$CuSO_4$-Mediated Homocoupling of Arylboronic Acids under Ligand- and Base-Free Conditions in Air

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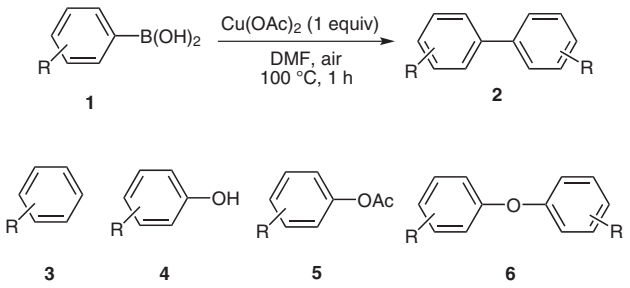
Abstract: The homocoupling of arylboronic acids mediated by very inexpensive and air stable copper(II) sulfate in *N*,*N*-dimethylformamide affords the corresponding symmetrical biaryls in moderate to good yields. The homocoupling reaction proceeds in air at 50 °C in the presence of molecular sieves without any additives such as base and ligand.

Key words: homocoupling, arylboronic acids, copper(II) sulfate, biaryls

Biaryl linkage is present in a range of important compounds including a number of potential pharmaceuticals and biologically active compounds.[1] The synthesis of biaryls through C–C bond formation reactions is of great interest because of their presence in many natural products and functional materials.[2] The transition-metal-catalyzed formation of the C–C bond by cross-coupling reactions have thus been developed in the past decades.[3] Among the various biaryl coupling methods, the Suzuki–Miyaura coupling has attracted attention due to its stability and the lower toxicity of the boronic acids than other organometallic reagents used.[4] Therefore, the homocoupling of arylboronic acids is a valuable method to obtain symmetrical biaryls. Recently, many studies have reported on the homocoupling of arylboronic acids for the synthesis of symmetrical biaryls.[5] A commonly applied method for the synthesis of symmetrical biaryls relies on palladium catalysis in the presence of different ligands, bases, and solvents.[6] In these catalytic methods, to restore the catalytically active palladium(II) species, metal salts and organic halides or benzoquinone are used as oxidizing agants.[7] Therefore, researchers have recently reported on the homocoupling of boronic acids in air or under an oxygen atmosphere.[8] Although some significant achievements in the palladium-catalyzed homocoupling arylboronic acids have been made, the drawbacks of the catalyst systems, such as sensitivity to air, high costs, and toxicity, limit their applications.

Recently, Demir et al. reported that copper(II) acetate is able to mediate the homocoupling of arylboronic for the synthesis of biaryls (Scheme 1).[9] This method is expedient and practical for the synthesis of symmetrical biaryls through the use of a copper(II) acetate mediator without any additives; however, it requires a high reaction temperature, and the reaction in the presence of molecular sieves gave the acetoxylation product **5** as a major product.[9] It has been shown that the presence of water results in the formation of side products **4** and **6** and molecular sieves trap the water released by arylboronic acids through triarylboroxine formation.[10] Therefore, despite the advantages of this method a number of limitations still remain. In this paper, we report on a very inexpensive and air stable copper(II) sulfate mediated homocoupling of boronic acids. The reaction proceeds in *N*,*N*-dimethylformamide at 50 °C in air in the presence of molecular sieves.



Scheme 1

Initially, the homocoupling of phenylboronic acid (**1a**) was chosen as the model reaction and the experimental data for the screening conditions are listed in Table 1. When the reaction was carried out using copper(II) acetate for one hour at 100 °C, biaryl (**2a**) was obtained in 46% isolated yield (TLC showed 100% conversion, Table 1, entry 1). The homocoupling reaction of 2 equivalents of **1a** with 0.1 equivalent of copper(II) acetate gave **2a** in 14% yield (entry 2). Reaction yield decreased to 30% when the reaction was carried out using three equivalents of copper(II) acetate for one hour at 100 °C (entry 3). As expected, the reaction in the presence of molecular sieves gave a low yield of the desired product **2a** (entries 4 and 5). Next, various copper salts were screened in the homocoupling reaction of **1a** (entries 6–13). Copper(I) chloride with or without molecular sieves gave a lower yield than copper(II) acetate (entries 6 and 7). On the other hand, the reaction failed to produce any desired products when copper(II) chloride was used as the mediator (entries 8 and 9).

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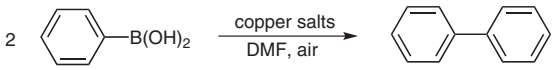
Table 1 Homocoupling of Pheylboronic Acid in Different Reaction Conditions



1a **2a**

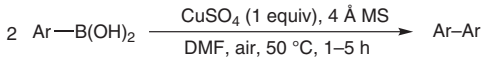
Entry	Copper salt[a]	Temp (°C)	Time (h)	Yield of **2a** (%)[b]
1	$Cu(OAc)_2$ (1 equiv)	100	1	46
2	$Cu(OAc)_2$ (0.1 equiv)	100	1	14
3	$Cu(OAc)_2$ (3 equiv)	100	1	30
4	$Cu(OAc)_2$ (1 equiv)/MS	100	1	<5
5	$Cu(OAc)_2$ (0.1 equiv)/MS	100	3	<5[c]
6	CuCl (1 equiv)	100	1	26
7	CuCl (1 equiv)/MS	100	1	26
8	$CuCl_2$ (1 equiv)	100	1	NR
9	$CuCl_2$ (1 equiv)/MS	100	1	NR
10	CuTC (1 equiv)	100	1	13
11	CuTC (1 equiv)/MS	100	1	7
12	$CuSO_4$ (1 equiv)	100	1	<5
13	$CuSO_4$ (1 equiv)/MS	100	1	62
14	$CuSO_4$ (1 equiv)/MS	50	1	80
15	$CuSO_4$ (3 equiv)/MS	50	1	81
16	$CuSO_4$ (1 equiv)/MS	r.t.	6	66

[a] CuTC = copper(I) thiophene-2-carboxylate.
[b] Yield refers to the isolated pure product **2a**. The conversion for all entries was 100% except for entries 8 and 9. NR = no reaction.
[c] The reaction was carried out under an oxygen atmosphere.

CuTC[11] afforded a low amount of product **2a** in addition to an inseparable mixture of unknown products (entries 10 and 11). When the reaction was carried out using copper(II) sulfate for one hour at 100 °C, biaryl (**2a**) was obtained in a very low yield (entry 12). The presence of molecular sieves 4Å (MS 4Å) significantly influenced the homocoupling reaction **1a** with one equivalent of copper(II) sulfate (62% isolated yield **2a**, entry 13). When the reaction was carried out using one equivalent of copper(II) sulfate for one hour at 50 °C, biaryl (**2a**) was obtained in 80% isolated yield (entry 14). When **1a** was reacted with one equivalent of copper(I) sulfate for six hours at room temperature, yield of **2a** did not increase and was formed only in 66% (isolated yield, entry 16). It should be noted that the homocoupling of **1a** in tetrahydrofuran or dichloromethane as a solvent gave lower yields of 10 and 7%, respectively. According to these results, the homocoupling of various arylboronic acids was examined using copper(II) sulfate in *N*,*N*-dimethylformamide at 50 °C in the presence of molecular sieves in air.

Under the above optimized conditions, arylboronic acids were employed in the homocoupling reactions. The obtained results are summarized in Table 2. The homocoupling of different *para*-substituted arylboronic acids gave corresponding biaryls in good to excellent yields (entries 2-5). *meta*-Substituted arylboronic acids produced the corresponding products **2f**[12] and **2g**[5a] in moderate to good yields (entries 6 and 7). Arylboronic acid bearing a weakly coordinating nitro group could also be used to obtain the desired product **2g** in 58% yield (entry 7). It is also possible to carry out this homocoupling for *ortho*-substituted arylboronic acids. The homocoupling of different *ortho*-substituted arylboronic acids gave corresponding biaryls in moderate to good yields (entries 8–10).

Table 2 $CuSO_4$-Promoted Homocoupling of Various Arylboronic Acids



1 **2**

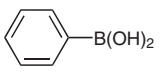
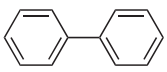
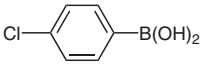
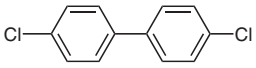
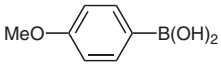
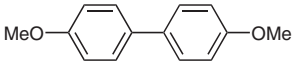
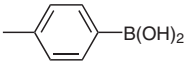
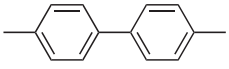
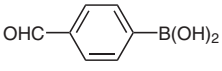
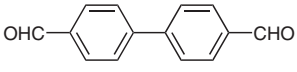
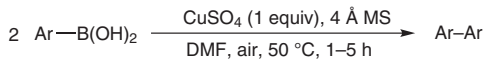
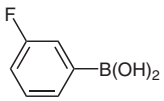
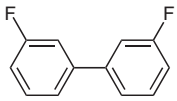
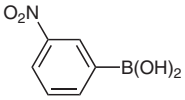
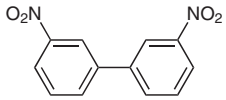
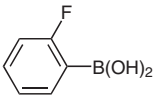
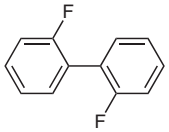
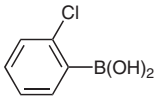
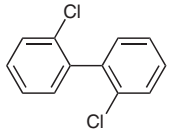
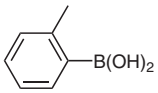
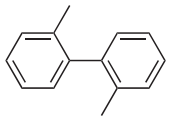
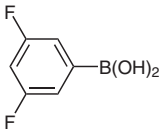
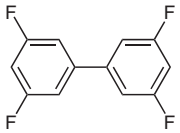
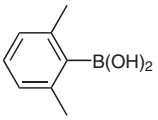
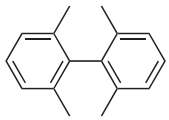
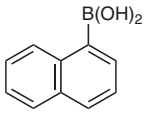
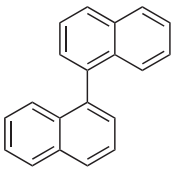
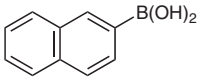
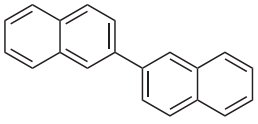
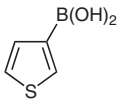
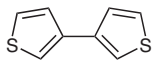
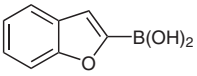
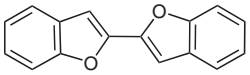
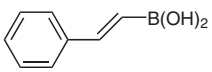
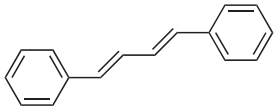
Entry	Compound **1**	Product **2**		Time (h)	Yield (%)[a]
1		**2a**		1	80
2		**2b**		1	91
3		**2c**		1	90
4		**2d**		1	71
5		**2e**		3	77

Table 2 $CuSO_4$-Promoted Homocoupling of Various Arylboronic Acids (continued)



1 **2**

Entry	Compound **1**	Product **2**	Time (h)	Yield (%)[a]
6		**2f** 	1	70
7		**2g** 	1	58
8		**2h** 	4	63
9		**2i** 	4	68
10		**2j** 	4	88
11		**2k** 	1	67
12		**2l** 	–	–[b]
13		**2m** 	5	47
14		**2n** 	2	63
15		**2o** 	1	56
16		**2p** 	3	35
17		**2q** 	5	40

[a] Yields refers to the isolated pure products after short column chromatography. When the yields were low, the corresponding arenes were obtained together with biaryls.
[b] No homocoupling products were obtained after 24 h at 50 °C.

Whereas 3,5-difluorophenylboronic acid provided the corresponding biaryl **2k**[13] in 67% yield (entry 12), sterically hindered 2,6-dimethylphenylboronic acid gave unknown products without formation of the corresponding biaryl **2l**,[14] due to the steric congestion around the arylboronic acid (entry 13). This method was also applied to homocoupling of 1- and 2-naphthylboronic acid. 2-Naphthylboronic acid gave the corresponding binaphthyl (**2n**)[15] in 63% yield; however, 1-naphthylboronic acid produced corresponding product **2m**[15] in lower yield 47%, which is possibly due to the steric effect (entries 13 and 14).

The homocoupling of thiophen-3-ylboronic acid, as an heteroarylboronic acid, gave 56% desired product **2o**[5a](entry 15), whereas with benzofuran-2-ylboronic acid around 35% yield of the desired product **2p**[5a] was obtained (entry 16). Finally, the reaction of *trans*-2-phenylvinylboronic acid, as a styrylboronic acid, in the presence of copper(II) sulfate and molecular sieves gave **2q**[16] in 40% yield (entry 17). Thus, the conditions reported herein tolerate homocoupling reaction of a wide variety of arylboronic acids. Of particular note is the homocoupling reaction of *ortho*-substituted arylboronic acids in moderate to good yields.

Notice that the color of the reaction mixture changes as the reaction progresses. In most cases, the color of the reaction mixture is white, which when heated at 50 °C turns to yellow after five minutes. This color smoothly changes to greenish-blue as the reaction progresses (Figure 1).

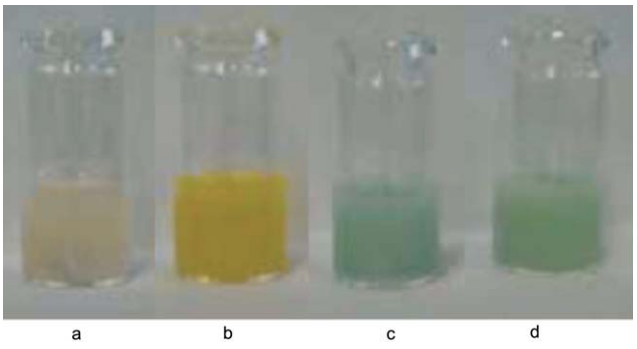
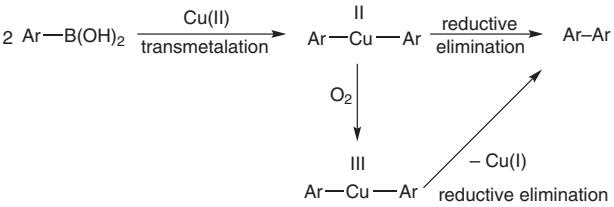


Figure 1 Color of the reaction mixture of **1k** using $CuSO_4$: a) before the reaction, b) after 5 min at 50 °C, c) after 10 min at 50 °C, d) after 1 h at 50 °C.

A plausible mechanism is outlined in Scheme 2 for copper(II) sulfate mediated homocoupling reaction of arylboronic acids. We believe that the present process proceeded via the transmetalation of arylboronic acids with copper(II) giving an arylcopper intermediate, which undergoes subsequent reductive elimination to the symmetrical biaryl compound. Alternatively, and most probably, the arylcopper intermediate undergoes air oxidation to yield higher-oxidation-state copper(III), which undergoes more efficient reductive elimination (Scheme 2).[10]

In summary, we have developed a simple and practical method for the synthesis of symmetrical biaryl compounds. Through a homocoupling reaction of arylboronic



Scheme 2

acids using very inexpensive and air stable copper(II) sulfate in the presence of molecular sieves, symmetrical biaryl compounds can be synthesized in moderate to good yields. This method is useful, in comparison with previously reported methods, because it allows for the use of readily available inexpensive copper sources.

In addition, by carrying out the reaction in air, biaryl formation was achieved at 50 °C without any additives such as base, ligand, or oxidant. With this novel feature, the present copper system is superior to the known unlike palladium catalyst protocols and the method has particular relevance to the fields of drug discovery and manufacturing.

All melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. Mass spectra were recorded on a VG Auto Spec using electron impact ionization (EI) techniques. NMR spectra were obtained on a Bruker DPX400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz). The chemical shift data for each signal on ^{1}H NMR are recorded relative to residual $CHCl_3$ (δ = 7.26 ppm). For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are recorded relative to the $CDCl_3$ resonance (δ = 77.0 ppm). Analytical TLC was carried out with Merck plates precoated with silica gel 60 F_{254} (0.25 mm thick). Unless otherwise noted, all arylboronic acids are commercially available.

Homocoupling of Arylboronic Acids 1 to Biaryls 2; General Procedure

To a mixture of $CuSO_4$ (80 mg, 0.5 mmol) and MS 4Å (0.5 g) in DMF (2 mL) was added the arylboronic acid **1** (1 mmol), and the resulting mixture was stirred at 50 °C for 1–5 h (Table 2). During this time the color changed from white to greenish-blue. The product was purified by immediate flash chromatography (silica gel 60, particle size 230–400 mesh, hexanes) to afford biaryls **2a**–**q** in 35–91% isolated yields (for compounds **2c**, **2e**, and **2g** a mixture of hexane–EtOAc, 10:1 was used as an eluent) (Table 2). All products are known,[5a,b,9,12–18] and most of them are commercially available.

Biphenyl (2a)

White solid; mp 68–71 °C (Lit.[5a] mp 67–69 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (4 H, d, *J* = 7.1 Hz), 7.44 (4 H, d, *J* = 7.8 Hz), 7.36 (2 H, d, *J* = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2, 128.7, 127.2, 127.1.

EI-MS: *m*/*z* = 154 (M^+).

4,4′-Dichlorobiphenyl (2b)

White solid; mp 146–148 °C (Lit.[5a] mp 149–154 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (4 H, d, *J* = 8.6 Hz), 7.40 (4 H, d, *J* = 8.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 133.8, 129.1, 128.3.

EI-MS: *m*/*z* = 222 (M^+).

4,4′-Dimethoxybiphenyl (2c)
White solid; mp 173–175 °C (Lit.[5a] mp 173–174 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (4 H, d, *J* = 8.8 Hz), 6.96 (4 H, d, *J* = 8.8 Hz), 3.84 (6 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 133.6, 127.8, 114.3, 55.4.

EI-MS: *m*/*z* = 214 (M^+).

4,4′-Dimethylbiphenyl (2d)
White solid; mp 118–120 °C (Lit.[5a] mp 122–124 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (4 H, d, *J* = 7.9 Hz), 7.24 (4 H, d, *J* = 7.9 Hz), 2.39 (6 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 136.8, 129.5, 126.9, 21.2.

EI-MS: *m*/*z* = 182 (M^+).

4,4′-Biphenyldicarboxyaldehyde (2e)
White solid; mp 150–151 °C (Lit.[5a] mp 148–150 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.0 (2 H, s), 8.01 (4 H, d, *J* = 8.3 Hz), 7.81 (4 H, d, *J* = 8.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 145.6, 136.0, 130.4, 128.1.

EI-MS: *m*/*z* = 210 (M^+).

3,3′-Difluorobiphenyl (2f)
Colorless liquid.[12]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.34 (4 H, m), 7.28–7.24 (2 H, m), 7.09–7.04 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2 (d, *J* = 244.6 Hz), 142.3 (dd, *J* = 7.7, 2.2 Hz), 130.5 (d, *J* = 8.0 Hz), 122.8 (d, *J* = 2.9 Hz), 114.8 (d, *J* = 21.0 Hz), 114.1 (d, *J* = 21.0 Hz).

EI-MS: *m*/*z* = 190 (M^+).

3,3′-Dinitrobiphenyl (2g)
Yellow solid; mp 201–202 °C (Lit.[5a] mp 201–202 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (2H, t, *J* = 1.9 Hz), 8.31 (2H, dq, *J* = 8.2, 1.9 Hz), 7.98 (2H, dq, *J* = 8.2, 1.9 Hz), 7.72 (2H, t, *J* = 8.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 140.3, 133.1, 130.3, 123.3, 122.1.

EI-MS: *m*/*z* = 244 (M^+).

2,2′-Difluorobiphenyl (2h)
White solid; mp 118–120 °C (Lit.[18] mp 117–118 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.35 (4 H, m), 7.24–7.15 (4 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (dd, *J* = 248.6, 13.1 Hz), 131.7 (t, *J* = 2.6 Hz), 129.9 (t, *J* = 4.0 Hz), 124.2 (d, *J* = 2.2 Hz), 115.9 (d, *J* = 6.4 Hz), 115.6 (d, *J* = 6.4 Hz).

EI-MS: *m*/*z* = 190 (M^+).

3,3′-Dichlorobiphenyl (2i)
White solid; mp 59–62 °C (Lit.[5a] mp 57–58 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.47 (2 H, m), 7.37–7.33 (4 H, m), 7.30–7.26 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 133.6, 131.3, 129.6, 129.2, 126.7.

EI-MS: *m*/*z* = 222 (M^+).

2,2′-Dimethylbiphenyl (2j)
Colorless liquid.[5a]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.20 (6 H, m), 7.10 (2 H, d, *J* = 7.0 Hz), 2.05 (6 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 135.9, 129.9, 129.4, 127.2, 125.6, 19.9.

EI-MS: *m*/*z* = 182 (M^+).

3,3′-5,5′-Tetrafluorobiphenyl (2k)
White solid; mp 82–84 °C (Lit.[13] mp 85.5–87 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09–7.03 (4 H, m), 6.89 (2 H, tt, *J* = 8.8, 2.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2 (dd, *J* = 247.6, 13.1 Hz), 142.2 (t, *J* = 11.9 Hz), 110.3 (d, *J* = 26.2 Hz), 103.4 (t, *J* = 25.4 Hz).

EI-MS: *m*/*z* = 226 (M^+).

1,1′-Binaphthyl (2m)
White solid; 142–144 °C (Lit.[15] mp 141–143 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.94 (4 H, m), 7.62–7.58 (2 H, m), 7.51–7.46 (4 H, m), 7.42–7.37 (2 H, m), 7.27–7.24 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 133.6, 132.9, 128.2, 128.0, 127.9, 126.6, 125.9, 125.7, 125.5.

EI-MS: *m*/*z* = 254 (M^+).

2,2′-Binaphthyl (2n)
White solid; mp 184–186 °C (Lit.[15] mp 188 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (2 H, s), 7.97–7.92 (4 H, m), 7.90–7.87 (4 H, m), 7.54–7.47 (4 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 133.8, 132.8, 128.6, 128.4, 127.8, 126.5, 126.2, 126.1, 125.8.

EI-MS: *m*/*z* = 254 (M^+).

3,3′-Bithiophene (2o)
White solid; mp 130–131 °C (Lit.[17] mp 130 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (2 H, d, *J* = 1.4 Hz,), 7.38–7.33 (4 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.3, 126.5, 126.2, 119.9.

EI-MS: *m*/*z* = 166 (M^+).

2,2′-Bibenzofuran (2p)
White solid; mp 197–199 °C (Lit.[5a] mp 198–200 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.63 (2 H, m), 7.56–7.54 (2 H, m), 7.35 (2 H, dt, *J* = 7.3, 1.4 Hz), 7.28 (2 H, dt, *J* = 7.3, 0.9 Hz), 7.18 (2 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 147.8, 128.6, 125.2, 123.5, 121.5, 111.4, 103.8.

EI-MS: *m*/*z* = 234 (M^+).

(1*E*,3*E*)-1,4-Diphenylbuta-1,3-diene (2q)
White solid; mp 150–152 °C (Lit.[16] mp 151–152 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.45 (4 H, m), 7.36–7.32 (4 H, m), 7.28–7.24 (2 H, m), 6.99–6.93 (2 H, m), 6.72–6.66 (2 H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 132.9, 129.3, 128.7, 127.6, 126.5.

EI-MS: *m*/*z* = 206 (M^+).

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