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Scope and Limitations of Auxiliary-Assisted, Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 C-H Bonds

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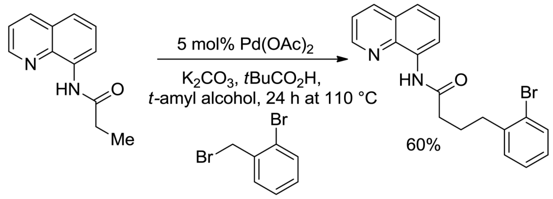
Abstract

Auxiliary-Assisted C-H Bond Functionalization.



The scope of palladium-catalyzed, auxiliary-assisted direct arylation and alkylation of sp^2 and sp^3 C-H bonds of amine and carboxylic acid derivatives has been investigated. The method employs a palladium acetate catalyst, substrate, aryl, alkyl, benzyl, or allyl halide, and inorganic base in *t*-amyl alcohol or water solvent at 100-140 °C. Aryl and alkyl iodides as well as benzyl and allyl bromides are competent reagents in this transformation. Picolinic acid auxiliary is used for amine γ-functionalization and 8-aminoquinoline auxiliary is used for carboxylic acid β-functionalization. Some optimization of base, additives, and solvent is required for achieving best results.

1. Introduction

Transition-metal-catalyzed functionalization of carbon-hydrogen bonds is becoming an important synthetic tool that allows to create carbon-carbon bonds efficiently.[1] Regioselective, intermolecular arylation and alkylation of heterocycles and other arenes can be efficiently accomplished by employing first- and second-row transition-metal catalysis.[2] A recent report by Ackerman shows that meta-alkylation of 2-phenylpyridine derivatives is feasible.[2l] In contrast, intermolecular functionalization of unactivated (not benzylic or α to heteroatom) sp^3 C-H bonds has attracted less attention.[3] Many of the published examples of sp^3 C-H bond functionalization involve positions adjacent to quaternary centers.[3a-f] Fewer reports deal with functionalization of sp^3 C-H bonds in systems where β-hydride elimination from metalated intermediates is possible. Ohno has prepared indolines from *N*-alkyl-2-bromoanilines.[3i] Yu has developed methods for palladium-catalyzed olefination, carbonylation, and arylation of sp^3 C-H bonds by employing perfluoroaniline auxiliaries and utilized pyridine as a directing group in an example of sp^3 C-H bond alkylation by alkylboronic acids.[3g-l] Sanford has reported an aerobic sp^3 C-H bond olefination by using a pyridine directing group.[3m] A direct Pd-catalyzed γ-arylation of amino acid esters bearing a removable *N*-(2-pyridyl)sulfonyl directing group has been described by Fernández-Ibáñez.[3n]

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Supporting Information Available. Spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

In 2005, we reported the β-arylation of carboxylic acid and γ-arylation of amine derivatives by employing an 8-aminoquinoline or picolinic acid auxiliary, catalytic $Pd(OAc)_2$, stoichiometric AgOAc, and an aryl iodide coupling partner.[4a] Subsequently, a number of auxiliaries were investigated for carboxylic acid β-arylation and it was shown that silver salts can be replaced by simple inorganic bases (Scheme 1).[4b] Omission of silver allowed catalytic alkylation of sp^2 and sp^3 C-H bonds. Functionalization regiochemistry is determined by a double five-membered palladacycle intermediate **1** that is formed in C-H bond activation step. The electron-rich dianionic pincer-type ligand on palladium facilitates oxidative addition of aryl halide to the Pd(II) intermediate **1** and stabilizes the presumed high-valent Pd intermediates.[4b,6] We have also reported auxiliary-directed synthesis of unnatural amino acids as well as picolinic acid-directed heterocycle formation.[4c,d] Aminoquinoline and picolinic acid can also direct copper-catalyzed carbon-heteroatom bond formation.[4e-g] Subsequently, several other groups have used these auxiliaries for new reaction development and synthetic purposes. Corey has used the 8-aminoquinoline auxiliary to arylate sp^3 C-H bonds in amino acid derivatives.[5a] Chen has employed 8-aminoquinoline auxiliary in total synthesis of Celogentin C.[5b] Synthesis of the Leu-Trp component of the celogentin family of cyclic peptides via C-H bond functionalization methodology has also been disclosed.[5c] Elegant total syntheses of piperborenines and the proposed structure of pipercyclobutanamide A by using 8-aminoquinoline and 2-thiomethylaniline directing groups have been developed by Baran.[5d,e] Carbocycles have been constructed by using 8-aminoquinoline directing group.[5f] Chen has employed picolinic acid directing group for arylation, alkenylation, and alkylation of sp^2 and sp^3 C-H bonds.[5g,h,l,m] Quinolinecarboxylic acid naphthylamide arylation has been recently disclosed.[3k] Picolinamide and 8-aminoquinoline-directed alkynylation of sp^2 and sp^3 C-H bonds has also been reported.[5i,j] Furthermore, iron, nickel, copper, and ruthenium catalysis has been used for 8-aminoquinoline-containing carboxamide functionalization.[4e-g, 5n-q] These examples show that monoanionic, chelating auxiliaries have found wide applications for C-H to C-C bond conversion in a variety of catalytic systems. Significantly, application of these auxiliaries in the construction of complex natural products shows that C-H bond functionalization methodology has been introduced into mainstream organic synthesis. Consequently, further methodological and mechanistic investigations that would increase the scope and understanding of C-H bond functionalization processes are warranted. We report here the scope and limitations of auxiliary-assisted, palladium-catalyzed arylation and alkylation of sp^2 and sp^3 C-H bonds in amine and carboxylic acid derivatives (Scheme 2).

2. Results and Discussion

2.1 Picolinamide Arylation Optimization

Based on our previous results with carboxylic acid derivative functionalization, the initial optimization experiments were aimed at replacing silver acetate with other stoichiometric additives for arylation of cumylamine picolylamide (Table 1). Potassium phosphate and cesium carbonate bases were inefficient (entries 1 and 2). Better results were obtained with cesium acetate in *t*-amyl alcohol (entry 4). Addition of 10 mol % of $CuBr_2$ allowed achieving full conversion to diarylation product (entry 6). Thus, the optimized arylation conditions include 4 equivalents of CsOAc base in *t*-amyl alcohol solvent, 5 mol % $Pd(OAc)_2$, 10 mol % $CuBr_2$, and 4 equivalents of ArI at 140 °C.

2.2. Benzylpicolinamide arylation

The silver-free conditions were applied to arylation of a number of benzylpicolinamides (Table 2). Benzylamine derivatives are arylated in excellent yields (entries 1-3). Diarylated products are obtained if unsubstituted benzylamines are employed (entries 1-2). We are interested in synthesis of 8-aryl-1-naphthylamines that could be used in the synthesis of ligands for Brookhart-type transition-metal catalyzed olefin polymerization.[7] Consequently, arylation of picolinamide of 1-naphthylamine was investigated in depth (entries 4-12). The reaction is successful both by using AgOAc base and by using CsOAc base. Thus, reaction with 4-iodoanisole gives 98% isolated yield if AgOAc is used, and 73% yield if CsOAc is employed (entry 6). 4-Bromophenylation of 1-naphthylamine picolinamide affords nearly identical yield of product in both cases (entry 10). However, AgOAc conditions allow for a lower $Pd(OAc)_2$ loading (2% vs. 5% for CsOAc base). Three large scale reactions (entries 4, 11, and 12) afforded excellent product yields showing that scale-up to at least 50 mmol is possible. Phenethylamine derivative is arylated in moderate yield, presumably due to requirement for less favorable six-membered palladacycle intermediate (entry 13). In contrast to this result, our previous benzylamine arylation methodology is not applicable to arylation of phenethylamines.[8] Alkenylation of sp^2 C-H bonds is also possible, and benzylamine picolinamide was reacted with iodostyrene to give coupling product in 86% yield. The ester, chloro, bromo, ether, and trifluoromethyl functionalities are compatible with the arylation conditions. The reaction fails if aryl bromide coupling partners are used. Benzylamine picolinamide was reacted with bromobenzene under conditions of entry 2 and arylation product was not detected in the reaction mixture.

Directing groups can be removed by using *n*-butylamine and $AlCl_3$ in toluene at 90 °C or NaOH in ethanol (Scheme 3).[9] Free arylated amines are obtained in good to excellent yields.

Synthesis of even more hindered amines is possible. Acylation of 8-(*p*-tolyl)-1-naphthylamine by propionyl chloride followed by palladium-catalyzed arylation affords 2-(4-carbethoxyphenyl)-8-8-(*p*-tolyl)-1-naphthylamine derivative in a good yield (Scheme 4).[10] Recently, a method for 1-aminonaphthalene quinolinecarboxamide arylation has been reported; however, it requires use of 15 mol% $Pd(OAc)_2$.[5k]

2.3 Arylation of Alkylpicolinamides

Arylation of unactivated sp^3 C-H bonds can be accomplished by employing conditions developed for sp^2 C-H bond functionalization (Table 3). Comparison of the arylation yields for propyl (entry 1), *s*-butyl (entry 2), and 2-(2-methylbutyl) derivatives (entry 3) shows that the reaction is most efficient for the substrates possessing the most α–methyl groups. The increase in yield is likely due to Thorpe-Ingold effect.[11] Arylation of secondary aliphatic C-H bonds is also feasible and proceeds in good yield (entry 4). An amide derived from *t*-octylamine was arylated in modest yield. A mixture of mono- and diarylation products was obtained, with functionalization occurring at δ-positions (entry 5). Sixmembered palladacycle intermediate may be responsible for less efficient arylation. 2-Iodotoluene was unreactive in all reactions tested as shown before for arylations proceeding via high-valent palladium intermediates.[4a,b,10]

2.4 Picolinamide alkylation

The alkylation of picolinamide C-H bonds is presented in Table 4. Short optimization showed that the best results are obtained by employing potassium carbonate base in conjunction with water solvent. α-Methylbenzylamine derivatives can be alkylated by various alkyl iodides such as butyl iodide (entry 1), 4,4,4-trifluorobutyl iodide (entry 2), isobutyl iodide (entry 3), and 2-phenethyl iodide (entry 4) in good yields. However, if butyl iodide was replaced with butyl bromide, no product was obtained. Benzylation can be performed by employing benzyl iodide (entry 5). α,α-Dimethylbenzylamine picolinamide reaction with *n*-butyl iodide gave the dialkylation product in a good yield (entry 6). Unexpectedly, secondary alkyl iodides are also reactive. Cyclohexylation of benzyl picolinamide affords a 20% yield of monoalkylation product in addition to 14% of dialkylation (entry 7). Similarly, alkylation of a 2-methoxybenzylamine derivative gives the product in 14% yield (entry 8). 1-Naphthylamine derivative is alkylated by *n*-octyl iodide in moderate yield (entry 6). The alkylation of unactivated sp^3 C-H bonds is inefficient. Reaction of picolinic acid 2-(2-methyl)butylamide with *n*-amyl iodide yielded only 27% of the product (entry 10). Chen has recently reported method for picolinamide sp^3 C-H bond alkylation.[51] We have previously shown that α-methylbenzylamines do not racemize under palladium-catalyzed arylation conditions.[4h]

2.5 Alkylation of 8-Aminoquinoline Benzamides

Our initial conditions reported in 2005 that use AgOAc for iodide removal were not successful for C-H bond alkylation. Silver acetate reacts with alkyl iodides competing with *C*-alkylation. The new silver-free conditions, developed in 2010, are successful since the competitive destruction of alkyl iodides is slow.[4b] We have determined that the optimal auxiliary for C-H bond alkylation of benzamide derivatives is 8-aminoquinoline. As reported earlier, alkylation conditions involve heating of the substrate with alkyl iodide or benzyl bromide to 100 - 110° C in *t*-amyl alcohol in the presence of K_2CO_3 base and catalytic amount of pivalic acid. We have previously reported 3 examples of 8-aminoquinoline benzamide alkylation.[4b] Table 5 shows the alkylation scope and functional group tolerance. Benzylation of alkoxy- (entries 1, 5 and 6), bromo- (entry 2), and trifluoromethyl-substituted (entry 4) benzoic acid amides occurs with good to excellent yields. The reaction cleanly affords dialkylation products if benzamide is substituted at 4-position or possesses a small substituent at 3-position (entry 6). The alkylation of 4-*t*-butylbenzoic acid derivative can be accomplished by employing ethyl iodide (entry 7), *i*-butyl iodide (entry 8), 2-phenethyl iodide (entry 9), and ethyl-7-iodoheptanoate (entry 10). Phthaloyl-protected 6-amino-1-iodohexane is also reactive (entry 15). Furthermore, a variety of benzyl bromides can be employed in the alkylation. Thus, reaction is successful with benzyl bromides possessing chloro (entry 11), ester (entry 12), trifluoromethoxy (entry 13), and nitro (entry 14) substituents, attesting to the functional group tolerance of C-H bond alkylation methodology. Allylation is also possible by employing 1-bromo-3-methylbut-2-ene, although the isolated yield of the product is low (entry 16).

2.6 Alkylation of 8-Aminoquinoline Amide sp^3 C-H Bonds

We have previously determined that the optimal auxiliary for carboxamide C-H bond alkylation is 8-aminoquinoline. Two examples of 8-aminoquinoline propionylamide α-alkylation were published.[4b] Alkylation conditions involve heating of the substrate with 5% $Pd(OAc)_2$ and alkyl iodide or benzyl bromide to 100 - 110° C in *t*-amyl alcohol in the presence of K_2CO_3base and catalytic amount of pivalic acid (Table 6). 8-Aminoquinoline propionamide can be alkylated with simple alkyl iodides such as ethyl (entry 1), butyl (entry 2), octyl (entry 3), and phenetyl iodide (entry 4). Allylation by 1-bromo-3-methylbut-2-ene is also possible, affording the product in a low yield (entry 5). Isobutyl iodide is reactive and the alkylation proceeds in a good yield (entry 6). Benzylation with 2-bromobenzyl bromide is successful and product is obtained in 60% yield (entry 7). 2-Methylbutyric acid derivative is selectively alkylated in the α-methyl group (entry 8). Flurbiprofen[12] amide can also be alkylated in a moderate yield (entry 9). Finally, alkylation of a secondary C-H bond proceeds in a low yield (entry 10).

3. Summary

In this paper, we report the scope and limitations of auxiliary-assisted, palladium-catalyzed arylation and alkylation of sp^2 and sp^3 C-H bonds in amine and carboxylic acid derivatives. The method employs a palladium acetate catalyst, substrate, aryl, alkyl, benzyl, or allyl halide, and inorganic base in *t*-amyl alcohol or water solvent at 100-140 °C. Aryl and alkyl iodides as well as benzyl and allyl bromides are competent reagents in this transformation.

Picolinic acid auxiliary is used for amine γ-functionalization and 8-aminoquinoline auxiliary is used for carboxylic acid β-functionalization. Some optimization of base, additives, and solvent is required for achieving best results. The arylation is possible for both secondary and primary sp^3 C-H bonds; however, alkylation of secondary sp^3 C-H bonds in aminoquinoline derivatives and primary C-H bonds in picolinamides is low-yielding.

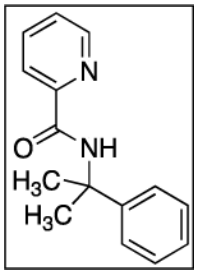
4. Experimental Section

General considerations—Flash chromatography was performed on 60 Å silica gel. Preparative TLC was performed on TLC plates, 20 x 20 cm, 2000 μm thick, with fluorescent indicator. GC analyses were performed on a Restek column (Rtx®-5, 15 m, 0.25 mm ID). Residual solvent peaks were used as reference in ^1H NMR and ^{13}C NMR spectra. Melting points are uncorrected. The following starting materials were obtained from commercial sources and were used without further purification: picolinic acid, triethylamine, dichloromethane, ethyl chloroformate, $MgSO_4$, hexanes, ethyl acetate, cumylamine, α-methylbenzylamine, benzylamine, 1-naphthylamine, pyridine, triphenylphosphite, H_2SO_4, 2-methoxybenzylamine, 3,4-dimethoxyphenethylamine, *tert*-pentylamine, 2-aminobutane, 1-propylamine, cyclohexylamine, *tert*-butylamine, palladium (II) acetate, copper (II) bromide, cesium acetate, *tert*-amyl alcohol, iodo-4-methylbenzene, iodobenzene, 1-iodo-4-methoxybenzene, 1-bromo-4-iodobenzene, ethyl 4-iodobenzoate, iodoethane, 1,1,1-trifluoro-4-iodobutane, 1-iodo-2-methylpropane, (2-iodoethyl)benzene, benzyl bromide, octyl iodide, iodobutane, iodocyclohexane, iodopentane, aluminum chloride. Mass spectra were performed on a Micromass Ultima Magnetic Sector.

Synthesis of starting materials

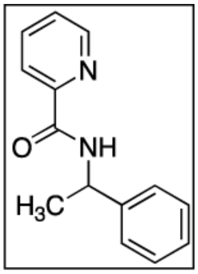
General procedure for the preparation of the picolinamides from amines[13]— Picolinic acid (35 mmol, 4.3 g) and triethylamine (70 mmol, 9.70 mL) were dissolved in dry dichloromethane (80 mL). The solution was cooled to 0 °C followed by addition of ethyl chloroformate (35 mmol, 3.30 mL). The mixture was subsequently stirred for 30 minutes in ice bath. The amine (20 mmol) was added dropwise via a syringe and the suspension was stirred for 1 hour. The solution was warmed to room temperature and stirred for 24 hours. After that, water (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The organic layers were combined, dried with $MgSO_4$, concentrated. The residue was purified by a silica gel column chromatography using hexanes/ethyl acetate eluent.

***N*-(2-Phenylpropan-2-yl)picolinamide (SM01)—**



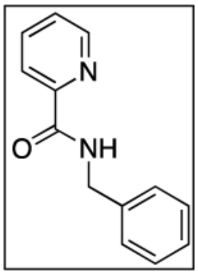
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and cumylamine (20 mmol, 2.7 g). After chromatography (hexanes/ethyl acetate 70/30), white crystalline material was obtained (4.44 g, 93 %). R_f = 0.40 (hexanes/ethyl acetate 70/30), mp = 87–88 °C (hexanes). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.54 (m, 1H), 8.48 (br s, 1H), 8.15–8.13 (m, 1H), 7.84–7.80 (m, 1H), 7.48–7.45 (m, 2H), 7.44–7.40 (m, 1H), 7.36–7.31 (m, 2H), 7.25–7.21 (m, 1H), 1.85 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.3, 150.6, 147.9, 146.9, 137.5, 128.5, 126.8, 126.1, 124.9, 122.0, 55.7, 29.3. FT-IR (neat, cm^{-1}) ν 3381, 1682, 15.13, 1570, 1436, 1384, 1365, 1280. Anal. Calcd. for $C_{15}H_{16}N_2O$ (240.30 g/mol): C, 74.97; H, 6.71; N, 11.66; Found: C, 75.02; H, 6.71; N, 11.62.

N-(1-Phenylethyl)picolinamide (SM02, 11)—



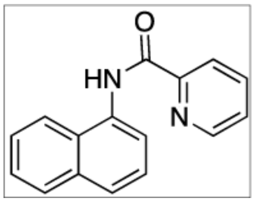
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and α-methylbenzylamine (20 mmol, 2.60 mL). After chromatography (hexanes/ethyl acetate 70/30), white crystals were obtained (4.35 g, 96 %). R_f = 0.31 (hexanes/ethyl acetate 70/30). This compound is known.[14] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.54–8.52 (m, 1H), 8.32 (d, J = 6.31H), 8.20–8.18 (m, 1H), 7.84–7.80 (m, 1H), 7.41–7.38 (m, 3H), 7.36–7.31 (m, 2H), 7.28–7.23 (m, 1H), 5.38–5.26 (m, 1H), 1.62 (d, J=6.9 Hz, 3H).

N-Benzylpicolinamide (SM03)—



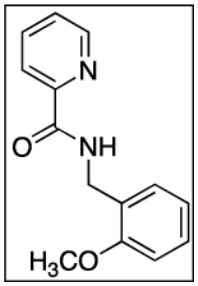
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and benzylamine (20 mmol, 2.18 mL). After chromatography (hexanes/ethyl acetate 60/40), white crystals were obtained (3.81 g, 90 %). R_f = 0.36 (hexanes/ethyl acetate 60/40). This compound is known.[15] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53–8.51 (m, 1H), 8.37 (br s, 1H), 8.23 (d, J=7.8 Hz, 1H), 7.87–7.83 (m, 1H), 7.43–7.40 (m, 1H), 7.38–7.32 (m, 4H), 7.30–7.26 (m, 1H), 4.67 (d, J=6.0 Hz, 2H).

N-(Naphthalen-1-yl)picolinamide (SM04, 3)—



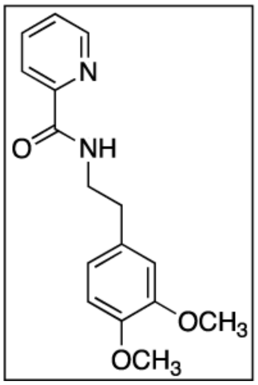
1-Naphthylamine (7.2 g, 50 mmol) in pyridine (10 mL) was added dropwise in 15 minutes to a stirred solution of picolinic acid (6.2 g, 50 mmol) in pyridine (14 mL) at 50 °C. Triphenylphosphite (13 mL, 50 mmol) was added to the resulting mixture followed by stirring at 110 °C for 4 hours. The mixture was cooled to room temperature followed by addition of distilled water (50 mL) and dichloromethane (50 mL). The mixture was placed in a 500 mL Erlenmeyer flask and aqueous H_2SO_4 (150 mL; concentrated H_2SO_4/water 1/1 v/v) was added. The mixture was shaken and the layers were separated. The organic layer was washed with aqueous H_2SO_4 (2 × 100 ml). The acidic aqueous layers were combined and neutralized with solid sodium bicarbonate. The tan solids formed were filtered and washed thoroughly with distilled water, then recrystallized from methanol to afford tan needles (10.9 g, 87 %). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.77 (s, 1H), 8.70 (d, *J* = 8.2 Hz, 1 H), 8.36 (d, *J* = 8.2 Hz, 1 H), 8.36 (d, *J* = 7.8 Hz, 1 H), 8.09 (d, *J* = 8.2 Hz, 1 H), 7.95–7.88 (m, 2 H), 7.70 (d, *J* = 8.2 Hz, 1 H), 7.61–7.50 (m, 4H).

***N*-(2-Methoxybenzyl)picolinamide(SM05)—**



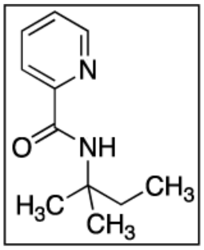
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 2-methoxybenzylamine (20 mmol, 2.74 g). After chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (3.2 g, 71 %). R_f = 0.34 (hexanes/ethyl acetate 60/40). This compound is known.[17] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53–8.52 (m, 1H), 8.45 (br s, 1H), 8.21–8.19 (m, 1H), 7.85–7.77 (m, 1H), 7.35 (dd, *J* = 7.45, 1.7 Hz, 2H), 7.27–7.24 (m, 2H), 6.93–6.88 (m, 2H), 4.67 (d, *J*=6.3 Hz, 2H), 3.88 (s, 3H).

***N*-(3,4-Dimethoxyphenethyl)picolinamide(SM06)—**



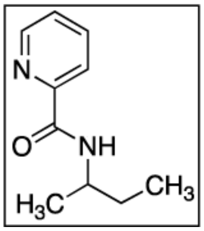
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.7 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 3,4-dimethoxyphenethylamine (20 mmol, 3.4 mL). After chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (5.56 g, 97 %). R_f = 0.30 (hexanes/ethyl acetate 60/40). This compound is known.[18] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52–8.51 (m, 1H), 8.21–8.16 (m, 2H), 7.87–7.82 (m, 1H), 7.43–7.39 (m, 1H), 6.84–6.78 (m, 3H), 3.87–3.85 (m, 6H), 3.74–3.69 (m, 2H), 2.91–2.87 (m, 2H).

***N*-(*tert*-Pentyl)picolinamide(SM07)—**



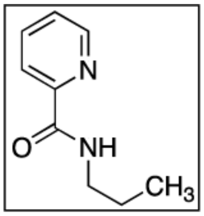
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-pentylamine (20 mmol, 2.19 mL). After chromatography (hexanes/ethyl acetate 70/30), colorless liquid was obtained (3.77 g, 98 %). R_f = 0.55 (hexanes/ethyl acetate 70/30). This compound is known.[5l] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52-8.51 (m, 1H), 8.19–8.16 (m, 1H), 7.97 (br s, 1H), 7.85–7.81 (m, 1H), 7.41–7.38 (m, 1H), 1.87 (q, *J*=7.3 Hz, 2H), 1.45 (s, 6H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 150.8, 147.8, 137.4, 125.9, 121.7, 53.7, 33.0, 26.4, 8.5.

N-(sec-Butyl)picolinamide(SM08)—



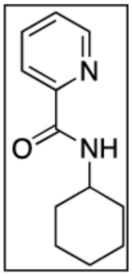
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-aminobutane (20 mmol, 2.01 mL). After chromatography (hexanes/ethyl acetate 70/30), white powder was obtained (3.27 g, 92 %). R_f = 0.35 (hexanes/ethyl acetate 70/30). This compound is known.[4a] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56–8.55 (m, 1H), 8.21 (d, *J*=7.8 Hz, 1H), 7.87–7.83 (m, 2H), 7.35–7.40 (m, 1H), 4.15–4.08 (m, 1H), 1.65–1.58 (m, 2H), 1.26 (d, *J*=6.4 Hz, 3H), 0.97 (t, *J*=7.5 Hz, 3H).

N-Propylpicolinamide (SM09)—



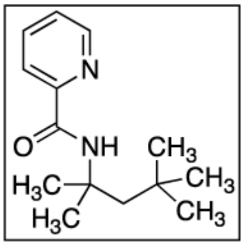
Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 1-propylamine (20 mmol, 1.64 mL). After chromatography (hexanes/ethyl acetate 70/30), colorless liquid was obtained (3.11 g, 95 %). R_f = 0.31 (hexanes/ethyl acetate 70/30). This compound is known.[4a] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.53 (m, 1H), 8.21 (d, *J*=7.8 Hz, 1H), 8.15 (br s, 1H), 7.86–7.82 (m, 1H), 7.35–7.40 (m, 1H), 3.46 (q, *J*=6.4 Hz, 2H), 1.71–1.64 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).

N-Cyclohexylpicolinamide(SM10)—



Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and cyclohexylamine (20 mmol, 2.29 mL). After chromatography (hexanes/ethyl acetate 70/30), white needles were obtained (4.30 g, 98 %). R_f = 0.32 (hexanes/ethyl acetate 70/30). This compound is known.[19] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.53 (m, 1H), 8.22–8.20 (m, 1H), 7.96 (s, J=3.7 Hz, 1H), 7.86–7.82 (m, 1H), 7.43–7.40 (m, 1H), 4.01–3.94 (m, 1H), 2.04–2.00 (m, 2H), 1.80–1.75 (m, 2H), 1.68–1.63 (m, 1H), 1.49–1.19 (m, 5H).

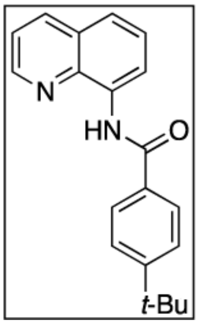
***N*-(2,4,4-Trimethylpentan-2-yl)picolinamide(SM11)—**



Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.7 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-octylamine (20 mmol, 3.2 mL). After column chromatography (hexanes/ethyl acetate 70/30), colorless oil was obtained (3.2 g, 62 %). R_f = 0.56 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, J=4.0 Hz, 1H), 8.18 (d, J=8.0, Hz, 1H), 8.12 (br s, 1H), 7.84–7.81 (m, 1H), 7.40–7.38 (m, H), 1.87 (s, 2H), 1.56 (s, 6H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.1, 151.0, 148.9, 137.4, 125.8, 121.7, 54.7, 52.0, 31.8, 31.6, 29.2. FT-IR (neat, cm^{-1}) ν 2956, 1681, 1522, 1464, 1432, 1365, 1228. Anal. Calcd. for $C_{14}H_{22}N_2O$ (234.34 g/mol): C, 71.76; H, 9.46; N, 11.95; Found: C, 71.46; H, 9.29; N, 11.86.

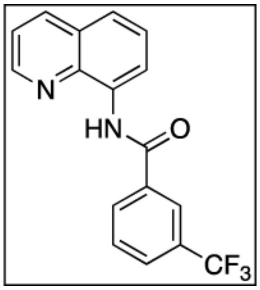
General procedure for the preparation of the 8-aminoquinoline amides—A round-bottom flask was charged with 8-aminoquinoline and triethylamine in dichloromethane. The respective benzoyl chloride was added as a solution in dichloromethane (35 mL). The mixture was stirred overnight at room temperature. The reaction mixture was transferred into separatory funnel and washed with water (2x35 mL). The water layer was extracted with dichloromethane (3x30 mL). Organic layers were combined, washed with saturated aqueous $NaHCO_3$ (30 mL), and dried over $MgSO_4$. Filtration and evaporation under reduced pressure gave the product. Amides not reported are known.[4b]

4-*tert*-Butyl-*N*-(quinolin-8-yl)benzamide (SM12, 12)—



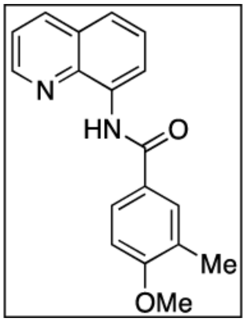
8-Aminoquinoline (13.1 mmol, 1.9 g) and Et_3N (15.8 mmol, 2.2 mL) in dichloromethane (35 mL), followed by 4-*tert*-butylbenzoyl chloride (13.1 mmol, 2.6 g) in dichloromethane (25 mL). The mixture was stirred for 24 h at room temperature. After chromatography (hexanes/ethyl acetate 7/1), tan crystalline compound (6.92 g, 99 % yield) was obtained. R_f = 0.33 (hexanes/ethyl acetate 7/1), mp = 93–94 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.73 (s, 1H), 8.95 (dd, J = 7.4, 1.1 Hz, 1H), 8.85 (dd, J = 4.3, 1.6 Hz, 1H), 8.19 (dd, J = 8.3, 1.4 Hz, 1H), 8.05–8.01 (m, 2H), 7.62–7.52 (m, 4H), 7.50–7.46 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.5, 155.4, 148.3, 138.8, 136.4, 134.8, 132.4, 128.0, 127.5, 127.2, 125.8, 121.8, 121.6, 116.5, 35.1, 31.3. FT-IR (neat, cm-1) ν 3349, 1665, 1531, 1485. Anal. Calcd. for $C_{20}H_{20}N_2O$ (304.35 g/mol): C, 78.92; H, 6.62; N, 9.20. Found: C, 78.88; H, 6.68; N, 9.22.

***N*-(Quinolin-8-yl)-3-(trifluoromethyl)benzamide (SM13)—**



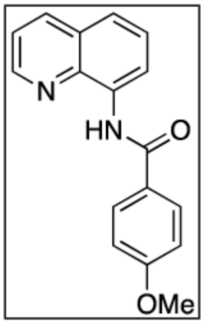
8-Amino-quinoline (13.1 mmol, 1.9 g) and Et_3N (15.8 mmol, 2.2 mL) in dichloromethane (35 mL), followed by 3-(trifluoromethyl)benzoyl chloride (23.4 mmol, 3.4 g) in dichloromethane (25 mL). The mixture was stirred for 16 h at room temperature. After recrystallization (ethanol/water), tan crystalline compound (4.9 g, 96 % yield) was obtained. R_f = 0.25 (toluene/ethyl acetate 50/1), mp = 86–87 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 10.84(s, 1H), 8.93 (dd, J = 7.4, 1.4 Hz, 1H), 8.90 (dd, J = 4.3, 1.5 Hz, 1H), 8.37 (s, 1H), 8.33–8.28 (m, 2H), 7.87–7.84 (m, 1H), 7.74–7.62 (m, 3H), 7.59–7.55 (m, IH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.0, 148.5, 138.7, 136.6, 136.0, 134.2, 131.5 (q, $J_{C\text{-}F}$ = 32.8 Hz), 130.3, 129.5, 128.5 (q, $J_{C\text{-}F}$ = 3.6 Hz), 128.0, 127.5, 124.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 122.4, 122.2, 121.9, 116.9. F NMR (376 MHz, $CDCl_3$, ppm) δ-62.5 (s). Anal. Calcd for $C_{17}H_{11}F_3N_2O$ (316.28 g/mol): C, 64.56; H, 3.51; N, 8.86. Found: C, 64.58; H, 3.45; N, 8.80.

4-Methoxy-3-methyl-*N*-(quinolin-8-yl)benzamide (SM14)—



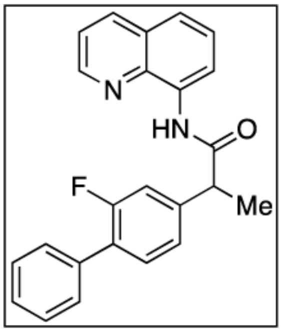
8-Amino-quinoline (10.9 mmol, 1.6 g) and Et_3N (14.7 mmol, 2.0 mL) in dichloromethane (20 mL), followed by 4-methoxy-3-methylbenzoyl chloride (12 mmol, 2.2 g) in dichloromethane (15 mL). The mixture was stirred for 16 h at room temperature. After recrystallization (ethanol/water), tan crystalline compound (3.18 g, 99 % yield) was obtained, mp = 121-123 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.64 (s, IH) 8.97 (dd, J = 7.4, 1.3 Hz, 1H), 8.83 (dd, J = 4.4, 1.5 Hz, 1H), 8.14 (dd, J = 8.3, 1.8 Hz, 1H), 7.95–7.86 (m, 2H), 7.60–7.47 (m, 2H), 7.46–7.42 (m, 1H), 6.92 (d, J = 8.5 Hz, 1H), 1.55 (s, 3H), 0.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 165.4, 160.8, 148.2, 138.8, 136.5, 134.9, 129.9, 128.1, 127.6, 127.1, 126.9, 126.7, 121.7, 121.4, 116.4, 109.5, 55.6, 16.5. Anal. Calcd for $C_{18}H_{16}N_2O_2$ 292.33 g/mol): C, 73.95; H, 5.52; N, 9.58. Found: C, 74.00; H, 5.50; N, 9.53.

4-Methoxy-*N*-(quinolin-8-yl)benzamide (SM15)—



8-Aminoquinoline (20.8 mmol, 3.0 g) and Et_3N (25 mmol, 3.50 mL), in dichloromethane (35 mL), followed by 4-methoxybenzoyl chloride (21.8 mmol, 3.7 g) in dichloromethane (20 mL). The mixture was stirred for 24 h at room temperature. A crystalline compound (5.6 g, 98 % yield) was obtained, mp = 117–118 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.67 (s, IH), 8.92 (dd, J = 7.3, 1.4 Hz, 1H), 8.84 (dd, J = 4.3, 1.5 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 8.08–8.03 (m, 2H), 7.60–7.49 (m, 2H), 7.48-7.43 (m, 1H), 7.05–7.01 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.0, 162.5, 148.3, 138.8, 136.4, 134.8, 129.2, 128.0, 127.6, 127.5, 121.7, 121.5, 116.4, 114.0, 55.5. Anal. Calcd for $C_{17}H_{14}N_2O_2$ (278.31 g/mol): C, 73.37; H, 5.07; N, 10.07. Found: C, 73.35; H, 5.09; N, 9.95.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)propan-amide (SM16)—

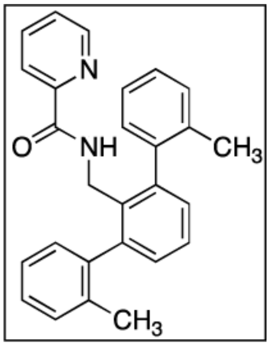


8-Aminoquinoline (7.4 mmol, 1.1 g) and Et_3N (8.2 mmol, 1.2 mL) in dichloromethane (25 mL), followed by 2-(2-fluorobiphenyl-4-yl)propanoyl chloride (8.2 mmol, 2.1 g) in dichloromethane (20 mL). The mixture was stirred for 16 h at room temperature. After chromatography (toluene/ethyl acetate 25/1), tan crystalline compound (2.6 g, 84 % yield) was obtained. R_f = 0.40 (toluene/ethyl acetate 25/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.98 (s, 1H), 8.81–8.69 (m, 2H), 8.11 (dd, J = 8.3, 0.9 Hz, 1H), 7.57–7.27 (m, 11H), 4.00–3.92 (m, 1H), 1.72 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm; list of signals, C-F coupling not assigned) δ 172.1, 161.2, 158.7, 147.4, 142.6, 142.5, 138.5, 136.4, 135.6, 134.5, 131.3, 131.2, 129.1, 129.0, 128.6, 128.4, 128.1, 128.0, 127.8, 127.4, 123.8, 123.7, 121.8, 127.7, 116.5, 115.6, 115.4, 48.2, 18.7. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -117.3 (m). HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{24}H_{19}FN_2O$, 393.13792; found, 393.13782, error=1.16 ppm.

Optimization of reaction conditions for arylation of*N*-(2-phenylpropan-2-yl)picolinamide—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1.0 mmol, 246 mg), and 1-iodo-4-methylbenzene (4.0 mmol, 896 mg). The reactants and solvent were added to this mixture (Table 7). The resulting suspension was stirred in an oil bath at the specified temperature. After the designated time, the reaction mixture was cooled, diluted with dichloromethane (4 mL) and analyzed by GC-MS.

Determination of the GC conversion using internal standard—The GC conversion for the optimization experiments was calculated based on an internal standard (dodecane) as described here. First, a 1:1 molar mixture of dodecane and the pure target compound was dissolved in ethyl acetate and injected into GC to determine detector response ratio $F = A_{tc}/A_{do}$ (A_{tc}: area of target compound peak, A_{do}: area of dodecane peak). Second, the reaction is set up as usual on 1 mmol scale with the addition of dodecane as internal standard (0.3 mmol). After the completion of reaction, 1 drop of reaction mixture is diluted with CH_2Cl_2 and injected into GC to determine area of dodecane (A_{dor}) and the target compound (A_{tcr}). The amount of target compound in reaction mixture can be calculated by the following equation: $n_{tcr} = 0.3.A_{tcr}/(A_{dor}.F)$ (mmol). The conversion is derived based on the amount of starting material added (n_{sm}): $C = (n_{tcr}/n_{sm})*100\%$.

Attempted synthesis of*N*-((2,2''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)picolinamide—



A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-benzylpicolinamide (1.0 mmol, 224 mg), 2-iodotoluene (4.0 mmol, 872 mg), CsOAc (4.0 mmol, 794 mg), and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. An aliquot of the reaction mixture was diluted with ethyl acetate and passed though a short silica plug. GC-MS analysis indicated that no product was formed.

Solvent optimization for the alkylation of*N*-(1-phenylethyl)picolinamide—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg), *N*-(1-phenylethyl)picolinamide (0.5 mmol, 134 mg), iodobutane (2 mmol, 367 mg), and K_3PO_4 (2 mmol, 424 mg). The solvent (0.50 mL) was added to this mixture (Table 8). The resulting suspension was stirred in an oil bath at 140 °C. After 24 hours, the reaction mixture was cooled and diluted with dichloromethane (4 mL) followed by analysis with GCMS using dodecane as an internal standard as described earlier.

Optimization of the additive used for the alkylation of*N*-(1-phenylethyl)picolinamide—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg), *N*-(1-phenylethyl)picolinamide (0.5 mmol, 134 mg), iodobutane (2 mmol, 367 mg), and K_3PO_4 (2.0 mmol, 424 mg). The additive (10 mol %) was added to this mixture (Table 9). The resulting suspension was stirred in an oil bath at 120 °C. After 24 hours, the reaction mixture was cooled and diluted with dichloromethane (4 mL) followed by GC-MS analysis using dodecane as an internal standard as described earlier.

Optimization of the base used for the alkylation of*N*-(1-phenylethyl)picolinamide—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg), $CuBr_2$ (10 mol %, 11 mg) *N*-(1-phenylethyl)picolinamide (0.5 mmol, 134 mg), iodobutane (2 mmol, 367 mg), base (2 mmol), and water (0.30 mL). The resulting suspension was stirred in oil bath at 120 °C. After 24 hours, the reaction mixture was cooled and diluted with dichloromethane (4 mL) followed by analysis with GC-MS using dodecane as an internal standard as described earlier.

General procedure for the arylation of sp^2 C-H bonds of picolinamides—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), picolinamide (1 mmol), aryl iodide (4 mmol), CsOAc (4 mmol, 794 mg), and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hours. The reaction mixture was then extracted with dichloromethane (3x4 mL). The extracts were combined, filtered through pad of cotton, concentrated, and then loaded onto a chromatography column with hexanes/ethyl acetate mixture as an eluent and subjected to column chromatography. After concentration of the fractions containing the product, the residue was dried under reduced pressure.

General procedure for the arylation of*N*-(naphthalen-1-yl)picolinamide using $Pd(OAc)_2$ catalyst and AgOAc base—A 2-dram screw-cap via was charged with $Pd(OAc)_2$ (2 mol%, 4.4 mg), AgOAc (166 mg, 1 mmol), aryl iodide (2 mmol), and *N*-(naphthalen-1-yl)picolinamide (0.5 mmol, 125 mg). The resulting solution was stirred at 140 °C for 24 hours. The reaction mixture was then diluted with dichloromethane (2 mL), filtered through pad of celite, concentrated, then loaded on a chromatography column with hexane/ethyl acetate mixture as an eluent.

***N*-(2-(4,4"-Dimethyl-[1,1':3',1"-terphenyl]-2'-yl)propan-2-yl)-picolinamide(Table 2, Entry 1)—**A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 246 mg), 1-iodo-4-methylbenzene (4 mmol, 896 mg), CsOAc (4 mmol, 794 mg), and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), tan powder (425 mg, 99 % yield) was obtained. $R_f = 0.45$ (hexanes/ethyl acetate 70/30), mp=164–165 °C (hexanes). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21–8.20 (m, 1H), 7.99–7.97 (m, 1H), 7.76–7.72 (m, 1H), 7.58 (*br* s, 1H), 7.31-7.28 (m, 1H), 7.17–7.13 (m, 5H), 7.02 (d, J=7.3 Hz, 2H), 6.90 (d, J=7.3 Hz, 2H), 2.25 (s, 6H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 150.7, 147.1, 143.4, 141.8, 141.7, 136.9, 135.7, 132.8, 128.7, 128.2, 125.4, 124.9, 121.5, 57.5, 33.4, 21.2. FT-IR (neat, cm^{-1}) ν 3369, 1679, 1527, 1444, 1224, 1042. Anal. Calcd for $C_{29}H_{28}N_2O$ (420.55 g/mol): C, 82.82; H, 6.71; N, 6.66; Found: C, 82.47; H, 6.69; N, 6.55.

***N*-([1,1':3',1"-Terphenyl]-2'-ylmethyl)picolinamide(Table 2, Entry 2)—**A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-benzylpicolinamide (1 mmol, 212 mg), iodobenzene (4 mmol, 816 mg), CsOAc (4 mmol, 794 mg), and *t*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), white needles (360 mg, 99 % yield) were obtained. $R_f = 0.34$ (hexanes/ethyl acetate 70/30), mp = 119–120 °C (hexanes). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.44–8.43 (m, 1H), 7.98–7.96 (m, 1H), 7.78–7.72 (m, 2H), 7.43–7.29 (m, 14H), 4.49 (d, $J = 5.1$ Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.9, 149.8, 147.9, 143.9, 141.2, 137.1, 132.7, 129.8, 129.1, 128.3, 127.5, 127.4, 125.9, 122.0, 39.4. FT-IR (neat, cm^{-1}) ν 3378, 1678, 1510, 1464, 1435, 1000. Anal. Calcd for $C_{25}H_{20}N_2O$ (364.44 g/mol): C, 82.39; H, 5.53; N, 7.69; Found: C, 82.50; H, 5.45; N, 7.68. When bromobenzene (4 mmol, 628 mg) was used instead of iodobenzene, product was not detected by GC-MS.

Ethyl 3'-methoxy-2'-(picolinamidomethyl)-[1,1'-biphenyl]-4-carboxylate(Table 2, Entry 3)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-methoxybenzyl)picolinamide (1 mmol, 247 mg), ethyl-4-iodobenzoate (4 mmol, 1104 mg), CsOAc (4 mmol, 794 mg), and *t*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 60/40), white needles (353 mg, 92 % yield) were obtained. $R_f = 0.33$ (hexanes/ethyl acetate 60/40), mp=163–164 °C (hexanes). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.48 (m, 1H), 8.33–8.36 (m, 1H), 8.16–8.13 (m, 1H), 8.10–8.07 (m, 2H), 7.81–7.76 (m, 1H), 7.43–7.41 (m, 2H), 7.38–7.31 (m, 2H), 6.96 (d, J=7.8 Hz, 1H), 6.89 (dd, $J = 7.8$, 0.9 Hz, 1H), 4.58 (d, $J = 5.5$ Hz, 2H), 4.37 (q, $J = 7.3$ Hz, 2H), 3.94 (s, 3H), 1.38 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 163.4, 158.8, 150.3, 148.1, 145.3, 143.0, 137.3, 129.6, 129.5, 128.7, 126.0, 123.6. 122.5, 122.3, 110.2, 61.0, 56.0, 38.6, 14.5. FT-IR (neat, cm^{-1}) ν 3396, 1709, 1668, 1584. 1512, 1462, 1271, 1176, 1023. Anal. Calcd for $C_{23}H_{22}N_2O_4$ (390.43 g/mol): C, 70.75; H, 5.68; N, 7.17; Found: C, 70.86; H, 5.65; N, 7.16.

N-(8-p-Tolylnaphthalen-1-yl)picolinamide (Table 2, Entry 4)—*N*-(Naphthalen-1-yl)picolinamide (5.1 g, 20.5 mmol), 4-iodotoluene (17.5 g, 80.3 mmol), AgOAc (5.1 g, 30.5 mmol), and Pd(OAc)$_2$ (101 mg, 0.45 mmol). The resulting suspension was stirred at 140 °C for 24 h. After column chromatography (hexanes/ethyl acetate 90/10 then hexanes/ethyl acetate 65/35), the solvent was evaporated to give light brown crystals (6.45 g, 91 % yield). R_f = 0.50 (hexanes/ethyl acetate 65/35), mp=123-124 °C (hexanes). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 9.61 (s, 1H), 8.23 (dd, J = 7.7, 1.5 Hz, 1H), 8.18–8.16 (m, 1H), 8.10–8.08 (m, 1H), 7.86 (dd, J = 8.4, 1.5 Hz, 1H), 7.80–7.74 (m, 2H), 7.58–7.54 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.24 (m, 4H), 6.96 (d, J = 7.7 Hz, 2H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 162.0, 150.0, 147.4, 139.9, 137.8, 137.0, 136.6, 135.6, 133.0, 130.5, 129.2, 128.9, 128.6, 126.5, 126.0, 125.7, 125.1, 125.0, 122.6, 121.9, 21.2. FT-IR (neat, cm^{-1}) ν 1689, 1493, 1433. Anal. Calcd for $C_{23}H_{18}N_2O$ (388.4 g/mol): C, 81.63; H, 5.36; N, 8.28; Found: C, 81.54; H, 5.35; N, 8.23.

N-(8-(4-tert-Butylphenyl)naphthalen-1-yl)picolinamide (Table 2, Entry 5)—*N*-(Naphthalen-1-yl)picolinamide (124, 0.5 mmol), 4-*t*-butyliodobenzene (mg, 2 mmol), AgOAc (166 mg, 1.0 mmol), and Pd(OAc)$_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 80/20), the solvent was evaporated to give white powder (190 mg, 99 % yield). R_f = 0.34 (hexanes/ethyl acetate 80/20), mp=136-137 °C (hexanes). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 9.60 (s, 1H), 8.32–8.18 (m, 2H), 8.11–8.10 (m, 1H), 7.88 (dd, J = 8.2, 0.9 Hz, 1H), 7.81–7.73 (m, 1H), 7.59–7.55 (m, 2H), 7.50–7.47 (m, 2H), 7.36–7.34 (m, 3H), 7.31–7.28 (m, 1H), 7.21–7.17 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 161.7, 149.8, 149.7, 147.6, 139.6, 137.8, 137.1, 135.6, 133.1, 130.7, 128.9, 128.4, 126.3, 126.0, 125.9, 125.2, 124.8, 122.3, 121.9, 34.3, 31.3. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) ν 1690, 1521, 1495. HRMS (m/z): [M$^+$] calcd for $C_{26}H_{24}N_2O$, 380.1889; found, 380.1885, error=−1.1 ppm.

N-(8-(4-Methoxyphenyl)naphthalen-1-yl)picolinamide (Table 2, Entry 6)—A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (5 mol %, 11 mg), CuBr$_2$ (10 mol %, 22 mg), *N*-(naphthalen-1-yl)picolinamide (1.0 mmol, 247 mg), 1-iodo-4-methoxybenzene (4.0 mmol, 936 mg), CsOAc (4.0 mmol, 794 mg), and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexanes/ethyl acetate 50/50), a beige powder (260 mg, 73 % yield) was obtained. R_f = 0.31 (hexane/ethyl acetate 50/50), mp = 107–108 °C (hexanes). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 9.71 (s, 1H), 8.30–8.28 (dd, J = 7.8, 1.4 Hz, 1H), 8.20–8.19 (d, J = 5.0, 1H), 8.11 (d, J = 7.8, 1H), 7.86 (dd, J = 8.2, 0.9 Hz, 1H), 7.86 (dd, J = 8.2, 0.9 Hz, 1H), 7.80–7.56 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.45 (m, 1H), 7.34–7.30 (m, 4H), 6.75–6.67 (m, 2H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 162.0, 158.9, 150.1, 147.5, 137.4, 137.0, 135.5, 135.1, 133.1, 130.7, 130.4, 128.6, 126.4, 126.0, 125.8, 125.0, 122.3, 122.0, 113.6, 55.0. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) ν 1683, 1494, 1515, 1433, 1243, 1176, 1036. Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.40 g/mol): C, 77.95; H, 5.12; N, 7.90; Found: C, 77.68; H, 5.09; N, 7.78.

N-(8-(4-Methoxyphenyl)naphthalen-1-yl)picolinamide (Table 2, Entry 6)—*N*-(Naphthalen-1-yl)picolinamide (127 mg, 0.5 mmol), 4-iodoanisole (468 mg, 2 mmol), AgOAc (166 mg, 1.0 mmol), and Pd(OAc)$_2$ (4.4 mg, 0.01 mmol). The resulting suspension was stirred at 140 °C for 24 h. After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (176 mg, 98 % yield). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 9.71 (s, 1H), 8.30–8.28 (dd, J = 7.8, 1.4 Hz, 1H), 8.20–8.19 (d, J = 5.0, 1H), 8.11 (d, J = 7.8, 1H), 7.86 (dd, J = 8.2, 0.9 Hz, 1H), 7.86 (dd, J = 8.2, 0.9 Hz, 1H), 7.80–7.56 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.45 (m, 1H), 7.34–7.30 (m, 4H), 6.75–6.67 (m, 2H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 162.0, 158.9, 150.1, 147.5, 137.4, 137.0, 135.5, 135.1, 133.1, 130.7, 130.4, 128.6, 126.4, 126.0, 125.8, 125.0, 122.3, 122.0, 113.6, 55.0. Signal for one carbon could not be located. Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.4 g/mol): C, 77.95; H, 5.12; N, 7.90; Found: C, 77.68; H, 5.09; N, 7.78.

N-(8-(3-Methoxyphenyl)naphthalen-1-yl)picolinamide (Table 2, Entry 7)—*N*-(Naphthalen-1-yl)picolinamide (125 mg, 0.5 mmol), 3-iodoanisole (468 mg, 2 mmol), AgOAc (166 mg, 1.0 mmol), and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (178 mg, 99 % yield). $R_f = 0.30$ (hexanes/ethyl acetate 70/30), mp=99–100 °C (hexanes). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.60 (s, 1H), 8.23–8.18 (m, 2H), 8.10–8.08 (m, 1H), 7.88 (dd, $J = 8.2$, 1.4 Hz, 1H), 7.82–7.75 (m, 2H), 7.60–7.56 (m, 1H), 7.47 (dd, $J = 8.2$ Hz, 7.3 Hz, 1H), 7.34–7.31 (m, 2H), 7.07–7.04 (m, 2H), 6.91–6.93 (m, 2H), 6.52–6.49 (m, 1H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.2, 159.4, 149.9, 147.5, 144.2, 137.6, 137.1, 135.5, 132.9, 130.3, 129.2, 128.9, 126.6, 126.0, 125.9, 125.3, 125.0, 123.1, 121.9, 121.7, 114.0, 113.3, 55.2. FT-IR (neat, cm^{-1}) ν 1682, 1521, 1577, 1498, 1427, 1215, 1160, 1041. Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.4 g/mol): C, 77.95; H, 5.12; N, 7.90; Found: C, 77.69; H, 5.10; N, 7.83.

Ethyl 4-(8-(picolinamido)naphthalen-1-yl)benzoate (Table 2, Entry 8)—*N*-(Naphthalen-1-yl)picolinamide (122 mg, 0.5 mmol), ethyl 4-iodobenzoate (122 mg, 2 mmol), AgOAc (166 mg, 1.0 mmol), and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (179 mg, 92 % yield). $R_f = 0.28$ (hexanes/ethyl acetate 70/30), mp=82–83 °C (hexanes). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.35 (s, 1H), 8.12–8.10 (m, 2H), 8.06 (d, $J = 7.8$ Hz, 1H), 7.90 (d, $J = 8.3$ Hz, 1H), 7.83–7.80 (m, 3H), 7.76–7.70 (m, 1H), 7.60–7.56 (m, 1H), 7.50–7.46 (m, 1H), 7.43 (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 7.4$ Hz, 1H), 7.24–7.22 (m, 1H), 4.29 (q, $J = 7.3$, 2H), 1.32 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 162.0, 149.6, 147.7, 147.5, 137.1, 136.8, 135.5, 132.5, 130.2, 129.4, 129.2, 128.8, 126.9, 126.2, 125.9, 125.4, 125.0, 123.8, 122.0, 60.8, 14.5. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) ν 1710, 1682, 1495, 1266, 1102. Anal. Calcd for $C_{25}H_{20}N_2O_3$ (396.4 g/mol): C, 75.74; H, 5.08; N, 7.07; Found: C, 75.63; H, 5.05; N, 7.00.

N-(8-(3-Chlorophenyl)naphthalen-1-yl)picolinamide (Table 2, Entry 9)—*N*-(Naphthalen-1-yl)picolinamide (135 mg, 0.5 mmol), 1-chloro-3-iodobenzene (476 mg, 2 mmol), AgOAc (166 mg, 1.0 mmol), and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 80/20), the solvent was evaporated to give white powder (190 mg, 98 % yield). $R_f = 0.30$ (hexanes/ethyl acetate 80/20), mp=120–121 °C (hexanes). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.50 (s, 1H), 8.30 (d, $J = 4.6$ Hz, 1H), 8.18 (dd, $J = 7.8$, 0.9 Hz, 1H), 8.10 (d, $J = 7.8$ Hz, 1H), 7.89 (dd, $J = 8.2$, 1.4 Hz, 1H), 7.82–7.76 (m, 2H), 7.60–7.56 (m, 1H), 7.49–7.47 (m, 2H), 7.37–7.34 (m, 1H), 7.28 (dd, $J = 7.4$, 1.4 Hz, 1H), 7.18–7.15 (m, 1H), 7.01–6.96 (m, 1H), 6.92–6.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.9, 149.6, 147.5, 144.7, 137.2, 136.2, 135.5, 134.2, 132.6, 130.4, 129.3, 129.1, 129.0, 127.8, 126.8, 126.2, 126.1, 125.2, 125.0, 123.3, 122.0. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) ν 1684, 1526, 1498, 1432. Anal. Calcd for $C_{22}H_{15}ClN_2O$ (358.8 g/mol): C, 73.64; H, 4.21; N, 7.81; Found: C, 73.89; H, 4.09; N, 7.76.

N-(8-(4-Bromophenyl)naphthalen-1-yl)picolinamide (Table 2, entry 10)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(naphthalen-1-yl)picolinamide (1.0 mmol, 251 mg), 1-bromo-4-iodobenzene (4.0 mmol, 1.13 g), CsOAc (4.0 mmol, 794 mg), and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 80/20), light brown powder (342 mg, 84 % yield) was obtained. $R_f = 0.33$ (hexanes/ethyl acetate 80/20), mp = 134–135 °C (hexanes). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 9.56 (s, 1H), 8.32–8.30 (m, 1H), 8.21–8.20 (m, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.91 (dd, J = 8.3, 0.9 Hz, 1H), 7.84–7.80 (m, 2H), 7.61–7.57 (m, 1H), 7.50–7.46 (m, 1H), 7.42–7.39 (m, 1H), 7.32–7.28 (m, 5H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 162.0, 149.5, 147.9, 141.9, 137.2, 136.4, 135.6, 132.6, 131.3, 130.9, 130.5, 129.2, 129.7, 126.3, 126.2, 125.0, 123.2, 122.0, 121.4. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) ν 1687, 1498, 1433, 1009. Anal. Calcd for $C_{22}H_{15}BrN_2O$ (403.3 g/mol): C, 65.52; H, 3.75; N, 6.95; Found: C, 65.10; H, 3.54; N, 6.82.

N-(8-(4-Bromophenyl)naphthalen-1-yl)picolinamide (Table 2, Entry 10)—*N*-(Naphthalen-1-yl)picolinamide (121 mg, 0.5 mmol), 1-bromo-4-iodobenzene (564 mg, 2 mmol), AgOAc (166 mg, 1.0 mmol), and Pd(OAc)$_2$ (4.4 mg, 0.01 mmol). The resulting suspension was stirred at 140 °C for 24 h. After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (161 mg, 82 % yield). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 9.56 (s, 1H), 8.32–8.30 (m, 1H), 8.21–8.20 (m, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.91 (dd, J = 8.3, 0.9 Hz, 1H), 7.84–7.80 (m, 2H), 7.61–7.57 (m, 1H), 7.50–7.46 (m, 1H), 7.42–7.39 (m, 1H), 7.32–7.28 (m, 5H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 162.0, 149.5, 147.9, 141.9, 137.2, 136.4, 135.6, 132.6, 131.3, 130.9, 130.5, 129.2, 129.7, 126.3, 126.2, 125.0, 123.2, 122.0, 121.4. Signal for one carbon could not be located. Anal. Calcd for $C_{22}H_{15}BrN_2O$ (403.3 g/mol): C, 65.52; H, 3.75; N, 6.95; Found: C, 65.10; H, 3.54; N, 6.82.

Large Scale Synthesis of *N*-(8-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)picolinamide (Table 2, Entry 11)—*N*-(Naphthalen-1-yl)picolinamide (12.4 g, 50 mmol), 4-iodobenzotrifluoride (27.2 g, 100 mmol), AgOAc (12.45 g, 75 mmol), and Pd(OAc)$_2$ (224 mg, 1.0 mmol). The flask was sealed with rubber septum and then heated with stirring at 140 °C for 24 hours. After the reaction was complete, the mixture was cooled and 150 mL of ethyl acetate was added. The mixture was filtered and the filtrate was washed with brine (150 mL). The layers were separated and the aqueous solution was extracted with ethyl acetate (2×50 mL). The organic layers were combined, dried with MgSO$_4$, and concentrated. The residue was subjected to column chromatography (hexanes/ethyl acetate 65/35), and the solvent was evaporated to give light orange crystals (16.3 g, 84 % yield). R$_f$ = 0.48 (hexanes/ethylacetate 70/30), mp = 155–156 °C (hexanes). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 9.34 (s, 1H), 8.15 (d, J = 4.1 Hz, 1H), 8.09–8.07 (m, 2H), 7.93 (dd, J = 8.2, 2.3 Hz, 1H), 7.84 (dd, J = 8.2, 1.3 Hz, 1H), 7.79–7.75 (m, 1H), 7.62–7.58 (m, 1H), 7.52–7.48 (m, 3H), 7.39 (d, J = 7.8 Hz, 2H), 7.34–7.30 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 162.0, 149.3, 147.6, 146.7, 137.3, 136.3, 135.6, 132.4, 130.5, 129.5, 129.1, 128.7, 127.0, 126.3, 125,5, 125.1, 124.9, 124.8 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.1, 122.7, 121.9. FT-IR (neat, cm^{-1}) ν 1670, 1491, 1320, 1185, 1141, 1111, 1070, 1058, 1018. Anal. Calcd for $C_{23}H_{15}F_3N_2O$ (392.4 g/mol): C, 70.40; H, 3.85; N, 7.14; Found: C, 70.59; H, 3.65; N, 7.14.

Large Scale Synthesis of *N*-(1,2'-Binaphthyl-8-yl)picolinamide (Table 2, Entry 12)—*N*-(Naphthalen-1-yl)picolinamide (8.68 g, 35 mmol), 2-iodonaphthalene (26.7 g, 105 mmol), AgOAc (8.71 g, 52.5 mmol), and Pd(OAc)$_2$ (392 mg, 1.75 mmol). The flask was sealed with rubber septum and then heated with stirring at 140 °C for 24 hours. After the reaction was complete, the mixture was cooled and ethyl acetate (150 mL) was added. The mixture was filtered and the filtrate was washed with brine (150 mL). The layers were separated and the aqueous solution was extracted with ethyl acetate (2x50 mL). The organic layers were combined, dried with MgSO$_4$, and concentrated. The residue was subjected to column chromatography (dichloromethane/ethyl acetate 50/50), and the solvent was evaporated and the residue obtained was recrystallized from methanol to give light brown crystals (8.5 g, 65 % yield). R$_f$ = 0.32 (dichloromethane/ethyl acetate 50/50), mp = 155–156

°C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.56 (s, 1H), 8.31 (dd, J = 7.8, 1.4 Hz, 1H), 8.03 (s, 1H), 7.94–7.87 (m, 3H), 7.81 (dd, J = 8.3, 0.9 Hz, 1 H), 7.61–7.47 (m, 6H), 7.41–7.34 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.1, 149.4, 146.8, 140.7, 137.6, 136.6, 135.5, 133.8, 133.1, 132.7, 130.7, 129.0, 128.1, 128.0, 127.7, 127.6, 127.4, 126.4, 126.3, 126.1, 125.8, 125.7, 125.1, 125.0, 122.3, 121.5. FT-IR (neat, cm^{-1}) ν 1692, 1496. Anal. Calcd for $C_{26}H_{18}N_2O$ (374.4 g/mol): C, 83.40; H, 4.85; N, 7.48; Found: C, 83.19; H, 4.88; N, 7.39.

Ethyl 4',5'-dimethoxy-2'-(2-(picolinamido)ethyl)-[1,1'-biphenyl]-4-carboxylate(Table 2, entry 13)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(3,4-dimethoxyphenethyl)picolinamide (1.0 mmol, 265 mg), ethyl 4-iodobenzoate (4.0 mmol, 1.10 g), CsOAc (4.0 mmol, 794 mg), and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 40/60), white powder (207 mg, 52 % yield) was obtained. R_f = 0.39 (hexanes/ethyl acetate 40/60), mp = 133–134 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.49 (m, 1H), 8.14–8.11 (m, 1H), 8.06–8.03 (m, 2H), 7.97–7.95 (m, 1H), 7.84–7.80 (m, 1H), 7.42–7.37 (m, 3H), 6.86 (s, 1H), 6.72 (s, 1H), 4.34 (q, J=7.3 Hz, 3.87 (s, 3H), 3.86 (s, 3H), 3.52 (q, J=7.3 Hz, 2H), 2.85 (t, J=7.3 Hz, 2H), 1.41 (t, J=7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 164.2, 149.9, 148.7, 148.0, 147.4, 146.2, 137.5, 133.6, 129.6, 129.1, 128.5, 126.3, 122.3, 113.1, 112.7, 61,1, 56.1, 56.0, 40.6, 32.6, 14.5. Signal for one carbon could not be located. δ. FT-IR (neat, cm^{-1}) ν 3364, 1706, 1666, 1520, 1502, 1440, 1272, 1237, 1212, 1139, 1097, 1032. Anal. Calcd for $C_{25}H_{26}N_2O_5$ (434.48 g/mol): C, 69.11; H, 6.03; N, 6.45; Found: C, 69.08; H, 5.95; N, 6.44.

***N*-(2,6-Di((*E*)-styryl)benzyl)picolinamide (Table 2, Entry 14)—**A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-benzylpicolinamide (1 mmol, 194 mg), (*E*)-(2-iodovinyl)benzene (4 mmol, 0.92 g), CsOAc (4 mmol, 794 mg), and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 h. After chromatography (hexanes/ethyl acetate 70/30), tan needles (269 mg, 86 % yield) were obtained. R_f = 0.35 (hexanes/ethyl acetate 70/30), mp=145–146 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43-8.41 (m, 1H), 8.23–8.21 (m, 1H), 8.14–8.12 (m, 1H), 7.82–7.78 (m, 1H), 7.61–7.53 (m, 8H), 7.40–7.34 (m, 6H), 7.27–7.24 (m, 2H), 7.02 (d, J=16.0 Hz, 2H), 4.98 (d, J=5.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) ϕ 163.9, 149.8, 148.1, 138.3, 137.4, 137.3, 132.5, 132.4, 128.7, 128.5, 127.9, 126.9, 126.2, 126.0, 125.9, 122.4, 37.4. FT-IR (neat, cm^{-1}) ν 3395, 1677, 1515. Anal. calcd for $C_{29}H_{24}N_2O$ (416.51g/mol): C, 83.63; H, 5.81; N, 6.73; Found: C, 83.89; H, 5.70; N, 6.57.

General procedure for the hydrolysis of the arylated picolinamides—The *N*-(8-arylnaphthalen-1-yl)picolinamide was dissolved in ethanolic NaOH solution (NaOH in $EtOH/H_2O$ 10/1) and refluxed for 6 hours. The reaction mixture was cooled and diluted with an equal volume of water. The product was extracted with dichloromethane (3×60 mL). The combined organic layers were combined, dried with $MgSO_4$, and concentrated. The crude compound was subjected to column chromatography and the fractions containing the product were combined and the solvent was evaporated to give pure 8-arylnaphthalen-1-amines.

8-*p*-Tolylnaphthalen-1-amine (6)—*N*-(8-*p*-tolylnaphthalen-1-yl)picolinamide (10.1 g, 30 mmol), ethanolic NaOH solution (12 g NaOH, 300 mmol in $EtOH/H_2O$ 10/1 v/v, 120 mL). After chromatography (hexane/ethyl acetate/triethylamine 94/5/1), beige crystals were obtained (7.0 g, quantitative yield). R_f = 0.16 (hexane/ethyl acetate/triethylamine 94/5/1), mp=73–74 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.75 (d, J = 8.1 Hz, 1H), 7.38−7.22 (m, 7H), 7.13 (d, J = 7.0 Hz, 1H), 6.60 (d, J = 7.3 Hz, 1H), 3.74 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.8, 140.6, 138.4, 137.3, 135.9, 129.2, 128.8, 128.6, 128.4, 126.6, 124.7, 121.0, 119.1, 111.4, 21.4. FT-IR (neat, cm^{-1}) ν 3490, 3393. 1615, 1579, 1522. Anal. Calcd for $C_{17}H_{15}N$ 233.3 g/mol): C, 87.52; H, 6.48; N, 6.00; Found: C, 87.44; H, 6.42; N, 5.96.

8-(4-(Trifluoromethyl)phenyl)naphthalen-1-amine (7)—*N*-(8-(4-(Trifluoromethyl)-phenyl)-naphthalene-1-yl)picolinamide (16.3 g, 42 mmol), NaOH (16.8 g, 420 mmol) in EtOH/H_2O (10/1 v/v, 200 mL). After chromatography (hexane/ethyl acetate/triethylamine 94/5/1), beige crystals were obtained (9.0 g, 75%). R_f = 0.21 (hexane/ethyl acetate/ triethylamine 94/5/1), mp=108–109 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (dd, J = 8.2, 0.9 Hz, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.56 (d, 7.8 Hz, 2 H), 7.41–7.28 (m, 3H), 7.12 (dd, J = 8.7, 1.4, 1H), 6.64 (dd, J = 8.7, 1.4 Hz, 1H), 3.56 (s, 2 H).^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.3, 143.4, 136.9, 135.9, 129.8, 129.5, 128.5, 126.9, 125.7, 125.0 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.7, 123.0, 120.4, 119.4, 111.8. FT-IR (neat, cm^{-1}) ν 3707, 3618, 2973, 2922, 2865, 2844, 1323, 1057, 1032, 1015. Anal. Calcd for $C_{17}H_{12}F_3N$ (287.3 g/mol): C, 71.07; H, 4.21; N, 4.88; Found: C, 71.23; H, 4.12; N, 4.82.

1,2'-Binaphthyl-8-amine (8)—*N*-(1,2'-Binaphthyl-8-yl)picolinamide (8.23 g, 22 mmol), NaOH (8.8 g, 220 mmol) in EtOH/H_2O (10/1 v/v, 100 mL). After chromatography (hexane/ dichloromethane 50/50), light brown crystals were obtained (5.2 g, 88% yield). R_f = 0.26 (hexane/dichloromethane 50/50), mp=113–114 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.91–7.84 (m, 4H), 7.81–7.79 (m, 1H), 7.57–7.51 (m, 3H), 7.41–7.26 (m, 3H), 7.22–7.20 (m, 1H), 6.60 (dd, J = 7.3, 1.4 Hz, 1H), 3.71 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.9, 141.3, 138.3, 136.0, 132.9, 132.6, 128.9, 128.7, 128.2, 128.0, 127.9, 127.6, 127.5, 126.8, 126.7, 126.4, 124.7, 120.9, 119.1, 111.3. FT-IR (neat, cm^{-1}) ν 3707, 3681, 2972, 2922, 2865, 2844, 1055, 1032, 1014. Anal. Calcd for $C_{20}H_{15}N$ (269.2 g/mol): C, 89.19; H, 5.61; N, 5.20; Found: C, 8.39; H, 5.56; N, 5.18.

Cleavage of the picolinic acid auxiliary: [1,1':3',1″-Terphenyl]-2'-ylmethanamine (4)—A known procedure was followed.[20] *N*-([1,1':3',1"-Terphenyl]-2'-ylmethyl)picolinamide (0.5 mmol, 182 mg), (0.5 mmol, 67 mg), *n*-butylamine (5 mmol, 0.5 mL), and toluene (1.5 mL) were mixed in a 2-dram vial inside glovebox. The mixture was shaken until the contents dissolved. Anhydrous $AlCl_3$ (0.5 mmol, 67 mg) was then added to the mixture. The vial was capped, taken outside the glovebox, heated and stirred at 90 °C for 24 h. After the reaction was complete, water (2 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (3×5 mL). The organic layers were combined, concentrated, and purified by column chromatography in hexanes/ethyl acetate 60/40. The fractions containing the product were combined, concentrated and the solvent was evaporated to give white crystals (118 mg, 91 % yield). R_f = 0.12 (hexanes/ethyl acetate 60/40), mp=70–72 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44–7.30 (m, 12 H), 7.23–7.22 (m, 1H), 3.71 (s, 2H), 1.01 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.6, 141.8, 138.7, 129.8, 129.3, 128.4, 127.2, 126.5, 40.8. FT-IR (neat, cm^{-1}) ν 3060, 3031, 2937, 1603, 1580, 1498, 1454, 1443, 1185, 1157, 1074, 1031. Anal. Calcd for $C_{19}H_{17}N$ (259.34 g/mol): C, 87.99; H, 6.61; N, 5.40; Found: C, 87.79; H, 6.70; N, 5.36.

Installation of the propanamide auxiliary: *N*-(8-*p*-Tolylnaphthalen-1-yl)propionamide (9)—8-*p*-Tolylnaphthalen-1-amine **6** (2.02 g, 8.7 mmol) and triethylamine (1.34 mL, 9.57 mol) were dissolved in dichloromethane (35 mL). The resulting mixture was cooled in ice bath. Propionyl chloride (1.55 mL, 17.4 mmol) in dichloromethane (10 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was diluted with water (25 mL) and the layers were separated. The organic layer was dried with $MgSO_4$, concentrated and subjected to column chromatography (hexane/ethyl acetate 75/25) to give 2.50 g (99 % yield) of a white powder. R_f = 0.29 (hexane/ethyl acetate 75/25), mp=134-135 °C (hexanes).^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14 (d, *J* = 7.1 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.81 (d, *J* =7.8 Hz, 1H), 7.50–7.42 (m, 2H), 7.33–7.28 (m, 4H), 7.26–7.25 (m, 1H), 7.15 (s, 1H), 2.45 (s, 3H), 1.57 (q, *J* = 7.3 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 140.6, 137.7, 136.8, 135.2, 133.3, 129.9, 129.4, 129.0, 126.1, 125.7, 124.7, 124.0, 121.2, 30.5, 21.3, 9.4. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) ν 1651, 1378, 1219. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{20}H_{19}NO$, 312.13644; found, 312.13589, error=0.87 ppm.

Arylation of naphthyl propanamide: Ethyl 4-(1-propionamido-8-*p*-tolylnaphthalen-2-yl)benzoate (10)—A 2-dram screw-cap via was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) AgOAc (166 mg, 1 mmol), ethyl 4-iodobenzoate (0.52 g, 2 mmol), *N*-(8-*p*-tolylnaphthalen-1-yl)propionamide (149.9 mg, 0.5 mmol), and trifluoroacetic acid (0.5 mL). The resulting solution was stirred at 110 °C for 3 h. The reaction mixture was diluted with dichloromethane (2 mL), filtered through pad of Celite® and concentrated. Purification by chromatography (hexanes/ethyl acetate 80/20) gave white powder (180 mg, 80 % yield). R_f = 0.09 (hexanes/ethyl acetate 80/20), mp=259-260 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.94–7.89 (m, 2H), 7.50–7.45 (m, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.30 (dd, *J* = 7.2, 0.7 Hz, 1H), 7.26–7.21 (m, 4H), 6.38 (s, 1H), 4.36 (q, *J* =7.3 Hz, 2H), 2.40 (s, 3H), 1.39 (t, *J* = 7.3 Hz, 3H), 1.22 (q, *J* = 7.4 Hz, 2H), 0.57 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.6, 166.6, 145.7, 142.0, 138.6, 138.4, 136.6, 135.1, 131.0, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 127.9, 125.4, 61.0, 29.1, 21.2, 14.5, 9.0. FT-IR (neat, cm^{-1}) ν 3710, 3680, 2956, 2844, 1716, 1662, 1266, 1055, 1033, 1014. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{29}H_{27}NO_3Na$, 460.18831; found, 460.18870, error=0.84 ppm.

General procedure for the arylation of sp^3 C-H bonds of picolinamides—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), picolinamide (1 mmol), aryl iodide (4 mmol), CsOAc (4 mmol, 794 mg), and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hours. The reaction mixture was extracted with dichloromethane (3×4 mL). The extracts were combined, filtered through pad of cotton, concentrated, and then loaded onto a chromatography column with hexanes/ethyl acetate mixture as eluent and subjected to column chromatography. After concentration of the fractions containing the product, the residue was dried under reduced pressure.

***N*-(3-(4-Methoxyphenyl)propyl)picolinamide(Table 3, Entry 1)—**A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-propylpicolinamide (1 mmol, 199 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), CsOAc (4 mmol, 794 mg), and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), yellowish oil (168 mg, 56 % yield) was obtained. R_f = 0.19 (hexanes/ethyl acetate 70/30). This compound is known.[4a] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (d, *J*=4.6 Hz, 1H), 8.18 (d, *J*=8.0 Hz, 1H), 8.09 (br s, 1H), 7.82–7.80 (m, 1H), 7.40–7.38 (m, 1H), 7.11 (d, *J*=8.0 Hz, 2H), 6.81 (d, *J*=8.0 Hz, 2H), 3.76 (s, 3H), 3.50–3.46 (m, 2H), 2.68–2.64 (m, 2H), 1.97–1.94 (m, 2H).

***N*-(4-(4-Methoxyphenyl)butan-2-yl)picolinamide (Table 3, Entry 2)—**A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-methylpropan-2-yl)picolinamide (1 mmol, 221 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), K_2CO_3 (4 mmol, 794 mg), and *tert*-amyl alcohol (2.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), pale yellow oil (255 mg, 75 % yield) was obtained. R_f= 0.27 (hexanes/ethyl acetate 70/30). This compound is known.[4a] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49–8.47 (m, 1H), 8.17–8.16 (m, 1H), 7.92 (*br* d, *J*=8.7 Hz, 1H), 7.79–7.75 (m, 1H), 7.36–7.33 (m, 1H), 7.09–7.05 (m, 2H), 6.78–6.75 (m, 2H), 4.25–4.15 (m, 1H), 3.70 (s, 3H), 2.61 (t, *J*=8.2 Hz, 2H), 1.91–1.75 (m, 1H), 1.25 (d, *J*=6.9 Hz, 3H).

N-(4-(4-Methoxyphenyl)-2-methylbutan-2-yl)picolinamide (Table 3, Entry 3)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-methylpropan-2-yl)picolinamide (1 mmol, 198 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), CsOAc (4 mmol, 794 mg), and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), pale yellow oil (278 mg, 91 % yield) was obtained. R_f = 0.26 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.49 (m, 1H), 8.17–8.15 (m, 1H), 8.00 (br s, 1H), 7.82–7.78 (m, 1H), 7.39–7.36 (m, 1H), 7.12–7.09 (m, 2H), 6.80–6.76 (m, 2H), 3.73 (s, 3H), 2.61–2.56 (m, 2H), 2.16–2.12 (m, 2H), 1.50 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 157.8, 150.7, 147.9, 137.4, 134.4, 129.4, 126.0, 121.8, 113.8, 55.3, 53.5, 42.4, 29.9, 27.2. FT-IR (neat, cm^{-1}) ν 2963, 1675, 1510, 1464, 1247, 1178, 1033. Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38 g/mol): C, 72.46; H, 7.43; N, 9.39; Found: C, 72.15; H, 7.31; N, 9.37.

Ethyl 4-(3-(picolinamido)cyclohexyl)benzoate (Table 3, Entry 4)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-cyclohexylpicolinamide (1 mmol, 194 mg), ethyl 4-iodobenzoate (4 mmol, 1.10 g), CsOAc (4 mmol, 794 mg), and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hr. After chromatography (hexane/ethyl acetate 70/30), light yellow powder (269 mg, 86 %) was obtained. R_f=0.35 (hexanes/ethyl acetate 70/30), mp=117–118 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.45–8.43 (m, 1H), 8.13–8.11 (m, 1H), 7.97 (*br* d, *J*=8.7 Hz, 1H), 7.91 (d, *J*=8.2 Hz, 2H), 7.76–7.72 (m, 1H), 7.34–7.30 (m, 1H), 7.20 (d, *J*=8.2 Hz, 2H), 4.27 (q, *J*=6.9 Hz, 2H), 4.12–4.02 (m, 1H), 2.75–2.67 (m, 1H), 2.20 (d, *J*=12.4 Hz, 1H), 2.07 (d, *J*=12.4 Hz, 1H), 1.91–1.80 (m, 2H), 1.57–1.26 (m. 7H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.7, 163.5, 151.4, 150.0, 148.1, 137.5, 129.8, 128.5, 126.9, 126.2, 122.3, 60.9, 48.7, 43.3, 40.4, 33.1, 32.7, 25.2, 14.4. FT-IR (neat, cm^{-1}) ν 3371, 1713, 1656, 1519, 1276, 1110. Anal. Calcd for $C_{21}H_{24}N_2O_3$ (352.43 g/mol): C, 71.57; H, 6.86; N, 7.95; Found: C, 71.31; H, 6.69; N, 7.73.

N-(4-(3-Methoxybenzyl)-5-(3-methoxy-phenyl)-2,4-dimethylpentan-2-yl)picolinamide (A) and N-(5-(3-methoxyphenyl)-2,4,4-trimethylpentan-2-yl)picolinamide (B) (Table 3, Entry 5)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1 mmol, 245 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), K_2CO_3 (6 mmol, 794 mg), and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hr. The following products were obtained after column chromatography in hexanes/ethyl acetate 70/30.

Product **A** was obtained as a light yellow oil (138 mg, 29 % yield). R_f = 0.69 (hexanes/ethyl acetate 70/30), ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49 (m, 1H), 8.17–8.15 (m, 2H), 7.82–7.79 1H), 7.38–7.35 (m, 1H), 7.17–7.14 (m, 2H), 6.76–6.72 (m, 4H), 6.68–6.67 (m, 2H), 3.76 (s, 6H), (d, *J*=13.0 Hz, 2H), 2.60 (d, *J*=13.0, 2H), 2.10 (s, 2H), 1.56 (s, 6H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.3, 159.1, 150.8, 147.9, 140.5, 137.5, 134.4, 128.6, 125.9, 123.7, 121.7, 116.9, 111.3, 55.2, 54.7, 48.3, 48.0, 39.0, 29.9, 24.8. FT-IR (neat, cm^{-1}) ν 2955, 1679, 1582, 1521, 1488, 1263, 1154, 1043. Anal. Calcd for $C_{28}H_{34}N_2O_3$ (446.58 g/mol): C, 75.31; H, 7.67; N, 6.27; Found C, 74.96; H, 7.67; N, 6.22.

Product **B** was obtained as a colorless oil (46 mg, 13 %). R_f = 0.64 (hexane/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51–8.49 (m, 1H), 8.18–8.16 (m, 1H), 8.14 (*br* s, 1H), 7.83–7.79 (m, 1H), 7.38–7.35 (m, 1H), 7.17–7.14 (m, 1H), 6.75–6.71 (m, 2H), 6.68–6.72 (m, 1H), 3.77 (s, 3H), 2.58 (s, 2H), 1.97 (s, 2H), 1.57 (s, 6H), 1.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.2, 159.0, 150.8, 147.9, 140.62, 137.4, 128.5, 125.9, 123.5, 121.7, 116.9, 111.1, 55.2, 54.7, 51.2, 51.1, 35.5, 29.6, 27.8. FT-IR (neat, cm^{-1}) ν 2916, 1679, 1583, 1520, 1488, 1463, 1264, 1045. Anal. Calcd for $C_{21}H_{28}N_2O_2$ (340.46 g/mol): C, 74.08; H, 8.29; N, 8.23; Found: C, 73.79; H, 8.28; N, 8.11.

General procedure for the alkylation of sp^2 and sp^3 C–H bonds of picolinamides—A Kontes flask or a 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol %, 22 mg), $CuBr_2$ (20 mol %, 44 mg), picolinamide (1 mmol), alkyl iodide (4–6 mmol), K_2CO_3 (4 mmol, 794 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and filtered through a pad of cotton. The residue was then washed with dichloromethane (2×4 mL). The organic solvents were combined, concentrated, and then loaded onto a chromatography column with hexanes/ethyl acetate mixture as eluent and subjected to column chromatography. After concentration of the fractions containing the product, the residue was dried under reduced pressure.

***N*-(1-(2,6-Dibutylphenyl)ethyl)picolinamide (Table 4, Entry 1)—**A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 11 mg), $CuBr_2$ (20 mol %, 22 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 239 mg), *n*-butyl iodide (4 mmol, 736 mg), K_2CO_3 (4 mmol, 552 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (336 mg, 99 % yield) was obtained. R_f = 0.60 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.62 (*br* d, J=7.8 Hz, 1H), 8.52–8.50 (m, 1H), 8.19–8.17 (m, 1H), 7.80 (td, J=7.5, 1.37 Hz, 1H), 7.40–7.36 (m, 1H), 7.14–7.10 (m, 2H), 7.06–7.04 (m, 1H), 5.76 (q, J=7.3, 1H), 2.98–2.90 (m, 2H), 2.80–2.73 (m, 2H), 1.70–1.60 (m, 7H), 1.52–1.43 (m, 4H), 0.93 (t, J=7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 150.1, 148.0, 141.0, 138.3, 137.4, 128.6, 127.1, 126.1, 122.2, 45.1, 34.5, 34.2, 23.2, 22.2, 14.1. FT-IR (neat, cm^{-1}) ν 2956, 1678, 1511, 1432, 1462, 1374, 1206. Anal. Calcd for $C_{22}H_{30}N_2O$ (338.49g/mol): C, 78.06; H, 8.93; N, 8.28; Found: C, 77.84; H, 8.92; N, 8.19.

When *n*-butyl bromide (4 mmol, 548 mg) was used as an alkylating agent, no product was detected by GC-MS.

***N*-(1-(2,6-Bis(4,4,4-trifluorobutyl)phenyl)ethyl)picolinamide (Table 4, Entry 2)—** A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 229 mg), 1,1,1-trifluoro-4-iodobutane (4 mmol, 948 mg), K_2CO_3 (4 mmol, 552 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (356 mg, 79 % yield) was obtained. R_f = 0.52 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.54–8.51 (m, 2H), 8.17–8.14 (m, 1H), 7.84–7.80 (m, 1H), 7.42–7.39 (m, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.06 (d, J=7.8 Hz, 1H), 5.69 (q, J = 7.3 Hz, 3.10–3.01 (m, 1H), 2.88–2.80 (m, 2H), 2.29–2.16 (m, 4H), 1.95–1.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 149.7, 148.1, 139.3, 138.8, 137.6, 129.1, 127.5, 127.2 (q, J = 276.1 Hz), 126.4, 122.2, 45.1, 33.8 (q, J = 28.8 Hz), 33.1, 24.1, 22.1. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ 66.1. FT-IR (neat, cm^{-1}) ν 1678, 1512, 1465, 1434, 1388, 1251, 1132, 1005. Anal. Calcd for $C_{22}H_{24}F_6N_2O$ (446.43g/mol): C, 59.19; H, 5.42; N, 6.27; Found: C, 59.28; H, 5.48; N, 6.24.

***N*-(1-(2,6-Diisobutylphenyl)ethyl)picolinamide (Table 4, Entry 3)—**A 10-mL Kontes flask was charged with Pd(OAc)$_2$ (10 mol %, 22 mg), CuBr$_2$ (20 mol %, 44 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 239 mg), 1-iodo-2-methylpropane (6 mmol, 1.10 g), K$_2$CO$_3$ (4 mmol, 552 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexane/ethyl acetate 70/30), light yellow oil (301 mg, 84 % yield) was obtained. R_f = 0.39 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 8.61 (*br* d, *J*=8.0 Hz, 1H) 8.52–8.51 (m, 1H), 8.19–8.17 (m, 1H), 7.79 (td, *J*7.5, 1.7 Hz, 1H), 7.39–7.36 (m, 1H), 7.12–7.10 (m, 1H), 7.05–7.04 (m, 2H), 5.76 (q, *J*=8.0 Hz, 1H), 2.91 (dd, *J*=13.8, 6.87 Hz, 2H), 2.62 (dd, *J*=13.8, 5.7 Hz, 2H), 2.04 (m, 2H), 1.67 (d, *J*=6.9 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 6H), 0.96 (d, *J*= 6.9 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 163.4, 150.1, 148.0, 139.7, 139.2, 137.4, 129.3, 126.4, 126.1, 122.2, 45.2, 43.3, 29.7, 23.0, 22.6, 22.3. FT-IR (neat, cm^{-1}) ν 2954, 1677, 1509, 1464, 1432, 1383. Anal. Calcd for C$_{22}$H$_{30}$N$_2$O (338.49 g/mol): C, 78.06; H, 8.93; N, 8.28; Found: C, 78.03; H, 9.11; N, 8.37.

***N*-(1-(2,6-Diphenethylphenyl)ethyl)picolinamide (Table 4, Entry 4)—**A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (10 mol %, 22 mg), CuBr$_2$ (20 mol %, 44 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 228 mg), (2-iodoethyl)benzene (4 mmol, 984 mg), K$_2$CO$_3$ (4 mmol, 552 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), light yellow oil (375 mg, 86 % yield) was obtained. R_f = 0.33 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 8.68 (br d, *J*=7.8 Hz, 1H), 8.45–8.43 (m, 1H), 8.20–8.18 (m, 1H), 7.77 (td, *J*=7.8, 1.8 Hz, 1H), 7.36–7.27 (m, 9H), 7.22–7.13 (m, 5H), 5.88 (q, *J*=7.8 Hz, 1H), 3.31–2.99 (m, 6H), 1.68 (d, *J*=6.87 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ□ 163.6, 150.0, 148.2, 142.1, 140.2, 138.8, 137.6, 129.2, 128.7, 128.6, 127.5, 126.4, 126.2, 122.4, 45.4, 38.5, 36.6, 22.2. FT-IR (neat, cm^{-1}) ν 1676, 1509, 1453, 1432. Anal. Calcd for C$_{30}$H$_{30}$N$_2$O (434.57 g/mol): C, 82.91; H, 6.96; N, 6.45; Found: C, 82.71; H, 7.22; N, 6.41.

***N*-(1-(2,6-Dibenzylphenyl)ethyl)picolinamide (Table 4, Entry 5)—**A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (5 mol %, 11 mg), CuBr$_2$ (10 mol %, 22 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 228 mg), benzyl iodide (4 mmol, 872 mg), K$_2$CO$_3$ (4 mmol, 552 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 hours. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (349 mg, 85 % yield) was obtained. R_f = 0.43 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, CDCl$_3$, 50 °C, ppm) δ 8.34 (br d, *J*=6.87 Hz, 1H), 8.30–8.28 (m, 1H), 8.04 (d, *J*=7.5 Hz, 1H), 7.71 (td, *J*= 7.5, 1.7 Hz, 1H), 7.28–7.26 (m, 1H), 7.19–7.03 (m, 13H), 5.72 (q, *J*=7.5 Hz, 1H), 4.45 (d, *J*=16.0 Hz, 2H), 4.21 (d, *J*=16.0 Hz, 2H), 1.24 (d, *J*=7.5 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 163.6, 149.8, 147.9, 141.2, 139.9, 138.9 (br), 137.1, 130.7 (br), 129.0, 128.4, 127.3, 125.9, 125.8, 121.9, 45.6, 40.1 (br), 20.6. FT-IR (neat, cm^{-1}) ν 3381, 1676, 1497, 1462, 1431. Anal. Calcd for C$_{28}$H$_{26}$N$_2$O (406.52 g/mol): C, 82.73; H, 6.45; N, 6.89; Found: C, 82.54; H, 6.44; N, 6.79.

***N*-(2-(2,6-Dibutylphenyl)propan-2-yl)picolinamide (A) and *N*-(2-(2-butylphenyl)-propan-2-yl)picolinamide (B) (Table 4, Entry 6)—**A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (5 mol %, 11 mg), CuBr$_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 224 mg), iodobutane (6 mmol, 1.10 g), K$_2$CO$_3$ (4 mmol, 552 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), two products were obtained.

Product **A** was obtained as a light yellow oil (178 mg, 54 % yield). R_f = 0.44 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ 8.54 (br s, 1H), 8.51–8.49 (m, 1H), 8.15 (d, *J*=7.8 Hz, 1H), 7.80 (td, *J*=9.2, 1.4 Hz, 1H), 7.40–7.36 (m, 1H), 7.10–7.02 (m, 3H), 2.90–2.86 (m, 4H), 2.08 (s, 6H), 1.56–1.48 (m, 4H), 1.29–1.20 (m, 4H), 0.74 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.1, 150.9, 147.8, 141.9, 141.5, 137.4, 130.5, 126.5, 125.9, 121.8, 59.1, 36.5, 35.5, 31.0, 23.3, 14.0. FT-IR (neat, cm^{-1}) ν 2956, 1678, 1510, 1463. Anal. Calcd for $C_{23}H_{32}N_2O$ (352.51 g/mol): C, 78.36; H, 9.15; N, 7.95; Found: C, 78.12; H, 9.31; N, 7.83.

Product **B** was obtained as a light yellow oil (38 mg, 14 % yield). R_f = 0.31 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51–8.47 (m, 2H), 8.14–8.12 (m, 1H), 7,82–7.79 (m, 1H), 7.50–7.48 (m, 1H), 7.41–7.37 (m, 1H), 7.23–7.15 (m, 3H), 2.82–2.78 (m, 2H), 1.92 (s, 6H), 1.47–1.40 (m, 2H), 1.18–1.12 (m, 2H), 0.61 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.8, 150.7, 147.8, 143.2, 140.8, 137.4, 131.6, 127.4, 127.2, 126.0, 125.7, 121.8, 56.3, 34.8, 33.8, 29.0, 23.4, 13.9 Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) ν 2930, 1678, 1511, 1463, 1432. HRMS (m/z): [M$^+$] calcd for $C_{19}H_{24}N_2O$, 296.1889; found, 296.1883, error=−2.0 ppm.

_N_-(2,6-Dicyclohexylbenzyl)picolinamide (A) and _N_-(2-cyclohexylbenzyl)picolinamide (B) (Table 4, Entry 7)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol %, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-benzylpicolinamide (1 mmol, 223 mg), iodocyclohexane (4 mmol, 840 mg), K_2CO_3 (4 mmol, 552 mg), and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexane/ethyl acetate 80/20), two products were obtained.

Product **A** was obtained as a light yellow oil (42 mg, 11 % yield). R_f = 0.31 (hexanes/ethyl acetate 80/20). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.45–8.44 (m. 1H), 8.24 (d, *J*=7.8 Hz, 1H), 7.89–7.82 (m, 2H), 7.40–7.37 (m, 1H), 7.30–7.27 (m, 1H), 7.18–7.16 (m, 1H), 4.73 (d, *J*=4.6 Hz, 2H), 2.83–2.75 (m, 2H), 1.80–1.69 (m, 12H), 1.49–1.18 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7, 149.9, 148.7, 147.5, 137.4, 131.4, 128.3, 126.2, 124.2, 122.2, 40.5, 36.6, 35.0, 27.1, 26.3. FT-IR (neat, cm^{-1}) ν 2925, 2850, 1673, 1521, 1568, 1433, 1242. Anal. Calcd for $C_{25}H_{32}N_2O$ (376.53 g/mol): C, 79.75; H, 8.57; N, 7.44; Found: C, 79.89; H, 8.21; N, 7.48.

Product **B** was obtained as a light yellow oil (62 mg, 20 % yield). R_f = 0.50 (hexanes/ethyl acetate 80/20). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.48 (m, 1H), 8.25–8.19 (m, 2H), 7.86–7.82 (m, 1H), 7.42–7.38 (m, 1H), 7.33–7.30 (m, 1H), 7.19–7.15 (m, 1H), 4.71 (d, *J*=5.5 Hz, 2H), 2.81–2.74 (m, 1H), 1.81–1.70 (m, 5H), 1.49–1.19 (m, 5H. ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.9, 149.9, 148.2, 146.6, 137.4, 134.7, 129.3, 128.2, 126.6, 126.2, 126.0, 122.3, 41.5, 39.7, 34.5, 27.0, 26.3. FT-IR (neat, cm^{-1}) ν 2926, 2851, 1674, 1568, 1522, 1241. Anal. Calcd for $C_{19}H_{22}N_2O$ (294.39 g/mol): C, 77.52; H, 7.53; N, 9.52; Found: C, 77.13; H, 7.67; N, 9.40.

_N_-(2-Cyclohexyl-6-methoxybenzyl)picolinamide (Table 4, Entry 8)—A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol %, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-(2-methoxybenzyl)-picolinamide (1 mmol, 217 mg), iodocyclohexane (4 mmol, 840 mg), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (47 mg, 14 % yield) was obtained. R_f = 0.39 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49–8.47 (m, 1H), 8.23–8.20 (m, 1H), 7.81 (td, *J*=9.52, 2.00 Hz, 1H), 7.38–7.35 (m, 1H), 7.27–7.23 (m, 1H), 6.93–6.91 (m, 1H), 6.77–6.74 (m, 1H), 4.76 (d, *J*=5.49 Hz, 2H), 3.87 (s, 3H), 3.02–2.97 (m, 1H), 1.78–1.72 (m, 5H), 1.51–1.36 (m, 4H), 1.27–1.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7, 158.3, 150.4, 148.4, 148.1, 137.3, 128.7, 125.9, 123.5, 122.3, 118.8, 108.0, 55.7, 39.9, 34.6, 34.4, 27.0, 26.3. FT-IR (neat, cm^{-1}) ν 2926, 1674, 1582, 1518, 1464, 1249, 1136, 1096. Anal. Calcd for $C_{20}H_{24}N_2O_2$ (324.42 g/mol): C, 74.04; H, 7.46; N, 8.64; O, 9.86 Found: C, 73.76; H, 7.50; N, 8.49.

***N*-(8-Octylnaphthalen-1-yl)picolinamide (Table 4, Entry 9)—**A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (5 mol%, 11 mg), CuBr$_2$ (10 mol %, 22 mg), *N*-(naphthalen-1-yl)picolinamide (1 mmol, 217 mg), octyl iodide (4 mmol, 960 mg), CsOAc (3 mmol, 594 mg), and *tert*-amyl alcohol (0.50 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), light yellow oil (153 mg, 49 % yield) was obtained. $R_f = 0.33$ (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, CDCl$_3$, ppm) γ 10.56 (s, 1H), 8.64–8.62 (m, 1H), 8.39–8.36 (m, 1H), 8.02 (d, J=7.8 Hz, 1H), 7.89 (td, J=7.6, 1.6 Hz, 1H), 7.77–7.72 (m, 2H), 7.52–7.45 (m, 2H), 7.38–7.30 (m, 2H), 3.30–3.26 (m, 2H), 1.68–1.61 (m, 2H), 1.27-1.13 (m, 10H), 0.86 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$, ppm) δ 162.5, 150.3, 148.1, 137.9, 137.8, 136.3, 132.7, 126.9, 128.0, 127.9, 127.5, 126.6, 125.6, 125.2, 122.8, 37.8, 32.9, 31.9, 29.8, 29.6, 29.4, 22.8, 14.3. FTIR (neat, cm^{-1}) ν 2926, 1686, 1522, 1498, 1431, 1339. Anal. Calcd for $C_{24}H_{28}N_2O$ (360.49 g/mol): C, 79.96; H, 7.83; N, 7.77; Found: C, 79.78; H, 7.93; N, 7.79.

***N*-(2-Methylnonan-2-yl)picolinamide(Table 4, Entry 10)—**A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (10 mol %, 11 mg), CuBr$_2$ (20 mol %, 22 mg), *N*-(*tert*-pentyl)picolinamide (1 mmol, 192 mg), iodopentane (4 mmol, 792 mg), K$_2$CO$_3$ (4 mmol, 552 mg), pivalic acid (2 mmol, 202 mg), and *tert*-amyl alcohol (0.7 mL). The resulting suspension was stirred at 110 °C for 24 h. After chromatography (hexanes/ethyl acetate 80/20), colorless oil (67 mg, 27 % yield) was obtained. $R_f = 0.31$ (hexanes/ethyl acetate 80/20), ^{1}H NMR (400 MHz, CDCl$_3$, ppm) γ 8.53–8.52 (m, 1H), 8.19–8.16 (m, 1H), 7.97 (br s, 1H), 7.83 (td, J=9.6, 1.8 Hz, 1H), 7.41–7.38 (m, 1H), 1.88–1.79 (m, 2H), 1.46 (s, 6H), 1.34-1.26 (m, 10H), 0.87 (t, J=6.9 Hz, 3H) ^{13}C NMR (100 MHz, CDCl$_3$, ppm) γ 163.3, 150.9, 147.8, 137.4, 125.9, 121.7, 53.6, 40.7, 32.0, 30.1, 29.4, 26.9, 24.3, 22.7, 14.2. FT-IR (neat, cm^{-1}) ν 2926, 1681, 1520, 1464, 1432, 1363, 1287. Anal. Calcd for $C_{16}H_{26}N_2O$ (262.39 g/mol): C, 73.24; H, 9.99; N, 10.68; Found: C, 73.04; H, 10.04; N, 10.38.

General procedure for the alkylation of sp^2 C–H bonds of 8-aminoquinoline amides—A 2– dram screw—capped vial was charged with Pd(OAc)$_2$ (5 mol%), K$_2$CO$_3$ (2.5 equiv), substrate, pivalic acid (20 mol%), and alkyl bromide or iodide (3–4 equiv). The *t*-amyl alcohol (0.7–3.0 mL) solvent was added and the resulting mixture was stirred at 100–110 °C for 12–96 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 mL), followed by washing with water (10 mL). The aqueous layer was extracted with ethyl acetate (3x10 mL). The organic layers were combined, dried over MgSO$_4$, and filtered. The filtrate was concentrated under vacuum. The crude product was purified flash column chromatography.

2-Benzyl-6-methoxy-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 1)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 2-methoxy-*N*-(quinolin-8-yl)benzamide (206 mg, 0.74 mmol), K$_2$CO$_3$ (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.148 mmol), and benzyl bromide (380 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 70/1), 166 mg (61 % yield) of a crystalline material was obtained. $R_f = 0.19$ (toluene/ethyl acetate 70/1), mp = 137–139 °C (hexanes). ^{1}H NMR (500 MHz, CDCl$_3$, ppm) δ 9.98 (s, 1H), 8.99-8.95 (dd, 1H, J = 7.7, 1.3 Hz), 8.71-8.68 (dd, 1H, J = 4.0, 1.3 Hz), 8.17–8.14 (dd, 1H, J = 8.3, 1.2 Hz), 7.61–7.57 (m, 1H), 7.55–7.52 (m, 1H), 7.44–7.41 (m, 1H), 7.33–7.29 (m, 1H), 7.21–7.17 (m, 2H), 7.13–7.09 (m, 2H), 7.04–7.00 (m, 1H), 6.89–6.81 (m, 2H), 4.13 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (500 MHz, CDCl$_3$, ppm) γ 166.4, 156.5, 148.1, 140.5, 140.4, 138.5, 136.2, 134.7, 130.3, 129.2, 128.3, 128.0, 127.5, 127.2, 126.0, 122.6, 121.7, 121.5, 116.8, 109.0, 55.9, 38.9. FT-IR (neat, cm^{-1}) ν 3330, 1670, 1525, 1483. Anal. calcd. for $C_{24}H_{20}N_2O_2$ (368.43 g/mol): C, 78.24; H, 5.47; N, 7.60. Found: C, 78.27; H, 5.54; N 7.46.

2,6-Dibenzyl-4-bromo-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 2)—$Pd(OAc)_2$ (8.3 mg, 0.037 mmol), 4-bromo-*N*-(quinolin-8-yl)benzamide (242 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and benzyl bromide (380 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 12 h. After column chromatography (toluene), 285 mg (76 %) of a crystalline material was obtained. R_f = 0.27 (toluene), mp = 118–119 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.74 (s, 1H), 8.91–8.87 (dd, 1H, J = 7.4, 1.5 Hz), 8.63–8.60 (dd, 1H, J = 4.3, 1.5 Hz), 8.17–8.13 (dd, 1H, J = 8.6, 1.7 Hz), 7.61–7.53 (m, 2H), 7.44–7.40 (m, 1H), 7.22 (s, 2H), 7.18–7.11 (m, 8H), 7.06–7.02 (m, 2H), 4.07 (s, 4H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 167.5, 148.2, 140.4, 139.3, 138.4, 136.8, 136.2, 134.0, 131.0, 129.21, 128.6, 127.9, 127.3, 126.4, 123.5, 122.2, 121.7, 116.8, 39.0. FT-IR (neat, cm^{-1}) ν 3358, 1677, 1524, 1485. Anal. calcd. for $C_{30}H_{23}BrN_2O$ (507.42 g/mol): C, 71.01; H, 4.57; N; 5.52. Found: C, 71.19; H, 4.52; N 5.48.

2,6-Dibenzyl-4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 3)— $Pd(OAc)_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and benzyl bromide (380 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 100 °C for 20 h. After column chromatography (toluene/ethyl acetate 100/1 to 50/1), 318 mg (88 % yield) of a crystalline material was obtained. R_f = 0.22 (toluene/ethyl acetate 70/1), mp = 136–137 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.64 (s, 1H), 8.93–8.90 (dd, J = 7.4, 1.3 Hz, 1H), 8.57–8.54 (dd, J = 4.1, 1.7 Hz, 1H), 8.14–8.11 (dd, J = 8.6, 1.6 Hz, 1H), 7.59–7.51 (m, 2H), 7.40–7.37 (m, 1H), 7.17–7.12 (m, 6H), 7.10–7.05 (m, 4H), 7.01–6.97 (m, 2H), 4.10 (s, 4H), 1.25 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 168.7, 152.2, 148.0, 140.5, 138.4, 137.6, 136.1, 135.4, 134.4, 129.1, 128.3, 127.9, 127.4, 125.9, 125.4, 121.9, 121.5, 116.7, 39.6, 34.7, 31.3. FT-IR (neat, cm^{-1}) ν 3363, 1676, 1521, 1485. Anal. calcd. for $C_{34}H_{32}N_2O$ (507.42 g/mol): C, 84.26; H, 6.66; N, 5.78. Found: C, 84.26; H, 6.68; N 5.82.

2-Benzyl-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide(Table 5, Entry 4)— $Pd(OAc)_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)-3-(trifluoromethyl)benzamide (234 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and benzyl bromide (380 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (hexanes/ethyl acetate 10/1), 212 mg (71 %) of crystalline material was obtained. R_f = 0.27 (hexanes/ethyl acetate 10/1), mp = 124-126 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.11 (s, 1H), 8.91–8.87 (d, J = 7.1 Hz, 1H), 8.75–8.72 (dd, J = 4.1, 1.5 Hz, 1H), 8.21–8.17 (dd, J = 8.5, 1.2 Hz, 1H), 7.90 (s, 1H), 7.67–7.57 (m, 3H), 7.48–7.45 (m, 1H), 7.40–7.37 (m, 1H), 7.21–7.18 (m, 4H), 7.12–7.08 (m, 1H), 4.34 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 196.8, 148.4, 143.8, 139.6, 138.5, 137.6, 136.4, 134.3, 131.5, 129.3, 128.9 (q, $J_{C–F}$ = 32.0 Hz), 128.6, 128.5, 128.0, 127.0 (q, $J_{C–F}$ = 3.5 Hz), 126.5, 124.3 (q, $J_{C–F}$ = 3.5 Hz), 123.9 (q, $J_{C–F}$ = 271.5 Hz), 122.4, 121.8, 116.9, 38.9. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ-62.3 (s). FT-IR (neat, cm^{-1}) ν 3361, 1674, 1525, 1485. Anal. calcd. for $C_{24}H_{17}F_3N_2O$ (406.40 g/mol): C, 70.93; H, 4.22; N, 6.89. Found: C, 70.83; H, 4.33; N 6.69.

2,6-Dibenzyl-4-methoxy-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 5)— $Pd(OAc)_2$ (8.3 mg, 0.037 mmol), 4-methoxy-*N*-(quinolin-8-yl)benzamide (206 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and benzyl bromide (380 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 ºC for 15 h. After column chromatography (toluene/ethyl acetate 40/1), 198 mg (58 %) of crystalline material was obtained. R_f = 0.33 (toluene/ethyl acetate 40/1), mp = 137-138 ºC (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.74 (s, 1H), 8.92 (dd, J =

7.5, 1.1 Hz, 1H), 8.61 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.60-7.51 (m, 2H), 7.42-7.38 (m, 1H), 7.20-7.17 (m, 4H), 7.14-7.10 (m, 4H), 7.06-7.01 (m, 2H), 6.59 (s, 2H), 4.09 (s, 4H), 3.70 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 168.5, 159.9, 148.0, 140.1, 140.0, 138.4, 136.1, 134.4, 131.1, 129.2, 128.4, 127.9, 127.4, 126.1, 121.8, 121.5, 116.6, 113.5, 55.2, 39.4. FT-IR (neat, cm-^{1}) ν 3344, 1669, 1521, 1485. Anal. calcd. for $C_{31}H_{26}N_2O_2$ (458.55 g/mol): C, 81.20; H, 5.72; N, 6.11. Found: C, 80.94; H, 5.73; N 6.10.

2,6-Dibenzyl-4-methoxy-3-methyl-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 6)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-methoxy-3-methyl-*N*-(quinolin-8-yl)benzamide (216 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and benzyl bromide (380 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (1.0 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 40/1), 258 mg (74 %) of crystalline material was obtained. TLC R_f = 0.35 (toluene/ethyl acetate 40/1), mp = 138–139 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.70 (s, 1H), 8.87 (dd, *J* = 7.5, 1.3 Hz, 1H,), 8.53 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.56–7.46 (m, 2H), 7.39–7.34 (m, 1H), 7.25–7.13 (m, 3H), 7.13–7.08 (m, 5H), 7.07–6.96 (m, 2H), 6.63 (s, 1H), 4.15 (s, 2H), 4.11 (s, 2H), 3.76 (s, 3H), 2.07 (s, 3H).^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ169.2, 158.3, 147.9, 140.6, 140.0, 138.4, 136.6, 136.3, 136.0, 134.4, 132.1, 129.1, 128.4, 128.3, 128.3, 127.8, 127.3, 126.0, 125.6, 124.5, 121.7, 121.4, 116.5, 110.2, 55.5, 39.5, 36.9, 11.9. FT-IR (neat, cm^{-1}) ν 3353, 1671, 1521, 1482. HRMS (m/z): [M^{+}] calcd for $C_{32}H_{28}N_2O_2$, 472.2151; found, 472.2152, error=0.2 ppm.

4-*tert*-Butyl-2,6-diethyl-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 7)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and iodoethane (346 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (1.0 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 50/1), 240 mg (90 %) of crystalline material was obtained. R_f = 0.33 (toluene/ethyl acetate 50/1), mp = 125–127 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.94 (s, 1H), 9.00 (dd, *J* = 7.5, 1.3 Hz, 1H), 8.72 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.19–8.15 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.63–7.54 (m, 2H), 7.45–7.41 (m, 1H), 7.19–7.16 (m, 2H), 2.78–2.71 (m, 4H), 1.35 (s, 9H), 1.25 (t, *J* = 7.8 Hz, 6H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 169.3, 152.2, 148.3, 140.4, 138.6, 136.3, 134.6, 134.5, 128.1, 127.5, 123.3, 121.8, 121.7, 116.8, 34.8, 31.4, 26.9, 16.2. FT-IR (neat, cm^{-1}) ν 3341, 1673, 1520, 1487. Anal. calcd. for $C_{24}H_{28}N_2O$ (360.49 g/mol): C, 79.96; H, 7.83; N, 7.77. Found: C, 79.81; H, 7.88; N 7.66.

4-*tert*-Butyl-2,6-diisobutyl-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 8)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and l-iodo-2-methylpropane (408 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (1.0 mL). Resulting mixture was stirred at 110 °C for 40 h. After column chromatography (toluene/ethyl acetate 50/1), 229 mg (75 %) of crystalline material was obtained. R_f = 0.37 (toluene/ethyl acetate 50/1), mp = 114–116 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.86 (s, 1H), 8.98 (dd, *J* = 7.5, 1.4 Hz, 1H), 8.71 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64–7.54 (m, 2H), 7.46–7.42 (m, 1H), 7.10 (s, 2H) 2.59 (d, *J* = 7.3 Hz, 4H), 2.04–1.93 (m, 2H), 1.35 (s, 9H), 0.85 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 169.3, 151.1, 148.2, 138.6, 137.8, 136.3, 135.7, 134.6, 128.1, 127.5, 124.7, 121.7, 121.6, 116.7, 43.0, 34.6, 31.3, 30.1, 22.7. FT-IR (neat, cm^{-1}) ν 3348, 1677, 1519, 1483. Anal. calcd. for $C_{28}H_{36}N_2O$ (416.60 g/mol): C, 80.73; H, 8.71; N, 6.72. Found: C, 80.66; H, 8.68; N 6.69.

4-*tert*-Butyl-2,6-diphenethyl-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 9)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74

mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and (2—iodoethyl)benzene (515 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 50/1), 350 mg (92 %) of crystalline material was obtained. $R_f = 0.30$ (toluene/ethyl acetate 50/1), mp = 160–161 °C (hexanes). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 9.98 (s, 1H), 9.04 (dd, $J = 7.6$, 1.0 Hz, 1H), 8.72 (dd, $J = 4.1$, 1.7, Hz, 1H), 8.18 (dd, $J = 8.4$, 1.4 Hz, 1H), 7.66–7.57 (m, 2H), 7.45–7.41 (m, 1H), 7.17–7.13 (m, 4H), 7.10–7.06 (m, 6H), 7.03 (s, 2H), 3.05–2.98 (m, 8H), 1.25 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 169.0, 151.8, 148.3, 141.8, 138.5, 138.0, 136.4, 135.0, 134.5, 128.6, 128.3, 128.1, 127.5, 125.8, 124.7, 122.0, 121.7, 116.9, 38.3, 36.3, 34.6, 31.3. FT-IR (neat, cm^{-1}) ν 3350, 1670, 1519, 1484. Anal. calcd. for $C_{36}H_{36}N_2O$ (512.68 g/mol): C, 84.34; H, 7.08; N, 5.46. Found: C, 84.35; H, 7.10; N 5.56.

Diethyl 7,7'-(5-(*tert*-butyl)-2-(quinolin-8-ylcarbamoyl)-1,3-phenylene)diheptanoate (Table 5, Entry 10)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and ethyl 7-iodoheptanoate (630 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (1.0 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 40/1 to 200/1), 353 mg (77 %) of a yellow oil was obtained. TLC $R_f = 0.08$ (toluene/ethyl acetate 40/1). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 9.90 (s, 1H), 8.97 (dd, $J = 7.5$, 1.4 Hz, 1H), 8.72 (dd, $J = 4.4$, 1.6 Hz, 1H), 8.17 (dd, $J = 8.3$, 1.7 Hz, 1H), 7.63–7.54 (m, 2H), 7.47–7.43 (m, 1H), 7.14 (s, 2H), 4.11–4.04 (m, 4H), 2.72–2.66 (m, 4H), 2.16–2.10 (m, 4H), 1.73–1.64 (m, 4H), 1.53–1.45 (m, 4H), 1.35 (s, 9H), 1.33–1.18 (m, 14H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 173.8, 169.2, 151.9, 148.3, 139.0, 138.5, 136.3, 134.8, 134.5, 128.1, 127.5, 123.9, 121.8, 121.7, 116.7, 60.1, 34.7, 34.2, 33.8, 31.7, 31.4, 29.3, 28.9, 24.8, 14.3. FT-IR (neat, cm^{-1}) ν 3344, 1734, 1519, 1482. Anal. calcd. for $C_{38}H_{52}N_2O_5$ (616.83 g/mol): C, 73.99; H, 8.50; N, 4.54. Found: C, 73.75; H, 8.61; N, 4.43.

4-(*tert*-Butyl)-2,6-bis(2-chlorobenzyl)-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 11)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and 1-(bromomethyl)-2-chlorobenzene (456 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 50/1 to 25/1), 286 mg (70 %) of crystalline material was obtained. $R_f = 0.38$ (toluene/ethyl acetate 50/1), mp = 140–141 °C (hexanes). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 9.86 (s, 1H), 8.91 (dd, $J = 7.3$, 1.7 Hz, 1H), 8.61 (dd, $J = 4.3$, 1.6 Hz, 1H), 8.14 (dd, $J = 8.3$, 1.8 Hz, 1H), 7.59–7.50 (m, 2H), 7.42–7.37 (m, 1H), 7.24–7.17 (m, 4H), 7.12–6.99 (m, 6H), 4.25 (s, 4H), 1.20 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 168.4, 152.3, 148.0, 138.5, 138.2, 136.2, 136.1, 135.6, 134.3, 134.2, 131.4, 129.3, 127.9, 127.6, 127.4, 126.8, 125.3, 121.9, 121.5, 116.8, 36.8, 34.7, 31.1. FT-IR (neat, cm^{-1}) ν 3341, 1670, 1524, 1486. Anal. calcd. for $C_{34}H_{30}Cl_2N_2O$ (553.52 g/mol): C, 73.78; H, 5.46; N, 5.06;. Found: C, 73.58; H, 5.57; N 5.05.

Dimethyl 3,3'-((5-(*tert*-butyl)-2-(quinolin-8-ylcarbamoyl)-1,3-phenylene)bis-(methylene))-dibenzoate (Table 5, Entry 12)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and methyl 3-(bromomethyl)benzoate (508 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (1.0 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 25/1 to 15/1), 318 mg (94 %) of crystalline material was obtained. $R_f = 0.18$ (toluene/ethyl acetate 25/1), mp = 110-112 °C (hexanes). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 9.43 (s, 1H), 8.87 (dd, $J = 7.4$, 1.6 Hz, 1H), 8.44 (dd, , J = 4.5, 1.7 Hz, 1H), 8.12 (dd, J = 8.2, 1.5 Hz, 1H), 7.78 (s, 2H), 7.63–7.60 (m, 2H), 7.58–7.50 (m, 2H), 7.39–7.32 (m, 3H), 7.18 (s, 2H), 7.16–7.11 (m, 2H), 4.13 (s, 4H), 3.71 (s, 6H), 1.29 (s, 9H).^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 168.3, 166.9, 152.5, 147.9, 140.7, 138.2, 137.2, 136.0 (q, Hz=187.8), 135.4, 134.0, 133.6, 130.1, 130.0, 128.4, 127.8, 127.3, 127.2, 125.7, 121.9, 121.5, 116.7, 51.9, 39.5, 34.8, 31.2. FT-IR (neat, cm^{-1}) ν 3328, 1673, 1520, 1484. Anal. calcd. for $C_{38}H_{36}N_2O_5$ (600.70 g/mol): C, 75.98; H, 6.04; N, 4.66. Found: C, 75.86; H, 6.08; N 4.67.

4-(*tert*-Butyl)-*N*-(quinolin-8-yl)-2,6-bis(4-(trifluoromethoxy)benzyl)benzamide (Table 5, Entry 13)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and 1-(bromomethyl)-4-(trifluoromethoxy)benzene (566 mg, 2.22 mmol) were dissolved in 1.0 ml of *t*-amyl alcohol. Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 25/1), 433 mg (90 %) of a crystalline material was obtained. R_f = 0.27 (toluene/ethyl acetate 70/1), mp = 118–119 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.52 (s, 1H), 8.86 (dd, J = 7.1, 1.9 Hz, 1H), 8.50 (dd, J = 4.3, 1.8 Hz, 1H), 8.14 (dd, J = 8.5, 1.6 Hz, 1H), 7.60–7.51 (m, 2H), 7.42–7.37 (m, 1H), 7.19–7.11 (m, 6H), 6.92–6.86 (m, 4H), 4.08 (s, 4H), 1.30 (s, 9H). FT-IR (neat, cm^{-1}) ν 3335, 1670, 1523, 1485. ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 168.3, 152.6, 148.1, 147.5, 139.2, 138.1, 137.2, 136.2, 135.4, 134.0, 130.1, 127.9, 127.2, 125.7, 122.1, 121.6, 120.8, 119.1, 116.5, 39.0, 34.8, 31.2. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ-57.9. Anal. calcd. for $C_{36}H_{30}F_6N_2O_3$ (652.63 g/mol): C, 66.25; H, 4.63; N, 4.29. Found: C, 66.51; H, 4.58; N 4.33.

4-(*tert*-Butyl)-2,6-bis(3-nitrobenzyl)-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 14)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and 1-(bromomethyl)-3-nitrobenzene (479 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 20 h. After column chromatography (toluene/ethyl acetate 40/1 to 30/1), 365 mg (86 %) of a yellow solid was obtained. R_f = 0.31 (toluene/ethyl acetate 40/1), mp = 122–123 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.39 (s, 1H), 8.76 (q, J = 5.6 Hz, 1H), 8.44 (q, J = 4.2 Hz, 1H), 8.13 (q, J = 8.4 Hz, 1H), 7.97–7.94 (m, 2H), 7.77–7.73 (m, 2H), 7.557.51 (m, 2H), 7.48–7.44 (m, 2H), 7.41–7.37 (m, 1H), 7.26–7.25 (m, 2H), 7.21–7.15 (m, 2H), 4.19 (s, 4H), 1.34 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$, ppm) δ 167.8, 153.2, 148.1, 148.1, 142.4, 138.0, 136.5, 136.3, 135.6, 135.2, 133.5, 129.2, 127.8, 127.3, 126.3, 123.7, 122.4, 121.7, 121.2, 116.6, 39.5, 34.9, 31.3. FT-IR (neat, cm^{-1}) ν 3369, 1671, 1517, 1481. Anal. calcd. for $C_{34}H_{30}N_4O_5$ (574.63 g/mol): C, 71.07; H, 5.26; N, 9.75. Found: C 71.02, H 5.27, N 9.74.

4-(*tert*-Butyl)-2,6-bis(6-(1,3-dioxoisoindolin-2-yl)hexyl)-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 15)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and 2-(6-iodohexyl)isoindoline-l,3-dione (792 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (3.0 mL). Resulting mixture was stirred at 110 °C for 40 h. After column chromatography (toluene/ethyl acetate 30/1 to 20/1), 420 mg (74 %) of a yellow oil was obtained. R_f = 0.13 (toluene/ethyl acetate 30/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.88 (s, 1H), 8.96 (dd, J = 7.4, 1.3 Hz, 1H), 8.68 (dd, J = 4.4, 1.6 Hz, 1H), 8.13 (dd, J = 8.4, 1.5 Hz, 1H), 7.82–7.78 (m, 4H), 7.71–7.66 (m, 4H), 7.61–7.51 (m, 2H), 7.39–7.35 (m, 1H), 7.11 (s, 2H), 3.51 (t, J = 7.3 Hz, 4H), 2.63 (t, J = 8.1 Hz, 4H), 1.65 (q, J = 7.8 Hz, 4H), 1.53–1.47 (m, 4H), 1.32 (s, 9H), 1.31–1.19 (m, 8H).^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 169.2, 168.4, 151.8, 148.2, 138.9, 138.5, 136.3, 134.8, 134.5, 133.8, 132.2, 128.0, 127.5, 124.0, 123.2, 121.8, 121.6, 116.8, 38.0, 34.7, 33.8, 31.8, 31.4, 29.3, 28.5, 26.7. FT-IR (neat, cm^{-1})

ν 3370, 1674, 1519, 1482. Anal. calcd. for $C_{48}H_{50}N_4O_5$ (762.93 g/mol): C, 75.57; H, 6.61; N, 7.34. Found: C, 75.29; H, 6.74; N 7.27.

4-(*tert*-Butyl)-2,6-bis(3-methylbut-2-en-1-yl)-*N*-(quinolin-8-yl)benzamide (Table 5, Entry 16)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 4-*tert*-butyl-*N*-(quinolin-8-yl)benzamide (225 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (14.8 mg, 0.15 mmol), and 1-bromo-3-methylbut-2-ene (330 mg, 2.22 mmol) were dissolved in *t*-amyl alcohol (1.0 mL). Resulting mixture was stirred at 110 °C for 96 h. After column chromatography (hexanes/ethyl acetate 15/1), 72 mg (22 %) of yellow oil was obtained. R = 0.31 (hexanes/ethyl acetate 15/1). ^{1}fH NMR (500 MHz, $CDCl_3$, ppm) *δ* 9.89 (s, 1H), 9.02–8.98 (m, 1H), 8.73–8.69 (m, 1H), 8.19–8.14 (m, 1H), 7.61–7.52 (m, 2H), 7.45–7.43 (m, 1H), 7.15 (s, 2H), 5.33–5.27 (m, 2H), 3.45 (d, *J* = 6.9 Hz, 4H), 1.50 (s, 6H), 1.46 (s, 6H), 1.34 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) *δ* 169.1, 152.2, 148.1, 138.5, 138.2, 136.3, 134.9, 134.8, 132.4, 127.9, 127.5, 124.2, 123.3, 121.7, 121.6, 116.7, 34.7, 32.6, 31.3, 25.6, 17.8. FT-IR (neat, cm^{-1}) *ν* 3339, 1675, 1520, 1482. HRMS (m/z): [M$^+$] calcd for $C_{30}H_{36}N_2O$, 440.2828; found, 440.2827, error=0.2 ppm.

General procedure for alkylation of 8-aminoquinoline amide sp^3 C-H bonds— A 2-dram screw—cap vial was charged with Pd(OAc)$_2$ (5 mol%), K_2CO_3 (3 equiv), substrate, pivalic acid (2 equiv), and alkyl bromide or iodide (4 equiv). *t*-Amyl alcohol solvent (0.5–1.0 mL) was added and the resulting mixture was stirred and heated at 110 °C for 12–96 h. The conversion was monitored by TLC. After completion of reaction, ethyl acetate was added to reaction mixture followed by extraction with water. Aqueous layer was washed with ethyl acetate (3x5 mL). Combined organic extracts were dried over $MgSO_4$. Filtration and evaporation under reduced pressure followed by purification by flash chromatography gave pure product.

***N*-(Quinolin-8-yl)pentanamide (Table 6, Entry 1)—**Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)propionamide (148 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and iodoethane (461 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.5 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 20/1), 133 mg (78 %) of a yellow oil was obtained. R_f = 0.20 (toluene/ethyl acetate 20/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) *δ* 9.80 (s, 1H), 8.77–8.82 (m, 2H), 8.13 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.41–7.55 (m, 3H), 2.56 (t, 7.5 Hz, 2H), 1.76–1.85 (m, 2H), 1.41–1.51 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) *δ* 172.1, 148.2, 138.4, 136.5, 134.7, 128.0, 127.5, 121.7, 121.4, 116.5, 38.1, 27.9, 22.6, 14.0. FT-IR (neat, cm^{-1}) *ν* 3355, 1688, 1524, 1486. This compound is known.[21]

***N*-(Quinolin-8-yl)heptanamide (Table 6, Entry 2)—**Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)propionamide (148 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and 1-iodobutane (544 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.6 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 20/1), 101 mg (53 %) of yellow oil was obtained. R_f = 0.56 (toluene/ethyl acetate 20/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) *δ* 9.80 (s, 1H), 8.79–8.77 (m, 2H), 8.13 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.53–7.41 (m, 3H), 2.54 (t, J = 7.3 Hz, 2H), 1.84–1.77 (m, 2H), 1.44–1.41 (m, 2H), 1.35–1.31 (m, 4H), 0.91–0.87 (m, 3H). This compound is known.[22]

***N*-(Quinolin-8-yl)undecanamide (Table 6, Entry 3)—**Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)propionamide (148 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and 1-iodooctane (710 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.5 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 25/1), 126 mg (52 %) of yellow oil was obtained. R_f = 0.46 (toluene/ethyl acetate 20/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.80 (s, 1H), 8.77–8.82 (m, 2H), 8.13 (dd, J = 8.2, 1.5 Hz, 1H), 7.41–7.55 (m, 3H), 2.52–2.59 (t, J = 7.6 Hz, 2H), 1.82 (q, J = 15.0, 7.6 Hz, 2H), 1.19–1.46 (m, 14H), 0.84–0.91 (m, 3H). This compound is known.[4b]

5-Phenyl-*N*-(quinolin-8-yl)pentanamide (Table 6, Entry 4)—$Pd(OAc)_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)propionamide (148 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and (2—iodoethyl)benzene (686 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.5 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 20/1), 138 mg (64 %) of yellow oil was obtained. R_f = 0.45 (toluene/ethyl acetate 20/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.72 (s, 1H), 8.75–8.81 (m, 2H), 8.13 (dd, J = 8.3 ,1.8 Hz, 1H), 7.40–7.54 (m, 3H), 7.14–7.29 (m, 5H), 2.68 (t, J = 7.5 Hz, 2H), 2.58 (t, J = 7.5 Hz, 2H), 1.82–1.92 (m, 2H), 1.71–1.81 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 171.7, 148.2, 142.3, 138.4, 136.5, 134.61, 128.6, 128.4, 128.0, 127.5, 125.9, 121.7, 121.5, 116.5, 38.2, 35.9, 31.2, 25.5. FT-IR (neat, cm^{-1}) ν 3353, 1687, 1524, 1485. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{20}H_{20}N_2O$, 327.14733; found, 327.14703, error=0.75 ppm.

6-Methyl-*N*-(quinolin-8-yl)hept-5-enamide (Table 6, Entry 5)—$Pd(OAc)_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)propionamide (148 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and 1-bromo-3-methylbut-2-ene (441 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.5 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 25/1) 58 mg (29 %) of yellow oil was obtained. R_f = 0.43 (toluene/ethyl acetate 25/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.79 (s, 1H), 8.76–8.81 (m, 2H), 8.15 (dd, J = 8.3, 1.7 Hz, 1H), 7.42–7.55 (m, 3H), 5.12–5.19 (m, 1H), 2.55 (t, J = 7.6 Hz, 2H), 2.09–2.16 (m, 2H), 1.81–1.91 (m, 2H), 1.69 (d, J = 0.9 Hz, 3H), 1.59 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 172.1, 148.3, 138.5, 136.5, 134.7, 132.8, 128.1, 127.6, 123.8, 121.7, 121.5, 116.6, 37.8, 27.6, 25.9, 25.9, 17.9. FT-IR (neat, cm^{-1}) ν 3357, 1687, 1524, 1486. HRMS electrospray (m/z): [M^+ + Na] calcd for $C_{17}H_{20}N_2O$, 291.14734; found, 291.14693, error=0.48 ppm.

5-Methyl-*N*-(quinolin-8-yl)hexanamide (Table 6, Entry 6)—$Pd(OAc)_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)propionamide (148 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and l-iodo-2-methylpropane (544 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.5 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 10/1), 133 mg (78 %) of yellow oil was obtained. R_f = 0.45 (toluene/ethyl acetate 10/1). ^{1f}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.81 (s, 1H), 8.83–8.76 (m, 2H), 8.14 (dd, J = 8.2, 1.6 Hz, 1H), 7.56–7.41 (m, 3H), 2.55 (t, J = 7.6 Hz, 2H), 1.87–1.77 (m, 2H), 1.56 (m, 2H), 1.68 (m, 1H), 1.36–1.27 (m, 2H), 0.94-0.88 (d, J = 6.6 Hz, 6H). This compound is known.[4b]

4-(2-Bromophenyl)-*N*-(quinolin-8-yl)butanamide (Table 6, Entry 7)—$Pd(OAc)_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)propionamide (148 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and 1-bromo-2-(bromomethyl)benzene (739 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.5 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (toluene/ethyl acetate 15/1), 166 mg (60 %) of yellow oil was obtained. R_f = 0.41 (toluene/ethyl acetate 15/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.81 (s, 1H), 8.82–8.76 (m, 2H), 8.14 (dd, J = 8.2, 1.8 Hz, 1H), 7.55–7.40 (m, 4H), 7.30–7.20 (m, 2H), 7.08–7.02 (m, 1H), 2.87 (t, J = 7.7 Hz, 2H), 2.63 (t, J = 7.3 Hz, 2H), 2.20–2.11 (m, Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 171.4, 148.3, 140.9, 138.4, 136.5, 134.6, 132.9, 130.7, 128.0, 127.9, 127.6, 127.5, 124.6, 121.7, 121.5, 116.6, 37.4, 35.5, 25.6. FT-IR (neat, cm^{-1}) ν 3344, 1688, 1524, 1486. HRMS electrospray (m/z): [M$^+$ + Na] calcd for $C_{19}H_{17}BrN_2O$, 391.04221; found, 391.04175, error=0.27 ppm.

2-Ethyl-*N*-(quinolin-8-yl)undecanamide (Table 6, Entry 8)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 2-methyl-*N*-(quinolin-8-yl)butanamide (169 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and 1-iodooctane (710 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (hexanes/ethyl acetate 12/1), 101 mg (40 %) of yellow oil was obtained. TLC R_f = 0.54 (hexanes /ethyl acetate 12/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.85 (s, 1H), 8.87–8.78 (m, 2H), 8.15 (dd, J = 8.3,1.8 Hz, 1H), 7.56–7.41 (m, 3H), 2.43–2.34 (m, 1H), 1.87–1.74 (m, 2H), 1.69–1.53 (m, 2H), 1.43–1.12 (m, 14H), 1.03-0.96 (t, J=7.4 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 175.1, 148.3, 138.6, 136.5, 134.7, 128.1, 127.6, 121.7, 121.5, 116.6, 51.2, 33.1, 32.0, 29.9, 29.7, 29.6, 29.4, 27.8, 26.4, 22.8, 14.3, 13.0. FT-IR (neat, cm^{-1}) ν 3356, 2926, 2854, 1689, 1524, 1486, 1324. HRMS electrospray (m/z): [M$^+$ + Na] calcd for $C_{24}H_{19}FN_2O$, 393.13792; found, 393.13782, error=1.16 ppm.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)undecanamide (Table 6, Entry 9)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), 2-(2-fluoro-[1,1'-biphenyl]-4-yl)-*N*-(quinolin-8-yl)propanamide (274 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and 1-iodooctane (710 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (hexanes/ethyl acetate 7/1), 162 mg (45 %) of yellow oil was obtained. R_f = 0.29 (hexanes/ethyl acetate 7/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.98 (s, 1H), 8.81–8.74 (m, 2H), 8.13 (dd, J = 8.3, 1.8 Hz, 1H), 7.56–7.29 (m, 11H), 3.77–3.70 (t, J = 7.6 Hz, 1H), 2.37–2.25 (m, 1H), 2.02–1.90 (m, 1H), 1.49–1.15 (m, 14H), 0.89–0.82 (t, J = 6.8 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm; list of signals, C–F coupling not assigned) δ 171.7, 161.2, 158.7, 148.3, 141.6, 141.5, 138.5, 136.4, 135.7, 134.5, 131.1, 131.0, 129.1, 129.0, 128.5, 128.0, 127.9, 127.7, 127.5, 124.2, 124.1, 121.8, 121.7, 116.5, 115.8, 115.6, 54.6, 33.6, 32.0, 29.7, 29.6, 29.4, 27.9, 22.8, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ-117.3. FT-IR (neat, cm^{-1}) ν 2927, 2854, 1688, 1525, 1484, 1424, 1325. HRMS electrospray (m/z): [M$^+$ + Na] calcd for $C_{24}H_{19}FN_2O$, 393.13792; found, 393.13782, error=1.16 ppm.

2-Octyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide (Table 6, Entry 10)—Pd(OAc)$_2$ (8.3 mg, 0.037 mmol), *N*-(quinolin-8-yl)cyclohexanecarboxamide (188 mg, 0.74 mmol), K_2CO_3 (256 mg, 1.85 mmol), pivalic acid (151 mg, 1.48 mmol), and 1-iodooctane (710 mg, 2.96 mmol) were dissolved in *t*-amyl alcohol (0.7 mL). Resulting mixture was stirred at 110 °C for 24 h. After column chromatography (hexanes/ethyl acetate 12/1), 42 mg (15 %) of yellow oil was obtained. TLC R_f = 0.29 (hexanes/ethyl acetate 12/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.82 (s, 1H), 8.85–8.79 (m, 2H), 8.16 (dd, J = 8.2, 1.7 Hz, 1H), 7.57–7.43 (m, 3H), 2.22–2.12 (m, 1H), 2.06–1.93 (m, 2H), 1.87–1.05 (m, 20 H), 1.04–0.92 (m, 1H), 0.83–0.78 (t, J = 6.9 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 175.2, 148.3, 138.6, 136.5, 134.8, 128.1, 127.6, 121.7, 121.4, 116.6, 54.2, 39.5, 35.0, 32.0, 31.3, 31.1, 30.0, 29.7, 29.4, 26.7, 26.1, 26.0, 22.8, 14.3. FT-IR (neat, cm^{-1}) ν 3354, 2924, 2855, 1685, 1523, 1485, 1327, 1160. HRMS electrospray (m/z): [M$^+$ + Na] calcd for $C_{24}H_{34}N_2O$, 389.25689; found, 389.25660, error=0.69 ppm.

Cleavage of the 8-aminoquinoline auxiliary: 5-Phenylpentanoic acid—5-Phenyl-*N*-(quinolin-8-yl)pentanamide (1.0 mmol, 304 mg), NaOH (2.5 mmol, 100 mg), and ethanol (2.0 mL) were mixed in a 2-dram vial. The vial was capped, heated and stirred at 70 °C for 3 h. After the reaction was complete, the contents of the vial was transferred to flask and water (10 mL) was added to the reaction mixture. The mixture was acidified with HCl (20 %

aqueous solution) to pH=1. The product was extracted with ethyl acetate (5x5 mL). The organic layers were combined, concentrated and subjected to column chromatography in hexanes/ethyl acetate 80/20. After concentration of the fractions containing the product, the residue was dried under reduced pressure. Product was obtained as tan crystals (155 mg, 87 % yield). R_f = 0.30 (hexanes/ethyl acetate 80/20). This compound is known.[23] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.82 (*br* s, 1H)7.33–7.14 (m, 5H), 2.52–2.40 (t, *J* = 7.0 Hz, 2H), 2.10–2.04 (t, *J* = 5.5 Hz, 2H), 1.85-1.54 (m, 4H).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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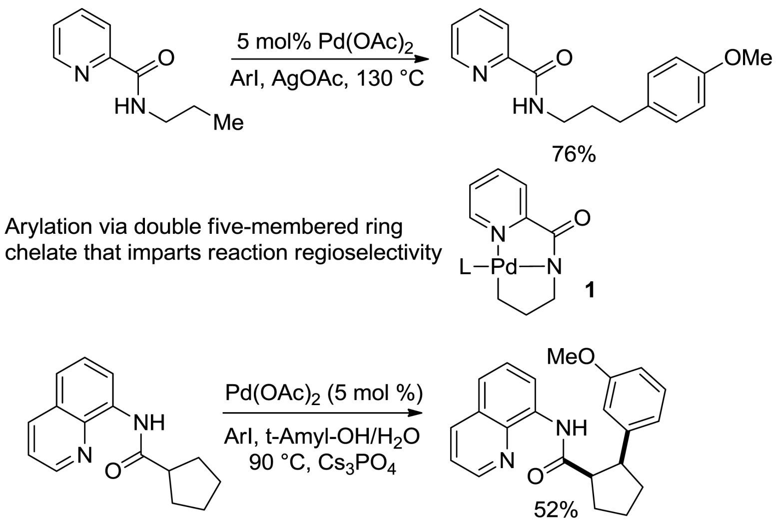
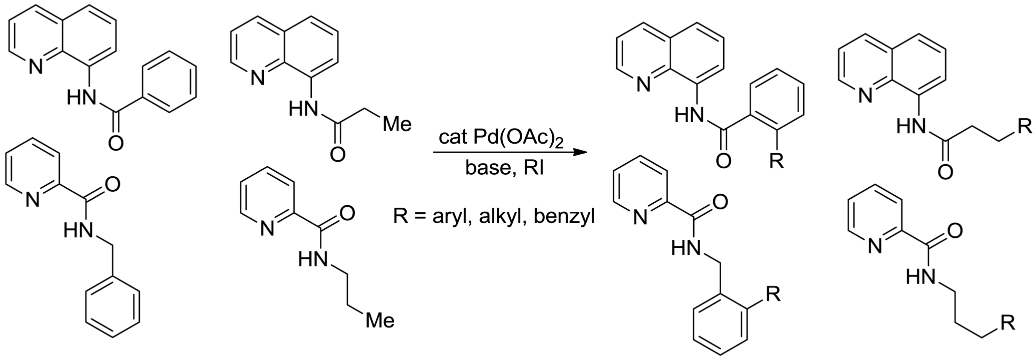


Arylation via double five-membered ring chelate that imparts reaction regioselectivity

1

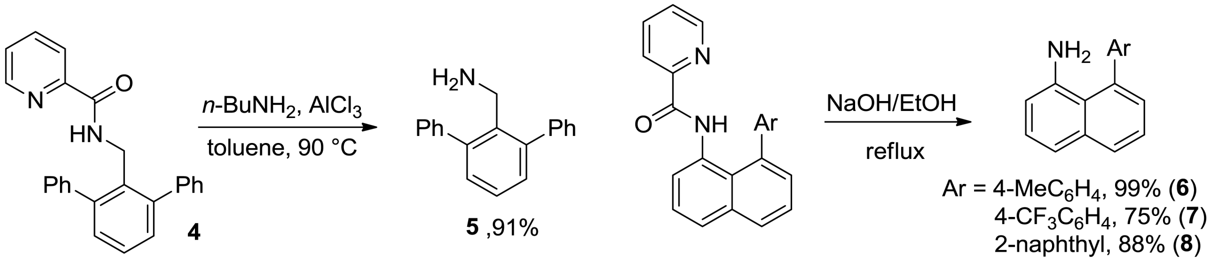
Scheme 1.

Auxiliary-Assisted Arylation



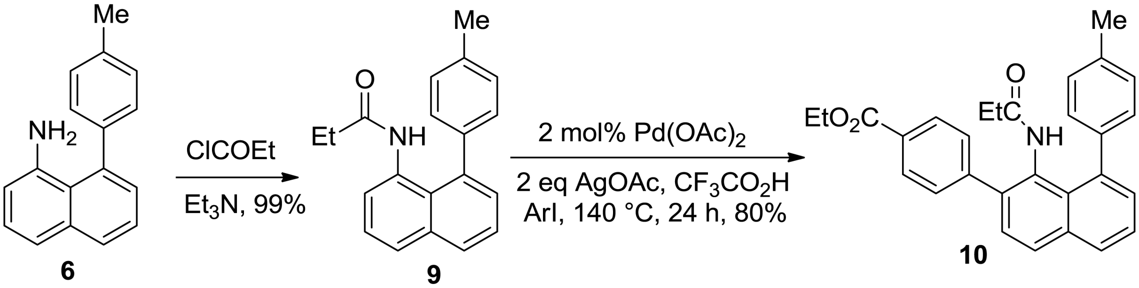
Scheme 2.

Auxiliary-Assisted, Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 C-H Bonds



Scheme 3.

Directing Group Removal

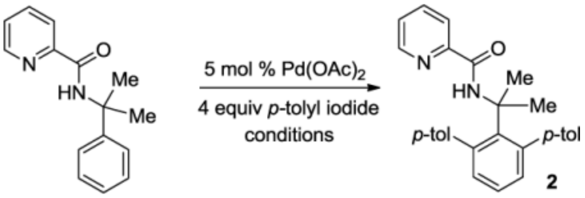


Scheme 4.

Introduction of Second Aryl Group

Table 1

Arylation Optimization[a]



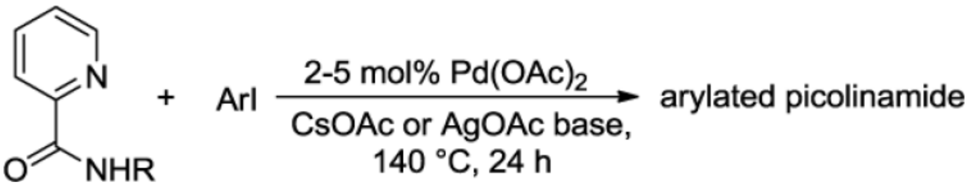
entry	reaction conditions	conv, %
1	K_3PO_4, toluene/CH_3CN, 140 °C, 16 h	15
2	Cs_2CO_3, toluene/CH_3CN, 140 °C, 16 h	15
3	CsOAc, toluene/CH_3CN, 140 °C, 16 h	30
4	CsOAc, *t*-amyl alcohol, 140 °C, 24 h	90
5	CsOAc, 10 % $CuBr_2$, *t*-amyl alcohol, 110 °C, 24 h	75 (70)[b]
6	CsOAc, 10 % $CuBr_2$, *t*-amyl alcohol, 140 °C, 24 h	>99 (99)[b]

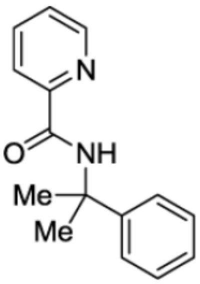
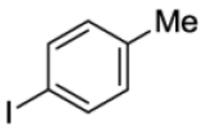
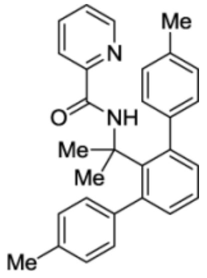
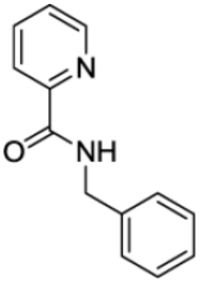
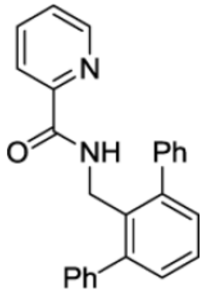
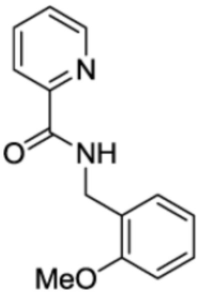
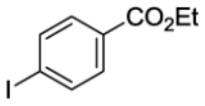
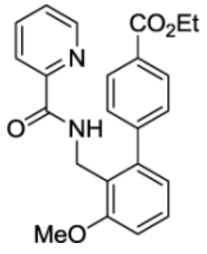
[a] conversion measured by GC with internal standard. Please see Experimental Section for details.

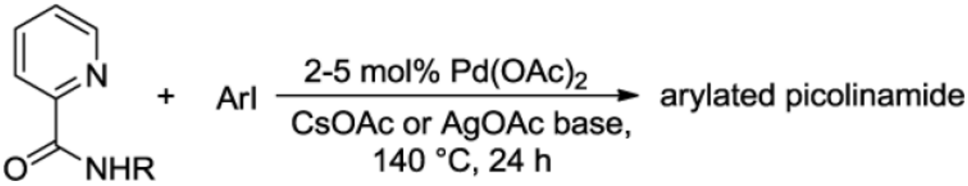
[b] Isolated yield.

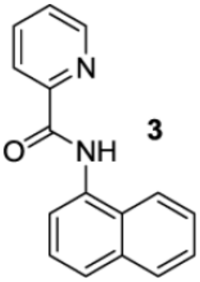
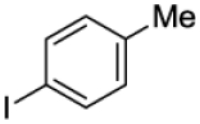
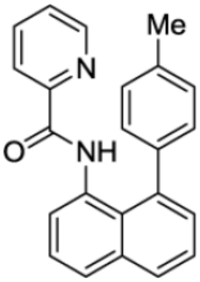
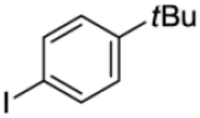
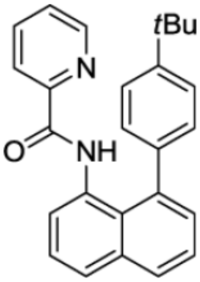
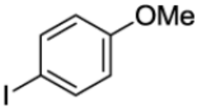
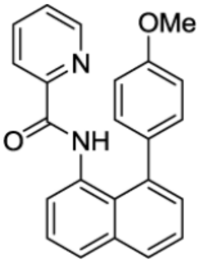
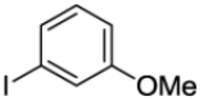
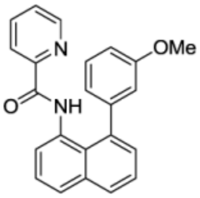
Table 2

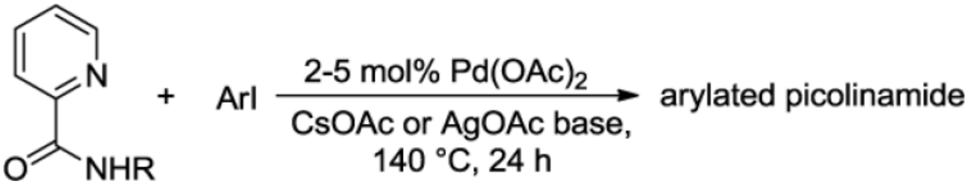
Arylation of Benzylpicolinamide[a]

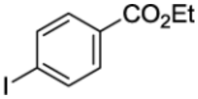
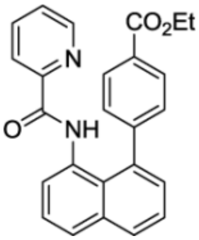
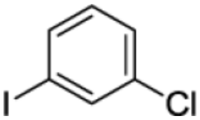
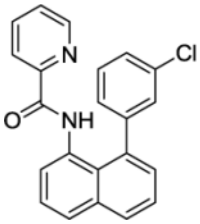
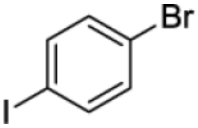
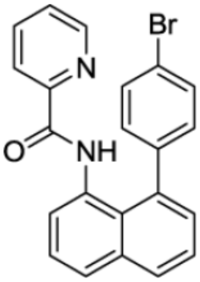
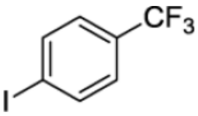
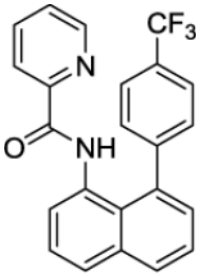


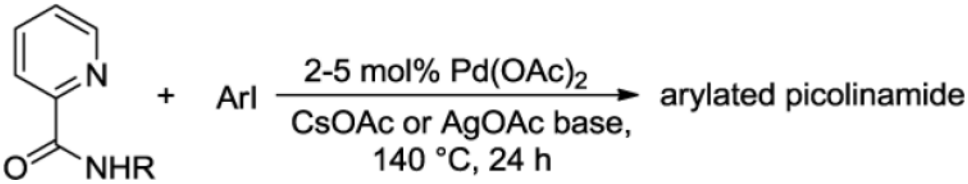
entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
1[b]				99%
2[b]		PhI		99%
3[b]				92%

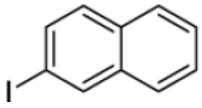
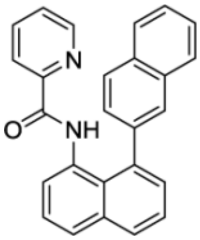
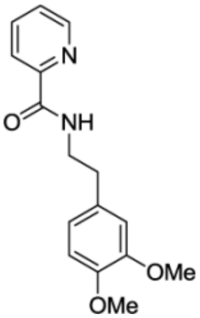
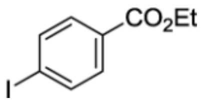
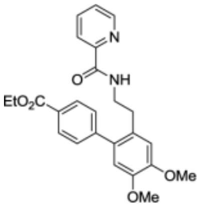
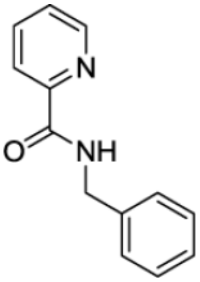
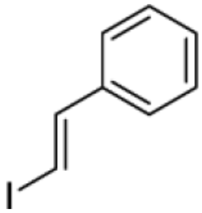
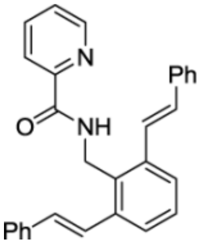


entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
4[c,d]	 **3**			91%
5[c]	**3**			99%
6	**3**			73%[b] 98%[c]
7[c]	**3**			99%



entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
8[c]3	**3**			92%
9[c]	**3**			98%
10	**3**			98%
11[c,e]	**3**			84%



entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
12[c,f]	**3**			65%
13[b]				52%
14[b]				86%

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[a] For CsOAc base: 5 mol % Pd(OAc)2, 10 mol% CuBr2 additive, 4 equiv CsOAc, tAmOH solvent, 4 equiv ArI, 1 mmol scale. For AgOAc base: 2 mol% Pd(OAc)2, 2 equiv AgOAc, no solvent, 4 equiv ArI, 0.5 mmol scale. Yields are isolated yields. Please see Experimental Section for details.

[b] CsOAc base.

[c] AgOAc base.

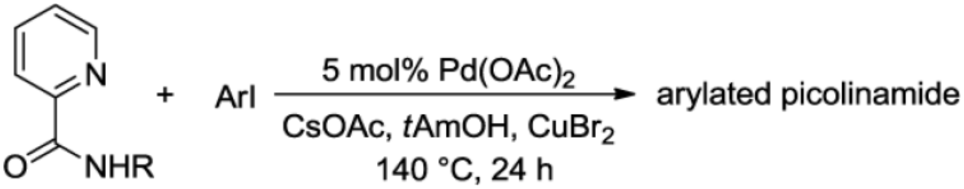
[d] 20 mmol scale, 1.5 equiv AgOAc.

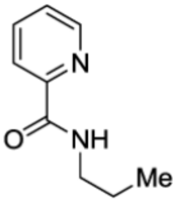
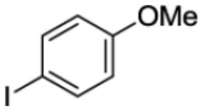
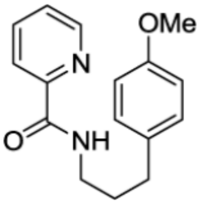
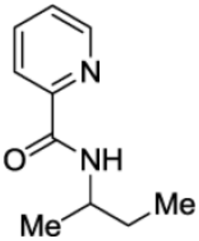
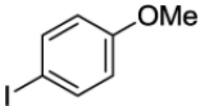
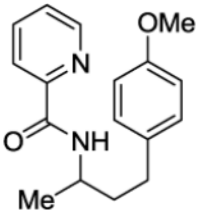
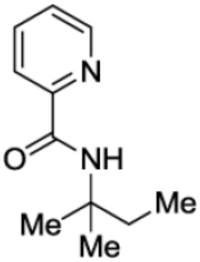
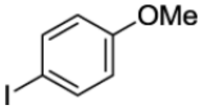
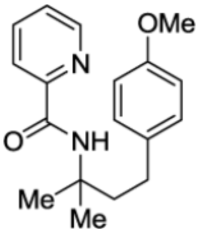
[e] 50 mmol scale, 2 equiv ArI, 1.5 equiv AgOAc.

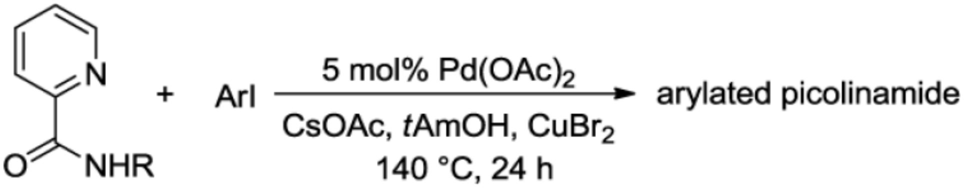
[f] 35 mmol scale, 3 equiv ArI, 1.5 equiv AgOAc.

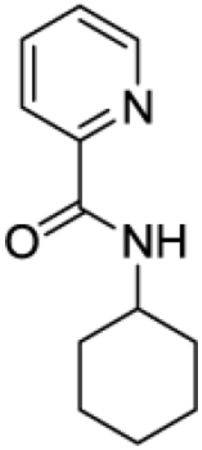
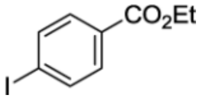
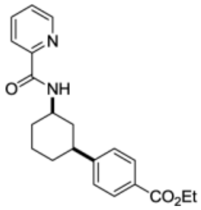
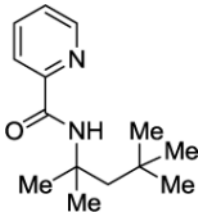
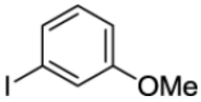
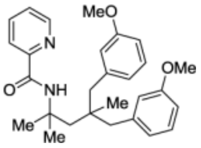
Table 3

Arylation of Alkyl Picolinamides[a]



Entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
1				56%
2				75%
3				91%



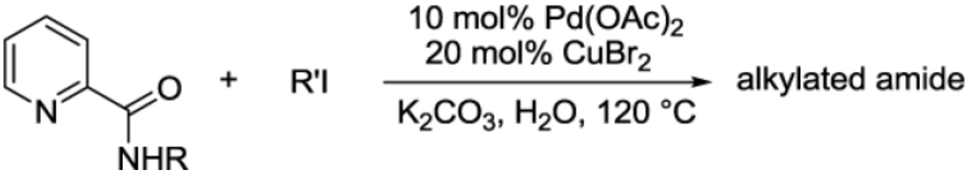
Entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
4				86%
5[b]				29%

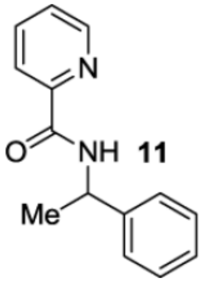
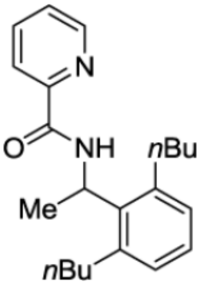
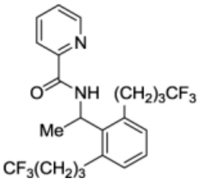
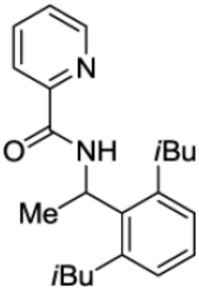
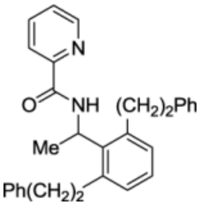
[a] Palladium acetate (5 mol %), 10 mol% $CuBr_2$ additive, 4 equiv CsOAc, *t*-amyl alcohol solvent, 4 equiv ArI, 1 mmol scale. Yields are isolated yields. Please see Experimental Section for details.

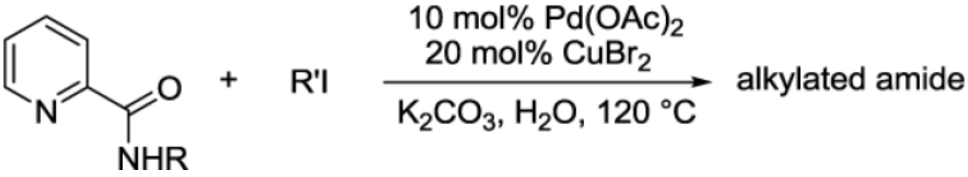
[b] Palladium acetate (10 mol %), 20 mol % $CuBr_2$, and K_2CO_3 base used. Monoarylation product also isolated in 13% yield.

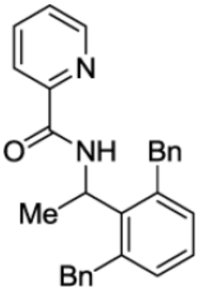
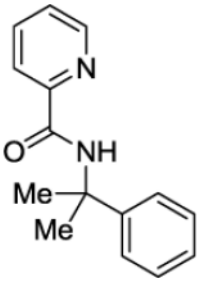
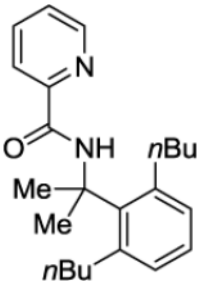
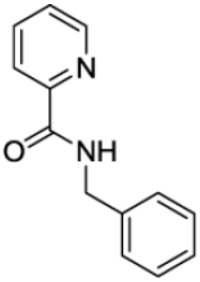
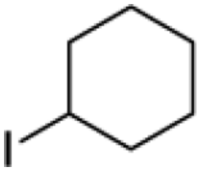
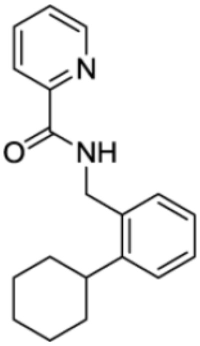
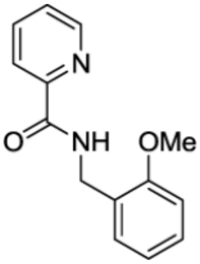
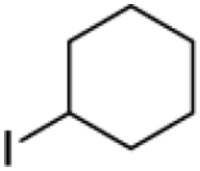
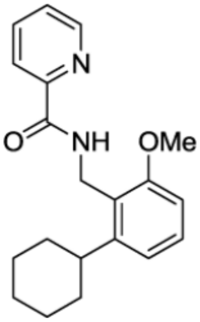
Table 4

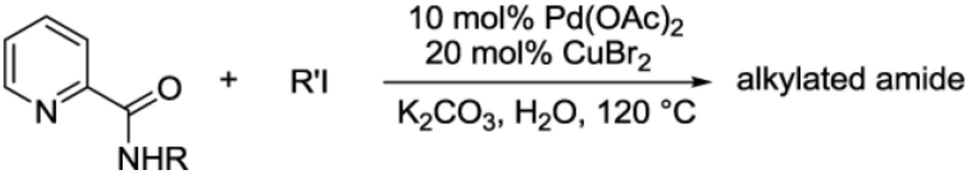
Alkylation of aryl and alkylpicolinamides[a]

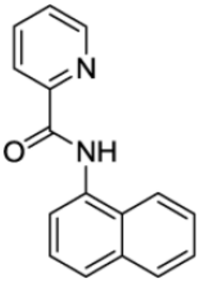
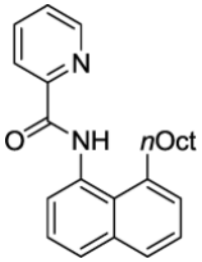
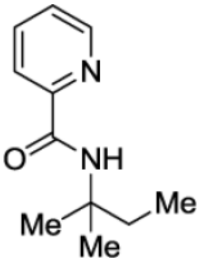
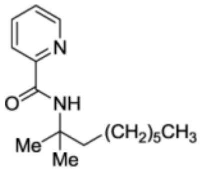


Entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
1[b]	 **11**	*n*BuI		99%
2[b]	**11**	$CF_3(CH_2)_3I$		79%
3[c]	**11**	$(CH_3)_2CHCH_2I$		84%
4	**11**	$PhCH_2CH_2I$		86%



Entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
5[b]	**11**	BnI		85%
6[b,c,d]		*n*BuI		54%
7[e]				20%
8				14%



Entry	Picolinamide	Aryl Iodide	Arylated Picolinamide	Yield
9[b,f]		*n*OctylI		49%
10[g]		*n*AmylI		27%

[a] Picolinamide (1 mmol), RI (4 mmol), Pd(OAc)$_2$ (10 mol%), CuBr$_2$ (20 mol%), K$_2$CO$_3$ (4 mmol), H$_2$O solvent, 24 h at 120 °C. Yields are isolated yields. Please see Experimental Section for details.

[b] Palladium acetate (5 mol%), CuBr$_2$ (10 mol%).

[c] Six equiv RI.

[d] Monoalkylation product also isolated (14 %).

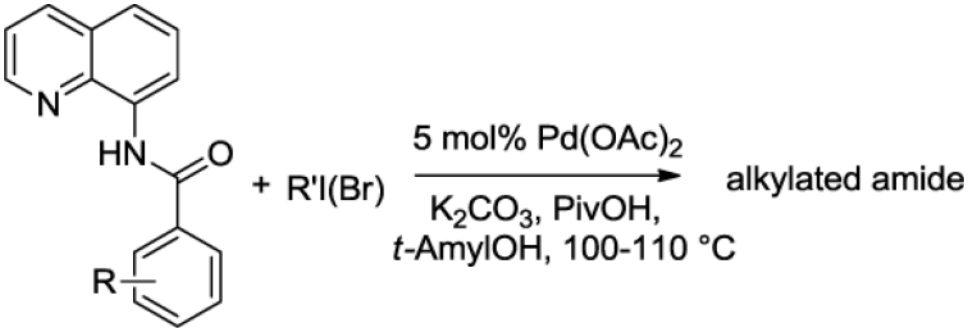
[e] Dialkylation product also isolated (11 %).

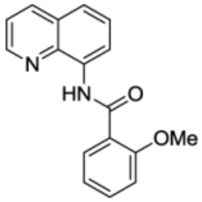
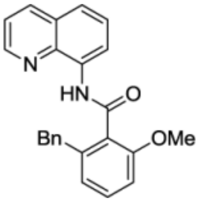
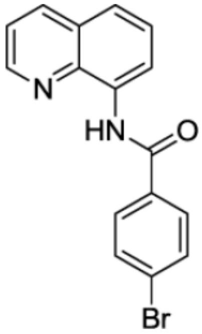
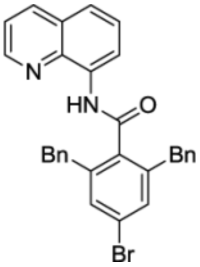
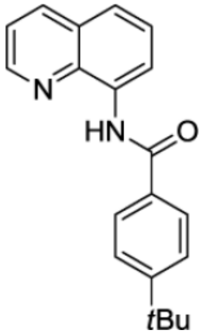
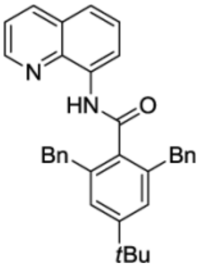
[f] *t*-Amyl alcohol solvent, CsOAc base, 140 °C.

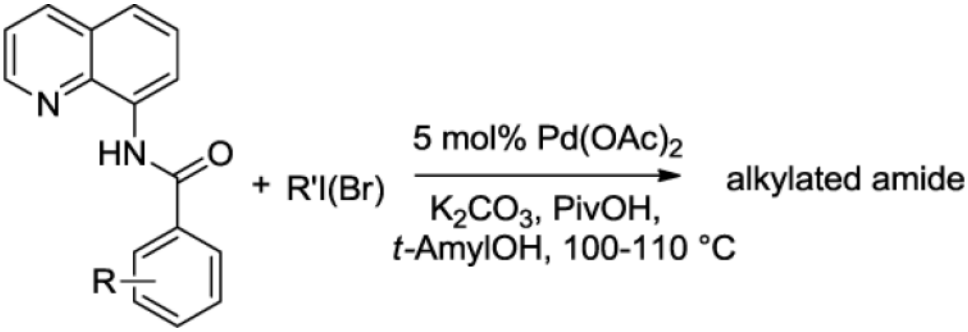
[g] Pivalic acid additive, *t*-amyl alcohol solvent, 110 °C.

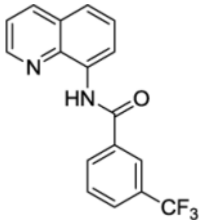
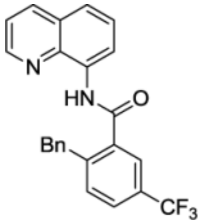
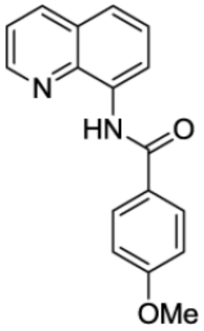
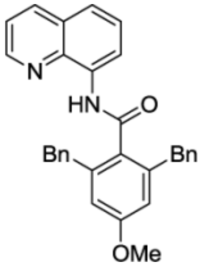
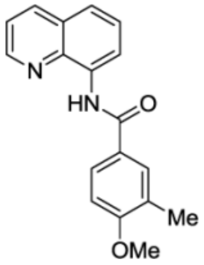
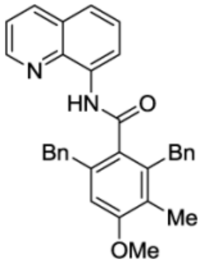
Table 5

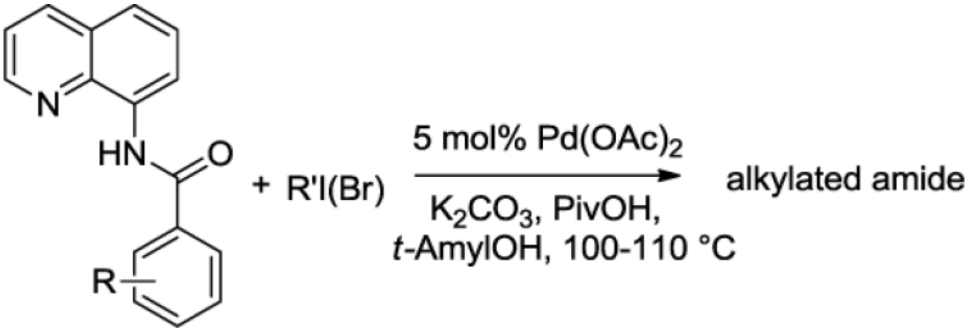
Alkylation of 8-Aminoquinoline Benzamides

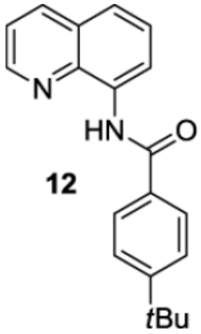
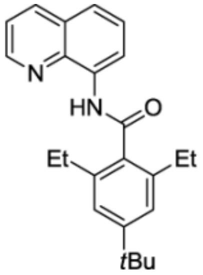
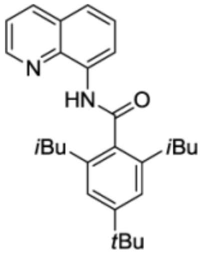
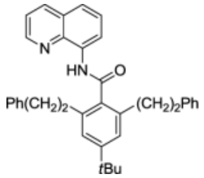
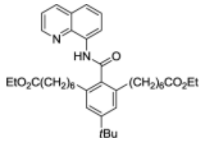


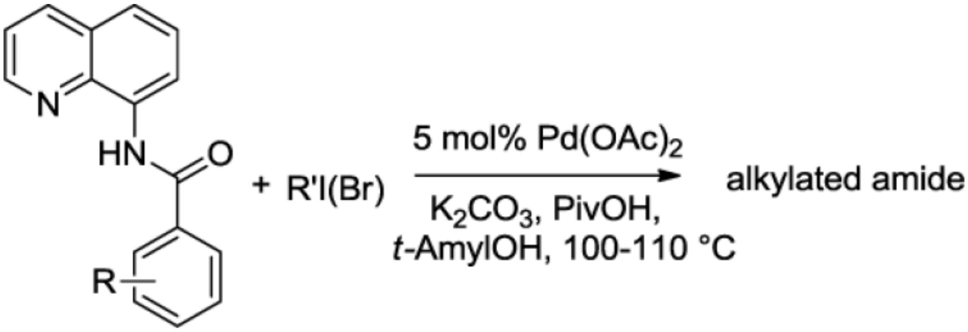
Entry	Amide	Alkyl Halide	Product	Yield
1		BnBr		61%
2		BnBr		76%
3		BnBr		88%

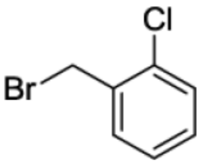
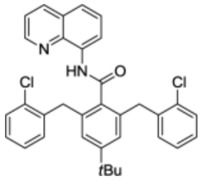
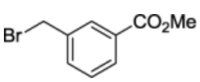
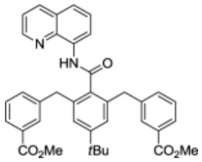
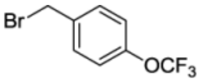
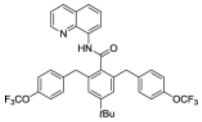
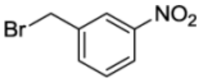
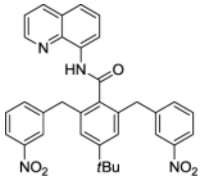
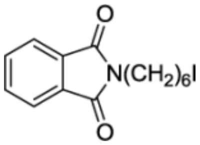
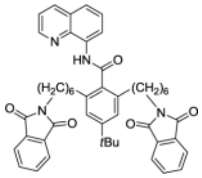
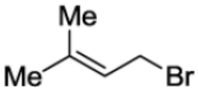
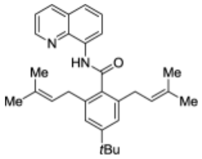


Entry	Amide	Alkyl Halide	Product	Yield
4		BnBr		71%
5		BnBr		58%
6		BnBr		74%



Entry	Amide	Alkyl Halide	Product	Yield
7	 **12**	EtI		90%
8	**12**	*i*BuI		75%
9	**12**	$Ph(CH_2)_2I$		92%
10	**12**	$EtO_2C(CH_2)_6I$		77%

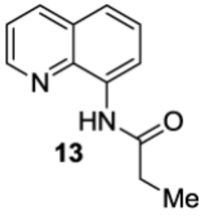
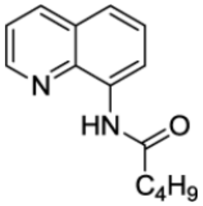
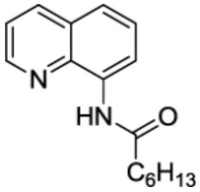
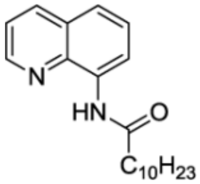
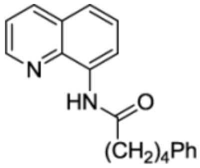
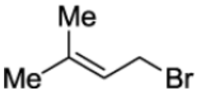
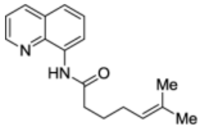


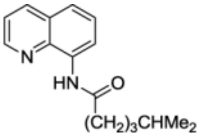
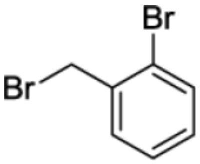
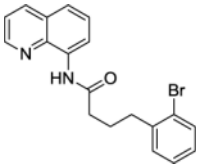
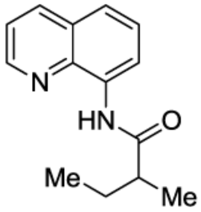
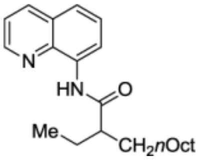
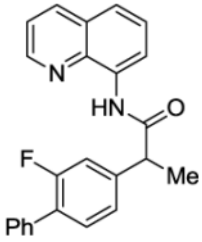
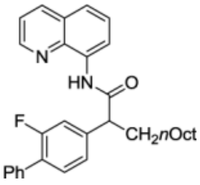
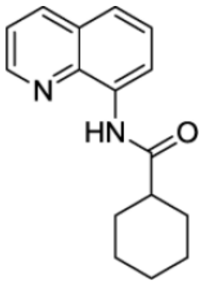
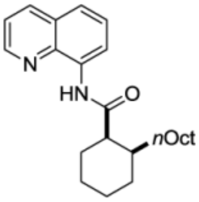
Entry	Amide	Alkyl Halide	Product	Yield
11	**12**			70%
12	**12**			94%
13	**12**			90%
14	**12**			86%
15	**12**			74%
16	**12**			25%

[a] Pd(OAc)$_2$ (5 mol %), K$_2$CO$_3$ (2.5 equiv), substrate (0.74 mmol), pivalic acid (2 mol %), alkyl bromide or iodide (3–4 equiv), *t*-amyl–OH solvent, 12–96 h at 110– °C. Yields are isolated yields. Please see Experimental section for details.

Table 6

Alkylation of 8-Aminoquinoline Amide sp^3 C-H Bonds

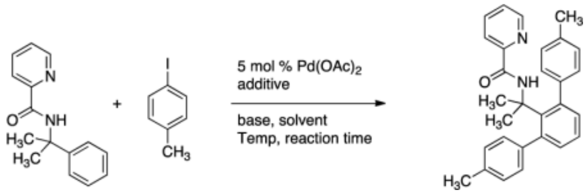
Entry	Amide	Alkyl Halide	Product	Yield
1	 **13**	EtI		78%
2	**13**	*n*BuI		
3	**13**	*n*OctI		52%
4	**13**	$Ph(CH_2)_2I$		64%
5	**13**			29%

Entry	Amide	Alkyl Halide	Product	Yield
6	**13**	*i*BuI		78%
7	**13**			60%
8		*n*OctI		40%
9		*n*OctI		45%
10		*n*OctI		15%

[a] Pd(OAc)$_2$ (5 mol %), K$_2$CO$_3$ (2.5 equiv), substrate (0.74 mmol), pivalic acid (2 equiv), alkyl bromide or iodide (4 equiv), *t*-amyl alcohol solvent, 24 h at 110 °C. Yields are isolated yields. Please see Experimental section for details.

Table 7

Optimization of Picolinamide Arylation[a]

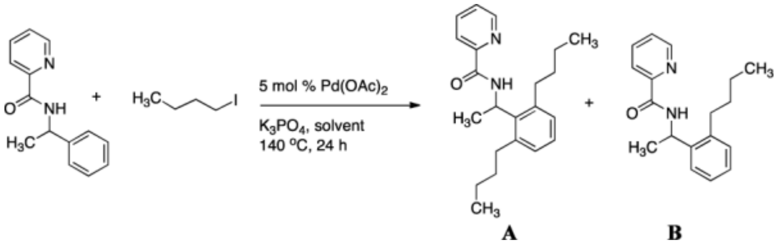


Entry	Reaction conditions	% GC Yield (isolated)
1	4 eq NaOAc, 2 mL MeCN, 60 °C, 16 h	0
2	4 eq NaOAc, 2 mL toluene, 140 °C, 16 h	10
3	4 eq CsOAc, 1.6 mL toluene, 0.4 mL MeCN, 140 °C, 16 h	30
4	2 eq K_3PO_4, 1.6 mL toluene, 0.4 mL MeCN, 140 °C, 16 h	15
5	2 eq Cs_2CO_3, 1.6 mL toluene, 0.4 mL MeCN, 140 °C, 16 h	15
6	3 eq K_3PO_4, 1.6 mL *t*-amyl alcohol, 0.4 mL H_2O, 90 °C, 16 h	70
7	3 eq K_2CO_3, 2 mL *t*-amyl alcohol, 90 °C, 20 h	80
8	4 eq K_2CO_3, 2 mL *t*-amyl alcohol, 110°C, 24 h	90 (86)
9	4 eq K_2CO_3, 2 mL *t*-amyl alcohol, 140°C, 24 h	80
10	4 eq CsOAc, 1 mL *t*-amyl alcohol, 110°C, 24 h	85
11	4 eq CsOAc, 1 mL t-amyl alcohol, 140°C, 24 h	90
12	10 % $CuBr_2$, 4 eq CsOAc, 1 mL t-amyl alcohol, 110°C, 24 hr	75 (70)
13	**10 % $CuBr_2$, 4 eq CsOAc, 1 mL t-amyl alcohol, 140°C, 24 h**	**99 (99)**

[a] a Dodecane as internal standard; amide (0.5 mmol), ArI (4 mmol).

Table 8

Alkylation of Picolinamides – Optimization of Solvent[a]

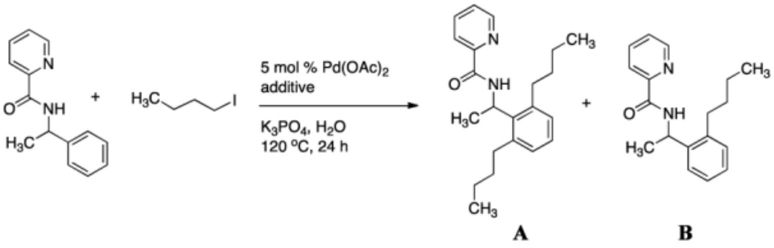


Entry	Solvent, 0.50 mL	% GC Yield	
		A	B
1	CF_3CH_2OH	26	19
2	$CF_3CH(OH)CF_3$	52	13
3	CH_3COOH	36	13
4	Piv-OH	20	5
5	H_2O, m-xylene	50	24
6	H_2O	47	23
7	**H_2O (0.15 mL)**	**50**	**14**

[a] Dodecane internal standard, amide (1 mmol), BuI (4 mmol)

Table 9

Alkylation of Picolinamides – Optimization of Additives[a]

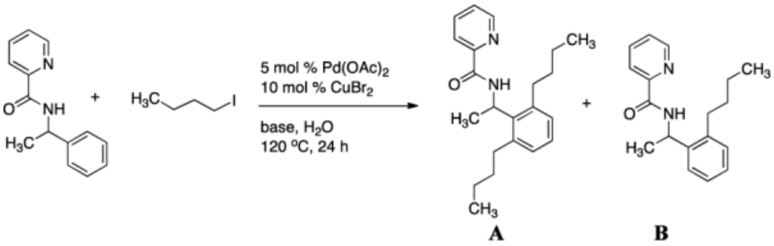


Entry	Additive	% GC Yield	
		A	B
1	No additive	45	15
2	**10 % $CuBr_2$**	**95**	**5**
3	20 % $CuBr_2$	76	14
4	10 % $Cu(NO_3)_2$	65	17
5	20 % $Cu(NO_3)_2$	95	4
6	10 % $CuCl_2$	55	20
7	10 % $CuCO_3$	58	19
8	10 % CuOAc	84	10
9	10 % MnO_2	70	17

[a] Dodecane internal standard; amide (0.5 mmol), BuI (4 mmol).

Table 10

Alkylation of Picolinamides – Optimization of Base[a]



Entry	Base	% GC Yield	
		A	B
1	K_3PO_4	95	5
2	Na_3PO_4	49	20
3	**K_2CO_3**	**99**	**0**
4	Na_2CO_3	54	20
5	Cs_2CO_3	28	10
6	CsOAc	7	14
7	K_2HPO_4	32	10
8	NaOAc	6	18

[a] Dodecane internal standard; amide (0.5 mmol), BuI (4 mmol).