Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Copper-catalyzed *ortho*-C–H amination of protected anilines with secondary amines

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Experimental procedures and data

General Methods. The corresponding starting materials were synthetized using oven-dried glassware under a nitrogen atmosphere containing a teflon-coated stirrer bar and dry septum. All halogenation reactions were performed at ambient N_2 pressure in oven-dried 20 mL vessel containing a teflon-coated stirrer bar and dry septum. All reactions were monitored by GC using *n*-hexadecane as an internal standard. Response factors of the products with regard to *n*-hexadecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3) and a time program beginning with 2 min at 60 ºC followed by 30 ˚C/min ramp to 300 ºC, then 3 min at this temperature. Flash column chromatography was performed using 230-400 mesh ultra-pure silica gel. NMR spectra were obtained on Bruker AC-300 or on Bruker AMX-500 systems using acetone-d_6 and $CDCl_3$ as solvents, with proton and carbon resonances at 300/500 MHz and 75/125 MHz, respectively. Mass spectral data were acquired on a VG *AutoSpec* mass spectrometer.

Solvents were purified by standard procedures prior to use. Copper salts were dried *in vacuo* at 60 ºC prior to use. All other compounds are commercially available and were used without further purification.

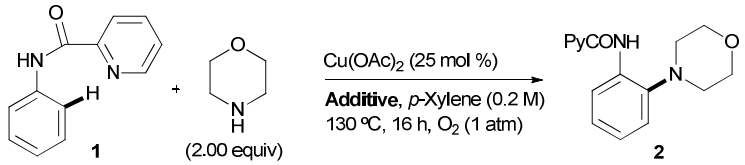
All oxidation reactions involving sodium hypochlorite were carried out with rapid continuous magnetic stirring in Erlenmeyer flasks open to the atmosphere. Sodium hypochlorite was commercial “ultra” laundry bleach containing a stated concentration of 6% NaOCl.

All microwave irradiation experiments were carried out in a mono mode microwave apparatus equipped with a pressure control system and a vertically-focused IR temperature sensor (Biotage).

1. Optimization studies

Table S1 Evaluation of different basic oxidants using O_2 as oxidant

In our initial experiments, we observed that the model reaction of picolinamide **1** with morpholine gave 41% of the *ortho*-amination product **2** using $Cu(OAc)_2$ in *p*-xylene as solvent at 130 ºC for 16 hours under an O_2 atmosphere (Table 1, entry 1). In fact, the reaction only led to 25% of **2** in the absence of O_2. In this case, the rest of the starting material was recovered unaltered (entry 2). Further experiments allowed us to conclude that the use of a basic additive was not improving the reactivity (entries 3-10).

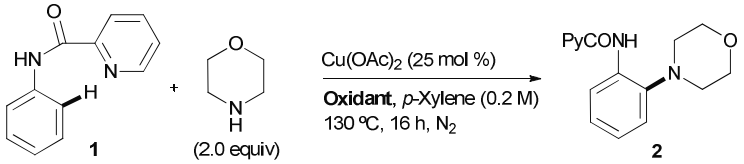


	Additive	Yield [%][a]
1	–	41
2[b]	–	25
3[c]	Na_2CO_3	50
4[c]	Na_2CO_3	53
5	K_2CO_3	44
6	Cs_2CO_3	41
7	K_3PO_4	40
8	KH_2PO_4	48
9	CsOPiv	48
10	NaOAc	49

Conditions: aniline **1** (0.20 mmol), morpholine (0.40 mmol), $Cu(OAc)_2$ (25 mol %), additive (25 mol %), *p*-xylene (0.2 M), 130 °C, 16 h, O_2. [a] GC yields (n-$C_{16}H_{34}$ as internal standard). [b] Under N_2. [c] Using 2.0 equiv. of the additive.

Table S2 Evaluation of different oxidants

Following the above conclusions, we next examined different oxidants. Among them, the use of NMO, $K_2S_2O_8$ and *N*-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate resulted in minor conversion of the starting material while $Ce(SO_4)_2$ and AgOAc provided comparable efficiency in terms of reactivity to the O_2. However, the use of $PhI(OAc)_2$ finally led to a 85% of the desired product **2**.

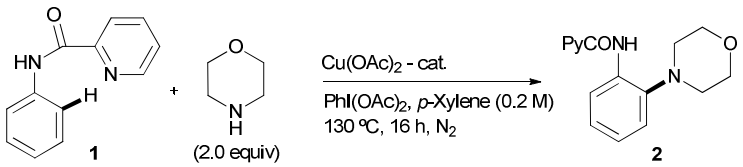


	Oxidant	Yield [%][a]
1	–	25
2	O_2	41
3	NMO	4
4	$K_2S_2O_8$	4
5	$Ce(SO_4)_2$	34
6	AgOAc	50
7	$[F^+]$	–
8	$PhI(OAc)_2$	85

Conditions: aniline **1** (0.20 mmol), morpholine (0.40 mmol), $Cu(OAc)_2$ (25 mol %), oxidant (0.40 mmol), *p*-xylene (0.2 M), 130 °C, 16 h, N_2. [a] GC yields (n-$C_{16}H_{34}$ as internal standard). $[F^+]$ = *N*-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate.

Table S3 Evaluation of the amounts of catalyst and oxidant

The encouraging 85% of **2** obtained when using $Cu(OAc)_2$ (25 mol %), $PhI(OAc)_2$ (2.0 equiv) as oxidant in *p*-xylene at 130 ºC for 16 hours was thus our starting point to adjust the amount of catalyst and oxidant. Thus, we were able to reduce the loading of $Cu(OAc)_2$ to a 15 mol%, using only 1.2 equiv. of $PhI(OAc)_2$. Under these conditions, the desired product was isolated in 74% yield (entry 4). Note that no product is formed in the absence of the $Cu(OAc)_2$ (entry 5).



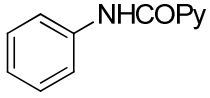
	$Cu(OAc)_2$ [mol %]	$PhI(OAc)_2$[equiv.]	Yield [%][a]
1	25	2.0	85 (84) [b]
2	20	2.0	83
3	15	2.0	72
4	15	1.2	75 (74) [b]
5	–	2.0	–

Conditions: aniline **1** (0.20 mmol), morpholine (0.40 mmol), $Cu(OAc)_2$, $PhI(OAc)_2$, *p*-xylene (0.2 M), 130 °C, 16 h, N_2. [a] GC yields (*n*-$C_{16}H_{34}$ as internal standard). [b] Isolated yield.

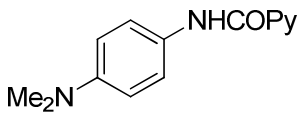
2. Typical procedure for the *N*-protection of anilines

2.1. Synthesis of *N*-aryl-2-pyridinecarboxamide derivatives

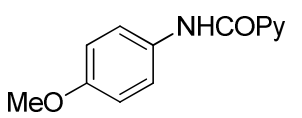
Synthesis of *N*-phenylpicolinamide (1).[1] A 50 mL round-bottomed flask immersed in a 0 °C bath (ice and water) was charged with picolinic acid (616 mg, 5.00 mmol) and CH_2Cl_2 (10 mL). To the stirred suspension was added oxalyl chloride (0.472 mL, 5.50 mmol) dropwise over a 15 minute period followed by addition of DMF (0.1 mL, catalytic amount) in one portion, producing a rust-red color and the evolution of a gas. The mixture was kept in the cooling bath for 1 h and then allowed to warm to room temperature. After gas evolution ceased, the mixture was again cooled to 0 °C and NEt_3 (1.40 mL, 10.0 mmol) was added dropwise over a 15 minute period followed by aniline (0.50 mL, 5.50 mmol) added dropwise over a 15 minute period. The brown mixture was left in the cooling bath for 30 minutes and then allowed to warm to room temperature. Stirring was continued at room temperature for 2 h. Removal of solvent in vacuo gave the crude product as a brown solid that was extracted with H_2O-AcOEt. The organic phases were combined and concentrated under reduced pressure to give **1** as a yellow solid; yield: 1.05 g (53%); mp= 76-77 ºC. The analytical data (NMR, HRMS analysis) matched those reported in the literature for *N*-phenyl-2-pyridinecarboxamide [CAS: 10354-53-7]. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.03 (s, 1H), 8.65 – 8.60 (m, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.92 (td, *J* = 7.7, 1.7 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.49 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H). **EI$^+$** calcd. for $C_{12}H_{10}N_2O$ $(M)^+$: 198.0793; Found: 198.0794.



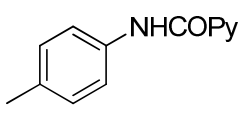
***N*-(4-(Dimethylamino)phenyl)picolinamide (11).** Compound **11** was prepared following the typical procedure from *N*,*N*-dimethylbenzene-1,4-diamine (681 mg, 5.00 mmol), to give **11** as a white solid; yield: 0.724 g (87%); mp= 131-132 ºC **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 9.85 (s, 1H), 8.61 (dd, *J* = 4.7, 0.7 Hz, 1H), 8.32 – 8.26 (m, 1H), 7.89 (td, *J* = 7.4, 1.2 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.49 – 7.49 (m, 1H), 6.78 (d, *J* = 9.0 Hz, 2H), 2.95 (s, 6H). **^{13}C NMR (acetone-d_6, 75 MHz)** δ: 162.1, 151.5, 149.1, 148.8, 138.7, 129.4, 127.2, 122.7, 121.8, 113.7, 40.9. **ESI$^+$** calcd. For $C_{14}H_{15}N_3O$ $(M+H)^+$: 242.1215; Found: 242.1289.



***N*-(4-Methoxyphenyl)picolinamide (12).** Compound **12** was prepared following the typical procedure from 4-methoxyaniline (615 mg, 5.00 mmol), to give **12** as a pale brown solid; yield: 0.495 g (44%); mp= 94-95 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 9.92 (s, 1H), 8.61 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.30 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.69 (d, *J* = 9, 2H), 7.47 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.92 (d, *J* = 9, 2H), 3.82 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.9, 156.6, 150.2, 148.1, 137.8, 131.2, 126.4, 122.5, 121.4, 114.4, 55.7. **ESI$^+$** calcd. for $C_{13}H_{12}N_2O_2$ $(M+H)^+$: 229.0899; Found: 229.0960.



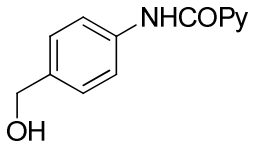
***N*-(*p*-Tolyl)picolinamide (13).** Compound **13** was prepared following the typical procedure from *p*-toluidine (0.606 mL, 5.50 mmol), to give **13** as a yellow solid; yield: 0.645 g (61%); mp= 105-107 ºC. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ: 9.96 (s, 1H), 8.60 (d, *J* = 4.7 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.46 (s, 1H), 7.18 (s, 2H), 2.34 (s, 3H). **^{13}C NMR ($CDCl_3$, 125**



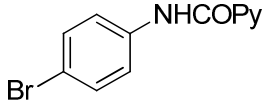
[1] (a) A. Jóźwiak, J. Z. Brzeziński, M. W. Płotka, A. K. Szcześniak, Z. Malinowski and J. Epsztajn, *Eur. J. Org. Chem.* 2004, 3254; (b) H. Brunner, B. Nuber and M. Prommesberger, *J. Organomet. Chem.* 1996, **523**, 179.

MHz) δ: 161.9, 150.1, 148.0, 137.7, 135.3, 134.0, 129.7, 126.4, 122.4, 119.8, 21.0. **EI** $^+$ calcd. for $C_{13}H_{12}N_2O$ $(M)^+$: 212.0950; Found: 212.0950.

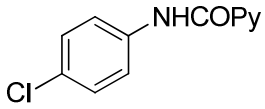
***N*-(4-(Hydroxymethyl)phenyl)picolinamide (14)**. Compound **14** was prepared following the typical procedure from (4-aminophenyl)methanol (615 mg, 5.00 mmol). The crude was purified by column chromatography (using *n*-hexane-ethyl acetate 2:1) to give **14** as a white solid; yield: 121 mg (11%); mp= 110-111 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.03 (s, 1H), 8.61 (d, *J* = 4.2 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.7, 1.6 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.51 – 7.42 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.67 (s, 2H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.1, 149.7, 147.9, 137.7, 137.3, 136.9, 127.9, 126.5, 122.4, 119.8, 64.7. **ESI**$^+$ calcd. for $C_{13}H_{12}N_2O_2$ $(M+H)^+$: 229.0899; Found: 229.0964.



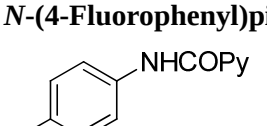
***N*-(4-Bromophenyl)picolinamide (15)**. Compound **15** was prepared following the typical procedure from 4-bromoaniline (946 mg, 5.50 mmol), to give **15** as a pale yellow solid; yield: 1.14 g (83 %); mp= 147-148 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.03 (s, 1H), 8.61 (dd, *J* = 4.8, 0.9 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.52 – 7.47 (m, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.2, 149.7, 148.2, 137.9, 137.0, 132.2, 126.8, 122.6, 121.4, 117.0. **EI**$^+$ calcd. for $C_{12}H_9BrN_2O$ $(M)^+$: 275.9898; Found: 275.9903.



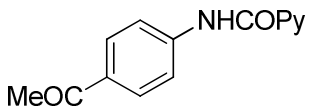
***N*-(4-Chlorophenyl)picolinamide (16)**. Compound **16** was prepared following the typical procedure from 4-chloroaniline (702 mg, 5.50 mmol), to give **16** as a pale yellow solid; yield: 866 mg (75%); mp= 139-140 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.04 (s, 1H), 8.66 – 8.57 (m, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.92 (td, *J* = 7.7, 1.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.49 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.2, 149.7, 148.1, 137.9, 136.5, 129.4, 129.3, 126.8, 122.6, 121.0. **EI**$^+$ calcd. for $C_{12}H_9ClN_2O$ $(M)^+$: 232.0403; Found: 232.0400.



***N*-(4-Fluorophenyl)picolinamide (17)**. Compound **17** was prepared following the typical procedure from 4-fluoroaniline (611 mg, 5.50 mmol), to give **17** as a brown solid; yield: 522 mg (48%); mp= 104-105 ºC. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ: 10.00 (s, 1H), 8.59 (d, *J* = 4.7 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.89 (td, *J* = 7.7, 1.6 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.47 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 7.09 – 7.09 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ: 162.0, 159.5 (d, $J_{C\text{-}F}$ = 243.4 Hz), 149.8, 148.1, 137.8, 133.9 (d, $J_{C\text{-}F}$ = 2.7 Hz), 126.6, 122.5, 121.4 (d, $J_{C\text{-}F}$ = 7.9 Hz), 115.8 (d, $J_{C\text{-}F}$ = 22.5 Hz). **^{19}F RMN ($CDCl_3$, 471 MHz)** δ: -117.9. **EI**$^+$ calcd. for $C_{12}H_9FN_2O$ $(M)^+$: 216.0699; Found: 216.0697.



***N*-(4-Acetylphenyl)picolinamide (18)**. Compound **18** was prepared following the typical procedure from 4-aminoacetophenone (743 mg, 5.50 mmol), to give **18** as a white solid; yield: 950 mg (79%); mp = 172-173 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.26 (s, 1H), 8.64 (d, *J* = 3.9 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 8.07 – 7.86 (m, 5H), 7.53 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.26 (s, 1H), 2.60 (s, 3H) **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 197.0, 162.3, 149.4, 148.1, 142.1, 138.0, 133.1, 130.0, 127.0, 122.8, 119.1, 26.6. **EI**$^+$ calcd. for $C_{14}H_{12}N_2O_2$ $(M)^+$: 240.0899; Found: 240.0892.



Methyl 4-(picolinamido)benzoate (19). Compound **19** was prepared following the typical procedure from methyl 4-aminobenzoate (831 mg, 5.50 mmol), to give **19** as a white solid; yield: 915 mg (71%); mp = 189-190 ºC. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 10.22 (s, 1H), 8.63 (d, *J* = 4.7 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 2H), 7.97 – 7.85 (m, 3H), 7.51 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 166.7, 162.3, 149.5, 148.1, 142.0, 137.9, 131.0, 126.9, 125.8, 122.7, 119.0, 52.1. **EI$^+$** calcd. for $C_{14}H_{12}N_2O_3$ $(M)^+$: 256.0848; Found: 256.0847.

***N*-(4-Cyanophenyl)picolinamide (20)**. Compound **20** was prepared following the typical procedure from 4-aminobenzonitrile (650 mg, 5.50 mmol), to give **20** as a pale yellow solid; yield: 895 mg (80%); mp= 164-166 ºC. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 10.25 (s, 1H), 8.64 (d, *J* = 4.0 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.93 (m, 3H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.53 (m, 1H). **^{13}C NMR (acetone-d$_6$, 75 MHz)** δ: 163.6, 150.3, 149.3, 143.5, 138.9, 133.9, 128.1, 123.3, 120.9, 119.5, 107.6. **EI$^+$** calcd. for $C_{13}H_9N_3O$ $(M)^+$: 223.0746; Found: 223.0737.

***N*-(3,5-Dimethoxyphenyl)picolinamide (21)**. Compound **21** was prepared following the typical procedure from 3,5-dimethoxyaniline (766 mg, 5.00 mmol), to give **21** as an orange solid; yield: 804 mg (63%); mp = 78-79 ºC. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 9.98 (s, 1H), 8.53 (d, *J* = 4.5 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.40 (dd, *J* = 6.7, 5.5 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 2H), 6.25 (s, 1H), 3.77 (s, 6H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 162.1, 149.7, 147.9, 137.7, 137.3, 136.9, 127.9, 126.5, 122.4, 119.8, 64.7. **ESI$^+$** calcd. for $C_{14}H_{14}N_2O_3$ $(M+H)^+$: 259.1004; Found: 259.1062.

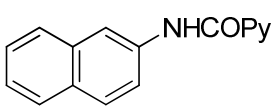
***N*-(3-Methoxyphenyl)picolinamide (22)**. Compound **22** was prepared following the typical procedure from 3-methoxyaniline (615 mg, 5.00 mmol), to give **22** as an orange oil; yield: 475 mg (42%). **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 10.11 (s, 1H), 8.53 (d, *J* = 7.8 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.5, 1H), 7.65 (t, *J* = 2.0 Hz, 1H), 7.45 – 7.22 (m, 3H), 6.74 (d, *J* = 7.9 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 161.6, 159.8, 149.2, 147.5, 138.7, 137.1, 129.3, 126.0, 121.8, 111.6, 109.7, 104.9, 54.7. **ESI$^+$** calcd. for $C_{13}H_{12}N_2O_2$ $(M+H)^+$: 229.0899; Found: 229.0962.

***N*-(*m*-Tolyl)picolinamide (23)**. Compound **23** was prepared following the typical procedure from *m*-toluidine (589 mg, 5.50 mmol), to give **23** as an orange oil; yield: 583 mg (55%). **^{1}H NMR (acetone-d$_6$, 300 MHz)** δ: 10.17 (s, 1H), 8.62 (d, *J* = 7.0 Hz, 1H,), 8.25 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.97 (td, *J* = 7.7, 1.7 Hz, 1H), 7.75 (d, *J* = 11.5 Hz, 2H), 7.54 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.0 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 162.0, 150.0, 148.0, 139.0, 137.7, 137.7, 128.9, 126.4, 125.2, 122.4, 120.4, 116.8, 21.6. **EI$^+$** calcd. for $C_{13}H_{12}N_2O$ $(M)^+$: 212.0950; Found: 212.0944.

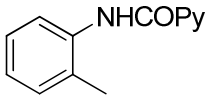
Methyl 3-(picolinamido)benzoate (24). Compound **24** was prepared following the typical procedure from methyl 3-aminobenzoate (831 mg, 5.50 mmol), to give **24** as an orange oil; yield: 483 mg (38%). **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 10.15 (s, 1H), 8.63 (d, *J* = 3.7 Hz, 1H), 8.36 – 8.28 (m, 2H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.93 (td, *J* = 7.7, 1.6 Hz, 1H),

7.83 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.56 – 7.43 (m, 2H), 3.94 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 166.8, 162.3, 149.6, 148.1, 138.1, 137.9, 131.2, 129.4, 126.8, 125.5, 124.1, 122.6, 120.7, 52.3. **EI$^+$** calcd. for $C_{14}H_{12}N_2O_3$ $(M)^+$: 256.0848; Found: 256.0853.

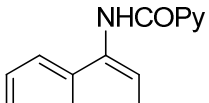
***N*-(Naphthalen-2-yl)picolinamide (25)**. Compound **25** was prepared following the typical procedure from naphthalen-2-amine (788 mg, 5.5 mmol), to give **25** as a pale brown solid; yield: 868 mg (70%); mp = 180-181 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.21 (s, 1H), 8.65 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.51 (d, *J* = 1.9 Hz, 1H), 8.35 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.93 (tt, *J* = 6.2, 3.1 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.55 – 7.40 (m, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.3, 149.9, 148.1, 137.8, 135.3, 134.1, 130.8, 128.9, 127.9, 127.7, 126.6, 126.6, 125.1, 122.5, 119.9, 116.5. **EI$^+$** calcd. for $C_{16}H_{12}N_2O$ $(M)^+$: 248.0950; Found: 248.0958.



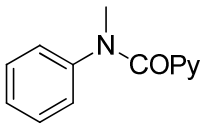
***N*-(*o*-Tolyl)picolinamide (26)**. Compound **26** was prepared following the typical procedure from *o*-toluidine (589 mg, 5.50 mmol), to give **26** as a white solid; yield: 502 mg (47 %); mp = 65-66 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.09 (s, 1H), 8.63 (d, *J* = 4.8, 1H), 8.30 (dd, *J* = 9.5, 8.4 Hz, 2H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.33 – 7.20 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.0, 150.3, 148.2, 137.8, 136.0, 130.5, 128.1, 127.0, 126.5, 124.7, 122.5, 121.4, 17.8. **EI$^+$** calcd. for $C_{13}H_{12}N_2O$ $(M)^+$: 212.0950; Found: 212.0949.



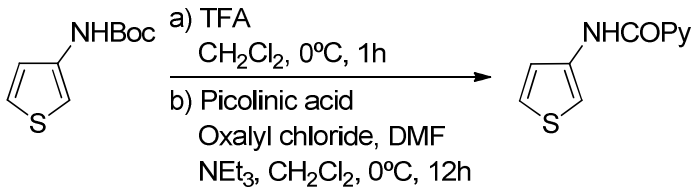
***N*-(Naphthalen-1-yl)picolinamide (27)**. Compound **27** was prepared following the typical procedure from naphthalen-1-amine (788 mg, 5.50 mmol), to give **27** as a pale brown solid; yield: 843 mg (68%); mp = 128-129 ºC. **^{1}H NMR (acetone-d_6, 300 MHz)** δ: 10.83 (s, 1H), 8.83 – 8.76(m, 1H), 8.38 (d, *J* = 7.6 Hz, 1H), 8.30 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.16 – 8.07 (m, 2H), 8.03 – 7.94 (m, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.74 – 7.54 (m, 4H). **^{13}C NMR (acetone-d_6, 75 MHz)** δ: 162.9, 151.0, 149.4, 139.0, 135.1, 133.8, 129.6, 127.8, 127.4, 127.2, 126.9, 126.6, 125.7, 123.0, 121.4, 119.4. **EI$^+$** calcd. for $C_{16}H_{12}N_2O$ $(M)^+$: 248.0950; Found: 248.0955.



***N*-Methyl-*N*-phenylpicolinamide (8)**. Compound **8** was prepared following the typical procedure from *N*-methylaniline (535 mg, 5.00 mmol), to give **8** as an orange oil; yield: 636 mg (60%). **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 8.26 (s, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.21 – 6.91 (m, 6H), 3.44 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 168.6, 154.1, 148.3, 144.1, 136.1, 128.8, 126.6, 126.4, 123.8, 123.4, 37.9. **EI$^+$** calcd. For $C_{13}H_{12}N_2O$ $(M)^+$: 212.0950; Found: 212.0951.



2.1.1. Synthesis of *N*-(thiophen-3-yl)picolinamide (28).



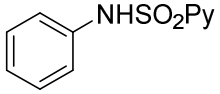
a) Deprotection of tert-butyl thiophen-3-ylcarbamate

A 50 mL round-bottomed flask immersed in a 0 °C bath (ice and water) was charged with *tert*-butyl thiophen-3-ylcarbamate (200 mg, 1.00 mmol) and CH_2Cl_2 (2 mL). To the stirred solution was added trifluoracetic acid (1.50 mL, 24.0 mmol) in one portion. After stirring at room temperature for 1 h, the removal of solvent *in vacuo* gave the salt of the unprotected aniline as a yellow oil.

b) Synthesis of the N-aryl-2-pyridinecarboxamide derivative

A 50 mL round-bottomed flask immersed in a 0 °C bath (ice and water) was charged with picolinic acid (123 mg, 1.00 mmol) and CH_2Cl_2 (8 mL). To the stirred suspension was added oxalyl chloride (93.0 µL, 1.10 mmol) dropwise over a 15 minute period followed by addition of DMF (20.0 µL, catalytic amount) in one portion, producing a rust-red color and the evolution of a gas. The mixture was kept in the cooling bath for 1 h and then allowed to warm to room temperature. After gas evolution ceased, the mixture was again cooled to 0 °C and pyridine (2.00 mL) was added dropwise over a 15 minute period followed by the solution of the salt of the thiophen-3-amine in CH_2Cl_2 (2 mL) added dropwise over a 15 minute period. The brown mixture was left in the cooling bath for 30 minutes and then allowed to warm to room temperature. Stirring was continued at room temperature for 12 h. Removal of solvent *in vacuo* gave the crude product as a brown solid that was extracted with H_2O-AcOEt. The organic phases were combined and concentrated under reduced pressure to give **28** as a red solid; yield: 153 mg (70%); mp = 104-105 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.18 (s, 1H), 8.59 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.79 (dd, *J* = 3.2, 1.4 Hz, 1H), 7.47 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.31 – 7.16 (m, 1H), 7.25 – 7.17 (m, 1H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.4, 149.5, 148.0, 137.6, 135.4, 126.4, 124.6, 122.4, 121.2, 110.4. **EI$^+$** calcd. for $C_{10}H_8N_2OS$ $(M)^+$: 204.0357; Found: 204.0352

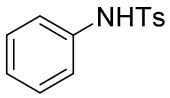
2.2. Synthesis of *N*-phenylpyridine-2-sulfonamide (5).[2] To a solution of aniline (364 µL, 4.00 mmol, 1.00 equiv) in THF (40 mL), pyridine (388 µL, 4.80 mmol, 1.20 equiv) and 2-pyridylsulfonyl chloride (852 mg, 4.80 mmol, 1.20 equiv) were successively added dropwise at 0 ºC and under N_2 atmosphere. The mixture was warmed to room temperature and stirred overnight. During this time, a gradual formation of a precipitate was observed. The resulting mixture was then suction filtered through a 6-cm fritted glass funnel (coarse) into a round-bottomed flask, and the filter cake was rinsed with THF (3 x 10 mL). To the resulting filtrate and the washes, water (20 mL) was added and the THF was removed by evaporation at reduced pressure, yielding a suspension of a white solid in the aqueous medium. This solid was collected by filtration, washed



[2] A. García-Rubia, B. Urones, R. Gómez Arrayás, and J. C. Carretero, *Angew. Chem. Int. Ed.* 2011, **50**, 10927.

sequentially with toluene (2 x 5 mL) and diethyl ether (2 x 5 mL). Then it was transferred to a round-bottomed flask, and dried at 1.0 mmHg to provide **5** as a white powder; yield: 862 mg (92%); mp = 170-172 ºC. The analytical data (NMR, HRMS analysis) matched those reported in the literature for *N*-phenylpyridine-2-sulfonamide [CAS: 103863-00-9]. **^{1}H NMR (acetone-d_6, 300 MHz)** δ: 9.19 (s, 1H), 8.69 (dd, *J* = 3.6, 1.2, 1H), 8.02 (m, 1H), 7.94 (m, 1H), 7.59 (ddd, *J* = 7.2, 4.8, 1.5, 1H), 7.24 (m, 4H), 7.03 (t, *J* = 7.2 Hz, 1H). **ESI$^+$** calcd. for $C_{11}H_{11}N_2O_2S$ $(M+H)^+$: 235.0535; Found: 235.0537.

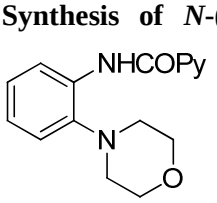
2.3. Synthesis of 4-methyl-*N*-phenylbenzenesulfonamide (6). Compound **6** was prepared following the typical procedure from aniline (364 µL, 4.00 mmol) and 4-methylbenzenesulfonyl chloride (915 mg, 4.80 mmol, 1.20 equiv) to give **6** as a white solid; yield: 752 mg (76%); mp = 96-97 ºC. The analytical data (NMR, GC-MS analysis) matched those reported in the literature for 4-methyl-*N*-phenylbenzenesulfonamide [CAS: 68-34-8]. **^{1}H NMR (acetone-d_6, 300 MHz)** δ: 8.90 (s, 1H), 7.67 (d, *J*=8.3, 2H), 7.31 (d, *J*=7.9, 2H), 7.21 (m, 4H), 7.06 (m, 1Hc), 2.35 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 144.0, 136.7, 136.2, 129.8, 129.4, 127.4, 125.4, 121.6, 21.6.



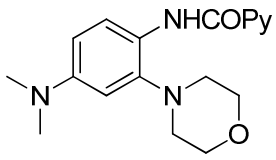
3. General procedures for the copper-catalyzed *ortho*-amination

3.1. Copper-catalyzed reaction of morpholine with aniline derivatives (Scheme 1)

Synthesis of *N*-(2-morpholinophenyl)picolinamide (2). An oven-dried, nitrogen-flushed 20 mL vessel was charged with *N*-phenylpicolinamide (**1**) (39.6 mg, 0.20 mmol, 1.00 equiv), (diacetoxyiodo)benzene (77.3 mg, 0.24 mmol, 1.20 equiv), and copper (II) acetate (5.45 mg, 0.03 mmol, 0.15 equiv).The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with nitrogen three times. Under the atmosphere of nitrogen, *p*¬xylene (1.00 mL), morpholine (0.31 mL, 0.40 mmol, 2.00 equiv) and the internal standard *n*¬hexadecane (10 µL) were added *via* syringe. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (*n*-hexane-EtOAc 5:1), yielding **2** as a white solid; yield: 46.9 mg (83%); mp= 108-109 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.15 (s, 1H), 8.66 (ddd, *J* = 4.7, 1.5, 0.9 Hz, 1H), 8.59 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.30 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7. 23 – 7.07 (m, 3H), 4.05 – 3.93 (m, 4H), 3.02 – 2.91 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.9, 150.7, 148.3, 141.9, 137.7, 133.2, 126.4, 125.4, 124.2, 122.5, 120.2, 119.7, 67.7, 52.6. **EI$^+$** calcd. for $C_{16}H_{17}N_3O_2$ $(M)^+$: 283.1321; Found: 283.1317. **Anal**. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 6752; H, 6.08; N, 14.82.

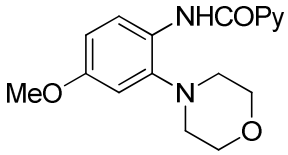


***N*-(4-(Dimethylamino)-2-morpholinophenyl)picolinamide (29).** Compound **29** was prepared following the general protocol from *N*-(4-(dimethylamino)phenyl)picolinamide (**11**) (48.3 mg, 0.20 mmol), to give **29** as a yellow solid; yield: 28.2 mg (43%); mp= 116-117 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.85 (s, 1H), 8.70 – 8.59 (m, 1H), 8.44 (d, *J* = 8.7 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.88 (td, *J* = 7.7, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.65 – 6.52 (m, 2H), 4.05 – 3.91 (m, 4H), 3.07 – 2.88 (m, 10H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.2, 151.1, 148.3, 148.0, 143.2, 137.6, 126.1,

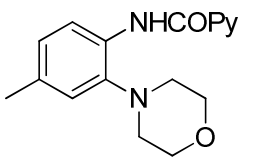


123.5, 122.3, 120.9, 109.3, 105.1, 67.8, 52.6, 41.2. **EI**$^+$ calcd. for $C_{18}H_{22}N_4O_2$ $(M+H)^+$: 327.1743; Found: 327.1812.

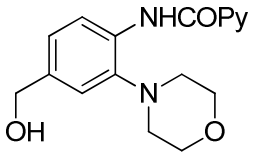
***N*-(4-Methoxy-2-morpholinophenyl)picolinamide (30).** Compound **30** was prepared following the general protocol from *N*-(4-methoxyphenyl)picolinamide (**12**) (45.7 mg, 0.20 mmol), to give **30** as a pale yellow solid; yield: 46.5 mg (74%); mp= 146-147 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.87 (s, 1H), 8.69 – 8.59 (m, 1H), 8.54 – 8.44 (m, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 6.80 – 6.67(m, 2H), 4.04 – 3.90 (m, 4H), 3.81 (s, 3H), 3. 02 – 2.87 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.5, 156.5, 150.7, 148.3, 143.5, 137.7, 126.5, 126.3, 122.3, 120.7, 108.8, 107.4, 67.6, 55.6, 52.5. **ESI**$^+$ calcd. for $C_{17}H_{19}N_3O_3$ $(M+H)^+$: 314.1426; Found: 314.1499. **Anal**. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.13; H, 6.21; N, 13.16.



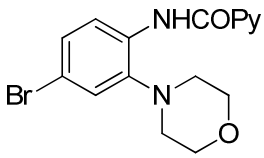
***N*-(4-Methyl-2-morpholinophenyl)picolinamide (31).** Compound **31** was prepared following the general protocol from *N*-(*p*-tolyl)picolinamide (**13**) (42.5 mg, 0.20 mmol), to give **31** as an orange solid; yield: 45.1 mg (76%); mp= 121-122 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.04 (s, 1H), 8.65 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.46 (d, *J* = 8.2 Hz, 1H), 8.29 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.05 – 6.92 (m, 2H), 4.06 – 3.90 (m, 4H), 3.01 – 2.87 (m, 4H), 2.34 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.8, 150.8, 148.3, 141.9, 137.7, 133.9, 130.5, 126.3, 125.8, 122.4, 120.9, 119.6, 67.8, 52.6, 21.3. **EI**$^+$ calcd. for $C_{17}H_{19}N_3O_2$ $(M)^+$: 297.1477; Found: 297.1488. **Anal**. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.00; H, 6.51; N, 13.91.



***N*-(4-(Hydroxymethyl)-2-morpholinophenyl)picolinamide (32).** Compound **32** was prepared following the general protocol from *N*-(4-(hydroxymethyl)phenyl)picolinamide (**14**) (36.0 mg, 0.15 mmol), to give **32** as an orange solid; yield: 28.8 mg (46%); mp= 116-117 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.10 (s, 1H), 8.66 (d, *J* = 4.7 Hz, 1H), 8.55 (d, *J* = 8.2 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (dd, *J* = 6.5, 4.8 Hz, 1H), 7.21 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 4.67 (s, 2H), 4.05 – 3.88 (m, 4H), 3.01 – 2.88 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.0, 150.5, 148.3, 142.2, 137.7, 136.9, 132.4, 126.5, 124.1, 122.5, 119.7, 119.1, 67.7, 65.3, 52.6. **ESI**$^+$ calcd. for $C_{17}H_{19}N_3O_3$ $(M+H)^+$: 314.1426; Found: 314.1502.



***N*-(4-Bromo-2-morpholinophenyl)picolinamide (33).** Compound **33** was prepared following the general protocol from *N*-(4-bromophenyl)picolinamide (**15**) (55.4 mg, 0.20 mmol), to give **33** as a pale orange solid; yield: 58.5 mg (81%); mp= 139-140 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.02 (s, 1H), 8.63 – 8.51 (m, 1H), 8.49 (dd, *J* = 8.7, 1.5 Hz, 1H), 8.29 (d, *J* = 7.4 Hz, 1H), 7.92 (tt, *J* = 7.8, 1.7 Hz, 1H), 7.50 (ddt, *J* = 7.5, 4.7, 1.4 Hz, 1H), 7.32 (d, *J* = 8.7 Hz 1H), 7.26 (s, 1H), 3.97 – 3.83 (m, 4H), 2.94 – 2.80 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.9, 150.3, 148.4, 143.3, 137.8, 132.2, 128.3, 126.6, 123.7, 122.6, 121.0, 116.6, 67.6, 52.4. **ESI**$^+$ calcd. for $C_{16}H_{16}BrN_3O_2$ $(M+H)^+$: 362.0426; Found: 362.0496.



***N*-(4-Chloro-2-morpholinophenyl)picolinamide (34).** Compound **34** was prepared following the general protocol from *N*-(4-chlorophenyl)picolinamide (**16**) (46.5 mg, 0.20 mmol), to give **34** as a pale yellow solid; yield: 49.4 mg (78%); mp= 147-148 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.01 (s, 1H), 8.72 – 8.62 (m, 1H), 8.53 (dd, *J* = 8.7, 3.1 Hz, 1H), 8.33 – 8.25 (m, 1H), 7.91 (tdd, *J* = 7.8, 3.3, 1.7 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.21 – 7.08 (m, 2H), 4.03 – 3.91 (m, 4H), 3.01 – 2.87 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 161.9, 150.4, 148.4, 143.1, 137.8, 131.7, 129.0, 126.6, 125.3, 122.6, 120.8, 120.7, 67.6, 52.4. **ESI$^+$** calcd. for $C_{16}H_{16}ClN_3O_2$ $(M+H)^+$: 318.0931; Found: 318.1007.

***N*-(4-Fluoro-2-morpholinophenyl)picolinamide (35).** Compound **35** was prepared following the general protocol from *N*-(4-fluorophenyl)picolinamide (**17**) (43.2 mg, 0.20 mmol), to give **35** as a pale yellow solid; yield: 36.2 mg (60%); mp= 144-145 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.91 (s, 1H), 8.65 (m, 1H), 8.58 – 8.49 (m, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.5, 1.5 Hz, 1H), 7.49 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.94 – 6.83 (m, 2H), 4. 05 – 3.92 (m, 4H), 2.99 – 2.88 (m, 4H). **^{13}C RMN ($CDCl_3$, 75 MHz)** δ: 161.8, 159.4 (d, *J* = 244.2 Hz), 150.5, 148.4, 143.6 (d, *J* = 7.6 Hz), 137.8, 129.2 (d, *J* = 3.1 Hz), 126.5, 122.5, 120.9 (d, *J* = 8.7 Hz), 111.4 (d, *J* = 21.8 Hz), 107.8 (d, *J* = 23.3 Hz), 67.5, 52.4. **^{19}F RMN ($CDCl_3$, 282 MHz)** δ: -116.7 (s). **EI$^+$** calcd. for $C_{16}H_{16}FN_3O_2$ $(M)^+$: 301.1227; Found: 301.1303. **Anal**. Calcd. for $C_{16}H_{16}FN_3O_2$: C, 63.78; H, 5.35; N, 13.95. Found: C, 63.59; H, 5.67; N, 12.98.

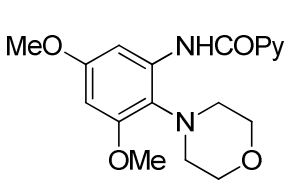
***N*-(4-Acetyl-2-morpholinophenyl)picolinamide (36).** Compound **36** was prepared following the general protocol from *N*-(4-acetylphenyl)picolinamide (**18**) (36 mg, 0.15 mmol). In this case, use of $Cu(OAc)_2$ (25 mol%) and $PhI(OAc)_2$ (2.00 equiv) is necessary to obtain **36** as a pale yellow solid; yield: 20.0 mg (32%); mp= 196-197 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.34 (s, 1H), 8.73 – 8.65 (m, 2H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.94 (t, *J* = 7.0 Hz, 1H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.52 (dd, *J* = 7.5, 4.8 Hz, 1H), 4.05 – 3.95 (m, 4H), 3.05 – 2.91 (m, 4H), 2.60 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 197.3, 162.1, 150.5, 148.4, 142.0, 137.8, 137.6, 133.1, 126.9, 126.8, 122.7, 119.9, 118.7, 67.6, 52.5, 26.5. **EI$^+$** calcd. for $C_{18}H_{19}N_3O_3$ $(M)^+$: 325.1426; Found: 325.1437.

Methyl 3-morpholino-4-(picolinamido)benzoate (37). Compound **37** was prepared following the general protocol from methyl 4-(picolinamido)benzoate (**19**) (38.4 mg, 0.15 mmol). In this case, use of $Cu(OAc)_2$ (25 mol%) and $PhI(OAc)_2$ (2.00 equiv) is necessary to give **37** as a white solid; yield: 30.6 mg (45%); mp= 157-159 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.32 (s, 1H), 8.73 – 8.65 (m, 2H), 8.31 (d, *J* = 7.9 Hz, 1H), 7.99 – 7.84 (m, 3H), 7.57 – 7.48 (m, 1H), 4.01 (m, 4H), 4.07 – 3.97 (s, 3H), 3.06 – 2.96 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 166.8, 162.3, 150.2, 148.4, 141.7, 137.8, 137.4, 127.5, 126.8, 125.5, 122.7, 121.8, 118.9, 67.6, 52.5, 52.2. **EI$^+$** calcd. for $C_{18}H_{19}N_3O_4$ $(M)^+$: 341.1376; Found: 341.1385.

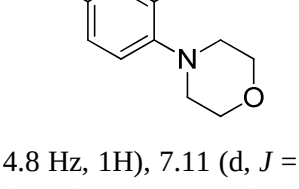
***N*-(4-Cyano-2-morpholinophenyl)picolinamide (38).** Compound **38** was prepared following the general protocol from *N*-(4-cyanophenyl)picolinamide (**20**) (44.6 mg, 0.20 mmol). In this case, use of $Cu(OAc)_2$ (25 mol%) and $PhI(OAc)_2$ (2.00 equiv) is necessary to obtain **38** as a white solid; yield: 30.8 mg (79%); mp= 180-181 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)**

δ: 11.27 (s, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.68 (d, *J* = 4.7 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.94 (td, *J* = 7.7, 1.6 Hz, 1H), 7.58 – 7-46 (m, 2H), 7.41 (d, *J* = 1.8 Hz, 1H), 4.05 – 3.96 (m, 4H), 3.01 – 2.92 (m, 4H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 162.5, 149.8, 148.5, 142.2, 137.9, 137.4, 129.9, 127.0, 124.1, 122.8, 119.8, 119.1, 107.0, 67.5, 52.4. **IE$^+$** calcd. para $C_{17}H_{16}N_4O_2$ $(M)^+$: 308.1273; Found: 308.1282.

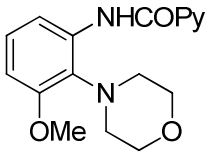
***N*-(3,5-Dimethoxy-2-morpholinophenyl)picolinamide (39).** Compound **39** was prepared following the general protocol from *N*-(3,5-dimethoxyphenyl)picolinamide (**21**) (51.7 mg, 0.20 mmol), to give **39** as a brown solid; 62.0 mg (92%); mp= 171-173 ºC. **^{1}H NMR (acetone-d$_6$, 300 MHz)** δ: δ 11.82 (s, 1H), 8.82 (d, *J* = 4.7 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 8.08 (t, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.70 – 7.63 (m, 1H), 6.35 (d, *J* = 2.6 Hz, 1H), 3.94 – 3.78 (m, 10H), 3.63 – 3.51 (m, 2H), 2.59 (d, *J* = 11.7 Hz, 2H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 162.4, 159.1, 159.0, 150.8, 148.4, 137.6, 137.4, 126.3, 122.4, 121.7, 95.4, 95.3, 68.5, 55.7, 55.3, 50.8. **ESI$^+$** calcd. for $C_{18}H_{21}N_3O_4$ $(M+H)^+$: 344.1532; Found: 344.1590. **Anal**. Calcd. for $C_{18}H_{21}N_3O_4$: C, 63.59; H, 5.67; N, 12.98. Found: C, 61.47; H, 6.15; N, 11.38.



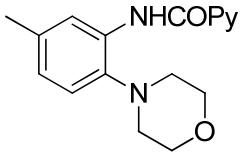
***N*-(5-Methoxy-2-morpholinophenyl)picolinamide (40).** Compound **40** was prepared following the general protocol from *N*-(3-methoxyphenyl)picolinamide (**22**) (45.6 mg, 0.20 mmol), to give **40** as a pale brown solid; yield: 23.1 mg (37%); mp= 102-103 ºC. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 11.31 (s, 1H), 8.66 (d, *J* = 4.8 Hz, 1H), 8.35 – 8.24 (m, 2H), 7.90 (td, *J* = 7.7, 1.2 Hz, 1H), 7.48 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.05 – 3.91 (m, 4H), 3.84 (s, 3H), 2.96 – 2.84 (m, 4H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 162.2, 157.4, 150.6, 148.4, 137.7, 135.1, 134.4, 126.5, 122.4, 121.3, 110.0, 104.8, 67.9, 55.7, 53.0. **ESI$^+$** calcd. for $C_{17}H_{19}N_3O_3$ $(M+H)^+$: 314.1426; Found: 314.1486. **Anal**. Calcd. for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 64.61; H, 6.17; N, 13.30.



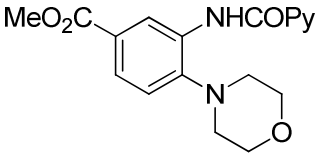
In the same experiment, ***N*-(3-Methoxy-2-morpholinophenyl)picolinamide (41)** was also isolated as a pale brown solid; yield: 10.2 mg (16%); mp= 180-181 ºC. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 11.84 (s, 1H), 8.69 (d, *J* = 3.9 Hz, 1H), 8.29 (dd, *J* = 7.3, 6.4 Hz, 2H), 7.90 (td, *J* = 7.7, 1.1 Hz, 1H), 7.47 (dd, *J* = 7.5, 4.7 Hz, 1H), 7.21 (t, *J* = 8.3 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.03 – 3.93 (m, 4H), 3.86 (s, 3H), 3.78 – 3.58 (m, 2H), 2.66 (d, *J* = 11.6 Hz, 2H). **^{13}C NMR (CDCl$_3$, 75 MHz)** δ: 162.34 158.5, 150.9, 148.4, 137.6, 137.2, 128.2, 127.6, 126.3, 122.5, 111.6, 107.2, 68.5, 55.4, 50.5. **ESI$^+$** calcd. for $C_{17}H_{19}N_3O_3$ $(M+H)^+$: 314.1426; Found: 314.1514.



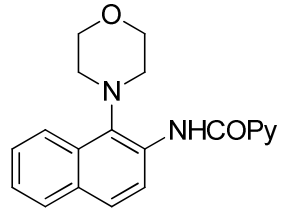
***N*-(5-Methyl-2-morpholinophenyl)picolinamide (42).** Compound **42** was prepared following the general protocol from *N*-(*m*-tolyl)picolinamide (**23**) (42.5 mg, 0.20 mmol), to give **42** as a yellow solid; yield: 36.0 mg (61%); mp= 136-137 ºC. **^{1}H NMR (CDCl$_3$, 300 MHz)** δ: 11.16 (s, 1H), 8.71 – 8.64 (m, 1H), 8.45 (s, 1H), 8.30 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.07 – 3.91 (m, 4H), 3.07 – 2.89 (m, 4H), 2.38 (s, 3H). **^{13}C NMR (acetone-d$_6$, 75 MHz)** δ: 162.2, 151.4, 149.4, 140.5, 138.8, 135.3, 134.0, 127.5, 125.1, 122.8, 121.0, 120.3, 68.0, 53.4, 21.4. **EI$^+$** calcd. for $C_{17}H_{19}N_3O_2$ $(M)^+$: 297.1477; Found: 297.2490. **Anal**. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.09; H, 6.51; N, 13.97.



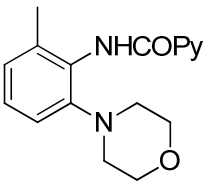
Methyl 4-morpholino-3-(picolinamido)benzoate (43). Compound **43** was prepared following the general protocol from methyl 3-(picolinamido)benzoate (**24**) (38.4 mg, 0.15 mmol), to give **43** as a pale yellow solid; yield: 41.0 mg (61%); mp= 183-184 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.92 (s, 1H), 9.19 (d, *J* = 2.0 Hz, 1H), 8.66 (dd, *J* = 4.7, 0.9 Hz, 1H), 8.31 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.98 – 7.88 (m, 1H), 7.82 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.50 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 4.07 – 3.97 (m, 4H), 3.91 (s, 3H), 3.07 - 2.95 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 166.9, 161.9, 150.2, 148.3, 146.1, 137.8, 132.4, 126.7, 126.6, 126.1, 122.6, 120.9, 119.5, 67.4, 52.1, 52.1. **ESI$^+$** calcd. for $C_{18}H_{19}N_3O_4$ $(M+H)^+$: 341.1376; Found: 341.1360.



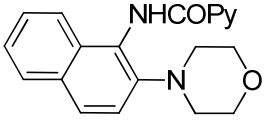
***N*-(1-Morpholinonaphthalen-2-yl)picolinamide (44).** Compound **44** was prepared following the general protocol from *N*-(naphthalen-2-yl)picolinamide **(25)** (49.7 mg, 0.20 mmol), to give **44** as a white solid; yield: 47.3 mg (71%); mp = 188-189 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 12.00 (s, 1H), 8.93 (d, *J* = 9.0 Hz, 1H), 8.81 – 8.71 (m, 1H), 8.35 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.02 – 7.90 (m, 1H), 7.83 (dd, *J* = 18.6, 8.5 Hz, 2H), 7.60 – 7.35 (m, 3H), 4.17 (tt, *J* = 7.8, 3.9 Hz, 2H), 4.05 (d, *J* = 10.4 Hz, 2H), 3.96 – 3.86 (m, 2H), 2.95 (d, *J* = 11.6 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.3, 150.8, 148.3, 137.7, 134.8, 133.3, 132.3, 131.7, 129.3, 127.8, 126.4, 126.1, 124.3, 123.4, 122.6, 119.0, 68.5, 51.1. **EI$^+$** calcd. For $C_{20}H_{19}N_3O_2$ $(M)^+$: 333.1477; Found: 333.1487. **EI$^+$** calcd. For $C_{20}H_{19}N_3O_2$ $(M)^+$: 333.1477; Found: 333.1487.



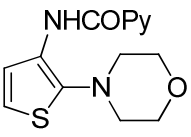
***N*-(2-Methyl-6-morpholinophenyl)picolinamide (45).** Compound **45** was prepared following the general protocol from *N*-(*o*-tolyl)picolinamide (**26**) (42.5 mg, 0.20 mmol), to give **45** as a pale brown solid; yield: 16.0 mg (27%); mp = 109-110 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.04 (s, 1H), 8.69 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.29 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.50 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 3.81 – 3.73 (m, 4H), 2.91 – 2.83 (m, 4H), 2.35 (s, 3H). **^{13}C NMR (acetone-d_6, 75 MHz)** δ: 162.8, 151.1, 149.4, 148.3, 138.7, 136.4, 132.0, 127.6, 127.4, 126.8, 123.0, 117.5, 67.8, 53.0, 19.7. **EI$^+$** calcd. For $C_{17}H_{19}N_3O_2$ $(M)^+$: 297.1477; Found: 297.1476. **Anal**. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.35; H, 6.60; N, 13.54.



***N*-(2-Morpholinonaphthalen-1-yl)picolinamide (46).** Compound **46** was prepared following the general protocol from *N*-(naphthalen-1-yl)picolinamide (**27**) (49.7 mg, 0.20 mmol), to give **46** as an orange solid; yield: 33.3 mg (50%); mp = 161-162 ºC. **^{1}H NMR (acetone-d_6, 300 MHz)** δ: 10.31 (s, 1H), 8.83 (dd, *J* = 3.3, 2.4 Hz, 1H), 8.30 – 8.35 (m, 1H), 8.10 (td, *J* = 7.7, 1.7 Hz, 1H), 7.94 – 7.85 (m, 3H), 7.70 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.52 – 7.39 (m, 3H), 3.78 – 3.70 (m, 4H), 3.02 – 2.95 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 163.5, 150.1, 148.4, 144.2, 137.7, 131.3, 129.8, 128.1, 128.0, 126.6, 126.3, 126.3, 125.0, 124.6, 122.9, 118.7, 67.6, 52.2. **EI$^+$** calcd. For $C_{20}H_{19}N_3O_2$ $(M)^+$: 333.1477; Found: 333.1464.



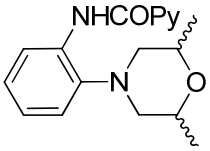
***N*-(2-Morpholinothiophen-3-yl)picolinamide (47).** Compound **47** was prepared following the general protocol from *N*-(thiophen-3-yl)picolinamide (**28**) (30.6 mg, 0.15 mmol). In this case, use of $Cu(OAc)_2$ (25 mol%) and $PhI(OAc)_2$ (2.00 equiv) is necessary to give **47** as a yellow oil; yield: 15.0 mg (35%). **^{1}H**



NMR ($CDCl_3$, 300 MHz) δ: 10.33 (s, 1H), 8.65 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.28 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.94 (d, *J* = 5.8 Hz, 1H), 7.93 – 7.86 (m, 1H), 7.48 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.02 (d, *J* = 5.9 Hz, 1H), 3.97 – 3.88 (m, 4H), 3.01 – 2.93 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 160.7, 150.1, 148.4, 140.9, 137.7, 127.9, 126.4, 122.5, 120.7, 118.5, 67.4, 54.7. **ESI$^+$** calcd. For $C_{14}H_{15}N_3O_2S$ $(M+H)^+$: 289.0885; Found: 289.0887.

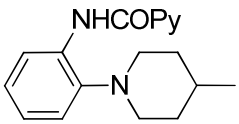
3.2. Scope with regard to the amine (Scheme 2)

Synthesis of *N*-(2-(2,6-dimethylmorpholino)phenyl)picolinamide (48). Into a 20 mL glass vial, were weighed *N*-phenylpicolinamide **(1)** (39.6 mg, 0.20 mmol, 1.00 equiv), (diacetoxyiodo)benzene (77.3 mg, 0.24 mmol, 1.2 equiv), and copper(II) acetate (5.45 mg, 0.03 mmol, 0.15 equiv). The vial was capped with a Teflon septum cap, evacuated and refilled with nitrogen via a needle through the septum two or three times. The solvent used in this reaction was *p*-xylene. Solvent (1.00 mL) and 2,6-dimethylmorpholine (49.3 µL, 0.40 mmol, 2.00 equiv) were added via syringe. The reaction vial was then placed in a reaction block heated at 80 ºC. After stirring for 16 hours, an aliquot of reaction mixture was loaded onto a $MgSO_4$ column and analyzed by GC, using *n*-hexadecane (0.01 mL) as internal standard. The product was concentrated in vacuo and purified by column chromatography to give **48** as a white solid; yield: 24.3 mg (39%); mp = 124-125 ºC. **^{1}H NMR (acetone-d6, 300 MHz)** δ: 11.14 (s, 1H), 8.77 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.60 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.25 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.08 (td, *J* = 7.7, 1.7 Hz, 1H), 7.66 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.25 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.23 – 7.06 (m, 2H), 4.05 (dqd, *J* = 12.5, 6.3, 2.1 Hz, 2H), 2.96 (dd, *J* = 8.9, 1.8 Hz, 2H), 2.49 (dd, *J* = 11.6, 10.0 Hz, 2H), 1.17 (s, 3H), 1.15 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.04, 150.77, 148.32, 141.75, 137.70, 133.25, 126.42, 125.38, 124.17, 122.53, 120.36, 119.68, 72.64, 58.19, 19.09. **EI$^+$** calcd. For $C_{18}H_{21}N_3O_2$ $(M)^+$: 311.1634; Found: 311.1643.



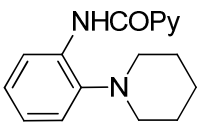
***N*-(2-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)picolinamide (49).** Compound **49** was prepared following the typical procedure from 1,4-dioxa-8-azaspiro[4.5]decane (51.3 µL, 0.40 mmol), to give **49** as a pale yellow solid; yield: 48.2 mg (71%); mp = 101-102 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.14 (s, 1H), 8.67 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.58 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.30 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.23 – 7.13 (m, 2H), 7.12 – 7.03 (m, 1H), 4.02 (s, 4H), 3.09 – 2.97 (m, 4H), 2.08 – 1.94 (m, 4H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.0, 150.7, 148.4, 142.6, 137.6, 133.0, 126.3, 125.0, 124.0, 122.4, 120.3, 119.5, 107.1, 64.4, 50.7, 35.9. **EI$^+$** calcd. For $C_{19}H_{21}N_3O_3$ $(M)^+$: 339.1583; Found: 339.1584. **Anal**. Calcd. for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.01; H, 6.40; N, 12.08.

***N*-(2-(4-Methylpiperidin-1-yl)phenyl)picolinamide (50).** Compound **50** was prepared following the typical procedure from 4-methylpiperidine (47.6 µL, 0.40 mmol), to give **50** as a yellow oil; yield: 37.6 mg (64%). **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.15 (s, 1H), 8.65 (d, *J* = 4.1 Hz, 1H), 8.61 – 8.56 (m, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.20 – 7.04 (m, 3H), 3.08 (d, *J* = 11.9 Hz, 2H), 2.72 (t, *J* = 11.2 Hz, 2H), 1.84 – 1.74 (m, 2H), 1.70 – 1.53 (m, 3H), 1.06 (d, *J* = 5.8 Hz, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.0, 150.8, 148.2, 143.5, 137.5, 133.2, 126.2, 124.6, 123.99, 122.4, 120.2, 119.4,

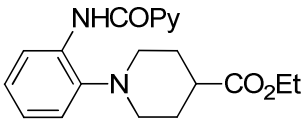


53.1, 35.2, 30.8, 22.3. **EI**$^+$ calcd. For $C_{18}H_{21}N_3O$ $(M)^+$: 295.1685; Found: 295.1686. **Anal**. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 72.89; H, 7.20; N, 14.16.

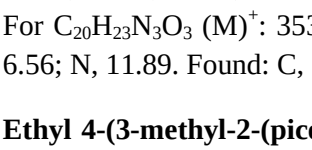
***N*-(2-(Piperidin-1-yl)phenyl)picolinamide (51).** Compound **51** was prepared following the typical procedure from piperidine (39.5 µL, 0.40 mmol) to give **51** as a yellow oil; yield: 41.6 mg (74%). **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.14 (s, 1H), 8.67 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.62 – 8.55 (m, 1H), 8.34 – 8.28 (m, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.21 – 7.03 (m, 3H), 2.93 – 2.82 (m, 4H), 1.92 – 1.78 (m, 4H), 1.70 – 1.55 (m, 2H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.1, 150.9, 148.3, 143.8, 137.5, 133.2, 126.2, 124.7, 124.0, 122.4, 120.2, 119.5, 53.8, 26.9, 24.5. **EI**$^+$ calcd. for $C_{17}H_{19}N_3O$ $(M)^+$: 281.1528; Found: 281.1537.



Methyl 1-(2-(picolinamido)phenyl)piperidine-4-carboxylate (52). Compound **52** was prepared following the typical procedure from ethyl piperidine-4-carboxylate (57.3 µL, 0.40 mmol). The crude was purified by column chromatography using *n*-hexane-EtOAc-CH_2Cl_2 (5:1:1) as eluent to give **52** as a yellow oil; yield: 54.4 mg (77%). **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.16 (s, 1H), 8.72 – 8.65 (m, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.90 (td, *J* = 7.7, 1.2 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.23 – 7.05 (m, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.14 (d, *J* = 11.8 Hz, 2H), 2.84 – 2.70 (m, 2H), 2.56 – 2.42 (m, 1H), 2.25 – 2.01 (m, 4H), 1.31 (t, *J*= 3H). **^{13}C NMR (acetone-d6, 75 MHz)** δ: 175.1, 162.2, 151.4, 149.3, 143.7, 138.8, 134.2, 127.6, 125.5, 124.6, 122.8, 121.2, 119.6, 60.7, 52.7, 41.4, 14.6. **EI**$^+$ calcd. For $C_{20}H_{23}N_3O_3$ $(M)^+$: 353.1739; Found: 353.1736. **Anal**. Calcd. for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.01; H, 6.70; N, 11.50.



Ethyl 4-(3-methyl-2-(picolinamido)phenyl)cyclohexanecarboxylate (53). Compound **53** was prepared following the typical procedure using *N*-(*o*-tolyl)-picolinamide (42.6 mg, 0.20 mmol) and piperidine-4-carboxylate (57.3 µL, 0.40 mmol) to give **53** as a pale yellow oil; yield: 15.7 mg (21%). **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 10.01 (s, 1H), 8.69 (d, *J* = 4.7 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.12 – 3.02 (m, 2H), 2.71 – 2.58 (m, 2H), 2.34 (s, 4H), 1.93 – 1.79 (m, 4H), 1.28 – 1.19 (m, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 175.2, 162.6, 150.2, 148.4, 148.1, 137.5, 135.8, 130.3, 126.6, 126.4, 126.2, 122.6, 116.8, 60.4, 52.0, 41.1, 29.0, 19.7, 14.3. **EI**$^+$ calcd. For $C_{21}H_{25}N_3O_3$ $(M)^+$: 367.1896; Found: 367.1894.



***N*-(2-(4-Cyanopiperidin-1-yl)phenyl)picolinamide (54).** Compound **54** was prepared following the typical procedure from piperidine-4-carbonitrile (44.6 µL, 0.40 mmol), using *p*-xylene:NMP (1:1) as solvent to give **54** as a pale orange solid; yield: 47.7 mg (78%); mp = 122-123 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.02 (s, 1H), 8.67 (dd, *J* = 4.7, 0.7 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.92 (td, *J* = 7.7, 1.1 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.15 (tt, *J* = 15.0, 7.6 Hz, 3H), 3.21 – 3.08(m, 2H), 2.93 – 2.78 (m, 3H), 2.26 – 2.15 (m, 4H). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ: 161.9, 150.6, 148.3, 142.1, 137.7, 133.0, 126.5, 125.6, 124.1, 122.5, 121.7, 120.3, 119.7, 50.8, 29.7, 26.2. **EI**$^+$ calcd. For $C_{18}H_{18}N_4O$ $(M)^+$: 306.1481; Found: 306.1469. **Anal**. Calcd. for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.16; H, 5.98; N, 18.32.

tert-Butyl 4-(2-(picolinamido)phenyl)piperazine-1-carboxylate (55). Compound **55** was prepared following the typical procedure from tert-butyl piperazine-1-carboxylate[3] (74.4 mg, 0.40 mmol), using $Cu(OAc)_2$ (9.08 mg, 25 mol%) and $PhI(OAc)_2$ (128 mg, 2.00 equiv) to give **55** as a pale orange solid; yield: 53.5 mg (70%); mp = 161-162 ºC. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ: 11.11 (s, 1H), 8.66 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.60 (dd, *J* = 8.1, 1.3 Hz, 1H), 8.31 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.18 – 7.07 (m, 2H), 3.72 (s, 4H), 2.95 – 2.85 (m, 4H), 1.51 (s, 9H). **^{13}C NMR ($CDCl_3$, 126 MHz)** δ: 162.0, 154.9, 150.6, 148.4, 142.0, 137.7, 133.0, 126.4, 125.4, 124.1, 122.5, 120.2, 119.7, 80.0, 52.1, 28.6. **ESI$^+$** calcd. For $C_{21}H_{26}N_4O_3$ $(M+H)^+$: 383.2005; Found: 383.2089.

***N*-(2-(Benzyl(methyl)amino)phenyl)picolinamide (56).** Compound **56** was prepared following the typical procedure from *N*-methyl-1-phenylmethanamine (51.5 µL, 0.40 mmol). This reaction proceeds at 130 ºC under O_2 atmosphere, using $Cu(OAc)_2$ (25 mol%) and $PhI(OAc)_2$ (2.00 equiv) to give **56** as a white solid; yield: 21.6 mg (34%); mp = 117-118 ºC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ: 11.38 (s, 1H), 8.73 – 8.62 (m, 3H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 (d, *J* = 6.8 Hz, 3H), 7.49 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.39 – 7.27 (m, 4H), 7.25 – 7.18 (m, 1H), 7.12 (td, *J* = 7.6, 1.6 Hz, 1H), 4.04 (s, 2H), 2.63 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ: 162.3, 150.7, 148.2, 143.2, 138.3, 137.6, 133.8, 129.1, 128.3, 127.3, 126.3, 125.5, 124.0, 122.5, 121.7, 119.6, 61.7, 41.7. **ESI$^+$** calcd. For $C_{20}H_{19}N_3O$ $(M+H)^+$: 318.1528; Found: 318.1600.

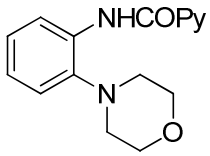
***N*-(2-(Methyl(propyl)amino)phenyl)picolinamide (57).** Compound **57** was prepared following the typical procedure from *N*-methylpropan-1-amine (41.0 µL, 0.40 mmol). This reaction proceeds at 130 ºC under O_2 atmosphere, using $Cu(OAc)_2$ (25 mol%) and $PhI(OAc)_2$ (2.00 equiv) to give **57** with a 10% GC-yield; MS (EI 70 eV) m/z: 269.1 (M^+, 8%), 251.1 (25%), 240.1 (19%), 163.0 (30%), 133.0 (90%), 105.9 (35%), 78.0 (100%).

3.3. General procedure for Cu-catalyzed amination under microwave-assisted conditions

Synthesis of *N*-(2-morpholinophenyl)picolinamide (2). An oven-dried, argon flushed 10 mL microwave vessel was charged with *N*-phenylpicolinamide (**1**) (39.6 mg, 0.20 mmol, 1.00 equiv) and copper (II) acetate (5.45 mg, 0.03 mmol, 0.15 equiv).The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen, *p*-xylene (1.00 mL), morpholine (0.31 mL, 0.40 mmol, 2.00 equiv) and the internal standard *n*-hexadecane (10 µL) were added via syringe. The resulting solution was then stirred for 5 min at room temperature followed by microwave irradiation at 130 ºC for 5 h. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (*n*-hexane-EtOAc 5:1), yielding **2** as a white solid; yield: 33.2 mg (60%); mp= 108-109 ºC. The analytical data (NMR and HRMS analysis) matched those obtained previously for compound **2**.

[3] H. Naito, T. Hata and H. Urabe, *Org. Lett.* 2010, **12**, 1228−1230.

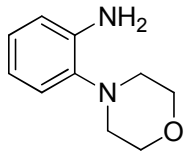
4. 1.00 gram-scale of the copper-catalyzed *ortho*-amination of 1



An oven-dried, nitrogen-flushed 50 mL vessel was charged with *N*¬phenylpicolinamide (**1**) (694 mg, 3.50 mmol, 1.00 equiv), (diacetoxyiodo)benzene (1.35 g, 4.20 mmol, 1.20 equiv), and copper (II) acetate (94.5 mg, 0.525 mmol, 0.15 equiv).The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with nitrogen three times. Under the atmosphere of nitrogen, *p*-xylene (20.0 mL), morpholine (0.61 mL, 7.00 mmol, 2.00 equiv) and the internal standard *n*-hexadecane (10 µL) were added *via* syringe. The resulting mixture was stirred at 80 °C for 24 h. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (*n*-hexane-EtOAc 5:1), yielding **2** as a white solid; yield: 832 mg (84%); mp= 108-109 ºC. The analytical data (NMR and HRMS analysis) matched those obtained previously for compound **2**.

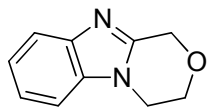
5. Typical procedure for the auxiliary cleavage

Synthesis of 2-morpholinoaniline (58). A 20 mL vessel was charged with *N*-(2-morpholinophenyl)picolinamide (**2**) (80.0 mg, 0.28 mmol, 1.00 equiv) and NaOH (167 mg, 4.20 mmol, 15.0 equiv). The reaction vessel was sealed with a Teflon lined cap, and ethanol (4.00 mL) was added *via* syringe. The resulting mixture was stirred at 80 °C for 3 h. After the reaction was complete, the reaction mixture was cooled down to room temperature, diluted by 50 mL of ethyl acetate and washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo* to give **58** as a yellow solid; yield: 48.0 mg (96%); mp = 96-97 ºC. **^{1}H NMR (acetone-d_6, 500 MHz)** δ: 6.94 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.86 – 6.81 (m, 1H), 6.73 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.64 – 6.59 (m, 1H), 4.51 (s, 2H), 3.81 – 3.73 (m, 4H), 2.89 – 2.75 (m, 4H). **^{13}C NMR (acetone-d_6, 125 MHz)** δ: 143.4, 139.4, 125.2, 120.0, 118.2, 115.5, 67.9, 52.2. **EI$^+$** calcd. For $C_{10}H_{14}N_2O$ $(M)^+$: 178.1106; Found: 178.1107.



6. Oxidative cyclization:

Synthesis of 3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazine (59).

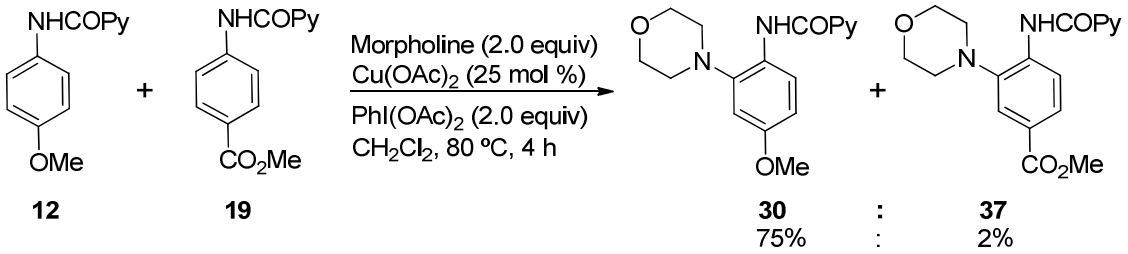


Method A: Starting from the 2-morpholinoaniline (58). An oven-dried, nitrogen-flushed 20 mL vessel was charged with a solution of 2-morpholinoaniline (**58**) (40.0 mg, 0.24 mmol, 1.00 equiv) in 1.00 mL of purified methylene chloride. Then, trifluoroacetic acid (185 µL, 2.4 mmol, 10.0 equiv) and hydrogen peroxide 30% (37 µL) were added dropwise. An exothermic reaction took place and the color darkened. After addition was complete, the solution was stirred under reflux for 15-30 min, during which time the color gradually faded. The solution was cooled, the organic solvent washed with aqueous sodium carbonate and with water, dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane-EtOAc 1:1), yielding **58** as an oil; yield: 25.1 mg (72%); mp = 126-127 ºC. **^{1}H NMR (acetone-d_6, 500 MHz)** δ: 7.60 – 7.57 (m, 1H), 7.46 – 7.43 (m, 1H), 7.24 – 7.19 (m, 2H), 4.93 (s, 2H), 4.23 – 4.21 (m, 4H). **^{13}C NMR (acetone-d_6, 125 MHz)** δ: 148.9, 144.0, 135.3, 122.7,

122.5, 119.8, 110.0, 65.8, 64.6, 42.8. **EI**$^+$ calcd. For $C_{10}H_{10}N_2O$ $(M)^+$: 174.0793; Found: 174.0788.

Method B: Starting from *N*-(2-morpholinophenyl)picolinamide (2). An oven-dried, nitrogen-flushed 20 mL vessel was charged with a solution of *N*-(2-morpholinophenyl)picolinamide (**2**) (67.9 mg, 0.24 mmol, 1.00 equiv) in 1.00 mL of purified methylene chloride. Then, formic acid (330 μL, 8.6 mmol, 36.0 equiv) and hydrogen peroxide 30% (170 μL, 5.5 mmol, 23.0 equiv) were added dropwise. After addition was complete, the solution was stirred for 1 h. The solution was then cooled, the organic solvent washed with aqueous sodium carbonate and with water, dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by column chromatography (*n*-hexane-EtOAc 1:1), yielding **58** as an oil; yield: 27.8 mg (80%).

7. Electronic effects: Competitive experiment



12 **19** **30** : **37**
75% : 2%

An oven-dried, nitrogen-flushed 20 mL vessel was charged with *N*-(4-methoxyphenyl)picolinamide (**12**) (34.2 mg, 0.15 mmol, 1.00 equiv), methyl 4-(picolinamido)benzoate (**19**) (38.4 mg, 0.15 mmol, 1.00 equiv), (diacetoxyiodo)benzene (96.6 mg, 0.30 mmol, 2.00 equiv), and copper (II) acetate (6.81 mg, 0.04 mmol, 0.25 equiv). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with nitrogen three times. Under the atmosphere of nitrogen, *p*-xylene (1.00 mL), morpholine (0.30 mL, 0.30 mmol, 2.00 equiv) and the internal standard *n*-hexadecane (10 μL) were added *via* syringe. The resulting mixture was stirred at 80 °C for 4 h. Then, an aliquot checked by GC analysis indicates that compound **30** is formed in 75% while only 2% of compound **37** can be detected.