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Nickel-catalyzed regioselective arylation of aromatic amides with aryl iodides enabled by an *N,O*-bidentate directing group†

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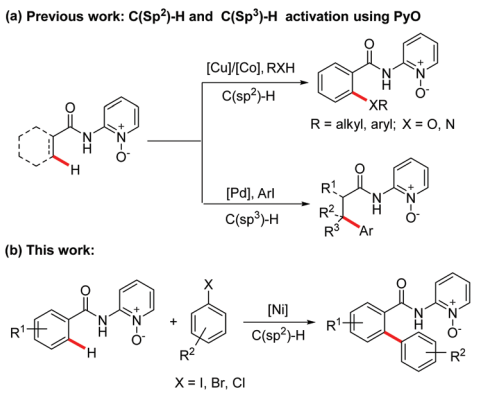
A bidentate directing group enabled regioselective arylation of C(sp^2)–H bonds in aromatic carboxamides with aryl iodides under nickel-catalysis is reported, which provides the corresponding products in moderate to good yields. This protocol using the inexpensive and low-toxic Ni catalyst can tolerate a wide range of functional groups.

Introduction

Over the past decade, the transition metal-catalyzed C–H bond activation has achieved tremendous advancement largely due to its broad applications in constructing C–C and C–X bonds in synthetic chemistry.[1] Generally, the combination of one suitable directing group and metal catalyst is requisite for the high efficiency and selectivity that is obtained from the chelation between the metal ion and heteroatom.[1,2] Therefore, a number of monodentate directing groups containing N, O or unsaturated bonds has been developed for facilitating the C–H activation event.[3] In recent years, a new strategy of the bidentate-type directing group pioneered by Daugulis has been developed for the challenging inert C–H activation and functionalization, which has achieved considerable success that could not be achieved by employing the common monodentate directing groups.[4] Then several typical bidentate directing groups containing the core of 8-aminoquinoline, picolinamide or pyridine developed by Chatani, Shi and some others have been successively applied for the selective activation of C(sp^2)–H and C(sp^3)–H bonds.[5,6] As a typical example, Song and co-workers in 2014 reported the first example of regioselective aryloxylation by using a copper catalyst and 2-aminopyridine 1-oxide (PyO) as the *N,O*-bidentate directing group.[7a] On the basis of the strategy, this group and others have established some efficient approaches for alkoxylation, amination, arylation and other reactions through transition metal catalysis.[7b–k] These elegant studies demonstrated that PyO as a powerful directing group could be capable of challenging more inert C–H activation (Scheme 1a).

Currently, chelation assistance has been one of the efficient and reliable strategies to enable the regioselective C–H activation. Especially for the bidentate directing group, it was found that the transition metal catalysts such as Pd,[8] Ru,[9] Cu,[10] Fe[11] and Ni[12] have been used to activate the inert C–H bonds. Among them, nickel catalysis in recent years has received increasing attention in organic synthesis for the advantage of natural abundance and low-toxicity. In fact, nickel has been used to catalyze the classical cross-couplings, such as the Suzuki, Negishi, and Kumada reactions.[13] Recently, nickel-catalysis is in the forefront in synthetic chemistry for new application in C–H functionalization with the assistance of bidentate directing groups. For example, Chatani *et al.* realized the nickel catalyzed oxidative coupling between C(sp^2)–H in benzamides and C(sp^3)–H in toluene derivatives,[12n] and they also developed the direct arylation of C(sp^3)–H



Scheme 1 C–H activation enabled by an *N,O*-bidentate directing group.

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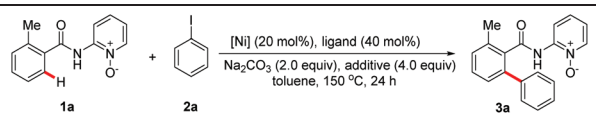
bonds in aliphatic amides with aryl halides catalyzed by nickel.[12p] Ge and co-workers reported the nickel-catalyzed site-selective alkylation of unactivated C(sp^3)–H bonds with alkyl halides.[12o] In 2016, Song, Niu and co-workers developed a nickel-catalyzed alkynylation/annulation cascade reaction using PyO as a removable *N*,*O*-bidentate group.[7i] Despite this progress, the nickel-catalyzed C–H functionalization has not been fully understood, at least the reaction scope has been extremely limited. Inspired by the recent studies on Ni catalysis,[12] we herein report a new nickel-catalyzed *ortho*-arylation of benzamides with the assistance of the *N*,*O*-bidentate group, which produced a series of desired products in good yields with broad functional group tolerance (Scheme 1b).

Aiming to realize the new nickel-catalyzed reactions, we initially focused our research on regioselective C(sp^2)–H bond arylation of benzamide (**1a**) with iodobenzene (**2a**). As shown in Table 1, the reaction was firstly performed in toluene at 150 °C for 24 hours in the presence of $NiCp_2$/PPh_3 as a catalyst and Na_2CO_3 as a base. However, only a trace amount of the desired product was obtained (Table 1, entry 1). To our delight, the reaction proceeded well when the ligand PPh_3 was replaced by 2-nitrobenzoic acid (*o*-NBA), providing the desired product **3a** in 37% isolated yield (entry 2). The structure of **3a** was characterized by ^1H and ^{13}C NMR, and the structure of **3b** was further confirmed by X-ray single crystal analysis.[14] Next, TBAB was added as an additive to this system, and the yield was promoted to 48% (entry 3). TBAB may act as a phase transfer reagent to improve the solubility of the substrates in toluene. To further examine the catalyst effect, various nickel salts were tested. It is evident that $NiBr_2$ was the most effective catalyst for the reaction, while $Ni(acac)_2$ and $Ni(OTf)_2$ failed in this catalytic transformation (entries 4–8). Curiously, not only Ni(II) salts but also a Ni(0)-complex showed a good catalytic activity, resulting in 37% yield of the desired product (entry 9). In the absence of a nickel catalyst, no desired product was formed, and only 11% yield of the product was detected without the addition of 2-nitrobenzoic acid (entries 10 and 11). Further investigation revealed that the addition of benzoic acid and some sterically bulky carboxylic acids, such as 2-biphenylcarboxylic acid (2-$PhC_6H_4CO_2H$), pivalic acid (PivOH) and 2,4,6-trimethylbenzoic acid (MesCOOH), also improved the product yields (entries 12–15). Among the additives examined, TBAB showed the highest reactivity (entries 16–18). The efficiency of the reaction was also significantly affected by the choice of the base used, and Na_2CO_3 was determined to be the best base for this reaction (see the ESI† for details). Among the solvents examined, toluene was the best (ESI†). The loading of the nickel catalyst, the reaction temperature, and the reaction time were optimized, which are outlined in Table 1 (entries 19–21).

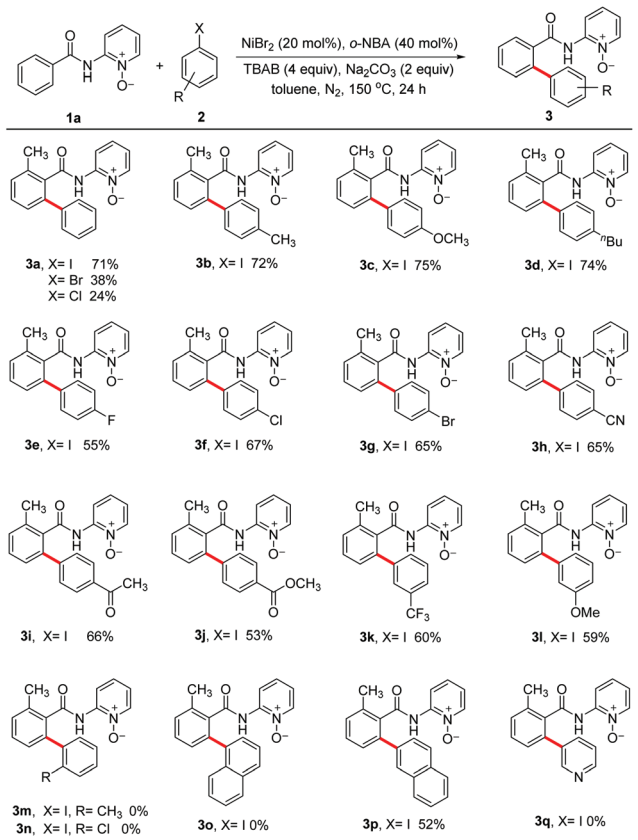
Table 1 Optimization of reaction conditions[a]



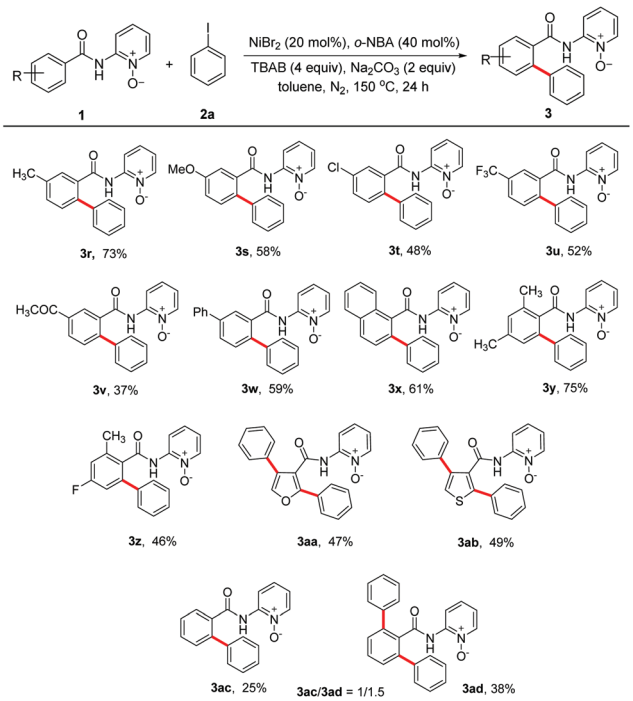
Entry	Catalyst	Ligand	Additive	Yield[b] (%)
1	$NiCp_2$	PPh_3	None	Trace
2	$NiCp_2$	*o*-NBA	None	37
3	$NiCp_2$	*o*-NBA	TBAB	48
4	$NiCl_2$	*o*-NBA	TBAB	43
5	$Ni(OAc)_2$	*o*-NBA	TBAB	27
6	$Ni(acac)_2$	*o*-NBA	TBAB	Trace
7	$Ni(OTf)_2$	*o*-NBA	TBAB	Trace
8	$NiBr_2$	*o*-NBA	TBAB	71
9	$Ni(COD)_2$	*o*-NBA	TBAB	37
10	None	*o*-NBA	TBAB	n.r.
11	$NiBr_2$	None	TBAB	11
12	$NiBr_2$	PhCOOH	TBAB	37
13	$NiBr_2$	2-$PhC_6H_4CO_2H$	TBAB	41
14	$NiBr_2$	PivOH	TBAB	45
15	$NiBr_2$	$MesCO_2H$	TBAB	50
16	$NiBr_2$	*o*-NBA	TBAI	55
17	$NiBr_2$	*o*-NBA	TBAC	43
18	$NiBr_2$	*o*-NBA	TBAF	41
19	$NiBr_2$	*o*-NBA	TBAB	61[c], 32[d]
20	$NiBr_2$	*o*-NBA	TBAB	43[e], 70[f]
21	$NiBr_2$	*o*-NBA	TBAB	51[g], 71[h]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (0.04 mmol, 20 mol%), ligand (0.08 mmol, 40 mol%), Na_2CO_3 (0.4 mmol, 2.0 equiv.), additive (0.8 mmol, 4 equiv.), toluene (1.5 mL) under an N_2 atmosphere at 150 °C for 24 h. [b] Isolated yields. [c] 15 mol% $NiBr_2$ was used. [d] 10 mol% $NiBr_2$ was used. [e] At 140 °C. [f] At 160 °C. [g] For 16 h. [h] For 30 h. *o*-NBA = 2-nitrobenzoic acid; TBAB = tetrabutylammonium bromide; TBAI = tetrabutylammonium iodide; TBAC = tetrabutylammonium chloride; TBAF = tetrabutylammonium fluoride; n.r. = no reaction.

With the optimal reaction conditions in hand, the generality of this *ortho*-arylation was investigated. As shown in Scheme 2, a variety of aryl iodides were tested under the optimized conditions. It should be noted that bromobenzene and chlorobenzene could also be used in this reaction, providing the corresponding product **3a** in 38% and 24% yield, respectively. Generally, *m*- and *p*-substituted iodobenzene with electron-donating and electron-withdrawing groups on the benzene rings could be applied to the reaction with **1a** affording the desired products (**3b–l**) in moderate to good yields. It should be noted that aryl iodide with an electron-rich group at the *para*-position on the phenyl rings, such as methyl, methoxy and *n*-butyl, generated the corresponding products (**3b–d**) in higher yields (72–75%), while aryl iodide with an electron-poor group at the *para*-position on the phenyl rings, such as fluoro, chloro, bromo, cyano, acetyl and CO_2CH_3 groups, afforded the corresponding products (**3e–j**) in the yields of 55–66%. However, 3-iodoanisole and 3-iodobenzotrifluoride showed a comparable reactivity in the reactions with **1a**, providing the desired products **3k** and **3l** in 60% and 59% yield, respectively. Unfortunately, *ortho*-substituted aryl iodides, such as 2-iodotoluene and 2-chloroiodobenzene failed to undergo *ortho*-arylation under the current catalyst system. Moreover, the fused-aryl halides and heteroaryl iodides, such as 1-iodine naphthalene, 2-iodine naphthalene and 3-iodopyridine, were used as substrates in this transformation. However, 1-iodine naphthalene and 3-iodopyridine exhibited the negative effect and none of the desired products were obtained.



Scheme 2 The substrate scope of aryl halides. Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $NiBr_2$ (0.04 mmol, 20 mol%), *o*-NBA (0.08 mmol, 40 mol%), Na_2CO_3 (0.4 mmol, 2.0 equiv.), TBAB (0.8 mmol, 4 equiv.), toluene (1.5 mL) under an N_2 atmosphere at 150 °C for 24 h.

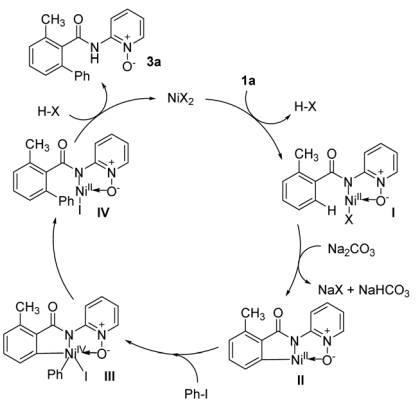


Scheme 3 The substrate scope of aromatic amides. Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $NiBr_2$ (0.04 mmol, 20 mol%), *o*-NBA (0.08 mmol, 40 mol%), Na_2CO_3 (0.4 mmol, 2.0 equiv.), TBAB (0.8 mmol, 4 equiv.), toluene (1.5 mL) under an N_2 atmosphere at 150 °C for 24 h.

When 2-iodine naphthalene was involved in the arylation reaction, the desired product **3p** was isolated in 52% yield.

To further investigate the substrate generality, we explored the substrate scope of aromatic amides. As shown in Scheme 3, different kinds of functionalized aromatic amides were well tolerated under the optimal reaction conditions, and the desired products (**3r–w**) were obtained in moderate to good yields (37–73%). For instance, benzamides with electron-donating groups, such as methyl, methoxy and phenyl substituents at the *meta*-position, underwent direct arylation with **2a** smoothly to afford the desired products **3r**, **3s** and **3t** in good yields, while benzamides with electron-withdrawing groups, such as chloro, trifluoromethyl and acetyl substituents at the *meta*-position, reacted with **2a** to give the corresponding products (**3t–v**) in lower yields. Moreover, α-naphthalimide could also be involved in the arylation reaction, providing the desired product **3x** in good yield. Notably, the reactions of *o*,*p*-disubstituted benzamides with **2a** generated moderate to good yields of the corresponding products **3y** and **3z**. Interestingly, di-arylation products **3aa** and **3ab** were obtained in moderate yields when furan-3-carboxamide and thiophene-3-carboxamide were introduced into the reaction, and none of the mono-substituted product was observed. Particularly, when 2-benzamidopyridine-1-oxide was used as a substrate, a separable mixture of mono- and di-arylation products **3ac** and **3ad** was obtained in 25% and 38% yield, respectively.

Further studies found that the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO, 2.0 equiv.) as a radical scavenger had a negligible effect on the model reaction outcome under the standard conditions (67% yield of **3a**), which is incompatible with the radical mechanism.[12n,o,p] Based on this result of the reaction and relevant literature reports,[7i,12p,s] a plausible mechanism was proposed to explain this process, although the exact mechanism of the reaction is unclear at present (Scheme 4). The catalytic cycle initiates with the



Scheme 4 A proposed mechanism.

coordination of **1a** to the Ni centre followed by ligand exchange with the concomitant generation of HX giving the Ni complex **I**, which undergoes cyclometalation to generate intermediate **II**. Then the oxidative addition of iodobenzene gives the high-valent Ni(IV) complex **III**. Subsequently, the Ni(IV) complex **III** undergoes reductive elimination to give **IV**, which affords the desired arylation product **3a** by protonation with the regeneration of Ni(II) for the next catalytic cycle.

Conclusions

In summary, a nickel-catalyzed direct *ortho*-arylation of 2-benzamidopyridine 1-oxide was developed. With the assistance of the PyO directing group, a variety of 2-benzamidopyridine 1-oxides and aryl iodides were tolerated, providing the corresponding products in moderate to good yields. This protocol using the inexpensive and low-toxic Ni catalyst can tolerate a wide range of functional groups. Further studies on the novel nickel-catalyzed reaction and detailed mechanism are currently underway in our laboratory.

Experimental section

General remarks

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometer (400 MHz and 100 MHz, respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, J, are reported in hertz (Hz). High resolution mass spectroscopy data of the product were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI). All the solvents and commercially available reagents were purchased from commercial suppliers. Products were purified by flash chromatography on 200–300 mesh silica gels, SiO_2.

Typical procedure for *ortho*-arylation of aromatic amides

In a glove-box, a 10 mL Schlenk tube was charged with **1a** (45.6 mg, 0.2 mmol), **2a** (122.4 mg, 0.6 mmol), $NiBr_2$ (8.7 mg, 0.04 mmol, 20 mol%), *o*-NBA (13.4 mg, 0.08 mmol, 40 mol%), Na_2CO_3 (42.4 mg, 0.4 mmol, 2 equiv.), TBAB (257.9 mg, 0.8 mmol, 4 equiv.), and toluene (1.5 mL) under an N_2 atmosphere. The reaction was carried out at 150 °C for 24 hours in an oil bath. After the reaction was completed, the reaction solution was washed with CH_2Cl_2 and concentrated under reduced pressure to yield a crude product, which was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 1 : 1, v/v) to give the desired product **3a** in 71% yield as a white solid.

Characterization data for all products

2-(3-Methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3a). White solid (43.2 mg, 71% yield), m.p. 202–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 7.6 Hz, 2H), 7.40–7.37 (m, 1H), 7.32–7.29 (m, 2H), 7.25–7.21 (m, 4H), 6.89–6.86 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 143.7, 139.8, 139.5, 136.9, 135.3, 135.2, 129.6, 129.3, 128.4, 128.2, 127.52, 127.47, 127.46, 118.5, 114.3, 19.4. HRMS (ESI) ($[M + H]^+$) calcd for $C_{19}H_{17}N_2O_2$: 305.1290, found: 305.1294.

2-(3,4′-Dimethyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3b). Yellow solid (45.8 mg, 72% yield), m.p. 199–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 6.4 Hz, 1H), 7.39–7.32 (m, 3H), 7.26–7.22 (m, 3H), 7.11 (d, J = 7.6 Hz, 2H), 6.91–6.87 (m, 1H), 2.44 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6, 143.9, 139.5, 137.2, 137.0, 136.9, 135.24, 135.23, 129.6, 129.14, 129.07, 128.3, 127.6, 118.5, 114.4, 21.0, 19.5. HRMS (ESI) ($[M + H]^+$) calcd for $C_{20}H_{19}N_2O_2$: 319.1447, found: 319.1444.

2-(4′-Methoxy-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3c). Yellow solid (50.1 mg, 75% yield), m.p. 151–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 6.4 Hz, 1H), 7.40–7.36 (m, 3H), 7.30–7.27 (m, 1H), 7.23 (d, J = 7.6 Hz, 2H), 6.94–6.91 (m, 1H), 6.86–6.84 (m, 2H), 3.75 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 159.1, 143.9, 139.2, 137.0, 135.34, 135.25, 132.3, 129.69, 129.67, 129.0, 127.8, 127.6, 118.6, 114.5, 113.9, 55.1, 19.5. HRMS (ESI) ($[M + H]^+$) calcd for $C_{20}H_{19}N_2O_3$: 335.1396, found: 335.1393.

2-(4′-Butyl-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3d). Yellow solid (53.3 mg, 74% yield), m.p. 241–242 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 6.4 Hz, 1H), 7.41–7.37 (m, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.28–7.24 (m, 3H), 7.11 (d, J = 8.0 Hz, 2H), 6.92–6.89 (m, 1H), 2.54 (t, J = 7.6 Hz, 2H), 2.45 (s, 3H), 1.54–1.46 (m, 2H), 1.27–1.18 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 143.9, 142.2, 139.8, 137.2, 136.9, 135.4, 135.3, 129.7, 129.2, 128.45, 128.40, 127.60, 127.55, 118.5, 114.4, 35.1, 33.3, 22.1, 19.6, 13.9. HRMS (ESI) ($[M + H]^+$) calcd for $C_{23}H_{25}N_2O_2$: 361.1916, found: 361.1912.

2-(4′-Fluoro-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3e). White solid (35.4 mg, 55% yield), m.p. 242–243 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 6.4 Hz, 1H), 7.42–7.38 (m, 3H), 7.33–7.26 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03–6.98 (m, 2H), 6.97–6.93 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 162.4 (d, J_{C-F} = 245.5 Hz), 143.7, 138.5, 137.1, 135.9 (d, J_{C-F} = 3.2 Hz), 135.5, 135.4, 130.2 (d, J_{C-F} = 8.0 Hz), 129.8, 129.6, 128.1, 127.5, 118.8, 115.3 (d, J_{C-F} = 21.2 Hz), 114.5, 19.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.3 (s). HRMS (ESI) ($[M + H]^+$) calcd for $C_{19}H_{16}FN_2O_2$: 323.1196, found: 323.1195.

2-(4′-Chloro-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3f). White solid (45.3 mg, 67% yield), m.p. 144–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 6.4 Hz, 1H), 7.42–7.37 (m, 3H), 7.32–7.27 (m, 4H), 7.21 (d, J = 7.6 Hz, 1H), 6.97–6.93 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 143.7, 138.35, 138.28, 137.1, 135.5, 135.3 133.8, 129.9, 129.82, 129.77,

128.6, 127.8, 127.5, 118.9, 114.5, 19.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{19}H_{16}ClN_2O_2$: 339.0900, found: 339.0895.

2-(4′-Bromo-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3g). White solid (49.7 mg, 65% yield), m.p. 234–237 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 6.4 Hz, 1H), 7.46–7.38 (m, 3H), 7.33–7.27 (m, 4H), 7.21 (d, J = 7.6 Hz, 1H), 6.98–6.94 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 143.7, 138.8, 138.3, 137.1, 135.5, 135.2, 131.6, 130.2, 129.9, 129.8, 127.9, 127.5, 122.1, 118.9, 114.5, 19.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{19}H_{16}BrN_2O_2$: 383.0395, found: 383.0392.

2-(4′-Cyano-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3h). Yellow solid (42.8 mg, 65% yield), m.p. 187–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.90 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 6.4 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.47–7.44 (m, 1H), 7.35–7.31 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 7.01–6.98 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 144.6, 143.5, 137.7, 137.1, 135.8, 135.2, 132.2, 130.6, 130.1, 129.3, 128.1, 127.3, 119.1, 118.6, 114.5, 111.5, 19.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{20}H_{16}N_3O_2$: 330.1243, found: 330.1240.

2-(4′-Acetyl-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3i). Yellow solid (45.7 mg, 66% yield), m.p. 206–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.89 (s, 1H), 8.42 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 6.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.46–7.42 (m, 1H), 7.32–7.25 (m, 3H), 6.97–6.94 (m, 1H), 2.56 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.6, 168.1, 144.7, 143.7, 138.4, 137.0, 136.1, 135.6, 135.2, 130.2, 129.9, 128.8, 128.5, 127.9, 127.5, 118.9, 114.5, 26.5, 19.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{21}H_{19}N_2O_3$: 347.1396, found: 347.1394.

2-(4′-(Methoxycarbonyl)-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3j). Yellow solid (38.4 mg, 53% yield), m.p. 159–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 8.42 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 6.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.44–7.40 (m, 1H), 7.31–7.25 (m, 3H), 6.95–6.92 (m, 1H), 3.87 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 166.6, 144.5, 143.6, 138.5, 137.0, 135.5, 135.2, 130.1, 129.8, 129.6, 129.2, 128.6, 127.8, 127.4, 118.8, 114.5, 51.9, 19.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{21}H_{19}N_2O_4$: 363.1345, found: 363.1341.

2-(3-Methyl-3′-(trifluoromethyl)-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3k). Yellow oil (44.6 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 6.4 Hz, 1H), 7.73 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.53–7.52 (m, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.33–7.27 (m, 3H), 6.97–6.93 (m, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 143.7, 140.6, 138.0, 137.0, 135.7, 135.4, 132.0 (d, J_{C-F} = 1.2 Hz), 130.7 (d, J_{C-F} = 32.2 Hz), 130.0, 129.0, 128.9 (d, J_{C-F} = 270.0 Hz), 127.8, 125.4 (q, J_{C-F} = 3.8 Hz), 125.2, 124.3 (q, J_{C-F} = 3.8 Hz), 122.5, 118.9, 114.6, 19.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7 (s). HRMS (ESI) ([M + H]$^+$) calcd for $C_{20}H_{16}F_3N_2O_2$: 373.1164, found: 373.1162.

2-(3′-Methoxy-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3l). Yellow oil (39.4 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 6.4 Hz, 1H), 7.41–7.38 (m, 1H), 7.29–7.20 (m, 4H), 7.03 (d, J = 7.6 Hz, 1H), 6.99 (s, 1H), 6.94–6.90 (m, 1H), 6.81–6.78 (m, 1H), 3.74 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.5, 159.4, 143.9, 141.2, 139.5, 137.0, 135.4, 135.2, 129.7, 129.5, 129.4, 127.7, 127.5, 121.0, 118.7, 114.4, 113.9, 113.6, 55.1, 19.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{20}H_{19}N_2O_3$: 335.1396, found: 335.1397.

2-(2-Methyl-6-(naphthalen-2-yl)benzamido)pyridine-1-oxide (3p). White solid (36.8 mg, 52% yield), m.p. 219–221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (br, 1H), 8.39 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.03 (d, J = 6.4 Hz, 1H), 7.93 (s, 1H), 7.82–7.77 (m, 3H), 7.59 (dd, J_1 = 8.5 Hz, J_2 = 1.6 Hz, 1H), 7.47–7.43 (m, 3H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.21 (td, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.86 (td, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 143.9, 139.6, 137.4, 137.0, 135.5, 133.3, 132.6, 129.8, 129.6, 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 126.7, 126.2, 126.1, 118.7, 114.5, 19.6. HRMS (ESI) ([M + H]$^+$) calcd for $C_{23}H_{19}N_2O_2$: 355.1447, found: 355.1448.

2-(4-Methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3r). White solid (44.4 mg, 73% yield), m.p. 203–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 6.4 Hz, 1H), 7.59 (s, 1H), 7.42–7.32 (m, 7H), 7.27–7.24 (m, 1H), 6.91–6.88 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 144.1, 139.5, 137.8, 137.4, 136.8, 134.1, 131.8, 130.7, 129.1, 128.6, 128.4, 127.7, 127.6, 118.4, 114.4, 20.8. HRMS (ESI) ([M + H]$^+$) calcd for $C_{19}H_{17}N_2O_2$: 305.1290, found: 305.1293.

2-(4-Methoxy-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3s). White solid (37.1 mg, 58% yield), m.p. 130–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 6.4 Hz, 1H), 7.59 (s, 1H), 7.42–7.32 (m, 7H), 7.27–7.24 (m, 1H), 6.91–6.88 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 144.1, 139.5, 137.8, 137.4, 136.8, 134.1, 131.8, 130.7, 129.1, 128.6, 128.4, 127.7, 127.6, 118.4, 114.4, 20.8. HRMS (ESI) ([M + H]$^+$) calcd for $C_{19}H_{17}N_2O_3$: 321.1239, found: 321.1236.

2-(4-Chloro-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3t). Pale solid (31.1 mg, 48% yield), m.p. 153–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 6.0 Hz, 1H), 7.78–7.77 (m, 1H), 7.55–7.52 (m, 1H), 7.39–7.30 (m, 7H), 6.97–6.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 143.8, 139.0, 138.4, 137.2, 135.6, 133.8, 132.1, 131.2, 128.84, 128.77, 128.6, 128.5, 128.4, 118.8, 114.7. HRMS (ESI) ([M + H]$^+$) calcd for $C_{18}H_{14}ClN_2O_2$: 325.0744, found: 325.0743.

2-(4-(Trifluoromethyl)-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3u). Yellow solid (37.2 mg, 52% yield), m.p. 161–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.05 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 6.4 Hz, 1H), 8.07 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.44–7.42 (m, 5H), 7.32–7.27 (m, 1H), 6.97–6.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 144.0 (q, J_{C-F} = 1.2 Hz), 143.8, 138.1, 137.0, 135.0, 130.1 (q, J_{C-F} = 257.5 Hz), 130.0 (q, J_{C-F} = 33.1 Hz), 128.9, 128.6, 127.8, 127.7 (q, J_{C-F} = 3.6 Hz), 126.0 (q, J_{C-F} = 3.8 Hz), 124.9, 122.2, 118.9, 114.7; ^{19}F NMR (376 MHz, $CDCl_3$)

δ −62.8 (s). HRMS (ESI) ([M + H]$^+$) calcd for $C_{19}H_{14}F_3N_2O_2$: 359.1007, found: 359.1005.

2-(4-Acetyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3v). Yellow solid (24.6 mg, 37% yield), m.p. 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.05 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 8.36 (d, J = 1.2 Hz, 1H), 8.16–8.11 (m, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.46–7.41 (m, 5H), 7.33–7.28 (m, 1H), 6.97–6.93 (m, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.5, 167.0, 144.9, 143.9, 138.5, 137.0, 136.1, 134.8, 131.2, 130.5, 129.0, 128.8, 128.7, 128.5, 127.7, 118.8, 114.6, 26.6. HRMS (ESI) ([M + H]$^+$) calcd for $C_{20}H_{17}N_2O_3$: 333.1239, found: 333.1236.

2-([1,1′:4′,1″-Terphenyl]-2′-ylcarboxamido)pyridine-1-oxide (3w). White solid (43.2 mg, 59% yield), m.p. 147–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.08 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 6.4 Hz, 1H), 8.02–8.01 (m, 1H), 7.80–7.78 (m, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.49–7.45 (m, 4H), 7.43–7.36 (m, 4H), 7.31–7.25 (m, 1H), 6.94–6.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 144.1, 140.6, 139.44, 139.39, 139.2, 137.0, 134.8, 131.3, 129.7, 128.9, 128.7, 128.6, 128.0, 127.9, 127.8, 127.4, 127.0, 118.4, 114.6. HRMS (ESI) ([M + H]$^+$) calcd for $C_{24}H_{19}N_2O_2$: 367.1447, found: 367.1440.

2-(2-Phenyl-1-naphthamido)pyridine 1-oxide (3x). White solid (41.5 mg, 61% yield), m.p. 212–215 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.99 (s, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 6.4 Hz, 1H), 8.07–8.04 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.94–7.92 (m, 1H), 7.59–7.57 (m, 5H), 7.41–7.37 (m, 2H), 7.33–7.30 (m, 2H), 6.95–6.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2, 143.9, 139.8, 137.4, 137.1, 132.4, 132.0, 130.3, 129.9, 128.9, 128.5, 128.2, 127.9, 127.8, 127.7, 127.5, 126.5, 124.9, 118.8, 114.6. HRMS (ESI) ([M + H]$^+$) calcd for $C_{22}H_{17}N_2O_2$: 341.1290, found: 341.1285.

2-(3,5-Dimethyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3y). White solid (47.7 mg, 75% yield), m.p. 231–233 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.42 (d, J = 8.24 Hz, 1H), 8.07 (d, J = 6.4 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.33–7.22 (m, 4H), 7.08–7.07 (m, 2H), 6.91–6.87 (m, 1H), 2.43 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7, 143.9, 140.0, 139.7, 139.6, 136.9, 135.4, 132.6, 130.2, 128.5, 128.3, 128.2, 127.6, 127.4, 118.5, 114.3, 21.1, 19.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{20}H_{19}N_2O_2$: 319.1447, found: 319.1442.

2-(5-Fluoro-3-methyl-[1,1′-biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3z). White solid (29.6 mg, 46% yield), m.p. 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.81 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 6.4 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.34–7.25 (m, 4H), 6.97 (d, J = 9.2 Hz, 2H), 6.93–6.90 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 162.6 (d, J_{C-F} = 248.6 Hz), 143.7, 142.2 (d, J_{C-F} = 8.7 Hz), 138.8 (d, J_{C-F} = 1.9 Hz), 138.7 (d, J_{C-F} = 8.7 Hz), 137.0, 131.6 (d, J_{C-F} = 3.2 Hz), 128.4 (d, J_{C-F} = 16.9 Hz), 128.1, 127.7, 118.7, 116.2 (d, J_{C-F} = 21.3 Hz), 114.5, 114.4, 114.3, 19.7 (d, J_{C-F} = 1.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −118.0 (s) HRMS (ESI) ([M + H]$^+$) calcd for $C_{19}H_{16}FN_2O_2$: 323.1196, found: 323.1199.

2-(2,4-Diphenylfuran-3-carboxamido)pyridine-1-oxide (3aa). Yellow solid (33.5 mg, 47% yield), m.p. 224–225 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 6.4 Hz, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.58 (s, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.44–7.35 (m, 6H), 7.31–7.26 (m, 1H), 6.94–6.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 155.1, 144.1, 139.2, 137.1, 130.4, 129.4, 128.8, 128.6, 128.4, 128.2, 127.6, 127.4, 127.2, 118.7, 116.6, 114.9. HRMS (ESI) ([M + H]$^+$) calcd for $C_{22}H_{17}N_2O_3$: 357.1239, found: 357.1236.

2-(2,4-Diphenylthiophene-3-carboxamido)pyridine-1-oxide (3ab). Yellow solid (36.4 mg, 49% yield), m.p. 205–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.91 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 6.4 Hz, 1H), 7.57–7.55 (m, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.36–7.30 (m, 6H), 7.26–7.21 (m, 2H), 6.89–6.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.4, 146.0, 143.8, 142.6, 136.9, 135.2, 132.5, 132.3, 128.80, 128.76, 128.73, 128.5, 128.2, 127.8, 127.6, 122.9, 118.6, 114.5. HRMS (ESI) ([M + H]$^+$) calcd for $C_{22}H_{17}N_2O_2S$: 373.1011, found: 373.1009.

2-([1,1′-Biphenyl]-2-ylcarboxamido)pyridine-1-oxide (3ac). White solid (14.5 mg, 25% yield), m.p. 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.00 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 6.4 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.59–7.56 (m, 1H), 7.49–7.35 (m, 7H), 7.31–7.26 (m, 1H), 6.95–6.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 144.1, 140.8, 139.6, 137.0, 134.4, 131.2, 130.9, 128.8, 128.7, 128.6, 128.0, 127.8, 127.6, 118.6, 114.6. HRMS (ESI) ([M + H]$^+$) calcd for $C_{18}H_{15}N_2O_2$: 291.1134, found: 291.1133.

2-([1,1′:3′,1″-Terphenyl]-2′-ylcarboxamido)pyridine-1-oxide (3ad). White solid (27.8 mg, 38% yield), m.p. 193–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.79 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 6.4 Hz, 1H), 7.57–7.53 (m, 1H), 7.47–7.41 (m, 6H), 7.34–7.30 (m, 4H), 7.28–7.25 (m, 2H), 7.15–7.11 (m, 1H), 6.83–6.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.7, 143.6, 140.4, 139.8, 136.8, 134.6, 129.8, 129.3, 128.6, 128.3, 127.60, 127.55, 118.4, 114.1. HRMS (ESI) ([M + H]$^+$) calcd for $C_{24}H_{19}N_2O_2$: 367.1447, found: 367.1441.

Conflicts of interest

There are no conflicts to declare.

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