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Aminocarbonylation of *N*-Containing Heterocycles with Aromatic Amines Using $Mo(CO)_6$

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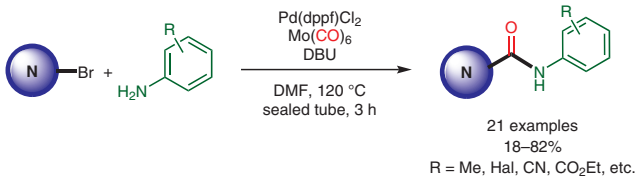

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Abstract We describe herein the palladium-catalyzed aminocarbonylation of nitrogen-containing heterocycles with aniline derivatives using molybdenum hexacarbonyl as a CO solid source, expanding the scope of the limited examples. This method is compatible with a variety of substitutions on the aniline moiety. The simple reaction conditions include easily available $Pd(dppf)Cl_2$ catalyst, DBU as base in DMF at 120 °C for 3 hours in sealed tube thereby leading to the isolation of 21 compounds with yields ranging from 18 to 82%. We also show that double aminocarbonylation reactions are possible in satisfactory yields regarding both coupling partners.

Key words heterocycles, nitrogen, aromatic amines, amide, carbonylation, palladium, catalysis

The amide motif is an ubiquitous feature in both biological systems and synthetic compounds such as pharmaceuticals agents, agrochemicals, and polymers.[1] Indeed, about 25% of commercially available drugs have an amide bond in their backbone (Figure 1). The prevalence of the amide motif is mainly linked to its unique hydrogen bonding ability as both acceptor and donor. Amide bond formation is a long standing goal in organic synthesis. It generally relies on the coupling of activated or non-activated carboxylic acids with amines mediated by coupling agents (e.g., EDC, HOBt, CDI, HATU, etc.) despite having poor atom economy and producing substantial waste.[2] Therefore, alternative approaches for amide bond formation with more respect to the green chemistry concepts are still being pursued.[3]

Since the pioneering work of Schoenberg and Heck in 1974, Pd-catalyzed carbonylation has gained increasing attention in the past decade and several procedures have been reported using CO gas as carbonyl donor.[4] However, the requirement for specific equipment as well as the use of odorless, toxic and flammable CO gas, are still major drawbacks in this approach.[5,6] Therefore, solid or liquid CO surrogates such as chloroform, DMF, formic acid derivatives or metal carbonyls have been explored and represent very efficient alternatives.[7,8] In 2002, Larhed and co-workers published the first palladium-catalyzed aminocarbonylation of aryl halides with primary and secondary amines using $Mo(CO)_6$ as a solid CO source and a 2:1 mixture of BINAP/Herrmann's palladacycle precatalyst under microwave irradiation.[9] In 2003, an improved protocol using DBU as base and THF as solvent was reported.[10] This DBU-accelerated CO release allowed the use of poor nucleophilic amines like aniline. Since then, $Mo(CO)_6$ has gained increasing attention as a CO precursor in palladium and non-palladium-

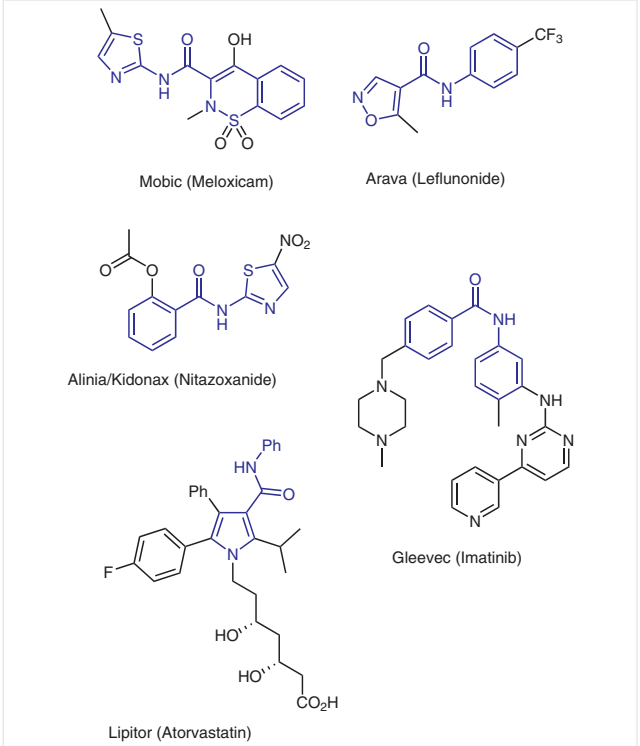


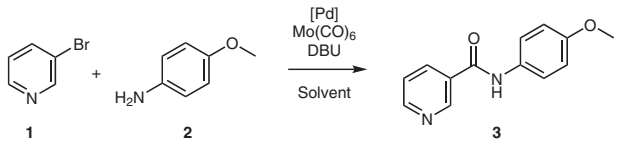
Figure 1 Selection of FDA-approved drugs containing *N*-arylbenzamides and *N*-arylheteroarenecarboxamides

catalyzed aminocarbonylation processes.[11] The utmost importance of nitrogen-containing heterocycles in many fields has inspired a wide array of synthetic work including aminocarbonylation reactions, mainly with aliphatic amines. Indeed, scarce examples of aminocarbonylation involving both nitrogen-containing heterocycles and aromatic amines have been reported and no systematic methods have been developed.

In 2007, Letavic and Ly reported the aminocarbonylation of various heteroaryl bromides with aliphatic amines using Larhed's procedure.[12] In 2009, Queiroz and Begouin detailed a single example of the aminocarbonylation of 2-bromopyridine with *p*-anisidine according to Larhed's procedure using excess heterocycle, leading to a 60% yield of the arylamide.[13] A palladium-free method was also developed using a mixture of norbornadiene, DABCO, and TBAB in diglyme at 140 °C and a single example of the aminocarbonylation of 5-bromopyrimidine with benzylamine was described.[14] More recently, in 2014, Langer and co-workers developed a convenient procedure using low nucleophilic amines such as 2-aminobenzonitrile and the duet $Pd(OAc)_2$/cataCXium as catalyst in DMF. Interestingly, heteroaryl bromides such as 5-bromoindole and 3-bromopyridine were coupled albeit in moderate yield, 61% and 49% yield, respectively, based on the deficit amine.[15] In this context, we report our efforts to expand the palladium-catalyzed aminocarbonylation process to various nitrogen-containing heteroarenes and aniline derivatives using molybdenum hexacarbonyl as a CO solid source.

As bromo derivatives are more easily available than their iodo counterparts, they were initially used in these reactions. Initially, Lahred's conditions[10] for the aminocarbonylation of 3-bromopyridine (**1**) with *p*-anisidine using $Mo(CO)_6$ as solid CO source and DBU as base in THF were not suitable as no reaction was observed (Table 1, entry 1). The system Herrmann's palladacycle/*t*-Bu_3PHBF_4 used by Letavic and Ly[12] delivered the desired product **3** in a low yield (Table 1, entry 2). The subsequent screening of palladium/ligand sources under microwave irradiation in dioxane at 150 °C with a large excess of *p*-anisidine (5 equiv) was investigated (Table 1). The use of electron-rich phosphine was really favorable for the reaction. Indeed, P(*o*-tolyl)$_3$ gave a moderate yield of 46% which was increased to 77% with XPhos [2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl] and 80% with cataCXium A [di(1-adamantyl)-*n*-butylphosphine] (entries 3–5). With bidentate dppb [1,4-bis(diphenylphosphino)butane], a slightly lower yield of compound **3** was obtained (entry 6). Decreasing both the

Table 1 Aminocarbonylation of 3-Bromopyridine



1 2 3

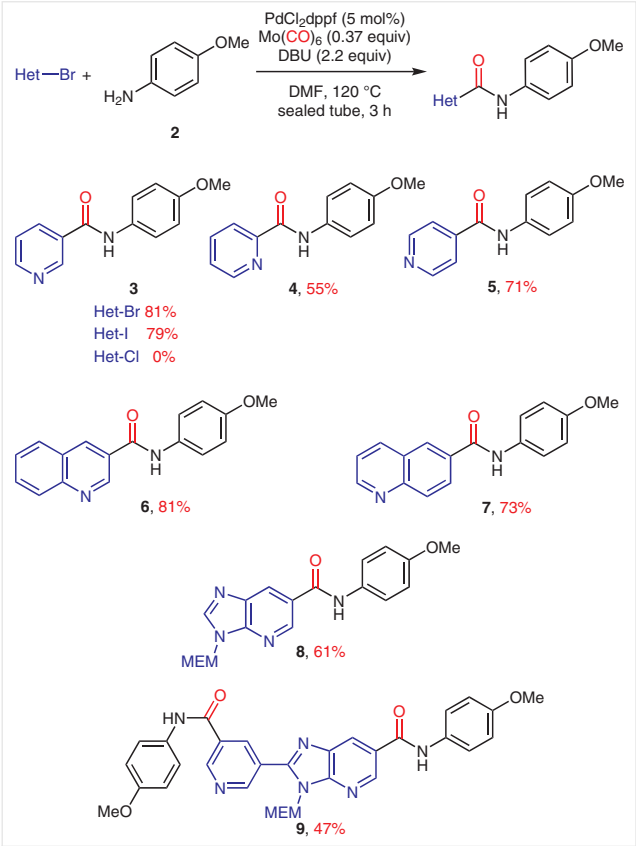
Entry	Pd source	Ligand	Solvent, temp	Yield (%)[c]
1[a]	$Pd(OAc)_2$ (10 mol%)	–	THF, 100 °C	0
2[a]	Herrmann's palladacycle	*t*-Bu_3PHBF_4	THF, 125 °C	30
3[a]	$Pd(OAc)_2$ (10 mol%)	P(*o*-tolyl)$_3$ (20 mol%)	dioxane, 150 °C	46
4[a]	$Pd(OAc)_2$ (10 mol%)	cataCXium A (20 mol%)	dioxane, 150 °C	80
5[a]	$Pd(OAc)_2$ (10 mol%)	XPhos (20 mol%)	dioxane, 150 °C	77
6[a]	$Pd(OAc)_2$ (10 mol%)	dppb (20 mol%)	dioxane, 150 °C	64
7[a]	$Pd(OAc)_2$ (5 mol%)	XPhos (10 mol%)	dioxane, 150 °C	47[d]
8[b]	$Pd(dppf)Cl_2$ (5 mol%)	–	DMF, 120 °C	81
9[b]	Herrmann's palladacycle (5 mol%)	–	DMF, 120 °C	67
10[b]	dppf Pd G3	–	DMF, 120 °C	43
11[b]	$Pd(dppf)Cl_2$ (5 mol%)	–	dioxane, 120 °C	46
12[b]	$Pd(dppf)Cl_2$ (2.5 mol%)	–	DMF, 120 °C	39
13[b]	$Pd(dppf)Cl_2$ (1 mol%)	–	DMF, 120 °C	<10
14[b]	$Pd(dppf)Cl_2$ (5 mol%)	–	DMF, 100 °C	39
15[b]	$Pd(dppf)Cl_2$ (5 mol%)	–	DMF, 80 °C	21

[a] Reaction conditions: 3-bromopyridine (0.5 mmol), *p*-anisidine (5 equiv), $Mo(CO)_6$ (0.37 equiv), Pd/ligand, solvent, 150 °C, microwaves, 1 h.
[b] Reaction conditions: 3-bromopyridine (0.63 mmol), *p*-anisidine (2 equiv), $Mo(CO)_6$ (0.37 equiv), [Pd], DBU (2.2 equiv), DMF, 120 °C, 3 h, sealed tube.
[c] Isolated yield.
[d] 2 equiv of amine were used.

catalyst loading to 5 mol% and the amount of amine to 2 equiv were deleterious for the reaction, giving amide **3** in only 47% yield (entry 7). Although good yields were obtained, all the above conditions required both excess amine (5 equiv) and high catalyst loading. Concurrently, we investigated conventional heating conditions along with a reduced quantity of amine. We performed aminocarbonylation using 'precatalyst' Pd–ligand complex Pd(dppf)Cl_2 [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium) with DBU as base and only 2 equiv of amine in DMF at 120 °C. The desired product **3** was isolated in 81% yield after 3 hours only (entry 8). Replacing Pd(dppf)Cl_2 by Herrmann's palladacycle or Buchwald's palladium precatalyst[5a] resulted in a lower yield of aminocarbonylation (respectively 67% and 43%, entries 9 and 10). DMF proved to be the best solvent as reaction in dioxane afforded compound **3** in only 46% yield (entry 10). Decreasing the catalytic loading to 1 mol% and the temperature dramatically affected the outcome of the reaction (entries 12–13 and 14–15). Finally, we identified Pd(dppf)Cl_2 (5 mol%), Mo(CO_6) and DBU in DMF at 120 °C as the optimum conditions for the aminocarbonylation of 3-bromopyridine (**1**) with 2 equiv of *p*-anisidine (**2**) since they do not require any additional phosphine ligand and large excess of amine.

Having determined the optimal conditions for the aminocarbonylation, we first set out to probe the scope of this protocol regarding the nitrogen-containing heteroarene partner. The results are shown in Scheme 1. The reactivity of 3-iodopyridine and 3-chloropyridine was also studied. The aminocarbonylation reaction of 3-iodopyridine gave the amide derivative **3** in a slightly lower yield (79%), whereas no product was formed when using the corresponding chloride. In addition, all positions of the pyridine ring can efficiently be functionalized, 2-bromopyridine being the least reactive furnishing product **4** in 55% yield; 3- and 6-bromoquinoline were also reactive giving compounds **6** and **7** in 81% and 73% yields, respectively. Interestingly, 6-bromo-3-MEM-3*H*-imidazo[4,5-*b*]pyridine was also compatible with the reaction conditions afforded the expected compound **8** in 61% yield. Noteworthy was the more complex dihalogenated heteroaryl, 6-bromo-2-(5-bromopyridin-3-yl)-3-MEM-3*H*-imidazo[4,5-*b*]pyridine, which underwent a double aminocarbonylation to afford the di-amidated compound **9** in a satisfactory 47% yield, highlighting the efficacy of the amidation process on two different heterocycles. Unfortunately, with other nitrogen-containing heterocycles such as 6-chloro-9-methyl-9*H*-purine or 2-bromobenzimidazole, either the aminated product was isolated or no reaction occurred even after prolonged reaction time (not shown).

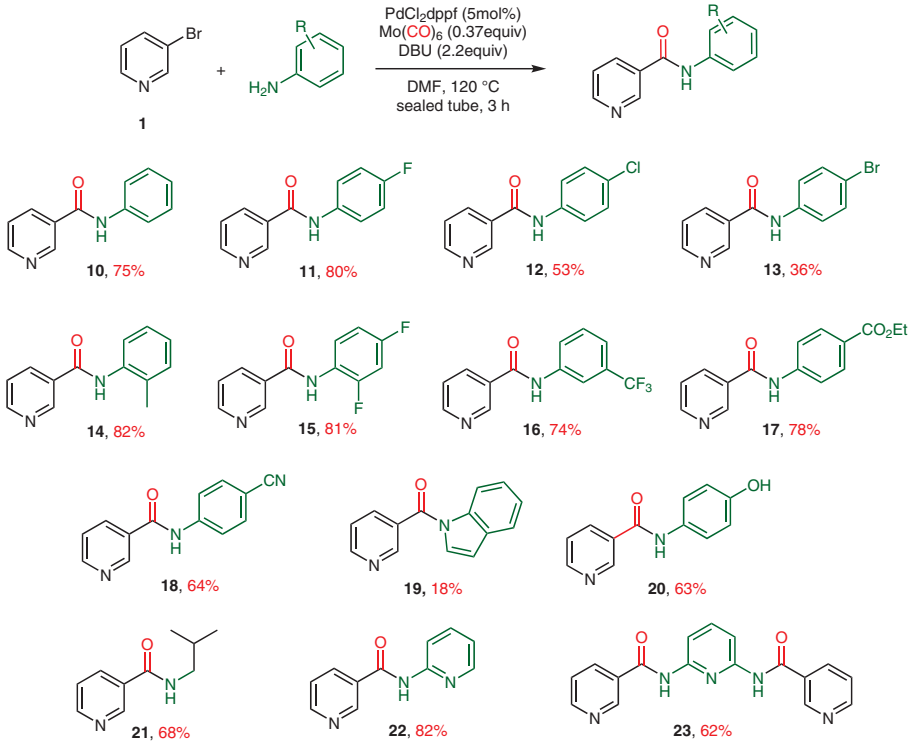
Then, we investigated the scope of aminocarbonylation with various substituted anilines. The results are reported in Scheme 2. The reaction with aniline gave the *N*-phenylnicotinamide (**10**) with a good yield of 75%. Both electron-



Scheme 1 Aminocarbonylation of heteroaryl bromides with *p*-anisidine; yields are calculated on isolated products (average of two runs)

rich and electron-deficient anilines reacted with 3-bromopyridine in good yields, with substitution being tolerated at each of the *ortho*, *meta* and *para* positions. These conditions proved to be compatible with the presence of important functional groups such as ester (78%), a cyano group (64%) and halides (36–80%) on the aniline moiety, which may be subject to further transformations.

Nitrogen-containing heteroaryl like indole seems to be less reactive and only 18% of the coupling product **19** was isolated with incomplete conversion even after a prolonged reaction time. Interestingly, starting from the 4-aminophenol, the aminocarbonylation product **20** was obtained exclusively and no traces of alkoxycarbonylation were detected. This result is in sharp contrast to the work of Alper and co-workers who carried out the selective alkoxycarbonylation of aryl iodines using Pd($OAc)_2$ and 1,3-bis(diphenylphosphino)propane (dppp), an electron-poor phosphine ligand. Conversely, the use of electron-rich ligands, in addition of DBU, was in favor of aminocarbonylation.[16] An aliphatic amine was also reactive in these conditions leading to amide **21** in 68% yield. Finally, 2-aminopyridine and 2,6-diaminopyridine proved to be really good substrates for this reaction. In particular, the double aminocarbonylation



Scheme 2 Aminocarbonylation of 3-bromopyridine with various (hetero)arylamines

took place in a very good 62% yield with 2,6-diaminopyridine giving a new and easy access to polypyridine-type ligands **23**.

In conclusion, optimized palladium-catalyzed aminocarbonylation conditions were applied to various nitrogen-containing heterocycles with aniline derivatives expanding the scope of the limited examples. This methodology relies on the use of $Mo(CO)_6$ as solid CO source and DBU as base and does not require additional ligand or sophisticated palladium complexes. The reaction tolerates a wide range of functional groups on the aniline moieties thereby leading to 21 *N*-arylamides with 18–82% yields. We also showed that double aminocarbonylation reactions can be accomplished in satisfactory yields regarding both coupling partners thereby giving a new access to more complexes molecules.

Commercially available reagents and solvents were used without further purification. Yields refer to isolated and purified products. Reactions were monitored by TLC carried out on 60F-254 silica gel plates and visualized under UV light at 254 and 365 nm. Column chromatography was performed using silica gel 60 (40–63 mm, 230–400 mesh ASTM) at medium pressure. ^{1}H and ^{13}C NMR use residual non-deuterated solvents as references. Melting points were measured with a Stuart SMP30. HRMS were measured by a TOF spectrometer using electrospray ionization (ESI).

Compounds **3**,[17] **4**,[13] **5**,[18] **10**,[19] **11**,[20] **12**,[21] **14**,[22] **18**,[23] **19**,[19] **21**,[24] and **22**[25] showed satisfactory spectroscopic data in agreement with those reported in the literature.

Aminocarbonylation; General Procedure

In a sealed tube and under argon inlet, aryl halide (1 equiv), $PdCl_2$dppf (5 mol%), $Mo(CO)_6$ (0.37 equiv), and the amine (2.0 equiv) were mixed. The tube was evacuated and backfilled with argon (3 ×). Anhyd DMF (2 mL) was added and the mixture was stirred at r.t. for 1 min. DBU (2.2 equiv) was added and the reaction vessel was then capped. The mixture was stirred at 120 °C for 3 h in a preheated oil bath. After cooling to r.t., CH_2Cl_2 was added to the mixture, which was filtered through Celite. The solvent was evaporated under reduced pressure and the mixture was extracted (EtOAc) and the organic layers dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH).

N-(4-Methoxyphenyl)quinoline-3-carboxamide (6)

Starting from 3-bromoquinoline (132 mg, 0.63 mmol), flash chromatography afforded **6** (143 mg, 81%) as a white solid; mp 175 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.39 (s, 1 H), 9.36 (d, J = 2.2 Hz, 1 H), 8.93 (d, J = 1.8 Hz, 1 H), 8.12 (dd, J = 7.5, 5.7 Hz, 2 H), 7.93–7.85 (m, 1 H), 7.76–7.67 (m, 3 H), 7.01–6.92 (m, 2 H), 3.77 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.6, 155.8, 149.1, 148.5, 135.9, 132.0, 131.3, 129.2, 128.8, 127.8, 127.5, 126.5, 122.0, 113.9, 55.2.

MS (ES+): m/z (%) = 279.1 (100) $[M + H]^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{17}H_{15}N_2O_2$: 279.1134; found: 279.1125.

N-(4-Methoxyphenyl)quinoline-6-carboxamide (7)

Starting from 6-bromoquinoline (132 mg, 0.63 mmol), flash chromatography afforded **7** (128 mg, 73%) as a white solid; mp 194 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.41 (s, 1 H), 9.01 (dd, *J* = 4.0, 1.3 Hz, 1 H), 8.62 (d, *J* = 1.1 Hz, 1 H), 8.53 (d, *J* = 8.1 Hz, 1 H), 8.27 (dd, *J* = 8.8, 1.6 Hz, 1 H), 8.13 (d, *J* = 8.8 Hz, 1 H), 7.79–7.70 (m, 2 H), 7.63 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.01–6.90 (m, 2 H), 3.76 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.7 and 164.6, 155.7, 152.2, 148.8, 137.2, 132.9 and 132.9, 132.2 and 132.1, 129.1, 128.3, 128.1, 127.1, 122.3, 122.0 and 121.9, 113.8, 55.2.

MS (ES+): *m*/*z* (%) = 279.1 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{17}H_{15}N_2O_2$: 279.1134; found: 279.1134.

3-[(2-Methoxyethoxy)methyl]-*N*-(4-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine-6-carboxamide (8)

Starting from 6-bromo-3-[(2-methoxyethoxy)methyl]-3*H*-imidazo[4,5-*b*]pyridine (184 mg, 0.64 mmol), flash chromatography afforded **8** (140 mg, 61%) as a white solid; mp 122 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (d, *J* = 1.4 Hz, 1 H), 8.58 (d, *J* = 1.2 Hz, 1 H), 8.28 (s, 1 H), 8.24 (s, 1 H), 7.63–7.55 (m, 2 H), 6.96–6.88 (m, 2 H), 5.78 (s, 2 H), 3.83 (s, 3 H), 3.75–3.70 (m, 2 H), 3.53–3.49 (m, 2 H), 3.33 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 156.3, 148.4, 145.8, 145.2, 133.7, 131.2, 126.6, 126.4, 122.5, 113.8, 72.9, 71.3, 68.9, 58.8, 55.2.

MS (ES+): *m*/*z* (%) = 357.2 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{18}H_{21}N_4O_4$: 357.1563; found: 357.1555.

3-[(2-Methoxyethoxy)methyl]-*N*-(4-methoxyphenyl)-2-{5-[(4-methoxyphenyl)carbamoyl]pyridin-3-yl}-3*H*-imidazo[4,5-*b*]-pyridine-6-carboxamide (9)

Starting from 6-bromo-2-(3-bromophenyl)-3-[(2-methoxyethoxy)methyl]-3*H*-imidazo[4,5-*b*]pyridine (114 mg, 0.26 mmol), flash chromatography afforded **9** (71 mg, 47%) as a white solid; mp 209 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.55 (s, 1 H), 10.37 (s, 1 H), 9.38 (d, *J* = 1.8 Hz, 1 H), 9.31 (d, *J* = 1.7 Hz, 1 H), 9.05 (d, *J* = 1.7 Hz, 1 H), 8.95–9.91 (m, 1 H), 8.77 (d, *J* = 1.7 Hz, 1 H), 7.72 and 7.71 (2d, *J* = 9.0 Hz, 4 H), 6.97 and 9.96 (2d, *J* = 9.0 Hz, 4 H), 5.84 (s, 2 H), 3.83–3.78 (m, 2 H), 3.76 (s, 6 H), 3.50–3.45 (m, 2 H), 3.17 (s, 3 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 163.8, 163.7, 162.9, 162.8, 155.9, 155.7, 153.2, 151.6, 150.2, 150.2, 145.0, 136.0, 133.5, 132.1, 131.8, 130.8, 126.9, 126.7, 125.3, 122.0, 121.9, 113.9, 113.8, 72.0, 70.9, 68.3, 66.7, 66.7, 58.1, 55.2.

MS (ES+): *m*/*z* (%) = 583.2 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{31}H_{31}N_6O_6$: 583.2305; found: 583.2309.

N-(4-Bromophenyl)nicotinamide (13)

Starting from 3-bromopyridine (100 mg, 0.63 mmol), flash chromatography afforded **13** (63 mg, 36%) as a beige solid; mp 174 °C.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 9.08 (d, *J* = 1.6 Hz, 1 H), 8.73 (dd, *J* = 4.9, 1.4 Hz, 1 H), 8.38–8.32 (m, 1 H), 7.71–7.64 (m, 2 H), 7.59 (dd, *J* = 7.5, 5.0 Hz, 1 H), 7.56–7.48 (m, 2 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 166.3, 152.9, 149.4, 138.9, 137.2, 132.8, 132.5, 125.1, 123.8, 118.3.

MS (ES+): *m*/*z* (%) = 279 (100) [M + 2 H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{12}H_{10}N_2OBr$: 276.9976; found: 276.9983.

N-(2,5-Difluorophenyl)nicotinamide (15)

Starting from 3-bromopyridine (100 mg, 0.63 mmol), flash chromatography afforded **13** (121 mg, 81%) as a white solid; mp 146 °C.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 9.09 (d, *J* = 1.7 Hz, 1 H), 8.74 (dd, *J* = 4.9, 1.5 Hz, 1 H), 8.37–8.32 (m, 1 H), 7.76 (ddd, *J* = 9.5, 6.0, 3.2 Hz, 1 H), 7.59 (dd, *J* = 7.9, 5.0 Hz, 1 H), 7.11 (dt, *J* = 9.6, 4.9 Hz, 1 H), 7.04–6.92 (m, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 166.6, 159.7 (dd, *J* = 240.3, 2.4 Hz), 153.1, 152.6 (dd, *J* = 242.5, 2.9 Hz), 149.6, 137.5, 131.85, 127.9 (dd, *J* = 14.1, 11.4 Hz), 125.2, 117.4 (dd, *J* = 22.8, 9.7 Hz), 113.6 (dd, *J* = 24.5, 7.9 Hz), 113.1 (dd, *J* = 28.3, 1.6 Hz).

MS (ES+): *m*/*z* (%) = 235.1 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{12}H_9N_2OF_2$: 235.0683; found: 235.0685.

N-[3-(Trifluoromethyl)phenyl]nicotinamide (16)

Starting from 3-bromopyridine (100 mg, 0.63 mmol), flash chromatography afforded **16** (126 mg, 74%) as a white solid; mp 149 °C.

^{1}H NMR (300 MHz, MeOH-d_4): δ = 9.10 (d, *J* = 1.6 Hz, 1 H), 8.73 (dd, *J* = 4.9, 1.4 Hz, 1 H), 8.41–8.31 (m, 1 H), 8.15 (br s, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 7.63–7.52 (m, 2 H), 7.45 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 166.5, 153.0, 149.5, 140.6, 137.4, 132.4, 132.2 (q, *J* = 32.2 Hz), 130.8, 125.5 (q, *J* = 271.5 Hz), 125.2, 125.1, 122.0 (q, *J* = 3.9 Hz), 118.4 (q, *J* = 4.1 Hz).

MS (ES+): *m*/*z* (%) = 267.1 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{13}H_{10}N_2OF_3$: 267.0745; found: 267.0750.

Ethyl 4-(Nicotinamido)benzoate (17)

Starting from 3-bromopyridine (100 mg, 0.63 mmol), flash chromatography afforded **17** (133 mg, 78%) as a grey solid; mp 125 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.89 (br s, 1 H), 9.20 (s, 1 H), 8.83 (d, *J* = 4.2 Hz, 1 H), 8.45 (d, *J* = 7.9 Hz, 1 H), 7.97 (s, 4 H), 7.69 (dd, *J* = 7.8, 5.0 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.32 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.3, 164.0, 151.0, 147.7, 143.2, 137.2, 130.8, 130.1, 125.0, 124.1, 119.7, 60.5, 14.2.

MS (ES+): *m*/*z* (%) = 271.1 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1075.

N-(4-Hydroxyphenyl)nicotinamide (20)

Starting from 3-bromopyridine (100 mg, 0.63 mmol), flash chromatography afforded **20** (133 mg, 63%) as a grey solid; mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.22 (s, 1 H), 9.31 (s, 1 H), 9.08 (d, *J* = 1.4 Hz, 1 H), 8.74 (dd, *J* = 4.7, 1.2 Hz, 1 H), 8.29–8.23 (m, 1 H), 7.59–7.49 (m, 3 H), 6.79–6.71 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.5, 154.0, 151.9, 148.6, 135.3, 130.8, 130.4, 123.5, 122.3 (2 C), 115.1 (2 C).

MS (ES+): *m*/*z* (%) = 215.1 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{12}H_{11}N_2O_2$: 215.0821; found: 215.0816.

***N*,*N*′-(Pyridine-2,6-diyl)dinicotinamide (23)**

Starting from 3-bromopyridine (200 mg, 1.27 mmol), flash chromatography afforded **23** (126 mg, 62%) as a white solid; mp 254 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.85 (s, 1 H), 9.12 (d, *J* = 1.8 Hz, 1 H), 8.77 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.35–8.30 (m, 1 H), 7.98–7.87 (m, 1 H), 7.56 (dd, *J* = 7.9, 4.8 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.7, 152.4, 150.3, 149.0, 140.2, 135.7, 129.9, 123.5, 111.7.

MS (ES+): *m*/*z* (%) = 320.2 (100) [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $C_{17}H_{14}N_5O_2$: 320.1147; found: 320.1151.

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Supporting Information

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