Highly Selective Room Temperature Copper-Catalyzed C-N Coupling Reactions

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Supporting Information

General Information. Copper(I) iodide was purchased from Strem. Anhydrous K_3PO_4 (Fluka brand) was purchased from Aldrich. Anhydrous Cs_2CO_3 (“fine”) was a gift from Chemetall. These inorganic bases were stored in a nitrogen-atmosphere glovebox; required amounts were removed from the glovebox immediately prior to use. Anhydrous N,N-dimethylformamide (DMF) was purchased from Aldrich in SureSeal™ bottles. The ligands N,N-diethylsalicylamide, 2,4-pentanedione, 2,2,6,6-tetramethylheptanedione and 2-acetylcyclohexanone were purchased from Aldrich and were used as received. Amines were purchased from commercial sources and in most cases were used without further purification. Occasionally a particularly air-sensitive amine was distilled from NaOH and was stored under nitrogen. Aryl halides were purchased from commercial sources and in most cases used without further purification. In cases where significant discoloration of the aryl halide was observed, recrystallization or passage through a short plug of basic alumina was employed.

Chromatographic silica gel was obtained from VWR (EMD chemicals, “Silica gel 60” 230-240 mesh). While most compounds were eluted using an ethyl acetate/hexane mixture, occasionally CH_2Cl_2 *saturated with* NH_3 in combination with MeOH was used for the separation of particularly basic compounds. This mixture was prepared by placing a 3:1 mixture of CH_2Cl_2 : NH_4OH (40%) in a separatory funnel, carefully shaking the mixture for 1-2 min and then collecting the organic layer. The addition of MeOH results in the formation of a clear homogeneous solvent mixture.

NMR spectra were recorded using a Bruker DRX 400 instrument. All 1H NMR chemical shifts were reported in ppm relative to the residual protonated solvent peak (7.27 ppm for $CDCl_3$). Proton-decoupled ^{13}C chemical shifts were reported relative to the solvent peak (7.26 ppm for $CDCl_3$). Gas chromatographic (GC) analyses were performed on a Hewlett-Packard 6890 Series GC System with a capillary column with cross-linked methyl siloxane as the stationary phase (25 m x 0.20 mm). Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, Georgia).

Preparation of 2-Acylcyclohexanone Ligands.

The ligands were prepared either *via* the bismuth/zinc-mediated C-acylation of enoxysilanes¹ or via the direct acylation of cyclohexanone.²

Preparation of 2-Propionylcyclohexanone. This procedure was adapted from the synthesis reported by Le Roux and coworkers.¹

An oven-dried 100 mL Schlenk flask equipped with a stirbar was transferred into glovebox and charged with BiCl₃ (283 mg, 0.9 mmol, 5 mol%) and ZnI₂ (421 mg, 1.32 mmol, 7.5 mol%). The flask was removed from the glovebox and under a counterflow of argon and dry ether (2.0 mL) and dry dichloromethane (18 mL) were added. Propionyl chloride (1.80 g, 1.70 mL, 19.4 mmol) was added and the mixture was allowed to stir for 5 min. At this point the enol ether (3.00 g, 3.43 mL, 17.6 mmol) was added all at once. The mixture became warm and an orange oil formed after ~ 5min. The mixture was allowed to stir an additional 40 min, at which point it was quenched with a saturated aqueous NaHCO₃ solution. The mixture was partitioned between water and dichloromethane. The organic fraction was collected, dried over MgSO₄ and filtered. Solvent was removed and the resulting orange oil was purified by column chromatography (silica gel, 10:1 hexane: ethyl acetate) affording 2.06 g (76%) of the desired product as slightly yellow oil. The product was distilled under vacuum affording a colorless liquid. ¹H NMR (CDCl₃) (99:1 *enol*: *ketone*, only data for the major *enol* form is given): δ 15.87 (s, 1H, *OH*), 2.44 (q, 2H, *J* = 7.3 Hz, CH₂CH₃), 2.32 (m, 4H, ring CH₂), 1.68 (m, 4H, ring CH₂), 1.10 (t, 3H, *J* = 7.3 Hz, CH₂CH₃) ppm.

Preparation of 2-Isobutyrylcyclohexanone. This procedure was adapted from the synthesis reported by Nasipuri and Biswas.²

A 3-neck 500 mL flask was charged with dry NaH (10.6 g, 442 mmol). The flask was fitted with a mechanical stirrer, a reflux condenser and a pressure-equalizing addition funnel. The top of the reflux condensor was fitted with an argon inlet. The flask was flushed with argon and a solution of methyl isobutyrate (30.0 g, 293 mmol) in THF (90 mL) was added, followed by MeOH (200 μL). A solution of cyclohexanone (19.6 g, 200 mmol) in THF (90 mL) was placed in the addition funnel. The reaction mixture was heated to 70 °C and with vigorous stirring cyclohexanone was added dropwise. When all of cyclohexanone was added (~1.5 h) the mixture was brought to reflux. After ~3h a thick yellow mixture had formed; the heating was continued for an additional 15 h. At this point the suspension was allowed cool and was quenched at 0 °C with water (40 mL), followed by 10% HCl to bring the pH to ~5. The resulting mixture was transferred to a separatory funnel and was partitioned between H₂O and Et₂O. The Et₂O fraction was

separated and the aqueous layer was extracted with an additional portion of Et₂O. The combined organic fraction was dried over MgSO₄. The product was isolated by fractional distillation. Yield: 13.5 g (40%). ¹H NMR (CDCl₃) (96:4 enol: ketone, only data for the major enol form is given): δ 16.36 (s, 1H, OH), 2.87 (hept, 1H, *J* = 6.8 Hz, CH), 2.35 (m, 4H, two CH₂), 1.67 (m, 4H, two CH₂), 1.08 (d, 6H, *J* = 6.8 Hz, CH₃) ppm. ¹³C{¹H} NMR (CDCl₃) (only the major enol form): δ 205.7, 183.4, 106.0, 33.6, 31.8, 27.4, 24.0, 23.4, 22.1, 19.1, 18.8 ppm. Anal. Calcd for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.86.

Preparation of 2-(1-Benzylimino-ethyl)-cyclohexanone.

2-Acetylcyclohexanone (280 mg, 260 μL, 2.0 mmol) was dissolved in EtOH (5mL). Molecular sieves (4 Å, 150 mg) and benzylamine (214 mg, 218 μL, 2.0 mmol) were added, followed by 3 drops of glacial acetic acid. The mixture was allowed to stir for 12 h at room temperature. At this point the solvent was removed under reduced pressure affording a yellow oil. The ¹H NMR analysis showed the oil to be a mixture of the desired product (90%) and the isomeric product where imine formation took place at the cyclohexanone C=O group (10%). Column chromatography on silica gel (1:1 hexane: ethyl acetate, leading band) afforded the desired as a yellow oil; Yield: 233 mg (50%). ¹H NMR (CDCl₃, the product is fully enolized) δ 11.83 (br s, 1H, NH), 7.35-7.23 (m, 5H, all Ph), 4.42 (d, 2H, *J* = 6.2 Hz, CH₂Ph), 2.34-2.33 (m, 4H, CH₂), 2.11 (s, 3H, CH₃), 1.63-1.58 (m, 4H, CH₂) ppm.

Experimental Procedure for Kinetic Studies Using Reaction Calorimetry.

Reaction procedure. Reactions were performed in an Omnical SuperCRC reaction calorimeter. The instrument contains an internal magnetic stirrer and a differential scanning calorimeter (DSC), which compares the heat released or consumed in a sample vessel to that of an empty reference vessel. The reaction vessels were 16 mL borosilicate screw-thread vials fit with opentop black phenolic screw caps and white PTFE septa (KimbleBrand) charged with Teflon stir bars. Sample volumes did not exceed 2.5 mL. In a typical calorimetry experiment, an oven-dried 16 mL vial was transferred into the glovebox where it was charged with CuI (9.5 mg, 0.05 mmol, 5 mol%), Cs₂CO₃ (650 mg, 2.0 mmol), *n*-hexylamine (151 mg, 1.5 mmol) and 400 µL of anhydrous DMF. The vial was then capped and placed in the calorimeter where the mixture was stirred (1000 rpm) at 25 °C. Simultaneously, two syringes, one containing a solution of the ligand (0.2 mmol) in 100 µL DMF and another containing 5-iodo-*m*-xylene were placed in the two injection ports of the calorimeter. After thermal equilibration at 25 °C (~1 h), the ligand was injected resulting in a heat spike. When the heat flow returned to baseline (~20 min), the reaction was initiated by injecting the aryl iodide. The temperature of the DSC was held constant at 25 °C using the internal temperature controller in the calorimeter, ensuring that the reaction would proceed under isothermal conditions. A raw data curve was produced by measuring the heat flow from the sample vessel every three seconds during the reaction. Due to the delay between the instantaneous moment heat evolved from the reaction vessel and the time the thermophile sensor detects the heat flow, a correction was applied to the raw data curve. The correction is based on the time constant that was measured by passing a constant amount of current through a resistor in the sample chamber of the calorimeter thereby producing a known quantity of heat. This process results in a response curve, which is then transformed into a square wave allowing for the response time of the instrument to be calculated using the WinCRC software. Time constant on the order of 2 seconds were generally measured. Application of the response time to the raw data results in a “tau corrected data curve.” The tau corrected data curve is a plot of heat flow (mJ s⁻¹) versus time. The reaction rate, which is directly proportional to the heat flow (eq 1), fraction conversion (eq 2), and instantaneous concentrations of reactants/products can all be calculated from this tau-corrected data curve.

$$q = \Delta H_{\text{rxn}} \bullet V \bullet r \quad (1)$$

where *q* is the instantaneous heat flow, ΔH_{rxn} is the heat of reaction, *V* is the reaction volume and *r* is the reaction rate. Fractional conversion can be calculated according to the following equation:

$$\text{fractional conversion} = \frac{\int_0^t q \bullet dt}{\int_0^{t_f} q \bullet dt} \quad (2)$$

where the numerator represents the area under the heat flow to any time point *t* and the denominator represents the total area under the heat flow curve.

General Procedure A: Room Temperature Coupling of Aryl Iodides with Amines.

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, CuI (10 mg, 0.05 mmol, 5 mol %), Cs₂CO₃ (650 mg, 2 mmol) and any remaining solids (amine and/or aryl halide). The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, amine (if liquid), aryl halide (if liquid) and DMF (0.5 mL) were added by syringe. Finally, **L4** (34 mg, 0.2 mmol, 20 mol%) was added *via* syringe, the tube was sealed and the mixture was allowed to stir under argon at ambient temperature (18-22 °C) for the indicated period of time. In cases where GC analysis of the mixture was required, dodecane (227 mL, 1.0 mmol) was added at the end of the reaction as an internal standard. Upon completion of the reaction, the mixture was diluted with ethyl acetate, passed through a fritted glass filter to remove the inorganic salts and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 1 h.

General Procedure B: Coupling of Aryl Bromides with Amines. An oven-dried Schlenk tube equipped with a Teflon valve (Kontes) was charged with a magnetic stir bar, CuI (10 mg, 0.05 mmol, 5 mol%) and the inorganic base (2 mmol): Cs₂CO₃ (650 mg) *or* K₃PO₄ (425 mg). Any remaining solids (amine and/or aryl halide) were added at this point. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counterflow of argon, amine (if liquid), aryl halide (if liquid) and DMF (0.5 mL) were added by syringe. Finally, the **L4** (34 mg, 0.2 mmol, 20 mol%) was added *via* syringe, the tube was sealed and the mixture was heated at the indicated temperature (90 °C – 110 °C) for the indicated period of time. Upon completion of the reaction, the mixture allowed to cool to room temperature and then was diluted with ethyl acetate, passed through a fritted glass filter to remove the inorganic salts and solvent was removed with the aid of rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under vacuum for at least 1 h.

Room Temperature Amination of Aryl Iodides: Table 1.

N-Benzyl-3,5-dimethylaniline (entry 1).³ Following Procedure A, 5-iodo-*m*-xylene (232 mg, 1.0 mmol) was allowed to react with benzylamine (161 mg, 1.5 mmol) for 2 h. Column chromatography: silica gel, 20:1 hexane: ethyl acetate (*R*_f = 0.28). Pale-yellow oil; yield: 202 mg (96%). ¹H NMR (CDCl₃): δ 7.37-7.27 (m, 5H, *all Ph resonances*), 6.38 (s, 1H, *p*-xylyl), 6.28 (s, 2H, *m*-xylyl), 4.29 (s, 2H, CH₂), 3.88 (br s, 1H, NH), 2.22 (s, 6H, CH₃) ppm. ¹³C{¹H} NMR (CDCl₃): δ 148.5, 139.8, 139.1, 128.8, 127.7, 127.4, 119.8, 110.9, 48.5, 21.7 ppm.

Using L2: The same procedure was followed using **L2** (28 mg, 0.2 mmol) instead of **L4**. After a 3 h reaction time the product was isolated in 94% yield.

[4-(3,5-Dimethylphenylamino)-butyl]-carbamic acid tert-butyl ester (entry 2).

Following Procedure A, 5-iodo-*m*-xylene (232 mg, 1.0 mmol) was allowed to react with mono-*N*-BOC-1,4-diaminobutane (282 mg, 1.5 mmol) for 4 h. Column chromatography: silica gel, 4:1 hexane: ethyl acetate ($R_f = 0.22$). Pale-yellow oil; yield: 290 mg (98%). Mp = 99-101 °C. ^1H NMR (CDCl_3): δ 6.36 (s, 1H, *p*-xylyl), 6.24 (s, 2H, *m*-xylyl), 4.59 (br s, 1H, NH), 3.5 (br s, 1H, NH), 3.17-3.09 (m, 4H, CH_2), 2.23 (s, 6H, 3,5- CH_3), 1.64-1.57 (m, 4H, CH_2), 1.44 (s, 9H, tBu) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 156.4, 148.8, 139.3, 119.7, 111.1, 79.6, 44.1, 40.8, 28.9, 28.2, 27.3, 21.9, 21.5 ppm. IR (CDCl_3 , cm^{-1}): 3375, 2975, 2932, 2843, 1698, 1602, 1515, 1455, 1250, 1172.

Using L2: The same procedure was followed using **L2** (28 mg, 0.2 mmol) instead of **L4**. After a 6 h reaction time the product was isolated in 97% yield. The characterization data matched that of compound obtained using **L4**.

5-(3,5-Dimethylphenylamino)-pentanoic acid (entry 3). The compound was prepared by a modification of Procedure A using 3.0 mmol of Cs_2CO_3 to couple 5-iodo-*m*-xylene (232 mg, 1.0 mmol) with 4-aminobutyric acid (155 mg, 1.5 mmol) at 40 °C for 6 h. After cooling to room temperature, the reaction mixture was partitioned between water and Et_2O and the aqueous phase was separated. The organic fraction was extracted with an additional 3 x 10 mL of 10% NaOH. The combined aqueous fractions was neutralized with a 20% HCl to a pH = 4 and extracted with 3 x 20 mL Et_2O . The resulting organic fraction was dried with MgSO_4 . Removal of the solvent afforded the product as a white microcrystalline solid, which was further dried under high vacuum at 70 °C to remove residual DMF. Yield: 182 mg (88%). Mp = 187-188 °C. ^1H NMR (CDCl_3): δ 8.27 (br s, 2H, NH and COOH), 6.47 (s, 1H, *p*-xylyl), 6.36 (s, 2H, *m*-xylyl), 3.21 (t, 2H, $J = 6.9$ Hz, CH_2), 2.50 (t, 2H, $J = 7.2$ Hz, CH_2), 2.29 (s, 6H), 1.97 (m, 2H, CH_2) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 179.7, 147.8, 139.4, 120.9, 112.1, 44.3, 32.3, 24.7, 21.9 ppm. IR (CDCl_3 , cm^{-1}): 3411, 3024, 2921, 1709, 1602, 1514, 1437, 1414, 1337, 1252, 1190, 907.

(4-Bromophenyl)-cyclopropylmethylamine (entry 4). Following Procedure A, 1-bromo-4-iodobenzene (282 mg, 1.0 mmol) was allowed to react with aminomethylcyclopropane (92 mg, 1.5 mmol, 115 μL) for 3 h. Column chromatography: silica gel, 40:1 hexane: ethyl acetate ($R_f = 0.1$). Pale-yellow liquid; yield: 222 mg (98%). Mp = 74-75 °C. ^1H NMR (CDCl_3): δ 7.24 (d, 2H, $J = 8.9$ Hz, *ArH*), 6.48 (d, 2H, $J = 8.9$ Hz), 3.81 (br s, 1H, NH), 2.91 (d, 2H, $J = 6.9$ Hz, NCH_2), 1.05-0.90 (m, 1H, CH), 0.58-

0.53 (m, 2H, *HCH*), 0.25-0.21 (m, 2H, *HCH*) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 147.6, 132.1, 114.4, 108.9, 49.2, 18.9, 10.9, 3.7 ppm. Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{BrN}$: C, 53.12; H, 5.35. Found: C, 53.36; H, 5.43. IR (CDCl_3 , cm^{-1}): 3423, 3081, 3007, 1884, 1595, 1497, 1472, 1316, 1252, 1178, 907, 731.

Using L2: The same procedure was followed as above using **L2** (28 mg, 0.2 mmol) instead of **L4**. After a 3 h reaction time the product was isolated in 96% yield. The characterization data matched that of compound obtained using **L4**.

(3,4-Difluoro-phenyl)-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine (entry 5). Following procedure A, 1,2-difluoro-4-iodo-benzene (240 mg, 1.0 mmol) was allowed to react with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine (192 mg, 1.5 mmol) for 1 h. Column chromatography: silica gel, 50:1 CH_2Cl_2 (sat'd with NH_3):MeOH (see General Information). Yellow oil; yield: 235 mg (98%). ^1H NMR (CDCl_3): δ 6.91 (m, 1H, *ArH*), 6.36-6.31 (m, 1H, *ArH*), 6.21 (m, 1H, *ArH*), 4.32 (br s, 1H, *NH*), 3.08-3.02 (m, 3H, overlapping CH_2 and CH), 2.31 (s, 3H, CH_3), 2.22-2.09 (m, 2H, CH_2), 1.97-1.75 (m, 2H, CH_2), 1.73-1.40 (m, 4H, CH_2) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 151.2 (d, $J_{\text{HF}} = 224$ Hz), 146.1, 143.1 (d, $J_{\text{HF}} = 234$ Hz), 117.7, 108.1, 101.3, 64.9, 57.6, 42.1, 41.0, 32.2, 30.3, 22.6 ppm. IR (neat, cm^{-1}): 3423, 3268, 2948, 2786, 1630, 1605, 1522, 1458, 1339, 1221, 1256, 1174, 1109, 827, 797, 771.

N-Allyl-benzene-1,3-diamine (entry 5). [2 mmol scale] Following procedure A, 3-iodoaniline (438 mg, 2.0 mmol) was allowed to react with allylamine (171 mg, 3.0 mmol) for 6 h. Column chromatography: silica gel, 4:1 hexane: ethyl acetate (*under N*₂). Yellow oil, became green upon exposure to air; yield: 267 mg (90%). ^1H NMR (CDCl_3): δ 7.00 (t, 1H, *ArH*), 6.11 (m, 2H, *ArH*), 6.03-5.94 (m, 2H, overlapping *ArH* and $\text{CH}_2\text{CH}=\text{CH}_2$), 5.32 (m, 1H, $\text{CH}_2\text{CH}=\text{CHH}$), 5.20 (m, 1H, $\text{CH}_2\text{CH}=\text{CHH}$), 3.76 (d, 2H, $J = 5.3$ Hz, $\text{CH}_2\text{CH}_2=\text{CH}_2$), 3.65 (br s, 3H, *NH* and *NH*₂) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 149.8, 148.0, 136.1, 130.5, 116.5, 105.5, 104.6, 100.2, 47.0 ppm. IR (CDCl_3 , cm^{-1}): 3362, 3215, 3045, 2839, 1583, 1511, 1499, 1454, 1337, 1212, 1165, 991, 910, 830, 762.

4-Benzylaminophenol (entry 7).⁴ The compound was prepared by a modification of Procedure A using 2.6 mmol Cs_2CO_3 (845 mg). Thus, 4-iodophenol (220 mg, 1.0 mmol) was allowed to react with benzylamine (160 mg, 1.5 mmol) for 8 h. The mixture was diluted with ethyl acetate and was neutralized with a 10% HCl solution until a pH of ~4 was reached. The mixture was transferred to a separatory funnel and the organic layer was separated. After additional extractions with two portions of ethyl acetate (10 mL), the combined organic fractions were concentrated. The residue was adsorbed onto silica

gel, transferred on top of a silica gel column and was eluted with 4:1 hexane ethyl acetate. Yellow solid, yield: 159 mg (80%). Mp = 91-93 (dec). ^1H NMR (CDCl_3): δ 7.41-7.26 (m, 5H, *Ph*), 6.68 (d, 2H, $J = 8.6$ Hz, *ArH*), 6.57 (d, 2H, $J = 8.6$, *ArH*), 4.62 (br s, 2H, *NH and OH*), 4.31 (s, 2H, CH_2), ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 148.5, 142.5, 139.9, 129.1, 128.1, 127.7, 116.7, 115.2, 50.0 ppm. IR (CDCl_3 , cm^{-1}): 3599, 3396, 3031, 1500, 1453, 1359, 1241, 1176.

3-Cyclohexylaminophenylmethanol (entry 8). Following Procedure A, 3'-iodobenzyl alcohol (234 mg, 1.0 mmol) was allowed to react with cyclohexylamine (150 mg, 1.5 mmol) for 7 h. Column chromatography: silica gel, 4:1 hexane: ethyl acetate ($R_f = 0.18$). White solid; yield: 177 mg (88%). Mp = 139-141 $^{\circ}\text{C}$. ^1H NMR (CDCl_3): δ 7.15 (t, 1H, $J = 7.8$ Hz, *ArH*), 6.64 (d, 1H, $J = 7.5$ Hz, *ArH*), 6.60 (s, 1H, *ArH*), 6.52 (dd, 1H, $J = 8.7$ Hz, 2 Hz, *ArH*), 4.59 (s, 2H, CH_2OH), 3.27 (tt, 1H, $J = 10.2$ Hz, 3.7 Hz, *NCH*), 2.07-2.03 (m, 2H, CH_2), 1.79-1.75 (m, 2H, CH_2), 1.67-1.63 (m, 1H, CH_2), 1.42-1.33 (m, 2H, CH_2), 1.27-1.05 (m, 3H, CH_2) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 147.9, 142.3, 129.7, 115.6, 112.7, 111.7, 65.9, 51.8, 33.7, 26.1, 25.2 ppm. IR (CDCl_3 , cm^{-1}): 3607, 3424, 2933, 2856, 1607, 1474, 1382. Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}$: C, 76.06; H, 9.33. Found: C, 76.10; H, 9.20.

1-(*m*-tolyl)pyrrolidine (entry 9).⁵ Following Procedure A, 3-iodotoluene (218 mg, 1.0 mmol) was allowed to react with pyrrolidine (107 mg, 1.5 mmol) for 6 h. Column chromatography: silica gel, 40:1 hexane : ethyl acetate. Yellow oil; yield: 145 mg (90%). ^1H NMR (CDCl_3): δ 7.25-7.21 (m, 1H, *ArH*), 6.60 (d, 1H, $J = 7.5$ Hz, *ArH*), 6.51-6.49 (m, 2H, *ArH*), 3.37 (m, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.09 (m, 2H, CH_2) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 148.6, 139.3, 129.5, 116.9, 112.9, 109.4, 47.8, 26.0, 22.4 ppm. IR (neat, cm^{-1}): 3041, 2966, 2832, 1579, 1603, 1498, 1458, 1368, 1321, 1173, 1022, 991, 830, 763, 690.

Amination of Heterocycle-Containing Substrates: Table 2.

3-(N-cyclohexyl)-aminopyridine.⁶ Following Procedure A, 3-iodopyridine (205 mg, 1.0 mmol) was allowed to react with cyclohexylamine (150 mg, 1.5 mmol) for 10 h. Column chromatography: silica gel, 1:1 hexane: ethyl acetate (R_f = 0.12). White solid; yield: 159 mg (90%). Mp = 105-107 °C (lit. Mp = 108-109).⁶ ¹H NMR (CDCl₃): δ 7.97 (s, 1H, *pyr H*), 7.88 (d, 1H, J = 4.1 Hz, *pyr H*), 7.03 (dd, 1H, *pyr H*), 6.82 (m, 1H, *pyr H*), 3.63 (br s, 1H, *NH*), 3.22 (m, 1H, *NCH*), 2.02 (m, 2H, *Cy*), 1.74 (m, 2H, *Cy*), 1.62 (m, 1H, *Cy*), 1.33 (m, 2H, *Cy*), 1.54 (m, 3H, *Cy*) ppm. ¹³C{¹H} NMR (CDCl₃): δ 143.8, 138.6, 136.8, 124.1, 119.0, 51.8, 33.6, 26.2, 25.3 ppm. IR (CDCl₃, cm⁻¹) 3419, 3273, 3154, 3047, 2934, 2856, 1588, 1500, 1482, 1416, 1318, 1262, 1248, 1147, 1117, 1100, 910, 793, 738, 650. Anal. Calcd for C₁₁H₁₆N₂: C, 74.96; H, 9.15. Found: C, 74.88; H, 9.25.

2,2-Dimethyl-5-(pyridin-3-ylamino)-pentan-1-ol (entry 2). [Note: Et₂O was used in the initial work up to prevent transesterification by ethyl acetate] Following Procedure A, 3-iodopyridine (205 mg, 1.0 mmol) was allowed to react with 5-amino-2,2-dimethylpentanol (196 mg, 1.5 mmol) for 20 h. The mixture was diluted with Et₂O and was filtered to remove inorganic salts. The solvent was removed using rotary evaporation and the residue was purified by column chromatography. Silica gel, pure ethyl acetate (R_f = 0.05 in ethyl acetate). Yellow solid; yield: 177 mg (85%). Mp = 102-103 °C. ¹H NMR (CDCl₃): δ 7.94 (d, 1H, *pyr H*), 7.86 (dd, 1H, *pyr H*), 7.03 (dd, 1H, *pyr H*), 6.80 (m, 1H, *pyr H*), 3.94 (br s, 1H, *NH or OH*), 3.52 (br s, 1H, *NH or OH*), 3.30 (s, 2H, *CH₂OH*), 3.03 (m, 2H, *CH₂*), 1.55 (m, 2H, *CH₂*), 1.33 (m, 2H, *CH₂*), 0.85 (s, 6H, *CH₃*) ppm. ¹³C{¹H} NMR (CDCl₃): δ 145.0, 138.4, 136.0, 124.2, 118.8, 71.5, 44.7, 36.2, 35.4, 24.4, 24.2 ppm. IR (CDCl₃, cm⁻¹) 3625, 3311, 2956, 2870, 2251, 1591, 1504, 1474, 1320, 1300, 1243, 1041, 908, 733, 649. Anal. Calcd for C₁₂H₂₀N₂O: C, 69.19; H, 9.68. Found: C, 69.01; H, 9.78.

(3-Imidazol-1-yl-propyl)-pyridin-2-ylamine (entry 3). Following Procedure A, 2-iodopyridine (205 mg, 1.0 mmol) was allowed to react with 1-(3-aminopropyl)-imidazole (188 mg, 1.5 mmol) for 14 h. Column chromatography: silica gel, 20:1 CH₂Cl₂ (sat'd with NH₃):MeOH (R_f = 0.15; see General Information). Yellow solid; yield: 182 mg (90%). Mp = 92-93. ¹H NMR (CDCl₃): δ 8.07 (ddd, 1H, *pyr H*), 7.48 (s, 1H, *imid H*), 7.39 (ddd, 1H, *pyr H*), 7.06 (s, 1H, *imid H*), 6.92 (s, 1H, *imid H*), 6.57 (ddd, 1H, *pyr H*), 6.33 (d, 1H, J = 8.4 Hz, *pyr H*), 4.60 (br s, 1H, *NH*), 4.05 (t, 2H, J = 6.9 Hz, *CH₂*), 3.31

(pseudo q, 2H, CH_2), 2.09 (t, 2H, $J = 6.8$ Hz, CH_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 159.0, 148.4, 137.8, 137.6, 129.9, 119.3, 113.4, 107.8, 44.9, 39.1, 31.4 ppm. IR ($CDCl_3$, cm^{-1}) 3437, 3278, 2940, 1602, 1572, 1506, 1448, 1327, 1287, 1230, 1152, 1109, 1078, 909, 817, 773, 733, 662, 650, 624. Anal. Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98. Found: C, 65.22; H, 7.02.

Pyrazin-2-ylthien-2-ylmethylamine (entry 4). Following Procedure A, iodopyrazine (206 mg, 1.0 mmol) was allowed to react with 2-thienemethylamine (158 mg, 1.4 mmol) for 30 min. Column chromatography: silica gel, 1:1 hexane: ethyl acetate ($R_f = 0.22$ in 1:1 hexane:ethyl acetate). Yellow crystalline solid; yield: 186 mg (97%). Mp = 189-191 (dec). 1H NMR ($CDCl_3$): δ 8.02 (br s, 1H, *pyr CH*), 7.91 (br s, 1H, *pyr CH*), 7.84 (br s, 1H, *pyr CH*), 7.22 (dd, 1H, $J = 5.1$ Hz, 1 Hz, *thiophene CH*), 7.02 (dd, 1H, $J = 3.4$ Hz, 1 Hz, *thiophene CH*), 6.96 (dd, 1H, $J = 5.0$ Hz, 3.5 Hz, *thiophene CH*), 5.07 (br s, 1H, *NH*), 4.74 (d, 2H, $J = 5.6$ Hz, CH_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 154.4, 142.3, 141.9, 133.8, 132.9, 127.3, 126.2, 125.5, 40.7 ppm. IR ($CDCl_3$, cm^{-1}) 3435, 3277, 3061, 2929, 1589, 1537, 1502, 1427, 1326, 1294, 1201, 1148, 1040, 1003, 910, 825, 826, 739, 650, 420. Anal. Calcd for $C_9H_9N_3S$: C, 56.52; H, 4.74. Found: C, 56.72; H, 4.70.

Allyl-thiophen-3-yl-amine (entry 5). [2 mmol scale] Following procedure A, 3-iodothiophene (420 mg, 2.0 mmol) was allowed to react with allylamine (171 mg, 3 mmol) for 17 h. Column chromatography: silica gel, 30:1 hexane: ethyl acetate ($R_f = 0.17$ in 20:1 hexane:ethylacetate). Yellow oil, rapidly became dark-red upon exposure to air; yield: 230 mg (83%). 1H NMR ($CDCl_3$): δ 7.17 (dd, 1H, *thiophene CH*, $J = 5.1$ Hz, 3.1 Hz), 6.64 (dd, 1H, $J = 5.1$ Hz, 1.5 Hz, *thiophene CH*), 6.04-5.94 (m, 2H, overlapping *thiophene CH* and vinylic CH_2CH), 5.31 (doublet of *pseudo* quartets, 1H, $J = 17.2$ Hz, *apparent* second $J = 1.6$ Hz, terminal $C=CH$), 5.19 (doublet of *pseudo* quartets, 1H, $J = 10.3$ Hz, *apparent* second $J = 1.4$ Hz, terminal $C=CH$), 3.74 (dt, 2H, $J = 5.6$ Hz, 1.5 Hz, CH_2), 3.75 (br s, 1H, *NH*) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.7, 136.0, 125.6, 120.4, 116.8, 96.5, 49.4 ppm. IR (neat, cm^{-1}) 3381, 3100, 3081, 2979, 2916, 2827, 1644, 1560, 1488, 1420, 1366, 1331, 1230, 1189, 1077, 995, 925, 865, 833, 749, 625, 526. Anal. Calcd for C_7H_9NS : C, 60.39; H, 6.52. Found: C, 60.22; H, 6.42.

Thiophen-3-yl-(2-thiophen-2-yl-ethyl)-amine (entry 6). Following Procedure A, 3-iodothiophene (210 mg, 1.0 mmol) was allowed to react with 2-thiopheneethylamine (191 mg, 1.5 mmol) for 17 h. Column chromatography: silica gel, 20:1 hexane: ethyl

acetate ($R_f = 0.20$ in 10:1 hexane: ethyl acetate). Yellow oil, rapidly became dark-red upon exposure to air; yield: 168 mg (80%). ^1H NMR (CDCl_3): δ 7.20-7.14 (m, 2H, two overlapping *CH*), 6.99-6.96 (m, 1H, *CH*), 6.89-6.88 (m, 1H, *CH*), 6.62 (dd, 1H, $J = 4.8$ Hz, 1.5 Hz, *CH*), 6.02-6.01 (m, 1H, *CH*), 3.77 (br s, 1H, *NH*), 3.40 (t, 2H, $J = 6.7$ Hz, CH_2), 3.16 (t, 2H, $J = 6.7$ Hz, CH_2) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 148.4, 142.2, 127.4, 125.8, 125.7, 12.3, 120.5, 96.5, 47.9, 30.1 ppm. IR (CDCl_3 , cm^{-1}) 3599, 3343, 2924, 1619, 1568, 1514, 1489, 1424, 1308, 1242, 1219, 1184, 1021, 909, 822, 788. Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{NS}_2$: C, 57.38; H, 5.30. Found: C, 57.60; H, 5.24.

4-[(5-Methyl-furan-2-ylmethyl)-amino]-phenol (entry 7). The compound was prepared by a modification of Procedure A using 2.6 mmol of Cs_2CO_3 . Thus, 4-iodo-phenol (220 mg, 1.0 mmol) was coupled with 5-methylfurfurylamine (166 mg, 1.5 mmol) in the presence of 845 mg of Cs_2CO_3 (2.6 mmol) for 14 h. Mixture was diluted with ethyl acetate and was neutralized with a 10% HCl solution until a pH of ~ 4 was reached. The mixture was transferred to a separatory funnel and the organic layer was separated. After additional extractions with two 10 mL portions of ethyl acetate, the combined organic fraction was concentrated. Column chromatography: silica gel, 2:1 hexane: ethyl acetate. Yellow oil, became red upon exposure to air, yield: 162 mg (80%). ^1H NMR (CDCl_3): δ 6.69 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.60 (d, 2H, $J = 8.8$ Hz, *ArH*), 6.08 (d, 1H, $J = 3.0$ Hz, *fur CH*), 5.88 (d, 1H, $J = 3.0$ Hz, *fur CH*), 4.52 (br s, 2H, *NH and OH*), 4.16 (s, 2H, CH_2), 2.26 (s, 3H, *Me*) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 152.1, 151.2, 148.9, 141.9, 116.6, 115.7, 108.4, 106.6, 106.5, 43.2, 14.0 ppm. IR (CDCl_3 , cm^{-1}) 3599, 3343, 3024, 2942, 2253, 1619, 1568, 1514, 1424, 1308, 1242, 1218, 1184, 1021, 906, 822, 788, 650.

***N,N'*-Bis-(2-thiophen-2-yl-ethyl)-benzene-1,4-diamine (entry 8).** [0.5 mmol scale, using 3-fold excess of amine] Following Procedure A, 1,4-di-iodobenzene (165 mg, 0.5 mmol) was coupled with 2-thiopheneethylamine (191 mg, 1.5 mmol) for 3 h. Column chromatography: silica gel, 4:1 hexane: ethyl acetate ($R_f = 0.10$). Yellow crystalline solid (slowly became red upon exposure to air); yield: 154 mg (94%). An analytically pure sample was obtained by recrystallization from ethyl acetate in 76% yield (slow cooling to -20 $^\circ\text{C}$; required scratching the bottom of the flask to induce crystallization). Mp = 123-124 $^\circ\text{C}$. ^1H NMR (CDCl_3): δ 7.18 (dd, 2H, $J = 5.13$ Hz, 1 Hz, *thiophene CH*), 6.97 (dd, 2H, $J = 5.1$ Hz, 3.4 Hz, *thiophene CH*), 6.87 (dd, 2H, $J = 3.3$ Hz, 1 Hz, *thiophene CH*), 6.59 (br s, 4H, *ArH*), 3.39 (br s, 6H, overlapping CH_2 and *NH*), 3.12 (t, 4H, $J = 6.7$ Hz, CH_2) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 142.4, 140.7, 127.4, 125.7, 124.2, 115.6, 46.9, 30.3 ppm. IR (CDCl_3 , cm^{-1}) 3370, 3027, 2921, 2844, 2252, 1516, 1474, 1243, 1129, 1191, 907, 650. Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{S}_2$: C, 65.81; H, 6.14. Found: C, 65.88; H, 6.11.

Intra vs. Intermolecular Amination: Scheme 2

Indoline from RT cyclization of (2'-bromo)-2-phenethylamine using CuI/L4.⁷

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, CuI (20 mg, 0.10 mmol, 5 mol %) and Cs₂CO₃ (1.30 g, 4 mmol). The tube was evacuated and backfilled with argon three times. Under counterflow of argon, substrate (400 mg, 2.0 mmol), DMF (1.0 mL) and **L4** (68 mg, 0.4 mmol) were added, the tube was sealed and the mixture was allowed to stir under argon at ambient temperature for 30 min. At this point the reaction mixture was diluted with ethyl acetate, filtered to remove inorganic salts and the solvent was evaporated. Residue was purified by column chromatography: silica gel, 10:1 hexane: ethyl acetate (*R_f* = 0.18). Yellow oil; yield: 219 mg (92%). ¹H NMR (CDCl₃): δ 7.14 (d, 1H, *J* = 7.2 Hz, *ArH*), 7.04 (m, 1H, *ArH*), 6.72 (m, 1H, *ArH*), 6.66 (d, 1H, *J* = 7.8 Hz), 3.77 (br s, 1H, *NH*), 3.57 (t, 2H, *J* = 8.4 Hz, *CH*₂), 3.06 (t, 2H, *J* = 8.4 Hz, *CH*₂) ppm. ¹³C{¹H} NMR (CDCl₃): δ 152.1, 129.8, 127.7, 119.1, 109.9, 47.8, 30.3 ppm.

Indoline from RT cyclization of (2'-bromo)-2-phenethylamine: no ligand. This procedure differed from the previous one only in that the ligand was omitted from the mixture. The reaction mixture was allowed to stir at ambient temperature for 3 h. Dodecane (1 mmol) was added as an internal standard and the mixture was analyzed by GC. Analysis indicated complete consumption of the starting material and a 91% GC yield (corrected) of the desired indoline.

Indoline: cyclization of (2'-chloro)-2-phenethylamine with CuI/L4.

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, CuI (20 mg, 0.05 mmol, 5mol%) and Cs₂CO₃ (1.30 g, 4 mmol). The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under counterflow of argon, substrate (310 mg, 2.0 mmol), 1.0 mL of DMF and **L4** (68 mg, 0.4 mmol, 20 mol%) were added, the tube was sealed and the mixture was allowed to stir under argon at 60 °C for 10 h. At this point the reaction mixture was diluted with ethyl acetate, filtered to remove inorganic salts and the solvent was removed. The residue was purified by column chromatography on silica gel (10:1 hexane: ethyl acetate mixture). Yield: 202 mg (85%). The characterization data matched that of compound obtained from the cyclization of the bromide derivative.

Intermolecular coupling: (4-Bromophenyl)-[2-(2-chloro-phenyl)-ethyl]-amine.

Following Procedure A, 1-bromo-4-iodobenzene (282 mg, 1.0 mmol) was allowed to react with 2-(2-chlorophenyl)-ethylamine (202 mg, 1.3 mmol) for 2 h. Column chromatography: silica gel, 20:1 hexane: ethyl acetate ($R_f = 0.17$). Beige oil; yield: 308 mg (99%). ¹H NMR (CDCl₃): δ 7.40-7.38 (m, 1H, *ArH*), 7.28-7.20 (m, 5H, *overlapping ArH*), 6.51 (d, 2H, $J = 8.9$ Hz, *ArH*), 3.78 (br s, 1H, *NH*), 3.40 (t, 2H, $J = 7.1$ Hz *CH*₂), 3.04 (t, 2H, $J = 7.1$ Hz, *CH*₂) ppm. ¹³C{¹H} NMR (CDCl₃): δ 147.3, 137.1, 134.5, 132.4, 131.4, 130.1, 128.5, 127.4, 114.9, 109.4, 43.8, 33.7 ppm. Anal. Calcd for C₁₄H₁₃BrClN: C, 54.13; H, 4.22. Found: C, 54.34; H, 3.99. IR (neat, cm⁻¹): 3412, 3322, 3300, 2989, 2959, 1576, 1512, 1467, 1337, 1212.

Copper-Catalyzed Amination of Aryl Bromides: Table 3

1-(3-Hexylamino-phenyl)-ethanone (entry 1). Following Procedure B, 3-bromoacetophenone (199 mg, 1.0 mmol) was allowed to react with *n*-hexylamine (151 mg, 1.5 mmol) in the presence of Cs₂CO₃ (650 mg, 2.0 mmol) at 90 °C for 3 h. Column chromatography: 10:1 hexane: ethyl acetate. Yellow oil; yield: 203 mg (93%). ¹H NMR (CDCl₃): δ 7.28 (m, 2H), 7.16 (s, 1H), 6.78 (m, 1H), 3.76 (br s, 1H, *NH*), 3.14 (t, 2H, *J* = 7.0 Hz), 2.57 (s, 3H, C(O)*CH*₃), 1.66-1.57 (m, 2H, *CH*₂), 1.45-1.25 (m, 6H, *CH*₂), 0.90 (t, 3H, *J* = 5.7 Hz, *CH*₃) ppm. ¹³C{¹H} NMR (CDCl₃): δ 199.2, 149.1, 138.5, 129.7, 117.9, 111.7, 44.3, 32.0, 29.8, 27.2, 27.1, 23.0, 14.5 ppm. IR (neat, cm⁻¹): 3390, 2955, 2928, 2857, 1678, 1603, 1584, 1515, 1489, 1469, 1432, 1337, 1355, 1269, 1237.

(3,4-Dimethoxy-benzyl)-(3-[1,3]dioxolan-2-yl-phenyl)-amine (entry 2). Following Procedure B, 2-(3-bromo-phenyl)-[1,3]dioxolane (229 mg, 1.0 mmol) was allowed to react with 3,4-dimethoxybenzylamine (250 mg, 1.5 mmol) in the presence of Cs₂CO₃ (650 mg, 2.0 mmol) at 90 °C for 6 h. Column chromatography: silica gel, 2:1 hexane: ethyl acetate (*R*_f = 0.12). White crystalline solid; yield: 290 mg (90%). Mp = 145-146 °C. ¹H NMR (CDCl₃): δ 7.18 (pseudo t, 1H, *ArH*), 6.92-6.75 (m, 5H, *ArH*), 6.61 (ddd, 1H, *ArH*), 5.75 (s, 1H, *ArCH*), 4.26 (s, 2H, *NCH*₂), 4.06-4.12 (m, 2H, *CH*₂), 3.98-4.04 (m, 3H, *NH* and *CH*₂), 3.88 (s, 3H, *CH*₃), 3.87 (s, 3H, *CH*₃) ppm. ¹³C NMR (CDCl₃): δ 149.5, 148.8, 148.6, 139.3, 132.2, 129.8, 120.1, 116.0, 114.0, 111.5, 111.2, 111.0, 104.3, 65.6, 56.6, 56.3, 48.6 ppm. IR (CDCl₃, cm⁻¹): 3420, 2891, 2838, 1610, 1594, 1515, 1465, 1263, 1028.

(3,5-Dimethyl-phenyl)-(1-phenyl-ethyl)-amine (entry 3).⁸ Following Procedure B, 5-bromo-*m*-xylene (185 mg, 1.0 mmol) was allowed to react with 1-phenylethylamine (181 mg, 1.5 mmol) in the presence of K₃PO₄ (425 mg, 2.0 mmol) at 90 °C for 10 h. Column chromatography: silica gel: gradient hexane → 20:1 hexane: ethyl acetate (*R*_f = 0.2 in 20:1 hexane : ethyl acetate). Yellow oil; yield: 204 mg (94%). ¹H NMR (CDCl₃): δ 7.39-7.29 (m, 4H), 7.22 (t, 1H, *J* = 7.2 Hz), 6.32 (s, 1H, *p*-*xylyl* H), 6.17 (s, 2H, *m*-*xylyl* H), 4.48 (q, 1H, *J* = 6.7 Hz, *NCH*), 3.9 (br s, 1H, *NH*), 2.17 (s, 6H, 3,5-Me), 1.50 (d, 3H, *J* = 6.7 Hz, *CH*₃) ppm. ¹³C NMR (CDCl₃): δ 147.9, 145.8, 139.2, 129.0, 127.2, 126.3, 119.7,

111.5, 53.7, 25.3, 21.9 ppm.

2-[4-(4-Amino-benzylamino)-phenyl]-ethanol (entry 5). Following Procedure B, 2-(4-bromo-phenyl)-ethanol (201 mg, 1.0 mmol) was allowed to react with 4-aminomethyl-phenylamine (185 mg, 1.5 mmol) in the presence of K_3PO_4 (425 mg, 2.0 mmol) at 90 °C for 19 h. Column chromatography: silica gel: gradient 1:1 -> 1:2 hexane: ethyl acetate (R_f = 0.2 in 1:2 hexane: ethyl acetate). Yellow powder; yield: 212 mg (87%). Mp = 167-168 °C. 1H NMR ($CDCl_3$): δ 7.16 (d, 2H, J = 8.4 Hz, *ArH*), 7.03 (d, 2H, J = 8.4 Hz, *ArH*), 6.67 (d, 2H, J = 8.4 Hz, *ArH*), 6.60 (d, 2H, J = 8.4 Hz, *ArH*), 4.17 (s, 2H, NCH_2), 3.79 (t, 2H, J = 6.5 Hz, CH_2OH), 3.65 (br s, 3H), 2.76 (t, 2H, J = 6.5 Hz, CH_2CH_2OH), 1.4 (br s, 1H, *NH or OH*) ppm. $^{13}C\{^1H\}$ NMR 147.4, 146.0, 130.3, 129.6, 129.3, 127.2, 115.7, 113.5, 64.4, 48.5, 38.7 ppm. Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49. Found: C, 74.40; H, 7.71.

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