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Palladium-Catalyzed Ortho-Arylation of Benzamides via Direct sp^2 C–H Bond Activation

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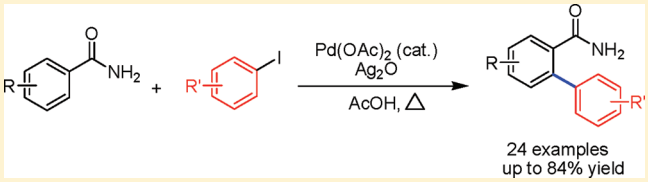
Supporting Information

ABSTRACT: The palladium-catalyzed ortho-arylation of benzamides by aryl iodides has been demonstrated with the simplest amide $CONH_2$ as a directing group for the first time. This protocol can be applied to various benzamides and aryl iodides with both electron-donating and electron-withdrawing groups. In addition, the synthesized biphenyl-2-carboxamides can be further transformed to other biphenyl derivatives such as nitriles, carboxylic acids, carbamates, and amines.



INTRODUCTION

The biaryl subunit is a key structural motif for the preparation of a wide range of natural products, biologically active pharmaceuticals, polymers, metal ligands for catalysis, and liquid crystals.[1] Over the past decades, cross-coupling reactions, i.e., Suzuki–Miyaura, Kumada, Negishi, Stille, and Hiyama reactions, have emerged as the most useful synthetic methods to construct aryl–aryl bonds.[2] Despite the widespread application, these methods usually require the prefunctionalized starting materials and auxiliary ligands that are often expensive or difficult to prepare. To overcome these drawbacks, transition-metal-catalyzed direct arylation via the cleavage of sp^2 C–H bond to construct C–C bonds has received extensive attention in recent years.[3] Directing group-assisted activation of ortho aromatic C–H bonds has been widely investigated, and various directing groups such as acylamino,[4] pyridyl,[5] carboxyl,[6] oxazolyl,[7] hydroxyl,[8] and oxime[9] groups have been used for palladium-catalyzed C–H bond activation. It is worthy of note that transition-metal-free processes to approach the cross coupling of aryl halides and arenes have been successfully realized.[10] In recent years, amide as a directing group has attracted substantial interest. Miura,[11] Daugulis,[12] Yu,[13] Dong,[14] and our group[15] have independently reported the Pd-catalyzed arylation reactions between *N*-substituted amides RCONHR′ and aryl halides or simple arenes. The Pd-catalyzed reaction of both *N*-aryl[11,13a,b] and *N*-alkyl[12] amides with aryl halides tended to afford significantly or even exclusively diarylation products and remains a challenge for selective monoarylation. Until now, extension to the simplest amide $CONH_2$ as a directing group to form arylation products catalyzed by palladium has never been reported. Herein, we report the palladium-catalyzed highly regioselective monoarylation of benzamides $ArCONH_2$ with aryl iodides directed by the $CONH_2$ group to afford biphenyl-2-carboxamides, which can be further converted to other biphenyl derivatives.

RESULTS AND DISCUSSION

Recently, we have reported palladium-catalyzed sp^2 C–H activation reactions using directing groups including the $-NHOCCH_3$ and $-CONHOCH_3$ groups to construct C–C, C–O, and C–N bonds.[15,16] Prompted by the success, we wondered whether the *N*-unsubstituted amide $-CONH_2$ could also be used as a directing group to facilitate the C–H arylation reaction with aryl iodides. In the initial study, we focused on benzamide (**1a**) and iodobenzene (**2a**) as the model substrates to screen the optimal conditions.

It is known that the combination of ArI and AgOAc has broad applications in the Pd-catalyzed arylation reactions of ArNHR, ArCONHR, and other substrates.[4f,12,17] Therefore, we first chose AgOAc as the additive. As desired, product **3aa** was isolated in 64% yield after 5 h (Table 1, entry 1). To our delight, when Ag_2O was used, the yield was improved to 74% (Table 1, entry 2) accompanied by 5% of diarylation product and ∼1% of the cyclized product, i.e., phenanthridinone. If the reaction time was prolonged to 36 h, the yield dropped to 44% (Table 1, entry 3) together with more byproducts (7% of diarylation product and 3% of phenanthridinone). Thus, we could conclude that the $CONH_2$ group behaved quite differently from the $CONHOCH_3$ group because the latter preferred to afford the cyclized product *N*-methoxyphenanthridinone in 76% yield under the same conditions.[15] The efficiency of other silver salts was also examined; Ag_2SO_4 and Ag_2CO_3 could promote the reaction, but both of them failed to give a better yield than Ag_2O (Table 1, entries 4 and 5).

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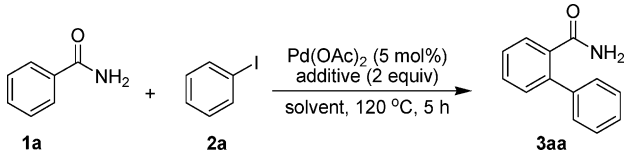
Table 1. Screening Conditions for the Pd-Catalyzed Reaction of Benzamide and Iodobenzene[a]



1a 2a 3aa

entry	additive	solvent	yield (%)
1	AgOAc	CH_3COOH	64
2	**Ag_2O**	**CH_3COOH**	**74**
3[b]	Ag_2O	CH_3COOH	44
4	Ag_2SO_4	CH_3COOH	61
5	Ag_2CO_3	CH_3COOH	73
6	Ag_2O	DCE	11
7	Ag_2O	toluene	17
8	Ag_2O	dioxane	18
9	Ag_2O	DMF	trace

[a]Unless otherwise specified, all reactions were carried out with 0.5 mmol of **1a**, 1.0 mmol of **2a**, 0.025 mmol of $Pd(OAc)_2$, and 1.0 mmol of additive in 5 mL of solvent at 120 °C for 5 h. [b]36 h.

In addition, the effect of solvent was explored. Disappointingly, when DCE, toluene, and 1,4-dioxane were employed as the solvent, the product was isolated in very low yield (Table 1, entries 6−9). Therefore, 1 equiv of **1a**, 2 equiv of **2a**, and 2 equiv of Ag_2O were chosen as the optimized conditions for the Pd-catalyzed reaction of **1a** with **2a** in refluxing AcOH at 120 °C.

With the optimized reaction conditions in hand, we started to investigate the scope and limitations of the reaction. The reaction conditions and product yields are listed in Table 2. Benzamides **1b−k** with either electron-donating or electron-withdrawing groups could react with iodobenzene (**2a**) to obtain the desired products **3ba−ka** (Table 2, entries 1−10). Substrates **1b−d** bearing a methyl group at the meta-position and/or para-position of the phenyl ring reacted with **2a** smoothly to give the corresponding products **3ba−da** in 58−68% yields (Table 2, entries 1−3). *O*-Methyl substitution on the phenyl ring of **1e** reduced the product yield only slightly (Table 2, entry 4 vs entries 1−3), not exhibiting an obvious "ortho-substituent" effect.[15,16] In comparison, the strong electron-donating methoxy group at the meta-position could also afford **3fa** in 68% yield (Table 2, entry 5), whereas the methoxy group at the para-position provided **3ga** in only 34% yield with some starting material remained unchanged even after prolonging the reaction time to 24 h (Table 2, entry 6). Substrates **1h−j** with halogen atoms including chlorine and bromine were tolerated under the employed reaction conditions and afforded **3ha−ja** in 34−54% yields (Table 2, entries 7−9). Gratifyingly, benzamide **3k** bearing the strong electron-withdrawing *p*-NO_2 group could also be functionalized to bring out the desired product, albeit at a relatively low yield even with a prolonged reaction time (Table 2, entry 10). The above substituent effects clearly disclose the electrophilic nature for the C−H activation process because substrates with electron-donating groups generally gave higher yields than those with electron-withdrawing groups (Table 2, entries 1−5 vs entries 7−10).

1-Iodo-4-methylbenzene (**2b**), 1-iodo-4-methoxybenzene (**2c**), 1-iodo-3-methoxybenzene (**2d**), and 1-chloro-4-iodobenzene (**2e**) were then chosen as other representative aryl iodides to examine the cross-coupling reaction (Table 2, entries 11−23). The Pd-catalyzed reaction of benzamide **1a** with **2b**, **2c**, **2d**, and **2e** produced **3ab**, **3ac**, **3ad**, and **3ae** in 84%, 71%, 68%, and 57% yields, respectively (Table 2, entries 11−14). Similarly, the reaction of *p*- and *m*-methyl-substituted benzamides **1b** and **1c** with **2b−d** afforded **3bb−bd** and **3cb−cd** in 50−78% yields (Table 2, entries 15−20). To our delight, when electron-rich substrate **1f** was allowed to react with **2b−d**, products **3fb−fd** were obtained in higher yields (70−82%) (Table 2, entries 21−23). It should be pointed out that the Pd-catalyzed arylation of benzamides **1** with aryl iodides **2** also gave a small amount of diarylated benzamides (0−9%) and phenanthridinones (<3%) as byproducts in most cases. However, the predominant monoarylation of *N*-unsubstituted benzamides $ArCONH_2$ with our protocol was intriguing because *N*-substituted benzamides ArCONHR usually afforded diarylation products except for sterically demanding meta-substituted benzamides.[11,12]

Aromatic amides and their derivatives are important intermediates of pharmaceuticals, pesticides, and dyes. The $CONH_2$ group is a valuable precursor for various functional groups such as nitrile, carboxylic acid, carbamate, and amine, as exemplified by **3aa** (Scheme 1). Treatment of **3aa** with a catalytic amount of $PdCl_2$ in a mixture of CH_3CN and H_2O at room temperature for 6 h afforded biphenyl-2-carbonitrile **4aa** in 95% yield. Hydrolysis of **3aa** in 30% H_2SO_4 at 120 °C for 24 h led to biphenyl-2-carboxylic acid **5aa** in 98% yield. Reaction of **3aa** with $PhI(OAc)_2$ in KOH−MeOH in the range of 0 °C to room temperature for 1 h generated methyl biphenyl-2-ylcarbamate **6aa**, which could be further converted to biphenyl-2-amine **7aa** in a total yield of 92%. Interestingly, when **3aa** was treated with 60% H_2SO_4 at 140 °C for 36 h, 9-fluorenone **8aa** was directly achieved in 87% yield. Fluorenones have been synthesized by the Pd-catalyzed ortho-arylation of *N*-propylbenzamides, followed by dehydration with $(CF_3CO)_2O$.[12b]

CONCLUSION

In summary, we have demonstrated the Pd-catalyzed regioselective ortho-arylation of benzamides by aryl iodides using the simplest amide $CONH_2$ as a directing group for the first time. Our protocol can be applied to a wide range of benzamides and aryl iodides with both electron-donating and electron-withdrawing groups. The obtained biphenyl-2-carboxamides can be further manipulated to construct a variety of biphenyl derivatives such as nitriles, carboxylic acids, carbamates, and amines and thus may provide a new strategy for the synthesis of drugs and natural products.

EXPERIMENTAL SECTION

General Procedure for the Direct Ortho-Arylation of Benzamide 1a (1b−k) Catalyzed by $Pd(OAc)_2$. To a stirred solution of benzamide **1a** (**1b−k**, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and aryl iodide **2a** (**2b−e**, 1 mmol) in AcOH (5 mL) at 120 °C was added Ag_2O (231.7 mg, 1 mmol). The reaction was monitored by TLC and stopped at the desired time. Then the solvent was evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate 2/1 as the eluent to give desired product **3aa** (**3ba−ka**, **3ab−ae**, **3bb−bd**, **3cb−cd**, and **3fb−fd**) along with small amounts of less polar diarylation products and phenanthridinones in most cases.

Biphenyl-2-carboxamide (3aa).[18] White solid; mp 176−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.2, 1.4 Hz, 1H), 7.51 (td, J = 7.6, 1.6 Hz, 1H), 7.47−7.39 (m, 6H), 7.37 (dd, J = 7.4, 1.0 Hz, 1H), 5.50 (1H, bs), 5.24 (1H, bs).

5-Methylbiphenyl-2-carboxamide (3ba). White solid; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.0, 3.0 Hz, 1H),

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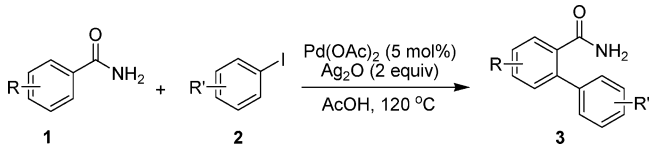
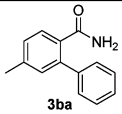
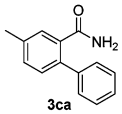
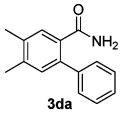
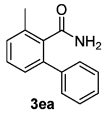
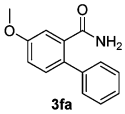
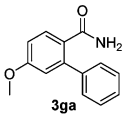
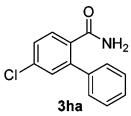
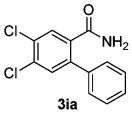
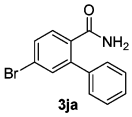
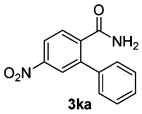
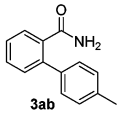
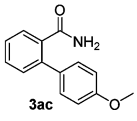
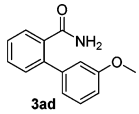
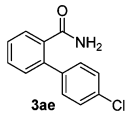
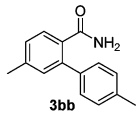
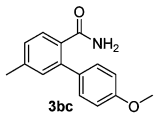
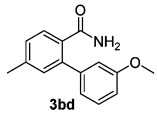
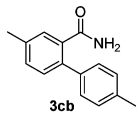
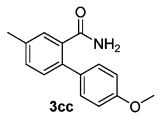
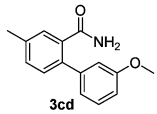
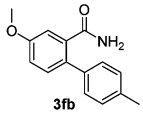
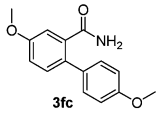
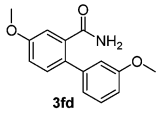
Table 2. Pd-Catalyzed Direct Ortho-Arylation of Benzamides[a]



1 2 3

entry	substrate 1	substrate 2	product	reaction time (h)	yield (%)[b]
1	1b	2a	 3ba	5	66 (9)
2	1c	2a	 3ca	5	68 (c)
3	1d	2a	 3da	5	58 (c)
4	1e	2a	 3ea	24	58 (0)
5	1f	2a	 3fa	5	68 (3)
6	1g	2a	 3ga	24	34 (7)
7	1h	2a	 3ha	24	38 (7)
8	1i	2a	 3ia	24	54 (c)
9	1j	2a	 3ja	24	34 (6)
10	1k	2a	 3ka	72	33 (6)
11	1a	2b	 3ab	5	84 (5)
12	1a	2c	 3ac	5	71 (3)
13	1a	2d	 3ad	5	68 (4)
14	1a	2e	 3ae	5	57 (6)
15	1b	2b	 3bb	5	50 (8)
16	1b	2c	 3bc	5	60 (5)
17	1b	2d	 3bd	5	69 (6)
18	1c	2b	 3cb	5	53 (c)
19	1c	2c	 3cc	5	78 (c)
20	1c	2d	 3cd	5	71 (c)
21	1f	2b	 3fb	5	70 (4)
22	1f	2c	 3fc	5	79 (3)
23	1f	2d	 3fd	5	82 (3)

[a]All reactions were carried out with 0.5 mmol of **1**, 1.0 mmol of **2**, 0.025 mmol of $Pd(OAc)_2$, and 1.0 mmol of Ag_2O in 5 mL of AcOH at 120 °C. [b]Isolated yield; the yield in parentheses corresponds to that of diarylation product. [c]Trace amount.

7.49−7.35 (m, 4H), 7.35−7.20 (m, 2H), 7.16 (s, 1H), 5.43 (bs, 1H), 5.19 (bs, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 141.0, 140.6, 140.1, 131.3, 129.5, 128.9 (2C), 128.8 (2C), 128.5, 128.0, 127.5, 21.5. IR (KBr) ν 3375, 3178, 1643, 1392, 1133, 822, 702,

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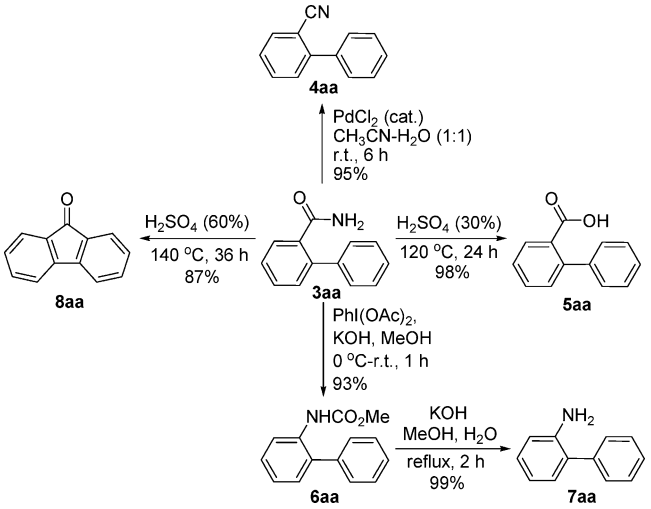
Scheme 1. Transformation of Biphenyl-2-carboxamide



668 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0991.

4-Methylbiphenyl-2-carboxamide (3ca). White solid; mp 172−174 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 1.2 Hz, 1H), 7.44−7.24 (m, 7H), 5.41 (bs, 1H), 5.19 (bs, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 140.4, 137.8, 137.2, 134.2, 131.5, 130.5, 129.8, 129.0 (2C), 128.8 (2C), 127.9, 21.1; IR (KBr) ν 3387, 3184, 1645, 1482, 1411, 1383, 822, 772, 702, 644 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0991.

4,5-Dimethylbiphenyl-2-carboxamide (3da). White solid; mp 139−140 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.47−7.35 (m, 5H), 7.12 (s, 1H), 5.51 (bs, 1H), 5.21 (bs, 1H), 2.34 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 140.4, 139.5, 137.6, 136.2, 131.8, 131.6, 130.5, 128.9 (2C), 128.7 (2C), 127.7, 19.7, 19.3; IR (KBr) ν 3385, 3186, 1643, 1486, 1448, 1400, 1101, 890, 773, 702, 653 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{15}H_{15}NO$ 225.1154, found 225.1147.

3-Methylbiphenyl-2-carboxamide (3ea). White solid; mp 124−126 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.32 (m, 6H), 7.22 (t, J = 7.4 Hz, 2H), 5.54 (bs, 1H), 5.27 (bs, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 140.5, 139.0, 135.8, 135.4, 129.5, 129.1, 128.7 (2C), 128.5 (2C), 127.6, 127.5, 19.6; IR (KBr) ν 3362, 3184, 1645, 1611, 1459, 1435, 1357, 758, 701 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{14}H_{13}NO$ 211.0997, found 211.0984.

4-Methoxybiphenyl-2-carboxamide (3fa). White solid; mp 161−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 5H), 7.34 (d, J = 2.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.4, 2.8 Hz, 1H), 5.42 (bs, 1H), 5.21 (bs, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 159.2, 140.1, 135.3, 132.5, 131.9, 129.1 (2C), 128.8 (2C), 127.8, 117.3, 113.7, 55.7; IR (KBr) ν 3382, 3173, 1646, 1599, 1486, 1409, 1388, 1298, 1276, 1233, 1041, 912, 866, 828, 771, 702 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{14}H_{14}NO_2^+$ 228.1019, found 228.1023.

5-Methoxybiphenyl-2-carboxamide (3ga). White solid; mp 183−184 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.8 Hz, 1H), 7.47−7.38 (m, 6H), 6.96 (dd, J = 8.8, 2.8 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 5.42 (bs, 1H), 5.13 (bs, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 161.3, 142.2, 140.5, 131.7, 128.91 (2C), 128.88 (2C), 128.3, 126.5, 115.9, 113.2, 55.6; IR (KBr) ν 3370, 3176, 1644, 1624, 1561, 1488, 1391, 1294, 1215, 1182, 1128, 1036, 1017, 887, 815, 769, 703, 594 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0942.

5-Chlorobiphenyl-2-carboxamide (3ha). White solid; mp 155−156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 1H), 7.45−7.39 (m, 6H), 7.36 (d, J = 2.0 Hz, 1H), 5.45 (bs, 1H), 5.18 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 141.7, 139.1, 136.7, 132.7, 130.9, 130.5, 129.0 (2C), 128.8 (2C), 128.7, 127.9; IR (KBr) ν 3378, 3189, 1644, 1382, 1090, 885, 832, 774, 703, 662, 549 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{13}H_{10}NO^{35}Cl$, 231.0451, found 231.0449.

4,5-Dichlorobiphenyl-2-carboxamide (3ia). White solid; mp 178−180 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.47−7.39 (m, 6H), 5.46 (bs, 1H), 5.20 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 139.8, 138.0, 134.9, 133.7, 132.33, 132.29, 131.4, 129.2 (2C), 128.9, 128.8 (2C); IR (KBr) ν 3386, 3189, 1645, 1472, 1392, 1346, 1150, 1023, 892, 773, 700, 648, 569 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{13}H_9NO^{35}Cl_2$ 265.0061, found 265.0053.

5-Bromobiphenyl-2-carboxamide (3ja). White solid; mp 158−159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 8.0, 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.48−7.40 (m, 5H), 5.47 (bs, 1H), 5.19 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 141.9, 138.9, 133.4, 133.2, 131.0, 130.9, 129.0 (2C), 128.8 (2C), 128.7, 125.0; IR (KBr) ν 3379, 3184, 1647, 1554, 1480, 1388, 1082, 887, 816, 772, 702, 660 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{13}H_{10}NO^{79}Br$ 274.9946, found 274.9940.

5-Nitrobiphenyl-2-carboxamide (3ka). Yellow solid; mp 182−184 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28−8.25 (m, 2H), 7.93 (dd, J = 7.4, 1.4 Hz, 1H), 7.51−7.47 (m, 5H), 5.61 (bs, 1H), 5.29 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 148.9, 141.5, 140.1, 138.0, 130.5, 129.30 (2C), 129.25 (2C), 128.8, 125.4, 122.5; IR (KBr) ν 3378, 3190, 1647, 1519, 1392, 1356, 912, 849, 796, 776, 732, 663, 549 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{13}H_{10}N_2O_3$ 242.0691, found 242.0691.

4′-Methylbiphenyl-2-carboxamide (3ab). White solid; mp 138−139 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.6, 1.6 Hz, 1H), 7.49 (td, J = 7.6, 1.6 Hz, 1H), 7.41 (td, J = 7.6, 1.2 Hz, 1H), 7.36−7.33 (m, 3H), 7.24 (d, J = 8.0 Hz, 2H), 5.41 (bs, 1H), 5.25 (bs, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 140.0, 138.0, 137.4, 134.4, 130.7, 130.6, 129.6 (2C), 129.3, 128.9 (2C), 127.6, 21.3; IR (KBr) ν 3372, 3183, 1643, 1483, 1396, 1130, 824, 756, 666, 631, 542, 512 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{14}H_{13}NO$ 211.0997, found 211.1001.

4′-Methoxybiphenyl-2-carboxamide (3ac). White solid; mp 102−104 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.6, 1.2 Hz, 1H), 7.48 (td, J = 7.6, 1.2 Hz, 1H), 7.39 (td, J = 7.6, 1.2 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 7.6, 1.2 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 5.65 (bs, 1H), 5.29 (bs, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 159.6, 139.6, 134.4, 132.6, 130.6, 130.5, 130.1 (2C), 129.2, 127.4, 114.3 (2C), 55.4; IR (KBr) ν 3368, 3186, 1650, 1574, 1478, 1445, 1392, 1096, 1004, 835, 759, 689, 633, 512 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{14}H_{14}NO_2^+$ 228.1019, found 228.1021.

3′-Methoxybiphenyl-2-carboxamide (3ad). White solid; mp 99−100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.6, 1.6 Hz, 1H), 7.50 (td, J = 7.6, 1.6 Hz, 1H), 7.44 (td, J = 7.6, 1.6 Hz, 1H), 7.36 (dd, J = 7.6, 1.6 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.02 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 6.98 (dd, J = 2.4, 1.6 Hz, 1H), 6.94 (ddd, J = 7.6, 2.4, 0.8 Hz, 1H), 5.43 (bs, 1H), 5.28 (bs, 1H), 3.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 159.8, 141.8, 139.9, 134.5, 130.6, 130.4, 129.9, 129.2, 127.8, 121.3, 114.4, 113.8, 55.4; IR (KBr) ν 3371, 3176, 1649, 1623, 1577, 1450, 1401, 1295, 1211, 1118, 1049, 874, 778, 689, 635, 530 cm^{-1}; HRMS (EI-TOF) m/z [M^+] calcd for $C_{14}H_{13}NO_2$ 227.0946, found 227.0941.

4′-Chlorobiphenyl-2-carboxamide (3ae). Pale yellow solid, mp 162−164 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 1H), 7.48−7.35 (m, 7H), 5.65 (bs, 1H), 5.21 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 140.3, 140.0, 134.5, 130.7, 130.5, 129.2, 128.9 (2C), 128.8 (2C), 128.1, 127.7; IR (KBr) ν 3385, 3174, 1643, 1618, 1450, 1398, 1113, 776, 742, 697, 634, 573 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{13}H_{11}NO^{35}Cl^+$ 232.0524, found 232.0533.

4′,5-Dimethylbiphenyl-2-carboxamide (3bb). White solid; mp 141−142 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.25−7.22 (m, 3H), 7.14 (d, J = 1.2 Hz, 1H), 5.72 (bs, 1H), 5.29 (bs, 1H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 140.9, 140.1, 137.9, 137.6, 131.4, 131.3, 129.6, 129.5 (2C), 128.8 (2C), 128.3, 21.4, 21.3; IR (KBr) ν 3370, 3178, 1642, 1497, 1393, 1264, 1136, 826, 745, 711, 664, 588, 550,

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517 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{15}H_{16}NO^+$ 226.1226, found 226.1218.

4′-Methoxy-5-methylbiphenyl-2-carboxamide (3bc). White solid; mp 142−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.13 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 5.84 (bs, 1H), 5.29 (bs, 1H), 3.84 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.6, 140.8, 139.7, 132.8, 131.4, 131.3, 130.1 (2C), 129.5, 128.1, 114.2 (2C), 55.4, 21.4; IR (KBr) ν 3376, 3178, 1647, 1605, 1474, 1431, 1406, 1382, 1299, 1270, 1217, 1134, 1054, 1047, 1022, 887, 855, 823, 789, 780, 701, 649 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{15}H_{16}NO_2^+$ 242.1176, found 242.1169.

3′-Methoxy-5-methylbiphenyl-2-carboxamide (3bd). White solid; mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.01−6.90 (m, 3H), 5.67 (bs, 1H), 5.29 (bs, 1H), 3.82 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.8, 142.0, 140.9, 140.0, 131.4, 131.1, 129.8, 129.5, 128.5, 121.3, 114.4, 113.7, 55.4, 21.4; IR (KBr) ν 3376, 3194, 1646, 1600, 1473, 1429, 1397, 1376, 1299, 1229, 1209, 1179, 1037, 862, 792, 699 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{15}H_{16}NO_2^+$ 242.1176, found 242.1165.

4,4′-Dimethylbiphenyl-2-carboxamide (3cb). White solid; mp 210−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.33−7.29 (m, 3H), 7.25−7.22 (m, 3H), 5.59 (bs, 1H), 5.29 (bs, 1H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 137.8, 137.5, 137.4, 137.2, 134.1, 131.5, 130.5, 129.9, 129.5 (2C), 128.9 (2C), 21.3, 21.1; IR (KBr) ν 3385, 3174, 1698, 1643, 1482, 1431, 1375, 1111, 1007, 895. 812, 728, 626, 595, 527 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{15}H_{16}NO^+$ 226.1226, found 226.1218.

4′-Methoxy-4-methylbiphenyl-2-carboxamide (3cc). White solid; mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.27 (dd, J = 8.0, 1.6 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 5.56 (bs, 1H), 5.25 (bs, 1H), 3.84 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 159.5, 137.3, 136.8, 134.1, 132.6, 131.4, 130.5, 130.1 (2C), 129.8, 114.2 (2C), 55.4, 21.0; IR (KBr) ν 3381, 3180, 1642, 1611, 1518, 1491, 1377, 1299, 1246, 1177, 1108, 1039, 818, 593, 534 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{15}H_{16}NO_2^+$ 242.1176, found 242.1169.

3′-Methoxy-4-methylbiphenyl-2-carboxamide (3cd). White solid; mp 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.62 (m, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.32−7.29 (m, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.00 (ddd, J = 7.8, 1.6, 1.0 Hz, 1H), 6.96 (dd, J = 2.4, 1.6 Hz, 1H), 6.92 (ddd, J = 8.4, 2.4, 1.0 Hz, 1H), 5.43 (bs, 1H), 5.26 (bs, 1H), 3.83 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 159.8, 141.8, 137.8, 137.1, 134.1, 130.4, 129.9, 129.8, 121.4, 114.5, 113.6, 55.4, 21.1; IR (KBr) ν 3392, 3180, 1640, 1518, 1490, 1427, 1375, 1300, 1245, 1177, 1108, 1040, 818, 594, 553 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{15}H_{16}NO_2^+$ 242.1176, found 242.1169.

4-Methoxy-4′-methylbiphenyl-2-carboxamide (3fb). White solid; mp 164−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 2.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.03 (dd, J = 8.4, 2.8 Hz, 1H), 5.41 (bs, 1H), 5.24 (bs, 1H), 3.88 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 159.1, 137.6, 137.2, 135.2, 132.5, 131.9, 129.6 (2C), 129.0 (2C), 117.4, 113.7, 55.7, 21.3; IR (KBr) ν 3385, 3185, 1650, 1600, 1493, 1385, 1298, 1232, 1094, 1038, 804, 647, 638 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{15}H_{16}NO_2^+$ 242.1176, found 242.1178.

4,4′-Dimethoxybiphenyl-2-carboxamide (3fc). White solid; mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 2.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 8.4, 2.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 5.50 (bs, 1H), 5.27 (bs, 1H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.4, 158.9, 135.2, 132.4, 132.2, 131.8, 130.2 (2C), 117.3, 114.3 (2C), 113.7, 55.7, 55.4; IR (KBr) ν 3385, 3171, 1643, 1608, 1490, 1429, 1245, 1175, 1038, 823, 612 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{16}NO_3^+$ 258.1125, found 258.1131.

3′,4-Dimethoxybiphenyl-2-carboxamide (3fd). White solid; mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 2.8 Hz, 1H), 7.32 (dd, J = 8.2, 7.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 1H), 7.03 (dd, J = 8.5, 2.8 Hz, 1H), 6.99 (ddd, J = 7.6, 1.5, 1.0 Hz, 1H), 6.94 (dd, J = 2.6, 1.5 Hz, 1H), 6.91 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 5.46 (bs, 1H), 5.28 (bs, 1H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 159.8, 159.2, 141.5, 135.4, 132.3, 131.7, 129.8, 121.4, 117.1, 114.5, 113.6, 113.4, 55.6, 55.4; IR (KBr) ν 3371, 3176, 1648, 1599, 1478, 1407, 1300, 1236, 1055, 1016, 861, 824, 780, 737, 702, 668 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{16}NO_3^+$ 258.1125, found 258.1117.

Synthesis of Biphenyl-2-carbonitrile (4aa).[19] By following a reported procedure,[20] **3aa** (49.3 mg, 0.25 mmol) in a mixture of H_2O/CH_3CN = 1:1 (6 mL) was treated with $PdCl_2$ (4.5 mg, 0.025 mmol) at room temperature for 6 h. The reaction mixture was quenched with water and extracted with diethyl ether (10 mL × 3). The solvent was removed in vacuo and the residual was separated on a silica gel column with petroleum ether/ethyl acetate 6/1 as the eluent to give **4aa** (42.7 mg, 95%) as a white solid: mp 35−37 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.8, 1.0 Hz, 1H), 7.65 (td, J = 7.6, 1.6 Hz, 1H), 7.58−7.42 (m, 7H).

Synthesis of Biphenyl-2-carboxylic Acid (5aa).[21] By following a modified procedure,[22] the solution of **3aa** (49.3 mg, 0.25 mmol) in 2.5 mL of 30% (v/v) sulfuric acid were heated at 120 °C with stirring for 24 h. After being cooled to room temperature, the reaction mixture was quenched with water and extracted with diethyl ether (10 mL × 3). The solvent was removed under vacuum and the residual was separated on a silica gel column with petroleum ether/ethyl acetate 3/1 as the eluent to afford **5aa** (48.4 mg, 98%) as a white solid: mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.6, 1.2 Hz, 1H), 7.56 (td, J = 7.6, 1.2 Hz, 1H), 7.45−7.32 (m, 7H).

Synthesis of Methyl Biphenyl-2-ylcarbamate (6aa). By following a reported process,[23] **3aa** (49.3 mg, 0.25 mmol) was added to a solution of KOH (35.3 mg, 0.63 mmol) in MeOH (2.5 mL) and was stirred at room temperature until a homogeneous solution was obtained, then cooled to 5−10 °C in an ice−water bath. Diacetoxyiodobenzene (80.9 mg, 0.25 mmol) was added in one portion and dissolved within 5 min. The reaction was stirred at ice-bath temperature for 15 min followed by warming to room temperature while stirring for an additional 45 min. Upon completion of the reaction (TLC), the methanol was removed in vacuo and the reaction mixture was quenched with water and extracted with CH_2Cl_2 (10 mL × 3). The solvent was removed in vacuo and the residual was separated on a silica gel column with petroleum ether/ethyl acetate 6/1 as the eluent to give methyl biphenyl-2-ylcarbamate **6aa** (52.6 mg, 93%) as a white solid: mp 184−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.43−7.34 (m, 4H), 7.21 (dd, J = 7.6, 1.6 Hz, 1H), 7.13 (td, J = 7.6, 1.2 Hz, 1H), 6.65 (bs, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 138.2, 135.0, 131.6, 130.3, 129.4 (2C), 129.3 (2C), 128.7, 128.1, 123.5, 119.7, 52.4; IR (KBr) ν 3422, 2952, 1740, 1586, 1522, 1449, 1305, 1213, 1069, 750, 704 cm^{-1}; HRMS (ESI) m/z (M + H^+) calcd for $C_{14}H_{14}NO_2^+$ 228.1019, found 228.1016.

Synthesis of Biphenyl-2-amine (7aa).[24] According to a reported procedure,[25] to a solution of **6aa** (48.1 mg, 0.21 mmol) in methanol (4 mL) was added 40% KOH solution (2 mL), and the mixture was refluxed for 2 h. After being cooled to room temperature, the mixture was diluted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate 6/1 as the eluent to obtain **7aa** (35.4 mg, 99%) as a white solid: mp 50−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 4H), 7.38−7.32 (m, 1H), 7.19−7.12 (m, 2H), 6.84 (td, J = 7.4, 1.2 Hz, 1H), 6.77 (dd, J = 7.6, 0.8 Hz, 1H), 3.76 (bs, 2H).

Synthesis of 9-Fluorenone (8aa).[9d] Product **8aa** was obtained by adapting the reported process.[26] The mixture of **3aa** (49.3 mg, 0.25 mmol) in 2.5 mL of 60% (v/v) sulfuric acid was heated with stirring at 140 °C for 36 h. After being cooled to room temperature, the reaction mixture was quenched with water and extracted with diethyl ether (10 mL × 3). The solvent was removed under vacuum, and the residual was separated on a silica gel column with petroleum ether/ethyl acetate 6/1 as the eluent to give **8aa** (39.0 mg, 87%) as a yellow solid: mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65

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(m, 2H), 7.54−7.51 (m, 2H), 7.49 (td, J = 7.4, 1.2 Hz, 2H), 7.30 (td, J = 7.2, 1.2 Hz, 2H).

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of products **3aa−ka**, **3ab−ae**, **3bb−bd**, **3cb−cd**, **3fb−fd**, and **4aa−8aa**. 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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