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Note

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Organic solvent-free, Pd(II)-salan complex-catalyzed synthesis of biaryls via Suzuki-Miyaura cross-coupling in water and air.

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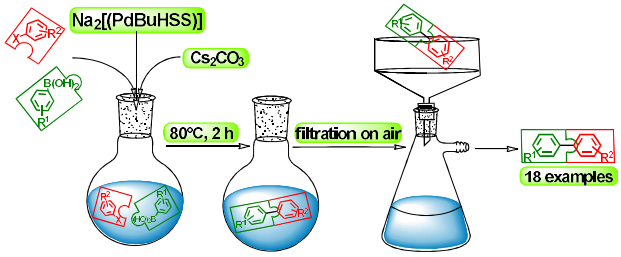
Abstract Graphic



Abstract

With use of a Pd(II)-sulfosalan complex as a water-soluble catalyst we have developed an efficient synthesis of biaryls via Suzuki-Miyaura cross-coupling in water under aerobic conditions. The water-insoluble target molecules were isolated by simple filtration in analytical purity after washing with 0.01 M aqueous HCl (20 examples). In most cases, palladium contamination was below 5 ppm considered acceptable for active pharmaceutical ingredients. The established method is scalable, reproducible, and provides biaryl products in isolated yields up to 91%.

Water plays an increasingly important role in development of environment-friendly methods of chemical synthesis.[1-4] In addition to its other advantageous features, water is relatively cheap, non-toxic and non-flammable so its use makes processes safer at reduced cost. Often the reactions are carried out in aqueous-organic biphasic mixtures or in mixed aqueous-organic homogeneous solutions. In other cases the chemical transformations can be performed in water, however, workup is based on extraction with organic solvents. In order to achieve most of the environmental benefits of an aqueous procedure, organic solvents should be avoided all along the synthesis pathway. For homogeneously catalyzed reactions in aqueous media water-soluble catalysts are required. Favorably, due to the exponential development of aqueous organometallic catalysis hydrosoluble catalysts are now available for most kind of reactions, including hydrogenation, hydroformylation, hydration, hydrocyanation, oxidation, C-C couplings, and many others.[1-4]

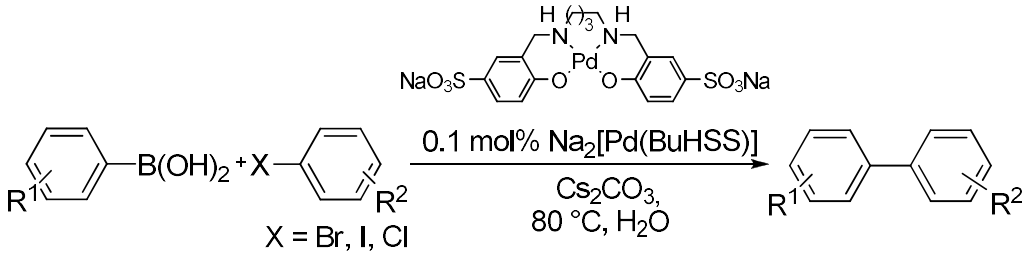
Transition-metal complex catalyzed C-C cross-coupling reactions have utmost importance in modern organic chemistry since they allow synthesis of complex molecules from relatively simple starting materials.[5-8] An important class of such reactions is the Suzuki-Miyaura cross-coupling of aryl halides and organoboronic acids. Numerous efforts have been made in order to apply water as solvent in this reaction, too, however, in most cases organic co-solvents had to be used, furthermore, isolation and purification of products often required organic solvents for extraction and column chromatography.[9-16] The use of a water-soluble Pd(II)-sulfonated triphenylphosphine complex to catalyze this process in aqueous reaction medium was first studied by Casalnuovo and Calabrese in 1990.[17] Main efforts of later research were focused on application of various water-soluble Pd-tertiary phosphine,[18-21] palladacycle,[22, 23] and Pd-N-heterocyclic carbene[24, 25] (Pd-NHC) complex catalysts in aqueous solution, often with microwave irradiation.[15] Procedures with ligandless Pd-catalysts (nanoparticles) with high catalytic activities were also developed.[26]

Water-insolubility of several biaryls leads to precipitation/crystallization of the products from aqueous reaction mixtures allowing isolation of target molecules by simple filtration.[27, 28] This approach helped also in keeping Pd-contamination low, even down to ppb level.[28] For example, with use of palladacycle catalysts, Eppinger and co-workers synthesized a large group of variously functionalized biaryls without the use of organic solvents.[29, 30] Lipshutz et al. applied various designer surfactants to facilitate Suzuki-Miyaura cross-couplings inside the core of micelles that allowed to perform the synthesis in water.[31-34] In several cases no organic solvent was added to the reaction mixture or applied during workup and the analytically pure products were isolated from the aqueous media by filtration.

Various metal complexes of Schiff-base ligands, including salens, bis(salicylaldiminato)-1,2-ethanediamines, are widely used in coordination chemistry and catalysis.[35-41] However, it has been reported ion several cases that in aqueous solvents they are degraded under catalytic conditions due to the hydrolytic instability of the C=N bond.[38,42-44] Hydrogenation of salens gives rise to structurally more flexible and hydrolytically stable *N*,*N*'-bis(2-hydroxybenzyl)alkylenediamines (salans) which, however, have been scarcely used as ligands in homogeneous catalysis.[42] Recently we have synthesized a series of Pd(II)-complexes with various water-soluble salan ligands (obtained via sulfonation of the respective tetrahydrosalens).[45, 46] Here we report a procedure capitalizing on the outstanding catalytic activity of a water-soluble Pd(II)-complex of *N*,*N*'-bis(2-hydroxy-5-sulfonatobenzyl)-1,4-diaminobutane, Na_2[Pd(BuHSS)] which allows performing Suzuki-Miyaura cross-couplings in water under aerobic conditions (Scheme 1). We have also synthesized similar catalysts with various bridges from 1,2-diamines derived from ethane, 1,2-diphenylethane, cyclohexane, and benzene. These Pd(II)-salan type complexes catalyzed the reaction of phenylboronic acid and bromobenzene with isolated yields between 13% and 93%; in the particular case of

Na_2[Pd(BuHSS)] with 82%; this catalyst was chosen for extensive scrutiny for its easy synthesis and for affording high yields.

Scheme 1. Suzuki-Miyaura cross-coupling of arylboronic acids and aryl halides with Na_2[Pd(BuHSS)] catalyst

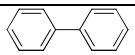
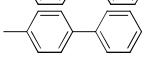
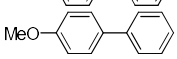
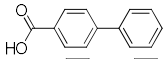
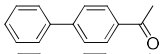
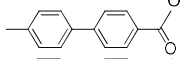
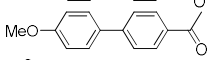
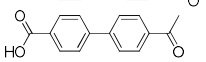
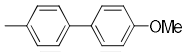
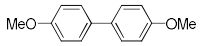
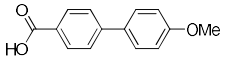
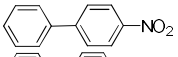
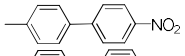
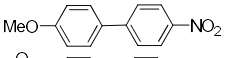
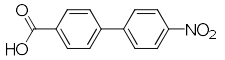
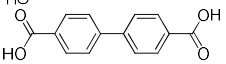
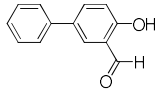
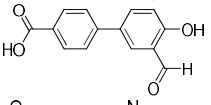
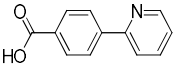
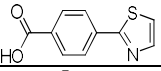


Cross-coupling of phenylboronic acids and aryl halides proceeded smoothly in air in the presence of bases at 80 °C with 0.1 mol% catalyst. Cs_2CO_3 and Et_3N promoted the reaction with the same efficiency, however, for environmental reasons and to avoid contamination of the products with any organics Cs_2CO_3 was used in the syntheses (Na_2CO_3 could be used, too, but see Table 3). Aryl halides showed the expected reactivity with conversions (GC) in 1 h: iodobenzene 100%, bromobenzene 71%, chlorobenzene 17%.

There has been an enduring interest in the activation of aryl chlorides in aqueous systems under phosphine-free conditions. Shahnaz et al.[36] recently reported a simple palladium Schiff-base catalyst that produced good-to-excellent yields of Suzuki-Miyaura cross-cross-coupling products using aryl chlorides in aqueous conditions. Note that employing our Pd(II)-salan catalyst high conversion, 82%, was achieved with chlorobenzene, too, when the reaction time was increased to 6 h. This results in a turnover number (TON) of 820, which is an order of magnitude higher than that obtained by Shahnaz et al. (TON = 12-96) in the cross-coupling of various aryl chlorides at 100 °C, underscoring the remarkable activity of Pd(II)-salan complexes.

Limited solubility of biaryls in water allowed to develop an efficient synthetic method including a simple workup. Suzuki-Miyaura cross-couplings were performed in water as solvent. After the desired time the reaction mixture was diluted with water, the solid product was isolated by filtration, washed thoroughly with 0.01 M HCl and dried to constant weight. The resulting compounds were characterized by their melting points, ^{1}H and ^{13}C NMR spectra. Previously unreported solid-state structures of five biaryls were determined by single crystal X-ray diffraction (see SI). For 20 examples, isolated yields and Pd-contents are shown in Table 1.

Table 1. Synthesis of biaryls with Suzuki-Miyaura cross-coupling of arylboronic acids and aryl halides in water under aerobic conditions catalyzed by the water-soluble Pd(II) complex Na_2[Pd(BuHSS)].

Entry/ Compound No.	Product	Isolated yield,%	Pd (ppm)
1[a]		82 (72[j])	8
2[a]		84	3
3[a]		77	1
4[a]		89	14
5[b]		78 (74[j])	<1
6[b]		70	1
7[b]		82	<1
8[b]		91	4
9[c]		59	1
10[c]		74	9
11[c]		90	2
12[d]		79 (82[e], 89[j])	4
13[d]		70 (72[e])	3
14[d]		70	2
15[d]		90 (89[e])	21
16[f]		92	4
17[g]		79	1
18[g]		91	3
19[h]		78	n.d.
20[i]		90	n.d.

Conditions: 5.0×10^{-7} mol Na_2[Pd(BuHSS)], 5.0×10^{-4} mol aryl halide, 7.5×10^{-4} mol boronic acid, 5.0×10^{-4} mol Cs_2CO_3, 3 mL water, 80 °C, 2 h.
[a]bromobenzene, [b]4-bromoacetophenone, [c]4-bromoanisole, [d]4-nitro-1-iodobenzene, [e]4-nitro-1-bromobenzene, Pd-content n.d., [f]4-bromobenzoic acid, [g]5-bromo-salicylaldehyde, [h]2-iodopyridine, [i]2-bromo-1,3-thiazole. [j]All quantities multiplied by 10, except V(H_2O)=15 mL; 80 °C, [a-g]2 h, [h,i]4 h.

Most biaryls were obtained in reactions of aryl bromides and/or aryl iodides; under conditions of Table 1 they reacted equally well. In general, the use of aryl halides as well as of arylboronic acids with either electron donating or electron withdrawing substituents resulted in high conversions with only 0.1 mol% of the Na_2[Pd(BuHSS)] catalyst. Due to the method of workup, the isolated yields depend also on the aqueous solubility of the respective biaryl so they may not reflect fine differences in reactivity. Organic solvents were not used at all, neither for the cross-coupling reaction nor for workup, furthermore, the products were not recrystallized before recording ^{1}H and ^{13}C NMR spectra (Supporting Information). It is of utmost importance, that despite the simple method of isolation, Pd-content of the products was found very low, in 14 cases below the 5 ppm limit[47] established for active pharmaceutical intermediates (API-s). Accordingly, thorough washing with 0.01 M aqueous HCl is highly effective for removal of palladium from the solid products. Only in cases of the 4-carboxy-1,1'-biphenyl (**4**) and 4-carboxy-4'-nitro-1,1'-biphenyl (**15**) were >10 ppm Pd-contents determined. Although formation of Pd-carboxylate complexes cannot be ruled out, **4** and **5** form water-insoluble dimers with strong H-bonds and their relatively high Pd-content may be due to inclusion of some of the reaction mixture during fast precipitation. The above synthesis can be scaled up easily; three biaryls (**1**, **5**, **12**; Table 1) were synthesized starting with 5 mmol of the respective aryl halides; quantities of other reactants were multiplied accordingly (but V(H_2O) = 15 mL). Small or no changes of the isolated yields (%) were observed (Table 1) so the synthesis proved applicable for several gram quantities of target molecules. In general, in terms of catalytic activity our findings are compare well to those obtained with similar N/O coordinated Pd complexes with the additional benefit of no use of organic solvents.[36-38, 40, 41]

Sodium tetraphenylborate and potassium phenyltrifluoroborate can serve as convenient phenyl sources in Suzuki-Miyaura cross-couplings.[26] Although their use limits the modularity of such processes to syntheses of biaryls with (at least) one unsubstituted phenyl ring, the water-

solubility of $Na[BPh_4]$ and $K[BPhF_3]$ leads to high reaction rates with hydrosoluble catalysts especially in cases (at temperatures) when the aryl halide is soluble in the aqueous reaction mixture (Table 2). For example, with $Na[BPh_4]$ poorly water-soluble 4-bromoacetophenone underwent only 5% conversion at room temperature while it reacted with 100% conversion at 80 °C. In contrast, 4-bromobenzoic acid afforded 4-carboxy-1,1'-biphenyl (**4**) with 100% conversion in short reaction times both at 80 °C (15 min) and at room temperature (30 min). Such high reaction rates demonstrate the efficiency of catalysis in purely aqueous reaction mixtures under proper conditions. Again, the water-insoluble products could be obtained in analytical purity after washing with 0.01 M HCl.

Table 2. Phenylboronic acid, Na-tetraphenylborate and K-phenyltrifluoroborate as phenyl-group donors in Suzuki-Miyaura cross-couplings catalyzed by $Na_2[Pd(BuHSS)]$ in water

	Conversion (%)		
	$PhB(OH)_2$[a]	$Na[BPh_4]$[b]	$K[PhBF_3]$[a]
bromobenzene	72	88	78
4-bromoanisole	28	73	47
4-bromoacetophenone	94	100	97
4-bromobenzoic acid	100	100	100
4-nitro-1-bromobenzene	55	100	80
4-iodotoluene	60	90	10

Conditions: 5.0×10^{-7} mol $Na_2[Pd(BuHSS)]$, 7.5×10^{-4} mol phenylboronic acid/Na-tetraphenylborate/K-phenyltrifluoro-borate, 5.0×10^{-4} mol aryl halide, 5.0×10^{-4} base ([a]Cs_2CO_3, [b]Na_2CO_3), 3 mL water, 80 °C, 1 h.

Table 3 shows the results of catalyst recycling experiments. At the end of each cycle the undiluted reaction mixture was filtered carefully to collect as much of the aqueous phase as possible, which was then supplied with new batches of 4-bromoacetophenone, phenylboronic acid and base. At the end of each cycle the yield was determined according to the mass of the isolated product. These results demonstrate that in the presence of Cs_2CO_3 the catalyst can be

recycled three times with no loss of activity. However, while the product biaryl precipitated nicely in the first three cycles, there was no precipitation in the 4th cycle. After extraction of the reaction mixture with $CHCl_3$, gas chromatography showed only 45% conversion of the aryl halide. When Na_2CO_3 was used as base, we observed a rapid loss of the catalyst's activity from cycle to cycle. Inorganic byproducts, such as bromide accumulate in the recycled catalyst solution (concentration of Br^- is 0.67 M at the end of the 4th cycle) and its complex formation with Pd(II) may be responsible for catalyst deactivation. In summary, while originally both Cs_2CO_3 and Na_2CO_3 are very effective as bases in the cross-coupling reaction, Na_2[Pd(BuHSS)] looses its activity much faster in Na_2CO_3 solutions than in the presence of Cs_2CO_3. In addition, the precipitates from Na_2CO_3-containing reaction mixtures are more sticky and can be collected by filtration with difficulties. Concerning the physical state of the catalyst during the reaction, a drop of conversion from 95% to 76% was observed in the presence of Hg (cross-coupling of 4-bromoacetophenone with phenylboronic acid, conditions as in Table 1, except 1 h reaction time). This may refer to participation of nanoparticles in catalysis, however, this question was not investigated in detail.

Table 3. Recycling of the Na_2[Pd(BuHSS)] catalyst in Suzuki-Miyaura cross-coupling of phenylboronic acid and 4-bromoacetophenone

No. of cycles	Yield (%)	
	Base: Cs_2CO_3	Base: Na_2CO_3
1	76	89
2	86	73[a]
3	81	15[a]
4	45[a]	0[a]

Conditions: 5.0×10^{-7} mol Na_2[Pd(BuHSS)], 7.5×10^{-4} mol phenylboronic acid, 5.0×10^{-4} mol 4-bromoacetophenone, 5.0×10^{-4} base, 3 mL water, 80 °C, 1 h each cycle. [a]No biaryl precipitates, conversions determined by GC.

In conclusion, a green method was developed for synthesis of biaryls by Suzuki-Miyaura cross-coupling of aryl halides and arylboronic acids in water in the presence of an inorganic base (Cs_2CO_3). An easily available, highly active salan-type water-soluble catalyst, Na_2[Pd(BuHSS)] (BuHSS = *N*,*N*'-bis(2-hydroxy-5-sulfonatobenzyl)-1,4-diaminobutane) was employed in 0.1 mol% and the various biaryls were isolated in high yields. No organic solvents were used in synthesis or workup; the water-insoluble products were isolated from the reaction mixture by simple filtration in high purity and –in most cases– with Pd-content below 5 ppm.

Experimental part

Na_2[Pd(BuHSS)] was synthesized as described in reference 45. All other reagents were commercial products of Sigma-Aldrich and were used as received. Solvents were obtained from Molar. Deionized water was used throughout. Melting points were determined on a Büchi melting point apparatus Model B-540 and are uncorrected. Pd contents were determined with use of an Agilent MP-AES spectrometer (biaryls were dissolved in *aqua regia* with the aid of an MLS 1200 microwave digestion equipment).

^{1}H- and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 360 MHz instrument at room temperature and were referenced to tetramethylsilane (TMS), as well as to ^{1}H or ^{13}C resonances of residual non-deuterated solvents in CH_3OD, $CDCl_3$ and dmso-d_6 (99.9% isotopic purity, Sigma-Aldrich), respectively (CH_3OH: ^{1}H NMR δ=3.34 ppm, ^{13}C{^{1}H} NMR δ=49.05 ppm; $CHCl_3$: ^{1}H NMR δ=7.24 ppm, ^{13}C{^{1}H} NMR δ=77.23 ppm; dmso: ^{1}H NMR δ=2.50 ppm, ^{13}C{^{1}H} NMR δ=39.51 ppm).

Single crystal X-Ray analyses were performed with the use of a Bruker D8 Venture system.

Conversions of aryl halides were determined by gas chromatography.

Typical procedure of Suzuki-Miyaura cross-couplings: Synthesis of biphenyl in reaction of iodobenzene and phenylboronic acid.

Bromobenzene (52 μL; 0.5 mmol), phenylboronic acid (92 mg; 0.75 mmol), and Cs_2CO_3 (163 mg, 0.5 mmol) were placed into a Schlenk tube or a screw cap vial. 300 μL of an aqueous solution of Na_2[Pd(BuHSS)] (1.7 mM; 0.51 μmol – synthesized according to reference 60) was added followed by addition of 2.7 mL distilled water. The reaction vesssel was closed with a septum and the reaction mixture was magnetically stirred at 80 °C (water bath) in air for 2 hours. After cooling to room temperature it was diluted with 15 mL water facilitating precipitation of the product. The white solid was collected on a filter, washed thoroughly with 0.01 M aqueous HCl and dried in air to constant weight. Yield: 63 mg (82%), mp: 74-75 °C (lit. mp: 69-73 °C).[48]

The following products were obtained by the above general method with 0.5mmol aryl halide (for reaction times and composition of the reaction mixtures see Table 1):

Biphenyl (**1**) from phenylboronic acid and bromobenzene: Yield 63 mg (82%), white solid, mp: 74-75 °C, after recrystallization from $CHCl_3$, mp: 70-71 °C (lit. mp: 69-73 °C).[48]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 7.62 (d, 4H, J_{HH} = 7.2 Hz), 7.46 (t, 4H, J_{HH} = 7.3 Hz), 7.37 (t, 2H, J_{HH} = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6): δ = 140.1, 128.8, 127.3, 126.5 ppm.

4-Methylbiphenyl (**2**) from *p*-tolylboronic acid and bromobenzene: Yield 71 mg (84%), white solid, mp: 49-50 °C (lit. mp: 49-50 °C).[49, 50]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 7.93-7.19 (m, 9H), 2.51 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$): δ = 141.4, 138.6, 137.2, 129.7, 128.9, 127.2, 21.3 ppm.

4-Methoxybiphenyl (**3**) from 4-methoxyphenylboronic acid and bromobenzene: Yield 71 mg (77%), white solid, mp: 91-92 °C (lit. mp: 91-92 °C).[50]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 7.51- 7.60 (m, 4H), 7.43 (t, 2H, J_{HH} = 7.8 Hz), 7.31 (t, 1H, J_{HH} = 7.0 Hz), 6.99 (d, 2H, J_{HH} = 8.7 Hz), 3.85 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$): δ =159.3, 141.0, 133.9, 128.9, 128.3, 126.9, 126.8, 114.3, 55.5 ppm.

4-Methoxybiphenyl (**3**) from phenylboronic acid and 4-bromoanisole: Yield 68 mg (74%), white solid, mp: 91-92 °C (lit. mp: 91-92 °C).[50]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 7.50-7.68 (m, 4H), 7.41 (t, 2H, J_{HH} = 7.8 Hz,, 7.29 (t, 1H, J_{HH} = 7.0 Hz), 6.97 (d, 2H, J_{HH} = 8.5 Hz), 3.84 (s, 3H) ppm. ^{13}C{^{1}H}NMR (90 MHz, 298 K, $CDCl_3$): δ = 159.3, 141.0, 133.9, 128.9, 128.3, 126.9, 126.8, 114.3, 55.5 ppm.

4-Carboxybiphenyl (**4**) from 4-carboxyphenylboronic acid and bromobenzene: Yield 88 mg (89%), white solid, mp: 228-230 °C (lit. mp: 228-230 °C).[51]

^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 12.97, 8.02 (d, J_{HH}= 7.8 Hz, 2H), 7.80 (d, J_{HH} = 7.8 Hz, 2H), 7.72 (d, J_{HH}= 8.1 Hz, 2H), 7.55-7.46 (m, 2H), 7.45-7.34 (m, 1H) ppm. ^{13}C{^{1}H} NMR (90 MHz, dmso-d_6): δ= 167.1, 144.3, 139.0, 129.9, 129.6, 129.1, 128.3, 127.0, 126.8 ppm.

4-Carboxybiphenyl (**4**) from phenylboronic acid and 4-bromobenzoic acid: Yield 83 mg (85%), white solid, mp: 228-230 °C (lit. mp: 228-230 °C).[51]

^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 12.96 (s), 8.02 (d, J_{HH} = 7.8 Hz, 2H), 7.79 (d, J_{HH} = 7.6 Hz, 2H), 7.73 (d, J_{HH} = 8.0 Hz, 2H), 7.56-7.46 (m, 2H), 7.46-7.34 (m,1H) ppm. ^{13}C{^{1}H} NMR (90 MHz, dmso-d_6): δ =167.3, 144.4, 139.1, 130.1, 129.7, 129.2, 128.4, 127.1, 126.9 ppm.

4-Acetylbiphenyl (**5**) from phenylboronic acid and 4-bromoacetophenone: Yield 76 mg (78%), white solid, mp: 127-128 °C (lit. mp: 126-128 °C).[52]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 8.02 (d, J_{HH} = 8.3 Hz, 2 H), 7.67 (d, J_{HH} = 8.0 Hz, 2 H), 7.61 (d, J_{HH} = 7.5 Hz, 2H), 7.53-7,34 (m, 3H), 2.63 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$): δ = 198.0, 146.1, 140.2, 136.2, 129.2 (d), 128.5, 127.5 (d), 26.69 ppm.

4-Methyl-4'-Acetylbiphenyl (**6**) from *p*-tolylboronic acid and 4-bromoacetophenone: Yield 74 mg (70%), white solid, mp: 127-128 °C (lit. mp: 126-128 °C).[52]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 8.03 (d, J_{HH} = 8.5 Hz, 2H), 7.68 (d, J_{HH} = 7.8 Hz, 2H), 7.54 (d, J_{HH} = 7.7 Hz, 2H), 7.29 (d, J = 7.7 Hz, 2H), 2.64 (s, 3H), 2.41 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$): δ = 197.9, 145.9, 138.4. 137.2, 135.8, 129.9, 129,1 127.3, 127.2, 26.8, 21.4 ppm.

4-Methoxy-4'-Acetylbiphenyl (**7**) from 4-methoxyphenylboronic acid and 4-bromoacetophenone: Yield 93 mg (82%), white solid, mp: 161-162 °C (lit. mp: 156.5-157.0 °C[53] and 156-158 °C[54]).

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 7.98 (d, J_{HH} = 8.9 Hz, 2H), 7.61 (d, J_{HH} = 8.8 Hz, 2H), 7.55 (d, J_{HH} = 8.9 Hz, 2H), 6.97 (d, J_{HH} = 8.8 Hz, 2H), 3.83 (s, 3H), 2.60 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$): δ = 197.9, 160.1, 145.5, 135.4, 132.3, 129.1, 128.5, 126.7, 114.6, 55.5, 26.8 ppm.

4-Carboxy-4'-Acetylbiphenyl (**8**) from 4-carboxyphenylboronic acid and 4-bromoacetophenone: Yield 109 mg (91%), white solid, mp >300 °C (lit. mp: 309-310 °C).[20]

^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 12.86 (bs), 8.16-7.99 (m, 4H), 7.96-7.81 (m, 4H), 2.62 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6): δ = 197.5, 167.0, 143.3, 142.9, 136.2, 130.5, 130.0, 128.9, 127.2, 127.1, 26.8 ppm.

4-Methyl-4′-Methoxybiphenyl (**9**) from *p*-tolylboronic acid and 4-bromoanisole:**:** Yield 58 mg (59%), white solid, mp: 112-113 °C; (lit. mp 111-112 °C).[50]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$) δ = 7.60-7.40 (md, 4H), 7.33-7.11 (md, 2H), 6.98 (md, J_{HH} = 8.7 Hz, 2H), 3.86 (s, 3H), 2.40 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$): δ = 159.0, 138.0, 136.4, 133.8, 129.5, 128.0, 126.7, 114.2, 55.4, 21.1 ppm.

4-Methoxy-4′-Methoxybiphenyl (**10**) from 4-methoxyphenylboronic acid and 4-bromoanisole: Yield 78 mg (74%), white solid, mp: 186-187 °C (lit. mp: 180-182 °C).[55]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 7.5 (d, J_{HH} = 8.8 Hz, 4H), 6.98 (d, J_{HH} = 8.8 Hz, 4H), 3.86 (s, 6H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$) δ = 158.9, 133.7, 127.9, 114.4, 55.5 ppm.

4-Carboxy-4′-Methoxybiphenyl (**11**) from 4-carboxyphenylboronic acid and 4-bromoanisole: Yield 96 mg (90%), white solid, mp: 250-253 °C (lit. mp: 250.0-251.7 °C).[56]

^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 8.04-7.94 (m, 2H), 7.81-7.63 (m, 4H), 7.15-6.96 (m, 2 H), 3.81 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6): δ =167.2, 159.6, 143.9, 131.2, 129.9, 128.8, 128.1, 126.1, 114.5, 55.2 ppm.

4-Carboxy-4′-Methoxybiphenyl (**11**) from 4-methoxyphenylboronic acid and 4-bromobenzoic acid: Yield 95 mg (89%), white solid, mp: 250-253 °C (lit mp: 250.0-251.7 °C).[56]

^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 8.04-7.94 (m, 2H), 7.81-7.63 (m, 4H), 7.15-6.96 (m, 2H), 3.81 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6): δ =167.2, 159.6, 143.9, 131.2, 129.9, 128.8, 128.1, 126.1, 114.5, 55.2 ppm.

4-Nitrobiphenyl (**12**) from phenylboronic acid and 4-nitro-1-iodobenzene: Yield 79 mg (79%), light yellow solid, mp: 118-119 °C. (lit. mp: 114.5-115.0 °C).[53]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 8.26 (d, J_{HH}= 8.4 Hz, 2H), 7.70 (d, J_{HH} = 8.6 Hz, 2H), 7.61 (d, J_{HH} = 7.0 Hz, 2H), 7.53–7.38 (m, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$) δ = 147.8, 147.3, 138.9, 129.3, 129.1, 127.9, 127.6, 124.3 ppm.

4-Methyl-4'-Nitrobiphenyl (**13**) from *p*-tolylboronic acid and 4-nitro-1-iodobenzene: Yield 75 mg (70%), yellow solid, mp: 142-143 °C (lit. mp: 142.5-143.0 °C).[53]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 8.28 (d, J_{HH} = 8.3 Hz, 2H), 7.72 (d, J_{HH} = 8.8 Hz, 2H), 7.54 (d, J_{HH} = 7.9 Hz, 2H), 7.32 (d, J_{HH} = 8.8 Hz, 2H), 2.44 (s, 3H) ppm. ^{13}C{^{1}H}NMR (90 MHz, 298 K, $CDCl_3$): δ = 147.6, 146.9, 139.2, 135.9, 130.0, 127.4(d), 124.2, 21.3 ppm.

4-Methoxy-4'-Nitrobiphenyl (**14**) from 4-methoxyphenylboronic acid and 4-nitro-1-iodobenzene: Yield 81 mg (70%), yellow solid, mp: 104-105 °C (lit. mp: 104-105 °C).[57]

^{1}H NMR (360 MHz, 298 K, $CDCl_3$): δ = 8.25 (d, J_{HH}= 8.8 Hz, 2 H), 7.67 (d, J_{HH} = 8.8 Hz, 2H), 7.58 (d, J_{HH} = 8.8 Hz, 2H), 7.00 (d, J_{HH} = 9.0 Hz, 2H), 3.86 (s, 3H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, $CDCl_3$): δ= 160.7, 147.3, 146.8, 131.4, 128.9, 127.4, 124.4, 114.9, 55.7 ppm.

4-Carboxy-4'-Nitrobiphenyl (**15**) from 4-carboxyphenylboronic acid and 4-nitro-1-iodobenzene: Yield 110 mg (90%), yellow solid, mp: >300 °C (lit. mp: 340 °C). [58, 59]

^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 13.27(s), 8.32 (d, J_{HH}=8.0, 2H), 8.15-7.96 (dd, J_{HH} = 8.0, 4H*)* 7.89 (d, J_{HH}=7.5, 2H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6) δ = 167.1, 147.1, 145.6, 141.2, 132.4, 130.0, 128.2, 127.3, 124.1 ppm.

4,4'-Dicarboxybiphenyl (**16**) from 4-carboxyphenylboronic acid and 4-bromobenzoic acid: Yield 111 mg (92%), white solid, mp >300 °C (lit. mp: 309-310 °C).[20]

^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 13.03 (2H), 8.05 (d, J_{HH} = 6.9 Hz, 4H), 7.86 (d, J_{HH} = 7.3 Hz, 4H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6) δ = 167.5, 143.6, 130.8, 130.5, 107.6 ppm.

4-Hydroxy-3-formylbiphenyl (**17**) from phenylboronic acid and 5-bromosalicylaldehyde: Yield 79 mg (79%), yellow solid, mp: 107-108 °C (lit. mp: 95-97 °C)[60]

^{1}H NMR (360 MHz, 298 K, dmso-d_6) δ = 10.87 (s, 1H,), 10.32 (s, 1H), 7.97-7.88 (m, 1H), 7.88-7.76 (m, 1H) 7.67-7.54 (m, 2H), 7.52-7.38 (bt, 2H), 7.37-7.26 (m, 1H), 7.10 (d, J = 9.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (90 MHz, dmso-d_6): δ = 191.7, 160.3, 138.9, 134.6, 131.5, 129.0, 127.1, 127.0, 126.1, 122.5, 118.0 ppm.

3'-Formyl-4'-hydroxy[1,1'-biphenyl]-4-carboxylic acid (**18**)[61] from 4-carboxyphenylboronic acid and 5-bromosalicylaldehyde: Yield 111 mg (91%), yellow solid, mp >300 °C (mp not available in reference 61).

^{1}H NMR (360 MHz, 298 K, dmso-d_6) δ = 12.03 (br), 10.27 (s, 1H), 8.04-7.89 (m, 3H), 7.88-7.82 (m, 1H), 7.75-7.65 (m, 2H), 7.09-7.06 (m, 1H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6) δ = 191.3, 167.2, 161.0, 143.2, 142.9, 134.7, 130.1, 130.0, 127.1, 126.0, 122.6, 118.2 ppm.

4-(Pyridin-2-yl)benzoic acid (**19**)[62] from 4-carboxyphenylboronic acid and 2-iodopyridine: Yield 72 mg (78%), white solid, mp: 230-232 °C (lit. mp: 238-240 °C) [63]. ^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 13.03 (s, 1H), 8.69-8.79 (m, 1H), 8.17-8.37 (m, 2H), 8.02-8.15 (m, 2H), 7.85-8.00 (q, 2H), 7.38-7.49 (m, 1H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, CH_3OD): δ= 169.4, 157.5, 150.3, 144.3, 139.4, 134.5, 132.6, 131.3, 129.7, 128.2, 124.6, 123.2 ppm.

4-(1,3-Thiazol-2-yl)benzoic acid (**20**)[64] from 4-carboxyphenylboronic acid and 2-bromothiazole: Yield 92 mg (90%), white solid, mp: 230-231 °C (lit. mp: 235-237 °C)[65]. ^{1}H NMR (360 MHz, 298 K, dmso-d_6): δ = 12.94 (s, 1H), 8.11-8.44 (m, 2H), 7.77-8.08 (m, 4H) ppm. ^{13}C{^{1}H} NMR (90 MHz, 298 K, dmso-d_6): δ= 167.3, 141.6, 133.9, 133.3, 131.8, 128.1, 127.9 ppm.

Supporting Information

^{1}H and ^{13}C NMR spectra of biaryls **1**-**20**; CIF files and X-ray structures of compounds **8**, **11**, **15**, **17**, **18**.

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