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Palladium-Catalyzed, *N*-(2-Aminophenyl)Acetamide-Assisted *Ortho*-Arylation of Substituted Benzamides—Application to the Synthesis of Urolithins B, M6 and M7

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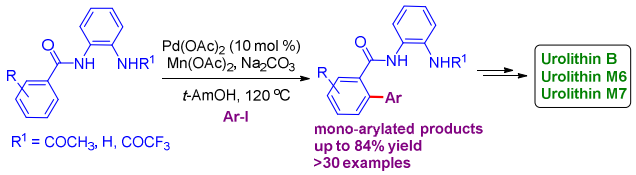


ABSTRACT: Pd-catalyzed, selective, monoarylation of *ortho*-C-H bonds of various benzamides with aryl/heteroaryl iodides has been realized using *N*-(2-aminophenyl)acetamide (APA) as a new bidentate directing group for the first time. The reaction was tolerant of a wide range of functional groups, and a variety of biaryl amide derivatives were successfully prepared in good to moderate yield. The utilization of *N*-(2-aminophenyl)acetamide as a novel directing group, $Mn(OAc)_2$ as a co-oxidant (silver free reaction conditions), and absolute *ortho*-monoaryl selectivity are notable features of this reaction. In addition, the obtained monoarylated products could be further transformed into the bioactive natural products and human microflora metabolites of dietary ellagic acid derivatives, urolithin B, urolithin M6 and urolithin M7.

INTRODUCTION

Transition metal-catalyzed carbon-carbon (C-C) and carbon-heteroatom (C-X) bond formation via C-H bond functionalization has emerged as a powerful and promising synthetic tool in organic synthesis in the past decade.[1-4] Although various transition metal complexes involving Pd, Ru, Rh, Ni, Co and Cu for C-H bond functionalization have been investigated,[2] Pd-catalyzed reactions to generate C-C and C-X bonds have recently seen tremendous advances due to broad functional group tolerance and the unique reactivity of palladium. The number of reports describing the utility of palladium-catalyzed C-C and C-X bond formation has dramatically increased in recent years.[3] Regioselective C-H functionalization is one of the key challenges in the development of synthetically useful reactions. In this line, substantial progress has been realized using directing group-assisted C-H activation/functionalization. Bidentate directing groups have proven particularly instrumental in position-selective C-H transformations under metal catalysis. Bidentate-type auxiliary groups have emerged as a new tool in metal-catalyzed C-H functionalizations due to their versatility and reliability. In addition, the bidentate directing group strongly coordinates the metal with a double coordination strategy and facilitates the C-H functionalization process.[4] In 2005, the pioneering discovery of 8-aminoquinoline as a bidentate directing group by Daugulis paved the way for site-selective C-H functionalization reactions, particularly *ortho*-arylation of benzamide derivatives.[5] Subsequently, various *N*,*N*-, *N*,*S*- and *N*,*O*-bidentate directing groups such as 8-aminoquinoline,[6] picolinamide,[7] pyridin-2-ylmethanamine/(pyridine-2-yl)isopropyl amine (PIP),[8] triazole,[9] 2-thiomethylaniline,[10] peptide derivatives,[11] 2-aminopyridine 1-oxide[12] and others were reported[13] and utilized for C-H activation/C-C bond formation. In particular, Q, PA and PIP were shown to be highly active bidentate directing groups with diverse substrates.[6-8,14] More recently, tremendous progress has been made by Daugulis,[5] Yu,[15] Chatani,[6f,16] Ackermann,[17] Nakamura,[18] Shi[19] and others[6e,13d,20] in

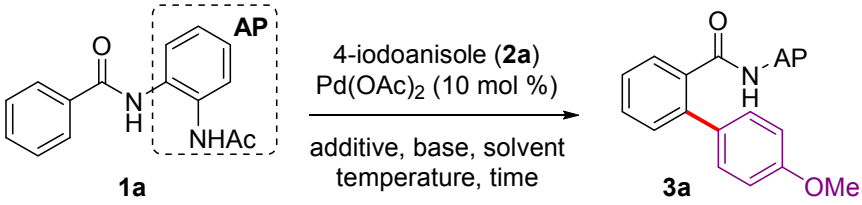
bidentate directing group-assisted C-H *ortho*-arylation reactions. Despite great success in this area, significant work remains to be done with respect to fully regioselective, *ortho*-monoarylation of benzamides using easily accessible bidentate assistance and further utilization of these products for the synthesis of biologically important molecules. In continuation of our research on C-C bond forming reactions using the C-H functionalization strategy,[21] herein, we describe the Pd-catalyzed, highly selective *ortho*-monoarylation of benzamides using commercially available *N*-(2-aminophenyl)acetamide (APA) as a bidentate directing group for the first time and apply this method to the preparation of several natural products of biological interest.

RESULTS AND DISCUSSION

Our initial investigations commenced by exploring *N*-(2-acetamidophenyl)benzamide (**1a**) and 4-iodoanisole (**2a**) model substrates under palladium-catalyzed conditions (table 1). Initially, the reaction of **1a** and **2a** was performed with 10 mol% $Pd(OAc)_2$ and 1 equiv of AgOAc in toluene at 110 ^oC for 24 h. To our delight, the expected monoarylated product (**3a**) could be isolated, although in very low yield (table 1, entry 1). Introduction of Na_2CO_3 as a base resulted in a modest increase to 14% of **3a** (entry 2). Encouraged by these results, we further examined various parameters for this reaction. Replacing toluene with other solvents such as *t*-AmOH or 1,4-dioxane, led to formation of the desired product in 31% and 18% yields, respectively (entries 3 and 4). Furthermore, the reaction of **1a** with **2a** using $Mn(OAc)_2$[22]and $Mn(OAc)_3 \cdot H_2O$ was examined under palladium-catalyzed conditions (entries 5 and 6).[23] $Mn(OAc)_2$ proved to be far superior to AgOAc and $Mn(OAc)_3$.[24] In the presence of $Mn(OAc)_2$ with 10 mol% $Pd(OAc)_2$ and 2 equiv of Na_2CO_3 in *t*-AmOH at 120 ^oC for 36 h, the arylated product **3a** was obtained in 82% yield (entry 5). Subsequently, the efficacy of other bases was also investigated under the

palladium/manganese system. Cs_2CO_3 and K_2CO_3 promoted the reaction with equal efficacy (entries 7 and 8) although in slightly lower yield, but KOAc and NaOAc proved nonviable in this transformation (entries 9 and 10). A variety of solvents were investigated, but all were inferior to *t*-AmOH (entries 11-14). Additionally, the influence of the co-oxidant was also investigated. When the reaction was carried out in the absence of $Mn(OAc)_2$, only 42% of the expected product **3a** was isolated (entry 15). With 0.5 equiv of $Mn(OAc)_2$, the desired product was isolated in 50% yield (entry 16), and with 2 equiv of $Mn(OAc)_2$, no significant improvement in the yield was effected (entry 17). Next, elevated temperature and longer reaction time provided no additional improvement in the yield of **3a** (entry 18). The arylation reaction proceeded smoothly in the absence of base, although **3a** was obtained in only 54% yield (entry 19). Similarly, no arylated product was isolated in the absence of Pd-catalyst (entry 20). Finally, lower yields of arylated products were obtained when the reactions were carried out with 2 and 5 mol % of $Pd(OAc)_2$ (entries 21 and 22). Therefore, the optimal conditions for the arylation reaction were identified as 10 mol% $Pd(OAc)_2$, 1 equiv of $Mn(OAc)_2$ and 2 equiv of Na_2CO_3 in *t*-AmOH at 120 ^oC for 36 h.

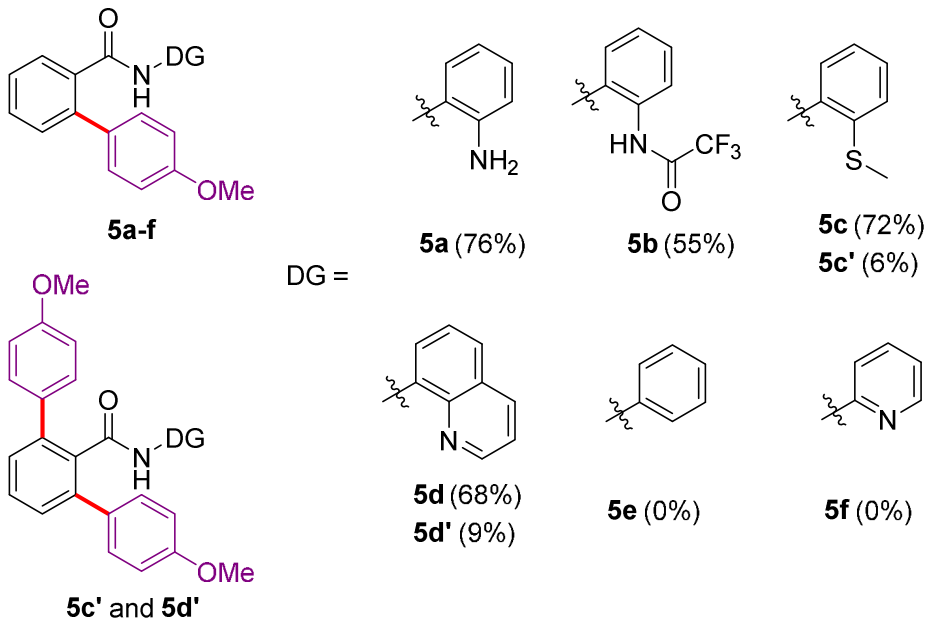
Table 1. Optimization of reaction conditions.[a]



entry	additive	base	solvent	temperature/time °C/hours	yield[b]
1	AgOAc	-	toluene	110/24	5 (79)
2	AgOAc	Na_2CO_3	toluene	110/36	14 (65)
3	AgOAc	Na_2CO_3	*t*-AmOH	120/36	31 (55)
4	AgOAc	Na_2CO_3	1,4-dioxane	110/36	18 (70)
5	**$Mn(OAc)_2$**	**Na_2CO_3**	***t*-AmOH**	**120/36**	**82 (12)[c]**
6	$Mn(OAc)_3.H_2O$	Na_2CO_3	*t*-AmOH	120/48	22 (65)
7	$Mn(OAc)_2$	Cs_2CO_3	*t*-AmOH	120/36	76 (15)
8	$Mn(OAc)_2$	K_2CO_3	*t*-AmOH	120/36	75 (15)
9	$Mn(OAc)_2$	KOAc	*t*-AmOH	120/36	12 (65)
10	$Mn(OAc)_2$	NaOAc	*t*-AmOH	120/36	10 (60)
11	$Mn(OAc)_2$	Na_2CO_3	1,4-dioxane	120/36	54 (26)
12	$Mn(OAc)_2$	Na_2CO_3	DMF	120/24	0 (24)
13	$Mn(OAc)_2$	Na_2CO_3	DMSO	120/24	0 (20)
14	$Mn(OAc)_2$	Na_2CO_3	CF_3CH_2OH	100/36	60 (15)
15	--	Na_2CO_3	*t*-AmOH	120/36	42 (40)
16[d]	$Mn(OAc)_2$	Na_2CO_3	*t*-AmOH	120/36	50 (35)
17[e]	$Mn(OAc)_2$	Na_2CO_3	*t*-AmOH	120/36	81 (10)
18	$Mn(OAc)_2$	Na_2CO_3	*t*-AmOH	150/48	65 (15)
19	$Mn(OAc)_2$	--	*t*-AmOH	120/36	54 (36)
20[f]	$Mn(OAc)_2$	Na_2CO_3	*t*-AmOH	120/48	0 (80)
21[g]	$Mn(OAc)_2$	Na_2CO_3	*t*-AmOH	120/36	32 (50)
22[h]	$Mn(OAc)_2$	Na_2CO_3	*t*-AmOH	120/36	60 (28)

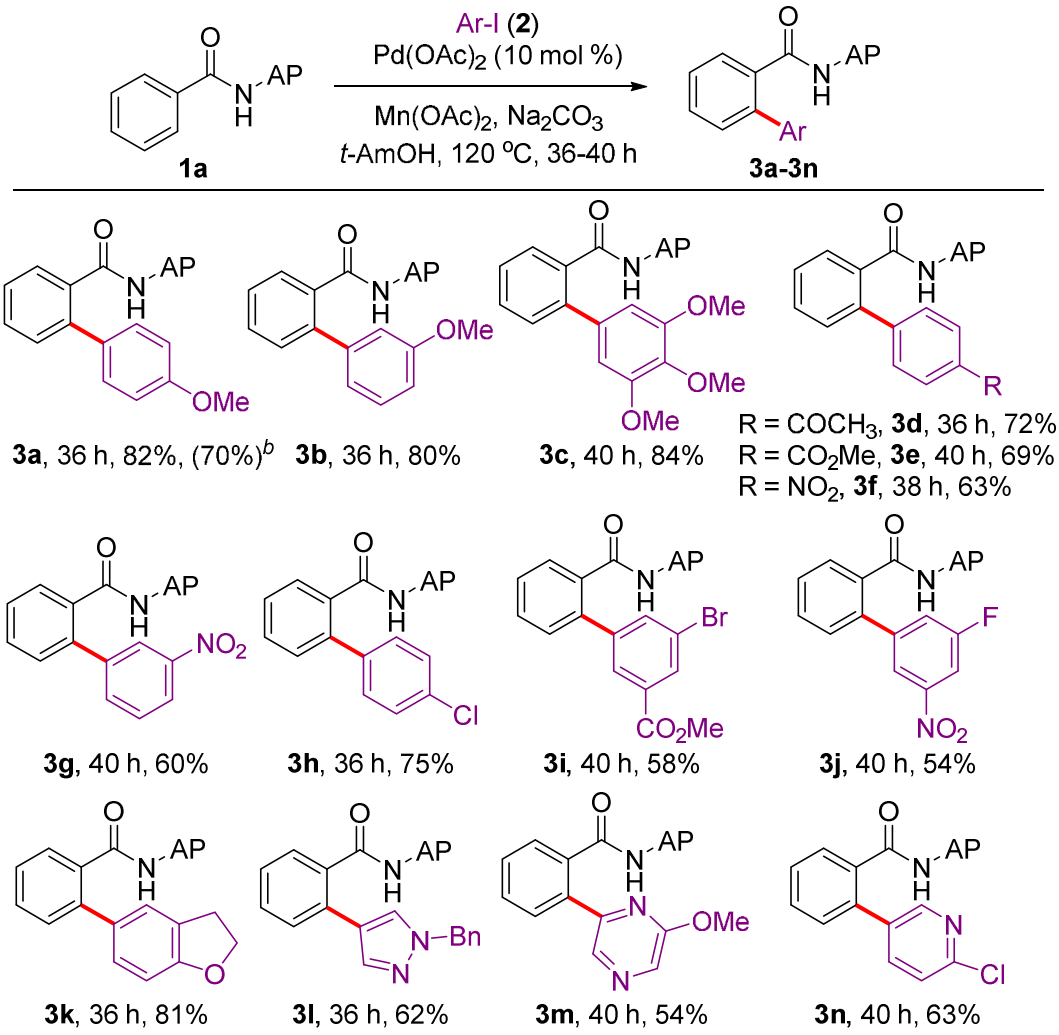
[a]Reaction conditions: benzamide **1a** (0.3 mmol), 4-iodoanisole (**2a**) (0.9 mmol), $Pd(OAc)_2$ (10 mol %), additive (0.3 mmol), base (0.6 mmol), solvent (5 mL); [b]All the products were characterized by ^1H, ^{13}C NMR, IR and MS; [c]0.3 mmol of Ar-I gave 49% while 0.6 mmol gave 68% yield; [d]0.15 mmol of $Mn(OAc)_2$ was used; [e]0.6 mmol of $Mn(OAc)_2$ was used; [f]no $Pd(OAc)_2$ used; [g]$Pd(OAc)_2$ (2 mol %); [h]$Pd(OAc)_2$ (5 mol %); The values in the parentheses refer to starting material recovered.

Having established the conditions for *ortho*-monoarylation using 2-APA, we screened other amide derivatives to differentiate reactivity and selectivity (scheme 1) to better understand the influence of the *N*-acetamide group. Monoarylated benzamide **5a** was isolated in 76% yield after 48 hours at 120 °C. The absence of the *N*-acetamide group allowed us to examine the impact of a pK_a change on reactivity and regioselectivity. Introduction of the electron-withdrawing *N*-trifluoroacetamide group gave the monoarylated compound **5b** in 55% yield. In both instances, no evidence of the presence of the di-arylated product was found. Next, we examined amides prepared from other bidentate ligands such as 2-(methylthio)aniline and 8-aminoquinoline under the standard conditions for the arylation reaction to afford the corresponding mixture of mono and di-*ortho*-arylated products in moderate yields (monoarylated products: **5c**, 72% and **5d**, 68% and di-arylated products: **5c′**, 6% and **5d′**, 9%).[25] As expected, benzamides of 2-aminopyridine and aniline gave no product formation (**5e** or **5f**) following treatment with aryl iodides after 48 h at 120 °C.



Scheme 1. Screening of directing groups.

Having established optimal reaction conditions, we next explored the scope of aryl iodides to test the compatibility of the present protocol (scheme 2). Evaluation of substituted aryl iodides established that the present method is viable with electron donating and withdrawing substituents including methoxy, ester, ketone, nitro- and chloro- functional groups at various positions, with all products being furnished in moderate to good yields (**3a**-**h**, 60-84%). Additionally, the methodology was utilized to prepare **3a** on a gram-scale to demonstrate its synthetic usefulness. Benzamide **1a** (4 mmol) and **2a** (12 mmol) were heated under the standard reaction conditions to furnish **3a** in 70% yield (1.0 g). Disubstituted aryl iodides (**2i** and **2j**) reacted smoothly with **1a** under standard conditions to give the corresponding arylated products **3i** and **3j**, respectively. The bicyclic heteroaromatic iodide, 5-iodo-2,3-dihydrobenzofuran (**2k**), was also transformed into the corresponding arylheteroaryl biarene (**3k**) in 81% yield. Gratifyingly, other heteroaromatic iodides **2l**, **2m** and **2n** provided the expected biaryl derivatives in moderate yields (**3l** in 62%, **3m** in 54% and **3n** in 63% yields, respectively). In contrast, *ortho*-substituted iodoarenes, aryl bromides/chlorides and (4-methoxyphenyl)boronic acid were not viable under the current catalytic conditions.



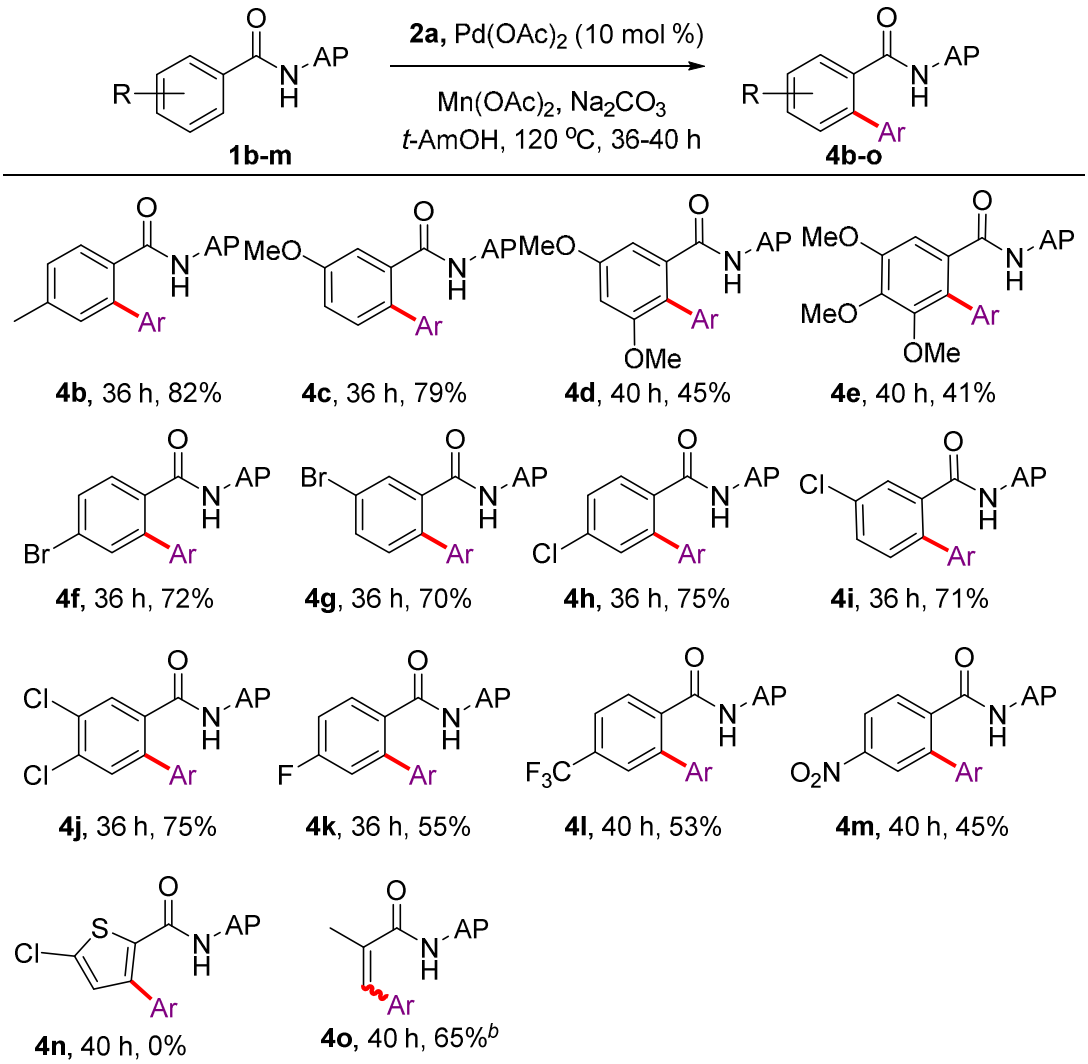
[a]Reaction conditions: benzamide **1a** (0.3 mmol), iodoarene **2** (0.9 mmol), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (0.3 mmol), Na_2CO_3 (0.6 mmol) *t*-AmOH (5 mL), 120 °C. All the products were characterized by ^1H, ^{13}C NMR, IR and MS. [b]The value in the parentheses refer to yield of the reaction on 4 mmol scale.

Scheme 2. Reactivity of various aryl/heteroaryl iodides with **1a**[a]

Encouraged by these results, we next explored the versatility of substituted benzamides in the selective C-H arylation protocol (scheme 3). Thus a range of amide derivatives (**1**) were prepared starting from commercially available *N*-(2-aminophenyl)acetamide (APA) and diverse benzoic acids/acid chlorides as coupling partners. Interestingly, considerable structural diversity of the benzamides was tolerated (scheme 3). Arylation of electron rich methyl and *mono*, *di*, *tri*-

methoxy-substituted benzamides gave the corresponding products in 45-84% yields (**4b-e**). Moreover, a variety of halogenated benzamides reacted well with **2a**, giving the biaryl amides in moderate to good yields (**4f-k**), thereby providing a complementary platform for further synthetic manipulation through cross-coupling reactions. Furthermore, C-H arylation of benzamides bearing electron-withdrawing groups (trifluoromethyl, **1l** and nitro, **1m**) proceeded under optimal conditions to provide biaryl derivatives, **4l** and **4m**, although the yields were somewhat lower (53% and 45%, respectively). In stark contrast, the heteroaromatic benzamide **1n**, when treated with **2a** under standard reaction conditions, failed to yield the corresponding arylated product (**4n**).

Next, to determine whether regioselective Z-cinnamoyl derivatives could be obtained under the current conditions, the alkenyl benzamide (**1o**) was prepared from methacryloyl chloride and 2-APA. Treatment of **1o** with **2a** gave a mixture of *E/Z* isomers that proved difficult to separate using column chromatography (65% yield of geometric isomers **4o**). The C-H arylation reaction of **1c**, **1g**, **1i** and **1j** revealed high position selectivity in favor of the sterically less crowded C-H bond cleavage to furnish *ortho*-arylated products **4c**, **4g**, **4i** and **4j**. In each instance, only monoarylated products were detected. Lower yields were observed and longer reaction times needed for substrates with electron-withdrawing substituents (**4l** and **4m**) or with increased steric hindrance (**1d**, and **1e**). In these instances, the reactions failed to reach completion, with unreacted benzamide remaining.

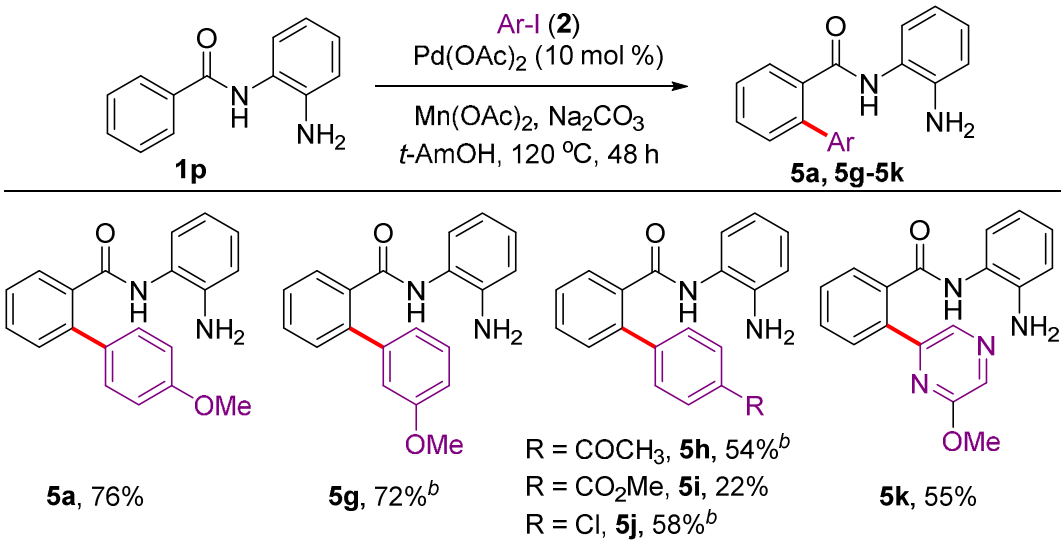


[a]Reaction conditions: benzamide **1** (0.3 mmol), 4-iodoanisole **2a** (0.9 mmol), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (0.3 mmol), Na_2CO_3 (0.6 mmol) *t*-AmOH (5 mL), 120 °C. All products were characterized by ^1H, ^{13}C NMR, IR and MS. [b]complex mixture of products with starting material.

Scheme 3. Scope of substituted benzamides in the arylation reaction.[a]

After investigating the AP-assisted Pd-catalyzed, selective, monoarylation of C(sp^2)-H bonds of benzamides (**3a-n** and **4b-o**), we further explored the arylation of benzamides using the benzene-1,2-diamine system as a bidentate auxiliary (scheme 4). In this line, we prepared benzamide **1p** from benzoyl chloride and benzene-1,2-diamine. The selective arylation of *ortho*-C(sp^2)-H bonds of benzamide **1p** with a set of aryl/heteroaryl iodides in the presence of 10 mol% $Pd(OAc)_2$,

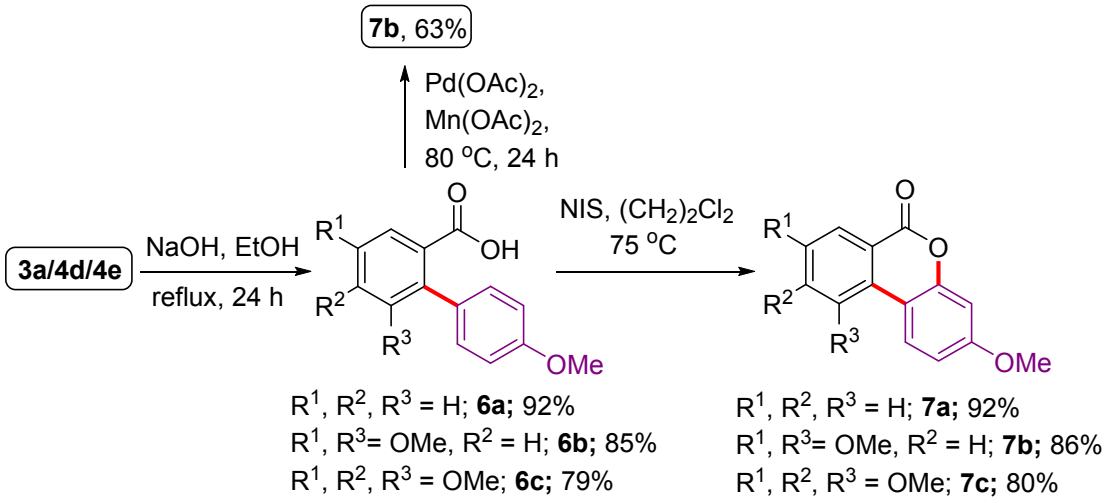
$Mn(OAc)_2$ and Na_2CO_3 in *t*-AmOH at 120 °C for 48 h gave the corresponding products (**5a** and **5g-k**). The reaction of **1p** with 4- and 3-methoxy iodobenzene proceeded smoothly to furnish the corresponding biaryl compounds (**5a** and **5g**) in 76% and 72% yields, respectively. Furthermore, aryl iodides with electron-withdrawing groups (**2d**, **e** and **2h**) were also tolerated in the present conditions with **1p** to afford the expected arylated aminobenzamide products (**5h-j**) although in lower yields (22%-58%). Finally, 2-iodo-6-methoxypyrazine (**2m**) with **1p** was found to undergo *ortho*-arylation to give the corresponding aryl/heteroaryl substrate **5k** in 55% yield. Interestingly, in each of these reactions, less than 15% of unreacted starting material was recovered. The remainder apparently decomposed to indistinguishable products as evidenced by TLC. Based on these results, the *N*-acetamide directing group is superior to the free amine under the current reaction conditions.



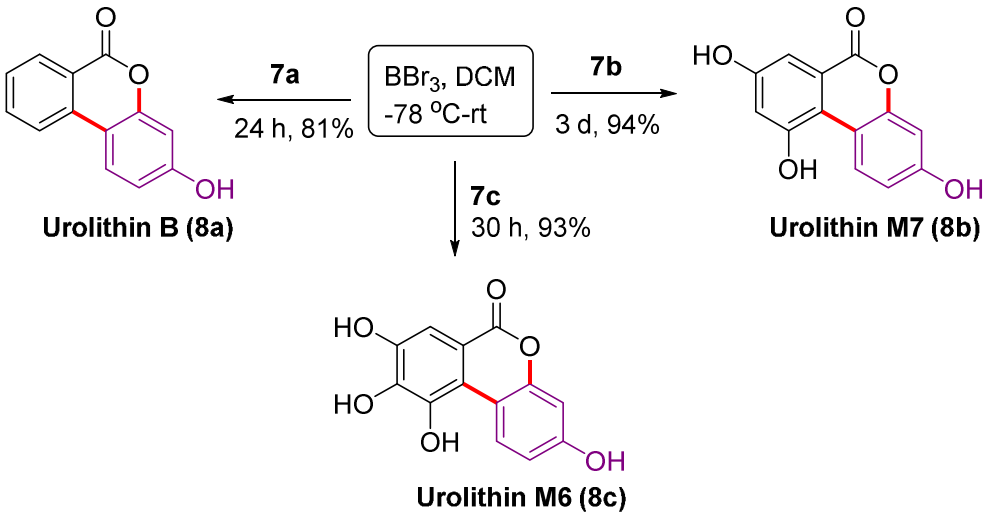
[a]Reaction conditions: benzamide **1p** (0.3 mmol), iodoarene **2** (0.9 mmol), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (0.3 mmol), Na_2CO_3 (0.6 mmol) *t*-AmOH (5 mL), 120 °C for 48 h. All the products were characterized by ^1H, ^{13}C NMR, IR and MS. [b]less than 15% of starting material was recovered.

Scheme 4. Scope of arylation reaction with *N*-(2-aminophenyl)benzamide.[a]

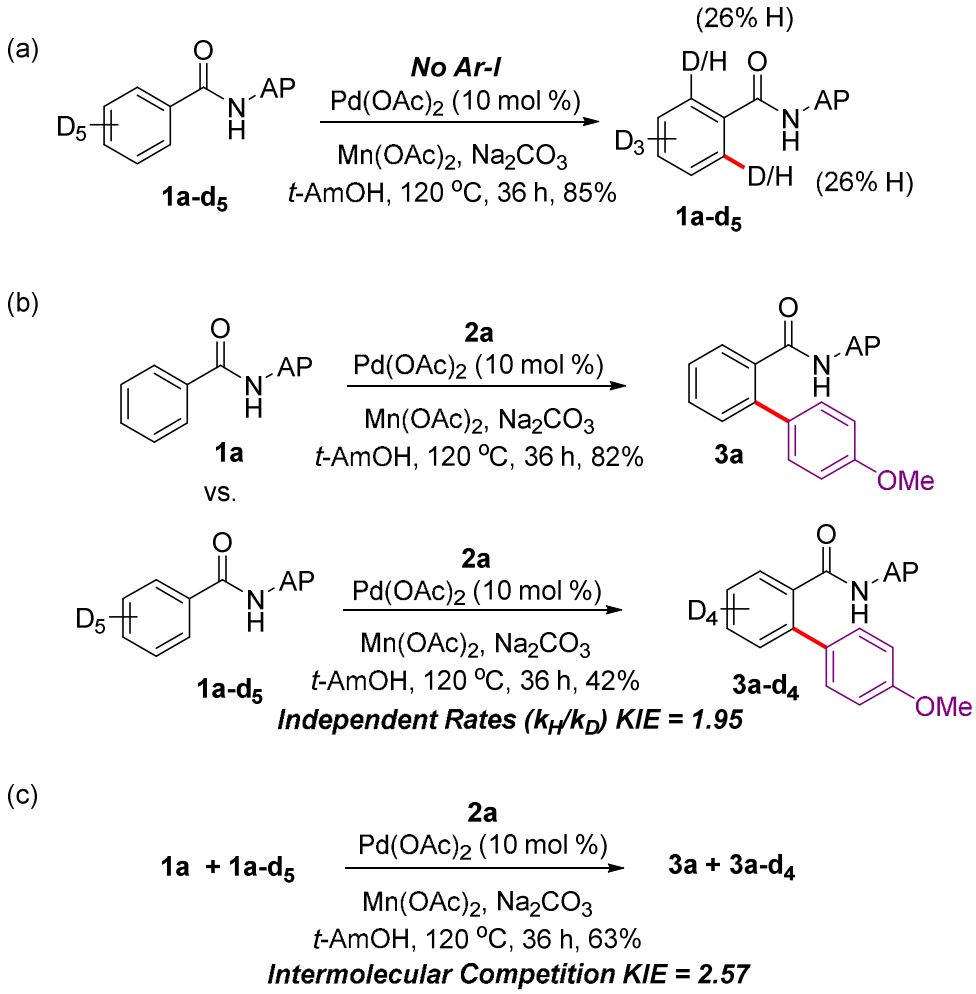
Additionally, to demonstrate the potential of the developed methodology, removal of the directing group was attempted on various products. *Ortho*-arylated benzamides (**3a**, **4d** and **4e**) were subjected to NaOH/EtOH under reflux conditions[24,26] to give biaryl acid derivatives (**6a-c**) in excellent yields (scheme 5). The obtained biaryl carboxylic acids were used as key structural motifs for the synthesis of bioactive urolithin natural products (**B**, **M6**, and **M7**).[27,28] Urolithins are human intestinal metabolites of ellagitannins, consisting of a benzopyranone core unit with phenolic hydroxy groups at various positions. Urolithins have been reported to exhibit strong antioxidant properties,[28a] anti-cancer,[28b] anti-inflammatory[28c,28d] and antiglycation activities.[28b] Additionally, these molecules also reduce triglyceride accumulation and increase the oxidation process of fatty acids in hepatocytes as well as adipocytes.[28e] Recent studies also suggest that urolithins may hold potential for the treatment of Type 2 diabetes. The biological significance and pharmacological potential of urolithins have made them attractive targets for both synthetic and medicinal chemists to study their medicinal properties. To this end, *N*-iodosuccinimide-mediated C(sp^2)-H functionalization/C-O cyclization[29] of **6a-c** led to the formation of the corresponding lactones (**7a-c**) in 80-92% yields. Alternatively, the cyclization could be conducted under palladium catalysis. To this end, **6b** was heated to 80 ^oC for 24 h in the presence of $Pd(OAc)_2$ (10 mol%) and $Mn(OAc)_2$ (1 equiv.), and the cyclized product (**7b**) was isolated in 63% yield. Finally, the phenolic natural products urolithin B (**8a**), urolithin M7 (**8b**) and urolithin M6 (**8c**) were isolated in excellent yields following deprotection of the methyl ethers in the presence of BBr_3/DCM[29] (scheme 6).



Scheme 5. Directing group removal and C-H functionalization/C-O cyclization.



Scheme 6. Synthesis of urolithins.

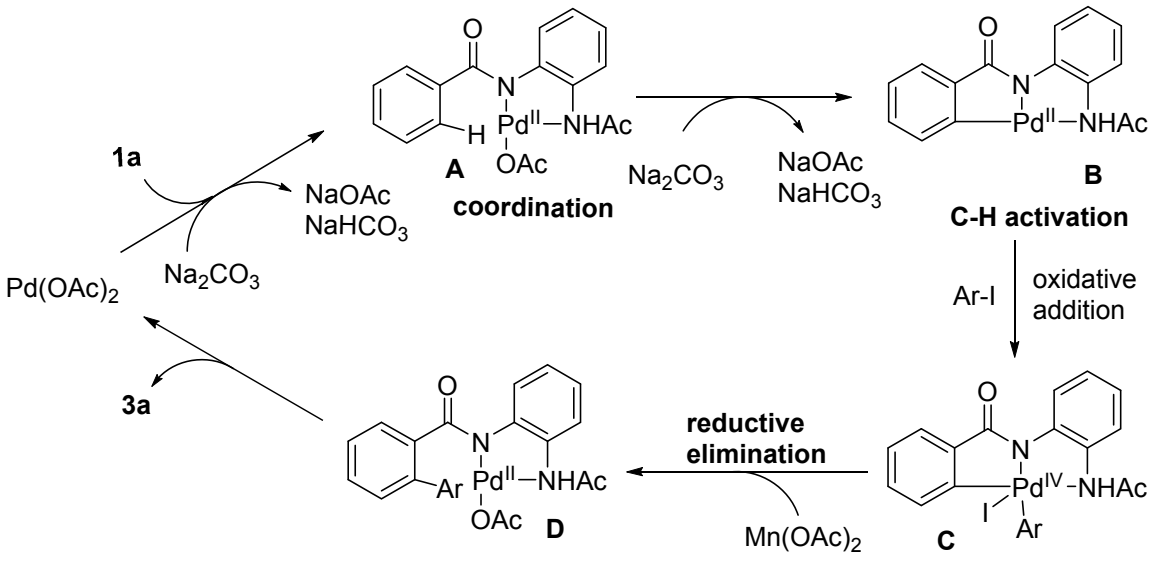


Scheme 7. Deuterium labeling studies.

Deuterium-labeling experiments were performed to gain insight into the mechanism of the monoarylation reaction (scheme 7). Heating **1a-d$_5$** under the reaction conditions in the absence of aryl iodide resulted in H/D exchange (26%, scheme 7c) at the *ortho* positions indicating that C-H cleavage is reversible. Kinetic isotope effects (KIE)[30] were determined from independent rates and intermolecular competition of **1a** and **1a-d$_5$** (scheme 7b and c). Separate reactions of **1a** and **1a-d$_5$** resulted in a KIE of 1.95 (scheme 7b), while the competition reaction yielded a similar KIE of 2.57 (scheme 7c).

In all the reactions conducted using the AP directing group under the optimized conditions, only monoarylated products were isolated. Analysis of **3a-d$_4$** (scheme 7b) revealed no detectable exchange at the *ortho* position of the benzamide, indicating that C-H activation does not occur, providing evidence for the observed mono-selectivity. Further investigation is underway to determine the precise barrier to C-H activation leading to di-arylation.

Based on the above observations and the known reports on bidentate directing group-assisted C-H activation under palladium-catalyzed conditions,[4a-c,4e,4g, 5, 10b,10c, 11a-c] a tentative reaction mechanism is proposed (scheme 8). Initially, the coordination of benzamide **1a** with $Pd(OAc)_2$ followed by ligand exchange provides bidentate-coordinated intermediate **A**, which undergoes rapid cyclometalation of the aryl group, resulting in the formation of **B**. Oxidative addition of the aryl iodide to complex **B** provides complex **C**, with a subsequent increase in oxidation state to Pd^{IV}. Finally, reductive elimination of **C** provides **D** followed by ligand exchange to give the *ortho*-arylated product **3a** and regeneration of $Pd(OAc)_2$.



Scheme 8. Plausible reaction mechanism.

CONCLUSION

In conclusion, we have developed a facile method for the regioselective synthesis of monoarylated benzamides under Pd-catalyzed conditions, with *N*-(2-aminophenyl)acetamide (APA) as a new *N*,*N*-bidentate directing group in a C-H functionalization reaction for the first time. Preliminary screening of directing groups for the arylation reaction revealed that APA is superior to the free amine (**1p**), trifluoroacetamide (**1q**) and other bidentate substrates under the present reaction conditions. Furthermore, we demonstrated the synthetic usefulness of the products by accomplishing the synthesis of natural products urolithin B, urolithin M6, and urolithin M7. Further application of the APA directing group in C-H functionalization reactions and the precise origin of its monoarylation selectivity are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. All reactions were conducted in glassware that was dried in an oven (120 °C), heated under reduced pressure, and cooled under a stream of argon before use. Reactions were monitored by thin-layer chromatography on silica gel plates using UV light (254 nm) and ceric sulfate or *β*-naphthol for visualization. Column chromatography was performed on a flash chromatography system with silica gel columns using *n*-hexane and ethyl acetate as eluent. Evaporation of solvents was conducted under reduced pressure at 50 °C using rotary evaporators. FTIR spectra were recorded neat, and wavenumbers are indicated in cm^{-1}. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C). Deuterated chloroform was used as the solvent, unless otherwise stated, and spectra were calibrated against the residual solvent peak at 7.26 ppm for ^{1}H and at 77.0 ppm for ^{13}C or against TMS. Chemical shifts (δ) and coupling

constants (*J*) are given in ppm (parts per million) and Hz (Hertz), respectively. The following abbreviations are used to describe the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet. Low-resolution mass spectra were obtained by electrospray ionization (ESI). High-resolution mass spectra (HRMS) were performed with an orbitrap mass analyzer by electrospray ionization (ESI).

Starting materials (**1r-u**) were prepared using literature procedures: *N*-(2-(methylthio)phenyl)benzamide (**1r**),[8e] *N*-(quinolin-8-yl)benzamide (**1s**),[8e,12a] *N*-phenylbenzamide (**1t**),[12a] *N*-(pyridin-2-yl)benzamide (**1u**).[12a]

General procedure for the synthesis of benzamides from acid chlorides (1a-c and 1f-o):[14a,24]

N-(2-Aminophenyl)acetamide (0.5 g, 3.33 mmol, 1 equiv) and triethylamine (0.7 mL, 4.99 mmol, 1.5 equiv) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 100 mL round-bottom flask, followed by dropwise addition of the aroyl chloride (3.66 mmol, 1.1 equiv, dissolved in 10 mL of DCM) via syringe over a period of 15 min at 0 ^oC. The reaction mixture was warmed to room temperature and stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (40 mL), washed with a saturated solution of $NaHCO_3$ (40 mL), 1 N aqueous HCl (40 mL), brine (40 mL), and dried over $MgSO_4$. The organic solvent was removed by evaporation. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 90:10 to 40:60) to afford the corresponding amide.

***N*-(2-Acetamidophenyl)benzamide**[30a] (**1a**)*:* From benzoyl chloride (0.515 g, 0.425 mL, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 80/20; R_f = 0.40 in hexanes/EtOAc = 3/1). The product was obtained as a brown solid (0.753 g, 89%); ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.49 (s,

1H), 8.71 (s, 1H), 7.98-7.93 (m, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.55-7.48 (m, 3H), 7.08-7.02 (m, 2H), 6.92 (t, J = 7.1 Hz, 1H), 2.04 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.3, 166.6, 133.5, 132.2, 130.8, 130.4, 128.8, 127.5, 126.3, 126.2, 126.0, 125.0, 23.6; FTIR (neat): 3231, 3091, 1646, 1512, 1431, 1329, 1292, 1155, 1090, 821 cm^{-1}; MS (ESI) *m/z* 255 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{15}O_2N_2$ 255.1128; Found: 255.1134.

***N*-(2-Acetamidophenyl)-4-methylbenzamide** (**1b**)*:* From 4-methylbenzoyl chloride (0.566 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 80/20; R_f = 0.42 in hexanes/EtOAc = 3/1). The product was obtained as a brown solid (0.767 g, 86%); mp = 166-168 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.77 (s, 1H), 9.71 (s, 1H), 7.86 (dd, J = 8.1, 2.2 Hz, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 7.9 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 2.24 (s, 3H), 2.16 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.1, 165.5, 142.2, 131.6, 131.4, 130.5, 129.2, 127.5, 125.8, 125.6, 125.3, 124.9, 23.7, 21.5; FTIR (neat): 3239, 3059, 1666, 1643, 1598, 1503, 1439, 1322, 1272, 1189, 1099, 822 cm^{-1}; MS (ESI) *m/z* 269 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$Calcd for $C_{16}H_{17}O_2N_2$ 269.1285; Found: 269.1291.

***N*-(2-Acetamidophenyl)-3-methoxybenzamide** (**1c**): From 3-methoxybenzoyl chloride (0.625 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.25 in hexanes/EtOAc = 3/1). The product was obtained as a white solid (0.598 g, 63%); mp = 185-186 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.82 (s, 1H), 9.64 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.59-7.52 (m, 2H), 7.39 (t, J = 8.1 Hz, 1H), 7.35 (dd, J = 7.8, 1.0 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 7.08 (dd, J = 8.2, 1.2 Hz, 1H), 3.88 (s, 3H), 2.19 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2

$CDCl_3$:DMSO-d_6): δ 170.1, 165.3, 159.6, 135.7, 131.2, 130.4, 129.5, 125.8, 125.5, 125.3, 124.8, 119.4, 117.9, 112.5, 55.3, 23.6; FTIR (neat): 3053, 1661, 1642, 1581, 1502, 1436, 1321, 1285, 1187, 1090, 822 cm^{-1}; MS (ESI) *m/z* 285 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{17}O_3N_2$ 285.1234; Found: 285.1238.

***N*-(2-Acetamidophenyl)-4-bromobenzamide** (**1f**): From 4-bromobenzoyl chloride (0.800 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.40 in hexanes/EtOAc = 3/1). The product was obtained as a white solid (0.830 g, 75%); mp = 210-211 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.96 (s, 1H), 9.76 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 2.18 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.3, 164.5, 133.4, 131.7, 131.0, 130.7, 129.3, 126.3, 125.8, 125.7, 125.5, 124.9, 23.7; FTIR (neat): 3308, 3128, 2995, 1640, 1592, 1493, 1370, 1269, 1144, 1071, 822 cm^{-1}; MS (ESI) *m/z* 333 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{14}BrO_2N_2$ 333.0233; Found: 333.0241.

***N*-(2-Acetamidophenyl)-3-bromobenzamide** (**1g**): From 3-bromobenzoyl chloride (0.800 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.40 in hexanes/EtOAc = 3/1). The product was obtained as a white solid (0.760 g, 69%); mp = 195-197 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.93 (s, 1H), 9.56 (s, 1H), 8.15 (d, *J* = 1.6 Hz, 1H), 7.90 (d, *J* = 7.0 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 6.9 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 2.19 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.1, 164.0, 136.4, 134.5, 130.8, 130.9, 130.7, 130.5, 130.0, 125.5, 125.8, 125.6, 124.8, 122.5, 23.6; FTIR (neat): 3241, 3058, 1646, 1598, 1513, 1443, 1375, 1283, 1162, 1063, 828 cm^{-1}; MS

(ESI) *m/z* 333 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{14}BrO_2N_2$ 333.0233; Found: 333.0241.

***N*-(2-Acetamidophenyl)-4-chlorobenzamide** (**1h**): From 4-chlorobenzoyl chloride (0.641 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.40 in hexanes/EtOAc = 3/1). The product was obtained as a brown solid (0.817 g, 85%); mp = 189-190 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.95 (s, 1H), 9.75 (s, 1H), 7.95 (dd, J = 8.5, 2.3 Hz, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.47 (dd, J = 8.6, 2.5 Hz, 2H), 7.37 (d, J = 6.3 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 2.18 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.2, 164.3, 137.7, 133.0, 131.0, 130.7, 129.1, 128.7, 125.8, 125.7, 125.5, 124.8, 23.7; FTIR (neat): 3301, 2935, 1702, 1645, 1580, 1495, 1332, 1275, 1151, 1030, 821 cm^{-1}; MS (ESI) *m/z* 289 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{14}ClO_2N_2$ 289.0738; Found: 289.0745.

***N*-(2-Acetamidophenyl)-3-chlorobenzamide** (**1i**): From 3-chlorobenzoyl chloride (0.641 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.38 in hexanes/EtOAc = 3/1). The product was obtained as a brown solid (0.675 g, 70%); mp = 199-200 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.97 (s, 1H), 9.67 (s, 1H), 7.99 (d, J = 1.5 Hz, 1H), 7.86 (d, J = 6.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.55-7.49 (m, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.27-7.14 (m, 2H), 2.19 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.2, 164.2, 136.4, 134.5, 131.7, 130.9, 130.7, 130.0, 128.0, 125.8, 125.7, 125.7, 125.6, 124.9, 23.8; FTIR (neat): 3238, 3059, 2933, 1647, 1565, 1493, 1315, 1284, 1126, 1067, 826 cm^{-1}; MS (ESI) *m/z* 289 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{13}ClO_2N_2Na$ 311.0558; Found: 311.0565.

***N*-(2-Acetamidophenyl)-3,4-dichlorobenzamide** (**1j**): From 3,4-dichlorobenzoyl chloride (0.763 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.36 in hexanes/EtOAc = 3/1). The product was obtained as a white solid (0.910 g, 85%); mp = 164-165 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 10.01 (s, 1H), 9.71 (s, 1H), 8.14 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 2.19 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.2, 163.3, 135.6, 134.3, 132.6, 130.6, 130.5, 130.4, 129.9, 126.6, 125.8, 125.7, 125.6, 124.6, 23.6; FTIR (neat): 3253, 3059, 1639, 1598, 1467, 1366, 1239, 1115, 1032, 826 cm^{-1}; MS (ESI) *m/z* 323 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{12}Cl_2O_2N_2Na$ 345.0168; Found: 345.0175.

***N*-(2-Acetamidophenyl)-4-fluorobenzamide** (**1k**): From 4-fluorobenzoyl chloride (0.581 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.40 in hexanes/EtOAc = 3/1). The product was obtained as a brown solid (0.640 g, 70%); mp = 195-196 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.87 (s, 1H), 9.64 (s, 1H), 8.05-7.96 (m, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.16 (m, 3H), 2.19 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.1, 165.9, 164.3, 163.4, 131.0, 130.4, 130.3, 129.8, 125.8, 125.4, 124.7, 115.5, 23.5; FTIR (neat): 3244, 3057, 2933, 2838, 1665, 1574, 1502, 1437, 1315, 1280, 1180, 1026, 821 cm^{-1}; MS (ESI) *m/z* 273 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{13}FO_2N_2Na$ 295.0853; Found: 295.0858.

***N*-(2-Acetamidophenyl)-4-(trifluoromethyl)benzamide** (**1l**): From 4-(trifluoromethyl)benzoyl chloride (0.764 g, 3.66 mmol) using the above general procedure. The crude residue was purified

by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.25 in hexanes/EtOAc = 3/1). The product was obtained as a brown solid (0.792 g, 74%); mp = 182-183 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 10.11 (s, 1H), 9.77 (s, 1H), 8.13 (d, J = 7.9 Hz, 2H), 7.81 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 7.8 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 2.19 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.3, 164.0, 138.0, 132.7, 130.7, 130.11, 128.1, 125.9, 125.7, 125.5, 125.5, 125.1, 122.5, 23.7; FTIR (neat): 3245, 3056, 2994, 1665, 1602, 1502, 1436, 1367, 1252, 1179, 1025, 822 cm^{-1}; MS (ESI) *m/z* 323 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{13}F_3O_2N_2Na$ 345.0821; Found: 345.0827.

***N*-(2-Acetamidophenyl)-4-nitrobenzamide** (**1m**): From 4-nitrobenzoyl chloride (0.680 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 60/40; R_f = 0.30 in hexanes/EtOAc = 2/1). The product was obtained as a brown solid (0.796 g, 80%); mp = 157-158 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 10.29 (s, 1H), 9.93 (s, 1H), 8.33 (dd, J = 8.7, 3.6 Hz, 2H), 8.22 (dd, J = 5.2, 3.4 Hz, 2H), 7.80 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.30-7.16 (m, 2H), 2.19 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.3, 163.4, 149.5, 140.3, 130.9, 130.6, 129.0, 125.9, 125.8, 125.7, 124.9, 123.7, 23.8; FTIR (neat): 3308, 3056, 2997, 1655, 1601, 1523, 1436, 1345, 1239, 1188, 1035, 821 cm^{-1}; MS (ESI) *m/z* 300 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{13}O_4N_3Na$ 322.0798; Found: 322.0804.

***N*-(2-Acetamidophenyl)-5-chlorothiophene-2-carboxamide** (**1n**): From 5-chlorothiophene-2-carbonyl chloride (0.655 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.30 in hexanes/EtOAc = 2/1). The product was obtained as a brown solid (0.850 g, 79%); mp = 186-

188 °C; ^{1}H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.97 (s, 1H), 9.74 (s, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.60-7.54 (M, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.26-7.14 (m, 2H), 6.99-6.94 (m, 1H), 2.21 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.4, 159.2, 138.6, 135.5, 130.5, 130.4, 128.1, 127.4, 125.9, 125.5, 125.4, 124.8, 23.8; FTIR (neat): 3300, 3056, 2977, 1652, 1623, 1525, 1436, 1361, 1239, 1188, 1034, 822 cm^{-1}; MS (ESI) *m/z* 295 $[M+H]^+$.

***N*-(2-Acetamidophenyl)methacrylamide** (**1o**): From methacryloyl chloride (0.380 g, 3.66 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 70/30; R_f = 0.45 in hexanes/EtOAc = 2/1). The product was obtained as a brown solid (0.574 g, 72%); mp = 157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.57 (s, 1H), 7.49 (dd, J = 6.8, 1.4 Hz, 1H), 7.14 (td, J = 7.4, 1.4 Hz, 1H), 7.07 (td, J = 8.0, 1.4 Hz, 1H), 7.03 (td, J = 10.0, 1.4 Hz, 1H), 5.95 (s, 1H), 5.52 (t, J = 2.3 Hz, 1H), 2.03 (s, 3H), 2.00 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 170.3, 167.6, 139.2, 130.7, 130.4, 126.3, 126.0, 125.9, 124.9, 122.3, 23.4, 18.6; FTIR (neat): 3312, 3052, 2977, 1644, 1621, 1525, 1434, 1361, 1240, 1180, 1034, 821 cm^{-1}; MS (ESI) *m/z* 219 $[M+H]^+$.

General procedure for the synthesis of benzamides (1d, 1e and 1a-d_5):[21a] Thionyl chloride (0.490 g, 0.300 mL, 4.12 mmol) was added slowly to a stirred solution of the carboxylic acid (0.50 g, 2.74 mmol) in toluene (15 mL) and DMF (0.05 mL) at room temperature. The mixture was stirred for 4 h at 110 °C and the solvent evaporated *in vacuo*. The residue was then dissolved in toluene (5 mL), evaporated *in vacuo* to give the crude acid chloride.

The acid chloride was dissolved in 10 mL of DCM and added dropwise to a solution of *N*-(2-aminophenyl)acetamide (412 mg, 2.74 mmol) and Et_3N (0.575 mL, 4.12 mmol) in CH_2Cl_2 (30 mL) at -10 °C over 15 min. The resulting solution was warmed to room temperature and stirred

overnight. The mixture was diluted with CH_2Cl_2 (40 mL) and washed successively with a saturated solution of $NaHCO_3$ (30 mL), 1 N aqueous HCl (30 mL), brine (30 mL), and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (10:90 to 50:50), to afford the corresponding amide **1**.

***N*-(2-Acetamidophenyl)-3,5-dimethoxybenzamide** (**1d**): From 3,5-dimethoxybenzoic acid (0.500 g, 2.74 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 60/40; R_f = 0.25 in hexanes/EtOAc = 2/1). The product was obtained as a brown solid (0.783 g, 91%); mp = 186-187 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.83 (s, 1H), 9.65 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.41-7.34 (m, 1H), 7.27-7.09 (m, 4H), 6.61 (d, J = 1.6 Hz, 1H), 3.85 (s, 6H), 2.17 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.0, 165.2, 160.8, 136.6, 131.2, 130.5, 125.8, 125.5, 125.4, 124.9, 105.3, 104.0, 55.6, 23.8; FTIR (neat): 3233, 3056, 1668, 1640, 1593, 1329, 1270, 1189, 1096, 821 cm^{-1}; MS (ESI) *m/z* 315 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}O_4N_2$ 315.1339; Found: 315.1343.

***N*-(2-Acetamidophenyl)-3,4,5-trimethoxybenzamide** (**1e**): From 3,4,5-trimethoxybenzoic acid (0.581 g, 2.74 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 60/40; R_f = 0.25 in hexanes/EtOAc = 2/1). The product was obtained as a brown solid (0.801 g, 85%); mp = 204-205 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.94 (s, 1H), 9.71 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.29 (s, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 3.94 (s, 6H), 3.88 (s, 3H), 2.18 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 170.2, 164.9, 153.0, 140.8, 131.4, 130.5, 129.6, 125.9, 125.4, 125.3, 124.9, 104.9, 60.8, 56.2, 23.8; FTIR (neat): 3239, 3072,

1658, 1642, 1599, 1431, 1324, 1272, 1185, 1098, 822 cm^{-1}; MS (ESI) *m/z* 345 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}O_5N_2$ 345.1445; Found: 345.1445.

N*-(2-Acetamidophenyl)benzamide-2,3,4,5,6-*d*$_5$ (1a-d$_5$):*** From benzoic-2,3,4,5,6-*d*$_5$ acid (0.348 g, 2.74 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 60/40; R_f = 0.25 in hexanes/EtOAc = 2/1). The product was obtained as a brown solid (0.589 g, 83%); mp = 256-257 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.73 (s, 1H), 7.51 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.09-7.00 (m, 2H), 6.95-6.88 (m, 1H), 2.04 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 170.3, 166.6, 133.4, 131.7, 130.8, 130.5, 128.3, 127.2, 126.3, 126.2, 126.0, 125.0, 23.6; FTIR (neat): 3231, 3091, 1646, 1512, 1431, 1329, 1292, 1155, 1090, 821 cm^{-1}; MS (ESI) *m/z* 260 $[M+H]^+$.

***N*-(2-Aminophenyl)benzamide**[31] (**1p**): To a stirred solution of benzene-1,2-diamine (4.00 g, 37 mmol, 2 equiv) in DCM (100 mL) Et_3N (2.6 mL, 18 mmol, 1 equiv) was added dropwise at room temperature. The solution was heated to reflux, and benzoyl chloride (2.15 mL, 18 mmol, 1 equiv) dissolved in DCM (80 mL) was added dropwise via dropping funnel over 90 min. The solution was refluxed for 2 h and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes: EtOAc 70:30) to afford the amide **1p** (2.86 g, 75 %) as a brown solid. ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.40 (s, 1H), 8.00 (d, *J* = 7.4 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 4.44 (bs, 2H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 166.0, 142.2, 134.7, 131.5, 128.4, 127.9, 126.9, 126.4, 124.3, 118.0, 117.3; FTIR (neat): 3400, 3265, 3060, 1640, 1577, 1522, 1313, 1252, 1062, 746 cm^{-1}; MS (ESI) *m/z* 213 $[M+H]^+$.

***N*-(2-(2,2,2-Trifluoroacetamido)phenyl)benzamide (1q)**: *N*-(2-aminophenyl)benzamide (**1n**, 212 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. Trifluoroacetic anhydride (315 mg, 0.212 mL, 1.5 mmol) and Et_3N (152 mg, 0.210 mL, 1.5 mmol) were added sequentially. The mixture was stirred at room temperature for 2 h, washed with water (20 mL), and dried over $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel (EtOAc/hexanes = 30/70) to afford the product **1q** as a white solid (265 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.61 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.56-7.49 (m, 3H), 7.24-7.20 (m, 1H), 7.14-7.08 (m, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 167.0, 156.2 (q), 132.7, 132.6, 130.1, 128.9, 128.4, 127.6, 127.5, 127.0, 125.8, 125.4, 117.3 (q); FTIR (neat): 3238, 3056, 1709, 1646, 1529, 1312, 1170, 915, 754 cm^{-1}; MS (ESI) *m/z* 309 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{12}F_3O_2N_2$ 309.0845; Found: 309.0848.

General procedure for the synthesis of arylated benzamides (**3a-n** and **4b-o**). To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added the benzamide (**1**, 0.3 mmol), iodoarene (**2**, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol), $Mn(OAc)_2$ (52 mg, 0.3 mmol) and *t*-AmOH (5 mL). The mixture was stirred for 36-40 h at 120 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (3:1 mixture of EtOAc: EtOH/hexanes = 10/90 to 50/50) to afford the desired arylated product (**3a-n** and **4b-o**).

***N*-(2-Acetamidophenyl)-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**3a**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc: EtOH = 90/10 to 60/40; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 4/1). The product **3a** was obtained as a brown solid (88 mg, 82%; 9 mg of starting material **1a** was recovered, 12%); mp = 197-198 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.44 (s, 1H), 9.23 (s, 1H), 7.65-7.56 (m, 2H), 7.55-7.50 (m, 1H), 7.47-7.36 (m, 5H), 7.16-7.07 (m, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 1.98 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.0, 167.8, 158.3, 138.4, 136.0, 131.6, 129.7, 129.6, 129.3, 129.2, 129.1, 128.9, 127.4, 126.1, 124.4, 124.2, 124.0, 113.2, 54.5, 23.0; FTIR (neat): 3362, 3046, 2989, 1685, 1600, 1512, 1482, 1367, 1243, 1082, 822 cm^{-1}; MS (ESI) *m/z* 361 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{21}O_3N_2$ 361.1547; Found: 361.1549.

***N*-(2-Acetamidophenyl)-3'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**3b**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-iodo-3-methoxybenzene **2b** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc: EtOH = 90/10 to 60/40; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 4/1). The product **3b** was obtained as a brown solid (86 mg, 80%); mp = 142-143 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.49 (s, 1H), 9.20 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.55 (t, J = 7.4 Hz, 2H), 7.51-7.44 (m, 3H), 7.28 (t, J = 7.8 Hz, 1H), 7.14-7.07 (m, 2H), 7.06-7.00 (m, 2H), 6.87 (d, J = 7.6 Hz, 1H), 3.75 (s, 3H), 1.99 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.1, 167.7, 158.6, 140.8, 138.7, 136.2, 129.8, 129.5, 129.4, 129.3, 128.7, 127.3, 126.7, 124.5, 124.2, 124.0, 123.9, 120.1, 113.6, 112.2, 54.4, 23.0; FTIR (neat): 3366, 3054, 2980, 1688, 1607, 1514, 1455, 1369, 1263, 1086, 821 cm^{-1};

MS (ESI) *m/z* 361 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{21}O_3N_2$ 361.1547; Found: 361.1549.

***N*-(2-Acetamidophenyl)-3',4',5'-trimethoxy-[1,1'-biphenyl]-2-carboxamide** (**3c**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 5-iodo-1,2,3-trimethoxybenzene **2c** (265 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc: EtOH = 70/30 to 40/60; R_f = 0.20 in hexanes/3:1 mixture of EtOAc:EtOH = 2/1). The product **3c** was obtained as a brown solid (106 mg, 84%); mp = 149-150 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.82 (s, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.50-7.43 (m, 1H), 7.42-7.35 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.61 (s, 2H), 3.80 (s, 3H), 3.68 (s, 6H), 1.93 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 168.2, 152.4, 138.5, 136.6, 134.5, 134.1, 129.7, 129.6, 129.2, 129.1, 128.9, 127.8, 126.8, 125.5, 124.9, 124.5, 123.4, 104.9, 59.9, 55.1, 22.8; FTIR (neat): 3341, 3019, 2920, 1647, 1605, 1513, 1481, 1313, 1245, 1179, 1032, 822 cm^{-1}; MS (ESI) *m/z* 421 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{24}O_5N_2Na$ 443.1577; Found: 443.1585.

***N*-(2-Acetamidophenyl)-4'-acetyl-[1,1'-biphenyl]-2-carboxamide** (**3d**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-(4-iodophenyl)ethan-1-one **2d** (221 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc: EtOH = 80/20 to 50/50; R_f = 0.25 in hexanes/3:1 mixture of EtOAc:EtOH = 4/1). The product **3d** was obtained as a white solid (80 mg, 72%; 12 mg of starting material **1a** was recovered, 16%); mp = 187-189 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.64 (s, 1H), 9.35 (s, 1H), 7.98 (d, J = 7.7 Hz, 2H), 7.73 (d, J = 7.0 Hz, 1H), 7.67-7.50 (m, 6H), 7.42 (t, J = 4.7 Hz, 1H), 7.19-7.08 (m, 2H), 2.58 (s, 3H), 1.97 (s,

3H); $^{13}C\{^{1}H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 198.0, 169.1, 168.0, 145.1, 138.7, 137.2, 136.0, 130.9, 130.7, 130.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 125.6, 125.3, 125.2, 27.2, 24.0; FTIR (neat): 3109, 3026, 2991, 1684, 1669, 1513, 1454, 1356, 1256, 1039, 822 cm^{-1}; MS (ESI) *m/z* 373 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{21}O_3N_2$ 373.1547; Found: 373.1549.

Methyl 2'-((2-acetamidophenyl)carbamoyl)-[1,1'-biphenyl]-4-carboxylate (**3e**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and methyl 4-iodobenzoate **2e** (236 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 80/20 to 50/50; R_f = 0.35 in hexanes/3:1 mixture of EtOAc:EtOH = 4/1). The product **3e** was obtained as a white solid (80 mg, 69%; 12 mg of starting material **1a** was recovered, 16%); mp = 215-216 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.37 (s, 1H), 9.22 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 2H), 7.70-7.32 (m, 8H), 7.18-7.06 (m, 2H), 3.90 (s, 3H), 2.02 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.9, 167.9, 166.0, 144.4, 138.2, 136.0, 129.8, 129.7, 129.6, 129.0, 128.5, 128.2, 128.1, 128.0, 127.6, 127.5, 125.0, 124.3, 124.2, 51.6, 23.2; FTIR (neat): 3091, 2929, 1654, 1600, 1527, 1466, 1348, 1272, 1180, 1035, 821 cm^{-1}; MS (ESI) *m/z* 389 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{21}O_4N_2$ 389.1496; Found: 389.1499.

***N*-(2-Acetamidophenyl)-4'-nitro-[1,1'-biphenyl]-2-carboxamide** (**3f**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-iodo-4-nitrobenzene **2f** (224 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 70/30 to 50/50; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **3f** was obtained as a white solid (71 mg, 63%; 13 mg of starting material **1a** was recovered, 18%); mp = 195-196 ^oC; ^1H NMR (400

MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.61 (s, 1H), 9.40 (s, 1H), 8.24 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.66-7.54 (m, 3H), 7.52 (d, J = 7.4 Hz, 1H), 7.39 (d, J = 6.5 Hz, 1H), 7.18-7.08 (m, 2H), 2.00 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.2, 167.6, 147.3, 147.1, 137.8, 137.0, 130.7, 130.6, 130.4, 130.3, 129.9, 128.9, 128.6, 125.5, 125.3, 125.2, 125.0, 123.8, 23.9; FTIR (neat): 3331, 3076, 2990, 1655, 1609, 1523, 1430, 1341, 1230, 1188, 1032, 822 cm^{-1}; MS (ESI) *m/z* 376 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{18}O_4N_3$ 376.1292; Found: 376.1295.

***N*-(2-Acetamidophenyl)-3'-nitro-[1,1'-biphenyl]-2-carboxamide** (**3g**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-iodo-3-nitrobenzene **2g** (224 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 70/30 to 50/50; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **3g** was obtained as a white solid (67 mg, 60%; 13 mg of starting material **1a** was recovered, 18%); mp = 206-207 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.58 (s, 1H), 9.39 (s, 1H), 8.83 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.64-7.51 (m, 4H), 7.49 (d, J = 7.4 Hz, 1H), 7.40 (dd, J = 5.9, 3.3 Hz, 1H), 7.17-7.08 (m, 2H), 2.06 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.5, 167.9, 148.0, 142.0, 137.7, 136.6, 134.9, 130.6, 130.5, 130.4, 130.3, 129.5, 128.5, 128.3, 125.6, 125.5, 125.0, 124.8, 123.4, 122.3, 23.7; FTIR (neat): 3309, 3043, 2927, 1642, 1605, 1517, 1441, 1313, 1240, 1179, 1035, 828 cm^{-1}; MS (ESI) *m/z* 376 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{18}O_4N_3$ 376.1292; Found: 376.1295.

***N*-(2-Acetamidophenyl)-4'-chloro-[1,1'-biphenyl]-2-carboxamide** (**3h**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-chloro-4-iodobenzene **2h** (215 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel

column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.40 in hexanes/3:1 mixture of EtOAc:EtOH = 4/1). The product **3h** was obtained as a white solid (82 mg, 75%); mp = 214-215 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.57 (s, 1H), 9.33 (s, 1H), 7.66 (dd, J = 7.5, 1.1 Hz, 1H), 7.59-7.53 (m, 2H), 7.52-7.42 (m, 5H), 7.42-7.37 (m, 2H), 7.17-7.09 (m, 2H), 2.01 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.1, 167.3, 138.2, 137.6, 136.1, 132.2, 129.9, 129.6, 129.4, 129.3, 127.8, 127.7, 127.4, 127.0, 124.5, 124.3, 124.2, 124.1, 23.0; FTIR (neat): 3308, 3056, 2997, 1654, 1601, 1523, 1436, 1349, 1232, 1188, 1035, 821 cm^{-1}; MS (ESI) *m/z* 365 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{18}O_2N_2Cl$ 365.1051; Found: 365.1054.

Methyl 2'-((2-acetamidophenyl)carbamoyl)-5-bromo-[1,1'-biphenyl]-3-carboxylate (3i): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and methyl 3-bromo-5-iodobenzoate **2i** (307 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.40 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **3i** was obtained as a white solid (81 mg, 58%; 18 mg of starting material **1a** was recovered, 24%); mp = 194-195 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.58 (s, 1H), 9.37 (s, 1H), 8.08 (s, 2H), 7.84 (s, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.63-7.43 (m, 5H), 7.19-7.10 (m, 2H), 3.89 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.7, 167.3, 164.5, 142.0, 136.8, 135.9, 134.9, 131.3, 130.5, 130.1, 129.8, 129.6, 129.5, 129.3, 127.8, 127.5, 125.0, 124.6, 124.5, 124.0, 121.5, 51.8, 23.1; FTIR (neat): 3333, 3050, 2997, 1656, 1601, 1582, 1437, 1345, 1211, 1180, 1033, 821 cm^{-1}; MS (ESI) *m/z* 467 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{20}O_4N_2Br$ 467.0601; Found: 467.0596.

***N*-(2-Acetamidophenyl)-3'-fluoro-5'-nitro-[1,1'-biphenyl]-2-carboxamide** (**3j**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-fluoro-3-iodo-5-nitrobenzene **2j** (240 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.35 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **3j** was obtained as a pale yellow solid (64 mg, 54%; 19 mg of starting material **1a** was recovered, 25%); mp = 204-205 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.64 (s, 1H), 9.48 (s, 1H), 8.15 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.67-7.52 (m, 4H), 7.47 (d, J = 7.1 Hz, 1H), 7.39 (d, J = 5.4 Hz, 1H), 7.14 (t, J = 3.5 Hz, 2H), 2.09 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.7, 167.5, 163.1, 160.7, 148.8, 144.2, 136.8, 136.5, 130.7, 130.6, 130.3, 129.0, 128.3, 125.7, 125.0, 124.8, 122.2, 121.9, 119.6, 110.1, 23.7; FTIR (neat): 3312, 3060, 2993, 1657, 1604, 1531, 1436, 1345, 1239, 1191, 1030, 821 cm^{-1}; MS (ESI) *m/z* 394 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{17}O_4N_3F$ 394.1198; Found: 394.1195.

***N*-(2-Acetamidophenyl)-2-(2,3-dihydrobenzofuran-5-yl)benzamide** (**3k**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 5-iodo-2,3-dihydrobenzofuran **2k** (221 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product was obtained as a white solid (91 mg, 81%); mp = 218-219 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.29 (s, 1H), 9.18 (s, 1H), 7.62-7.37 (m, 7H), 7.22 (d, J = 8.1 Hz, 1H), 7.16-7.07 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H), 4.55 (t, J = 8.6 Hz, 2H), 3.17 (t, J = 8.5 Hz, 2H), 2.00 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.5, 159.1, 139.0, 135.8, 131.7, 129.8, 129.7, 129.5, 129.4, 127.8, 127.4, 126.8, 126.1, 124.8, 124.7, 124.6, 124.2, 124.1, 108.4, 108.3, 70.7, 28.9, 23.1; FTIR (neat):

3309, 3042, 2928, 1645, 1609, 1513, 1441, 1313, 1249, 1179, 1032, 822 cm^{-1}; MS (ESI) *m/z* 373 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{20}O_3N_2Na$ 395.1366; Found: 395.1372.

***N*-(2-Acetamidophenyl)-2-(1-benzyl-1H-pyrazol-4-yl)benzamide** (**3l**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 1-benzyl-4-iodo-1*H*-pyrazole **2l** (256 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **3l** was obtained as a white solid (76 mg, 62%); mp = 191-192 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.45 (s, 1H), 9.19 (s, 1H), 7.78-7.59 (m, 3H), 7.58-7.49 (m, 4H), 7.39-7.11 (m, 8H), 5.28 (m, 2H), 2.00 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.6, 168.4, 137.7, 135.8, 135.2, 129.8, 129.6, 129.4, 129.3, 128.3, 128.0, 127.8, 127.3, 127.1, 127.0, 125.9, 124.8, 124.7, 124.4, 124.3, 120.0, 55.2, 23.0; FTIR (neat): 3330, 3058, 2997, 1657, 1601, 1531, 1437, 1345, 1232, 1193, 1035, 825 cm^{-1}; MS (ESI) *m/z* 411 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{22}O_2N_4Na$ 433.1635; Found: 433.1637.

***N*-(2-Acetamidophenyl)-2-(6-methoxypyrazin-2-yl)benzamide** (**3m**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 2-iodo-6-methoxypyrazine **2m** (212 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.32 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **3m** was obtained as a white solid (59 mg, 54%; 20 mg of starting material **1a** was recovered, 26%); mp = 201-202 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.59 (s, 1H), 9.35 (s, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 7.79-7.68 (m, 3H), 7.63-7.54 (m, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 6.5 Hz, 2H), 3.73 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.8, 167.8, 158.7, 148.8, 136.8,

134.8, 134.1, 133.1, 130.0, 129.6, 129.3, 129.0, 128.7, 128.0, 124.8, 124.6, 124.2, 123.8, 52.9, 23.0; FTIR (neat): 3313, 3055, 2989, 1651, 1603, 1523, 1445, 1346, 1234, 1186, 1034, 823 cm^{-1}; MS (ESI) *m/z* 363 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{18}O_3N_4Na$ 385.1271; Found: 385.1278.

***N*-(2-Acetamidophenyl)-2-(6-chloropyridin-3-yl)benzamide** (**3n**): From *N*-(2-acetamidophenyl)benzamide **1a** (76 mg, 0.30 mmol) and 2-chloro-5-iodopyridine **2n** (215 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.20 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **3n** was obtained as a white solid (69 mg, 63%; 11 mg of starting material **1a** was recovered, 15%); mp = 211-212 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.54 (s, 1H), 9.36 (s, 1H), 8.46 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 11.7 Hz, 1H), 7.65-7.48 (m, 3H), 7.42 (d, J = 6.4 Hz, 1H), 7.39-7.30 (m, 2H), 7.21-7.09 (m, 2H), 2.08 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.8, 167.8, 150.3, 149.0, 148.9, 139.0, 138.9, 136.6, 135.2, 130.6, 130.5, 130.4, 130.3, 128.6, 128.3, 125.7, 125.0, 124.9, 123.8, 23.7; FTIR (neat): 3332, 3055, 2989, 1657, 1603, 1523, 1435, 1245, 1187, 1038, 823 cm^{-1}; MS (ESI) *m/z* 366 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{16}O_2N_3ClNa$ 388.0823; Found: 388.0829.

***N*-(2-Acetamidophenyl)-4'-methoxy-[1,1'-biphenyl]-3,4,5,6-d_4-2-carboxamide** (**3a-d_4**): From *N*-(2-acetamidophenyl)benzamide-2,3,4,5,6-d_5 **1a-d_5** (78 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc: EtOH = 90/10 to 60/40; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 4/1). The product **3a-d_4** was obtained as a white solid (46 mg, 42%; 35 mg of starting material **1a-d_5** was recovered, 45%);

mp = 199-201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.55 (s, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 7.2 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 7.8 Hz, 1H), 3.75 (s, 3H), 1.97 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 169.2, 169.0, 159.6, 139.3, 136.0, 134.7, 132.2, 130.8, 130.0. 129.7, 126.6, 125.9, 125.8, 124.4, 114.4, 55.4, 24.0; FTIR (neat): 3361, 3046, 2989, 1688, 1600, 1512, 1481, 1367, 1243, 1076, 821 cm^{-1}. MS (ESI) *m/z* 365 $[M+H]^+$.

***N*-(2-Acetamidophenyl)benzamide-3,4,5-*d*$_3$, 2,6-D/H** (**1a-d$_5$**): To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added the *N*-(2-acetamidophenyl)benzamide-2,3,4,5,6-d_5 (**1a-d$_5$**, 78 mg, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol), $Mn(OAc)_2$ (52 mg, 0.3 mmol) and *t*-AmOH (5 mL). The mixture was stirred for 36 h at 120 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (3:1 mixture of EtOAc: EtOH/hexanes = 10/90 to 50/50) to afford the *ortho*-deuterium exchanged compound (**1a-d$_5$**, 67 mg) in 85% yield as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.70 (s, 1H), 7.96 (s, 0.54H; deuterium exchanged with hydrogens at *ortho* position); 7.52 (dd, J = 8.0, 1.0 Hz, 1H), 7.09-7.00 (m, 2H), 6.96-6.89 (m, 1H), 2.04 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 170.3, 166.5, 133.4, 131.7, 130.8, 130.5, 128.3, 127.5, 127.1, 126.3, 126.2, 126.0, 125.0, 23.6; FTIR (neat): 3231, 3091, 1646, 1512, 1431, 1329, 1292, 1155, 1090, 821 cm^{-1}. MS (ESI) *m/z* 260 $[M+H]^+$.

***N*-(2-Acetamidophenyl)-4'-methoxy-5-methyl-[1,1'-biphenyl]-2-carboxamide** (**4b**): From *N*-(2-Acetamidophenyl)-4-methylbenzamide **1b** (80 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene

2a (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc: EtOH = 90/10 to 60/40; R_f = 0.40 in hexanes/3:1 mixture of EtOAc: EtOH = 4/1). The product **4b** was obtained as a white solid (103 mg, 82%); mp = 175-176 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 8.31 (s, 1H), 7.67-7.59 (m, 2H), 7.46 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.6 Hz, 2H), 7.27-7.19 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 7.7 Hz, 1H), 3.82 (s, 3H), 2.43 (s, 3H), 2.03 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.3, 169.2, 159.3, 140.8, 139.4, 132.4, 131.1, 130.6, 130.0, 129.9, 129.8, 128.8, 127.9, 126.0, 125.6, 125.4, 124.5, 114.6, 55.3, 23.9, 21.4; FTIR (neat): 3309, 3043, 2927, 1649, 1605, 1513, 1441, 1313, 1245, 1179, 1035, 822 cm^{-1}; MS (ESI) *m/z* 375 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{22}O_3N_2Na$ 397.1523; Found: 397.1527.

***N*-(2-Acetamidophenyl)-4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxamide** (**4c**): From *N*-(2-acetamidophenyl)-3-methoxybenzamide **1c** (85 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.30 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4c** was obtained as a white solid (81 mg, 79%); mp = 180-182 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.76 (s, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.37-7.29 (m, 3H), 7.22 (d, J = 2.6 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.08-7.02 (m, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 7.7 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 2.02 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 169.2, 168.9, 159.2, 158.8, 135.7, 131.9, 131.8, 130.6, 130.0, 129.9, 129.8, 126.4, 125.9, 125.7, 124.4, 116.9, 114.3, 113.7, 55.5, 55.4, 24.0; FTIR (neat): 3328, 3045, 2928, 1648, 1605, 1515, 1449, 1312, 1245, 1178, 1032, 822 cm^{-1};

MS (ESI) *m/z* 391 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{22}O_4N_2Na$ 413.1472; Found: 413.1478.

***N*-(2-Acetamidophenyl)-4,4',6-trimethoxy-[1,1'-biphenyl]-2-carboxamide** (**4d**): From *N*-(2-acetamidophenyl)-3,5-dimethoxybenzamide **1d** (94 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.25 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4d** was obtained as a white solid (57 mg, 45%; 36 mg of starting material **1d** was recovered, 39%); mp = 212-213 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.60 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 1.7 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 2.04 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 169.0, 168.7, 160.0, 159.0, 158.1, 137.4, 131.5, 130.8, 129.6, 127.6, 126.5, 125.7, 125.6, 124.4, 121.2, 114.0, 104.3, 101.1, 56.0, 55.6, 55.3, 24.1; FTIR (neat): 3329, 3289, 3042, 2929, 1645, 1615, 1524, 1449, 1328, 1246, 1187, 1030, 825 cm^{-1}; MS (ESI) *m/z* 421 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{25}O_5N_2$ 421.1758; Found: 421.1760.

***N*-(2-Acetamidophenyl)-4,4',5,6-tetramethoxy-[1,1'-biphenyl]-2-carboxamide** (**4e**): From *N*-(2-acetamidophenyl)-3,4,5-trimethoxybenzamide **1e** (103 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.20 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4e** was obtained as a white solid (55 mg, 41%; 45 mg of starting material **1e** was recovered, 44%); mp = 214-215 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.02 (s, 1H), 8.79 (s, 1H), 7.42-7.35 (m, 2H),

7.33 (d, J = 8.2 Hz, 2H), 7.09 (t, J = 4.2 Hz, 2H), 7.01 (s, 1H), 6.89 (d, J = 8.1 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.3, 168.1, 158.8, 152.1, 151.5, 143.8, 132.5, 131.1, 130.4, 130.3, 127.8, 126.8, 125.5, 125.4, 124.9, 124.6, 113.5, 107.3, 61.0, 60.9, 56.1, 55.2, 55.3, 23.9; FTIR (neat): 3334, 3286, 3044, 2923, 1649, 1607, 1533, 1442, 1331, 1249, 1164, 1036, 823 cm^{-1}; MS (ESI) *m/z* 451 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{26}O_6N_2Na$ 473.1683; Found: 473.1684.

***N*-(2-Acetamidophenyl)-5-bromo-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**4f**): From *N*-(2-acetamidophenyl)-4-bromobenzamide **1f** (100 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.40 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4f** was obtained as a white solid (95 mg, 72%); mp = 206-208 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.33 (s, 1H), 9.18 (s, 1H), 7.60-7.49 (m, 4H), 7.43-7.37 (m, 3H), 7.16-7.08 (m, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.7, 167.3, 158.8, 140.7, 134.7, 132.6, 130.3, 129.7, 129.6, 129.2, 129.1, 129.0, 124.8, 124.7, 124.2, 124.1, 123.1, 113.4, 54.6, 23.1; FTIR (neat): 3321, 3059, 2954, 1653, 1601, 1524, 1439, 1347, 1232, 1088, 822 cm^{-1}; MS (ESI) *m/z* 439 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{19}BrO_3N_2Na$ 461.0471; Found: 461.0475.

***N*-(2-Acetamidophenyl)-4-bromo-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**4g**): From *N*-(2-acetamidophenyl)-3-bromobenzamide **1g** (100 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f =

0.40 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4g** was obtained as a white solid (92 mg, 70%); mp = 212-214 ^{o}C; ^{1}H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6 2): δ 9.13 (s, 1H), 8.95 (s, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.61 (dd, J = 8.3, 2.0 Hz, 1H), 7.47 (dd, J = 6.4, 4.0 Hz, 1H), 7.43-7.37 (m, 3H), 7.29 (d, J = 8.3 Hz, 1H), 7.14 (dd, J = 6.4, 4.1 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 2.02 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6 2): δ 169.3, 167.5, 159.3, 138.3, 137.7, 132.9, 131.8, 131.1, 131.0, 130.2, 130.0, 129.6, 125.7, 125.5, 124.9, 124.8, 120.7, 114.0, 55.2, 23.8; FTIR (neat): 3336, 3057, 2856, 1651, 1608, 1531, 1437, 1321, 1235, 1180, 1035, 821 cm^{-1}; MS (ESI) *m/z* 439 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{20}BrO_3N_2$ 439.0652; Found: 439.0655.

***N*-(2-Acetamidophenyl)-5-chloro-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**4h**): From *N*-(2-acetamidophenyl)-4-chlorobenzamide **1h** (87 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.40 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product obtained as a white solid (88 mg, 75%); mp = 202-204 ^{o}C; ^{1}H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.30 (s, 1H), 9.16 (s, 1H), 7.65-7.52 (m, 2H), 7.45-7.32 (m, 5H), 7.17-7.06 (m, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.81 (s, 3H), 2.01 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.7, 167.3, 158.8, 140.5, 134.9, 134.3, 130.4, 129.6, 129.3, 129.2, 129.0, 128.9, 126.2, 124.9, 124.8, 124.2, 124.1, 113.4, 54.7, 23.2; FTIR (neat): 3331, 3157, 2996, 1655, 1602, 1523, 1436, 1349, 1243, 1185, 1035, 827 cm^{-1}; MS (ESI) *m/z* 395 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{20}ClO_3N_2$ 395.1157; Found: 395.1159.

***N*-(2-Acetamidophenyl)-4-chloro-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**4i**): From *N*-(2-acetamidophenyl)-3-chlorobenzamide **1i** (87 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene

2a (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.40 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4i** was obtained as a white solid (84 mg, 71%); mp = 205-206 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 8.99 (s, 1H), 8.85 (s, 1H), 7.59 (d, J = 2.1 Hz, 1H), 7.45 (dd, J = 8.3, 2.2 Hz, 1H), 7.42-7.33 (m, 5H), 7.16-7.09 (m, 2H), 6.91 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.4, 167.7, 159.3, 137.8, 137.4, 132.7, 131.6, 131.1, 130.3, 130.0, 130.0, 129.7, 128.2, 125.8, 125.6, 124.9, 124.8, 114.0, 55.2, 23.8; FTIR (neat): 3308, 3056, 2997, 1655, 1601, 1523, 1436, 1345, 1239, 1188, 1035, 821 cm^{-1}; MS (ESI) *m/z* 395 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{19}ClO_3N_2Na$ 417.0976; Found: 417.0979.

***N*-(2-Acetamidophenyl)-4,5-dichloro-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**4j**): From *N*-(2-acetamidophenyl)-3,4-dichlorobenzamide **1j** (97 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.35 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4j** was obtained as a white solid (96 mg, 75%; 12 mg of starting material **1j** was recovered, 13%); mp = 218-219 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.48 (s, 1H), 9.26 (s, 1H), 7.76 (s, 1H), 7.57 (dd, J = 9.3, 3.8 Hz, 1H), 7.54 (s, 1H), 7.44-7.36 (m, 3H), 7.17-7.09 (m, 2H), 6.92 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.6, 165.7, 158.9, 138.7, 135.5, 132.7, 131.4, 129.8, 129.7, 129.4, 129.3, 129.3, 128.9, 124.9, 124.6, 124.4, 124.2, 113.4, 54.6, 23.1; FTIR (neat): 3323, 3050, 2992, 1655, 1601, 1526, 1464, 1343, 1235, 1187, 1035, 821 cm^{-1}; MS (ESI) *m/z* 451 $(M+Na)^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{18}Cl_2O_3N_2Na$ 451.0587; Found: 451.0590.

***N*-(2-Acetamidophenyl)-5-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**4k**): From *N*-(2-acetamidophenyl)-4-fluorobenzamide **1k** (82 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.40 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product obtained as a white solid (62 mg, 55%; 20 mg of starting material **1k** was recovered, 25%); mp = 205-206 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.23 (s, 1H), 9.14 (s, 1H), 7.66-7.52 (m, 2H), 7.44-7.34 (m, 3H), 7.17-7.05 (m, 4H), 6.95-6.86 (m, 2H), 3.81 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.3, 168.1, 164.4, 161.9, 159.5, 142.1, 142.0, 132.6, 131.3, 130.5, 130.4, 129.7, 125.5, 124.9, 116.9, 116.7, 114.0, 113.7, 55.3, 23.8; FTIR (neat): 3325, 3050, 2993, 1655, 1601, 1522, 1436, 1348, 1239, 1188, 1039, 821 cm^{-1}; MS (ESI) *m/z* 379 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{19}FO_3N_2Na$ 401.1272; Found: 401.1275.

***N*-(2-Acetamidophenyl)-4'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide** (**4l**): From *N*-(2-acetamidophenyl)-4-(trifluoromethyl)benzamide **1l** (97 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.38 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product obtained as a white solid (68 mg, 53%; 26 mg of starting material **1l** was recovered, 27%); mp = 200-201 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 8.99 (s, 1H), 8.77 (s, 1H), 7.67 (dd, J = 6.8, 4.6 Hz, 1H), 7.63-7.55 (m, 2H), 7.44-7.33 (m, 3H), 7.32-7.25 (m, 1H), 7.12-7.03 (m, 2H), 6.91-6.83 (m, 2H), 3.75 (s, 3H), 1.95 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.5, 167.9, 159.7, 140.0, 139.3, 132.0, 131.7, 130.9, 130.3, 130.0, 129.8, 128.8, 127.2, 125.9, 125.8, 125.0, 124.9, 123.6, 114.2, 55.3, 23.8; FTIR (neat): 3330, 3055, 2997, 1657, 1601, 1526,

1436, 1345, 1234, 1179, 1054, 827 cm^{-1}; MS (ESI) *m/z* 429 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{19}F_3O_3N_2Na$ 451.1240; Found: 451.1242.

***N*-(2-Acetamidophenyl)-4'-methoxy-5-nitro-[1,1'-biphenyl]-2-carboxamide** (**4m**): From *N*-(2-acetamidophenyl)-4-nitrobenzamide **1m** (90 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/3:1 mixture of EtOAc:EtOH = 90/10 to 60/40; R_f = 0.33 in hexanes/3:1 mixture of EtOAc:EtOH = 3/1). The product **4m** was obtained as a white solid (55 mg, 45%; 27 mg of starting material **1m** was recovered, 30%); mp = 215-216 °C; ^{1}H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.55 (s, 1H), 9.28 (s, 1H), 8.28-8.21 (m, 2H), 7.82 (dd, J = 8.3, 2.4 Hz, 1H), 7.61 (d, J = 7.1 Hz, 1H), 7.48 (dd, J = 8.7, 2.4 Hz, 2H), 7.37 (d, J = 7.1 Hz, 1H), 7.20-7.11 (m, 2H), 6.96 (dd, J = 8.8, 2.4 Hz, 2H), 3.83 (s, 3H), 2.01 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 169.5, 167.0, 159.9, 148.3, 142.1, 140.9, 130.7, 130.2, 129.9, 129.8, 129.5, 125.8, 125.5, 125.0, 124.9, 124.8, 121.6, 114.3, 55.4, 23.8; FTIR (neat): 3312, 3056, 2999, 1658, 1604, 1543, 1421, 1366, 1245, 1127, 1032, 821 cm^{-1}; MS (ESI) *m/z* 406 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{19}O_5N_3Na$ 428.1217; Found: 428.1218.

General procedure for the synthesis of arylated aminobenzamides (**5a-k**). To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added the benzamide (**1**, 0.3 mmol), iodoarene (**2**, 0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), Na_2CO_3 (64 mg, 0.6 mmol), $Mn(OAc)_2$ (52 mg, 0.3 mmol) and *t*-AmOH (5 mL). The mixture was stirred for 48 h at 120 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with

brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexanes = 10/90 to 50/50) to afford the desired arylated product (**5a-d** and **5g-k**).

***N*-(2-Aminophenyl)-4'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**5a**): From *N*-(2-aminophenyl)benzamide **1p** (64 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 90/10 to 60/40; R_f = 0.30 in hexanes/EtOAc = 4/1). The product obtained as a brown solid (73 mg, 76%); mp = 161-163 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, J = 7.5, 1.2 Hz, 1H), 7.50 (dd, J = 7.5, 1.4 Hz, 1H), 7.48-7.41 (m, 3H), 7.40 (d, J = 7.6 Hz, 1H), 7.02-6.95 (m, 4H), 6.82 (s, 1H), 6.73 (td, J = 7.6, 1.3 Hz, 1H), 6.67 (dd, J = 7.9, 1.5 Hz, 1H), 3.83 (s, 3H), 3.31 (bs, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 168.2, 159.6, 140.0, 138.8, 135.4, 132.5, 130.5, 130.3, 130.2, 129.4, 127.5, 126.8, 124.6, 124.1, 119.4, 117.7, 114.5, 55.5; FTIR (neat): 3395, 3319, 3207, 2996, 2841, 1657, 1597, 1515, 1456, 1247, 1178, 938, 836, 747 cm^{-1}; MS (ESI) *m/z* 319 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{19}O_2N_2$ 319.1441; Found: 319.1440.

4'-Methoxy-*N*-(2-(2,2,2-trifluoroacetamido)phenyl)-[1,1'-biphenyl]-2-carboxamide (**5b**): From *N*-(2-(2,2,2-trifluoroacetamido)phenyl)benzamide **1q** (64 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 90/10 to 60/40; R_f = 0.40 in hexanes/EtOAc = 4/1). The product **5b** was obtained as a white solid (68 mg, 55%; 19 mg of starting material **1q** was recovered, 30%); mp = 185-187 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.57 (td, J = 7.5, 1.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.27 (t, J = 8.7 Hz,

1H), 7.12 (s, 1H), 7.08 (td, *J* = 7.9, 1.4 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.14 (dd, *J* = 8.0, 1.3 Hz, 1H), 3.86 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 169.7, 159.9, 155.3, 139.5, 133.5, 131.7, 131.5, 130.6, 130.2, 129.8, 129.3, 127.8, 127.3, 126.9, 125.8, 123.9, 114.8, 114.8, 55.5; FTIR (neat): 3282, 3024, 1719, 1648, 1514, 1285, 1166, 1031, 903, 832, 760 cm^{-1}; MS (ESI) *m/z* 415 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{18}F_3O_3N_2$ 415.1264; Found: 415.1268.

4'-Methoxy-*N*-(2-(methylthio)phenyl)-[1,1'-biphenyl]-2-carboxamide (**5c**): From *N*-(2-(methylthio)phenyl)benzamide **1r** (64 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 98/2 to 80/20; R_f = 0.50 in hexanes/EtOAc = 5/1). The products obtained as a brown solid (75 mg, 72%); mp = 156-158 ^{o}C; The diarylated product (**5c′**) also isolated as a brown solid (8 mg, 6%; R_f = 0.42 in hexanes/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, *J* = 7.6 Hz, 1H), 8.30 (s, 1H), 7.77 (d, *J* = 6.7 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.46-7.41 (m, 4H), 7.38 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.02 (td, *J* = 7.6, 1.3 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 2.04 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 168.2, 159.5, 139.1, 138.6, 135.7, 133.2, 132.1, 130.6, 130.5, 130.1, 129.1, 128.9, 127.3, 125.3, 124.3, 120.1, 114.3, 55.3, 19.2; FTIR (neat): 3109, 2994, 2855, 1689, 1593, 1515, 1459, 1247, 1177, 922, 837, 776 cm^{-1}; MS (ESI) *m/z* 350 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{20}O_2NS$ 350.1209; Found: 350.1212.

4,4''-Dimethoxy-*N*-(2-(methylthio)phenyl)-[1,1':3',1''-terphenyl]-2'-carboxamide (**5c′**): mp = 186-187 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 8.07 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.50 (td, *J* = 8.2, 1.2 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 4H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.19 (td, *J* = 8.5, 1.4 Hz, 1H), 6.98 (td, *J* = 7.6, 1.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 4H), 3.77 (s, 6H), 1.92 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 167.8, 159.1, 139.7, 138.2, 135.7,

133.0, 132.7, 129.9, 129.3, 129.1, 128.8, 125.4, 124.3, 120.5, 113.9, 55.3, 18.9; FTIR (neat): 3109, 2991, 2894, 1693, 1597, 1517, 1463, 1244, 1178, 931, 837, 727 cm^{-1}.

4'-Methoxy-*N*-(quinolin-8-yl)-[1,1'-biphenyl]-2-carboxamide[32] (**5d**): From *N*-(quinolin-8-yl)benzamide **1s** (64 mg, 0.30 mmol) and 1-iodo-4-methoxybenzene **2a** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 98/05 to 80/20; R_f = 0.50 in hexanes/EtOAc = 5/1). The products obtained as a brown solid (72 mg, 68%); The diarylated product (**5d′**) also isolated as a brown solid (12 mg, 9%; R_f = 0.40 in hexanes/EtOAc = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 8.82 (dd, J = 7.6, 1.1 Hz, 1H), 8.53 (dd, J = 4.2, 1.6 Hz, 1H), 8.09 (dd, J = 8.3, 1.6 Hz, 1H), 7.90 (dd, J = 7.9, 1.2 Hz, 1H), 7.57-7.50 (m, 2H), 7.49-7.42 (m, 5H), 7.36 (dd, J = 8.2, 4.2 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 159.3, 147.7, 139.9, 138.5, 136.0, 135.9, 134.6, 132.4, 130.6, 130.5, 130.1, 129.2, 127.7, 127.3, 127.2, 121.5, 121.4, 116.3, 113.9, 55.1.

4,4''-Dimethoxy-*N*-(quinolin-8-yl)-[1,1':3',1''-terphenyl]-2'-carboxamide[32] (**5d′**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 8.62-8.50 (m, 2H), 8.06 (d, J = 8.3 Hz, 1H), 7.54-7.50 (m, 1H), 7.46 (t, J = 5.9 Hz, 4H), 7.42 (dd, J = 8.8, 6.1 Hz, 4H), 7.34 (dd, J = 7.9, 3.9 Hz, 1H), 6.78 (d, J = 8.1 Hz, 4H), 3.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 158.9, 147.8, 140.1, 138.3, 136.0, 136.0, 134.4, 132.9, 129.8, 129.2, 129.0, 127.8, 127.2, 121.4, 121.3, 116.4, 113.8, 55.1.

***N*-(2-Aminophenyl)-3'-methoxy-[1,1'-biphenyl]-2-carboxamide** (**5g**): From *N*-(2-aminophenyl)benzamide **1p** (64 mg, 0.30 mmol) and 1-iodo-3-methoxybenzene **2b** (211 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel

column chromatography (hexanes/EtOAc = 90/10 to 60/40; R_f = 0.30 in hexanes/EtOAc = 4/1). The product obtained as a brown solid (69 mg, 72%; 5 mg of starting material **1p** was recovered, 8%); mp = 197-198 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.3 Hz, 1H), 7.57-7.39 (m, 3H), 7.36 (t, J = 7.8 Hz, 1H), 7.08 (d, J = 7.3 Hz, 1H), 7.03 (s, 1H), 7.01-6.81 (m, 4H), 6.70 (t, J = 7.4 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 3.77 (s, 3H), 3.31 (bs, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 168.1, 160.0, 141.7, 140.3, 139.2, 135.5, 130.6, 130.2, 130.1, 129.4, 128.0, 127.0, 124.8, 123.9, 121.3, 119.3, 117.6, 114.2, 114.1, 55.4; FTIR (neat): 3391, 3315, 3170, 2965, 2841, 1667, 1492, 1309, 1295, 1168, 1050, 993, 757 cm^{-1}; MS (ESI) *m/z* 319 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{19}O_2N_2$ 319.1441; Found: 319.1440.

4'-Acetyl-*N*-(2-aminophenyl)-[1,1'-biphenyl]-2-carboxamide (**5h**): From *N*-(2-aminophenyl)benzamide **1p** (64 mg, 0.30 mmol) and 1-(4-iodophenyl)ethan-1-one **2d** (221 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 80/20 to 60/40; R_f = 0.30 in hexanes/EtOAc = 3/1). The product obtained as a brown solid (54 mg, 54%; 8 mg of starting material **1p** was recovered, 12%); mp = 190-192 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.4 Hz, 2H), 7.75 (dd, J = 7.8, 1.2 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.54 (dd, J = 7.6, 1.2 Hz, 1H), 7.10 (s, 1H), 6.98 (td, J = 7.5, 1.4 Hz, 1H), 6.91 (dd, J = 7.9, 1.3 Hz, 1H), 6.70 (td, J = 7.6, 1.2 Hz, 1H), 6.65 (dd, J = 7.9, 1.1 Hz, 1H), 3.39 (bs, 2H), 2.60 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 197.6, 167.9, 144.9, 140.3, 138.4, 136.3, 135.7, 130.6, 130.2, 129.2, 129.0, 128.8, 128.4, 127.1, 124.6, 123.9, 119.4, 117.9, 26.7; FTIR (neat): 3376, 3208, 1671, 1602, 1513, 1488, 1275, 934, 847, 740 cm^{-1}; MS (ESI) *m/z* 331 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{19}O_2N_2$ 331.1441; Found: 331.1444.

Methyl 2'-((2-aminophenyl)carbamoyl)-[1,1'-biphenyl]-4-carboxylate (**5i**): From *N*-(2-aminophenyl)benzamide **1p** (64 mg, 0.30 mmol) and methyl 4-iodobenzoate **2e** (236 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 80/20 to 60/40; R_f = 0.35 in hexanes/EtOAc = 3/1). The product obtained as a brown solid (23 mg, 22%); mp = 197-198 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 8.79 (s, 1H), 8.06 (d, J = 7.7 Hz, 2H), 7.72 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.59-7.44 (m, 3H), 7.07 (d, J = 7.8 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 3.98 (bs, 2H), 3.92 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.3, 166.6, 145.1, 141.3, 138.8, 136.8, 130.1, 130.0, 129.7, 129.1, 128.8, 128.5, 127.9, 126.8, 125.4, 123.7, 118.1, 117.1, 52.2; FTIR (neat): 3376, 3208, 2926, 1714, 1671, 1502, 1279, 1180, 847, 748 cm^{-1}; MS (ESI) *m/z* 347 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{19}O_3N_2$ 347.1390; Found: 347.1391.

***N*-(2-Aminophenyl)-4'-chloro-[1,1'-biphenyl]-2-carboxamide** (**5j**): From *N*-(2-aminophenyl)benzamide **1p** (64 mg, 0.30 mmol) and 1-chloro-4-iodobenzene **2h** (214 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 80/20 to 60/40; R_f = 0.35 in hexanes/EtOAc = 3/1). The product **5j** was obtained as a brown solid (56 mg, 58%; 9 mg of starting material **1p** was recovered, 14%); mp = 172-174 ^oC; ^1H NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 8.73 (s, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.58-7.34 (m, 7H), 7.07 (d, J = 7.8 Hz, 1H), 6.97 (t, J = 7.9 Hz, 1H), 6.76-6.64 (m, 2H), 3.90 (bs, 2H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 168.3, 141.0, 138.8, 138.4, 136.5, 133.4, 130.1, 130.0, 129.9, 128.5, 128.3, 127.5, 126.7, 125.2, 123.6, 118.2, 117.1; FTIR (neat): 3429, 3396, 3258, 3061, 1640, 1591, 1454, 1342, 1299, 1106, 855,

745 cm^{-1}; MS (ESI) *m/z* 323 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{16}ClON_2$ 323.0946; Found: 323.0950.

***N*-(2-Aminophenyl)-2-(6-methoxypyrazin-2-yl)benzamide** (**5k**): From *N*-(2-aminophenyl)benzamide **1p** (64 mg, 0.30 mmol) and 2-iodo-6-methoxypyrazine **2m** (212 mg, 0.90 mmol) using the above general procedure. The crude residue was purified by silica gel column chromatography (hexanes/EtOAc = 80/20 to 60/40; R_f = 0.30 in hexanes/EtOAc = 3/1). The product obtained as pale yellow solid (53 mg, 55%; mp = 169-170 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.14 (s, 1H), 7.79-7.46 (m, 5H), 7.08-6.97 (m, 2H), 6.80-6.68 (m, 2H), 3.79 (s, 3H), 3.69 (bs, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 168.3, 159.3, 149.5, 140.4, 136.5, 135.4, 134.9, 134.3, 130.5, 129.9, 129.4, 128.9, 127.2, 124.5, 124.4, 119.5, 118.4, 53.9; FTIR (neat): 3459, 3357, 3204, 2997, 1654, 1621, 1534, 1390, 1273, 1003, 863, 740 cm^{-1}; MS (ESI) *m/z* 321 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{17}O_2N_4$ 321.1346; Found: 321.1349.

General procedure for removal of directing group. Arylated benzamide (**3a**/**4d**/**4e**; 0.5 mmol) and NaOH (200 mg, 5.0 mmol) were dissolved in 10 mL of EtOH in a 30 mL dry screw cap vial, equipped with a magnetic stir bar. The resulting solution was heated at 120 ºC for 24 h. The organic solvent was evaporated, and 10 mL water was added. The mixture was acidified with 1 N HCl to adjust the pH to 4, then extracted with DCM (20 mL x 2). The combined organic layers were washed with water (20 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (3:1 mixture of EtOAc: EtOH/hexanes = 10/90 to 50/50) to afford the corresponding biaryl acid derivative (**6a-c**).

4'-Methoxy-[1,1'-biphenyl]-2-carboxylic acid[8d] (**6a**): 105 mg, 92%; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.74 (bs, 1H), 7.92 (d, J = 6.9 Hz, 1H), 7.52 (t, J = 6.6 Hz, 1H), 7.45-7.30 (m, 2H), 7.26 (d, J = 7.4 Hz, 2H), 6.91 (d, J = 7.3 Hz, 2H), 3.83 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 173.9, 159.1, 142.9, 133.3, 132.1, 131.2, 130.7, 129.6, 129.3, 126.9, 113.6, 55.3; FTIR (neat): 2958, 2837, 2536, 1694, 1669, 1608, 1514, 1480, 1300, 1178, 1030, 838, 730 cm^{-1}; MS (ESI) *m/z* 227 (M-H)$^{-}$; HRMS (ESI) *m/z*: [M-H]$^{-}$ Calcd for $C_{14}H_{11}O_3$ 227.0714; Found: 227.0713.

4,4',6-Trimethoxy-[1,1'-biphenyl]-2-carboxylic acid (**6b**): 122 mg, 85%; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.74 (bs, 1H), 7.16 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 6.67 (d, J = 2.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 173.9, 159.4, 158.6, 158.3, 132.1, 131.0, 128.2, 124.4, 113.4, 105.2, 102.7, 56.1, 55.6, 55.1; FTIR (neat): 3008, 2963, 2840, 1705, 1599, 1460, 1390, 1275, 1071, 862, 706 cm^{-1}; MS (ESI) *m/z* 289 [M+H]-; HRMS (ESI) *m/z*: [M-H]$^{-}$ Calcd for $C_{16}H_{15}O_5$ 287.0925; Found: 287.0921.

4,4',5,6-Tetramethoxy-[1,1'-biphenyl]-2-carboxylic acid[29] (**6c**): 125 mg, 79%; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.19 (bs, 1H), 7.30 (s, 1H), 7.16 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 3.84 (s, 3H), 3.53 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 172.5, 158.7, 152.1, 151.8, 146.1, 131.2, 130.6, 128.4, 124.9, 113.2, 109.7, 61.0, 60.9, 56.1, 55.1; FTIR (neat): 2969, 2843, 2595, 1679, 1610, 1486, 1391, 1333, 1243, 1177, 1031, 850, 700 cm^{-1}; MS (ESI) *m/z* 319 [M+H]+; HRMS (ESI) *m/z*: [M-H]$^{-}$ Calcd for $C_{17}H_{17}O_6$ 317.1031; Found: 317.1027.

Synthesis of 6*H*-benzo[*c*]chromen-6-one derivatives (**7a-c**).[29] To a solution of biaryl acid **6** (0.30 mmol) in 1,2-dichloroethane (15 mL), *N*-iodosuccinimide (169 mg, 0.75 mmol, 2.5 equiv) was added in one portion, and the mixture was heated to 75 °C for 3-6 h. After completion of the reaction (monitored by TLC), 1,2-dichloroethane was evaporated. The crude residue was dissolved in EtOAc (20 mL), and the mixture was washed with sat. $Na_2S_2O_3$ (20 mL), and then with water (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (3:1 mixture of EtOAc:EtOH/hexanes = 10/90 to 50/50) to afford the corresponding 6*H*-benzo[*c*]chromen-6-one derivative (**7a-c**).

3-Methoxy-6*H*-benzo[*c*]chromen-6-one[33] (**7a**): 62 mg, 92%; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J = 8.0, 1.8 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.77 (td, J = 8.0, 1.4 Hz, 1H), 7.49 (td, J = 7.0, 1.1 Hz, 1H), 6.89 (dd, J = 8.8, 2.6 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 3.87 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.4, 152.5, 135.1, 134.8, 130.5, 128.8, 127.7, 123.7, 121.0, 119.9, 112.4, 111.1, 101.6, 55.6; FTIR (neat): 3077, 3012, 2931, 1718, 1607, 1518, 1348, 1197, 1034, 960, 835 cm^{-1}; MS (ESI) *m/z* 227 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{11}O_3$ 227.0703; Found: 227.0704.

3,8,10-Trimethoxy-6*H*-benzo[*c*]chromen-6-one (**7b**): 74 mg, 86%; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 9.6 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 6.86-6.81 (m, 3H), 3.99 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.6, 159.7, 159.3, 157.9, 151.2, 128.5, 122.3, 118.8, 111.5, 111.0, 106.3, 103.0, 101.2, 55.9, 55.8, 55.5; FTIR (neat): 2933, 2840, 1719, 1619, 1559, 1458, 1353, 1287, 1174, 1039, 934, 816 cm^{-1}; MS (ESI) *m/z* 287 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{15}O_5$ 287.0914; Found: 287.0914.

3,8,9,10-Tetramethoxy-6*H*-benzo[*c*]chromen-6-one[29] (**7c**): 76 mg, 80%; pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 9.1 Hz, 1H), 7.68 (s, 1H), 6.88 (dd, J = 9.1, 2.7 Hz, 1H), 6.83 (d, J = 2.7 Hz, 1H), 4.04 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.3, 160.2, 152.9, 151.7, 150.4, 149.1, 127.6, 123.3, 116.0, 112.5, 110.6, 108.0, 101.4, 61.2, 60.4, 56.2, 55.5; FTIR (neat): 2950, 2923, 2848, 1719, 1614, 1481, 1401, 1205, 1162, 1082, 856, 750, 635 cm^{-1}; MS (ESI) *m/z* 317 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}O_6$ 317.1020; Found: 317.1019.

Palladium-catalyzed C-O bond formation for the synthesis of 7b: To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added the acid (**6b**, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $Mn(OAc)_2$ (52 mg, 0.3 mmol) and *t*-AmOH (5 mL). The mixture was stirred for 24 h at 80 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (3:1 mixture of EtOAc: EtOH/hexanes = 10/90 to 50/50) to afford the desired lactone **7b** in 63% yield.

Synthesis of urolithin B (8a). 3-Methoxy-6*H*-benzo[*c*]chromen-6-one **7a** (30 mg, 0.133 mmol, 1.0 equiv) was dissolved in dry DCM (6 mL) in a 50 mL round-bottom flask, and the mixture was cooled to −78 °C. BBr_3 (1.0 M in DCM, 0.27 mL, 0.27 mmol, 2 equiv) was added slowly dropwise. The reaction was allowed to warm to room temperature and stirred for 24 hours. MeOH (2 mL) was added, stirred for another 15 min, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (3:1 mixture of EtOAc:EtOH/hexanes = 60/40) to afford urolithin B (**8a**, 23 mg, 81%) as a brown solid. ^{1}H

NMR (400 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 9.88 (bs, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.91 (dd, J = 8.7, 2.4 Hz, 1H), 7.79 (t, J = 7.0 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 6.86 (td, J = 6.9, 2.4 Hz, 1H), 6.80 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, 8:2 $CDCl_3$:DMSO-d_6): δ 161.5, 160.0, 152.5, 135.6, 135.0, 130.1, 127.3, 124.1, 121.1, 119.4, 113.4, 109.8, 103.6; FTIR (neat): 3310, 2958, 2921, 2859, 1685, 1612, 1438, 1366, 1169, 1023, 808, 763 cm^{-1}; MS (ESI) *m/z* 213 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_9O_3$ 213.0546; Found: 213.0547.

Synthesis of urolithin M7 (8b). 3,8,10-Trimethoxy-6*H*-benzo[*c*]chromen-6-one **7b** (50 mg, 0.175 mmol, 1.0 equiv) was dissolved in dry DCM (10 mL) in a flame-dried 50 mL round-bottom flask, and the mixture was cooled to −78 °C. BBr_3 (1.0 M in DCM, 1.57 mL, 1.57 mmol, 9 equiv.) was added slowly dropwise. The reaction was allowed to warm to room temperature and stirred for 3 days. MeOH (6 mL) was added, stirred for another 30 min, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel [10% (MeOH in acetic acid 1:9) in EtOAc:hexanes = 50/50 to 100/0] to afford urolithin M7 (**8b**, 40 mg, 94%) as a pale green solid. ^1H NMR (400 MHz, DMSO-d_6): δ 10.81 (s, 1H), 10.06 (s, 1H), 10.02 (s, 1H), 8.76 (d, J = 8.8 Hz, 1H), 7.15 (s, 1H), 6.93 (s, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.73 (s, 1H); $^{13}C\{^1H\}$NMR (100 MHz, DMSO-d_6): δ 161.2, 157.7, 157.4, 156.5, 150.6, 128.4, 122.0, 115.1, 112.8, 110.4, 110.3, 106.4, 103.0; FTIR (neat): 3312, 2953, 2921, 2852, 1682, 1620, 1438, 1360, 1169, 1047, 1023, 803, 764 cm^{-1}; MS (ESI) *m/z* 245 $[M+H]^+$; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_9O_5$ 245.0444; Found: 245.0442.

Synthesis of urolithin M6 (8c). 3,8,9,10-Tetramethoxy-6*H*-benzo[*c*]chromen-6-one **7c** (50 mg, 0.158 mmol, 1.0 equiv) was dissolved in dry DCM (10 mL) in a flame-dried 50 mL round-bottom flask, and the mixture was cooled to −78 °C. BBr_3 (1.0 M in DCM, 1.27 mL, 1.27 mmol,

8 equiv) was added slowly dropwise. The reaction was allowed to warm to room temperature and stirred for 30 h. MeOH (6 mL) was added, stirred for another 30 min, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel [10% (MeOH in acetic acid 1:9) in EtOAc:hexanes = 50/50 to 100/0] to afford urolithin M7 (**8c**, 38 mg, 93%) as a pale green solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (bs, 1H), 9.96 (bs, 2H), 9.52 (bs, 1H), 8.80 (d, J = 8.9 Hz, 1H), 7.29 (s, 1H), 6.75 (dd, J = 8.9, 2.2 Hz, 1H), 6.68 (d, J = 2.2 Hz, 1H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d_6): δ 161.2, 158.8, 151.1, 145.7, 143.0, 140.8, 128.5, 116.4, 112.5, 111.1, 110.7, 107.3, 103.0; FTIR (neat): 3311, 1683, 1614, 1524, 1441, 1363, 1238, 1170, 1127, 1008, 840, 771 cm^{-1}; MS (ESI) *m/z* 259 $[M+H]^+$; HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{13}H_7O_6$ 259.0248; Found: 259.0246.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C{^{1}H}NMR 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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