mg, 30% yield; mp: 165.2−166.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.42 (d, J = 9.0 Hz, 1H), 8.25 (s, 1H), 7.30 (t, J = 7.4 Hz, 3H), 7.24−7.19 (m, 3H), 3.06 (t, J = 7.6 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 142.9,

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139.9, 136.2, 128.7, 128.3, 128.1, 126.5, 125.2, 114.5, 39.3, 30.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{14}ClN_2O_2$: 277.0738, found: 277.0740; IR (KBr): 2958, 1687, 1570, 1506, 1432, 1212, 769 cm^{-1}.

*5-Chloro-2-(3,3-diphenylpropanamido)pyridine 1-Oxide (**3−2e**).* Pale yellow; 21 mg, 30% yield; mp: 171.2−172.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.33 (d, J = 9.2 Hz, 1H), 8.20 (s, 1H), 7.27 (t, J = 6.3 Hz, 11H), 7.19 (t, J = 6.6 Hz, 2H), 4.67 (t, J = 7.8 Hz, 1H), 3.27 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.0, 136.1, 128.8, 128.1, 127.6, 126.8, 125.2, 46.9, 44.0; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{20}H_{18}ClN_2O_2$: 353.1051, found: 353.1048; IR (KBr): 3201, 2958, 1703, 1557, 1505, 1450, 1213, 749 cm^{-1}.

*5-Bromo-2-(3-phenylpropanamido)pyridine 1-Oxide (**3-2f**).* Pale yellow solid; 19 mg, 29% yield; mp: 189.4−190.8 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.37 (d, J = 9.3 Hz, 2H), 7.44 (d, J = 9.0 Hz, 1H), 7.33−7.27 (m, 2H), 7.23 (d, J = 7.3 Hz, 3H), 3.06 (t, J = 7.5 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 139.8, 138.1, 130.8, 128.7, 128.3, 126.6, 114.8, 111.5, 39.3, 30.8; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{14}H_{14}BrN_2O_2$: 321.0233, found: 321.0222; IR (KBr): 3228, 2959, 1701, 1556, 1502, 1378, 1210, 752 cm^{-1}.

*5-Bromo-2-(3,3-diphenylpropanamido)pyridine 1-Oxide (**3-2g**).* Pale yellow solid; 24 mg, 30% yield; mp: 196.4−197.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.35−8.28 (m, 2H), 7.40 (d, J = 9.1 Hz, 1H), 7.35−7.27 (m, 9H), 7.23 (d, J = 6.8 Hz, 2H), 4.70 (t, J = 7.8 Hz, 1H), 3.29 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.0, 138.0, 130.7, 128.8, 127.6, 126.8, 114.8, 111.5, 46.9, 44.0; HR-MS (ESI) calcd for $[M + Na]^+$: $C_{20}H_{17}BrN_2NaO_2$: 419.0371, found: 419.0366; IR (KBr): 2922, 1701, 1555, 1500, 1382, 1079, 698 cm^{-1}.

*5-Methyl-2-(3-phenylpropanamido)pyridine 1-Oxide (**3-2h**).* Pale yellow solid; 15 mg, 30% yield; mp: 127.2−128.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.33 (d, J = 8.6 Hz, 1H), 8.05 (s, 1H), 7.32−7.26 (m, 2H), 7.25−7.20 (m, 3H), 7.14 (d, J = 8.5 Hz, 1H), 3.06 (t, J = 7.6 Hz, 2H), 2.83 (t, J = 7.6 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 141.8, 140.1, 136.7, 129.4, 129.0, 128.6, 128.3, 126.4, 114.3, 39.3, 31.0, 17.9; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{15}H_{17}N_2O_2$: 257.1285, found: 257.1283; IR (KBr): 3209, 2924, 1695, 1576, 1531, 1452, 1113, 764 cm^{-1}.

*2-(3,3-Diphenylpropanamido)-5-methylpyridine 1-Oxide (**3-2i**).* Pale yellow solid; 23 mg, 35% yield; mp: 134.2−136.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.01 (s, 1H), 7.28 (d, J = 4.0 Hz, 9H), 7.19 (dd, J = 8.1, 3.8 Hz, 2H), 7.08 (d, J = 8.7 Hz, 1H), 4.69 (t, J = 7.7 Hz, 1H), 3.26 (d, J = 7.8 Hz, 2H), 2.23 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 143.2, 141.7, 136.6, 129.3, 129.0, 128.7, 127.7, 126.7, 114.3, 46.9, 43.9, 17.8; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{21}H_{21}N_2O_2$: 333.1598, found: 333.1595; IR (KBr): 2923, 1691, 1523, 1508, 1448, 1148, 699 cm^{-1}.

*2-(3-Phenylpropanamido)-5-(trifluoromethyl)pyridine 1-Oxide (**3-2j**).* Pale yellow solid; 20 mg, 30% yield; mp: 135.7−136.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.61 (d, J = 8.8 Hz, 1H), 8.54 (s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.37−7.20 (m, 5H), 3.10 (t, J = 7.4 Hz, 2H), 2.91 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 146.3, 139.7, 134.7, 128.7 (d, J = 43.6 Hz), 128.3, 126.6, 124.6, 123.3, 122.6 (q, J = 15.1 Hz), 122.3, 120.6, 114.4, 39.3, 30.7; HR-MS (ESI) calcd for $[M + Na]^+$: $C_{15}H_{13}F_3N_2O_2Na$: 333.0814, found: 333.0819; IR (KBr): 2931, 1698, 1526, 1510, 1448, 1138, 701 cm^{-1}.

*2-(3,3-Diphenylpropanamido)-5-(trifluoromethyl)pyridine 1-Oxide (**3-2k**).* Pale yellow solid; 23 mg, 28% yield; mp: 147.3−148.8 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.50 (d, J = 12.2 Hz, 2H), 7.47 (t, J = 8.2 Hz, 1H), 7.33−7.16 (m, 10H), 4.68 (t, J = 7.7 Hz, 1H), 3.32 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 146.2, 142.9, 134.7, 129.1, 128.8 (d, J = 43.6 Hz), 128.5, 128.4, 128.3, 127.6, 126.9, 124.7, 124.6, 123.3 (q, J = 35.4 Hz), 122.7, 122.3, 120.6, 114.5, 46.9, 44.0; HR-MS (ESI) calcd for $[M + Na]^+$: $C_{21}H_{17}F_3N_2O_2Na$: 409.1135, found: 409.1138; IR (KBr): 2935, 1694, 1536, 1512, 1450, 1148, 701 cm^{-1}.

*2-(3, 3-Diphenylpropanamido)-5-nitropyridine 1-Oxide (**3-2l**).* Pale yellow solid; 18 mg, 25% yield; mp: 145.1−146.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 9.10 (s, 1H), 8.55 (d, J = 9.3 Hz, 1H), 8.10 (d, J = 9.3 Hz, 1H), 7.35−7.28 (m, 8H), 7.24 (d, J = 6.1 Hz, 2H), 4.70 (t, J = 7.6 Hz, 1H), 3.36 (d, J = 7.6 Hz, 2H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 142.7, 133.5, 128.87, 127.6, 127.0, 122.7, 112.8, 46.9, 44.2; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{20}H_{18}N_3O_4$: 364.1292, found: 364.1293; IR (KBr): 2960, 1713, 1570, 1517, 1452, 1348, 1116, 700 cm^{-1}.

*2-(3-Benzyl-5,5-dimethylhexanamido)pyridine 1-Oxide (**3-2m**).* Pale yellow solid; 34 mg, 52% yield; mp: 132.4−133.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 6.3 Hz, 1H), 7.33−7.28 (t, 1H), 7.25 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.2 Hz, 2H), 7.15 (t, J = 7.0 Hz, 1H), 6.96 (t, J = 6.9 Hz, 1H), 2.75 (dd, J = 13.3, 6.2 Hz, 1H), 2.62 (dd, J = 13.2, 7.9 Hz, 1H), 2.46 (t, J = 5.9 Hz, 2H), 2.43−2.33 (m, 1H), 1.38 (dd, J = 14.1, 3.0 Hz, 1H), 1.32−1.24 (dd, 1H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 144.1, 140.2, 137.0, 129.4, 128.3, 128.1, 126.1, 118.4, 114.7, 47.3, 44.2, 42.8, 33.8, 31.1, 29.8; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{20}H_{27}N_2O_2$: 327.2067, found: 327.2068; IR (KBr): 2957, 1701, 1567, 1508, 1424, 1127, 759 cm^{-1}.

*2-(2-Phenylcyclohexanecarboxamido)pyridine 1-Oxide (**3-2n**).* Pale yellow solid; 9 mg, 15% yield; mp: 161.3−163.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 6.5 Hz, 1H), 7.23 (d, J = 3.2 Hz, 4H), 7.19 (t, J = 8.2 Hz, 1H), 7.15−7.10 (m, 1H), 6.87 (t, J = 7.0 Hz, 1H), 2.92 (t, J = 11.3 Hz, 1H), 2.68 (t, J = 11.4 Hz, 1H), 2.12 (d, J = 13.2 Hz, 1H), 1.91 (dd, J = 26.7, 12.3 Hz, 4H), 1.72 (dd, J = 24.3, 12.1 Hz, 1H), 1.55−1.50 (m, 1H), 1.48−1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 144.2, 136.9, 128.6, 128.0, 127.2, 126.6, 118.3, 114.6, 53.4, 46.5, 34.3, 30.8, 26.1, 25.4; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{18}H_{21}N_2O_2$: 297.1598, found: 297.1597; IR (KBr): 2925, 1699, 1567, 1506, 1425, 1207, 757, 699 cm^{-1}.

*2-(2,6-Diphenylcyclohexanecarboxamido)pyridine 1-Oxide (**3-2o**).* Pale yellow solid; 12 mg, 15% yield; mp: 162.3−163.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.09 (t, J = 6.9 Hz, 2H), 7.42−7.36 (m, 4H), 7.32 (t, J = 7.3 Hz, 2H), 7.26 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.0 Hz, 2H), 7.13 (t, J = 8.0 Hz, 1H), 6.82 (t, J = 7.0 Hz, 1H), 3.57 (dd, J = 12.9, 6.9 Hz, 2H), 3.41−3.35 (m, 1H), 2.23 (d, J = 11.8 Hz, 2H), 2.01 (dt, J = 20.1, 10.3 Hz, 2H), 1.80 (t, J = 10.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 144.8, 143.9, 142.6, 136.8, 128.7, 128.6, 128.3, 127.9, 127.4, 126.6, 126.4, 118.1, 114.5, 54.7, 42.8, 40.5, 32.4, 30.3, 21.4; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{24}H_{25}N_2O_2$: 373.1911, found: 373.1907; IR (KBr): 2959, 1705, 1567, 1502, 1424, 1206, 756, 699 cm^{-1}.

*2-(2-Phenylcyclopentanecarboxamido)pyridine 1-Oxide (**3-2p**).* Pale yellow solid; 34 mg, 60% yield; mp: 154.2−156.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.11 (t, J = 8.8 Hz, 2H), 7.23 (d, J = 7.5 Hz, 2H), 7.17 (t, J = 7.6 Hz, 3H), 7.07 (t, J = 7.2 Hz, 1H), 6.85 (t, J = 7.0 Hz, 1H), 3.52 (dd, J = 16.9, 8.5 Hz, 1H), 3.25 (dd, J = 14.3, 7.6 Hz, 1H), 2.32−2.19 (m, 2H), 2.13 (dd, J = 18.8, 13.1 Hz, 3H), 1.82 (dd, J = 18.7, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 143.8, 140.7, 136.8, 128.2, 127.9, 127.8, 126.6, 118.1, 114.3, 52.8, 49.9, 31.2, 28.6, 24.7; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{17}H_{19}N_2O_2$: 283.1441, found: 283.1443; IR (KBr): 2932, 1708, 1567, 1506, 1425, 1308, 699 cm^{-1}.

*2-(2-Phenylcyclobutanecarboxamido)pyridine 1-Oxide (**3-2q**).* Pale yellow solid; 11 mg, 20% yield; mp: 163.2−163.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.12 (dd, J = 11.7, 7.7 Hz, 2H), 7.25 (d, J = 7.6 Hz, 3H), 7.19 (dd, J = 16.2, 8.1 Hz, 2H), 7.08 (t, J = 7.0 Hz, 1H), 6.86 (t, J = 6.8 Hz, 1H), 4.08 (q, J = 8.7 Hz, 1H), 3.70 (d, J = 4.1 Hz, 1H), 2.67 (dt, J = 17.5, 8.9 Hz, 1H), 2.60−2.51 (m, 1H), 2.40 (dd, J = 23.7, 13.5 Hz, 1H), 2.29 (dd, J = 18.6, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.0, 136.8, 128.3, 127.9, 127.3, 126.7, 118.1, 114.3, 47.6, 43.3, 24.5, 20.2; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{16}H_{17}N_2O_2$: 269.1285, found: 269.1286; IR (KBr): 2923, 1698, 1567, 1505, 1425, 1311, 761, 699 cm^{-1}.

*2-(2,4-Diphenylcyclobutanecarboxamido)pyridine 1-Oxide (**3-2r**).* Pale yellow solid; 28 mg, 40% yield; mp: 170.1−171.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.06 (d, J = 6.4 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.30−7.19 (m, 8H), 7.12 (t, J = 6.3 Hz, 2H), 7.03 (t, J = 8.0 Hz, 1H), 6.78 (t, J = 7.0 Hz, 1H), 4.05 (dd, J = 17.6, 7.3 Hz, 4H), 3.45 (q, J = 10.4 Hz, 1H), 2.73−2.62 (m, 1H); ^{13}C NMR

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(100 MHz, $CDCl_3$) δ 169.5, 143.7, 140.0, 136.7, 128.2, 127.9, 126.8, 126.3, 118.1, 114.5, 54.5, 38.9, 29.3; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{22}H_{21}N_2O_2$: 345.1598, found: 345.1597; IR (KBr): 3272, 2938, 1700, 1567, 1506, 1425, 1208, 763, 697 cm^{-1}.

*2-(2-Phenylcyclopropanecarboxamido)pyridine 1-Oxide (**3-2s**).* Pale yellow solid; 28 mg, 55% yield; mp: 160.4−162.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.18 (d, J = 6.7 Hz, 2H), 7.27 (dd, J = 13.2, 6.8 Hz, 4H), 7.18 (d, J = 10.0 Hz, 2H), 6.89 (t, J = 7.0 Hz, 1H), 2.68 (dd, J = 16.9, 8.6 Hz, 1H), 2.26 (dd, J = 14.5, 7.7 Hz, 1H), 1.95−1.85 (m, 1H), 1.46 (dd, J = 13.4, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 144.1, 136.9, 135.8, 129.2, 128.1, 128.1, 126.8, 118.1, 114.6, 27.0, 25.0, 11.4; HR-MS (ESI) calcd for $[M + 1]^+$: $C_{15}H_{15}N_2O_2$: 255.1228, found: 255.1227; IR (KBr): 3203, 2924, 1691, 1567, 1508, 1425, 1209, 1136, 754, 695 cm^{-1}.

Several Examples about Removal of the Pyridine *N*-Oxide Group of 3. NaOH (0.30 mmol, 1.5 eqiv) was added to a solution of arylation product **3** (0.20 mmol, 1.0 equiv) in EtOH (2.0 mL), and the mixture was stirred at 85 °C for 8 h. After the solvent was removed *in vacuo*, the resulting residue was dissolved in aq. HCl solution (1.0 M, 3.0 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and then combined organic layers were washed with brine and dried over $MgSO_4$. The corresponding crude products were purified through flash chromatography on silica gel to provide the desired products.

*3-Phenylpropanoic Acid (**4a**):*[17] White solid; mp: 45−47.5 °C; 24 mg, 80% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 6.8 Hz, 2H), 7.20 (d, J = 6.8 Hz, 3H), 2.95 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 140.2, 128.6, 128.3, 126.4, 35.7, 30.6; LR- MS (ESI) m/z 151.1 $[M + H]^+$. IR (KBr) 3060, 1699, 1304, 1221, 696 cm^{-1}.

*3-Phenylbutanoic Acid (**4b**):*[18] Light yellow solid; mp: 35−37 °C; 25 mg, 75% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.3 Hz, 2H), 7.25−7.18 (m, 3H), 3.26 (dt, J = 13.9, 7.0 Hz, 1H), 2.67 (dd, J = 15.5, 6.7 Hz, 1H), 2.57 (dd, J = 15.4, 8.3 Hz, 1H), 1.31 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 145.5, 128.6, 126.7, 126.5, 42.6, 36.2, 21.9; MS (ESI) m/z 165.1 $[M + H]^+$; IR (KBr) 3030, 1604, 1453, 1297, 700 cm^{-1}.

*2, 4-Diphenylcyclobutanecarboxylic Acid (**4c**):*[19] Light yellow solid; mp: 171−173 °C; 39 mg, 78% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 8H), 7.22 (d, J = 6.0 Hz, 2H), 3.78 (q, J = 9.3 Hz, 2H), 3.31 (t, J = 9.5 Hz, 1H), 2.78 (q, J = 8.8 Hz, 1H), 2.31 (q, J = 10.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 142.7, 128.6, 126.7, 126.6, 52.4, 39.5, 32.7; MS (ESI) m/z 253.1 $[M + H]^+$; IR (KBr) 3015, 1623, 1456, 1260, 696 cm^{-1}.

Mechanistic Studies for Pd(II)-Catalyzed C(sp^3)−H Bond Arylation. *2-(N-Methylpropionamido)pyridine 1-Oxide (**1o**).* A mixture of 2-propionamidopyridine 1-oxide (0.5 mmol, 83 mg), K_2CO_3 (1.0 mmol, 138 mg), and methyl iodide (0.75 mmol, 106 mg) in CH_3CN (5 mL) was stirred at 85 °C for 3 h. After the reaction mixture was then filtrated, the corresponding filtrate was concentrated and purified by silica gel chromatography to give the desired product (**1o**) as a pale yellow oil (54 mg, 60% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 33.1, 6.1 Hz, 1H), 7.41−7.28 (m, 3H), 3.24 (s, 3H), 2.15 (q, J = 7.3 Hz, 2H), 1.10 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 148.8, 140.5, 126.2, 126.1, 125.1, 34.2, 26.9, 9.0; HR-MS (ESI) calcd for $[M + Na]^+$: $C_9H_{12}N_2NaO_2$: 203.0791, found: 203.0791; IR (KBr): 2980, 1700, 1570, 1507, 1432, 1209, 761 cm^{-1}.

*H/D Exchange of N-(1-Oxy-pyridin-2-yl)-propionamide (**1a**).* To an oven-dried Schlenk tube, *N*-(1-oxy-pyridin-2-yl)-propionamide (**1a**) (0.2 mmol, 33.2 mg), AcOD (1.0 mL), Pd $(OAc)_2$ (0.02 mmol, 4.5 mg), AgOAc (0.4 mmol, 66.4 mg), and *p*-xylene (2.0 mL) were added. The mixture was stirred at 130 °C for 6 h, then cooled down to room temperature, and filtered through a short plug of silica sand. The corresponding filtrate was further concentrated *in vacuo* and purified through flash chromatography on silica gel with ethyl acetate/petroleum (v/v = 1/2) as the eluent to afford the desired product ***D*-1a** (60% yield) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 6.4 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 6.99 (t, J = 6.7 Hz, 1H), 2.55 (s, 1H), 2.04 (s, 0.45 H); HR-MS (ESI) calcd for $[M + 1]^+$: $C_8H_8D_3N_2O_2$: 170.1003, found: 170.1002.

Kinetic Isotope Effect of This Transformation. Parallel individual reactions of **1a** and ***D*-1a**: The mixture of Pd $(OAc)_2$ (0.02 mmol, 4.5 mg), AgOAc (0.4 mmol, 66.4 mg), PhI(0.3 mmol, 61.0 mg), 2-propionamidopyridine 1-oxide (**1a**) (0.2 mmol, 33.2 mg), or the isotopically labeled substrate ***D*-1a** (0.2 mmol, 33.8 mg) in *p*-xylene (2.0 mL) was heated at 130 °C in a tube under an Ar atomosphere. Then aliquots (0.5 mL) of the reaction solution were taken at 80 min intervals. For each aliquot, the solvent was removed under reduced pressure, followed by analysis by ^1H NMR. The ^1H NMR raw data of the reactions of **1a** and ***D*-1a** were displayed (see SI; Figures 1 and 2). Comparison of the reaction progress in the early stage (0−320 min) indicated that the corresponding KIE value is 2.0 (see SI; Figure 3).

■ ASSOCIATED CONTENT

Supporting Information

Details for experiments conditions, copies of ^1H and ^{13}C NMR spectra for all isolated compounds, and single crystal data of **3-2q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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