Metal-Free Iodination of Arylboronic Acids and the Synthesis of Biaryl Derivatives

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Received: 25.12.2013; Accepted after revision: 05.02.2014

Abstract: A simple, general and efficient method is developed for the metal-free iodination of arylboronic acids. The protocol uses very cheap molecular iodine as the halide source and potassium carbonate as the base. The method is highly tolerant of various functional groups present in the substrates. Importantly, the iodination strategy can also be applied very effectively in the one-pot, two-step synthesis of biaryl derivatives.

Key words: arylboronic acids, iodination, cross-coupling, Suzuki coupling, biaryl derivatives

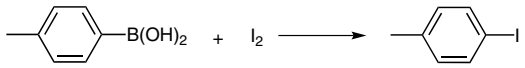
Iodine has generated significant attention in modern oxidation catalysis because of its safety, ease of storage and handling, and especially due to its chemical properties, which include the lowest homolytic dissociation energy and electronegativity among the halogens.[1] Aryl iodides usually show much higher reactivity than the corresponding aryl bromides and chlorides in transition metal catalyzed coupling reactions.[2] Unfortunately, the direct iodination of arenes with iodine is difficult because of the low reactivity of iodine toward electrophilic substitution.[3] Some alternative methods have been developed in which various auxiliary reagents[4] such as chromium(VI) oxide (CrO_3) in acidic solution,[4e,f] mercuric chloride ($HgCl_2$),[4h] and silver sulfate (Ag_2SO_4),[4j] were used in such iodinations of arenes. However, these reagents do not meet the following requirements: high efficiency, high regioselectivity, environmentally benign and mild reaction conditions. Organoboron derivatives have drawn considerable attention because they are generally nontoxic and stable under atmospheric conditions. With the development of transition metal catalyzed borylations from aryl triflates, tosylates and halides,[5] and the iridium-catalyzed direct borylations of arenes via C–H bond activation,[6] the ready availability of numerous organoboron derivatives enhances the significance of modern organoboron-based chemistry.[7] Boron–iodine exchange has emerged as a means by which iodinated arenes can be generated,[8] and they include copper-catalyzed methods with potassium iodide (KI)[8a,b] or iodine (I_2),[8c] and metal-free approaches with *N*-iodosuccinimide[8d] or sodium iodide in the presence of chloramine-T.[8e] Therefore, it is very desirable to develop highly efficient, environmentally benign and inexpensive approaches to aryl iodides. On the other hand, biaryl derivatives occur widely in biologically active and functional molecules,[9] and their significance is shown in the immense economic value of pharmaceuticals,[10] agrochemicals,[11] and liquid crystals for LCD screens.[12] Therefore, it is of high importance to develop convenient and general methods for the synthesis of biaryl derivatives. Herein, we report a simple, general and highly effective method for metal-free iodination of arylboronic acids with iodine in the presence of a base, and which can be used efficiently for the synthesis of biaryls from arylboronic acids.

In order to optimize the reaction conditions, *p*-tolylboronic acid (**1b**) was chosen as the model substrate, and the effects of bases, solvents, the amount of iodine, temperature and atmosphere were investigated. As shown in Table 1, the reaction did not occur in the absence of base (Table 1, entry 1). Four bases were screened in the presence of iodine in acetonitrile at 80 °C under a nitrogen atmosphere (Table 1, entries 2–5), and analytically pure potassium carbonate (K_2CO_3) (99%) provided the highest yield (Table 1, entry 3). Next the effect of solvents was studied (compare Table 1, entries 3 and 6–9), and acetonitrile gave the best result. The amounts of iodine and potassium carbonate were also changed (compare Table 1, entries 3 and 10–13), and 1.5 equivalents of iodine and two equivalents of potassium carbonate were the best combination. When the reaction temperature was decreased (Table 1, entries 14 and 15), lower yields were afforded. The reaction was less efficient under air or oxygen atmospheres (Table 1, entries 16 and 17). Highly pure potassium carbonate (99.997% purity) was used tested in this reaction, to avoid the possible involvement of other metals,[13] and an 80% yield of the iodide was obtained (Table 1, entry 18), which was similar to the yield achieved when the previous analytically pure potassium carbonate (99%) was used. Therefore, the optimal reaction conditions for the iodination are as follows: potassium carbonate (2 equiv) as the base, iodine (1.5 equiv) as the halide source, and acetonitrile as the solvent, with the reaction being carried out at 80 °C under a nitrogen atmosphere.

Next, the substrate scope of the metal-free iodination of various arylboronic acids was investigated under the optimized conditions described above. As shown in Table 2,

SYNLETT 2014, 25, 0995–1000
Advanced online publication: 14.03.2014
DOI: 10.1055/s-0033-1340871; Art ID: ST-2013-W1166-L

Table 1 Base-Promoted Iodination of *p*-Tolylboronic Acid (**1b**) to give 1-Iodo-4-methylbenzene (**2b**); Optimization of the Reaction Conditions[a]



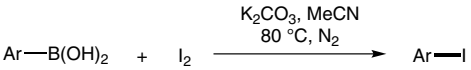
1b **2b**

Entry	Base (equiv)	Solvent	I_2 (equiv)	Temp (°C)	Yield (%)[b]
1	–	MeCN	1.5	80	0
2	Na_2CO_3 (2)	MeCN	1.5	80	30
3	**K_2CO_3 (2)**	**MeCN**	**1.5**	**80**	**81**
4	Cs_2CO_3 (2)	MeCN	1.5	80	50
5	KOH (2)	MeCN	1.5	80	0
6	K_2CO_3 (2)	DMF	1.5	80	22
7	K_2CO_3 (2)	DMSO	1.5	80	25
8	K_2CO_3 (2)	EtOH	1.5	80	trace
9	K_2CO_3 (2)	DCE	1.5	80	15
10	K_2CO_3 (2)	MeCN	1.0	80	51
11	K_2CO_3 (2)	MeCN	2.0	80	81
12	K_2CO_3 (1)	MeCN	1.5	80	21
13	K_2CO_3 (3)	MeCN	1.5	80	80
14	K_2CO_3 (2)	MeCN	1.5	r.t.	7
15	K_2CO_3 (2)	MeCN	1.5	45	38
16	K_2CO_3 (2)	MeCN	1.5	80	30[c]
17	K_2CO_3 (2)	MeCN	1.5	80	0[d]
18	K_2CO_3 (2)[e]	MeCN	1.5	80	80

[a] Reaction conditions: *p*-Tolylboronic acid (**1b**) (0.5 mmol), solvent (2 mL), 10 h, N_2 atmosphere.
[b] Yield of isolated product.
[c] Under an air atmosphere.
[d] Under an O_2 atmosphere.
[e] Highly pure K_2CO_3 (99.997% purity) from Alfa Aesar was used.

the examined substrates provided good to excellent yields of the iodinated products **2**.[14] Arylboronic acids containing electron-withdrawing groups displayed higher reactivity than those containing neutral or electron-donating groups. The iodination reaction exhibited wide generality and tolerated various functional groups including ether (Table 2, entries 7–9), carbon–chlorine bonds (Table 2, entries 10–12), carbon–fluorine bonds (Table 2, entry 13), amine (Table 2, entry 14), aldehyde (Table 2, entry 15), acetyl (Table 2, entry 16), cyano (Table 2, entry 17), ester (Table 2, entry 18), carboxyl (Table 2, entries 19 and 20), naphthalene (Table 2, entry 21), and O-heterocyclic (Table 2, entry 22) on the arylboronic acid.

Table 2 Potassium Carbonate Promoted Iodination of Arylboronic Acids[a]



1 **2**

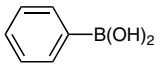
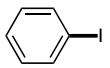
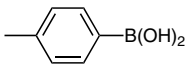
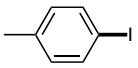
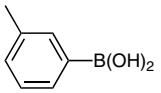
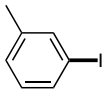
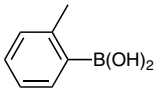
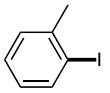
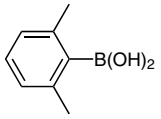
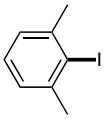
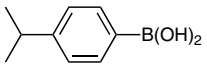
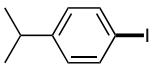
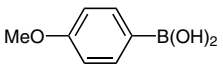
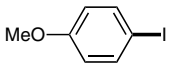
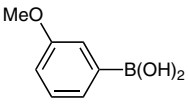
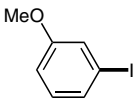
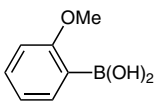
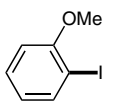
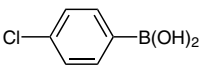
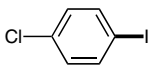
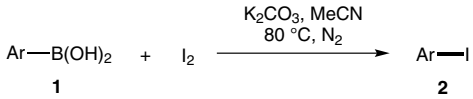
Entry	Boronic acid	Time (h)	Product	Yield (%)[b]
1	 **1a**	10	 **2a**	73
2	 **1b**	10	 **2b**	81
3	 **1c**	10	 **2c**	77
4	 **1d**	10	 **2d**	72
5	 **1e**	12	 **2e**	78
6	 **1f**	12	 **2f**	82
7	 **1g**	12	 **2g**	80
8	 **1h**	12	 **2h**	78
9	 **1i**	12	 **2i**	76
10	 **1j**	9	 **2j**	85

Table 2 Potassium Carbonate Promoted Iodination of Arylboronic Acids[a] (continued)



1 2

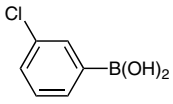
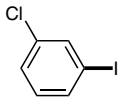
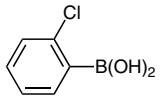
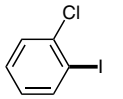
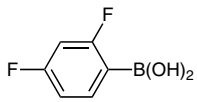
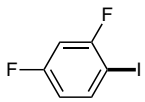
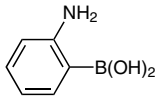
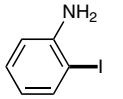
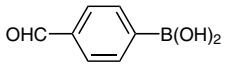
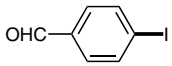
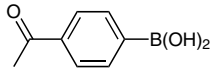
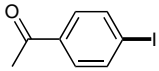
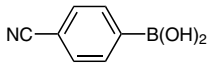
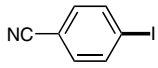
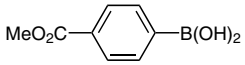
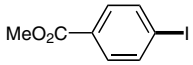
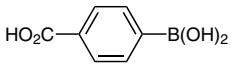
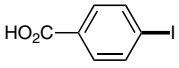
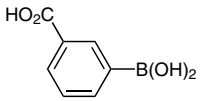
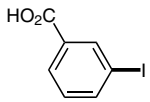
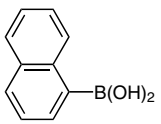
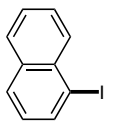
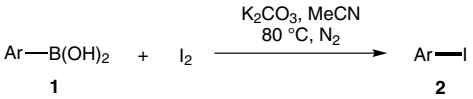
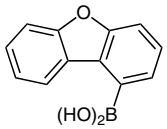
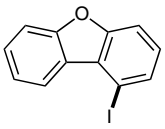
Entry	Boronic acid	Time (h)	Product	Yield (%)[b]
11	 **1k**	9	 **2k**	73
12	 **1l**	9	 **2l**	78
13	 **1m**	14	 **2m**	68
14	 **1n**	14	 **2n**	71
15	 **1o**	8	 **2o**	92
16	 **1p**	8	 **2p**	91
17	 **1q**	8	 **2q**	93
18	 **1r**	8	 **2r**	90
19	 **1s**	8	 **2s**	89
20	 **1t**	8	 **2t**	78
21	 **1u**	9	 **2u**	87

Table 2 Potassium Carbonate Promoted Iodination of Arylboronic Acids[a] (continued)

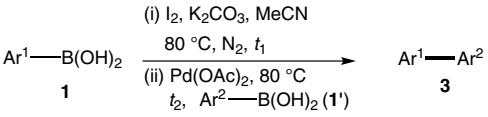


1 2

Entry	Boronic acid	Time (h)	Product	Yield (%)[b]
22	 **1v**	9	 **2v**	88

[a] Reaction conditions: $ArB(OH)_2$ (0.5 mmol), I_2 (0.75 mmol), K_2CO_3 (1.0 mmol), 80 °C, N_2 atmosphere.
[b] Yield of isolated product.

Table 3 One-Pot Synthesis of Biaryls via Iodination of Arylboronic Acids and Palladium-Catalyzed Cross-Coupling[a]



1 3

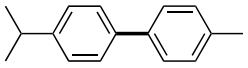
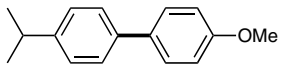
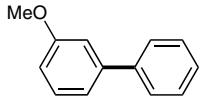
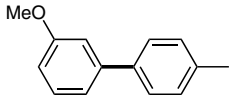
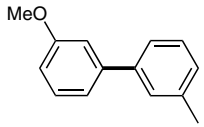
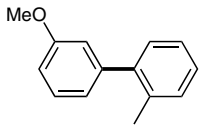
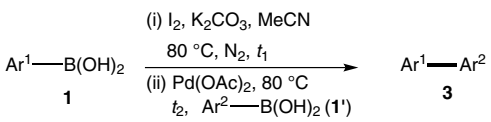
Entry	$Ar^1B(OH)_2$ (**1**)	$Ar^2B(OH)_2$ (**1′**)	Product (t_1, t_2,[b] yield)[c]
1	**1f**	**1b**	 **3a** (12 h, 16 h, 82%)
2	**1f**	**1g**	 **3b** (12 h, 16 h, 80%)
3	**1h**	**1a**	 **3c** (12 h, 14 h, 77%)
4	**1h**	**1b**	 **3d** (12 h, 14 h, 82%)
5	**1h**	**1c**	 **3e** (12 h, 14 h, 80%)
6	**1h**	**1d**	 **3f** (12 h, 14 h, 75%)

Table 3 One-Pot Synthesis of Biaryls via Iodination of Arylboronic Acids and Palladium-Catalyzed Cross-Coupling[a] (continued)



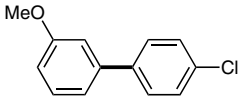
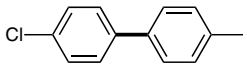
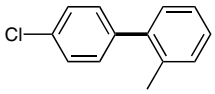
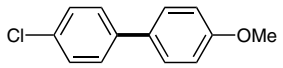
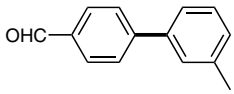
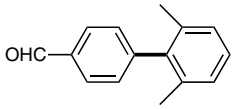
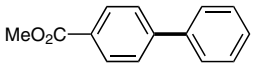
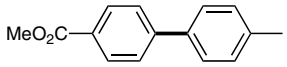
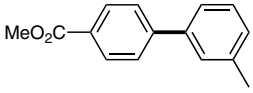
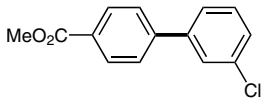
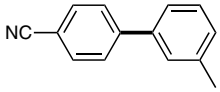
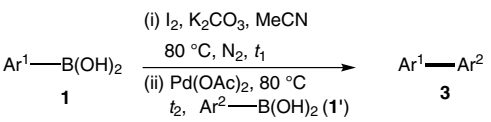
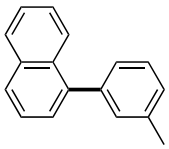
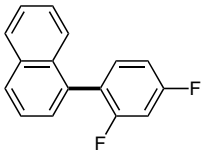
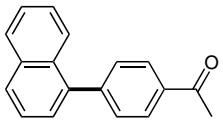
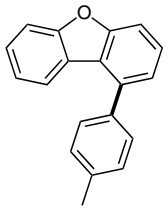
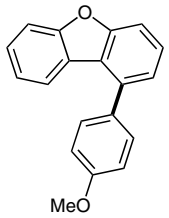
Entry	$Ar^1B(OH)_2$ (**1**)	$Ar^2B(OH)_2$ (**1′**)	Product (t_1, t_2,[b] yield)[c]
7	**1h**	**1j**	 **3g** (12 h, 14 h, 71%)
8	**1j**	**1b**	 **3h** (9 h, 15 h, 86%)
9	**1j**	**1d**	 **3i** (9 h, 15 h, 78%)
10	**1j**	**1g**	 **3j** (9 h, 15 h, 83%)
11	**1o**	**1c**	 **3k** (8 h, 12 h, 85%)
12	**1o**	**1e**	 **3l** (8 h, 12 h, 83%)
13	**1r**	**1a**	 **3m** (8 h, 14 h, 80%)
14	**1r**	**1b**	 **3n** (8 h, 14 h, 87%)
15	**1r**	**1c**	 **3o** (8 h, 14 h, 78%)
16	**1r**	**1k**	 **3p** (8 h, 12 h, 76%)
17	**1q**	**1c**	 **3q** (8 h, 12 h, 81%)

Table 3 One-Pot Synthesis of Biaryls via Iodination of Arylboronic Acids and Palladium-Catalyzed Cross-Coupling[a] (continued)



Entry	$Ar^1B(OH)_2$ (**1**)	$Ar^2B(OH)_2$ (**1′**)	Product (t_1, t_2,[b] yield)[c]
18	**1u**	**1c**	 **3r** (9 h, 16 h, 86%)
19	**1u**	**1m**	 **3s** (9 h, 16 h, 68%)
20	**1u**	**1p**	 **3t** (9 h, 16 h, 79%)
21	**1v**	**1b**	 **3u** (9 h, 16 h, 85%)
22	**1v**	**1g**	 **3v** (9 h, 16 h, 75%)

[a] Reaction conditions: $Ar^1B(OH)_2$ (0.5 mmol), I_2 (0.75 mmol), K_2CO_3 (1.0 mmol), $Ar^2B(OH)_2$ (0.75 mmol), $Pd(OAc)_2$ (0.025 mmol), 80 °C, N_2 atmosphere.
[b] The time taken for the iodination (step 1, t_1) is shown first, followed by that required for the cross-coupling (step 2, t_2).
[c] Yield of isolated product.

Inspired by these excellent results, we subsequently investigated a one-pot, two-step synthesis of biaryls from arylboronic acids by applying this iodination strategy. As shown in Table 3, the initial arylboronic acid was first converted into the corresponding aryl iodide under the established iodination conditions, and then the second arylboronic acid and palladium(II) acetate [$Pd(OAc)_2$] were added to the resulting solution. After 12–16 hours at 80 °C, the expected bi-

aryls **3** were obtained in good to excellent yields.[15] The method exhibited wide tolerance of functional groups including ether (Table 3, entries 2–7, 10 and 22), carbon–chlorine bonds (Table 3, entries 7–10 and 16), aldehyde (Table 3, entries 11 and 12), ester (Table 3, entries 13–16), cyano (Table 3, entry 17), naphthalene (Table 3, entries 18–20), carbon–fluorine bonds (Table 3, entry 19), acetyl (Table 3, entry 20), and O-heterocyclic (Table 3, entries 21 and 22) on the arylboronic acid.

In summary, we have developed a simple, general and efficient method for the metal-free iodination of arylboronic acids with iodine in the presence of potassium carbonate as the base. The method is highly tolerant toward various functional groups present in the substrates. Importantly, the iodination strategy could also be applied efficiently to the one-pot synthesis of biaryl derivatives. These convenient and practical methods should attract attention from industrial and academic research.

Acknowledgment

The authors wish to thank the National Natural Science Foundation of China (Grant Nos. 21172128, 21372139, 21105054 and 21221062), and the Ministry of Science and Technology of China (Grant No. 2012CB722605) for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) K_2CO_3 (99.997%) was purchased from Alfa Aesar and contains Si (1 ppm), Ca (2 ppm) and Na (4 ppm); other elements including: Al, Bi, Cr, Fe, Mn, Sr, V, Sb, B, Co, Pb, Mo, Te, Zn, As, Cd, Cu, Li, Ni, Ag, Sn, Zr, Ba, In, Mg, P and Ti were not detected by ICP/AA (data provided by Alfa Aesar).

(14) **Aryl Iodides (2); General Procedure**
Arylboronic acid **1** (0.5 mmol) and K_2CO_3 (1 mmol, 138.0 mg) were added to a 20 mL Schlenk-tube equipped with a magnetic stir bar. The tube was evacuated twice and backfilled with N_2. MeCN (2 mL) and I_2 (0.75 mmol, 191 mg) were added to the tube at r.t. under a stream of N_2, and the tube was sealed and placed into a pre-heated oil bath at 80 °C for 8–12 h. The resulting solution was cooled to r.t. and H_2O (10 mL) was added. The aq layer was extracted with EtOAc

(3 × 5 mL). For products **2s** and **2t**, HCl (1 M) was added to the aq solution until pH 2 before extraction. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated by rotary evaporation. Purification of the residue by column chromatography on silica gel provided the desired product **2a–v**. Data for three representative examples are provided. PE = petroleum ether.

1-Iodo-4-methoxybenzene (2g)[16]

Eluent: PE; yield: 93.6 mg (80%); white solid; mp 49–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.9 Hz, 2 H), 6.68 (d, *J* = 8.9 Hz, 2 H), 3.77 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 138.3, 116.5, 82.8, 55.4. EI-MS: *m*/*z* $[M]^+$ = 234.0.

1-Chloro-3-iodobenzene (2k)[17]

Eluent: PE; yield: 86.8 mg (73%); yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.33 (d, *J* = 7.9 Hz, 1 H), 7.02 (t, *J* = 7.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3, 135.8, 135.2, 131.1, 128.1, 94.3. EI-MS: *m*/*z* $[M]^+$ = 237.9.

1-Iododibenzo[*b*,*d*]furan (2v)[8a]

Eluent: PE–EtOAc, 20:1; yield: 129.4 mg (88%); white solid; mp 48–49 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.77 (m, 3 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.47 (d, *J* = 6.9 Hz, 1 H), 7.37 (d, *J* = 6.9 Hz, 1 H), 7.08 (t, *J* = 7.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 155.7, 136.0, 127.8, 124.6, 124.5, 124.4, 123.3, 121.3, 120.6, 112.2, 75.6. EI-MS: *m*/*z* $[M]^+$ = 294.0.

(15) **Biaryls (3); General Procedure**

Arylboronic acid **1** (0.5 mmol) and K_2CO_3 (1 mmol, 138.0 mg) were added to a 20 mL Schlenk-tube equipped with a magnetic stir bar. The tube was evacuated twice and back-filled with N_2. MeCN (2 mL) and I_2 (0.75 mmol, 191 mg) were added to the tube at r.t. under a stream of N_2, and the tube was sealed and placed into a pre-heated oil bath at 80 °C for 8–12 h. The resulting solution was cooled to r.t., and then arylboronic acid **1′** (0.75 mmol) and $Pd(OAc)_2$ (0.025 mmol, 5.6 mg) were added, and the mixture stirred at 80 °C for 12–16 h. The resulting solution was cooled to r.t. and H_2O (10 mL) was added. The aq layer was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated by rotary evaporation, and the residue was purified by column chromatography on silica gel to provide the desired product **3a–v**. Data for three representative examples are provided.

3-Methoxy-1,1′-biphenyl (3c)

Eluent: PE–EtOAc, 100:1; yield: 70.8 mg (77%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 6.9 Hz, 2 H), 7.47 (t, *J* = 7.3 Hz, 2 H), 7.41–7.37 (m, 2 H), 7.22 (d, = 8.2 Hz, 1 H), 7.17 (s, 1 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 3.89 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 142.9, 141.2, 129.9, 128.9, 127.5, 127.3, 119.8, 113.0, 112.8, 55.4. EI-MS: *m*/*z* $[M]^+$ = 184.1.

Methyl 4′-Methyl-[1,1′-biphenyl]-4-carboxylate (3n)

Eluent: PE–EtOAc, 100:1; yield: 98.4 mg (87%); white solid; mp 102–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.7 Hz, 2 H), 7.64 (d, *J* = 8.2 Hz, 2 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.7 Hz, 2 H), 3.93 (s, 3 H), 2.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 145.7, 138.2, 137.2, 130.2, 129.7, 128.7, 127.2, 126.9, 52.2, 21.2. EI-MS: *m*/*z* $[M]^+$ = 226.1.

3′-Methyl-[1,1′-biphenyl]-4-carbonitrile (3q)

Eluent: PE–EtOAc, 100:1; yield: 78.2 mg (81%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.2 Hz, 2 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.39–7.36 (m, 3 H), 7.23 (d, *J* = 6.0 Hz, 1 H), 2.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 139.3, 138.9, 132.6, 129.5, 129.1, 128.1, 127.8, 124.5, 119.1, 110.9, 21.6. EI-MS: *m*/*z* $[M]^+$ = 193.1.

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