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# Primary Amide Directed Regioselective *ortho*-C−H-Arylation of (Aryl)Acetamides

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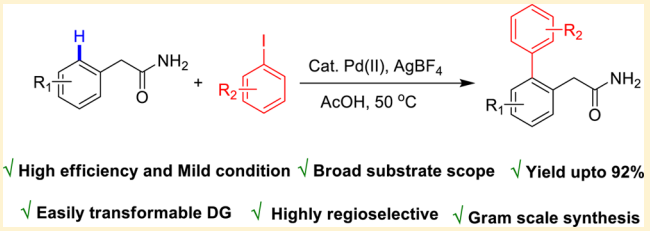
Supporting Information

**ABSTRACT:** An efficient and regioselective palladium(II)-catalyzed primary acetamide assisted *ortho* arylation of arylacetamide has been discovered. This is the first report where functionalizable primary acetamide ($-CH_2CONH_2$) is used as a directing group for C($sp^2$)−H activation/cross-coupling reactions, circumventing the extra steps of installation and subsequent removal of the directing groups. The synthetic utility of this transformation is demonstrated through the scale-up synthesis. In addition, the primary acetamide can be manipulated into synthetically important derivatives such as nitriles and carboxylic acids.

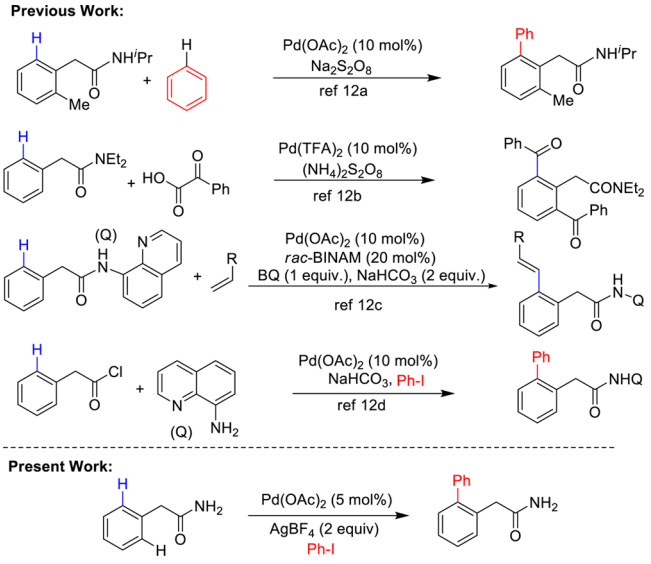



Directing group assisted transition metal catalyzed selective C−H bond functionalization has emerged as an efficient and robust synthetic tool for construction of C−C and C−X bonds for the synthesis of complex target molecules from ubiquitous C−H bonds.[1,2] In the past decade, a variety of directing groups such as acetanilides,[3] pyridyls,[4] oxazolyl,[5] oximes,[6] trizoles,[7] and *N*-substituted secondary and tertiary amides[8] have been introduced for regioselective C−H transformation. However, a major limitation of these strategies lie in requirements of preinstallation of directing groups followed by their uninstallation, which demands two extra steps, resulting in the eventual reduction in the atom and step economy of the complete transformation.[9] Hence, to make direct C−H functionalization transformation more appealing and attractive for the routine synthesis of organic compounds, developing new directing groups is still highly desirable.

Biaryl and its derivatives are key structural motifs present in many natural and synthetic products including light-emitting devices.[10] Biarylacetamide displays a broad range of biological activities.[11] This key scaffold can be procured by a cross-coupling reaction on using *N*-substituted amides as directing groups (Scheme 1).[12] Wang and co-workers first reported a method for *ortho*-arylation of benzamides, and later, Laha et al. attained chemo- and regioselective *ortho*-benzylation of benzamides by using a primary amide as a directing group.[13a,b]

In spite of the significant progress, regioselective *ortho*-arylation under the mild conditions and further utilization of the directing group are major challenges for organic chemists.[12a,14] Yu and a co-worker first reported the application of phenylacetic acid and its derivatives as a directing group for regio- and chemoselective C−H functionalization.[15,16] Inspired by the pioneer work of Yu et al. and our interest in transition metal catalyzed reactions,[17] we herein report a functionalizable

**Scheme 1. Different Synthetic Routes toward the Diverse Product of Arylacetamides**




primary acetamide directed palladium(II)-catalyzed regioselective *ortho*-arylation of aryl-acetamides. To the best of our knowledge, primary acetamide as a directing group to form arylation products has not been reported to date. Primary amides are widely available in nature and can be easily manipulated into a range of other functional groups such as acids, nitriles, and amines.[18] Use of primary acetamide as a

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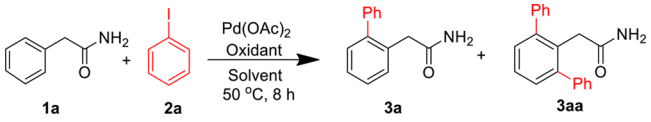
directing group for *ortho* C−H activation will be an exciting addition to the literature.

Phenylacetamide **1a** and iodobenzene **2a** were selected as the designed substrates to optimize the reaction conditions, and the results are summarized in Table 1. The reaction of **1a** and **2a**

**Table 1. Optimization of Reaction Conditions**[a]



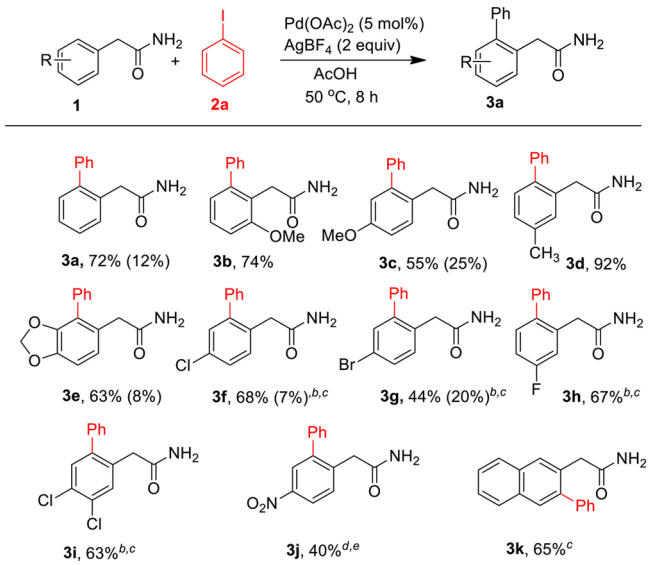

| entry | solvent | oxidant | yield[b] (%) | ratio (3a:3aa)[c] |
|---|---|---|---|---|
| 1 | AcOH | $Ag_2CO_3$ | 11 | n.d. |
| 2 | AcOH | AgO | trace | n.d. |
| 3 | AcOH | AgOAc | 11 | n.d. |
| 4 | AcOH | $AgSbF_6$ | 90 | 1.3:1 |
| **5** | **AcOH** | **$AgBF_4$** | **84** | **6:1** |
| 6 | AcOH | – | 0 | n.d. |
| 7 | HFIP | $AgBF_4$ | 66 | 5.6:1 |
| 8 | TFA | $AgBF_4$ | 30 | 10:1 |
| 9 | DMF | $AgBF_4$ | 8 | n.d. |
| 10 | DMSO | $AgBF_4$ | trace | n.d. |
| 11 | NMP | $AgBF_4$ | trace | n.d. |

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), $Pd(OAc)_2$ (5 mol %), oxidant (0.5 mmol), solvent (2.5 mL), at 50 °C for 8 h in pressure tube. [b]Combined yield of **3a** and **3aa**. [c]Ratio of **3a** and **3aa** was determined after isolation of product through column chromatography. n.d. = not determined.

was conducted in the presence of $Pd(OAc)_2$ as a catalyst and $Ag_2CO_3$ as an oxidant in acetic acid at 50 °C. The desired monoarylated product **3a** was obtained, albeit in a low yield of 11% (Table 1, entry 1). Inspired by the initial result, we optimized various parameters of the reaction conditions such as solvent and oxidants. The efficiency and regioselectivity of the reaction were significantly improved by using $AgBF_4$ as a suitable oxidant, and the monoaryalted compound **3a** was obtained as a major product in 72% yield with high selectivity (6:1) (Table 1, entry 5). Other silver salts such as AgO, AgOAc, and $AgSbF_6$ were less effective (entries 2−4). Although the use of $AgSbF_6$ allowed the formation of an arylated product in 90% yield, regioselectivity was compromised (1.3:1, entry 4). It is important to note that a control experiment in the absence of a silver salt yielded no product and the starting material remained intact (entry 6).[7f] Furthermore, the screening of the reaction solvent revealed that acetic acid is the best choice (entry 5) among other solvents such as HFIP, TFA, DMF, and DMSO (entries 7−11). It is noteworthy that other parameters such as the reaction time and temperature played a very important role in controlling the regioselective outcome. It was observed that a long reaction time and high temperature lead to the formation of a biarylated product as a major compound (for details, see the Supporting Information (SI), Table 1.1).[19] Additional experiments also revealed that the presence of a catalyst is essential for the progress of the reaction (see the SI, Table 1.2),[19] and an increase/decrease in the catalyst loading gave inferior yields. Finally, the reaction conditions described in entry 5 were selected as the standard conditions for further exploration.

With an optimized catalytic system in hand, we next investigated the scope of the palladium-catalyzed primary acetamide directed *ortho*-arylation of phenylacetamides (Scheme 2). We noted that various arylacetamides substituted with electron-donating groups (EDG) such as methyl, methoxy,

**Scheme 2. Scope of Aryl Acetamide Derivatives**[a]




[a]Reaction condition see: entry 5, Table 1. Yield of diarylated product is shown in parentheses. [b]75 °C. [c]15 h. [d]100 °C. [e]24 h.

and 3,4-dioxy at the *ortho*, *meta*, and *para* positions of the aryl ring underwent smooth an *ortho*-arylation reaction to afford the highly regiocontrolled monoarylated products in 55−92% yields (**3b**−**3e**). Interestingly, the substrate bearing a methyl group at the *meta*-position (**1d**) afforded *mono*-arylated product **3d** in 92% yield. Phenylacetamides containing *halo* groups such as *chloro*, *fluoro*, and *bromo* were also suitable substrates to yield the corresponding products, which enabled a potential application for further functionalization (**3f**−**3i**).

However, the presence of a strong electron-withdrawing group such as nitro **1j** at the *para* position of the phenyl ring of phenylacetamide reduced the reactivity and resulted in only a 40% yield of **3j** even at a higher temperature (100 °C). Under the standard conditions, when 2-naphthyl-acetamide was subjected, we obtained the desired product **3k** in 65% yield. In general, when the phenyl ring is substituted with electron-donating groups, the arylation products are afforded in higher yields (**3a**−**3e**) in comparison to the electron-withdrawing substituted groups (**3f**−**3j**) with higher selectivity.

Subsequently, the scope of the optimized strategy was further extended with various aryl iodide substrates (Scheme 3). Iodobenzene with electron-donating groups (EDG) such as methyl and methoxy at the *para* and *meta* position gave the required products in 55−75% yields (**3l**−**3o**). Interestingly, when 4-iodoanisole was reacted with phenylacetamide **1a**, monoarylated product **3o** was afforded in moderate yield (55%). This may be due to the self-coupling of 4-iodoanisole leading to the formation of 4,4′-dimethoxy biphenyl as a side product. Of note, the presence of a stronger electron-withdrawing group ($-CF_3$and $-NO_2$) at the *para*-position of iodobenzene resulted in moderate yields (35−60%) of required products (**3p**−**3q**, Scheme 3). Similarly, when 1-iodonaphthalene was used as the coupling partner, corresponding product **3r** was obtained in 52% yield. In addition, when phenylacetamide bearing a methyl group at the *meta*-position coupled with iodobenzene substituted with a methoxy, methyl,



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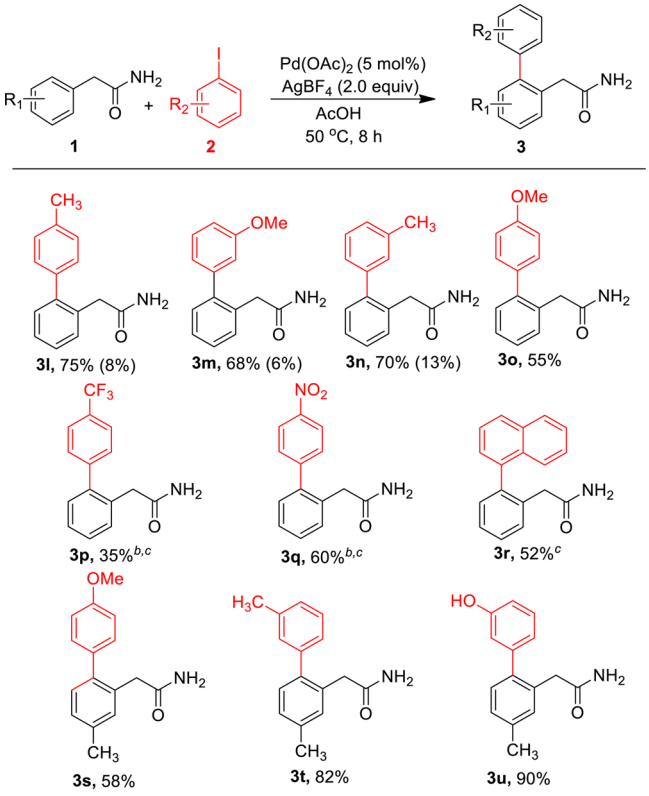
**Scheme 3. Substrate Scope for the Synthesis of Various Monoarylated Acetamide Products**[a]

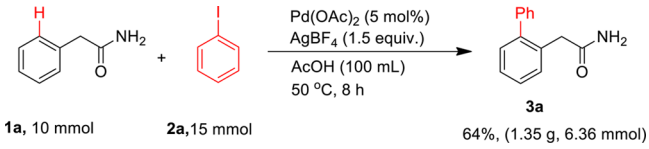



[a]For reaction condition: see entry 5, Table 1. Yield of diarylated product is shown in parentheses. [b]75 °C. [c]15 h.

and hydroxyl group under optimized conditions, the corresponding products were isolated in moderate to good (58–90%) yields with excellent selectivity (**3s**–**3u**).

Next, we sought to evaluate the scalability of the reaction under the established protocol (Scheme 4). The reactions

**Scheme 4. Gram-Scale Reaction**




involving 10 mmol of phenylacetamides **1a** and 15 mmol of the iodobenzene **2a** were subjected to the standard conditions. Subsequently, the product **3a** was procured in 1.35 g (64%), and there was no substantial drop in the yield. This result further demonstrates the robustness of the optimized strategy.

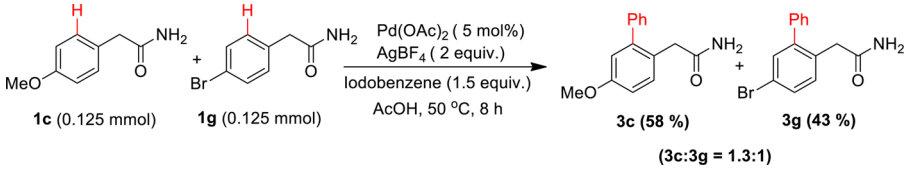
Furthermore, a competition experiment between electron-rich 4-methoxy phenylacetamide **1c** and electron-deficient 4-bromophenylacetamide **1g** revealed that catalytic *ortho*-arylation is slightly favored for the electron-rich arylacetamide over the electron-deficient arylacetamide (Scheme 5). The ratio of product was found in **3c:3g** = 1.3:1 (for details, see the SI).[19]

After successfully establishing the protocol for regioselective *ortho*-arylation of phenylacetamides, further transformation of monoarylacetamide **3a** was studied. Amides and their derivative are ubiquitous in nature and supply crucial intermediates to pharmaceuticals, dyes, and pesticides based industries. The functionalizable primary amide group can be easily hydrolyzed to the corresponding carboxylic acid **4a** by treatment with 40% $H_2SO_4$ at 100 °C (Scheme 6a). Dehydration of amide **3a** with $PPh_3$/NCS led to the formation of biphenylacetonitrile **4b** in 93% yield (Scheme 6b).

Although the reaction mechanism is not clear at this stage, we propose a plausible reaction mechanism based on earlier literature reports (Scheme 7).[12b,20] We believe that the reaction might have followed the Pd(II)/Pd(IV) catalytic pathway.[20a] The acetamide has two possible coordinating sites: (a) carbonyl oxygen and (b) electron-rich nitrogen ($-NH_2$) to form a six-membered palladacycle intermediate. To resolve the ambiguity, we tried to obtain the crystal of the six-membered palladacycle intermediate, but unfortunately, failed. Further, full quantum chemical calculations were done with density functional theory (DFT) using the Gaussian 09 program package in order to understand the coordination site of the directing group under standard conditions (for details, please see the SI).[19] The result revealed that the formation of complex **A** is more exothermic in comparison to the complex **A′** (Scheme 7). The exothermicity, $\Delta H$, equals −7.30 kcal/mol at the LANL2DZ level and is −6.51 kcal/mol using the LANL2TZ (f) basis set. The relative free energy change, $\Delta G$, is −7.42 kcal/mol at the LANL2DZ level and −6.73 kcal/mol at LANL2TZ (f) levels, respectively. This implies that the formation of complex **A** is more favored under reaction conditions (Equilibrium Constant = $3.6 \times 10^4$, $\Delta G$ = −6.73 kcal/mol). Based on *ab inito* calculation, we believe that the reaction would have started with coordination of the carbonyl oxygen[20b,d,21] of phenylacetamide with $Pd(OAc)_2$ to produce species **A** and, subsequently, C($sp^2$)–H bond activation at the *ortho*-position to form a six-membered palladacycle species **B**. Then, oxidative addition[22] of aryl iodide to Pd(II) species **B** would afford Pd(IV) intermediate **C**, followed by reductive elimination to afford the desired product **3a** and regenerate the Pd(II) catalyst. The silver salt may have acted as a halide scavenger to improve the efficacy of transformation.[23]

In conclusion, we have developed an efficient and robust strategy for Pd(II)-catalyzed *regio*-selective *ortho*-arylation of arylacetamides by using functionalizable primary acetamide ($-CH_2CONH_2$) as a directing group for the first time. The developed protocol has a series of advantages: (a) regioselective *ortho*-arylation, (b) simple catalytic system, (c) step economy, (d) broad substrate scope, (e) gram scale synthesis, and (f) no additional requirement of installation and removal of the

**Scheme 5. Competition Experiment**



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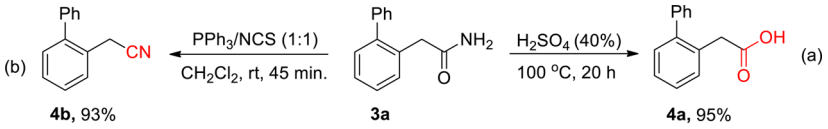
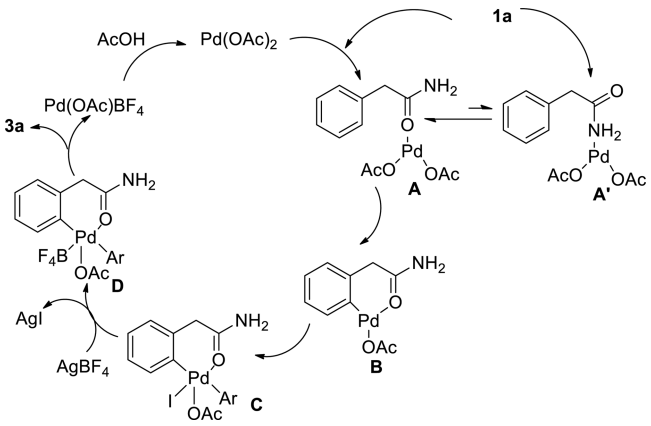
**Scheme 6. Transformation of Biarylacetamide**




**Scheme 7. Proposed Reaction Mechanism**




directing group. These advantages make acetamide a better directing group in comparison to the other reported *N*-substituted amides. Detailed mechanistic studies are in progress, and study of a new application of acetamide as a directing group in the construction of C−C or C−heteroatom bonds is underway in our laboratory.

## EXPERIMENTAL SECTION

**General Information.** All reagents were purchased from a commercial supplier and used without further purification unless specified. $^1$H NMR spectra were recorded at 400 MHz, and $^{13}$C{$^1$H} NMR spectra were recorded at 100 MHz. $CDCl_3$ and DMSO-$d_6$ were used as solvent. TMS was used for internal referencing. The chemical shift is reported in parts per million. Data were reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiple, br, broad singlet), coupling constant (hertz, Hz), integration. Infrared spectra were recorded by an FT-IR apparatus. HRMS spectra were performed on an ESI-TOF spectrometer, and acetonitrile was used to dissolve the sample. Column chromatography was performed on silica gel (100−200) mesh using ethyl acetate and hexanes as eluent in different ratios.

**Preparation of Starting Material.** Phenylacetamide and its derivatives **1a**−**1k** were synthesized by following a known reported precedure.[24]

**General Procedure for Pd-Catalyzed *ortho*-Arylation of Arylacetamides (GP-A).** In an oven-dried 15 mL pressure tube, aryl acetamide (0.25 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %, 2.8 mg), aryl iodide (0.375 mmol, 1.5 equiv), and acetic acid (2.5 mL) were added. Subsequently, silver tetrafluoroborate (0.5 mmol, 98.3 mg, 2.0 equiv) was added in the reaction mixture under a nitrogen atmosphere. The reaction mixture was further flushed with nitrogen and closed with a screw cap. The reaction mixture was stirred at 50 °C for 8−15 h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, solvent was evaporated under reduced pressure and the organic layer was neutralized with a saturated sodium bicarbonate solution and extracted with ethyl acetate (15 mL × 3). The organic layer was washed with a brine solution (10 mL) and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified using silica gel column chromatography with hexanes and EtOAc (70:30) as the eluent to afford the corresponding products.

*2-Biphenyl 2-yl Acetamide (**3a**).*[11] Following GP-A, **3a** was prepared in 8 h and isolated as white crystalline solid (37.9 mg, 72% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 169−171 °C; IR (ATR) 3371, 3185, 1656, 1396, 750 cm$^{-1}$; $^1$H NMR (400 MHz,$CDCl_3$) $\delta$ 7.36−7.25 (m, 6H), 7.25−7.18 (m, 3H), 5.74 (brs, 1H), 5.20 (brs, 1H), 3.45(s, 2H); $^{13}$C{$^1$H} NMR(100 MHz,$CDCl_3$) 173.8, 142.6, 140.8, 132.4, 130.6, 130.5, 129.0 (2C), 128.4 (2C), 128.0, 127.5, 127.4, 40.8.

*2-[1,1′3;1″]Terphenyl-2′-ylacetamide (**3aa**).* Following GP-A, **3aa** was prepared in 8 h and isolated as a white solid (8.6 mg, 12% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.5; Mp 222−224 °C; IR (ATR) 3384, 3194, 1657, 1626, 1397, 1280, 756 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.25 (m, 11H), 7.22−7.18 (m, 2H), 5.24 (brs, 1H), 4.94 (brs, 1H), 3.38 (s, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) 173.7, 143.6 (2C), 141.5 (2C), 130.3, 129.7 (2C), 129.2 (4C), 128.3 (4C), 127.3 (2C), 127.0, 38.1. HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{18}NO$ [M + H]$^+$ 288.1383, Found 288.1384.

*2-(3-Methoxy-biphenyl-2-yl)-acetamide (**3b**).* Following GP-A, **3b** was prepared in 8 h and isolated as a white solid (44.5 mg, 74% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 213−215 °C; IR (ATR) 3369, 3178, 1648, 1403, 697 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$ with $CDCl_3$) $\delta$ 7.41−7.31 (m, 5H), 7.26 (t, *J* = 15.8 Hz, 1H), 7.01 (brs, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.67 (brs, 1H), 3.81 (s, 3H), 3.33 (s, 2H); $^{13}$C{$^1$H}NMR (100 MHz, DMSO-$d_6$with $CDCl_3$) $\delta$ 172.7, 157.8, 143.3, 140.9, 128.9 (2C), 127.9 (2C), 127.1, 126.8, 122.3, 121.7, 109.2, 55.4, 34.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{15}NO_2Na$ [M + Na]$^+$ 264.0995, Found 264.1002.

*2-(5-Methoxy-biphenyl-2-yl)-acetamide (**3c**).* Following GP-A, **3c** was prepared in 8 h and isolated as a white solid (33.1 mg, 55% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.25; Mp 143−145 °C; IR(ATR) 3365, 3178, 1647, 1489, 705 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.31 (m, 3H), 7.31−7.26 (m, 3H), 6.93−6.90 (m, 1H), 6.84 (d, *J* = 2.8,1H), 5.63 (brs, 1H), 5.28 (brs, 1H), 3.82 (s, 3H) 3.45 (s, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) 174.1, 158.7, 143.8, 140.8, 131.7, 128.9 (2C), 128.5 (2C), 127.5, 124.5, 115.7, 113.8, 55.4, 40.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{15}NO_2Na$ [M + Na]$^+$ 264.0995, Found 264.1003.

*2-(5′-Methoxy-[1,1′3′;1″]terphenyl-2′-yl)-acetamide (**3cc**).* Following GP-A, **3cc** was prepared in 8 h and isolated as a white solid (19.8 mg, 25% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.55; Mp 201−203 °C; IR (ATR) 3385, 3183, 1656, 1595, 1338, 1431 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34−7.25 (m, 10H), 6.78 (s, 2H), 5.25 (brs, 1H), 4.99 (brs, 1H), 3.75 (s, 3H), 3.29 (s, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) 174.2, 157.9, 144.8 (2C), 141.5 (2C), 129.0 (4C), 128.3 (4C), 127.3 (2C), 122.6, 115.2 (2C), 55.4, 37.4. HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{20}NO_2$ [M + H]$^+$ 318.1489, Found 318.1487.

*2-(4-Methyl-biphenyl-2-yl)-acetamide (**3d**).*[11] Following GP-A, **3d** was prepared in 8 h and isolated as a white solid (52 mg, 92% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 160−162 °C; IR (ATR) 3402, 3201, 1651, 1485, 1396, 759 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.39 (m, 2H), 7.37−7.33 (m, 1H), 7.30−7.25 (m, 2H), 7.21−7.15 (m, 3H), 5.54 (brs, 1H), 5.26 (brs, 1H), 3.51 (s, 2H), 2.40 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) 173.7, 140.8, 139.7, 137.8, 132.1, 131.2 (2C), 130.5 (2C), 129.1, 128.42, 128.36, 127.2, 41.3, 21.0.

*2-(4-Phenyl-benzo(1,3)dioxol-5-yl)-acetamide (**3e**).* Following GP-A, **3e** was prepared in 8 h and isolated as a white solid (40.1 mg, 63% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 161−163 °C; IR (ATR) 3378, 3194, 1649, 1507, 1224, 767 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$ with $CDCl_3$) $\delta$ 7.39−7.30 (m, 5H), 6.83 (s, 2H), 6.67 (s, 1H), 6.56 (brs, 1H), 5.98 (s, 2H), 3.33 (s, 2H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$ with $CDCl_3$) 173.0, 146.4, 145.9, 140.6, 135.3, 129.0 (2C), 127.8 (2C), 126.5, 126.2, 109.9, 109.4, 100.6, 39.3; HRMS (ESI-



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TOF) $m/z$ calcd for $C_{15}H_{13}NO_3Na$ $[M + Na]^+$ 278.0788, Found 278.0794.

*2-(5-Chloro-biphenyl-2-yl)-acetamide (**3f**).*[11] Following GP-A, **3f** was prepared in 15 h and isolated as a white solid (43 mg, 68% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.35; Mp 176−178 °C; IR (ATR) 3377, 3188, 1653, 1417, 1392, 1288 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.45−7.34 (m, 3H), 7.33 (s, 2H), 7.31−7.27 (m, 3H), 5.61 (brs, 1H), 5.22 (brs, 1H), 3.48 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 173.0, 144.1, 139.6, 133.1, 131.9, 130.9, 130.3, 128.9 (2C), 128.6 (2C), 128.0, 127.9, 40.0.

*2-(5-Bromo-biphenyl-2-yl)-acetamide (**3g**).* Following GP-A, **3g** was prepared in 15 h and isolated as a white solid (31.9 mg, 44% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.27; Mp 186−188 °C; IR (ATR) 3390, 3196, 1653, 1417, 844 $cm^{-1}$; $^1H$ NMR(400 MHz, DMSO-$d_6$with $CDCl_3$) $\delta$ 7.46−7.35 (m, 7H), 7.27 (d, $J$ = 8.2 Hz, 1H), 7.19 (brs, 1H), 6.78 (brs, 1H), 3.36 (s, 2H); $^{13}C\{^1H\}$ NMR(100 MHz, DMSO-$d_6$ with $CDCl_3$) 172.2, 144.0, 139.4, 132.7, 132.3, 131.9, 129.7, 128.8 (2C), 128.0 (2C), 127.2, 119.4, 38.8; HRMS (ESI-TOF) $m/z$ calcd for $C_{14}H_{12}NBrONa$ $[M + Na]^+$ 311.9994, Found 311.9997.

*2-(5′-Bromo-[1,1′3′;1″]terphenyl-2′-yl)-acetamide (**3gg**).* Following GP-A, **3gg** was prepared in 15 h and isolated as a white solid (18.3 mg, 20% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.55; Mp 239−241 °C; IR (ATR) 3393, 3194, 1654, 1400, 873 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$ with $CDCl_3$) $\delta$ 7.39−7.32 (m, 10H), 7.31 (s, 2H), 6.77 (brs, 1H), 6.46 (brs, 1H), 3.19 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$ with $CDCl_3$) 172.8, 145.1 (2C), 140.0 (2C), 131.1 (2C), 130.6, 128.6 (4C), 127.9 (4C), 127.2 (2C), 119.1, 37.1; HRMS (ESI-TOF) $m/z$ calcd for $C_{20}H_{17}BrNO$ $[M + H]^+$ 366.0488, Found 366.0484.

*2-(4-Fluoro-biphenyl-2-yl)-acetamide (**3h**).*[11] Following GP-A, **3h** was prepared in 15 h and isolated as a white solid (38.3 mg, 67% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.35; Mp 146−148 °C; IR (ATR) 3334, 3203, 1651, 1481, 759 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$ with $CDCl_3$) $\delta$ 7.42−7.38 (m, 2H), 7.35−7.32 (m, 3H), 7.23−7.20 (m, 1H), 7.17 (brs, 1H), 7.13−7.10 (m, 1H), 7.04−6.99 (m, 1H), 6.76 (brs, 1H), 3.41 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$ with $CDCl_3$) 172.2, 162.4 and 160.0 ($J_{(C-F)}$ = 248 Hz), 139.8, 138.03 and 138.00, ($J_{(C-F)}$ = 3 Hz), 135.7 and 135.6 ($J_{(C-F)}$ = 8 Hz), 131.1 and 131.0 ($J_{(C-F)}$ = 8 Hz), 129.0, 127.9 (2C), 126.8 (2C), 116.7 and 116.4 ($J_{(C-F)}$ = 21 Hz), 113.2 and 113.0 ($J_{(C-F)}$ = 21 Hz), 39.4.

*2-(4,5-Dichloro-biphenyl-2-yl)-acetamide(**3i**).* Following GP-A, **3i** was prepared in 15 h and isolated as a white solid (44.2 mg, 63% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 191−193 °C; IR (ATR) 3403, 3208, 1652, 1465, 701 $cm^1$. $^1H$ NMR(400 MHz,DMSO-$d_6$ with $CDCl_3$) $\delta$ 7.54 (s, 1H), 7.44−7.33 (m, 7H), 6.89 (brs, 1H), 3.36 (s, 2H); $^{13}C\{^1H\}$NMR (100 MHz,DMSO-$d_6$with $CDCl_3$) 171.7, 142.2, 138.4, 134.3, 132.2, 130.9, 129.8, 129.0, 128.8 (2C), 128.1 (2C), 127.6, 38.5; HRMS (ESI-TOF) $m/z$ calcd for $C_{14}H_{11}Cl_2NONa$ $[M + Na]^+$ 302.0110, Found 302.0124.

*2-(5-Nitro-biphenyl-2-yl)-acetamide (**3j**).*[11] Following GP-A, **3j** was prepared in 24 h and isolated as a white solid (25.8 mg, 40% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.25; Mp 216−218 °C; IR (ATR) 3302, 3201, 1658, 1517, 1342, 578 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$ with $CDCl_3$) $\delta$ 8.16 (dd, $J$ = 8.5, 2.5 Hz, 1H), 8.02 (d, $J$ = 2.4 Hz,1H), 7.62 (d, $J$ = 8.5 Hz, 1H), 7.48−7.41 (m, 6H), 6.95 (brs, 1H), 3.53 (s, 2H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO-$d_6$ with $CDCl_3$) 171.4, 145.9, 143.0, 141.5, 138.7, 131.9, 128.8 (2C), 128.2 (2C), 127.8, 124.0, 121.6, 39.2.

*2-(3-Phenyl-naphtalen-2-yl)-acetamide (**3k**).* Following GP-A, **3k** was prepared in 15 h and isolated as a white solid (42.5 mg, 65% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.35; Mp 178−180 °C; IR(ATR) 3387, 3201, 1651, 1396, 640 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$with $CDCl_3$) $\delta$ 7.86−7.83 (m, 3H), 7.72 (s, 1H), 7.50−7.37 (m, 7H), 7.21 (brs, 1H), 6.84 (brs, 1H), 3.55 (s, 2H); $^{13}C\{^1H\}$NMR (100 MHz,DMSO-$d_6$ with $CDCl_3$) 172.5, 140.7, 140.5, 132.1, 132.0, 131.8, 129.2, 128.9 (2C), 128.2 (2C), 127.9, 127.3, 126.93, 126.91, 125.9, 125.7, 39.82; HRMS (ESI-TOF) $m/z$ calcd for $C_{18}H_{15}NONa$ $[M + Na]^+$ 284.1046, found 284.1062.

*2-(4′-Methyl-biphenyl-2-yl)-acetamide (**3l**).* Following GP-A, **3l** was prepared in 8 h and isolated as a white solid (42.1 mg, 75% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 168−170 °C; IR (ATR) 3382, 3191, 1655, 1396, 755 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.31 (m,3H), 7.29−7.25 (m, 1H), 7.23−7.17 (m, 4H), 5.69 (brs, 1H), 5.27 (brs, 1H), 3.54 (s, 2H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR(100 MHz, $CDCl_3$) 173.8, 142.6, 137.8, 137.1, 132.5, 130.63, 130.58, 129.1 (2C), 128.9 (2C), 127.8, 127.5, 40.9, 21.2; HRMS (ESI-TOF) $m/z$ Calcd for $C_{15}H_{16}NO$ $[M + H]^+$ 226.1226, Found 226.1230.

*2-(3′-Methoxy-biphenyl-2-yl)-acetamide (**3m**).* Following GP-A, **3m** was prepared in 8 h and isolated as a white solid (41 mg, 68% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.35; Mp 142−144 °C; IR (ATR) 3371, 3194, 1651, 1415, 1289, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.34−7.25 (m, 5H), 6.92−6.86 (m, 3H), 6.71 (brs, 1H), 6.48 (brs, 1H), 3.80 (s, 3H), 3.46 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 173.1, 158.7, 142.0, 141.7, 132.7, 130.1, 129.4, 128.7, 127.0, 126.3, 121.0, 114.2, 112.5, 54.7, 39.7; HRMS (ESI-TOF) $m/z$ calcd for $C_{15}H_{15}NO_2Na$ $[M + Na]^+$ 264.0995, Found 264.0997.

*2-(3′-Methyl-biphenyl-2-yl)-acetamide (**3n**).* Following GP-A, **3n** was prepared in 8 h and isolated as a white solid (39.5 mg, 70% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.35; Mp 159−161 °C; IR (ATR) 3377, 3188, 1653, 1406, 1277, 766 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.25 (m, 5H), 7.17 (d, $J$ = 7.64 Hz, 1H), 7.09 (d, $J$ = 7.92 Hz, 2H), 5.77 (brs, 1H), 5.27 (brs, 1H), 3.53 (s, 2H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 173.8, 142.7, 140.8, 138.0, 132.4, 130.56, 130.50 129.8, 128.3, 128.1, 127.9, 127.4, 126.1, 40.8, 21.4; HRMS (ESI-TOF) $m/z$ calcd for $C_{15}H_{15}NONa$ $[M + Na]^+$ 248.1046, Found 248.1049.

*2-(3,3″-Dimethyl-[1,1′3′;1″]Terphenyl-2′-yl)acetamide (**3nn**).* Following GP-A, **3nn** was prepared in 8 h and isolated as a white solid (10.2 mg, 13% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.5; Mp 194−196 °C; IR (ATR) 3399, 3175, 1651, 1415, 778 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) 7.29−7.25 (m, 1H), 7.21−7.17 (m, 4H), 7.08 (s, 4H), 7.07 (s, 2H), 5.48 (brs, 1H), 5.97 (brs, 1H), 3.38 (s, 2H), 2.29 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 174.0, 143.6 (2C), 141.4 (2C), 137.8 (2C), 130.2, 130.0 (2C), 129.6 (2C), 128.1 (2C), 128.0 (2C), 127.0, 126.2 (2C), 38.2, 21.5 (2C); HRMS (ESI-TOF) $m/z$ calcd for $C_{22}H_{22}NO$ $[M + H]^+$ 316.1696, Found 316.1698.

*2-(4′-Methoxy-biphenyl-2-yl)-acetamide (**3o**).* Following GP-A, **3o** was prepared in 8 h and isolated as a white solid (33.2 mg, 55% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.35; Mp 148−150 °C; IR (ATR) 3382, 3191, 1655, 1396, 755 $cm^{-1}$; $^1H$ NMR (400 MHz,$CDCl_3$) $\delta$ 7.38−7.28 (m, 4H), 7.22 (d, $J$ = 8.0 Hz, 2H), 6.95 (d, $J$ = 8.0 Hz, 2H), 5.65 (brs, 1H), 5.29 (brs, 1H), 3.85 (s, 3H), 3.55 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 174.0, 159.1, 142.2, 133.3, 132.8, 130.9, 130.8, 130.4 (2C), 127.9, 127.7, 114.0 (2C), 55.5, 41.0; HRMS (ESI-TOF) $m/z$ calcd for $C_{15}H_{15}NO_2Na$ $[M + Na]^+$ 264.0995, Found 264.0984.

*2-(4′-Trifluoromethyl-biphenyl-2-yl)-acetamide (**3p**).* Following GP-A, **3p** was prepared in 15 h and isolated as a white solid (24.3 mg, 35% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 208−210 °C; IR (ATR) 3390, 3199, 1651, 1324, 1169 $cm^{-1}$; $^1H$ NMR(400 MHz, DMSO-$d_6$ with $CDCl_3$) $\delta$ 7.77 (d, $J$ = 8.2 Hz, 2H), 7.61 (d, $J$ = 8.0 Hz, 2H), 7.38−7.31 (m, 4H), 7.24 (d, $J$ = 6.8 Hz, 1H), 6.8 (brs, 1H), 3.36 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$ with $CDCl_3$) 172.2, 145.06, 140.3, 133.6, 130.6, 129.9, 129.5, 127.8 and 127.5 ($J_{(C-F)}$ = 31 Hz) 126.6, 125.7 and 122.9 ($J_{(C-F)}$ = 270 Hz), 124.93 (q, $J_{(C-F)}$ = 4 Hz), 124.89, 39.1; HRMS (ESI-TOF) $m/z$ calcd for $C_{15}H_{12}F_3NONa$ $[M + Na]^+$ 302.0763, Found 302.0740.

*2-(4′-Nitro-biphenyl-2-yl)-acetamide (**3q**).* Following GP-A, **3q** was prepared in 15 h and isolated as a white solid (39 mg, 60% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 278−280 °C; IR (ATR) 3383, 3198, 1651, 1510, 1348, 854 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.29 (d, $J$ = 8 Hz, 2H), 7.52 (d, $J$ = 12 Hz, 2H), 7.48−7.39 (m, 3H), 7.30−7.28 (m, 1H), 5.61 (brs, 1H), 5.35 (brs, 1H), 3.51 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 172.8, 147.6, 147.2, 140.4, 132.0, 131.0, 130.15, 130.13(2C), 129.1, 127.9, 123.7 (2C), 40.5; HRMS (ESI-TOF) $m/z$ calcd for $C_{14}H_{13}N_2O_3$ $[M + H]^+$ 257.0921, found 257.0923.

*2-(2-Napthalane-1-yl-phenyl)-acetamide (**3r**).* Following GP-A, **3r** was prepared in 15 h and isolated as a white solid (34 mg, 52% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.45; Mp 148−150 °C; IR (ATR) 3384, 3185, 1659, 1388, 765 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (t, $J$



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J. Org. Chem. 2016, 81, 12499−12505

= 8.16, 2H), 7.53−7.31 (m, 9H), 5.37 (brs, 1H), 5.01 (brs, 1H), 3.34 (d, $J$ = 15.8, 1H), 3.21 (d, $J$ = 15.8, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 173.3, 140.4, 138.2, 133.8, 133.6, 132.0, 131.1, 130.3, 128.4, 128.3, 128.1, 127.4, 127.2, 126.4, 126.0, 125.7, 125.4, 40.7; HRMS (ESI-TOF) $m/z$ calcd for $C_{18}H_{15}NONa$ $[M + Na]^+$ 284.1046, found 284.1052.

*2-(4′-Methoxy-4-methyl-biphenyl-2-yl)-acetamide (**3s**).* Following GP-A, **3s** was prepared in 8 h and isolated as a white solid (37 mg, 58% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.35; Mp 154−156 °C; IR (ATR) 3338, 3196, 1653, 1489, 815 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.22−7.13 (m, 5H), 6.95−6.93 (m, 2H), 5.57 (brs,1H), 5.28 (brs, 1H), 3.84 (s, 3H), 3.52 (s, 2H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 173.8, 158.8, 139.3, 137.5, 133.1, 132.3, 131.2 (2C),130.7, 130.2, 128.4, 113.9 (2C), 55.3, 40.9, 21.0; HRMS (ESI-TOF) $m/z$ calcd for $C_{16}H_{17}NO_2Na$ $[M + Na]^+$ 278.1151, Found 278.1153.

*2-(4,3′-Dimethyl-biphenyl-2-yl)-acetamide (**3t**).* Following GP-A, **3t** was prepared in 8 h and isolated as a white solid (48 mg, 82% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.3; Mp 147−149 °C; IR (ATR) 3382, 3182, 1651, 1406, 663 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30−7.25 (m, 1H), 7.18−7.13 (m, 4H), 7.09−7.07 (m, 2H), 5.71 (brs, 1H), 5.27 (brs, 1H), 3.51 (s, 2H), 2.39 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 173.9, 140.7, 139.8, 138.0, 137.6, 132.1, 131.1, 130.4, 129.9, 128.2, 127.9 (2C), 126.1, 40.8, 21.5, 21.0; HRMS (ESI-TOF) $m/z$ calcd for $C_{16}H_{17}NONa$ $[M + Na]^+$ 262.1202, Found 262.1202.

*2-(4′-Hydroxy-4-methyl-biphenyl-2-yl)-acetamide (**3u**).* Following GP-A, **3u** was prepared in 8 h and isolated as a white solid (54.5 mg, 90% yield); $R_f$ (6:4 Hexane/EtOAc) = 0.25; Mp 157−159 °C; IR (ATR) 3469, 3327, 1653, 1456, 788, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$ with $CDCl_3$) $\delta$ 9.22 (s, 1H), 7.17−7.05 (m, 4H), 6.88 (brs, 1H), 6.75−6.73 (m, 3H), 6.63 (brs, 1H), 3.41 (s, 2H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$ with $CDCl_3$) 173.0, 156.8, 142.0, 139.2, 136.0, 132.7, 130.6, 129.3, 128.7, 127.0, 119.8, 116.0, 113.7, 39.46, 20.7; HRMS (ESI-TOF) $m/z$ calcd for $C_{15}H_{15}NO_2Na$ $[M + Na]^+$ 264.0995, Found 264.0993.

**Procedure for Synthesis of Biphenyl Acetic Acid (4a).** By following a reported literature method,[25] the solution of **3a** (53 mg, 0.25 mmol) in 3 mL of 40% (v/v) sulfuric acid was heated at 100 °C for 20 h. After reaction completion, the mixture was diluted with water and extract with diethyl ether (15 mL × 3). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a colorless solid.

*Biphenyl-2-yl Acetic Acid (**4a**).*[26] Colorless solid (50.5 mg, 95% yield); Mp 118−120 °C; IR (ATR) 3009 (br), 1694, 1419, 934, 697 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.27 (m, 9H), 3.62 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 178.3, 142.6, 140.9, 131.0, 130.4, 130.3, 129.2 (2C), 128.3 (2C), 127.6, 127.4, 127.2, 38.5.

**Procedure for Synthesis of Biphenyl-2-yl Acetonitrile (4b).** By following a known literature procedure,[27] a solution of triphenylphosphine (131.1 mg, 0.5 mmol) and *N*-chlorosuccinimide (66.7 mg, 0.5 mmol) in dichloromethane (4 mL) was prepared. Biphenyl acetamide (53 mg, 0.25 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 45 min. After reaction completion, solvent was dried in vacuum and crude product was purified by column chromatography using ethyl acetate and hexanes as eluent to give biphenyl-2-yl acetonitrile as a colorless liquid.

*Biphenyl-2-yl Acetonitrile (**4b**).*[28] Colorless liquid (45 mg, 93% yield); IR (ATR) 3050, 2255, 1460, 745 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.57−7.53 (m, 1H), 7.48−7.42 (m, 2H), 7.41−7.37 (m, 3H), 7.30−7.25 (m, 3H), 3.63 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 141.9, 139.9, 130.5, 128.9 (2C), 128.7 (2C), 128.24, 128.23, 127.8, 127.7, 118.3, 22.0.

**Procedure for Gram Scale Synthesis.** In an oven-dried 250 mL round-bottom flask, phenylacetamide (10 mmol, 1.35 g, 1 equiv), $Pd(OAc)_2$ (5 mol %, 112 mg), iodobenzene (15 mmol, 3.06 g, 1.5 equiv), and acetic acid (100 mL) were added. Subsequently, silver tetrafluoroborate (20 mmol, 3.9 g, 2.0 equiv) was added to the reaction mixture under a nitrogen atmosphere. The reaction mixture was flushed with nitrogen and tightly closed with a rubber septum. The reaction mixture was stirred at 50 °C for 8 h. After reaction completion, the solvent was evaporated under reduced pressure and the organic layer was neutralized with a saturated sodium bicarbonate solution and extracted with ethyl acetate (200 mL × 3). The organic layer was washed with a brine solution and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate and hexanes as eluent to give 64% (1.35 g) of biarylacetamide.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02353.

$^1H$ NMR and $^{13}C$ NMR spectra of products and optimization of reaction conditions, DFT calculation (PDF)

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### Notes

The authors declare no competing financial interest.

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