

Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling

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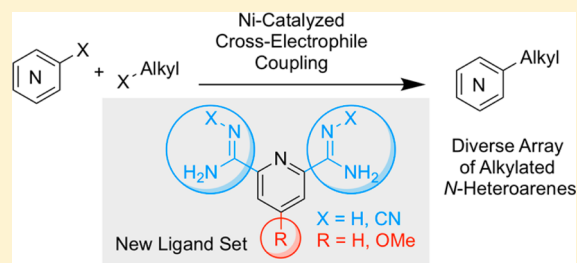
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S Supporting Information

ABSTRACT: Despite their importance, the synthesis of alkylated heterocycles from the cross-coupling of Lewis basic nitrogen heteroaryl halides with alkyl halides remains a challenge. We report here a general solution to this challenge enabled by a new collection of ligands based around 2-pyridyl-*N*-cyanocarboxamidines and 2-pyridyl-carboxamidines cores. Both primary and secondary alkyl halides can be coupled with 2-, 3-, and 4-pyridyl halides as well as other more complex heterocycles in generally good yields (41 examples, 69% average yield).



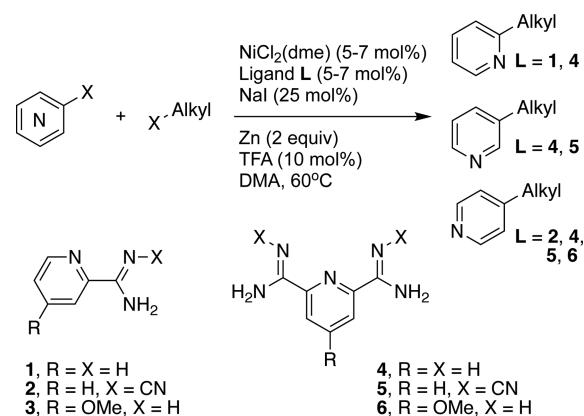
INTRODUCTION

Nitrogen heterocycles are common structures in pharmaceutical chemistry but often present challenges in transition-metal-catalyzed cross-coupling reactions.¹ While great advancements have been made in cross-coupling to make aryl–heteroaryl bonds (Csp²–Csp²), the corresponding synthesis of heteroaryl–alkyl bonds (Csp²–Csp³), while desired by industry, remains challenging.¹ Strategies starting from heteroaryl nucleophiles or alkyl nucleophiles have been examined in detail,² but the carbon nucleophile reagents can limit functional group compatibility, and fewer are commercially available than carbon electrophiles. Substrate-directed strategies, like Minisci chemistry³ or C–H functionalization,^{2b,4} can avoid the need for a prefunctionalized heteroarene, but the regiochemistry of the alkylation is dictated by the structure of the heteroarene. A useful compromise solution is the cross-coupling of two different electrophiles. Cross-electrophile coupling⁵ avoids the need for a carbon nucleophile, but reactions of heteroaryl halides with alkyl halides have not been extensively explored.^{6–8} The majority of examples with unactivated alkyl halides have been with simple 2-halopyridines, while Reisman has reported the coupling of mostly 3-halopyridines (and pyrimidines) with activated alkyl halides.⁷ A generalized approach with unactivated alkyl halides has not yet been realized but would greatly benefit drug discovery and development.⁹

Previously reported advances involved modification of the solvent and the use of additives but largely utilized the same small number of bipyridine and phenanthroline ligands that have been employed for simple aryl halides. This small ligand pool has been a limitation not only of reductive cross-electrophile coupling but also related photoredox cross-coupling¹⁰ and cross-couplings of redox active esters.¹¹

We recently reported a new approach to ligand discovery that uncovered pyridyl carboxamidines (**1–6**, Scheme 1) as

Scheme 1. General Heteroaryl Halide Alkylation



excellent ligands for cross-electrophile coupling.¹² In that study, the only tridentate ligand examined was **4**,¹³ and only 3-bromopyridines were examined. We considered that a slightly expanded set of ligands might allow a broad array of heteroaryl halides to be coupled. Herein, we show that a small collection of pyridyl carboxamidines suffices for the cross-coupling of a wide variety of basic nitrogen heterocycles with primary and secondary alkyl halides (Scheme 1).

Received: May 30, 2017

Published: July 6, 2017

RESULTS AND DISCUSSION

We began by examining substituted 4-halopyridines using a common alkyl halide (Table 1) using conditions developed

Table 1. Coupling of 4-Bromopyridine Derivatives

Entry	Ar-X	Product	Ligand: Isolated yield
1			1: 60% 2: 87% 3: 60% 4: 46% 5: 59% 6: 81%
2			5: 78% ^{a,b} 5: 84% ^{a,b,c,d}
3			2: 52% ^{c,e}
4			2: 75% ^{c,e}
5			2: 55% ^{c,e,f}

^a(3-Chloropropyl)benzene (**8b**) was used instead of **8a**. ^bReaction run at 80 °C. ^c2.0 equiv of alkyl halide was used. ^d7 mol % of NiCl₂(dme) and ligand were used. ^eNiL₂ (5 mol %) was used instead of NiCl₂-dme. ^fNaI was omitted.

previously by our groups.^{6b,11,14} 1-Bromo-3-phenylpropane **8a** was chosen due to the presence of a chromophore which allowed analysis of the reaction mixtures by HPLC methods. A survey of the ligands (entry 1) showed that a variety of ligands were effective, including *N*-cyano ligands **2** and **5** and *p*-methoxy-substituted ligand **6**. The optimal ligand for this reaction was the bidentate, *N*-cyano-substituted amidine **2**, prompting us to consider both the bi- and tridentate ligand series in our evaluations. In many reactions, the presence of a large amount of the byproduct arising from alkyl dimerization prompted us to switch from the 1-bromo-3-phenylpropane **8a** to 1-chloro-3-phenylpropane **8b**. This tended to minimize the formation of alkyl dimers and produced cross-coupled products in useful yields (>50%). This is a rare example of the use of an alkyl chloride in a cross-electrophile coupling reaction and the first example of an unactivated alkyl chloride being coupled with an aryl halide intermolecularly.¹⁵ These improvements have allowed the successful couplings of 4-chloro-, -bromo-, and -iodopyridines (entries 2–5).

Encouraged by these results, we expanded our survey to include both 3- and 2-halopyridines (Tables 2 and 3, respectively). All of the 3-bromopyridines examined coupled best with ligands **4** and **5**. While the reaction of simple 3-bromopyridine using ligand **4** gave the cross-coupled product in

Table 2. Coupling of 3-Bromopyridine Derivatives

Ar-X	Alk-X	Product	Ligand: Yield
	X = Br		4 : 93% 5 : 65%
	X = Br		5 : 80%
	X = Cl X = Br		5 : R = I, 86% ^{a,b,c} 5 : R = Br, 64% ^{a,d}
	X = Cl		5 : 50% ^{a,d}
	X = Cl		5 : 56% ^{a,d}
	X = Cl		5 : 54% ^{a,d}
	X = Br		4 : 95%
	X = Br		4 : 74%
	X = Cl		5 : 52% ^{a,b}
	X = Cl		5 : 51% ^{a,b}

^a7 mol % NiCl₂(dme) and ligand were used. ^b2.0 equiv of alkyl halide was used. ^cNaI was omitted. ^d2 equiv of alkyl halide was used at 80 °C.

excellent yield (Table 2, **11a**), functionalized 3-bromopyridines generally performed best with the new *N*-cyano-substituted ligand **5** (**11b–f**). In general, substitution with electron-donating groups gave higher yields, providing cross-coupled products in 80–86% yield.

Besides 3-halopyridines, several related heterocycles with additional nitrogen atoms also coupled effectively under these conditions (**11g–j**). This is in contrast to the use of bipyridine ligands, which provided low yields due to competing hydrodehalogenation and dimerization of the heteroaryl halide. While all of these cores are prevalent in the patent literature, we could find only a couple examples of alkylative cross-couplings with 6-halo[1,2,4]triazolo[1,5-*a*]pyridines (**11h**, 540 patents, three references with alkylative cross-coupling),¹⁶ 3-halo-1,5-naphthyridines (**11i**, 630 patents, two references with alkylative cross-coupling),¹⁷ and 6-halo-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridines (**11j**, 264 patents, one reference with alkylative cross-coupling).¹⁸ The few literature examples all used preformed organometallic reagents (zinc or boron) or enolates

Table 3. Coupling of 2-Bromopyridine Derivatives

Entry	Ar-X	Product	Ligand: Isolated yield
1			4: 46% 5: 50% 1: 85% ^{a,b}
2			5: 64% ^{c,d} 1: 76% ^{a,b}
3			1: 77% ^{a,b}
4			1: 65% ^{a,b}
5			1: 83% ^{a,b,e}
6			1: 90% ^{a,b}

^aNiI₂ was used in place of NiCl₂(dme). ^b2 equiv of **8a** was used. ^c(3-Chloropropyl)benzene (**8b**) was used instead of **8a**, and the reaction temperature was 80 °C. ^d7 mol % of NiCl₂(dme) and ligand were used. ^eReaction run at 40 °C.

instead of alkyl halides, demonstrating the potential of this new methodology to impact medicinal chemistry.

Successful coupling of pyridines in the 2-position occurred exclusively through the bromopyridine. In contrast to the other pyridines and our previous results,¹⁰ simple 2-pyridylcarboxamidine **1** was the best ligand. Yields could be further improved by increasing the amount of alkyl bromide to 2 equiv from 1.2 equiv. These results represent a large improvement over the previously reported coupling of 2-chloropyridines.^{6b}

To further demonstrate the utility of this reaction, we tested a variety of other substituted primary and secondary alkyl bromide coupling partners with functionality of use in medicinal chemistry (Table 4) using a minimal number of ligands. Synthetically useful yields could be obtained in all cases with ligands **1**, **2**, and **4**, despite the challenging nature of the substrate pairs chosen. Because the optimal ligand for a reaction depends on the structure and reactivity of the alkyl halide as well as the heteroaryl halide, it is difficult to make generalizations. At this time, ligand **4** appears to be the most general of the six, and ligand **3**, which was superior for difficult aryl bromides in our previous study,¹¹ was not among the best in this study of heteroaryl halides.

While isomerization of secondary alkyl groups to form primary alkylated products is a common problem in cross-coupling,¹⁹ we did not observe any isomerization in the coupling of *sec*-butyl bromide to form **14n**.^{13a}

Finally, not all tested heterocycles provided acceptable yields under these conditions: bromopyrazoles and bromoimidazoles

Table 4. Couplings with Functionalized Alkyl Halides

14a 1: 50% ^a	14b 1: 43%; 4: 62%	14c 1: 77% ^a ; 4: 73%	
14d 1: 74% ^a ; 4: 38%	14e 4: 49% ^b	14f 4: 49% ^b	
14g 4: 58%	14h 4: 82%	14i 4: 67%	
14j 4: 55% ^c	14k 4: 53%	14l 4: 64%	14m 4: 70%
14n 4: 58% ^b	14o 4: 72% ^c	14p 4: 72%	14q 2: 54% ^{a,d} ; 4: 56% ^d
14r 4: 86%	14s 2: 62% ^a ; 4: 54%	14t 2: 61% ^a ; 4: 93%	

^aNiI₂ was used in place of NiCl₂(dme). ^b2 equiv of alkyl halide was used. ^cCommercial chloromethyl pivalate was used. ^d1.5 equiv of alkyl halide was used.

provided low yields of the cross-coupled product (<50%). At this time, we hypothesize that this difference is related to the differences in the electronics of the corresponding heteroarylnickel(II) complexes¹³ or competing insertion of zinc into the heteroaryl-X bond.²⁰

CONCLUSIONS

This work, along with our initial report,¹⁰ shows that three to six ligands suffice to couple a broad range of aryl and heteroaryl halides with alkyl halides under a standard set of conditions. Notably, this work demonstrates that *N*-cyanocarboxamidine ligands can, in some cases, be superior to unsubstituted carboxamidine ligands. We anticipate that these catalysts will also prove useful for the growing number of reactions that use

bipyridine-ligated nickel catalysts.⁹ Studies to understand why these *N*-cyanocarboximidine catalysts perform better are ongoing.²¹

EXPERIMENTAL SECTION

General Information. All starting materials and solvents were purchased from Alfa Aesar, Aldrich, Acros, or TCI chemical companies or from the storehouse of Asychem Laboratories, Inc., and used as received. Ligands 1–4 were synthesized according to the known literature procedures.¹² ¹H and ¹³C NMR spectra were recorded on Varian Inova 500, Varian Mercury Plus 400, and Varian Mercury Plus 300 instruments, and the chemical shifts (δ) are expressed in parts per million relative to tetramethylsilane or residual solvent as internal standards. Proton magnetic resonance (¹H NMR) spectra were recorded at 500 or 400 MHz. Carbon magnetic resonance (¹³C NMR) spectra were recorded at 126 or 101 MHz. Fluorine magnetic resonance (¹⁹F NMR) spectra were recorded at 376 or 282 MHz, and the chemical shifts (δ) are expressed in parts per million relative to FCCL₃ as an internal standard. Melting points (mp) were determined using an open melting point capillary and are uncorrected. LC–MS was performed on an Agilent 1260 LC with an Agilent 6230 mass spectrometer (electrospray ionization, ESI) eluting with 0.05% trifluoroacetic acid in H₂O and 0.05% trifluoroacetic acid in CH₃CN.

Synthesis of (2Z,6Z)-N',N'-6-Dicyanopyridine-2,6-bis(carboximidamide) (5). To a 500 mL flask equipped with magnetic stirbar and N₂ purge were added, in order, dry methanol (200 mL), pyridine-2,6-dicarbonitrile (10 g, 77 mmol, 1.0 equiv), and 20 wt % sodium methoxide solution in methanol (2.1 g, 7.7 mmol, 0.10 equiv). The mixture was stirred for 4 h before solid cyanamide (95% potency, 10.3 g, 232 mmol, 3.00 equiv) was added, and the mixture was allowed to reflux for 6 h. The reaction mixture was then cooled to rt, the slurry was filtered, and the filtrate was dried under a stream of N₂ to give crude product. This material was stirred in 200 mL of hot methanol. The solid was collected on a Büchner funnel and dried on the funnel with an N₂ stream to give pure (2Z,6Z)-N',N'-6-dicyanopyridine-2,6-bis(carboximidamide) (14.5 g, 67.8 mmol, 88% yield) as a white solid. Mp > 300 °C. ¹H NMR (401 MHz, DMSO): δ 9.94 (br, 2H), 9.14 (br, 2H), 8.38 (d, *J* = 7.9 Hz, 2H), 8.19 (t, *J* = 7.9 Hz, 1H). ¹³C NMR (101 MHz, DMSO): δ 164.5, 147.4, 139.8, 125.6, 116.1. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₈H₈N₇ 214.0841, found 214.0836.

Synthesis of 4-Methoxyppyridine-2,6-bis(carboximidamide) Dihydrochloride (6). To a 250 mL flask equipped with magnetic stirbar and N₂ purge were sequentially added dry methanol (200 mL), 4-methoxyppyridine-2,6-dicarbonitrile (5.0 g, 31 mmol, 1.0 equiv), and 20 wt % sodium methoxide solution in methanol (0.85 g, 3.1 mmol, 0.10 equiv). The resulting mixture was stirred for 4 h before ammonium chloride (3.3 g, 63 mmol, 2.0 equiv) was added, and the mixture was stirred at rt overnight. The resulting slurry was filtered. The filtrate was concentrated to ~5 volumes and cooled to precipitate the product. This material was collected on a Büchner funnel and dried under a stream of N₂ to give crude product, pyridine-2,6-dicarboximidamide, as a white solid. This material was stirred in refluxing ethanol (40 volumes), collected on a Büchner funnel, and again dried under an N₂ stream to afford pure 4-methoxyppyridine-2,6-dicarboximidamide (4.3 g, 16 mmol, 52% yield). Mp: 248–250 °C dec. ¹H NMR (401 MHz, DMSO): δ 10.19 (br, 4H), 9.79 (br, 4H), 8.53 (s, 2H), 4.09 (s, 3H). ¹³C NMR (101 MHz, DMSO): δ 168.5, 160.4, 145.3, 113.7, 57.7. HRMS (ESI-TOF) (*m/z*): of free base [M + H]⁺ calcd for C₈H₁₂N₅O 194.1042, found 194.1023.

General Procedure for the Nickel-Catalyzed Cross-Electrophile Coupling of Alkyl Halides with Heteroaryl Halides. To a 25 mL test tube in an EZMax Reactor equipped with a small football-shaped magnetic stirbar and N₂ bubbler were added, in the following order, DMAc (10 mL, 20 mL/g), ligand (0.05 equiv), NiCl₂(DME) (0.05 equiv), sodium iodide (0.25 equiv), aryl halide (0.50 g), alkyl halide (1.20 equiv), zinc metal powder (<10 μ m, 2.00 equiv), and trifluoroacetic acid (0.10 equiv). The vial was capped, the atmosphere made inert, and the reaction mixture was heated to 60 °C with stirring (500 rpm) for several hours. Upon reaction completion (judged by

HPLC or TLC), the reaction mixture was filtered through a Celite pad, and the pad was washed with ethyl acetate (2 \times 12 mL). The filtrate was then washed with 5% aq NH₄OH (2 \times 20 mL). The organic layer was washed with brine (20 mL), dried over MgSO₄, and filtered to remove the drying agent. The resulting filtrate was then concentrated in vacuo (80 mmHg, 45 °C) to a residue and diluted with dichloromethane (3 mL). This solution was wet-loaded onto a silica column for flash chromatographic separation with a gradient between 5 and 30% ethyl acetate in heptane. The fractions containing product were then concentrated to dryness and analyzed.

2-Methyl-4-(3-phenylpropyl)pyridine (9a). Ligand 1: 17 h, 60% yield. Ligand 2: 16 h, 87% yield. Ligand 3: 17 h, 60% yield. Ligand 4: 29 h, 46% yield. Ligand 5: 28 h, 59% yield. Ligand 6: 17 h, 81% yield. Yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.37 (d, *J* = 5.0 Hz, 1H), 7.29 (m, 2H), 7.19 (m, 3H), 6.97 (s, 1H), 6.91 (d, *J* = 4.7 Hz, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.52 (s, 3H), 1.98–1.92 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 158.1, 151.4, 149.0, 148.8, 141.6, 128.4, 128.3, 125.9, 125.8, 123.4, 123.3, 121.0, 120.9, 35.2, 34.5, 31.7. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₈N 212.1439, found 212.1436.

2,6-Dimethyl-4-(3-phenylpropyl)pyridine (9b). Ligand 4: 16 h, 78% yield (from 2.0 equiv of (3-chloropropyl)benzene); 16 h, 84% yield (from 2.0 equiv of (3-chloropropyl)benzene at 80 °C, 7 mol % catalyst). Yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 7.29 (m, 2H), 7.19 (m, 3H), 6.78 (s, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.55 (t, *J* = 7.7 Hz, 2H), 2.48 (s, 6H), 1.96–1.90 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 157.5, 151.64, 141.8, 128.4, 128.3, 125.9, 120.4, 35.4, 34.5, 31.8, 24.3. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₆H₂₀N 226.1596, found 226.1595.

4-(3-Phenylpropyl)picolinonitrile (9c). Ligand 2: 30 h, 52% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.58 (d, *J* = 5.1 Hz, 1H), 7.51 (s, 1H), 7.30 (m, 3H), 7.17 (m, 3H), 2.68 (m, 4H), 2.02–1.96 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 152.9, 150.9, 140.9, 133.9, 128.6, 128.5, 128.3, 127.0, 126.2, 117.3, 35.1, 34.2, 31.4. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₅N₂ 223.1235, found 223.1223.

4-(3-Phenylpropyl)pyridine (9d). Ligand 2: 24 h, 75% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.48 (d, *J* = 4.9 Hz, 2H), 7.29 (m, 2H), 7.19 (m, 3H), 7.09 (d, *J* = 4.9 Hz, 2H), 2.64 (m, 4H), 1.99–1.93 (m, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 151.1 149.6, 141.5, 128.3, 125.9, 123.8, 35.2, 34.5, 31.7. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₄H₁₆N 198.1283, found 198.1275.

2-Fluoro-4-(3-phenylpropyl)pyridine (9e). Ligand 2: 6 h, 55% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂; NaI is omitted). Yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.09 (d, *J* = 5.1 Hz, 1H), 7.29 (m, 2H), 7.21 (m, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 4.3 Hz, 1H), 6.73 (s, 1H), 2.66 (t, *J* = 7.0 Hz, 4H), 2.00–1.94 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 164.1 (d, *J* = 235.6 Hz), 157.3 (d, *J* = 7.6 Hz), 147.3 (d, *J* = 12.6 Hz), 141.3, 128.4, 128.3, 126.0, 121.6, 109.1 (d, *J* = 36.5 Hz), 35.2, 34.4, 31.5. ¹⁹F NMR (377 MHz, CDCl₃): δ 62.9. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₄H₁₅FN 216.1189, found 216.1180.

3-(3-Phenylpropyl)pyridine (11a). Ligand 4: 19 h, 93% yield. Ligand 5: 21 h, 65% yield. Pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.44 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.20–7.17 (m, 4H), 2.65 (m, 4H), 1.97 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 149.9, 147.3, 141.6, 137.3, 135.6, 128.3 (2), 125.8, 123.2, 35.2, 32.5, 32.3. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₄H₁₆N 198.1283, found 198.1270.

2-Methoxy-3-(3-phenylpropyl)pyridine (11b). Ligand 5: 70 h, 80% yield. Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, *J* = 4.2 Hz, 1H), 7.33 (d, *J* = 6.6 Hz, 1H), 7.26 (m, 2H), 7.17 (m, 3H), 6.77 (dd, *J* = 6.6, 4.2 Hz, 1H), 3.93 (s, 3H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.95–1.88 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 162.6, 144.6, 142.7, 138.0, 128.8 (2), 126.2, 125.2, 117.0, 53.6, 36.0, 30.9, 30.0. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₈NO 228.1388, found 228.1386.

2-Methoxy-5-(3-phenylpropyl)pyridine (11c). Ligand 5: 18 h, 86% yield (from 5-iodo-2-methoxyppyridine and 2.0 equiv of (3-

chloropropyl)benzene, 7 mol % catalysts; NaI is omitted); From 5-bromo-2-methoxypyridine, 22 h, 64% yield (from 2.0 equiv of (3-bromopropyl)benzene at 80 °C, 7 mol % catalysts). Colorless oil. ¹H NMR (401 MHz, CDCl₃): δ 7.97 (d, *J* = 2.3 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.28 (m, 2H), 7.18 (m, 3H), 6.68 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 2.64 (t, *J* = 8.0 Hz, 2H), 2.56 (t, *J* = 8.0 Hz, 2H), 1.95–1.87 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 162.6, 146.0, 141.9, 138.9, 123.0, 128.4, 128.3, 125.8, 110.4, 53.3, 35.1, 32.8, 31.5. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₈NO 228.1388, found 228.1384.

2-Fluoro-5-(3-phenylpropyl)pyridine (11d). Ligand 5: 18 h, 50% yield (from 2.0 equiv of (3-chloropropyl)benzene at 80 °C, 7 mol % catalysts). Pale yellow oil. ¹H NMR (401 MHz, CDCl₃): δ 8.01 (d, *J* = 0.7 Hz, 1H), 7.58 (td, *J* = 8.4, 2.5 Hz, 1H), 7.29 (m, 2H), 7.19 (m, 3H), 6.84 (dd, *J* = 8.4, 2.5 Hz, 1H), 2.64 (m, 4H), 1.98–1.91 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 162.1 (d, *J* = 258 Hz), 147.0 (d, *J* = 17.6 Hz), 141.5, 141.0 (d, *J* = 10.8 Hz), 134.9 (d, *J* = 1.2 Hz), 128.4, 128.3, 126.0, 109.0 (d, *J* = 46.6 Hz), 35.1, 32.6, 31.4. ¹⁹F NMR (377 MHz, CDCl₃): δ 59.9. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₄H₁₅FN 216.1189, found 216.1178.

5-(3-Phenylpropyl)pyridin-2-yl Di-tert-butylcarbamate (11e). Ligand 5: 24 h, 56% yield (from 2.0 equiv of (3-chloropropyl)benzene at 80 °C, 7 mol % catalysts). White solid. Mp: 80–82 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.31 (s, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.29 (m, 2H), 7.20–7.13 (m, 4H), 2.65 (m, 4H), 1.99–1.93 (m, 2H), 1.43 (s, 18H). ¹³C NMR (126 MHz, CDCl₃): δ 151.4, 150.3, 148.6, 141.6, 137.8, 136.3, 135.7, 128.4, 125.9, 121.6, 82.9, 35.1, 32.5, 31.9, 27.9. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₂₄H₃₃N₂O₄ 413.2440, found 413.2420.

N-(5-(3-Phenylpropyl)pyridin-2-yl)acetamide (11f). Ligand 5: 24 h, 56% yield (from 2.0 equiv of (3-chloropropyl)benzene at 80 °C, 7 mol % catalysts). White solid. Mp: 118–120 °C. ¹H NMR (500 MHz, CDCl₃): δ 9.10 (s, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.08 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.28 (m, 2H), 7.19 (m, 3H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.19 (s, 3H), 1.94–1.91 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 168.7, 149.8, 147.1, 141.6, 138.4, 133.4, 128.3 (2), 125.9, 114.0, 35.1, 32.6, 31.8, 24.5. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₆H₁₉N₂O 255.1497, found 255.1486.

5-(3-Phenylpropyl)pyrimidine (11g). Ligand 4: 19 h, 95% yield. Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 9.07 (s, 1H), 8.57 (s, 2H), 7.30 (m, 2H), 7.19 (m, 3H), 2.69 (t, *J* = 7.6 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 1H), 2.02–1.96 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 156.7, 156.6, 141.0, 134.9, 128.4, 128.3, 126.0, 35.1, 32.0, 29.7. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₃H₁₅N₂ 199.1235, found 199.1232.

6-(3-Phenylpropyl)[1,2,4]triazolo[1,5-a]pyridine (11h). Ligand 4: 24 h, 74% yield. Pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.38 (s, 1H), 8.30 (s, 1H), 7.68 (d, *J* = 9.1 Hz, 1H), 7.37 (dd, *J* = 9.1, 1.4 Hz, 1H), 7.30 (m, 2H), 7.20 (m, 3H), 2.70 (m, 4H), 2.05–1.99 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 153.4, 149.1, 141.1, 131.3, 128.2 (2), 128.1, 128.1, 126.1, 125.8, 115.9, 34.8, 31.8, 31.5. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₆N₃ 238.1344, found 238.1340.

3-(3-Phenylpropyl)-1,5-naphthyridine (11i). Ligand 4: 17 h, 52% yield (from 2.0 equiv of (3-chloropropyl)benzene, 7 mol % catalysts). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.96 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.84 (d, *J* = 1.8 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 7.60 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.30 (m, 2H), 7.21 (m, 3H), 2.90 (t, *J* = 7.7 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.15–2.08 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 152.8, 151.1, 143.8, 142.1, 141.4, 138.8, 137.1, 135.4, 128.4, 128.4, 126.0, 123.6, 35.1, 32.5, 32.2. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₇H₁₇N₂ 249.1392, found 249.1375.

1-Methyl-6-(3-phenylpropyl)-1H-pyrazolo[4,3-b]pyridine (11j). Ligand 4: 24 h, 51% yield (from 2.0 equiv of (3-chloropropyl)benzene, 7 mol % catalysts). Pale yellow oil. ¹H NMR (401 MHz, CDCl₃): δ 8.43 (d, *J* = 1.4 Hz, 1H), 8.17 (s, 1H), 7.49 (s, 1H), 7.30 (m, 2H), 7.20 (m, 3H), 4.05 (s, 3H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.05 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 147.0, 141.5, 140.3, 135.0, 133.3, 133.0, 128.5, 128.4, 128.3, 125.9, 115.5, 35.7, 35.3,

32.9. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₆H₁₈N₃ 252.1501, found 252.1486.

2-(3-Phenylpropyl)pyridine (13a). Ligand 4: 18 h, 46% yield. Ligand 5: 22 h, 50% yield. Ligand 1: 5 h, 85% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.53 (d, *J* = 4.4 Hz, 1H), 7.57 (td, *J* = 7.7, 1.4 Hz, 1H), 7.27 (m, 2H), 7.18 (m, 3H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 7.2, 5.2 Hz, 1H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.10–2.04 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 161.9, 149.2, 142.1, 136.3, 128.4, 128.3, 125.7, 122.7, 121.0, 37.9, 35.5, 31.5. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₄H₁₆N 198.1283, found 198.1278.

2-Methoxy-6-(3-phenylpropyl)pyridine (13b). Ligand 5: 22 h, 64% yield (from 2.0 equiv of (3-chloropropyl)benzene, 7 mol % catalyst). Ligand 1: 20 h, 76% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.44 (t, *J* = 7.7 Hz, 1H), 7.27 (m, 2H), 7.18 (m, 3H), 6.68 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 2.07 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 159.7, 142.4, 138.6, 128.5, 128.2, 125.7, 115.2, 107.3, 53.1, 37.2, 35.4, 30.8. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₈NO 228.1388, found 228.1376.

2-(Benzyloxy)-6-(3-phenylpropyl)pyridine (13c). Ligand 1: 26 h, 77% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.45 (m, 3H), 7.35 (m, 2H), 7.28 (m, 3H), 7.18 (d, *J* = 7.4 Hz, 3H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.38 (s, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 2.09–2.03 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 163.1, 159.6, 142.4, 138.7, 137.8, 128.5, 128.3, 128.3, 128.1, 127.6, 125.7, 115.4, 107.9, 67.3, 37.2, 35.4, 30.8. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₂₁H₂₁NO 304.1701, found 304.1693.

5-Methoxy-2-(3-phenylpropyl)pyridine (13d). Ligand 1: 22 h, 65% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.23 (d, *J* = 2.4 Hz, 1H), 7.26 (m, 2H), 7.17 (m, 3H), 7.10 (m, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 3.80 (s, 3H), 2.77 (t, *J* = 7.7 Hz, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.06–2.00 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 153.88, 142.10, 136.32, 128.35, 128.17, 125.61, 122.69, 121.12, 55.47, 55.45, 36.73, 35.39, 31.56. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₈NO 228.1388, found 228.1378.

5-Fluoro-2-(3-phenylpropyl)pyridine (13e). Ligand 1: 20 h, 83% yield (from 2.0 equiv of (3-bromopropyl)benzene at 40 °C, 5 mol % NiL₂). White solid. Mp: 98–100 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.37 (d, *J* = 2.1 Hz, 1H), 7.26 (m, 3H), 7.18–7.15 (m, 3H), 7.08 (dd, *J* = 8.5, 4.3 Hz, 1H), 2.80 (t, *J* = 7.7 Hz, 2H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.07–2.01 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 157.9 (d, *J* = 253.3 Hz), 157.8 (d, *J* = 8.8 Hz), 141.8, 137.1 (d, *J* = 20.4 Hz), 128.3, 128.2, 125.7, 123.3, 122.9 (d, *J* = 17.6 Hz), 36.9, 35.3, 31.4. ¹⁹F NMR (377 MHz, CDCl₃): δ 0.5. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₄H₁₅FN, 216.1189, found 216.1179.

4-Methyl-2-(3-phenylpropyl)pyridine (13f). Ligand 1: 15 h, 90% yield (from 2.0 equiv of (3-bromopropyl)benzene, 5 mol % NiL₂). Pale yellow oil. ¹H NMR (401 MHz, CDCl₃): δ 8.37 (d, *J* = 5.0 Hz, 1H), 7.26 (m, 2H), 7.20–7.17 (m, 3H), 6.94 (s, 1H), 6.91 (d, *J* = 5.0 Hz, 1H), 2.78 (t, *J* = 8.0 Hz, 2H), 2.68 (t, *J* = 8.0 Hz, 2H), 2.30 (s, 3H), 2.09–2.02 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 161.7, 149.0, 147.2, 142.2, 128.4, 128.2, 125.7, 123.6, 122.0, 37.8, 35.6, 31.5, 20.9. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₁₅H₁₈N 212.1439, found 212.1428.

5-Fluoro-2-(oxetan-3-yl)pyridine (14a). Ligand 1: 14 h, 50% yield (NiL₂ was used in place of NiCl₂(dme)). White solid. Mp: 118–120 °C. ¹H NMR (401 MHz, CDCl₃): δ 8.49 (d, *J* = 2.8 Hz, 1H), 7.39 (td, *J* = 8.4, 2.9 Hz, 1H), 7.27 (dd, *J* = 8.6, 4.3 Hz, 1H), 5.06 (dd, *J* = 8.4, 5.9 Hz, 2H), 4.91 (t, *J* = 6.2 Hz, 2H), 4.42–4.34 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 158.3 (d, *J* = 255 Hz), 156.2 (d, *J* = 4.0 Hz), 137.7 (d, *J* = 23.2 Hz), 123.2 (d, *J* = 18.2 Hz), 122.3 (d, *J* = 4.0 Hz), 77.0, 41.0. ¹⁹F NMR (377 MHz, CDCl₃): δ 2.5. HRMS (ESI-TOF) (*m/z*): [M + H]⁺ calcd for C₈H₉FNO 154.0668, found 154.0658.

2-(4-Methylpyridin-2-yl)ethyl benzoate (14b). Ligand 1: 21 h, 43% yield. Ligand 4: 10 h, 62% yield. Colorless oil. ¹H NMR (500 MHz,

CDCl₃): δ 8.41 (d, J = 5.0 Hz, 1H), 7.99 (d, J = 7.3 Hz, 2H), 7.53 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.06 (s, 1H), 6.97 (d, J = 5.0 Hz, 1H), 4.70 (t, J = 6.9 Hz, 2H), 3.21 (t, J = 6.8 Hz, 2H), 2.31 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 166.4, 157.7, 149.2, 147.4, 132.8, 130.2, 129.5, 128.2, 124.3, 122.6, 64.1, 37.3, 20.9. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₅H₁₆NO₂ 242.1181, found 242.1170.

2-(2-(4-Methylpyridin-2-yl)ethyl)isoindoline-1,3-dione (14c). Ligand 1: 15 h, 77% yield (NiI₂ was used in place of NiCl₂(dme)). Ligand 4: 15 h, 73% yield. White solid. Mp: 94–96 °C. ¹H NMR (401 MHz, CDCl₃): δ 8.36 (d, J = 5.0 Hz, 1H), 7.83 (dd, J = 5.5, 3.0 Hz, 2H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 7.01 (s, 1H), 6.95 (d, J = 5.0 Hz, 1H), 4.09 (t, J = 8.0 Hz, 2H), 3.13 (t, J = 8.0 Hz, 2H), 2.29 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 167.9, 157.8, 149.0, 147.3, 133.6, 131.9, 123.9, 123.0, 122.5, 37.6, 36.4, 20.7. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₆H₁₅N₂O₂ 267.1134, found 267.1123.

Ethyl 4-(4-Methylpyridin-2-yl)butanoate (14d). Ligand 1: 21 h, 74% yield (NiI₂ was used in place of NiCl₂(dme)). Ligand 4: 24 h, 38% yield. Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.38 (d, J = 5.0 Hz, 1H), 6.98 (s, 1H), 6.94 (d, J = 5.0 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.32 (s, 3H), 2.06 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 173.3, 160.8, 148.8, 147.4, 123.7, 122.1, 60.1, 37.1, 33.6, 24.8, 20.9, 14.1. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₂H₁₈NO₂ 208.1338, found 208.1324.

4-Methyl-2-(oxetan-3-yl)pyridine (14e). Ligand 4: 22 h, 49% yield (from 2.0 equiv of 3-bromooxetane). Colorless oil. ¹H NMR (401 MHz, CDCl₃): δ 8.47 (d, J = 5.0 Hz, 1H), 7.11 (s, 1H), 7.01 (d, J = 5.0 Hz, 1H), 5.06 (dd, J = 8.4, 5.8 Hz, 2H), 4.93 (t, J = 7.5 Hz, 2H), 4.37–4.30 (m, 1H), 2.36 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 160.1, 149.2, 147.7, 122.9, 122.3, 76.9, 41.5, 20.9. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₉H₁₁NO 150.0919, found 150.0914.

2-Cyclopentyl-4-methylpyridine (14f). Ligand 4: 22 h, 49% yield (from 2.0 equiv of bromocyclopentane). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.38 (d, J = 5.0 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J = 5.0 Hz, 1H), 3.16–3.06 (m, 1H), 2.30 (s, 3H), 2.09–2.03 (m, 2H), 1.85–1.80 (m, 2H), 1.78–1.73 (m, 2H), 1.71–1.66 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 165.2, 148.7, 147.0, 122.4, 121.8, 47.7, 33.4, 25.7, 20.9. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₁H₁₆N 162.1283, found 162.1277.

2-(6-Methoxy-pyridin-3-yl)ethyl Benzoate (14g). Ligand 4: 22 h, 58% yield. Colorless oil. ¹H NMR (401 MHz, CDCl₃): δ 8.09 (d, J = 2.3 Hz, 1H), 8.01 (m, 2H), 7.55–7.50 (m, 2H), 7.42 (dd, J = 10.7, 4.7 Hz, 2H), 6.71 (d, J = 8.5 Hz, 1H), 4.48 (t, J = 6.7 Hz, 2H), 3.92 (s, 3H), 3.00 (t, J = 6.7 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 166.4, 163.1, 146.6, 139.2, 132.9, 130.0, 129.5, 128.3, 126.0, 110.7, 65.1, 53.3, 31.5. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₅H₁₆NO₃ 258.1130, found 258.1113.

5-Cyclopentyl-2-methoxypyridine (14h). Ligand 4: 9 h, 82% yield. Colorless oil. ¹H NMR (401 MHz, CDCl₃): δ 8.02 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 8.5, 2.4 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 3.91 (s, 3H), 2.96–2.88 (m, 1H), 2.07–2.00 (m, 2H), 1.84–1.75 (m, 2H), 1.73–1.62 (m, 2H), 1.56–1.47 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 162.5, 144.9, 137.4, 134.0, 110.3, 53.1, 42.4, 34.4, 25.3. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₁H₁₆NO 178.1232, found 178.1217.

Ethyl 4-(6-methoxypyridin-3-yl)butanoate (14i). Ligand 4: 20 h, 67% yield. Colorless oil. ¹H NMR (401 MHz, CDCl₃): δ 7.97 (d, J = 2.4 Hz, 1H), 7.41 (dd, J = 8.5, 2.4 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 2.57 (t, J = 7.6 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.95–1.87 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 173.1, 162.7, 146.0, 138.8, 129.1, 110.4, 60.2, 53.1, 33.3, 31.1, 26.3, 14.1. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₂H₁₈NO₃ 224.1287, found 224.1272.

(6-Methoxypyridin-3-yl)methyl Pivalate (14j). Ligand 4: 17 h, 55% yield (from chloromethyl pivalate). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.16 (s, 1H), 7.57 (dd, J = 8.4, 2.5 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.04 (s, 2H), 3.94 (s, 3H), 1.20 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 178.3, 164.1, 146.8, 139.0, 124.8, 110.8, 63.4, 54.1,

38.7, 27.1. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₂H₁₈NO₃ 224.1287, found 224.1282.

5-Cyclohexyl-2-fluoropyridine (14k). Ligand 4: 40 h, 53% yield. Pale yellow oil. ¹H NMR (401 MHz, CDCl₃): δ 8.04 (s, 1H), 7.61 (td, J = 8.2, 2.4 Hz, 1H), 6.84 (dd, J = 8.4, 2.8 Hz, 1H), 2.59–2.48 (m, 1H), 1.86 (d, J = 8.3 Hz, 4H), 1.77 (d, J = 12.8 Hz, 1H), 1.44–1.34 (m, 4H), 1.28–1.23 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 162.1 (d, J = 237 Hz), 145.8 (d, J = 14.1 Hz), 140.6 (d, J = 5.0 Hz), 139.3 (d, J = 4.0 Hz), 109.1 (d, J = 37.4 Hz), 41.1, 34.3, 26.6, 25.8. ¹⁹F NMR (377 MHz, CDCl₃): δ 59.6. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₁H₁₅FN 180.1189, found 180.1186.

3-Cyclohexylpyridine (14l). Ligand 4: 21 h, 64% yield. Pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.49 (s, 1H), 8.44 (d, J = 4.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.8, 4.8 Hz, 1H), 2.53 (m, 1H), 1.85 (m, 4H), 1.76 (m, 1H), 1.46–1.35 (m, 4H), 1.30–1.21 (m, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 148.6, 147.0, 143.0, 134.3, 123.3, 41.9, 34.0, 26.5, 25.8. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₁H₁₆N 162.1283, found 162.1277.

2-Fluoro-5-(oxetan-3-yl)pyridine (14m). Ligand 4: 15 h, 70% yield. White solid. Mp: 70–72 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.16 (s, 1H), 8.00 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 8.4, 2.6 Hz, 1H), 5.13 (m, 2H), 4.71 (m, 2H), 4.29–4.23 (m, 1H). ¹³C NMR (126 MHz, CDCl₃): δ 162.7 (d, J = 239 Hz), 146.0 (d, J = 15.1 Hz), 139.2 (d, J = 7.6 Hz), 134.7 (d, J = 3.8 Hz), 109.7 (d, J = 37.8 Hz), 78.2, 36.9. ¹⁹F NMR (377 MHz, CDCl₃): δ 61.9. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₈H₉FNO 154.0668, found 154.0658.

5-sec-Butyl-2-methoxypyridine (14n). Ligand 4: 70 h, 58% yield (from 2 equiv of 2-bromobutane, 7 mol % catalyst). Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.5, 2.4 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 3.94 (s, 3H), 2.58 (qt, J = 7.0 Hz, 1H), 1.67–1.49 (m, 2H), 1.24 (d, J = 7.0 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 162.8, 145.4, 137.3, 135.3, 110.6, 53.4, 38.4, 31.1, 21.9, 12.2. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₀H₁₆NO 166.1226, found 166.1224.

(2-Methylpyridin-4-yl)methyl Pivalate (14o). Ligand 4: 17 h, 72% yield (from chloromethyl pivalate). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.48 (d, J = 5.0 Hz, 1H), 7.09 (s, 1H), 7.05 (d, J = 5.0 Hz, 1H), 5.08 (s, 2H), 2.57 (s, 3H), 1.27 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 178.0, 158.6, 149.3, 145.6, 121.1, 118.7, 64.1, 38.8, 27.1, 24.4. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₂H₁₈NO₂ 208.1338, found 208.1331.

4-Cyclopentyl-2-methylpyridine (14p). Ligand 4: 8 h, 72% yield. Yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.40 (s, 1H), 7.02 (s, 1H), 6.98 (d, J = 4.3 Hz, 1H), 2.97–2.90 (m, 1H), 2.53 (s, 3H), 2.09–2.04 (m, 2H), 1.85–1.77 (m, 2H), 1.74–1.65 (m, 2H), 1.61–1.54 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 158.0, 156.2, 148.8, 122.3, 119.8, 45.1, 33.8, 25.5, 24.3. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₁H₁₆N 162.1283, found 162.1278.

2-Methyl-4-(oxetan-3-yl)pyridine (14q). Ligand 2: 21 h, 56% yield (from 1.5 equiv of 3-bromooxetane, 5 mol % NiI₂). Ligand 4: 21 h, 56% yield (from 1.5 equiv of 3-bromooxetane). Yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 8.48 (d, J = 5.0 Hz, 1H), 7.19 (s, 1H), 7.13 (d, J = 5.0 Hz, 1H), 5.08 (dd, J = 8.2, 6.2 Hz, 2H), 4.73 (t, J = 6.3 Hz, 2H), 4.18–4.13 (m, 1H), 2.57 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 158.6, 150.5, 149.2, 121.3, 118.9, 77.4, 39.3, 24.1. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₉H₁₂NO 150.0919, found 150.0906.

2-(2-(2-Methylpyridin-4-yl)ethyl)isoindoline-1,3-dione (14r). Ligand 4: 9 h, 86% yield. White solid. Mp: 122–124 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.39 (d, J = 4.8 Hz, 1H), 7.84 (dd, J = 5.0, 3.3 Hz, 2H), 7.72 (dd, J = 5.0, 3.3 Hz, 2H), 7.06 (s, 1H), 6.99 (d, J = 4.8 Hz, 1H), 3.94 (t, J = 7.6 Hz, 2H), 2.97 (t, J = 7.6 Hz, 2H), 2.51 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 168.0, 158.6, 149.2, 147.0, 134.0, 131.9, 123.6, 123.3, 121.1, 38.1, 33.7, 24.3. HRMS (ESI-TOF) (m/z): [M + H]⁺ calcd for C₁₆H₁₅N₂O₂ 267.1134, found 267.1119.

Ethyl 4-(2-Methylpyridin-4-yl)butanoate (14s). Ligand 2: 56 h, 62% yield (NiI₂ was used in place of NiCl₂(dme)). Ligand 4: 70 h, 54% yield. Colorless oil. ¹H NMR (401 MHz, CDCl₃): δ 8.38 (d, J = 5.0 Hz, 1H), 6.98 (s, 1H), 6.92 (d, J = 5.0 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.61 (m, 2H), 2.52 (s, 3H), 2.32 (t, J = 7.4 Hz, 2H), 1.99–1.92 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃): δ

172.9, 158.2, 150.5, 148.9, 123.3, 120.9, 60.2, 34.2, 33.3, 25.3, 24.1, 14.1. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{12}H_{18}NO_2$ 208.1338, found 208.1322.

2-(2-Methylpyridin-4-yl)ethyl Benzoate (**14t**). Ligand 2: 22 h, 61% yield (NiI₂ was used in place of NiCl₂(dme)). Ligand 4: 7 h, 93% yield. White solid. Mp: 48–50 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.43 (d, J = 5.0 Hz, 1H), 7.99 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.08 (s, 1H), 7.02 (d, J = 5.0 Hz, 1H), 4.55 (t, J = 6.7 Hz, 2H), 3.03 (t, J = 6.7 Hz, 2H), 2.54 (s, 3H). ¹³C NMR (126 MHz, CDCl₃): δ 166.2, 158.4, 149.1, 147.1, 133.0, 129.9, 129.4, 128.3, 123.7, 121.2, 64.0, 34.4, 24.2. HRMS (ESI-TOF) (m/z): $[M + H]^+$ calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1163.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01334.

¹H and ¹³C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Research reported in this publication was supported in part by the National Institute of General Medical Sciences of the National Institutes of Health under Award No. R01GM097243 (D.J.W.). This work was influenced by the ongoing efforts of the Non-Precious Metal Catalysis Alliance between Pfizer, Boehringer-Ingelheim, Abbvie, and Asymchem. We thank James Gage (Asymchem) for useful discussions and Don Batesky (University of Rochester) for synthesis of key ligand intermediates.

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