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Palladium-Catalyzed C(sp^2)–H Arylation Using Formamide as a Transformable Directing Group

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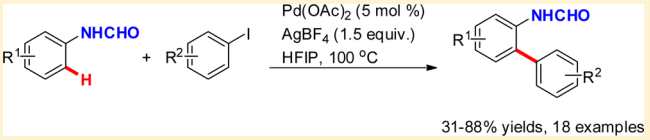
Supporting Information

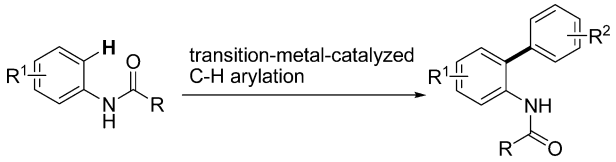
ABSTRACT: A new process for the ortho arylation of formanilides through palladium-catalyzed C–H activation is described. Formamide is reported as a transformable directing group in the transition-metal-catalyzed C–H functionalization reaction. The resulting biarylformanilide products can be readily transformed to the corresponding biarylisocyanides or N-heterocycles.



Transition-metal-catalyzed C–H functionalization is emerging as a promising strategy to construct new C–C or C–heteroatom bonds, as it employs ubiquitous C–H bonds as a latent functional group.[1] Generally, this strategy needs to have a directing group preinstalled in the substrate that is chelating with the transition-metal catalyst to achieve chemo- and regioselectivity. If the chelation group is not wanted after C–H functionalization, an extra step to remove it, which is normally a challenging task, is required. To solve this problem, many removable directing groups have been developed in C–H functionalization reactions.[2,3] However, simply removing the directing groups reduces the atom economy of the whole process, offsetting the advantages of C–H functionalization over traditional transformations starting from C–X bonds. To make C–H functionalization reactions more applicable in routine organic synthesis, developing new directing groups that are transformable to other functionalities under mild conditions is of great interest.

Aniline is one of the most important nitrogen-containing substances widely used in the manufacture of agrochemicals, pharmaceuticals, dyes, pigments, and polymers. Biarylaniline is an important building block used for the synthesis of many biologically active molecules and functional materials.[4] Ortho arylation of aniline derivatives through transition-metal-catalyzed C–H functionalization is undoubtedly a straightforward approach to prepare this structural motif. Therefore, a variety of amide,[5] sulfonamide,[6] and urea[7] derivatives of anilines have been used for chelation-assisted C–H arylation. Among them, various secondary anilides are the most frequently applied, including acetanilide, propionanilide, isobutyranilide, pivalanilide, trifluoroacetanilide, benzanilide, and others (Scheme 1). However, most of these directing groups are not easily removed or transformed. In this context, we report herein a new protocol for palladium-catalyzed C–H ortho arylation using formamide as the transformable directing group. Formamide can serve as a precursor of isocyanide or can be removed under relatively mild conditions (Scheme 1). It is important to note that Shi's group reported palladium-catalyzed ortho arylation of formamide using a mixture of copper and silver salts as co-oxidants and trialkoxylsilane as a coupling partner in 2007, but the efficiency of this transformation was low.[5c]

Scheme 1. Anilides in Chelation-Assisted C–H Arylation



previous work: R = CH_3, CH_3CH_2, $(CH_3)_2CH$, $(CH_3)_3C$, CF_3, Ph

this work: R = **H**

Isocyanides are versatile in organic reactions such as Ugi and Passerini multicomponent reactions,[8] transition-metal-catalyzed imidoylation,[9] and radical-based transformation.[10] One of the most common methods to prepare isocyanide is dehydration of the corresponding formamide. The amide bond in formamide is more flexible and labile than other amide bonds. Therefore, it is not surprising that there are few methods reported that use formamide as a directing group in transition-metal-catalyzed C–H functionalization in which the reaction conditions are usually harsh. Inspired by the palladium-catalyzed C–H ortho arylation of anilides,[5–7] we assumed that a palladium-catalyzed C–H ortho arylation using formamide as a directing group could be realized with iodobenzenes as a coupling partner. Remarkably, the arylated products can be readily converted to biaryl isocyanides, which have been extensively studied in the synthesis of phenanthridine derivatives.[11]

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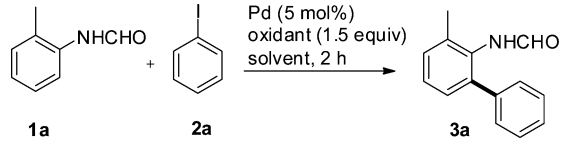
o-Methylformanilide **1a** and iodobenzene **2a** were chosen as substrates for an initial study, as summarized in Table 1. First,

Table 1. Screening of the Reaction Conditions[a]



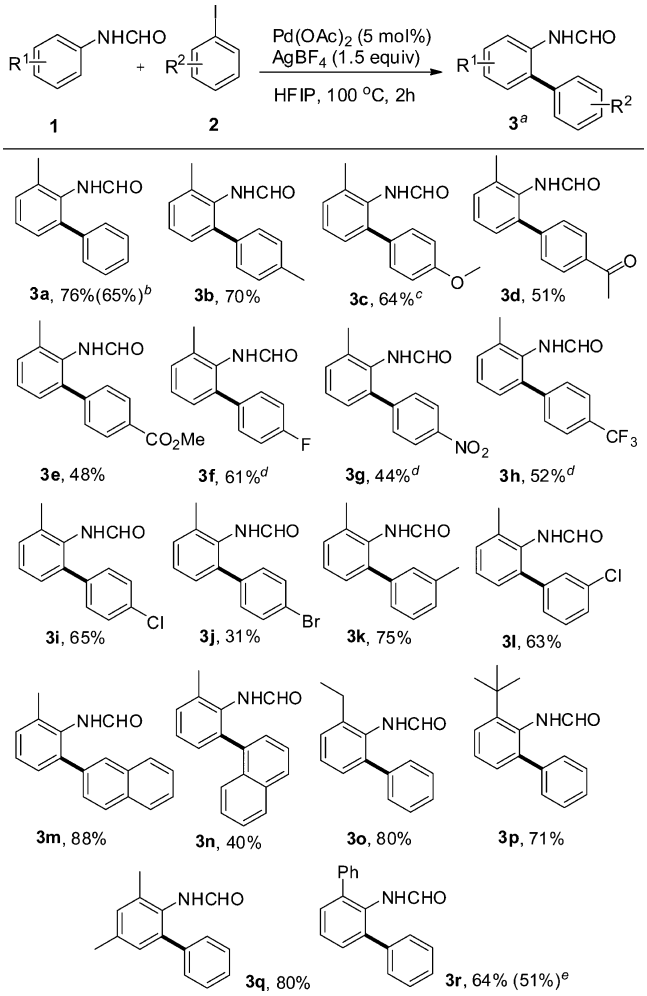
entry	catalyst	oxidant	solvent	T (°C)	yield (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	TFA	100	0
2	$Pd(OAc)_2$	O_2	TFA	100	0
3	$Pd(OAc)_2$	AgOAc	TFA	100	48
4	$Pd(OAc)_2$	Ag_2CO_3	TFA	100	trace
5	$Pd(OAc)_2$	$AgSbF_6$	TFA	100	44
6	$Pd(OAc)_2$	AgTFA	TFA	100	50
7	$Pd(OAc)_2$	Ag_2O	TFA	100	trace
8	$Pd(OAc)_2$	$AgBF_4$	TFA	100	56
9	Pd(OAc)2	$AgBF_4$	HBF_4	100	40
10	**$Pd(OAc)_2$**	**$AgBF_4$**	**HFIP**	**100**	**76**
11	$Pd(TFA)_2$	$AgBF_4$	HFIP	100	74
12	$PdCl_2$	$AgBF_4$	HFIP	100	trace
13	$Pd(CH_3CN)_2Cl_2$	$AgBF_4$	HFIP	100	40
14		$AgBF_4$	HFIP	100	n.d.
15	$Pd(OAc)_2$	$AgBF_4$	HFIP	80	71
16	$Pd(OAc)_2$	$AgBF_4$	HFIP	120	74

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (3.0 mmol), Pd catalyst (5 mol %), oxidants (0.3 mmol, 1.5 equiv), solvent (0.2 mL), 2 h. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [b]Isolated yields.

the reaction was conducted by examining a suitable oxidant in the presence of $Pd(OAc)_2$ as a catalyst in TFA. No desired arylation product was detected using $Cu(OAc)_2$ or O_2 as oxidants (entries 1 and 2). To our delight, arylation product **3a** was obtained in 48% yield using AgOAc as the oxidant (entry 3). Other silver salts, such as Ag_2CO_3, $AgSbF_6$, AgTFA, Ag_2O, and $AgBF_4$, were also screened, identifying all of these silver salts as being effective for this transformation (entries 4−8). Then, screening the reaction solvent revealed that HFIP is the solvent of choice and that the yield of **3a** could be improved to 76% (entry 10). Further study showed that other palladium salts, such as $PdCl_2$ and $Pd(MeCN)_2Cl_2$, are inferior to $Pd(TFA)_2$ and $Pd(OAc)_2$ in promoting this arylation process (entries 11−13). In a control reaction where the palladium catalyst was absent, no arylation product **3a** was detected. In addition, altering the reaction temperature (80−120 °C) gave no significant difference in reaction yield (entries 15 and 16).

With the optimized reaction conditions established, the substrate scope of this formamide-directed arylation reaction was investigated (Scheme 2). A variety of electron-withdrawing or -donating group-substituted aryl iodides, including methyl, methoxy, halogen, trifluoromethyl, and nitro groups, were compatible with the optimal conditions in reactions with *o*-methylformanilide **1a**. In general, aryl iodides bearing electron-rich groups afforded the arylation products in higher yields (**3a-c**) than those with electron-deficient ones (**3d−j**). It was found that switching from $AgBF_4$ to AgTFA as the oxidant in TFA for the reaction employing the electron-deficient aryl iodides led to a dramatic increase in yield at higher temperature. The reason for this is not clear, although the results do indicate that the new catalytic system is more effective with an electron-deficient coupling partner. When 1-bromo-4-iodobenzene was used as

Scheme 2. Scope of Formanilides and Aryl Iodides[a,b]



[a]Formanilide **1** (0.2 mmol), aryl iodide **2** (0.6 mmol), $Pd(OAc)_2$ (5 mol %), $AgBF_4$ (0.3 mmol, 1.5 equiv), HFIP (0.2 mL), 100 °C, 2 h. [b]Four millimoles of **1a** was used. [c]80 °C in N_2. [d]AgTFA (0.3 mmol, 1.5 equiv), TFA (1 mL), 110 °C, 5 h. [e]Yield of biarylation of formanilide.

the coupling partner, corresponding product **3j** was obtained in lower yield because of the formation of a significant amount of unidentified byproducts. The reaction was sensitive to the steric hindrance of aryl iodides. For example, meta-substituted aryl iodides generated the corresponding products in similar yields as their para analogues (**3k−m**), whereas ortho-substituted aryl iodides failed to afford the corresponding products except for 1-iodonaphthalenethe (**3n**). Other 2-substituted formanilides **1** were also applicable to this arylation process (Scheme 2). Electron-rich groups such as ethyl (**3o**), *tert*-butyl (**3p**), 2,4-dimethyl (**3q**), and phenyl (**3r**) substituted formanilides underwent the arylation reaction effectively with iodobenzene, affording the corresponding products in 64−80% yield. Unfortunately, selective monoarylation of 2-unsubstituted formanilide was not accessible, giving the diarylation product in 51% yield (**3r**). It is noteworthy that under the optimized conditions the reaction can be easily scaled up; for example, when 4 mmol of **1a** (0.54 g) was used, there was no appreciable drop in the yield (Scheme 2, **3a**).

After this formamide-directed ortho-arylation protocol was established, further transformation of biaryl formamide product

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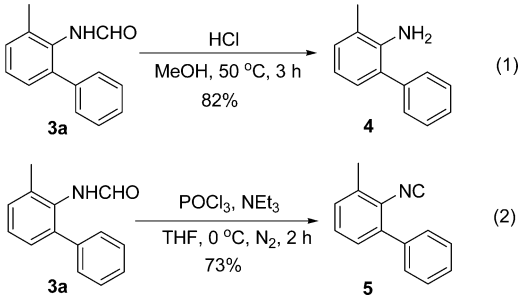
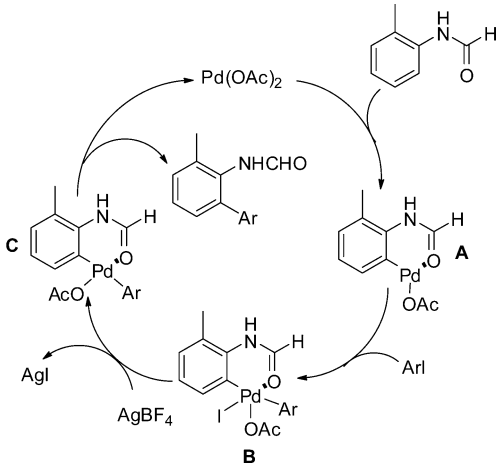
3a was studied. The formamide group can be readily removed with HCl (1.1 equiv, 36−38%), giving *ortho*-phenyl aniline **4** in 82% yield (1, Scheme 3).[12] Dehydration of **3a** with phosphorus oxychloride provided biphenyl isocyanide **5** in 73% yield (2, Scheme 3).[11b]

Scheme 3. Transformation of Biaryl Formamide



A plausible reaction mechanism is proposed in Scheme 4. First, formamide-directed electrophilic palladation generates a

Scheme 4. Proposed Reaction Mechanism



palladacycle intermediate, **A**. Then, oxidative addition of aryl iodide to Pd(II) in **A** gives a Pd(IV) intermediate, **B**, followed by reductive elimination to afford the arylation product and Pd(II). Silver salt may act as a halide scavenger to improve the transformation under the reaction conditions.[13−15] Another reaction pathway involving a Pd(0)/Pd(II) catalytic cycle is also possible.

In conclusion, we have developed an efficient method for Pd-catalyzed C(sp^2)−H arylation directed by a transformable formamide group. Formanilides react with various aryl iodides to give the corresponding ortho-arylated products in moderate to good yields. The corresponding biaryl formanilide products can be readily converted to biaryl isocyanides, which are useful building blocks in the synthesis of phenanthridine derivatives.

EXPERIMENTAL SECTION

General Information. The materials and solvents were purchased from common commercial sources and used without further purification unless otherwise noted. Reactions were monitored using thin-layer chromatography (TLC) on commercial silica gel plates (GF254). Visualization of the developed plates was performed under UV light (254 nm). Flash column chromatography was performed on silica gel (200−300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer using TMS as an internal standard. Infrared (IR) spectra were recorded as KBr pellets on an FTIR-8500 spectrophotometer. Melting points (mp) are uncorrected. The following abbreviations were used to describe peak splitting patterns when appropriate: br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Coupling constants, *J*, are reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on an ESI−LC−MS/MS spectrometer.

General Procedure for the Preparation of Formanilide Derivatives.[11a] To an oven-dried three-necked flask equipped with a dropping funnel were added aniline (2 mmol, 1.0 equiv) and THF (2 mL) under a N_2 atmosphere, and the mixture was cooled to 0 °C. Acetic formic anhydride (3 mmol, 1.5 equiv) was transferred to the dropping funnel and dropped into the solution of aniline at 0 °C. After the addition was completed, the mixture was warmed to room temperature and stirred for 2 h. Then, the mixture was quenched by a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc three times. The extract was dried over Na_2SO_4 and concentrated under reduced pressure to give formamide as a pale yellow solid.

General Procedure for the Arylation of Formanilide with Various Aryl Iodides. *Procedure A.* A Schlenk tube with a magnetic stir bar was charged with formanilide (0.2 mmol, 1.0 equiv), aryl iodide (0.6 mmol, 3.0 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg, 5 mol %), $AgBF_4$ (0.3 mmol, 58 mg, 1.5 equiv), and HFIP (0.2 mL). The mixture was heated at 100 °C, stirred for 2 h, and then cooled to room temperature. After addition of saturated $NaHCO_3$, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic layer was collected. The combined organic phases were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as the eluent to afford the corresponding products.

Procedure B. A Schlenk tube with a magnetic stir bar was charged with formanilide (0.2 mmol, 1.0 equiv), aryl iodide (0.6 mmol, 3.0 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg, 5 mol %), $AgBF_4$ (0.3 mmol, 58 mg, 1.5 equiv), and HFIP (0.2 mL). The mixture was heated at 80 °C, stirred for 2 h under a N_2 atmosphere, and then cooled to room temperature. After addition of saturated $NaHCO_3$, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic layer was collected. The combined organic phases were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as the eluent to afford the corresponding products.

Procedure C. A Schlenk tube with a magnetic stir bar was charged with formanilide (0.2 mmol, 1.0 equiv), aryl iodide (0.6 mmol, 3.0 equiv), $Pd(OAc)_2$ (0.01 mmol, 2.2 mg, 5 mol %), AgTFA (0.3 mmol, 77 mg, 1.5 equiv), and TFA (1 mL). The mixture was heated at 110 °C, stirred for 5 h, and then cooled to room temperature. After addition of saturated $NaHCO_3$, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic layer was collected. The combined organic phases were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as the eluent to afford the corresponding products.

Procedure for the Dehydration of *N*-(3-Methyl-[1,1′-biphenyl]-2-yl)formamide.[12] To a solution of *N*-(3-methyl-[1,1′-biphenyl]-2-yl)formamide (64 mg, 0.3 mmol) and triethylamine (0.25 mL, 6 equiv) in 2 mL of anhydrous THF was added $POCl_3$ (45 uL, 1.5 equiv) dropwise with constant magnetic stirring at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for about 2 h. Then, 5 mL of saturated aqueous $NaHCO_3$ was added carefully to quench the reaction, and the mixture was stirred for about 10 min. The mixture was then extracted with EtOAc. The organic layers were evaporated under vacuum. The residue was purified by column chromatography on silica gel to give **1**.

Procedure for the Deformylation of *N*-(3-Methyl-[1,1′-biphenyl]-2-yl)formamide.[11b] A mixture of *N*-(3-methyl-[1,1′-biphenyl]-2-yl)formamide (64 mg, 0.3 mmol) and concentrated hydrochloric acid (275 μL, 1.1 equiv, 12 N) in ethanol (2 mL) was

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heated at 75 °C for 12 h. Upon cooling the reaction mixture to room temperature, the mixture was neutralized with 2 N NaOH and extracted with ethyl acetate. The combined organic layers were washed with water and brine. The dried solution (over Na_2SO_4) was concentrated, and the residue was purified by flash chromatography to yield **2**.

***N*-(3-Methyl-biphenyl-2-yl)-formamide (3a).** Following general procedure A (white solid). Yield (32.1 mg, 76%). mp 159−160 °C (159−160 °C).[16] ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.21 (s, 0.51H), 7.94 (d, 0.44H, J = 12.0 Hz), 7.18−7.43 (m, 8H), 6.80 (d, 0.36H, J = 10.4 Hz), 6.69 (br s, 0.41H), 2.38 (s, 1.38H), 2.34 (s, 1.62H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 160.0, 139.4, 139.3, 138.7, 138.5, 136.3, 134.1, 131.9, 131.1, 130.3, 130.1, 129.4, 128.9, 128.7, 128.3, 127.9, 127.6, 127.4, 127.4, 127.1, 18.8, 18.7. HRMS (ESI): mass calcd for $C_{14}H_{13}NO$ $[M + H]^+$, 212.1075; found, 212.1071. IR (KBr pellet): 3187, 3062, 3005, 2918, 2893, 1668, 1657, 1530, 1466, 1440, 1387, 1263, 1156, 1071, 796, 757, 723, 702, 555 cm^{-1}.

***N*-(3,4′-Dimethyl-biphenyl-2-yl)-formamide (3b).** Following general procedure A (white solid). Yield (31.5 mg, 70%). mp 134−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.20 (s, 0.49H), 7.93 (d, 0.46H, J = 11.7 Hz), 7.16−7.26 (m, 7H), 6.86 (d, 0.40H, J = 10.6 Hz), 6.71 (br s, 0.46H), 2.39 (s, 1.44H), 2.38 (s, 3H). 2.33 (s, 1.56H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 159.9, 139.3, 138.4, 137.2, 137.2, 136.4, 136.3, 135.7, 133.9, 132.0, 131.1, 130.1, 130.0, 129.4, 129.2, 129.0, 128.9, 128.8, 128.0, 127.5, 127.1, 21.1, 18.9, 18.8. HRMS (ESI): mass calcd for $C_{15}H_{15}NO$ $[M + H]^+$, 226.1232; found, 226.1230. IR (KBr pellet): 3251, 2911, 2862, 1655, 1588, 1513, 1466, 1445, 1402, 1379, 1219, 1150, 1035, 826, 778, 731, 715, 577, 538, 512, 469 cm^{-1}.

***N*-(4′-Methoxy-3-methyl-biphenyl-2-yl)-formamide (3c).** Following general procedure B (pale yellow solid). Yield (30.9 mg, 64%). mp 143−144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.23 (s, 0.50H), 7.96 (d, 0.46H, J = 12.0 Hz), 7.16−7.26 (m, 5H), 6.95−6.96 (m, 2H), 6.80 (br s, 0.45H), 6.69 (br s, 0.44H), 3.84 (s, 3H), 2.37 (s, 1.41H), 2.33 (s, 1.59H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 159.9, 159.1, 159.0, 139.1, 138.2, 136.3, 133.9, 132.0, 131.6, 131.2, 130.9, 130.5, 130.1, 130.0, 129.9, 128.9, 128.0, 127.6, 127.1, 114.3, 113.8, 55.3, 18.9, 18.9. HRMS (ESI): mass calcd for $C_{15}H_{15}NO_2$ $[M + H]^+$, 242.1181; found, 242.1173. IR (KBr pellet): 3266, 2993, 2956, 2918, 2855, 2835, 1654, 1612, 1514, 1467, 1443, 1379, 1294, 1250, 1184, 1034, 834, 820, 784, 735, 546 cm^{-1}.

***N*-(4′-Acetyl-3-methyl-biphenyl-2-yl)-formamide (3d).** Following general procedure A (pale yellow solid). Yield (25.8 mg, 51%). mp 177−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.19 (s, 0.54H), 8.00 (t, 2H, J = 9.3 Hz), 7.88 (d, 0.44H, J = 11.6 Hz), 7.44 (d, 2H, J = 7.9 Hz), 7.18−7.32 (m, 3H), 7.00 (d, 0.40H, J = 11.1 Hz), 6.80 (br s, 0.51H), 2.63 (s, 3H), 2.39 (s, 1.31H), 2.34 (s, 1.69H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 197.6, 164.8, 160.0, 144.5, 143.8, 138.8, 137.4, 136.6, 135.9, 134.6, 131.8, 131.0, 130.7, 129.7, 129.2, 128.8, 128.7, 128.3, 127.8, 127.8, 127.4, 26.6, 18.7, 18.7. HRMS (ESI): mass calcd for $C_{16}H_{15}NO_2$ $[M + H]^+$, 254.1181; found, 254.1177. IR (KBr pellet): 3256, 2968, 2910, 1682, 1655, 1606, 1501, 1402, 1376, 1359, 1269, 840, 788, 605 cm^{-1}.

2′-Formylamino-3′-methyl-biphenyl-4-carboxylic Acid Methyl Ester (3e). Following general procedure A (white solid). Yield (25.8 mg, 48%). mp 188−190 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.20 (s, 0.54H), 8.09 (t, 2H, J = 8.4 Hz), 7.89 (d, 0.40H, J = 11.8 Hz), 7.41 (d, 2H, J = 7.4 Hz), 7.18−7.32 (m, 3H), 6.82 (d, 0.36H, J = 9.4 Hz), 6.67 (br s, 0.48H), 3.94 (s, 3H), 2.39 (s, 1.37H), 2.34 (s, 1.73H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.7, 164.7, 159.8, 144.2, 143.5, 138.8, 137.5, 136.6, 134.5, 131.8, 131.0, 130.9, 130.7, 130.0, 129.6, 129.5, 129.2, 129.2, 129.0, 128.7, 127.8, 127.8, 127.4, 52.1, 18.8, 18.7. HRMS (ESI): mass calcd for $C_{16}H_{15}NO_3$ $[M + H]^+$, 270.1130; found, 270.1128. IR (KBr pellet): 3263, 2954, 2911, 1718, 1655, 1610, 1500, 1438, 1316, 1286, 1119, 768, 709 cm^{-1}.

***N*-(4′-Fluoro-3-methyl-biphenyl-2-yl)-formamide (3f).** Following general procedure C (pale yellow solid). Yield (27.9 mg, 61%). mp 164−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.21 (s, 0.52H), 7.91 (d, 0.43H, J = 11.6 Hz), 7.07−7.31 (m, 7H), 6.91 (d, 0.45H, J = 11.7 Hz), 6.69 (br s, 0.45H), 2.38 (s, 1.35H), 2.33 (s, 1.65H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 162.3 (d, J = 245.5 Hz), 162.2 (d, J = 245.9 Hz), 159.9, 138.7, 137.6, 136.5, 135.3 (d, J = 3.5 Hz), 134.7 (d, J = 3.4 Hz), 134.4, 132.0, 131.1, 131.1, 130.6, 130.5, 130.3, 128.9, 128.0, 127.8, 127.3, 115.7 (d, J = 21.2 Hz), 115.3 (d, J = 21.2), 18.8, 18.8. HRMS (ESI): mass calcd for $C_{14}H_{12}FNO$ $[M + H]^+$, 230.0981; found, 230.0979. IR (KBr pellet): 3234, 2916, 1650, 1604, 1511, 1466, 1377, 1221, 1160, 842, 785, 538 cm^{-1}.

***N*-(3-Methyl-4′-nitro-biphenyl-2-yl)-formamide (3g).** Following general procedure C (pale yellow solid). Yield (22.5 mg, 44%). mp 221−223 °C. ^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 9.58 (s, 0.81H), 9.48 (d, 0.18H, J = 11.4 Hz), 8.28 (t, 2H, J = 9.6 Hz), 8.03 (s, 0.80H), 7.68 (d, 0.2H, J = 10.6 Hz), 7.58−7.64 (m, 2H), 7.22−7.42 (m, 3H), 2.31 (s, 0.57H), 2.23 (s, 2.43H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.9, 160.5, 147.1, 146.9, 146.8, 146.6, 138.1, 137.4, 136.7, 136.4, 133.3, 132.8, 131.6, 131.3, 131.1, 130.4, 128.7, 128.0, 127.8, 127.7, 123.9, 123.6, 18.7, 18.6. HRMS (ESI): mass calcd for $C_{14}H_{12}N_2O_3$ $[M + H]^+$, 257.0926; found, 257.0922. IR (KBr): 3249, 3074, 3006, 2954, 2920, 1686, 1668, 1599, 1515, 1469, 1393, 1348, 1109, 860, 846, 797, 755, 695 cm^{-1}.

***N*-(3-Methyl-4′-trifluoromethyl-biphenyl-2-yl)-formamide (3h).** Following general procedure C (pale yellow solid). Yield (29.0 mg, 52%). mp 176−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.21 (s, 0.58H), 7.91 (d, 0.41H, J = 11.7 Hz), 7.68 (t, 2H, J = 8.5 Hz), 7.45 (d, 2H, J = 7.8 Hz), 7.18−7.33 (m, 3H), 6.83 (d, 0.34H, J = 11.7 Hz), 6.65 (br s, 0.53H), 2.39 (s, 1.23H), 2.34 (s, 1.74). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 159.8, 143.1, 142.5, 138.6, 137.2, 136.7, 134.7, 131.8, 131.1, 130.9, 130.8, 129.9, 129.6, 129.6, 129.3, 128.8, 128.0, 127.9, 127.5, 125.7 (q, J = 3.7 Hz), 125.3 (q, J = 3.6 Hz), 124.1 (q, J = 270.1 Hz), 124.0 (q, J = 270.3 Hz). 18.7. HRMS (ESI): mass calcd for $C_{15}H_{12}F_3NO$ $[M + H]^+$, 280.0949; found, 280.0944. IR (KBr pellet): 3229, 2922, 1654, 1519, 1402, 1382, 1329, 1168, 1107, 1080, 1065, 782 cm^{-1}.

***N*-(4′-Chloro-3-methyl-biphenyl-2-yl)-formamide (3i).** Following general procedure A (white solid). Yield (31.9 mg, 65%). mp 185−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.21 (s, 0.55H), 7.92 (d, 0.42H, J = 11.6 Hz), 7.39 (t, 2H, J = 8.5 Hz), 7.29 (m, 2H), 7.15−7.27 (m, 3H), 6.85 (d, 0.34H, J = 11.0 Hz), 6.66 (br s, 0.46H), 2.38 (s, 1.34H), 2.33 (s, 1.66H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 159.9, 138.6, 137.8, 137.4, 137.2, 136.6, 134.4, 133.7, 133.6, 131.8, 131.0, 130.7, 130.7, 130.5, 130.2, 129.0, 128.8, 128.5, 127.9, 127.8, 127.4, 18.8, 18.8. HRMS (ESI): mass calcd for $C_{14}H_{12}NOCl$ $[M + H]^+$, 246.0686; found, 246.0681. IR (KBr pellet): 3227, 3053, 2949, 2914, 1651, 1496, 1463, 1377, 1149, 1091, 1016, 839, 781, 734, 719 cm^{-1}.

***N*-(4′-Bromo-3-methyl-biphenyl-2-yl)-formamide (3j).** Following general procedure A (white solid). Yield (17.9 mg, 31%). mp 194−196 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.22 (s, 0.53H), 7.92 (d, 0.40H, J = 11.2 Hz), 7.55 (t, 2H, J = 8.3 Hz), 7.15−7.30 (m, 5H), 6.76 (d, 0.38H, J = 12.3 Hz), 6.63 (br s, 0.49H), 2.38 (s, 1.29H), 2.33 (s, 1.71). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 159.8, 138.6, 138.3, 137.7, 137.4, 136.6, 134.4, 132.0, 131.7, 131.5, 131.0, 130.9, 130.8, 130.6, 130.5, 128.8, 127.9, 127.8, 127.4, 121.9, 121.8, 18.8, 18.8. HRMS (ESI): mass calcd for $C_{14}H_{12}BrNO$ $[M + H]^+$, 290.0181; found, 290.0176. IR (KBr pellet): 3226, 2949, 2913, 1651, 1493, 1462, 1377, 1012, 836, 780 cm^{-1}.

***N*-(3,3′-Dimethyl-biphenyl-2-yl)-formamide (3k).** Following general procedure A (white solid). Yield (33.8 mg, 75%). mp 118−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.18 (s, 0.50H), 7.92 (d, 0.47H, J = 11.5 Hz), 7.13−7.32 (m, 7H), 6.98 (d, 0.50H, J = 10.3 Hz), 6.78 (br s, 0.50H), 2.37 (s, 4.35H), 2.32 (s, 1.65H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 159.9, 139.5, 139.3, 138.7, 138.6, 138.4, 138.0, 136.3, 133.9, 132.0, 131.1, 130.2, 130.1, 130.0, 129.6, 128.9, 128.6, 128.3, 128.2, 128.2, 127.9, 127.5, 127.0, 126.4, 126.0, 21.4, 21.4, 18.9, 18.8. HRMS (ESI): mass calcd for $C_{15}H_{15}NO$ $[M + H]^+$, 226.1232; found, 226.1227. IR (KBr pellet): 3177, 3111, 3015, 2921, 2880, 1686, 1655, 1592, 1523, 1462, 1386, 1283, 1256, 1239, 782, 732, 707 cm^{-1}.

***N*-(3′-Chloro-3-methyl-biphenyl-2-yl)-formamide (3l).** Following general procedure A (white solid). Yield (30.9 mg, 63%). mp

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172−174 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.21 (s, 0.54H), 7.92 (d, 0.41H, J = 11.6 Hz), 7.30−7.34 (m, 5H), 7.15−7.21 (m, 2H), 6.85 (d, 0.36H, J = 10.2 Hz), 6.69 (br s, 0.48H), 2.38 (s, 1.31H), 2.33 (s, 1.69H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 159.9, 141.2, 140.6, 138.4, 137.2, 136.6, 134.6, 134.5, 134.1, 131.9, 131.0, 130.8, 130.6, 130.0, 129.6, 129.5, 128.9, 128.8, 127.9, 127.8, 127.7, 127.6, 127.6, 127.3, 127.2, 18.8, 18.7. HRMS (ESI): mass calcd for $C_{14}H_{12}ClNO$ $[M + H]^+$, 246.0686; found, 246.0681. IR (KBr pellet): 3269, 3060, 2913, 1655, 1565, 1504, 1460, 1401, 1380, 1147, 1110, 779, 737, 697 cm^{-1}.

***N*-(2-Methyl-6-naphthalen-2-yl-phenyl)-formamide (3m).** Following general procedure A (pale yellow solid). Yield (46.0 mg, 88%). mp 168−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.19 (s, 0.52H), 7.95 (d, 0.61H, J = 11.6 Hz), 7.86−7.90 (m, 3H), 7.79 (br s, 1H), 7.52 (br s, 2H), 7.44 (t, 1H, J = 6.8 Hz), 7.28−7.33 (m, 3H), 6.89 (d, 0.38H, J = 10.3 Hz), 6.71 (br s, 0.48H), 2.40 (s, 1.34H), 2.36 (s, 1.66H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 159.9, 139.4, 138.4, 136.9, 136.5, 136.3, 134.1, 133.5, 133.2, 132.5, 132.5, 132.1, 131.3, 130.5, 130.3, 129.2, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.7, 127.7, 127.7, 127.7, 127.2, 127.2, 126.5, 126.4, 126.3, 126.2, 18.9, 18.8. HRMS (ESI): mass calcd for $C_{18}H_{15}NO$ $[M + H]^+$, 262.1232; found, 262.1228. IR (KBr pellet): 3188, 3055, 2983, 2923, 2886, 1669, 1658, 1528, 1506, 1481, 1461, 1439, 1386, 1266, 828, 792, 748, 724, 481 cm^{-1}.

***N*-(2-Methyl-6-naphthalen-1-yl-phenyl)-formamide (3n).** Following general procedure A (pale yellow solid). Yield (20.9 mg, 40%). mp 193−195 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.88−7.92 (m, 3H), 7.48−7.54 (m, 3H), 7.20−7.43 (m, 5H), 6.63 (d, 0.40H, J = 11.2 Hz), 6.52 (br s, 0.49H), 2.43 (s, 1.32H), 2.38 (s, 1.68H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 159.2, 137.3, 137.1, 136.8, 136.2, 136.1, 133.8, 133.7, 133.5, 133.1, 132.4, 131.7, 131.5, 130.8, 130.5, 129.6, 128.6, 128.5, 128.3, 128.1, 127.4, 127.4, 127.0, 126.7, 126.6, 126.1, 126.1, 125.6, 125.4, 125.4, 125.0, 19.1, 18.9. HRMS (ESI): mass calcd for $C_{18}H_{15}NO$ $[M + H]^+$, 262.1232; found, 262.1229. IR (KBr pellet): 3217, 3058, 3012, 1683, 1657, 1589, 1519, 1462, 1439, 1385, 1281, 1240, 801, 779, 727 cm^{-1}.

***N*-(3-Ethyl-biphenyl-2-yl)-formamide (3o).** Following general procedure A (white solid). Yield (36.0 mg, 80%). mp 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.20 (s, 0.45H), 7.87 (d, 0.56H, J = 11.6 Hz), 7.19−7.42 (m, 8H), 6.87 (d, 0.43H, J = 11.8 Hz), 6.65 (br s, 0.38H), 2.71 (m, 2H), 1.28 (s, 1H), 1.26 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 160.4, 142.0, 140.4, 140.1, 139.6, 139.0, 138.9, 131.2, 130.4, 129.5, 128.9, 128.9, 128.7, 128.5, 128.3, 128.1, 128.1, 128.0, 127.6, 127.4, 127.4, 24.9, 24.8, 14.6, 14.1. HRMS (ESI): mass calcd for $C_{15}H_{15}NO$ $[M + H]^+$, 226.1232; found, 226.1227. IR (KBr pellet): 3195, 2965, 1671, 1658, 1530, 1456, 1435, 1390, 759, 729, 702 cm^{-1}.

***N*-(3-*tert*-Butyl-biphenyl-2-yl)-formamide (3p).** Following general procedure A (white solid). Yield (35.9 mg, 71%). mp 198−200 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.94 (s, 0.23H), 7.64 (d, 0.75H, J = 11.7 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.20−7.43 (m, 7H), 7.16 (d, 0.71H, J = 11.6 Hz), 6.87 (br s, 0.23H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 160.5, 147.9, 147.2, 143.5, 141.9, 140.6, 139.4, 131.8, 130.9, 129.8, 129.4, 129.0, 128.7, 128.1, 127.9, 127.8, 127.2, 127.0, 126.5, 35.5, 35.5, 31.2. HRMS (ESI): mass calcd for $C_{17}H_{19}NO$ $[M + H]^+$, 254.1545; found, 254.1542. IR (KBr pellet): 3237, 3059, 3006, 2965, 2864, 1690, 1667, 1516, 1447, 1421, 1381, 1303, 1267, 806, 761, 697 cm^{-1}.

***N*-[1,1′;3′,1″]Terphenyl-2′-yl-formamide (3q).** Following general procedure A (white solid). Yield (35.0 mg, 64%). mp 173−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.84 (s, 0.28H), 7.77 (d, 0.67H, J = 11.4 Hz), 7.38−7.47 (m, 13H), 6.77 (d, 0.58H, J = 10.2 Hz), 6.64 (br s, 0.23H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 159.9, 140.8, 139.6, 138.5, 137.0, 130.7, 130.6, 130.0, 129.7, 129.4, 129.0, 128.9, 128.2, 127.9, 127.8, 127.4, 126.5. HRMS (ESI): mass calcd for $C_{19}H_{15}NO$ $[M + H]^+$, 274.1232; found, 274.1225. IR (KBr pellet): 3240, 3058, 3026, 1663, 1497, 1459, 1441, 1423, 1383, 807, 756, 731, 703, 591 cm^{-1}.

***N*-(3,5-Dimethyl-biphenyl-2-yl)-formamide (3r).** Following general procedure A (white solid). Yield (36.0 mg, 80%). mp 170−172 °C (173−175 °C).[17] ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.18 (s, 0.51H), 7.89 (d, 0.44H, J = 11.7 Hz), 7.29−7.43 (m, 5H), 7.10 (s, 1H), 7.05 (s, 0.46H), 6.99 (s, 0.54H), 6.79 (d, 0.41H, J = 11.6 Hz), 6.65 (br s, 0.47H), 2.36 (s, 1.37H), 2.34 (s, 3H), 2.29 (s, 1.63H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 160.1, 139.5, 139.3, 138.9, 138.6, 137.4, 137.0, 136.1, 134.1, 131.0, 130.8, 129.5, 129.4, 129.3, 128.9, 128.7, 128.7, 128.4, 128.3, 127.4, 127.3, 20.9, 20.9, 18.7. HRMS (ESI): mass calcd for $C_{15}H_{15}NO$ $[M + H]^+$, 226.1232; found, 226.1226. IR (KBr pellet): 3235, 2915, 1680, 1652, 1602, 1513, 1440, 1383, 1146, 864, 773, 718, 703 cm^{-1}.

***N*-[1,1′;3′,1″]Terphenyl-2′-yl-formamide (3s).** Following general procedure A (white solid). Yield (27.9 mg, 51%). mp 173−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.85 (s, 0.29H), 7.82 (d, 0.70H, J = 11.4 Hz), 7.38−7.47 (m, 13H), 6.77 (d, 0.62H, J = 10.0 Hz), 6.64 (br s, 0.24H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 159.9, 140.8, 139.5, 138.5, 137.0, 130.7, 130.6, 130.0, 129.7, 129.3, 129.0, 128.8, 128.2, 127.9, 127.8, 127.4, 126.5. HRMS (ESI): mass calcd for $C_{19}H_{15}NO$ $[M + H]^+$, 274.1232; found, 274.1225. IR (KBr pellet): 3240, 3058, 3026, 1663, 1497, 1459, 1441, 1423, 1383, 807, 756, 731, 703, 591 cm^{-1}.

3-Methyl-biphenyl-2-ylamine (4). *N*-(3-Methyl-biphenyl-2-yl)-formamide (0.2 mmol) was used. Yield (30.0 mg, 82%) (white solid). mp 61−62 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.44 (d, 4H, J = 4.0 Hz), 7.33−7.35 (m, 1H), 7.07 (d, 1H, J = 7.4 Hz), 7.01 (d, 1H, J = 7.5 Hz), 6.76 (r, 1H, J = 7.4 Hz), 3.70 (br s, 2H), 2.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 139.9, 129.7, 129.3, 128.8, 128.3, 127.5, 127.1, 122.4, 118.1, 17.9. HRMS (ESI): mass calcd for $C_{13}H_{13}N$ $[M + H]^+$, 184.1126; found, 184.1122. IR (KBr pellet): 3457, 3376, 3075, 3047, 3026, 2979, 2929, 2852, 1622, 1590, 1465, 1430, 1275, 1241, 1080, 1072, 1016, 784, 757, 746, 701 cm^{-1}.

2-Isocyano-3-methyl-biphenyl (5). *N*-(3-Methyl-biphenyl-2-yl)-formamide (0.2 mmol) was used. Yield (28.2 mg, 73%) (pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.39−7.50 (m, 5H), 7.34 (t, 1H, J = 7.6 Hz), 7.23−7.28 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 139.0, 137.5, 135.8, 129.3, 129.0, 128.9, 128.5, 128.2, 128.0, 19.4. HRMS (ESI): mass calcd for $C_{14}H_{11}N$ $[M + H]^+$, 194.0970; found, 194.0963. IR (KBr pellet): 3061, 3032, 2923, 2117, 1593, 1500, 1469, 1442, 1420, 1101, 1070, 868, 793, 760, 738, 700, 665, 593 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all synthesized compounds. 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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