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Note

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Structure Ligation Relationship of Amino Acids for the Amination Cross-Coupling Reactions

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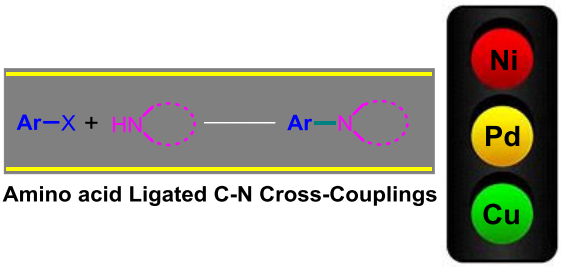
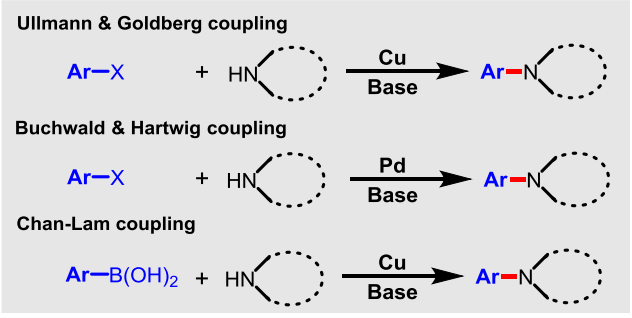


ABSTRACT: The **S**tructure **L**igation **R**elationship (SLR) of amino acids (AA) for the cross-coupling aminations was examined. While AA ligated C–N cross-coupling under Pd- and Ni- catalysis were minor or ineffective, the AA ligated Cu-catalyzed C–N cross-couplings were promising particularly with the use of L-Methionine. The role –NH_2, -CO_2H, and –S- of L-Methionine were investigated and found critical for their ligation efficiency. The finding was compatible with aromatic as well as aliphatic amines including tautomerizable *N*-heteroarenes.

Introduction of nitrogen functionality into carbocyclic frameworks has been the hot area of research owing to the ubiquity of amino compounds in pharmaceuticals, agrochemicals, and functional materials.[1] While traditional approaches to construct C–N bonds often require multi-steps procedure, the metal-catalyzed C–N bond formations has opened a new avenue in context of efficiency and applicability.[2] In this regard, the cross coupling of amine nucleophiles with prefunctionalized arene electrophiles (Ullmann reaction[3] and Buchwald–Hartwig reaction[4]) or nucleophiles (Chan–Lam reaction[5]) constitute the fundamental building blocks (Scheme 1). Recently, direct C–H aminations[6] emerged as valuable strategy for C–N bond formation complementing the classical cross coupling procedures.

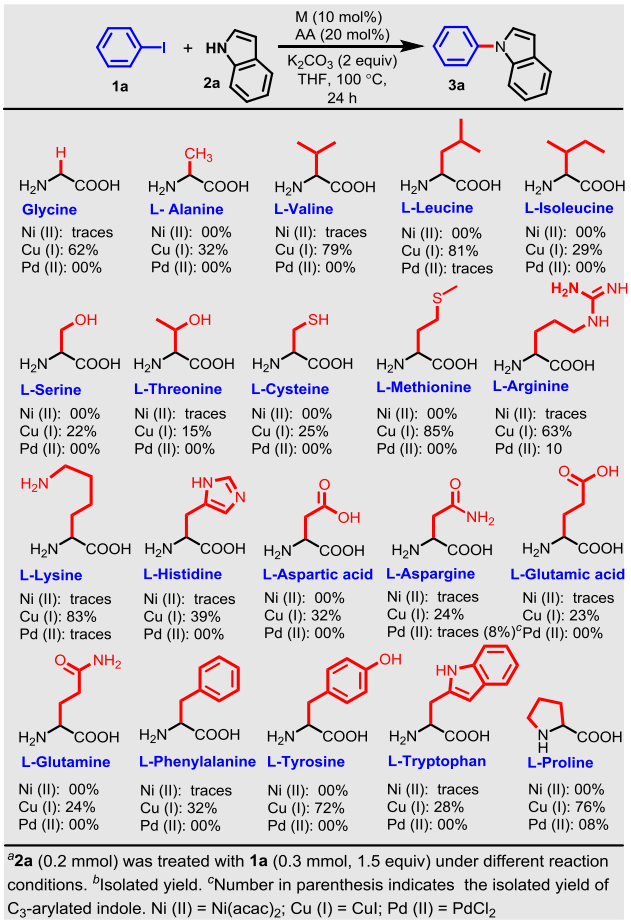
Scheme 1: Metal-catalyzed cross coupling C–N Bond Formation reactions.



Amino acids (AAs), the fundamental building blocks of life, have been exploited well in organic synthesis and catalysis including asymmetric reactions[7] and direct C-H functionalizations.[8] The ease of availability and its derivatizations (cost-effectiveness), tolerance toward aerial oxidation & moisture, and lack of general toxicity is the key advantages. The use of amino acid ligands in cross-coupling reactions including C-N bond formation is documented,[9] however their general **S**tructure **L**igation **R**elationship (**SLR**) or **S**tructure **E**fficiency **R**elationship (**SER**) have been not investigated. In this context, the present work aims to evaluate AA ligations (**SLR**) on C–N bond formation under Cu-, Pd-, and Ni-catalysis and subsequently translate the optimal catalytic combinations for the general amination cross-couplings.

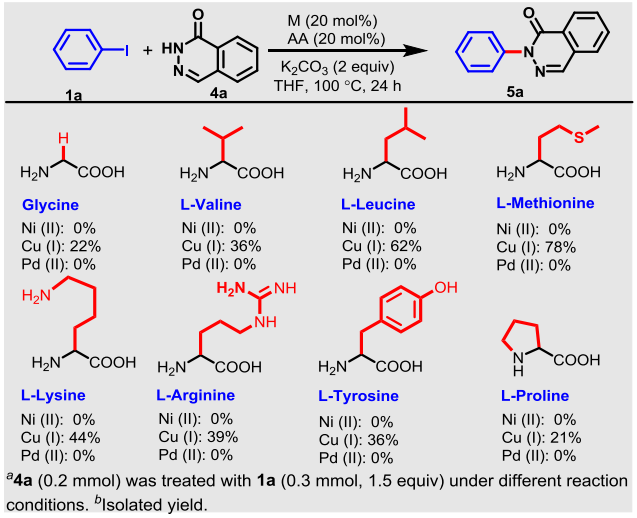
The study begun with evaluating different AAs for the C–N bond formation under metal catalysis (Scheme 2). For each AA, three parallel reactions were performed, representing Ni-, Pd-, and Cu-catalysis respectively. The reason being choosing indole as amine source is the challenges lie ahead in controlling selectivity as it represents a reactant with three distinct nucleophilic sites (NH, C3–H, and C2–H). We initially examined the cross-coupling of iodobenzene (**1a**) with indole (**2a**), employing Ni (II) as metal precursor. No C–N bond formation (**3a**) was observed in any case, the starting **2a** was found intact (no C-arylation was observed as well).

Scheme 2. Evaluation of AAs ligation for C–N cross-couplings under metal catalysis. [a, b, c]



[a]**2a** (0.2 mmol) was treated with **1a** (0.3 mmol, 1.5 equiv) under different reaction conditions. [b]Isolated yield. [c]Number in parenthesis indicates the isolated yield of C_3-arylated indole. Ni (II) = Ni(acac)$_2$; Cu (I) = CuI; Pd (II) = $PdCl_2$

Scheme 3. Ligation distinction of elected AAs for C–N cross-coupling reactions under metal catalysis. [a, b]



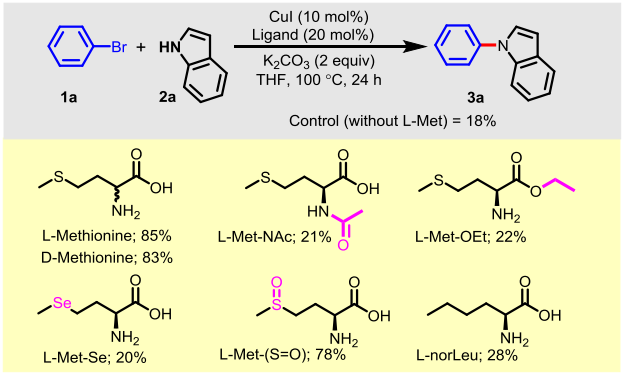
[a]**4a** (0.2 mmol) was treated with **1a** (0.3 mmol, 1.5 equiv) under different reaction conditions. [b]Isolated yield.

Next, the AA ligation for C–N bond formation was examined under Pd (II)-catalysis. The results were quite interesting as we observed the formation of both, the C–N bond (see, L-Arg, L-Lys, L-Pro) and C–C bond (see, L-Asp), however the yields were very poor (< 10%). The scope of AAs ligation for C–N bond formations under Cu (I)-catalysis was examined subsequently. The formation of C–N bond was observed with variable yields of **3a** in different AAs such as Gly (62%), L-Val (79%), L-Leu (81%), L-Met (92%), L-Arg (63%), L-Lys (83%), L-Tyrosine (72%), and L-Proline (76%). In order to obtain the ligation distinction between these elected AAs, cross coupling of **1a** with 1(2*H*)-phthalazinone (**4a**) were performed (Scheme 3). The results were promising, the use of L-Met was found distinctly superior over others, with 78% yield of **5a**.

The above studies concluded that AA ligation suits best with Cu-catalysis for C–N cross-coupling reactions, the L-Met being the distinctly superior over others notable AAs such as Gly, L-Val, L-Leu, L-Lys, L-Arg, L-Tyr, and L-Pro. The AA-ligated Pd-catalysis was capable of C–N bond formations; however selectivity was an issue as it forms the competitive side products (C–arylation) significantly. The AAs as ligand were ineffective for C–N cross-coupling reaction under Ni-catalysis.

For the catalytic system consisting of Cu (I)/α-amino acid, rate and yields is induced by the structure of the α-amino acid. The greater ability of L-Met, a sulfur-containing AA, to promote coupling reactions might be dependent on the presence of thioether sulfur donors in its structure, in addition to the N and O donor groups, which may lead to more active and stable Cu (I) species in the reaction medium. To gain insight further, structural analogs of L-Met such as N-Acetyl-L-Met (L-Met-NAc), L-Met ethyl ester (L-Met-OEt), L-Met sulfoxide [L-Met-(S=O)], Seleno-L-Met (L-Met-Se), and L-Norleucine were investigated under optimized conditions to elucidate the role of –NH2, -CO2H, and –S- (Scheme 4). The yield of **3a** was significantly decreased in case of L-Met-NAc (21%), L-Met-OEt (22%), L-Met-Se (20%), and L-norLeu (28%) suggesting the simultaneous involvement of free -NH2, -CO2H, and –S-. The L-Met-(S=O) was ligable to provide excellent yield (78%), however inferior compared to L-Met (85 %). A similar yield was obtained using isomeric D-Met (83%) indicating chirality of AAs insignificant.

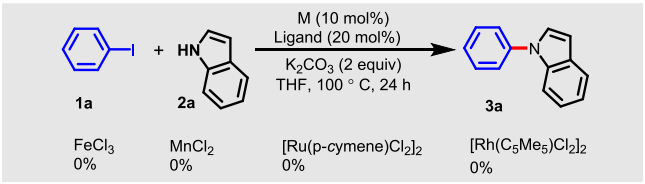
Scheme 4. Investigation of role of L-Met as ligand



Ligation of L-Met for the C–N cross-couplings with other metal-catalysis such as iron, manganese, rutheni-

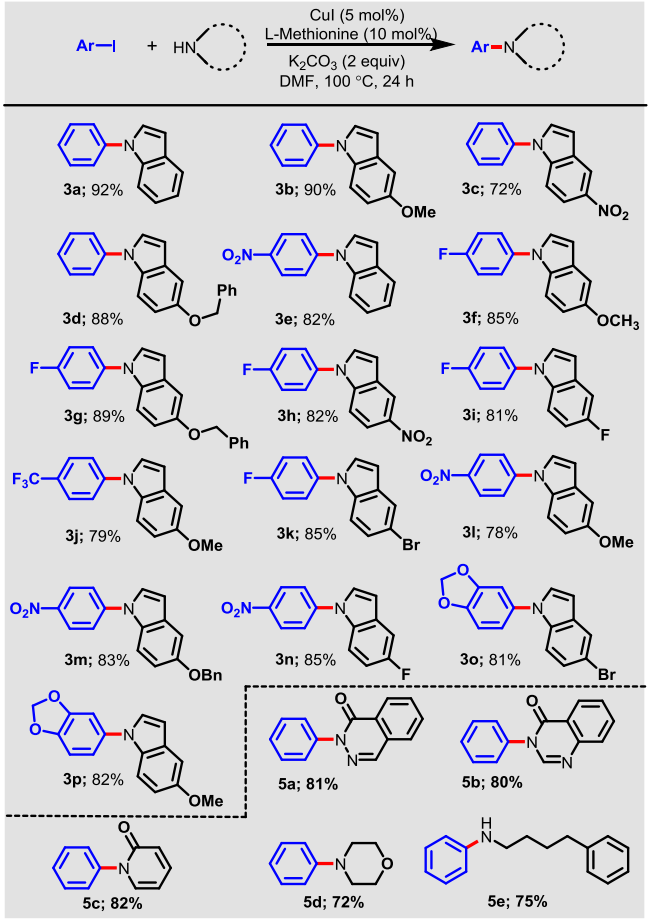
um, rhodium were re-investigated; however, it was discouraging as no desired **3a** was formed in any case as shown in scheme 5.

Scheme 5. Re-investigation of L-Met ligation for cross-coupling amination reaction under Fe-, Mn-, Ru-, Rh- catalysis.



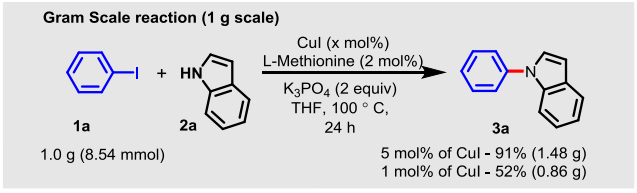
We took this opportunity to discover a general high yielding protocol for the synthesis of high value *N*-aryl indoles. A full optimization of different reaction parameters revealed the use of 5 mol % of CuI with 10 mol% of L-Met in presence of K_2CO_3 (2 equiv) at 100 °C in DMF was optimal with 92% yield of **3a**. Variations in the Cu-source using L-Met as ligand resulted inferior results (see ESI).

Scheme 6. C–N cross-couplings of various amines under optimized conditions unless otherwise noted.



With optimized conditions, the scope of developed protocol was examined. As summarized in Scheme 6, various indoles bearing e-withdrawing groups, e-releasing groups, halogens etc. were reacted well with electronically different iodobenzenes affording excellent yields of *N*-arylated indoles. Wide range of functional groups (–OMe, -OBn, –F, –Br, $–NO_2$,$–CF_3$, $–OCH_2O–$) tolerated well, validating the robustness of protocol. The applicability of this protocol was further extended to other biologically relevant *N*-heteroarenes. Gratifyingly, *N*-arylation of electron-deficient tautomerizable bioactive *N*-heteroarenes such as phthalazine **5a**, quinazoline **5b**, and pyridine **5c** proceeded well with excellent yields and chemoselectivity. The efficiency of the developed protocol with aliphatic amines was showcased using representative examples (**5d** and **5e**) with excellent yields.

Scheme 7. Demonstration of gram scale reaction



To demonstrate the scalability and utility of the protocol, the reaction was also performed on a gram scale. Treatment of **2a** (1 g, 8.54 mmol) with **1a** under optimized condition resulted the formation of **3a** in 91%. A 52% of **3a** was obtained using 1 mol% of CuI and 2 mol% of L-Met (Scheme 7).

In conclusion, the present work reports the scope and limitations of the amino acids (AAs) ligation for the cross-coupling amination reactions under commonly exercised metal (Cu-, Pd-, & Ni-) catalysis. While AAs were ineffective ligand for C–N cross-coupling under Ni-catalysis, their ligation under Pd- and Cu-catalysis were capable for C–N bond construction. However, AA-ligated C–N cross-coupling under Pd-catalysis is markedly inferior compared to Cu-catalysis in term of chemoselectivity and yields. While several AAs were found effective for C–N cross-couplings under Cu-catalysis, the use of L-Met is distinctly superior and versatile. The finding was applied to construct the varieties of *N*-aryl indoles in excellent yields with high functional group tolerance. Notably, the methodology was found effective for C–N cross-couplings using electron deficient tautomerizable *N*-heteroarenes and aliphatic amines as well. The mechanistic studies indicated the simultaneous involvement of the NH2, -CO2H, and –S- of L-Met is critical for effective ligation.

EXPERIMENTAL SECTION

Unless otherwise noted, all manipulations (reactions) were carried out in oven-dried glasswares under nitrogen conditions. All commercially obtained reagents/solvents were used as received; chemicals were purchased from Alfa Aesar®, Sigma-Aldrich®, Acros®, and were used as received without further purification. ^{1}NMR and ^{13}C NMR

spectra were recorded on Brukar 400 MHz and 100 spectrometers respectively using TMS as an internal standard. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane (δ = 0). Data for ^{1}H NMR are reported as chemical shift (δ ppm) with the corresponding integration values. Coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), b (broad), d (doublet), t (triplet), q (quartet) and m (multiplet). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). High-resolution mass spectra of unknown products were obtained at Agilent QTOFs spectrometer in positive (ESI$^+$) ion mode.

Representative procedure for C-N bond formation: To dried tube equipped with a stir bar, CuI (1.90 mg, 0.01 mmol, 5 mol%), L-Met (2.98 mg, 0.02 mmol, 10 mol%), Indole **2a** (23.43 mg, 0.2 mmol), iodobenzene **1a** (33.57 µL, 61.20 mg, 0.3 mmol, 1.5 equiv), K_2CO_3 (55.28 mg, 0.4 mmol, 2.0 equiv) followed by DMF (1 mL) was added and the resulting reaction mixture was stirred at 100 °C (oil bath). After 24 h, the reaction mixture was cooled to rt, adsorbed on to silica gel and purified by column chromatography using petroleum ether (PE) and ethyl acetate (EA) (6/1, R_f = 0.52) as mobile phase to get analytically pure **3a**[10a] (35.57 mg, 92%) as white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.65 (m, 4H), 7.54-7.49 (m, 2H), 7.47 – 7.38 (m, 2H), 6.90 (d, *J* = 3.2 Hz, 1H); ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 140.00, 136.04, 129.81, 129.57, 128.15, 126.61, 124.52, 122.60, 121.38, 120.61, 110.75, 103.83; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{12}N$ 194.0964, Found 194.0966.

5-Methoxy-1-phenyl-1*H*-indole[10b] **(3b):** White solid (40.18 mg, 90%); purified by column chromatography using PE/EA: 9/1, R_f = 0.58; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.39 (m, 5H), 7.33 – 7.23 (m, 2H), 7.12 (d, *J* = 2.5 Hz, 1H), 6.86 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.57 (dd, *J* = 3.3, 0.8 Hz, 1H), 3.83 (s, 3H); ^{13}C {**^{1}H**} NMR (101 MHz, $CDCl_3$) δ δ154.7, 140.0, 131.1, 130.0,129.71, 128.4, 126.3, 124.08, 112.6, 111.5, 103.4, 102.8, 55.9; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{14}NO$ 224.1075, Found 224.1078.

5-Nitro-1-phenyl-1H-indole[10c] **(3c):** White solid (50.40 mg, 72%); purified by column chromatography using PE/EA: 9/1, R_f = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 2.3 Hz, 1H), 8.10 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.59 – 7.44 (m, 7H), 6.85 (d, *J* = 3.3 Hz, 1H); ^{13}C {**^{1}H**} NMR (101 MHz, $CDCl_3$): δ 142.2, 138.7, 138.6, 131.3, 130.0, 128.5, 127.8, 124.7, 118.3, 117.9, 110.5, 105.6; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{11}N_2O_2$239.0821, Found 239.0807.

5-(Benzyloxy)-1-phenyl-1H-indole (3d): White solid (52.68 mg, 88%); purified by column chromatography using PE/EA: 6/1, R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.46 (m, 7H), 7.45 – 7.38 (m, 2H), 7.39 – 7.30 (m, 3H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.62 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.16 (s, 2H); ^{13}C {**^{1}H**} NMR (101 MHz, $CDCL_3$) δ 153.7, 139.9, 137.6, 131.2, 129.8, 129.6, 128.6, 128.4, 127.8, 127.6, 126.3, 124.1, 113.2, 111.4, 104.3, 103.3, 70.8; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{18}NO$ 300.1383, Found 300.1387.

1-(4-Nitrophenyl)-1H-indole[10d] **(3e):** White solid (39.23 mg, 82%); purified by column chromatography using PE/EA: 9/1, R_f = 0.45; NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 8.9 Hz, 3H), 7.36 (d, *J* = 3.4 Hz, 1H), 7.25 (dtd, *J* = 24.0, 7.1, 1.2 Hz, 2H), 6.76 (dd, *J* = 3.4, 0.9 Hz, 1H); ^{13}C {**^{1}H**} NMR (101 MHz, $CDCl_3$) δ 145.2, 145.0, 135.3, 130.1, 127.1, 125.5, 123.5, 123.3, 121.7, 121.6, 110.5, 106.2; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{11}N_2O_2$239.0821, Found 239.0807.

1-(4-Fluorophenyl)-5-methoxy-1H-indole[10e] **(3f):** White solid (41.00 mg, 85%); purified by column chromatography using PE/EA: 8/1, R_f = 0.57; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.38 (m, 2H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 3.2 Hz, 1H), 7.21 – 7.15 (m, 2H), 7.13 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.59 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.86 (s, 3H): ^{13}C {**^{1}H**} NMR (101 MHz, $CDCl_3$): δ 160.9 (d, *J* = 246.0 Hz), 154.6, 136.0 (d, *J* = 2.9 Hz), 131.3, 129.7, 128.5, 125.9 (d, *J* = 8.4 Hz), 116.5 (d, *J* = 22.8 Hz), 112.6, 111.1, 103.3, 102.7, 55.9; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{13}FNO$ 242.0981, Found 242.0977.

5-(Benzyloxy)-1-(4-fluorophenyl)-1H-indole (3g): White solid (56.47 mg, 89%); purified by column chromatography using PE/EA: 19/1, R_f = 0.56;^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.31 (m, 9H), 7.24 – 7.17 (m, 3H), 6.97 (d, *J* = 8.9 Hz, 1H), 6.60 (s, 1H), 5.14 (s, 2H); ^{13}C {**^{1}H**} NMR (101 MHz, $CDCl_3$) δ 160.9 (d, *J* = 245.8 Hz), 153.7, 137.5, 135.9, 131.4, 129.6, 128.5, 128.4, 127.7, 127.4, 125.8 (d, *J* = 8.6 Hz), 116.4 (d, *J* = 22.9 Hz), 113.3, 110.9, 104.3, 103.2, 70.8; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{17}FNO$ 318.1289, Found 318.1293.

1-(4-Fluorophenyl)-5-nitro-1H-indole[10f] **(3h):** White solid (61.72 mg, 82%); purified by column chromatography using PE/EA: 9/1, R_f = 0.47; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 2.3 Hz, 1H), 8.11 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.57 – 7.35 (m, 4H), 7.27 (t, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 3.4 Hz, 1H); ^{13}C {**^{1}H**} NMR (101 MHz, $CDCl_3$): δ 161.8 (d, *J* = 248.3 Hz), 142.2, 138.9, 134.6 (d, *J* = 3.1 Hz), 131.4, 128.3, 126.6 (d, *J* = 8.5 Hz), 118.4, 118.1, 116.9 (d, *J* = 23.1 Hz), 110.2, 105.7; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{14}H_{10}FN_2O_2$ 257.0726, Found 257.0727.

5-Fluoro-1-(4-fluorophenyl)-1*H*-indole[10g] **(3i):** White solid (37.13 mg, 81%); purified by column chromatography using PE/EA: 9/1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.26 (m, 4H), 7.24 (d, *J* = 3.3 Hz, 1H), 7.15 (t, *J* = 8.5 Hz, 2H), 6.92 (td, *J* = 9.0, 2.6 Hz, 1H), 6.59 (d, *J* = 3.2 Hz, 1H); ^{13}C {**^{1}H**} NMR (101 MHz, $CDCl_3$): δ 161.2 (d, *J* = 246.7 Hz), 159.5, 157.1, 135.7 (d, *J* = 3.0 Hz), 132.8, 129.6, 126.2 (d, *J* = 8.5 Hz), 116.6 (d, *J* = 22.8 Hz), 111.0 (d, *J* = 9.0 Hz), 110.7, 105.9 (d, *J* = 23.5 Hz), 103.5 (d, *J* = 4.5 Hz); HRMS (ESI-TOF) *m/z*: [M + H]$^+$Calcd for $C_{14}H_{10}F_2N$ 230.0781, Found 230.0785

5-Methoxy-1-(4-(trifluoromethyl)phenyl)-1*H*-indole (3j): White solid (45.83 mg, 79%); purified by column chromatography using PE/EA: 19/1, R_f = 0.56; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.17 (d, J = 2.5 Hz, 1H), 6.93 (dd, J = 9.0, 2.5 Hz, 1H), 6.67 (d, J = 3.3 Hz, 1H), 3.90 (s, 3H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 154.9, 142.9, 130.6, 130.4, 127.85 (q, J = 32.6 Hz), 127.82, 126.8 (q, J = 3.8 Hz), 124.0 (q, J = 275 Hz), 123.3, 112.9, 111.2, 104,6, 103.0, 55.8; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{16}H_{12}F_3NONa$ 314.0763, Found 314.0769.

5-Bromo-1-(4-fluorophenyl)-1*H*-indole[10h] (3k): White solid (50.80 mg, 85%); purified by column chromatography using PE/EA: 19/1, R_f = 0.57; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.43 (dd, J = 8.9, 4.7 Hz, 2H), 7.35 – 7.30 (m, 2H), 7.28 (d, J = 3.3 Hz, 1H), 7.22 (t, J = 8.5 Hz, 2H), 6.62 (d, J = 3.2 Hz, 1H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 161.3 (d, J = 247.0 Hz), 135.4 (d, J = 3.1 Hz), 134.8, 130.8, 129.2, 126.2 (d, J = 8.5 Hz), 125.3, 123.6, 116.6 (d, J = 22.8 Hz), 113.6, 111.7, 103.1; HRMS (ESI-TOF) m/z: [M + H]$^+$Calcd for $C_{14}H_{10}BrFN$ 298.9981, Found 298.9985.

5-Methoxy-1-(4-nitrophenyl)-1*H*-indole[10i] (3l): White solid (41.81 mg, 78%); purified by column chromatography using PE/EA: 4/1, R_f = 0.47; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 9.1 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.9 Hz, 1H), 7.36 (d, J = 3.4 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 6.94 (dd, J = 8.9, 2.6 Hz, 1H), 6.70 (d, J = 3.4 Hz, 1H), 3.89 (s, 3H); ^{13}C {^{1}**H**} NMR (101 MHz $CDCl_3$): δ 155.3, 145.4, 144.8, 130.9, 130.3, 127.5, 125.6, 122.8, 113.2, 111.4, 106.0, 103.3, 55.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{13}N_2O_3$ 269.0926, Found 269.0926

5-(Benzyloxy)-1-(4-nitrophenyl)-1*H*-indole (3m): White solid (55.50 mg, 83%); purified by column chromatography using PE/EA: 12/1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 7.1 Hz, 2H), 7.42 (t, J = 7.3 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.23 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 9.0, 2.5 Hz, 1H), 6.70 (d, J = 3.3 Hz, 1H), 5.15 (s, 2H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 154.5, 145.3, 144.8, 137.3, 130.9, 130.4, 128.6, 128.0, 127.6, 127.5, 125.6, 122.8, 113.9, 111.4, 106.1, 104.9, 70.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{17}N_2O_3$ 345.1234, Found 345.1236.

5-Fluoro-1-(4-nitrophenyl)-1*H*-indole (3n): White solid (43.55 mg, 85%); purified by column chromatography using PE/EA: 6/1, R_f = 0.5;^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.58 (dd, J = 9.0, 4.3 Hz, 1H), 7.44 (d, J = 3.4 Hz, 1H), 7.36 (dd, J = 9.1, 2.5 Hz, 1H), 7.06 (td, J = 9.0, 2.6 Hz, 1H), 6.76 (dd, J = 3.3, 0.8 Hz, 1H); ^{13}C {^{1}**H**} NMR (101 MHz $CDCl_3$): δ 158.6 (d, J = 237.5 Hz), 145.1 (d, J = 26.3 Hz), 131.8, 130.7 (d, J = 10.2 Hz), 128.7, 125.6, 123.4, 111.8, 111.5, 111.3 (d, J = 9.6 Hz), 106.6 (d, J = 23.5 Hz), 105.9 (d, J = 4.4 Hz); HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{14}H_9FN_2O_2Na$ 279.0546, Found 279.0549.

1-(Benzo[d][1,3]dioxol-5-yl)-5-bromo-1*H*-indole (3o): White solid (51.00 mg, 81%); purified by column chromatography using PE/EA: 30/1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 1.9 Hz, 1H), 7.38 – 7.21 (m, 4H), 6.97 – 6.88 (m, 3H), 6.60 (dd, J = 3.2, 0.8 Hz, 1H), 6.09 (s, 2H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 148.5, 146.6, 135.0, 133.4, 130.6, 129.4, 125.1, 123.5, 118., 113.4, 111. 9, 108.7, 106.2, 102.5, 101.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{11}BrNO_2$ 315.9968, Found 315.9972.

1-(Benzo[d][1,3]dioxol-5-yl)-5-methoxy-1*H*-indole (3p): White solid (43.83 mg, 82%); purified by column chromatography using PE/EA: 30/1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 3.2 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 6.97 (d, J = 1.7 Hz, 1H), 6.92 (d, J = 2.0 Hz, 2H), 6.88 (dd, J = 9.0, 2.6 Hz, 1H), 6.57 (d, J = 3.1 Hz, 1H), 6.05 (s, 2H), 3.88 (s, 3H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 154.5, 148.3, 146.2, 134.1, 131.5, 129.5, 128.7, 117.7, 112.5, 111.2, 108.6, 106.1, 102.7, 101.7, 55.9, 29.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{16}H_{14}NO_3$ 268.0968, Found 268.0969.

2-Phenylphthalazin-1(2*H*)-one[11a] (5a): White solid (36.00 mg, 81%); purified by column chromatography using PE/EA: 3/1, R_f = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dt, J = 7.6, 1.0 Hz, 1H), 8.28 (d, J = 0.8 Hz, 1H), 7.88 – 7.76 (m, 2H), 7.76 – 7.70 (m, 1H), 7.67 (dd, J = 8.6, 1.2 Hz, 2H), 7.49 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 159.2, 141.9, 138.5, 133.5, 132.0, 129.5, 128.8, 128.6, 127.8, 127.3, 126.2, 125.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{14}H_{11}N_2O$ 223.0871, Found 223.0873.

3-Phenylquinazolin-4(3*H*)-one[11b] (5b): White solid (35.55 mg, 80%); purified by column chromatography using PE/EA: 1/1, R_f = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 7.5 Hz, 1H), 8.14 (s, 1H), 7.84 – 7.74 (m, 2H), 7.59 – 7.52 (m, 3H), 7.52 – 7.47 (m, 1H), 7.46 – 7.40 (m, 2H); ^{13}C {^{1}**H**} NMR (101 MHz, ,$CDCl_3$): δ 160.7, 147.7, 146.1, 137.5, 134.6, 129.7, 129.2, 127.7, 127.5, 127.2, 127.0, 122.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{14}H_{11}N_2O$ 223.0871, Found 223.0873.

1-Phenylpyridin-2(1*H*)-one[11c] (5c): White solid (28.00 mg, 82%); purified by column chromatography using PE/EA: 1/9, R_f = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, J = 7.4 Hz, 2H), 7.45 – 7.35 (m, 4H), 7.33 (d, J = 6.9 Hz, 1H), 6.67 (d, J = 9.2 Hz, 1H), 6.24 (td, J = 6.7, 1.4 Hz, 1H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 162.4, 140.9, 139.9, 138.0, 129.4, 128.5, 126.5, 121.9, 105.9; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{11}H_{10}NO$ 172.0762, Found 172.0763.

4-Phenylmorpholine[11d] (5d): White solid (23.50 mg, 72%); purified by column chromatography using PE/EA: 4/1, R_f = 0.4;^{1}H NMR (400 MHz, $CDCl_3$): δ7.29 (dd, J = 8.7, 7.3 Hz, 2H), 6.91 (dd, J = 18.4, 7.7 Hz, 3H), 3.87 (t, J = 9.6 Hz, 4H), 3.16 (t, J = 10 Hz, 4H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 151.2, 129.2, 120.1, 115.7, 66.9, 49.4; HRMS (ESI-TOF) m/z: [M + H]$^+$Calcd for $C_{10}H_{14}NO$ 164.1075, Found 164.1077.

***N*-(3-Phenylpropyl)aniline**[ne] **(5e):** White solid (33.80 mg, 75%); purified by column chromatography using PE/EA: 9/1, R_f = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 2H), 7.24 – 7.15 (m, 5H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 7.7 Hz, 2H), 3.15 (t, *J* = 6.9 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.92 – 1.58 (m, 4H); ^{13}C {^{1}**H**} NMR (101 MHz, $CDCl_3$): δ 145.9, 139.7, 126.7, 125.9, 125.8, 123.3, 114.6, 110.2, 41.3, 33.1, 26.6, 26.4; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{15}H_{18}N$ 212.1439, Found 212.1436

3-Phenyl-1*H*-indole[nf] as white solid; purified by column chromatography using PE/EA: 4/1, R_f = 0.35; ^{1}H NMR (400 MHz $CDCl_3$): δ 8.16 (s, 1H, NH), 7.93 (d, *J* = 6.0 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.46-7.38 (m, 3H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.30-7.17 (m, 4H); ^{13}C {^{1}**H**} NMR (100 MHz, $CDCl_3$): δ 136.7, 135.6, 128.7, 127.5, 126.0, 125.7, 122.5, 121.8, 120.4, 119.8, 116.3, 111.4; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$Calcd for $C_{14}H_{12}N$ 194.0964, Found 194.0967.

Representative procedure for the gram-scale reaction: To dried tube equipped with a stir bar, CuI (81.32 mg, 0.43 mmol, 5 mol%), L-Met (126.82 mg, 0.85 mmol, 10 mol%, 2 equiv), Indole **2a** (1.0 g, 8.54 mmol), iodobenzene **1a** (1.43 mL, 2.61 g, 12.81 mmol, 1.5 equiv), K_2CO_3 (2.36 g, 17.08 mmol, 2.0 equiv) followed by DMF (10 mL) was added and the resulting reaction mixture was stirred at 100 °C (oil bath). After 24 h, the reaction mixture was cooled to rt, worked-up with water-EtOAC system, dried using anhydrous $MgSO_4$, adsorbed on to silica gel and purified by column chromatography (PE/EA: 6/1, R_f = 0.52) to get analytically **3a** (1.48 g, 91%) as white solid.

ASSOCIATED CONTENT

Supporting Information. Few experimental details and copy of ^{1}H NMR & ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest

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