JOC The Journal of Organic Chemistry

Note

Nickel-Catalyzed Cross-Electrophile Reductive Couplings of Neopentyl Bromides with Aryl Bromides

Soumik Biswas, Bo Qu, Jean-Nicolas Desrosiers, Younggi Choi, Nizar Haddad, Nathan K Yee, Jinghua J. Song, and Chris H Senanayake

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00549 • Publication Date (Web): 26 May 2020

Just Accepted

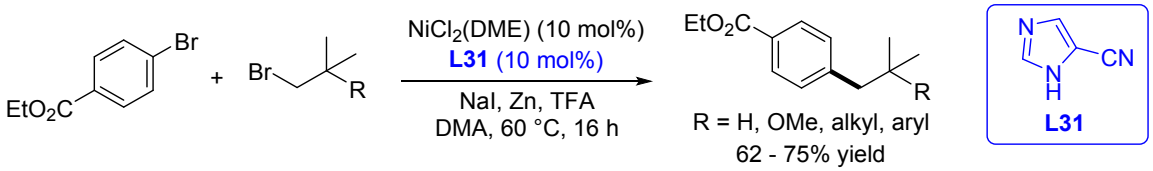
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Nickel-Catalyzed Cross-Electrophile Reductive Couplings of Neopentyl Bromides with Aryl Bromides

Soumik Biswas, Bo Qu*, Jean-Nicolas Desrosiers*,†, Younggi Choi‡, Nizar Haddad,

Nathan K. Yee, Jinghua J. Song, Chris H. Senanayake§

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, USA



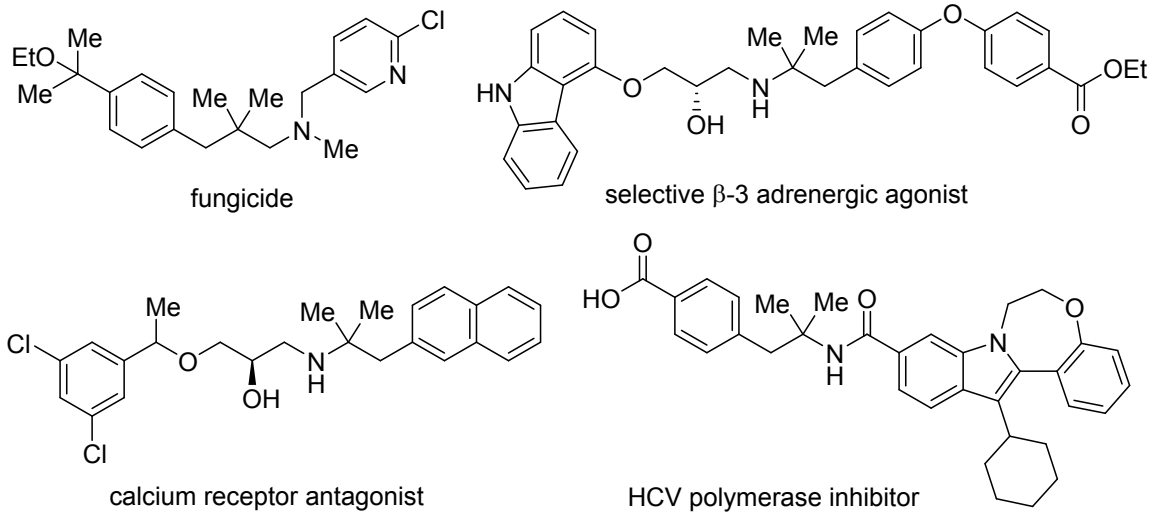
Abstract

5-Cyanoimidazole was identified as a new ligand for nickel-catalyzed cross-electrophile couplings by screening a diverse set of pharmaceutical compound library. A strategic screening approach led to the discovery of this novel ligand; which was successfully applied in the preparation of various alkylated arene products with good to high yields. Furthermore, the properties of this ligand allowed expanding the scope of reductive couplings to challenging substrates, such as sterically hindered neopentyl halides, which are known to generate motifs that are prevalent in biologically active molecules.

Ni-catalyzed cross-electrophile couplings have expanded the field of cross-coupling reactions which were dominated by typical palladium-catalyzed electrophile-nucleophile couplings. Such reductive transformation enables the direct coupling of two electrophiles between an sp^2-carbon and an sp^3-carbon without pre-functionalization of a requisite carbon nucleophile coupling partner.[1] Cross-electrophile coupling has become one of the most useful synthetic methods[2] to access sp^3-hybridized carbons in drug

molecules, which were correlated to improved biological and physicochemical properties comparing to the less saturated analogues.[3]

Nitrogen-based bidentate and tridentate ligands including carbenes,[4] bipyridines, 1,10-phenanthrolines[5], bisoxazoline[6] and Pybox[7] derivatives were proven to be effective ligands to facilitate nickel-catalyzed cross-electrophile reductive coupling reactions. Significant functional group tolerance was reported including substrates containing highly acidic protons such as alcohols and amines.[5b] Standard reaction conditions are chemoselective for electrophilic C-X bond in the presence of nucleophilic C-B, C-Si or C-Sn bonds,[5b] which in turn provide a handle for further functionalization. Ligands that complex nickel are essential for enabling the reactivity and selectivity of the desired cross-electrophile coupling reactions. However, unlike the diverse and large libraries of phosphine ligands, the development of nitrogen-based ligand libraries to complex first-row transition metals lags far behind. To speed up the ligand identification process and discover new ligand structures for effective Ni-catalyzed cross-electrophile coupling reactions, Hansen and Weix took a strategic approach of mining Pfizer's structurally diverse and nitrogen-heterocycle-rich discovery research compound libraries.[8] Indeed, these efforts enabled the identification of pyridyl carboxamidines as a new class of ligand, which effectively promotes the reductive coupling of two electrophiles with comparable or significantly improved yields.[8,9]



Scheme 1: Representative molecules containing neopentyl type fragments

Significant progress has been made to enable the coupling of Csp^2-Csp^3 for a direct synthesis of alkyl-aryl derivatives of biological importance. For example, neopentyl-type fragments are prevalent in biologically active molecules[11] due to their interesting sp^3 characters (Scheme 1). Despite their desirable properties, cross-coupling reactions involving alkyl halides with increased steric hindrance, such as neopentyl halides, remains a challenge. Low yields were reported from the coupling of aryl iodides and neopentyl iodides.[5a] Trace amount of product was detected with neopentyl bromide.[5b] Improved yield was realized for the synthesis of methyl 4-neopentylbenzoate under photoredox catalysis conditions with silyl radical activation of the neopentyl bromide.[10] To identify an effective ligand for the direct cross-electrophile coupling of neopentyl bromides and aryl bromides, we took a similar approach[8,12] mining Boehringer Ingelheim library of more than 2 million compounds (Figure 1).

The sub-structure search was first focused on bidentate ligand-like fragments including N-$(CH_2)_2$-N, N-$(CH_2)_3$-N and N-$(CH_2)_2$-O. Several filters[13] were applied including a starting point of molecular weight below 500 g/mol. Molecules containing undesired functional groups such as halides, isocyanates, acid chlorides were excluded (Figure 1). This resulted in 18,730 compounds that were considered for further clustering. Among these, a search of nitrogen-containing five-, or six-membered hereocycles narrowed down the selection to 28 compounds. Initial testing of these compounds as ligands for the reductive coupling of ethyl 4-bromobenzoate with (3-bromopropyl)benzene identified nitrile-containing imidazoles as a promising new class of ligand. Subsequent focused screens based on the initial hits led to the identification of 5-cyanoimidazole as an effective new ligand for Ni-catalyzed cross-electrophile couplings. Furthermore, 5-cyanoimidazole was found effective for the reductive coupling of challenging neopentyl halides with aryl halides.

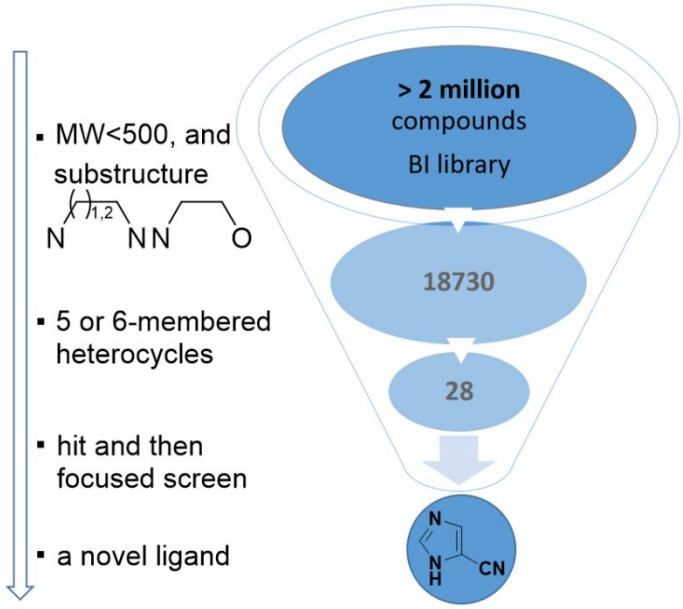
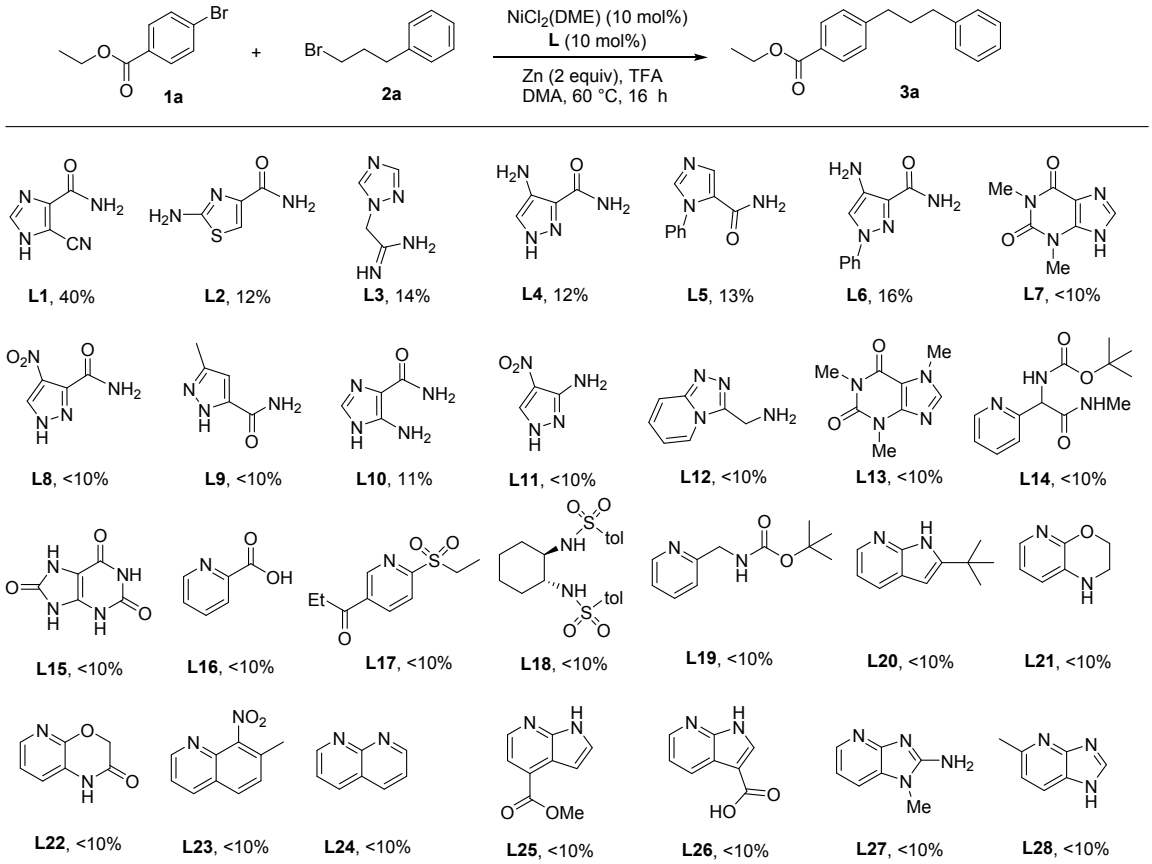


Figure 1. Strategies employed for mining BI compound library for new ligands

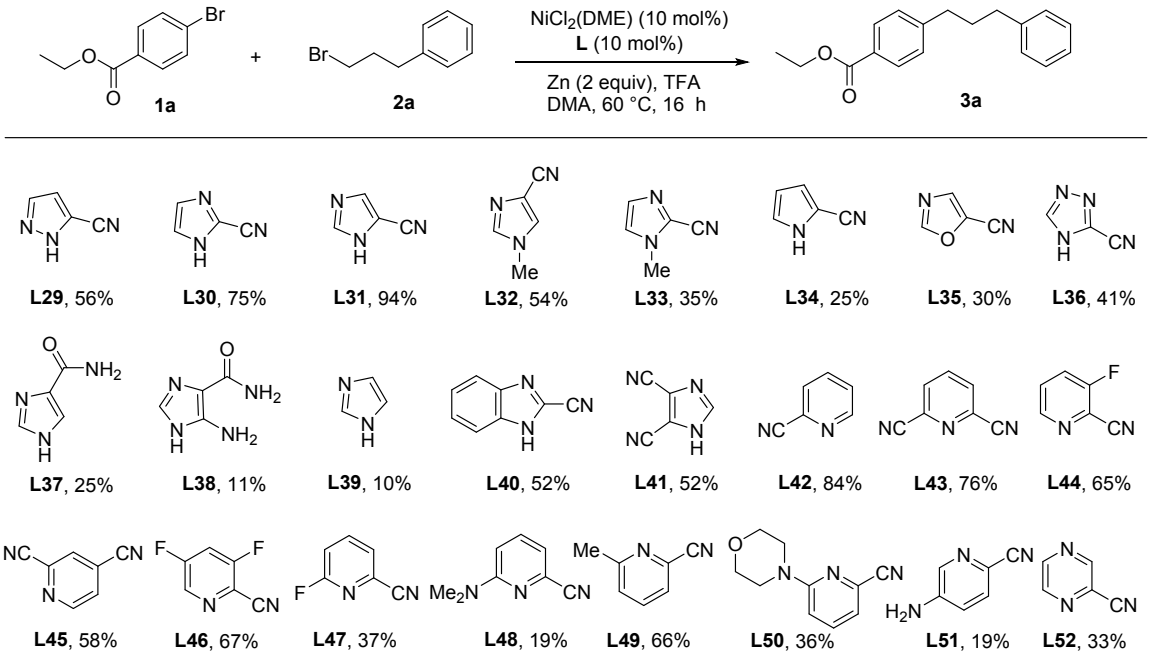
The results of the initial evaluation using model compounds ethyl 4-bromobenzoate and (3-bromopropyl)benzene with the first twenty eight ligand structures identified from the compounds library was shown in Scheme 2. Reaction conditions utilized for this screening were composed of 10 mol% $NiCl_2$(DME), 10 mol% ligand, 25 mol% NaI, 2 equiv Zn dust, and 10 mol% TFA in 0.3 M *N*,*N*-dimethylacetamide (DMA) at 60 °C for 16 h. Among the ligands tested, cyano-imidazole ligand **L1** resulted in a moderate yield of 40% for the desired cross coupling product. All other compounds tested within this initial subset provided low amount of product formation.



Scheme 2. Results of the initial evaluation of the twenty eight ligand structures. Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), $NiCl_2$(DME) (0.05 mmol), ligand (0.05 mmol), Zn dust (1.0 mmol), NaI (0.125 mmol), TFA (0.05 mmol) in DMA (0.3 M) at 60 °C for 16 h. The reaction yield was measured by GC with dodecane as the internal standard.

The encouraging result of the nitrile-containing heterocycle **L1** prompted us to evaluate additional compounds with a similar substitution pattern (Scheme 3). Interestingly, it was found that the nitrile functionality in the ligand structure is essential for increased reactivity. Unsubstituted imidazole **L39** provided 10% yield for **3a**. The 2-carbonitrile-substituted 1H-imidazole **L30** increased the yield to 75%. On the other hand, the *N*-Me-2-carbonitrile imidazole **L33** provided the product in 35% yield. The best result was obtained with 5-carbonitrile-substituted 1H-imidazole **L31** where 94% yield of the cross-coupling product **3a** was obtained. Low levels of impurities including homo-

dimerization, β-hydride elimination and hydrodehalogenation were observed with this ligand. Notably, the 6-membered heterocycle picolinonitrile **L42** also provided the product in 84% yield.

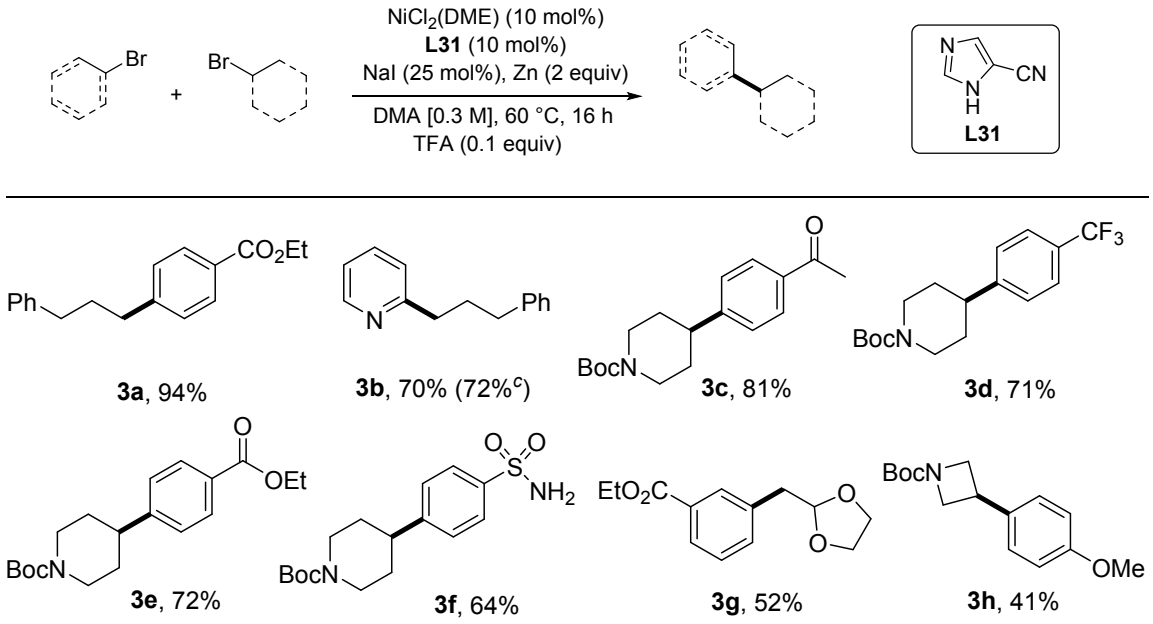


Scheme 3: Focused ligand screen with carbonitrile-containing molecules. Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), $NiCl_2$(DME) (0.05 mmol), ligand (0.05 mmol), Zn dust (1.0 mmol), NaI (0.125 mmol), TFA (0.05 mmol) in DMA (0.3 M) at 60 °C for 16 h. The reaction yield was measured on GC with dodecane as the internal standard.

With the identification of the new ligand 5-carbonitrile imidazole **L31**, we next tested the coupling reaction of heteroaryl 2-bromopyridine with (3-bromopropyl)benzene **2a**. The corresponding product **3b** was successfully isolated in 72% yield. We then decided to tackle more challenging substrates of un-activated secondary heteroatom-containing alkyl bromides (Figure 2). There are still limited methods to access aryl-substituted nonaromatic heterocycles including piperidines and azetidines.[14] Under the standard conditions using ligand **L31**, base-sensitive methyl ketone aryl bromide coupled efficiently with *N*-Boc-4-bromopiperidine to provide product **3c** in 81% yield. CF_3-, ester-, and sulfonamide-containing aryl bromides all worked well. Products **3d, 3e** and **3f**

were produced in 71%, 72% and 64% yields, respectively. Acetal group was tolerated to yield product **3g** in 52% yield. Coupling of *N*-Boc-3-bromoazetidine and 4-bromoanisole provided the product **3h** in 41% comparable yield.[13]

Figure 2: Substrate scope for Ni-catalyzed cross-electrophile couplings[a,b]

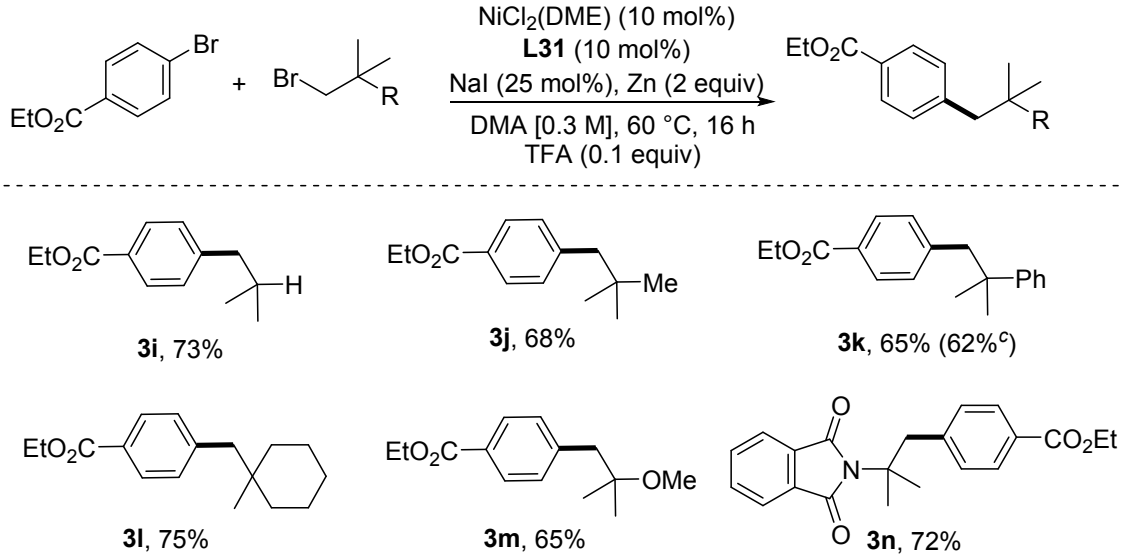


[a] Reaction conditions: Ar-Br (0.5 mmol), alkyl-Br (0.75 mmol), $NiCl_2$(DME) (0.05 mmol), **L31** (0.05 mmol), Zn dust (1.0 mmol), NaI (0.125 mmol), TFA (0.05 mmol) in DMA (0.3 M) at 60 °C for 16 h. [b] Isolated yields. [c] With 2.0 mmol of 2-bromopyridine.

The conditions with 5-cyanoimidazole ligand **L31** were also applied to the direct reductive coupling of 4-bromobenzoate bromide with more sterically challenging neopentyl-type alkyl bromides. Ligand **L31** effectively promoted the reductive coupling of hindered neopentyl-type bromides (Figure 3) that are typically known to lead to sluggish conversions. The reaction of 1-bromo-2-methylpropane with ethyl 4-bromobenzoate yielded product **3i** in 73% yield. Increasing the steric hindrance on alkyl bromides successfully furnished similar yields including 1-bromo-2,2-dimethylpropane (**3j**, 68% yield), (1-bromo-2-methylpropanyl)benzene (**3k**, 62% yield) and 1-(bromomethyl)-1-methylcyclohexane (**3l**, 75% yield). 1-bromo-2-methoxy2-methylpropane was tolerated to give 65% yield of product **3m**. 2-Methyl-2-phthalimido-

1-bromopropane coupled with ethyl 4-bromobenzoate to yield product **3n** in 72% yield. Upon deprotection, phentermine derivative is directly generated and could be applied for the synthesis of biologically active molecules such as the HCV Polymerase inhibitor listed in Scheme 1. The scope of neopentyl-derived products clearly exemplifies the new type of reactivity obtained from the use of the novel 5-cyanoimidazole ligand **L31**.[15]

Figure 3: Reductive Coupling of Aryl Bromides with Neopentyl-type Bromides[a,b]



[a] Reaction conditions: Ar-Br (0.5 mmol), alkyl-Br (0.75 mmol), $NiCl_2$(DME) (0.05 mmol), **L31** (0.05 mmol), Zn dust (1.0 mmol), NaI (0.125 mmol), TFA (0.05 mmol) in DMA (0.3 M) at 60 °C for 16 h. [b] Isolated yields. [c] With 2.0 mmol of Ar-Br.

In conclusion, we identified 5-cyanoimidazole as a new ligand for effective Ni-catalyzed cross-electrophile reductive couplings by mining Boehringer Ingelheim's diverse set of pharmaceutical compound library. The identified ligand was successfully applied in the preparation of various alkylated arene products with good to high yields including the sterically challenging neopenyl-type alkyl halides. Future efforts will be focused on determining the nickel-5-cyanoimidazole complex properties and its applications towards new transformations.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an atmosphere of argon or nitrogen in dry glassware with magnetic stirring. Commercially available Ar-Br and alkyl-Br, catalyst, ligand, Zn dust and solvents were used as received. NMR spectra were recorded on Bruker spectrometers (400, 500, and 600 MHz) and are reported relative to residual solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, non = nonet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, tt = triplet of triplet, br = broad), coupling constant (Hz) and integration are referenced to the residual solvent peak 7.26 ppm for $CDCl_3$. Data for ^{13}C NMR are reported in terms of chemical shift (at 100, 125 or 150 MHz) and are referenced to the residual solvent peak 77.15 for $CDCl_3$. High resolution mass spectra data (HRMS) were obtained on a LTQ FT Ultra Mass Spectrometer using DART source ionization at 50,000 resolving power with a Fourier Transform ion cyclotron resonance (FT-ICR) MS detector.

General experimental procedure: Anhydrous DMA was sparged with argon for 15 min prior to usage. Ar-Br (0.5 mmol), alkyl-Br (0.75 mmol), $NiCl_2$(DME) (0.05 mmol, 11.0 mg), **L31** (0.05 mmol, 4.7 mg), NaI (0.125 mmol, 19.0 mg) and Zn dust (1.0 mmol, 65.0 mg) were added to a vial on benchtop, followed by addition of DMA (1.7 mL). The vial was sealed with a septa cap. The mixture was evacuated and backfilled with argon five times. Then TFA (0.05 mmol, 4 uL, 0.1 equiv) was added to the vial. The reaction mixture was heated in a heating block on EASYMAX that was preheated to 60 °C. The mixture was stirred for 16 h before quenching with water (5 mL). The organic layer was extracted with DCM (3 x 5 mL), then washed with water (5 mL) and dried with anhydrous Na_2SO_4. The product was purified by column chromatography using silica gel.

Ethyl 4-(3-phenylpropyl)benzoate (3a): The title compound was prepared according to the general procedure and purified using hexanes as eluent to give the product as colorless oil, 126 mg, 94% yield. ^{1}H NMR spectrum was in accordance with the reported one:[16] (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.2 Hz, 2H), 7.17-7.29 (m, 7H), 4.36 (q, J = 7.1 Hz, 2H), 2.70 (t, J = 7.7 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 1.97 (quint, J = 7.7 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{18}H_{21}O_2$, 269.1542; found 269.1536.

2-(3-phenylpropyl)pyridine (3b): The title compound was prepared according to the general procedure and started with 2.0 mmol of 2-bromopyridine (316 mg). The other reagents were added accordingly: 3.0 mmol (3-bromopropyl)benzene (597 mg), 0.2 mmol $NiCl_2$(DME) (44.0 mg), 0.2 mmol **L31** (18.8 mg), 0.5 mmol NaI (76 mg), 4.0 mmol Zn dust (260 mg), 6.8 ml DMA and 0.2 mmol TFA (16 uL). The product was purified using 20% EtOAc in hexanes as eluent to give colorless oil, 284 mg, 72% yield. ^{1}H NMR spectrum was in accordance with the reported one:[17] (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.6 Hz, 1H), 7.59 (t, *J* = 7.5, 1H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.08-7.20 (m, 5H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.07 (quint, *J* = 7.5 Hz, 2H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_{16}N$, 198.1283; found 198.1277.

Tert-butyl 4-(4-acetylphenyl)piperidine-1-carboxylate (3c): The title compound was prepared according to the general procedure and purified using 10% EtOAc in hexanes as eluent to give the product as light yellow solid, 123 mg, 81% yield. ^{1}H NMR spectrum was in accordance with the reported one:[14] (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.28 (d, *J* = 13.1 Hz, 2H), 2.85 (dt, *J* = 13.1, 1.9 Hz, 2H), 2.73 (tt, *J* = 12.2, 3.5 Hz, 1H), 2.59 (s, 3H), 1.85 (m, 2H), 1.66 (dq, *J* = 12.5, 4.5 Hz, 2H), 1.49 (s, 9H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{18}H_{26}NO_3$, 304.1913; found 304.1908.

Tert-butyl 4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (3d): The title compound was prepared according to the general procedure and purified using 10% EtOAc in hexanes as eluent to give the product as colorless oil, 117 mg, 71% yield. ^{1}H NMR spectrum was in accordance with the reported one:[18] (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.27 (br s, 2H), 2.79-2.84 (br t, 2H), 2.69 (tt, *J* = 12.2, 3.6 Hz, 1H), 1.81-1.84 (m, 2H), 1.64 (dq, *J* = 12.6, 4.2 Hz, 2H), 1.49 (s, 9H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{17}H_{23}F_3NO_2$, 330.1681; found 330.1677.

Tert-butyl 4-(4-(ethoxycarbonyl)phenyl)piperidine-1-carboxylate (3e): The title compound was prepared according to the general procedure and purified using 20% EtOAc in hexanes as eluent to give the product as colorless liquid, 120 mg, 72% yield. ^{1}H NMR spectrum was in accordance with the reported one:[19] (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.26 (br d, *J* = 11.4 Hz, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 2.71 (tt, *J* = 12.1, 3.5 Hz, 1H), 1.81-1.84 (m, 2H), 1.64 (dq,

J = 12.6, 4.2 Hz, 2H), 1.49 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{19}H_{28}NO_4$, 334.2018; found 334.2013.

Tert-butyl 4-(4-sulfamoylphenyl)piperidine-1-carboxylate (3f): The title compound was prepared according to the general procedure and purified using 30% EtOAc in hexanes as eluent to give the product as white solid, 109 mg, 64% yield. ^{1}H NMR spectrum was in accordance with the reported one[14]: (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.02 (s, 2H), 4.25 (br s, 2H), 2.81 (br t, 2 H), 2.71 (tt, *J* = 12.4, 3.4 Hz, 1H), 1.80-1.83 (m, 2H), 1.64 (dq, *J* = 12.6, 4.2 Hz, 2H), 1.48 (s, 9H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{16}H_{25}N_2O_4S$, 341.1535; found 341.1531.

Ethyl 3-((1,3-dioxolan-2-yl)methyl)benzoate (3g): The title compound was prepared according to the general procedure and purified using 10% EtOAc in hexanes as eluent to give the product as colorless oil, 61 mg, 52% yield. ^{1}H NMR spectrum was in accordance with the reported one:[5a] (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 5.09 (t, *J* = 4.7 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.83-3.94 (m, 4H), 3.02 (d, *J* = 4.8 Hz, 2H) 1.39 (t, *J* = 7.2 Hz, 3H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{13}H_{17}O_4$, 237.1127; found 237.1122.

Tert-butyl 3-(4-methoxyphenyl)azetidine-1-carboxylate (3h): The title compound was prepared according to the general procedure and purified using 20% EtOAc in hexanes as eluent to give the product as colorless oil, 54 mg, 41% yield. ^{1}H NMR spectrum was in accordance with the reported one:[14] (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.23 (t, *J* = 8.6 Hz, 2H), 3.86 (dd, *J* = 8.6, 6.1 Hz, 2H), 3.73 (s, 3H), 3.58-3.63 (m, 1H), 1.39 (s, 9H). HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{15}H_{22}NO_3$, 264.1600; found 264.1595.

Ethyl 4-isobutylbenzoate (3i): The title compound was prepared according to the general procedure and purified using hexanes as eluent to give the product as colorless oil, 75 mg, 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.52 (d, *J* = 7.2 Hz, 2H), 1.89 (non, *J* = 6.7 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 147.1, 129.4, 129.1, 128.1, 60.7, 45.4, 30.1, 22.3, 14.4. ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 166.8, 147.1, 129.4, 129.1, 128.1, 60.7, 45.4, 30.1, 22.3, 14.4. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{13}H_{19}O_2$, 207.1385; found 207.1380.

Ethyl 4-neopentylbenzoate (3j): The title compound was prepared according to the general procedure and purified using 5% EtOAc in hexanes as eluent to give the product as colorless oil, yield: 76 mg, 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.47 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H), 0.83 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 166.8, 145.2, 130.4, 128.9, 128.1, 60.8, 50.2, 31.9, 29.4, 14.4. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_{21}O_2$, 221.1542; found 221.1536.

Ethyl 4-(2-methyl-2-phenylpropyl)benzoate (3k): The title compound was prepared according to the general procedure and started with 2.0 mmol of ethyl 4-bromobenzoate (458 mg). The other reagents were added accordingly: 3.0 mmol (3-bromopropyl)benzene (639 mg), 0.2 mmol $NiCl_2$(DME) (44.0 mg), 0.2 mmol **L31** (18.8 mg), 0.5 mmol NaI (76 mg), 4.0 mmol Zn dust (260 mg), 6.8 ml DMA and 0.2 mmol TFA (16 uL). The product was purified using hexanes as eluent to give colorless oil, 350 mg, 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.09-7.21 (m, 5H), 6.76 (d, J = 8.2 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 2.84 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.25 (s, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.8, 148.3, 144.3, 130.3, 128.7, 128.2, 128.0, 126.2, 125.9, 60.8, 51.1, 38.9, 28.3, 14.4. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{19}H_{23}O_2$, 283.1698; found 283.1693.

Ethyl 4-((1-methylcyclohexyl)methyl)benzoate (3l): The title compound was prepared according to the general procedure and purified using 5% EtOAc in hexanes as eluent to give the product as colorless oil, 98 mg, 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.2 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 2.51 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.16-1.50 (m, 10H), 0.75 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 166.8, 144.8, 130.6, 128.8, 128.1, 60.7, 48.8, 37.7, 34.3, 26.4, 24.6, 22.1, 14.4. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{17}H_{25}O_2$, 261.1849; found 261.1845.

Ethyl 4-(2-methoxy-2-methylpropyl)benzoate (**3m**): The title compound was prepared according to the general procedure and purified using 20% EtOAc in hexanes as eluent to give the product as colorless oil, 76 mg, 65% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.29 (s, 3H), 2.83 (s, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.15 (s, 6H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 166.7,

143.8, 130.4, 129.1, 128.4, 75.1, 60.7, 49.4, 46.3, 24.7, 14.3. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{14}H_{21}O_3$, 237.14852; found 237.14855.

Ethyl 4-(2-(1,3-dioxoisoindolin-2-yl)-2-methylpropyl)benzoate (3n): The title compound was prepared according to the general procedure and purified 20% EtOAc in hexanes as eluent to give the product as white solid, 126 mg, 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.74-7.76 (m, 2H), 7.67-7.69 (m, 2H), 7.15 (d, J = 8.2 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 3.32 (s, 2H), 1.76 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.8, 166.5, 142.8, 133.9, 131.8, 130.2, 129.3, 128.8, 122.8, 60.9, 60.8, 45.4, 27.6, 14.3. HRMS-ESI (m/z) $[M+H]^+$ calcd for $C_{21}H_{22}NO_4$, 352.1549; found 352.1544.

Corresponding Authors

*E-mail: bo.qu@boehringer-ingelheim.com
*E-mail: nick.desrosiers@pfizer.com

Supporting Information

NMR spectra of the products. The Supporting Information is available free of charge on the ACS Publications website.

Present address

† Chemical Research & Development, Pfizer Worldwide Research & Development, 558 Eastern Point Rd., Groton, CT 06340, USA

‡ Discovery, Alkermes, Inc., 852 Winter St., Waltham, MA 02451, USA

§ TCG Lifesciences USA, 737 North 5th St., Suite 501, Richmond, VA 23219, USA

Competing Financial Interests

The authors declare no competing financial interests.

Acknowledgements

This work was influenced by the on-going efforts of the Non-Precious Metal Catalysis Alliance between Abbvie, Boehringer Ingelheim Pharmaceuticals and Pfizer. We thank

Dr. Eric Hansen and Dylan Pedro from Pfizer for helpful discussions. We are grateful to Drs. Nina Gonnella and Dongyue Xin for NMR analysis of compounds **3l** and **3m**. HRMS analysis by Scott Pennino and purification of compounds **3j**, **3l** and **3m** by Dr. Xiaowen Hou and Amy Gao are greatly appreciated.

References

1. For reviews, see: (a) Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem*. **2014**, *79*, 4793−4798. (b) Moragas, T.; Correa, A.; Martin, R. Metal-Catalyzed Reductive Coupling Reactions of Organic Halides with Carbonyl-Type Compounds. *Chem. Eur. J*. **2014**, *20*, 8242−8258. (c) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem. Eur. J*. **2014**, *20*, 6828−6842. (d) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res*. **2015**, *48*, 1767−1775. (e) Gu, J.; Wang, X.; Xue, W.; Gong, H. Nickel-catalyzed reductive coupling of alkyl halides with other electrophiles: concept and mechanistic considerations. *Org. Chem. Front*. **2015**, *2*, 1411−1421. (f) Richmond, E.; Moran, J. Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents. *Synthesis*, **2018**, *50*, 499−513. (g) Campeau, L.-C.; Hazari, N. Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future. *Organometallics* **2019**, *38*, 3−35.
2. For selected reviews, see: (a) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev*. **2011**, *111*, 1417−1492. (b) Yan, M. Lo, J. C.; Edwards, J. T.; Baran, P. S. Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc*. **2016**, *138*, 12692−12714. (c) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The Merger of Transition Metal and Photocatalysis. *Nature Rev. Chem*. **2017**, *1*, 0052.
3. Lovering, F.; Bikker, J.; Humble, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem*. **2009**, *52*, 6752−6756.
4. Wang, X.; Wang, S.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides. *J. Am. Chem. Soc*. **2015**, *137*, 11562−11565.
5. (a) Everson, D. A.; Shrestha, R.; Weix, D. J. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc*. **2010**, *132*, 920−921. (b) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146−6159. (c) Wang, S.; Qian, Q.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Halides with Secondary Alkyl Bromides and Allylic Acetate. *Org. Lett*. **2012**, *14*, 3352−3355. (d) Olivares, A. M.; Weix, D. J. Multimetallic Ni- and Pd-Catalyzed Cross-Electrophile Coupling To Form Highly Substituted 1,3-Dienes. *J. Am. Chem. Soc*. **2018**, *140*, 2446−2449.

6. Cherney, A. H.; Kadunce, N. T.; Reisman. S. E. Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones. *J. Am. Chem. Soc*. **2013**, *135*, 7442−7445.
7. Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. Nickel-Catalyzed Reductive Cross-Coupling of Unactivated Alkyl Halides. *Org. Lett*. **2011**, *13*, 2138−2141.
8. Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. New Ligands for Nickel Catalysis from Diverse Pharmaceutical Heterocycle Libraries. *Nature Chem*. **2016**, *8*, 1126−1130.
9. Hansen, E. C.; Li, C.; Yang, S.; Pedro, D.; Weix, D. J. Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling. *J. Org. Chem*. **2017**, *82*, 7085−7092.
10. (a) Paul, A.; Smith, M. D.; Vannucci, A. K. Photoredox-Assisted Reductive Cross-Coupling: Mechanistic Insight into Catalytic Aryl−Alkyl Cross-Couplings. *J. Org. Chem*. **2017**, *82*, 1996−2003. (b) Zhang, P.; Le, C.; MacMillan, D. W. C. Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc*. **2016**, *138*, 8084−8087.
11. (a) Nishino, T.; Yui, M.; Asai, Y. Method for Producing Hematopoietic Stem Cells Using Pyrazole Compound. PCT Int. Appl. (2012), WO 2012074068 A1 20120607. (b) Oka, T.; Ikegashira, K.; Hirashima, S.; Yamanaka, H.; Noji, S.; Niwa, Y.; Matsumoto, Y.; Sato, T.; Ando, I.; Nomura, Y. Preparation of Fused Heterotetracyclic Compounds and Use Thereof as Hepatitis C Virus (HCV) Polymerase Inhibitors. PCT Int. Appl. (2005), WO 2005080399 A1 20050901. (c) Shinagawa, Y.; Katsushima, T.; Nakagawa, T. Preparation of Naphthalenylethylaminopropanol Derivatives as Calcium Receptor Antagonists. PCT Int. Appl. (2002), WO 2002014259 A1 20020221. (d) Ito, A.; Sudo, K.; Watanabe, T.; Kusano, N.; Araki, N.; Eizuka, T.; Niizeki, Y. Preparation of Nitrogen-containing Heterocyclic Compounds as Medical and Agrochemical Fungicides. PCT Int. Appl. (2001), WO 2001085684 A1 20011115. (e) Crowell, T. A.; Evrard, D. A.; Jones, C. D.; Muehl, B. S.; Rito, C. J.; Shuker, A. J.; Thorpe, A. J.; Thrasher, K. J. Preparation of Carbazole Derivatives as Selective β3 Adrenergic Agonists. PCT Int. Appl. (1998), WO 9809625 A1 19980312.
12. Chan, V. S.; Krabbe, S. W.; Li, C.; Sun, L.; Liu, Y.; Nett, A. J. Identification of an Oxalamide Ligand for Copper-Catalyzed C-O Couplings from a Pharmaceutical Compound Library. *ChemCatChem* **2019**, *11*, 5748−5753.
13. Molecular weight of the compounds was limited to be less than 500 g/mol so that the identified ligand would be a compound with low molecule weight. Initial compound selections were focused on molecules with structures not known as existing ligands. Further substructure search identified that, most of the times, one of the nitrogens is part of 5-, or 6-heterocycles.
14. Molander, G. A.; Traister, K. M.; O'Neill, B. T. Reductive Cross-Coupling of Nonaromatic, Heterocyclic Bromides with Aryl and Heteroaryl Bromides. *J. Org. Chem*. **2014**, *79*, 5711−5780.
15. The reaction conditions are not applicable to tert-butyl bromide; no cross coupling product was observed.

16. Amatore, M.; Gosmini, C. Direct Method for Carbon-Carbon Bond Formation: The Functional Group Tolerant Cobalt-Catalyzed Alkylation of Aryl Halides. *Chem. Eur. J.* **2010**, *16*, 5848–5852.
17. Guo, W.; Wang, Z. Iron-catalyzed Cross-coupling of Aryltrimethylammonium Triflates and Alkyl Grignard Reagents. *Tetrahedron* **2013**, *69*, 9580–9585.
18. Zhang, X.; MacMillan, D. W. C. Alcohols as Latent Coupling Fragments for Metallaphotoredox Catalysis: sp^3−sp^2 Cross-Coupling of Oxalates with Aryl Halides. *J. Am. Chem. Soc*. **2016**, *138*, 13862−13865.
19. Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. Direct Synthesis of 4-Arylpiperidines via Palladium/Copper(I)-Cocatalyzed Negishi Coupling of a 4-Piperidylzinc Iodide with Aromatic Halides and Triflates. *J. Org. Chem*. **2004**, *69*, 5120−5123.