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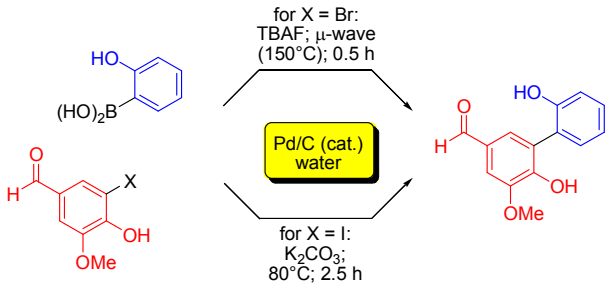
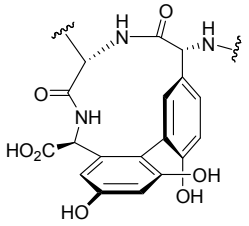


Abstract: User-friendly protocols for the protecting group free synthesis of 2,2'-biphenols via Suzuki-Miyaura coupling of *ortho*-halo phenols and *ortho* phenol boronic acid are presented. The reactions proceed in water in the presence of simple additives such as K_2CO_3, KOH, KF or TBAF and with commercially available Pd/C as precatalyst. Expensive or laboriously synthesized ligands or other additives are not required. In the case of bromo phenols, efficient rate acceleration and short reaction times were accomplished by microwave irradiation.

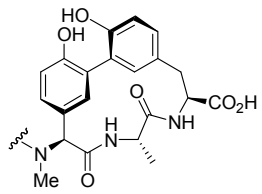
Introduction

The 2,2'-biphenol structure is a common motif in many natural products and in drugs or drug candidates.[1] Probably the most prominent example is vancomycin, often used as a last option antibiotic for the treatment of *staphylococcus aureus* infections.[2,3] More recently discovered were the arylomycins,[4,5] which share a 2,2'-biphenol bridged peptide structure and a high antibiotic activity with vancomycin. Structurally less complex are biphenols isolated from extracts of *magnolia officinalis*, such as magnolol,[6] which shows high activity as an anti-oxidant, or the diarylheptanoid acerogenin E, which has been isolated from the tree *acer nikoense* (**Figure 1**).[7]

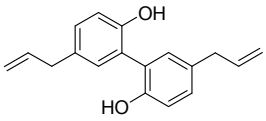
Figure 1. Selected natural products with a 2,2'-biphenol structure



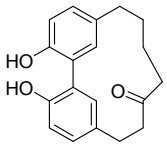
Biphenol unit of vancomycin



Biphenol unit of arylomycin A_2



Magnolol



Acerogenin E

Not surprisingly, the synthesis of 2,2'-biphenols has, like the synthesis of biaryls in general,[1,8] attracted considerable attention. Very recent contributions to this field are methods using radical cyclizations of acetal tethered phenols[9] or an oxidative copper mediated intramolecular biaryl formation, which was applied to the synthesis of strictinin.[10] Probably the most commonly used methods for biaryl formation are Pd-catalyzed cross coupling reactions, in particular the Suzuki-Miyaura coupling. In most cases when this reaction has been applied to the synthesis of 2,2'-biphenols, either one or both coupling partners are OH-protected, e. g. as a methyl ether[11,12] or as a MOM-ether.[13] Although scattered literature precedence for the successful cleavage of aryl methyl ethers in the late stages of total syntheses of target

molecules as complex as arylomycin[12] and vancomycin[11] exists, the harsh conditions normally required for this transformation, in particular the use of strong Lewis acids in large excess at elevated temperatures,[14] often in combination with strongly nucleophilic reagents such as thiols, makes the use of this protecting group impractical in many cases. A straightforward solution to avoid the difficulties associated with the deprotection of aryl methyl ethers would be the use of unprotected *ortho*-halo phenols and *ortho*-phenol boronic acids as coupling partners in the Suzuki-Miyaura reaction. This option has been pursued for surprisingly few examples. In most of these cases, $Pd(PPh_3)_4$[15-17] or $Pd(OAc)_2$[18] have been used as precatalysts in mixtures of organic solvents and water. The isolated yields of 2,2'-biphenols obtained via this fully protecting group-free route rarely exceed 50%.

A catalyst system which has attracted considerable attention for coupling and cross coupling reactions is palladium on charcoal.[19-24] It is not only conveniently available, but due to its heterogeneous nature easily removable from the reaction mixture. This is potentially very useful, because the catalyst might be recycled and reused, and the contamination of the reaction products with metal residues can be reduced. Examples for the successful application of Pd/C as a catalyst for Suzuki-Miyaura reactions of various halo phenols in aqueous media have been published by Hirao et al.[25] and by Freundlich and Landis.[26] We are, however, not aware of any reports describing the completely protecting group-free synthesis of 2,2'-biphenols via heterogeneously catalyzed Suzuki-Miyaura couplings. In this paper we report our results on the optimization and scope of cross coupling reactions between unprotected *ortho*-halo phenols and *ortho*-phenol boronic acids, catalyzed by easily removable Pd/C.

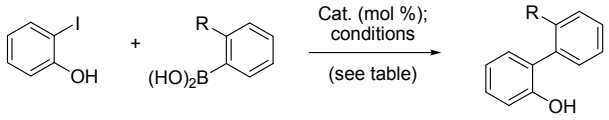
Results and discussion

Optimization of conditions for *ortho*-iodo phenols. In the initial experiments, equimolar amounts of 2-iodo phenol (**1a**) and 2-phenol boronic acid (**2a**) were subjected to cross coupling conditions, using $Pd(OAc)_2$ as a precatalyst in different solvents or solvent mixtures

commonly used for the Suzuki-Miyaura reaction (Table 1). The reaction mixtures were analyzed with GC-MS, revealing that neither DMSO/water nor DMF at a reaction temperature of 130°C in the presence of Na_2CO_3 or K_3PO_4 as a base gave complete conversion (Table 1, entries 1 and 3). Inspired by a literature report describing a beneficial effect of $Cu(OAc)_2$ as a co-catalyst[18] we tested this additive, unfortunately to no avail (entry 2). Similarly disappointing was the addition of $P(o\text{-}tol)_3$ as a ligand in DMF in the presence of K_3PO_4 as a base (entry 4). Interestingly, with $[\eta^3\text{-}(C_3H_5)PdCl]_2$ as a precatalyst (entry 5) full conversion was accomplished at 130°C. We then tested Pd/C under the conditions previously established by Hirao et al. for the coupling of non-phenolic aryl boronic acids,[25] i.e. using water as a solvent and K_2CO_3 as a base at ambient temperature (entry 6). Although some product formation could be observed, substantial amounts of the starting materials did not react. The reason for this incomplete conversion might be a significantly reduced reactivity of the 2-phenol boronic acid (**2a**) used by us, compared to the phenyl boronic acid (**2b**) used by Hirao et al., or a lower activity of the Pd/C used in our experiments. The reproducibility of transformations catalyzed by Pd/C depends to a certain extent on the method used for its preparation and in particular on the oxidation state of the Pd and its distribution on the solid support.[19,22] Both factors are difficult to control for commercial catalysts, as their exact nature is sometimes insufficiently documented by the supplier. To test the activity of the commercial Pd/C used by us, we decided to reproduce the coupling of **1a** and **2b** under the conditions previously described by Hirao et al., with the only exception being a somewhat higher catalyst loading of 2 mol % (entry 7). The conversion to the cross coupling product was quantitative at ambient temperature and **3ab** could be isolated in nearly quantitative yield. This observation suggests that the unsatisfactory result obtained for 2-phenol boronic acid (**2a**) is not caused by an insufficiently active catalyst, but more likely by a reduced reactivity of **2a** compared to **2b**. Therefore, the experiment listed in entry 6 was repeated at elevated temperature. Gratifyingly, an almost quantitative conversion to **3aa**, which was isolated in 91% yield, was observed at

80°C (entry 8). In the next step, the catalyst loading was lowered to 1 mol %, resulting again in a virtually quantitative conversion and a similar isolated yield under otherwise identical conditions (entry 9). Reducing the amount of catalyst further to 0.25 mol % resulted in incomplete conversion after 16 h, but the yield of isolated product **3aa** was still acceptable (entry 10). To ensure that the high conversions under these conditions do not originate from a coincidentally particularly well suited Pd/C catalyst, two other commercial samples were tested under the standard conditions (entries 11 and 12). In both cases high conversions and isolated yields of 2,2'-biphenol (**3aa**) could be obtained by using 2 mol % of the catalyst, which suggests that the established protocol should be robust and reliable irrespective of the batch of Pd/C catalyst chosen. Although for optimization purposes a standardized reaction time of 16 hours was applied, we observed complete conversion at 80°C already after 2.5 hours, if 2 mol % of catalyst were used. For these reasons, the reaction time was lowered to 2.5 hours in all further experiments.

Table 1. Optimization of conditions for Suzuki-Miyaura coupling of 2-iodophenol and 2-phenol boronic acid



1a **2a** (R = OH) **2b** (R = H) **3aa** (R = OH) **3ab** (R = H)

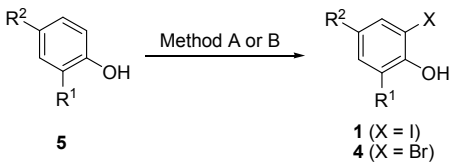
entry	**2**	Catalyst (mol %)	Cond.[a)]	Additive (equiv.)	T	Complete conversion?	Product (yield)[b)]
1	**2a**	$Pd(OAc)_2$ (5)	**A**	--	130°C	No	**3aa** (n. d.)
2	**2a**	$Pd(OAc)_2$ (5)	**A**	$Cu(OAc)_2$ (0.05)	130°C	No	**3aa** (n. d.)
3	**2a**	$Pd(OAc)_2$ (5)	**B**	--	130°C	No	**3aa** (n. d.)

4	**2a**	$Pd(OAc)_2$ (5)	**B**	$P(o\text{-}tol)_3$ (0.30)	130°C	No	**3aa** (n. d.)
5	**2a**	$[\eta^3\text{-}(C_3H_5)PdCl]_2$ (2.5)	**B**	--	130°C	No	**3aa** (n. d.)
6	**2a**	Pd/C (2)[c,d]	**C**	--	20°C	No	**3aa** (n. d.)
7	**2b**	Pd/C (2) [c,d]	**C**	--	20°C	Yes	**3ab** (97%)
8	**2a**	Pd/C (2) [c,d]	**C**	--	80°C	Yes[g]	**3aa** (91%)
9	**2a**	Pd/C (1) [c,d]	**C**	--	80°C	Yes	**3aa** (92%)
10	**2a**	Pd/C (0.25) [c,d]	**C**	--	80°C	Yes	**3aa** (82%)
11	**2a**	Pd/C (2) [c,e]	**C**	--	80°C	Yes[g]	**3aa** (98%)
12	**2a**	Pd/C (2) [c,f]	**C**	--	80°C	Yes[g]	**3aa** (84%)

[a]Reaction conditions: **A**: DMSO/water (1 : 1), Na_2CO_3 (4 equiv.), 16 h; **B**: DMF, K_3PO_4 (4 equiv.), 16 h; **C**: Water; K_2CO_3 (4 equiv.), 16 h. [b]n. d.: not determined. [c]Catalyst contains 10 wt-% Pd. [d]Catalyst batch 1. [e]Catalyst batch 2. [f]Catalyst batch 3; contains 50 wt-% water. [g]Conversion complete after 2.5 h.

Synthesis of *ortho*-halo phenols 1 and 4. To investigate the scope of the Suzuki-Miyaura reaction of *ortho*-halo phenols and *ortho*-phenol boronic acid further, various iodo phenols **1** and bromo phenols **4** were synthesized by halogenation of the corresponding phenols **5** using either the corresponding N-halo succinimides NIS or NBS[27] or, in the case of **1g**, ICl. The results are summarized in Table 2.

Table 2. Synthesis of *ortho*-halo phenols **1** and **4**



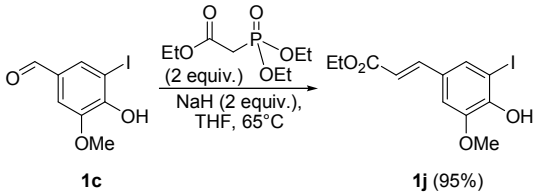
5 **1** (X = I) **4** (X = Br)

entry	**5**	R^1	R^2	Method (reagent, equiv.)[a)]	product	Yield
1	**5b**	H	Me	A (NIS, 1.05)	**1b**	81%
2	**5d**	H	CHO	A (NIS, 1.05)	**1d**	24%
3	**5e**	COMe	Me	A (NIS, 1.10)	**1e**	91%
4	**5f**	CHO	Br	A (NIS, 1.10)	**1f**	19%
5	**5g**	OMe	NO_2	B (ICl, 1.00)	**1g**	75%
6	**5b**	H	Me	A (NBS, 1.05)	**4b**	72%
7	**5d**	H	CHO	A (NBS, 1.05)	**4d**	76%

[a)]Method A: CH_3CN (5 mL/mmol), p-TSA (1 equiv.), NIS or NBS (1.05 equiv. – 1.10 equiv.), 20°C, 16 h. Method B: methanol/water (5 : 1, 4 mL/mmol), ICl (1 equiv.), 20°C, 16 h.

The 4-bromo- and 4-chloro-2-iodo phenols **1h**,**i** were synthesized similarly from 2-iodo phenol **1a** using *N*-chloro succinimide (NCS) or *N*-bromo succinimide (NBS), respectively. Precursor **1j** was synthesized from **1c** using a Horner-Wadsworth-Emons olefination with triethyl phosphonoacetate and NaH as a base (**Scheme 1**).

Scheme 1. Synthesis of precursor **1j**

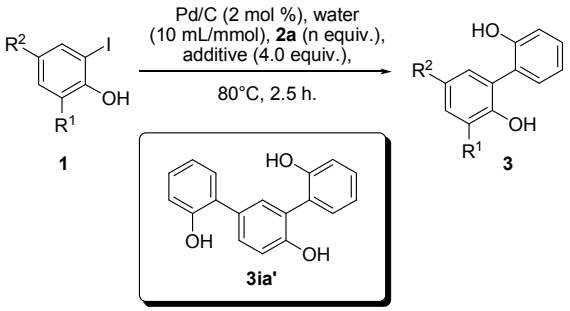


1c **1j** (95%)

Scope of the cross coupling reaction with *ortho*-iodo phenols. Various ortho iodo phenols **1a-j** were coupled with ortho phenol boronic acid (**2a**) under the optimized conditions (Table 3). In most cases high yields were obtained with equimolar amounts of the coupling partners. In the other cases, yields could be improved by increasing the amount of boronic acid to 1.3

equivalents. A notable exception is the 4-bromo derivative **3ia**, which was formed in high chemoselectivity but only moderate yield with 1.0 equivalents of **2a** (entry 10). Control of chemo- and site selectivity in Suzuki-Miyaura reactions has been accomplished by using leaving groups with different reactivity or by using identical leaving groups at electronically distinct sites of the aromatic core, even if the coupling partner was present in excess.[28] Therefore, we tested whether the bromo substituent can be effectively discriminated even in the presence of 1.3 equiv. of **2a** (entry 11), but the isolated yield of **3ia** could only be slightly improved to 52%. Under these conditions, 14% of the triphenol **3ia'** resulting from dual cross coupling were isolated as a byproduct. We tried to synthesize **3ia'** selectively by further increasing the amount of **2a** to 2.6 equivalents and the amount of base to 6 equivalents. This led to an increased yield of 43% of **3ia'**, but the mono coupling product **3ia** was still the major product with 50% isolated yield (entry 12). When ester **1j** was coupled with **2a** under standard conditions, ester hydrolysis occurred and the free carboxylic acid **3ka** was isolated in 68% yield (entry 13). The ester cleavage could be avoided by replacing K_2CO_3 by KF, and the expected product **3ja** was obtained in high yield (entry 14).

Table 3. Scope of Pd/C catalyzed Suzuki coupling of ortho iodo phenols **1**



entry	**1**	R^1	R^2	equiv. of **2a**	Additive	**3**	Yield
1	**1a**	H	H	1.0	K_2CO_3	**3aa**	98%

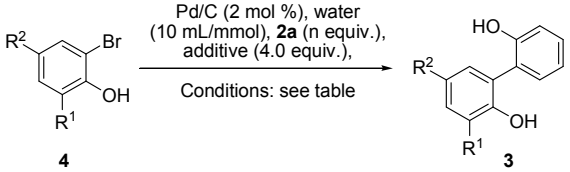
2	**1b**	H	Me	1.0	K_2CO_3	**3ba**	98%
3	**1c**	OMe	CHO	1.0	K_2CO_3	**3ca**	80%
4	**1c**	OMe	CHO	1.3	K_2CO_3	**3ca**	98%
5	**1d**	H	CHO	1.3	K_2CO_3	**3da**	86%
6	**1e**	COMe	Me	1.3	K_2CO_3	**3ea**	85%
7	**1f**	CHO	Br	1.0	K_2CO_3	**3fa**	65%
8	**1g**	OMe	NO_2	1.0	K_2CO_3	**3ga**	91%
9	**1h**	H	Cl	1.3	K_2CO_3	**3ha**	88%
10	**1i**	H	Br	1.0	K_2CO_3	**3ia**	47%
11	**1i**	H	Br	1.3	K_2CO_3	**3ia**	52%[a)]
12	**1i**	H	Br	2.6	K_2CO_3	**3ia**	50%[b)]
13	**1j**	OMe	$CH=CHCO_2Et$	1.0	K_2CO_3	**3ka**	68%[c)]
14	**1j**	OMe	$CH=CHCO_2Et$	1.0	KF	**3ja**	90%[d)]

[a)]Isolated along with 14% of triphenol **3ia'** resulting from double cross coupling. [b)]6.0 Equiv. of K_2CO_3 were used; product isolated along with 43% of **3ia'**. [c)]Hydrolysis of the ester group occurs under standard conditions, R^2 in **3ka** is $CH=CHCO_2H$. [d)]Addition of ethanol (4 mL/mmol) is required to dissolve substrate.

Optimization of conditions for *ortho*-bromo phenols. Aryl bromides are more stable and considerably cheaper than the corresponding aryl iodides, but on the other hand significantly less reactive in most Pd-catalyzed transformations. We investigated the Suzuki coupling of ortho bromo phenols **4b**,**c**,**d** with 2-phenol boronic acid (**2a**) under the standard conditions used for the corresponding iodides, but at a slightly higher temperature of 100°C. Under these conditions, the *para*-methyl derivative **3ba** was obtained in a moderate yield of 55% (Table 4, entry 1). Replacing K_2CO_3 by Cs_2CO_3 (entry 2) did not lead to an improvement. Under thermal conditions, the reaction failed completely with the electron deficient *para*-formyl

compound **4d**. Previous reports describing a rate accelerating effect of microwave irradiation[29-31] on Suzuki-Miyaura reactions in aqueous media[26] prompted us to investigate these conditions for the coupling of **4d** and **2a**, using otherwise identical conditions (entry 4). Gratifyingly, the expected product **3da** could be isolated in reaction times of 0.5 h in good yield and high selectivity. Unfortunately, these conditions do not appear to be generally applicable, as the microwave induced cross coupling of bromo phenol **4c** and boronic acid **2a** furnished the desired biphenol **3ca** only in poor selectivity, along with substantial amounts of 2,2'-biphenol resulting from oxidative homocoupling[32-34] of **2a**, and unreacted bromo phenol **4c** (entry 5).

Table 4. Optimization of conditions for Suzuki-Miyaura coupling of 2-bromo phenols **4**

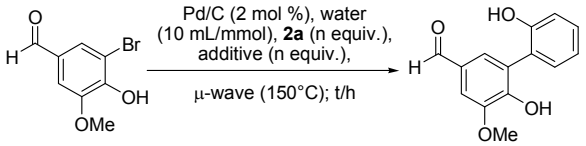


entry	**4**	R^1	R^2	**2a** (equiv.)	Additive	Conditions	Product	Yield
1	**4b**	H	Me	1.0	K_2CO_3	100°C; 16 h	**3ba**	55%
2	**4b**	H	Me	1.0	Cs_2CO_3	100°C; 16 h	**3ba**	53%
3	**4d**	H	CHO	1.0	K_2CO_3	100°C; 16 h	**3da**	--[a)]
4	**4d**	H	CHO	1.3	K_2CO_3	μ-wave irradiation at 150°C; 0.5 h	**3da**	78%
5	**4c**	OMe	CHO	1.3	K_2CO_3	μ-wave irradiation at 150°C; 0.5 h	**3ca**	--[b)]

[a)]No conversion. [b)]Substantial amount of oxidative boronic acid homocoupling product formed.

To suppress the undesired oxidative homocoupling, alternative additives were tested for the reaction of **4c** and **2a** under microwave irradiation (Table 5). These experiments revealed that synthetically useful yields and selectivities could be obtained with KF (entry 1), TBAF (entry 2) and KOH (entry 4) as additives, whereas only minor amounts of product were formed when Cs_2CO_3 (entry 3) or NaOTf (entry 6) were added to the reaction mixture. We also tested a combination of the Lewis acid BF_3•MeOH and K_2CO_3 as a base (entry 5), unfortunately to no avail. This additive combination was inspired by previous reports describing the mutual activation of coupling partners through formation of borates, which are presumably activated by additional Lewis acid.[35] Further attempts to improve the yield involved varying the amount of boronic acid and the equivalents of KOH, unfortunately to no avail (entries 7 – 11). Even by using the threefold amount of catalyst, no further improvement could be achieved (entry 12).

Table 5. Alternative additives for microwave induced cross coupling of **4c**



entry	**2a** (equiv.)	Additive (equiv.)	t/h	Conversion complete?	Yield[a)]
1	1.3	KF (4.0)	0.5	Yes	43%
2	1.3	TBAF (4.0)	0.5	Yes	63%
3	1.3	Cs_2CO_3 (4.0)	0.5	No	n. d.
4	1.3	KOH (4.0)	0.5	Yes	65%
5	1.3	BF_3•MeOH (2.0); K_2CO_3 (4.0)	0.5	No	n. d.
6	1.3	NaOTf (4.0)	0.5	No	n. d.

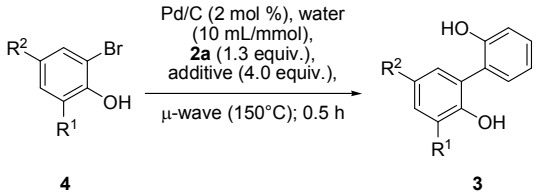
7	1.05	KOH (6.0)	1.0	No	19%
8	1.3	KOH (6.0)	1.0	No	43%
9	1.5	KOH (6.0)	1.0	No	46%
10	1.5	KOH (2.0)	1.0	No	46%
11	1.5	KOH (4.0)	1.0	No	65%
12[b)]	1.5	KOH (4.0)	1.0	No	65%

[a)]n. d.: not determined. [b)]Reaction performed with 6 mol % of Pd/C.

From these experiments we concluded that increasing the amount of catalyst beyond 2 mol % and the amount of boronic acid beyond 1.3 equivalents has no beneficial effect on the conversion of less reactive aryl bromides. With respect to the amount of base used, 4.0 equivalents of KOH appears to be the optimum, as both increasing and decreasing the equivalents of base leads to significantly lower yields. In addition to KOH, KF and TBAF are also suitable rate enhancing additives.

Scope of the cross coupling reaction with *ortho*-bromo phenols under microwave conditions. The optimized protocol for Suzuki-Miyaura coupling under microwave irradiation was then tested for several *ortho*-bromo phenols **4** (Table 6). In all cases, the oxidative dimerization of 2-phenol boronic acid could be efficiently suppressed, and in most cases good yields of the desired coupling products **3** were obtained by using KOH as an additive. Notable exceptions are the examples listed in entries 8 and 11, leading to products **3la** and **3na**, respectively, with hydrolyzable functional groups. In both cases, the yields could be significantly improved by using TBAF instead of KOH as an additive (entries 9 and 12). Similarly, the methyl ester **3ma** (entry 10) could also be isolated in good yield without concomitant saponification.

Table 6. Scope of microwave induced Suzuki-Miyaura couplings of *ortho*-bromo phenols **4** with *ortho*-phenol boronic acid (**2a**)



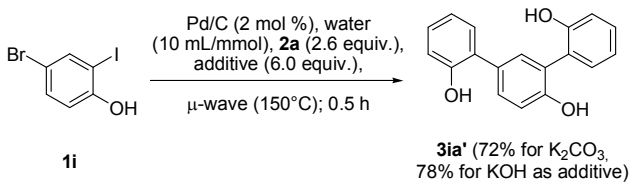
4 **3**

entry	**4**	R^1	R^2	Additive	Product **3**	Yield
1[a)]	**4a**	H	H	KOH	**3aa**	83%
2	**4b**	H	Me	KOH	**3ba**	88%
3	**4c**	OMe	CHO	KF	**3ca**	43%
4	**4c**	OMe	CHO	KOH	**3ca**	63%
5	**4c**	OMe	CHO	TBAF	**3ca**	65%
6	**4d**	H	CHO	KOH	**3da**	78%
7	**4h**	H	Cl	KOH	**3ha**	76%
8	**4l**	H	CN	KOH	**3la**	47%
9	**4l**	H	CN	TBAF	**3la**	77%
10	**4m**	H	CO_2Me	TBAF	**3ma**	78%
11	**4n**	H	NHAc	KOH	**3na**	22%
12	**4n**	H	NHAc	TBAF	**3na**	70%

a)1.0 Equiv. of boronic acid **2a** used.

Having established the beneficial effect of microwave irradiation on the rate of conversion for *ortho*-bromo phenols, we reinvestigated the dual Suzuki-Miyaura coupling of 4-bromo-2-iodo-phenol (**1i**), which was found to be unsuccessful with conventional heating (see Table 2, entry 12). The best yield obtained under optimized thermal conditions was 43% of triphenol **3ia'**, along with 50% of the bromo biphenol **3ia** (**Scheme 2**).

Scheme 2. Selective formation of triphenol **3ia'** via dual Suzuki-Miyaura coupling under microwave conditions

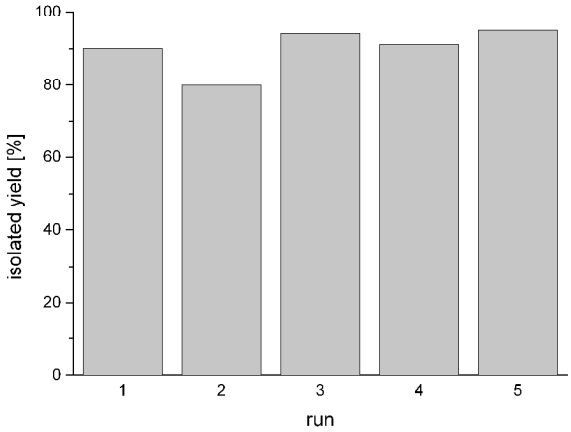


When one equivalent of **1i** was reacted with 2.6 equivalents of **2a** under the optimized conditions for microwave initiated Suzuki-Miyaura couplings in water, the triphenol **3ia'** was obtained in 72% yield, along with trace amounts of **3ia** if K_2CO_3 was used as a base. Replacing K_2CO_3 by KOH led to an even better selectivity, as no mono coupling product **3ia** could be detected in the crude reaction mixture, and a slightly increased yield of 78% of **3ia'**.

Recyclability of Pd/C used for the synthesis 2,2'-biphenols. The opportunity to recycle and reuse the catalyst is generally considered as one of the major advantages of heterogeneous catalysis. However, leaching and catalyst deactivation are sometimes serious obstacles, resulting in continuously decreasing rates of conversion and hence isolated yields of the desired product. Very recently, this issue has been investigated for Pd/C-catalyzed Suzuki-Miyaura coupling reactions of aryl bromides and aryl boronic acids.[36] In this study, 2-phenol boronic acid was not investigated. Interestingly, the authors found only trace amounts of the biaryl when the reaction was run in water, whereas water/ethanol mixtures gave up to quantitative yields. The isolated yield of coupling product and the reaction time decreased only very slightly with each run. This report prompted us to test the recyclability of the Pd/C catalyst under our conditions, because we were anxious that the chelating properties of 2,2'-biphenols, in particular under basic conditions, might lead to a substantial deactivation of the catalyst by the product. As a test reaction, the coupling of **1c** and **2a** to 2,2'-biphenol **3ca**

under the standard conditions outlined in table 3, entry 4 was chosen. To enable catalyst recovery, the workup procedure was modified: rather than aqueous extraction of the acidified mixture to isolate the product, the reaction mixture was filtered through a glas filter funnel. This procedure turned out to be inconvenient, because a considerable amount of the Pd/C was absorbed by the glas filter and could not be used in subsequent reactions. For these reasons, the catalyst was filtered off through a paper filter, which was added as a whole to the reaction mixture prepared for the next run. For the second and all following experiments the same amounts of **1c**, **2a** and base were used. The isolated yields of **3ca** for runs 1 to 5 are shown in **Figure 2**. In the first run, quantitative conversion was observed, but the isolated yield was somewhat lower compared to the aqueous workup procedure (90% vs. 98%, see table 3, entry 4), presumably due to absorption of small amounts of product on the filter. In the second run, set up immediately after recovery of the catalyst/filter paper mixture, the yield was lower than in the first run, but still acceptable. We then checked whether the performance of the recovered catalyst would be affected by storing it under air for a certain period of time before reusing it. Therefore, we waited for 16 h before starting the third run, which gave the desired product in 94% isolated yield. The yields obtained after runs 4 and 5 were virtually identical.

Figure 2. Yields of isolated **3ca** with recycled Pd/C



Conclusions

In summary, *ortho*-halo phenols and *ortho*-phenol boronic acids undergo the Suzuki-Miyaura coupling to 2,2'-biphenols in high yields and selectivities, using water as a solvent and commercially available Pd/C as a precatalyst. The protocols described herein are simple and therefore user friendly, because no elaborate precatalysts and ligands are required to obtain synthetically useful yields and short reaction times. While iodo phenols are coupled within 2.5 h in excellent yields under thermal conditions, the coupling of the analogous bromo phenols proceeds effectively under microwave irradiation within 0.5 h.

Experimental Section

General methods. All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. Deionized water was used for the cross coupling reactions. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with $CHCl_3$ (δ = 7.26 ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.0 ppm) as an internal standard. Whenever the solubility of the sample was insufficient in $CDCl_3$, one of the following solvents was used for NMR measurements: DMSO-d_6 (DMSO-d_5 as internal standard for ^{1}H NMR spectroscopy, δ = 2.50 ppm, DMSO-d_6 as internal standard for ^{13}C NMR spectroscopy, δ = 39.5 ppm); methanol-d_4 (CD_2HOD as internal standard for ^{1}H NMR spectroscopy, δ = 3.31 ppm, CD_3OD as internal standard for ^{13}C NMR spectroscopy, δ = 49.2 ppm; acetone-d_6 ($CD_2HC(O)CD_3$ as internal standard for ^{1}H NMR spectroscopy, δ = 2.05 ppm, $CD_3C(O)CD_3$ as internal standard for ^{13}C NMR spectroscopy, δ = 29.9 ppm). IR spectra were recorded as ATR-FTIR spectra. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m) or weak (w). Low- and high resolution mass spectra were obtained by EI/TOF. Microwave reactions were carried out in an Anton-Paar-monowave-300 reactor at 150°C (monowave, maximum power 850 W, temperature control

via IR-sensor, vial volume: 20 mL, pressure ca. 5 bar under these conditions). The following ortho-halo phenols were purchased and used without further purification: **1a**, **1c**, **4a**, **4c**, **4h**, **4l**, **4m**. Acetamide **4n** was synthesized as previously reported in the literature.[37]

General procedures for the synthesis of *ortho*-halo phenols 1 and 4. *General procedure A*: To a solution of the corresponding phenol **5** or **1a** (1.0 mmol) in CH_3CN (5 mL) was added p-TSA mono hydrate (1.0 mmol), followed by NIS, NBS, or NCS (1.05 mmol or 1.10 mmol) as indicated in the table. The mixture was stirred for 16 h at ambient temperature and then quenched by addition of aqueous Na_2SO_3 solution. It was acidified by addition of aqueous HCl (1 M), the organic solvent was evaporated, and the aqueous layer was extracted with MTBE. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish the halo or dihalo phenols **1** or **4**, using hexane/MTBE mixtures as eluent. *General procedure B*: To a solution of the appropriate phenol **5** (5.0 mmol) in methanol/water (20 mL, 5:1) was added ICl (810 mg, 5.0 mmol). The suspension was stirred for 16 h at ambient temperature, then quenched with an aqueous solution of Na_2SO_3 (3 mL) and acidified with aqueous HCl (1 M). The organic solvent was removed in vacuo, and the aqueous phase was extracted with MTBE. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica to furnish the 2-iodo phenol **1**, using hexane/MTBE as eluent.

2-Iodo-4-methylphenol (1b).[27] *General procedure A*: obtained from 4-methylphenol (**5b**, 540 mg, 5.0 mmol), *p*-TSA•H_2O (950 mg, 5.0 mmol), NIS (1.125 g, 5.0 mmol); yield 952 mg (4.1 mmol, 81 %). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 1H, J = 1.3 Hz), 7.04 (dd, 1H, J = 8.2, 1.5 Hz), 6.88 (d, 1H, J = 8.2 Hz), 5.21 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 138.4, 132.1, 131.0, 114.8, 85.5, 20.1; IR (ATR) ν 3480 (m), 2921

(w), 1485 (s), 1177 (s), 812 (s); HRMS (EI) calcd. for $C_7H_7OI^+$ [M^+]: 233.9542, found: 233.9538.

4-Hydroxy-3-iodobenzaldehyde (1d). *General procedure A*: obtained from 4-hydroxybenzaldehyde (**5d**, 610 mg, 5.0 mmol), *p*-TSA•H_2O (950 mg, 5.0 mmol), NIS (1.18 g, 5.25 mmol); yield 294 mg (1.2 mmol, 24%). Yellow solid, mp 108-110°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1 H), 8.22 (d, 1H, J = 1.9), 7.79 (dd, 1H, J = 8.4, 1.9 Hz), 7.1 (d, 1H, J = 8.4 Hz), 6.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 160.3, 140.9, 132.4, 131.6, 115.6, 86.2; HRMS (EI) calcd. for $C_7H_5O_2I^+$ [M^+]: 247.9334, found: 247.9322.

1-(2-Hydroxy-3-iodo-5-methylphenyl)ethanone (1e). *General procedure A*: obtained from 1-(2-hydroxy-5-methylphenyl)ethanone (**5e**, 900 mg, 6.0 mmol), *p*-TSA•H_2O (1.14 g, 6.0 mmol), NIS (1.35 g, 6.6 mmol); yield 1.51 g (5.5 mmol, 91%). Yellow solid, mp 101-102°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.95 (s, 1H), 7.80 (d, 1H, J = 2.0 Hz), 7.52 (d, 1H, J = 1.3 Hz), 2.64 (s, 3H), 2.30 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 159.2, 146.7, 131.1, 130.1, 119.4, 86.5, 26.5, 20.2; IR (ATR) ν 3017 (w), 1640(m), 1440 (m), 1247 (m), 746 (s); HRMS (EI) calcd. for $C_9H_9O_2I^+$ [M^+]: 275.9647, found: 275.9666. Anal. Calcd. for $C_9H_9O_2I$ (276.07): C, 39.2; H, 3.3. Found: C, 39.2; H, 3.1.

5-Bromo-2-hydroxy-3-iodobenzaldehyde (1f). *General procedure A*: obtained from 5-bromo-2-hydroxy-benzaldehyde (**5f**, 1.21g, 6.0 mmol), *p*-TSA•H_2O (1.14 g, 6.0 mmol), NIS (1.35 g, 6.6 mmol); yield 370 mg (1.1 mmol, 19%). Yellow solid, mp 80-81°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.72 (s, 1H), 9.72 (s, 1H), 8.10 (d, 1H, J = 2.3 Hz), 7.69 (d, 1H, J = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 159.8, 147.9, 136.0, 121.2, 112.3, 86.8; IR (ATR) ν 3191 (w), 1660 (s), 1276 (s), 1143 (s), 708; HRMS (EI) calcd. for $C_7H_4O_2{}^{79}BrI^+$ [M^+]: 325.8439, found: 325.8444. Anal. Calcd. for $C_7H_4O_2BrI$ (326.91): C, 25.7; H, 1.2. Found: C, 25.7; H, 1.1.

2-Iodo-6-methoxy-4-nitrophenol (1g). *General procedure B*: obtained from 2-methoxy-4-nitrophenol (**5g**, 843 mg, 5.0 mmol) and ICl (810 mg, 5.0 mmol); yield 1.11 g (3.8 mmol, 75%). Yellow solid, mp 142-143°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (d, 1H, J = 2.4 Hz), 7.75 (d, 1H, J = 2.4 Hz), 6.76 (s, 1H), 4.02 (s, 3H, J = 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 145.3, 127.5, 118.7, 114.1, 106.3, 57.0; IR (ATR) ν 3362 (w), 1509 (m), 1485 (m), 1237 (s), 1033 (s); HRMS (EI) calcd. for $C_7H_6O_4NI^+$ [M^+]: 294.9342, found: 294.9323.

4-Chloro-2-iodophenol (1h).[27] *General procedure A*: obtained from 2-iodophenol (**1a**, 2.20 g, 10.0 mmol), *p*-TSA•H_2O (1.90 mg, 10.0 mmol), NCS (1.46 g, 11.0 mmol) with a reaction time of 2 weeks; yield 1.68 g (6.6 mmol, 66%). Colourless solid, mp 76-77°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 2.5 Hz), 7.21 (dd, 1H, J = 8.7, 2.5 Hz), 6.92 (d, 1H, J = 8.7 Hz), 5.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 137.3, 130.3, 126.3, 115.8, 85.6; IR (ATR) ν 3281 (w), 1397 (m), 1211 (m), 1101 (m), 808 (s); HRMS (EI) calcd. for $C_6H_4O^{35}ClI^+$ [M^+]: 253.8995, found: 253.8984. Anal. Calcd. for C_6H_4OClI (254.45): C, 28.3; H, 1.6. Found: C, 28.6; H, 1.4.

4-Bromo-2-iodophenol (1i).[38] *General procedure B*: obtained from 2-iodophenol (**1a**, 1.10 g, 5 mmol), *p*-TSA•H_2O (950, 5.0 mmol), NBS (935 mg, 5.3 mmol); yield 970 mg (3.3 mmol, 65%). Colourless solid, mp 70-71°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 1H, J = 2.3 Hz), 7.36 (dd, 1H, J = 8.7, 2.3 Hz), 6.89 (d, 1H, J = 8.7 Hz), 5.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 140.0, 133.2, 116.5, 113.2, 86.2; IR (ATR) ν 3332 (s), 1402 (m), 1269 (m), 1030 (m), 808 (s); HRMS (EI) calcd. for $C_6H_4O^{79}BrI^+$ [M^+]: 297.8490, found: 297.8480. Anal. Calcd. for C_6H_4OBrI (298.90): C, 24.1; H, 1.4. Found: C, 24.1; H, 1.1.

2-Bromo-4-methylphenol (4b).[39] *General procedure A*: obtained from 4-methylphenol (**5b**, 2.16 g, 20.0 mmol), *p*-TSA•H_2O (3.79 g, 22.0 mmol), NBS (3.74 g, 21.0 mmol); yield 2.73 g (14.6 mmol, 72%). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, 1H, J = 1.3 Hz), 7.02 (dd, 1H, J = 8.3, 1.5 Hz), 6.94 (d, 1H, J = 8.3 Hz), 5.58 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 150, 132.2, 131.5, 129.8, 115.9, 109.9, 20.2; IR (ATR) ν 3502 (m), 1492 (s), 1177 (s), 1040 (m), 811 (s); HRMS (EI) calcd. for $C_7H_7O^{79}Br^+$ [M^+]: 185.9680, found: 185.9674.

3-Bromo-4-hydroxybenzaldehyde (4d).[40] *General procedure A*: obtained from 4-hydroxybenzaldehyde (**5d**, 1.22, 10.0 mmol), *p*-TSA•H_2O (1.90 g, 10.0 mmol), NBS (1.87 g, 10.5 mmol); yield 1.54 g (7.6 mmol, 76%). Colourless solid, mp 120-121°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.04 (s, 1H), 7.80 - 7.73 (m, 1H), 7.15 (d, 1H, J = 8.4 Hz), 6.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 157.8, 134.2, 131.5, 131.1, 116.7, 111.3; IR (ATR) ν 3093 (m), 1422 (s), 1274 (s), 1154 (s), 819 (s); HRMS (EI) calcd. for $C_7H_5O_2{}^{79}Br^+$ [M^+]: 199.9473, found: 199.9465.

(*E*)-Ethyl 3-(4-hydroxy-3-iodo-5-methoxyphenyl)acrylate (1j). To a solution of triethyl phosphonoacetate (8.96 g, 40.0 mmol) in dry and degassed THF (100mL) was added NaH (60 wt-% dispersion in mineral oil, 1.60 g, 40.0 mmol). The mixture was stirred at ambient temperature for 0.5 h, and aldehyde **1c** (5.56 g, 20.0 mmol) was added. The solution was heated to reflux for 5 hours, cooled to ambient temperature, and carefully acidified with aqueous HCl (1 M). The organic solvent was removed under reduced pressure, and the aqueous phase was extracted with MTBE. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica, using hexane/MTBE as eluent; yield 6.61 g (19.0 mmol, 95%). Colourless solid, mp 145-146°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 15.8 Hz), 7.49 (s, 1H) 6.97 (d, 1H, J = 1.7 Hz), 6.37 (s, 1H), 6.28 (d, 1H, J = 15.9 Hz), 4.25 (q, 2H, J = 7.1 Hz), 3.92 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 147.8, 146.3, 143.2, 131.7, 128.8, 117.1, 109.5, 81.6, 60.6, 56.5, 14.5; IR (ATR) ν 3251 (m), 1687

(s), 1629 (s) 1373 (m), 1182 (s); HRMS (EI) calcd. for $C_{12}H_{13}O_4I^+$ [M^+]: 347.9859, found: 347.9859.

General Procedure for the thermally initiated coupling of ortho-iodo phenols (1) and 2a (procedure A). The appropriate 2-iodo phenol **1** (0.75 mmol), boronic acid **2a** (104 mg, 0.75 mmol, 1.0 equiv. or 135 mg, 0.98 mmol, 1.3 equiv., as indicated in the table), K_2CO_3 (415 mg, 3.0 mmol) and Pd/C (10 wt-%, 15 mg, 2 mol %) were suspended in water (7.5 mL). The mixture was immersed for 2.5 h in an oilbath preheated at 80°C. After cooling the mixture to ambient temperature, it was carefully acidified by addition of HCl (aq., 1.0 M) and extracted three times with MTBE (50 mL for each extraction). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent to furnish the 2,2'-biphenols **3**.

General Procedure for the microwave initiated coupling of *ortho*-bromo phenols (4) and 2a (procedure B). The appropriate 2-bromo phenol **4** (0.75 mmol), boronic acid **2a** (104 mg, 0.75 mmol, 1.0 equiv. or 135 mg, 0.98 mmol, 1.3 equiv., as indicated in the table), the appropriate additive (KOH (168 mg, 3.0 mmol) or KF (174 mg, 3.0 mmol) or TBAF•$3H_2O$ (946 mg, 3.0 mmol), as indicated in the table) and Pd/C (10 wt-%, 15 mg, 2 mol %) were suspended in water (7.5 mL) in a vessel suited for microwave irradiation. The closed vessel was placed in a microwave reactor, and irradiated at 150°C for 0.5 h. After cooling the mixture to ambient temperature, it was carefully acidified by addition of HCl (aq., 1.0 M) and extracted three times with MTBE (50 mL for each extraction). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent.

Biphenyl-2-ol (3ab). *General procedure A*: obtained from **1a** (165 mg, 1.00 mmol), and **2b** (1.0 equiv.) at 20°C with a reaction time of 16 h; yield: 165 mg (0.97 mmol, 97%). Colourless solid, mp 56–57°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.38 (m, 5H), 7.31 – 7.24 (m, 2H), 7.07 – 6.97 (m, 2H), 5.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 137.2, 130.4, 129.4, 129.3, 129.2, 128.3, 128.0, 121.0, 116.0; IR (ATR) ν 3526 (m), 1434 (m), 1324 (m), 1100 (m), 753 (s); HRMS (EI) calcd. for $C_{12}H_{10}O^+$ [M^+]: 170.0732, found: 170.0738; Anal. calcd. for $C_{12}H_{10}O$ (170.21): C, 84.7; H, 5.9. Found: C, 84.3; H, 5.8.

Biphenyl-2,2'-diol (3aa). *General procedure A*: obtained from **1a** (165 mg, 0.75 mmol) and **2a** (1.0 equiv.); yield: 137 mg (0.74 mmol, 98%). *General procedure B*: obtained from **4a** (130 mg, 0.75 mmol) and **2a** (1.0 equiv.); yield: 116 mg (0.62 mmol, 83%). Colourless solid, mp 109-111°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (ddd, 2H, J = 9.2, 7.4, 1.7), 7.28 (dd, 2H, J = 6.1, 1.5), 7.11 – 7.00 (m, 4H), 5.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 131.5, 130.1, 123.9, 121.8, 116.8; IR (ATR) ν 3131 (w), 1483 (m), 1439 (m), 1225 (m), 745 (s); HRMS (EI) calcd. for $C_{12}H_{10}O_2^+$ [M^+]: 186.0681, found: 186.0672. Anal. Calcd. for $C_{12}H_{10}O_2$ (186.21): C, 77.4; H, 5.4. Found: C, 77.4; H, 5.5.

5-Methylbiphenyl-2,2'-diol (3ba). *General procedure A*: obtained from **1b** (176 mg, 0.75 mmol) and **2a** (1.0 equiv.); yield: 147 mg (0.74 mmol, 98%). *General procedure B*: obtained from **4b** (140 mg, 0.75 mmol) and **2a** (1.3 equiv.); yield: 132 mg (0.66 mmol, 88%). Colourless solid, mp 81-83°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, 1H, J = 7.6, 1.6), 7.29 (ddd, 1H, J = 7.4, 7.3, 1.4 Hz), 7.15 (d, 1H, J = 1.7), 7.13 – 7.04 (m, 2H), 7.00 (dd, 1H, J = 8.1, 1.0), 6.90 (d, 1H, J = 8.2), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 150.3, 132.0, 131.5, 131.1, 130.3, 129.7, 129.6, 124.9, 124.5, 121.8, 116.8, 116.7, 20.6; IR (ATR) ν 3297 (w), 1579 (w), 1489 (m), 1447 (s), 1101 (m); HRMS (EI) calcd. for $C_{13}H_{12}O_2^+$ [M^+]: 200.0837, found: 200.0825.

2',6-Dihydroxy-5-methoxybiphenyl-3-carbaldehyde (3ca). *General procedure A*: obtained from **1c** (209 mg, 0.75 mmol) and **2a** (1.3 equiv.); yield: 179 mg (0.73 mmol, 98%). *General*

procedure B: obtained from **4c** (173 mg, 0.75 mmol), **2a** (1.3 equiv.) and TBAF•3H_2O (4.0 equiv.) as additive; yield: 119 mg (0.58 mmol, 65%). Colourless solid, mp 130°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.50 (d, 1H, J = 1.8), 7.47 (d, 1H, J = 1.8), 7.40 – 7.29 (m, 2H), 7.12 – 7.02 (m, 2H), 6.84 (s, 1H), 5.96 (s, 1H), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 153.6, 147.8, 147.6, 131.2, 130.4, 130.2, 129.9, 124.7, 124.0, 121.5, 117.9, 108.0, 56.7; IR (ATR) ν 3334 (bw), 1672 (s), 1589 (s), 1148 (s), 867 (m); HRMS (EI) calcd. for $C_{14}H_{12}O_4^+$ [M^+]: 244.0736, found: 244.0742. Anal. Calcd. for $C_{14}H_{12}O_4$ (244.24): C, 68.8; H, 5.0. Found: C, 68.3; H, 5.0.

2',6-Dihydroxybiphenyl-3-carbaldehyde (3da). *General procedure A*: obtained from **1d** (124 mg, 0.50 mmol) and **2a** (1.3 equiv.); yield: 92 mg (0.86 mmol, 86%). *General procedure B*: obtained from **4d** (101 mg, 0.75 mmol), **2a** (1.3 equiv.); yield: 84 mg (0.39 mmol, 78%). Colourless solid, mp 119°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.15 (s, 1H), 7.81 (d, 1H, J = 2.1), 7.76 (dd, 1H, J = 8.4, 2.1), 7.33 – 7.23 (m, 2H), 7.10 (d, 1H, J = 8.4), 7.07 – 6.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 159.8, 152.8, 134.8, 131.9, 131.7, 130.2, 129.8, 126.6, 123.7, 121.9, 117.9, 116.9; IR (ATR) ν 3248 (bm), 1670 (s), 1592 (s), 1305 (m), 1182 (m); HRMS (EI) calcd. for $C_{13}H_{10}O_3^+$ [M^+]: 214.0630, found: 214.0628. Anal. Calcd. for $C_{13}H_{10}O_3$ (214.22): C, 72.9; H, 4.7. Found: C, 72.2; H, 5.0.

1-(2,2'-Dihydroxy-5-methylbiphenyl-3-yl)ethanone (3ea). *General procedure A*: obtained from **1e** (207 mg, 0.75 mmol) and **2a** (1.3 equiv.); yield: 155 mg (0.64 mmol, 85%). Colourless solid, mp 165°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.45 (s, 1H), 7.63 (d, 1H, J = 1.5), 7.43 (d, 1H, J = 2.1), 7.32 (td, 1H, J = 7.6, 7.6, 1.6), 7.26 (dd, 1H, J = 7.6, 1.6), 7.08 (dd, 1H, J = 7.8, 1.0), 7.02 (ddd, 1H, J = 7.5, 1.1), 6.69 (s, 1H), 2.71 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 156.0, 154.2, 140.2, 131.2, 130.6, 129.8, 129.5, 128.3, 125.6, 121.4, 119.7, 118.6, 27.0, 20.7; IR (ATR) ν 3370 (bw), 1635 (m), 1437 (m), 1329 (m), 1217 (m); HRMS (EI) calcd. for $C_{15}H_{14}O_3^+$ [M^+]: 242.0943, found: 242.0955. Anal. Calcd. for $C_{15}H_{14}O_3$ (242.27): C, 74.4; H, 5.8. Found: C, 74.6; H, 5.7.

5-Bromo-2,2'-dihydroxybiphenyl-3-carbaldehyde (3fa). *General procedure A*: obtained from **1f** (164 mg, 0.50 mmol) and **2a** (1.0 equiv.); yield: 95 mg (0.32 mmol, 65%). Colourless solid, mp 115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.94 (s, 1H), 9.92 (s, 1H), 7.76 (s, 2H), 7.35 (ddd, 1H, J = 8.2, 7.9, 1.6), 7.25 (dd, 1H, J = 8.0, 1.4), 7.13 – 6.97 (m, 2H), 6.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 156.5, 153.9, 141.9, 135.5, 131.2, 130.6, 130.3, 123.4, 121.9, 121.7, 118.5, 112.7; IR (ATR) ν 3402 (bw), 1656 (s), 1436 (m), 1415 (m), 1281 (s); HRMS (EI) calcd. for $C_{13}H_9O_3{}^{79}Br^+$ [M^+]: 291.9735, found: 291.9724. Anal. Calcd. for $C_{13}H_9O_3Br$ (293.11): C, 53.3; H, 3.1. Found: C, 53.4; H, 3.2.

3-Methoxy-5-nitrobiphenyl-2,2'-diol (3ga). *General procedure A*: obtained from **1g** (221 mg, 0.75 mmol) and **2a** (1.0 equiv.); yield: 179 mg (0.69 mmol, 91%). Colourless solid, mp 184-185°C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.88 (d, 1H, J = 2.7), 7.78 (d, 1H, J = 2.6), 7.30 (dd, 1H, J = 7.6, 1.6), 7.24 (ddd, 1H, J = 8.1, 7.4, 1.7), 7.00 (dd, 1H, J = 8.1, 0.9), 6.93 (ddd, 1H, J = 7.5, 7.5, 1.2); ^{13}C NMR (75 MHz, acetone-d_6) δ 155.5, 151.6, 148.6, 140.8, 132.3, 130.2, 126.3, 124.4, 121.1, 120.4, 117.0, 106.2, 57.0; IR (ATR) ν 3411 (bw), 1488 (m), 1332 (s), 1252 (s), 1094 (m); HRMS (EI) calcd. for $C_{13}H_{11}O_5N^+$ [M^+]: 261.0637, found: 261.0632. Anal. Calcd. for $C_{13}H_{11}O_5N$ (261.23): C, 59.8; H, 4.2; N, 5.4. Found: C, 59.6; H, 4.2; N, 5.3.

5-Chlorobiphenyl-2,2'-diol (3ha). *General procedure A*: obtained from **1h** (191 mg, 0.75 mmol) and **2a** (1.3 equiv.); yield: 146 mg (0.66 mmol, 88%). *General procedure B*: obtained from **4h** (127 mg, 0.50 mmol) and **2a** (1.3 equiv.); yield: 84 mg (0.38 mmol, 76%). Colourless solid, mp 154°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (ddd, 1H, J = 8.1, 7.4, 1.7), 7.28 – 7.21 (m, 3H), 7.07 (td, 1H, J = 7.5, 7.5, 1.1), 6.98 (dd, 1H, J = 8.1, 0.9), 6.95 (dd, 1H, J = 6.9, 2.2), 5.97 (s, 1H), 5.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.8, 131.6, 131.0, 130.5, 129.8, 126.5, 126.0, 123.0, 122.2, 118.4, 116.9; IR (ATR) ν 3278 (bw), 1484 (m), 1262 (m), 1220 (m), 1104 (w); HRMS (EI) calcd. for $C_{12}H_9O_2{}^{35}Cl^+$ [M^+]: 220.0291,

found: 220.0274. Anal. Calcd. for $C_{12}H_9O_2Cl$ (220.65): C, 65.3; H, 4.1. Found: C, 65.3; H, 4.0.

5-Bromobiphenyl-2,2'-diol (3ia) and 5-(phenyl-2''-ol)-biphenyl-2,2'-diol (3ia'). *General procedure A*: obtained from **1i** (224 mg, 0.75 mmol) and **2a** (1.3 equiv.); yield of **3ia**: 103 mg (0.39 mmol, 52%), along with byproduct **3ia'** (30 mg, 0.11 mmol, 14%). *Modified general procedure A*: obtained from **1i** (224 mg, 0.75 mmol), **2a** (2.6 equiv.), and K_2CO_3 (6.0 equiv.); yield: yield of **3ia**: 100 mg (0.38 mmol, 50%), along with byproduct **3ia'** (89 mg, 0.32 mmol, 43%). *Analytical data for 5-bromobiphenyl-2,2'-diol (**3ia**)*: colourless solid, mp ###°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.39 (dd, 1H, J = 9.5, 2.5), 7.32 (ddd, 1H, J = 9.6, 7.5, 1.7), 7.26 (dd, 1H, J = 7.7, 1.7), 7.07 (ddd, 1H, J = 7.6, 7.5, 1.1), 6.98 (dd, 1H, J = 8.1, 1.0), 6.89 (d, 1H, J = 8.2), 6.07 (s, 1H), 5.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152. 6, 152.3, 133.9, 132.7, 131.6, 130.5, 126.6, 123.0, 122.1, 118.8, 116.9, 113.7; IR (ATR) ν 3276 (bm), 1481 (m), 1447 (m), 1262 (m), 1219 (s); HRMS (EI) calcd. for $C_{12}H_9O_2{}^{79}Br^+$ [M^+] 263.9786, found: 263.9780. Anal. Calcd. for $C_{12}H_9O_2Br$ (265.10): C, 54.4; H, 3.4. Found: C, 54.9; H, 3.5. *Analytical data for 5-(phenyl-2''-ol)-biphenyl-2,2'-diol (**3ia'**)*: colourless solid, mp 64°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, 1H, J = 2.1), 7.36 (dd, 1H, J = 8.3, 2.2), 7.32 – 7.26 (m, 2H), 7.26 – 7.18 (m, 2H), 7.09 – 7.01 (m, 2H), 7.01 – 6.91 (m, 3H), 6.50 (s, 2H), 5.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 152.6, 152.5, 132.4, 131.7, 130.6, 130.5 (2C), 130.1, 129.0, 127.8, 125.3, 124.1, 122.0, 121.1, 117.6, 117.0, 116.1; IR (ATR) ν 3338 (bm), 1484 (s), 1400 (m), 1221 (s), 754 (s); HRMS (EI) calcd. for $C_{18}H_{14}O_3^+$ [M^+] 278.0943, found: 278.0953. Anal. Calcd. for $C_{18}H_{14}O_3$ (278.30): C, 77.7; H, 5.1. Found: C, 77.6; H, 5.3.

(*E*)-Ethyl 3-(2',6-dihydroxy-5-methoxybiphenyl-3-yl)acrylate (3ja). *General procedure A*: obtained from **1j** (696 mg, 2.00 mmol), **2a** (1.0 equiv.), KF (4.0 equiv.) as an additive instead of K_2CO_3, and ethanol (4 mL/mmol) as co-solvent; yield: 566 mg (1.80 mmol, 90%). Colourless solid, mp 110°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, J = 15.9), 7.37 – 7.26

(m, 2H), 7.14 (d, 1H, J = 1.8), 7.07 (d, 1H, J = 2.1), 7.07 – 7.00 (m, 2H), 6.59 (s, 1H), 6.34 (d, 1H, J = 15.9), 6.18 (s, 1H), 4.26 (q, 2H, J = 7.1), 3.98 (s, 3H), 1.33 (t, 3H, J = 7.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 153.6, 147.2, 144.4, 144.0, 131.1, 129.9, 127.9, 125.3, 124.8, 124.6, 121.4, 117.9, 116.9, 108.7, 60.6, 56.5, 14.5; IR (ATR) ν 3373 (bm), 1694 (m), 1632 (m), 1264 (s), 1159 (s); HRMS (EI) calcd. for $C_{18}H_{18}O_5^+$ [M^+] 314.1154, found: 314.1152. Anal. Calcd. for $C_{18}H_{18}O_5$ (314.33): C, 68.8; H, 5.8. Found: C, 68.9; H, 5.8.

(*E*)-3-(2',6-Dihydroxy-5-methoxybiphenyl-3-yl)acrylic acid (3ka). *General procedure A*: obtained from **1j** (261 mg, 0.75 mmol) and **2a** (1.0 equiv.) after a prolonged reaction time of 16 h; yield: 147 mg (0.51 mmol, 68%). Colourless solid, mp >300°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.77 – 7.63 (m, 1H), 7.51 (d, 1H, J = 15.9 Hz), 7.30 (d, 1H, J = 1.8 Hz), 7.18 – 7.09 (m, 2H), 7.02 (d, 1H, J = 1.7 Hz), 6.89 (d, 1H, J = 7.4 Hz), 6.82 (dd, 1H, J = 7.4, 1.0 Hz), 6.39 (d, 1H, J = 15.9 Hz), 3.89 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.0, 154.6, 148.0, 146.5, 144.7, 131.3, 128.3, 126.2, 125.3, 124.9, 124.8, 118.6, 115.7, 115.6, 109.1, 56.0, 39.5; IR (ATR) ν 3187 (bm), 1682 (s), 1627 (s), 1420 (s), 1263 (s); HRMS (EI) calcd. for $C_{16}H_{14}O_5^+$ [M^+]: 286.0841, found: 286.0837.

2',6-Dihydroxybiphenyl-3-carbonitrile (3la). *General procedure B*: obtained from **4l** (149 mg, 0.75 mmol), **2a** (1.3 equiv.) and TBAF•3H_2O (4.0 equiv.); yield: 122 mg (0.58 mmol, 77%). Colourless solid, mp 145°C; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.54 (d, 1H, J = 1.9), 7.51 (dd, 1H, J = 8.4, 2.2), 7.25 – 7.15 (m, 2H), 7.00 (d, 1H, J = 8.4), 6.95 – 6.87 (m, 2H); ^{13}C NMR (75 MHz, methanol-d_4) δ 160.3, 155.5, 137.0, 133.7, 132.5, 130.4, 128.9, 125.1, 120.9, 120.5, 118.0, 117.0, 103.4; IR (ATR) ν 3286 (s), 2230 (s), 1601 (m), 1488 (s), 1282 (s); HRMS (EI) calcd. for $C_{13}H_9O_2N^+$ [M^+]: 211.0633, found: 211.0631. Anal. Calcd. for $C_{13}H_9NO_2$ (211.22): C, 73.9; H, 4.3. Found: C, 74.4; H, 3.9.

Methyl 2',6-dihydroxybiphenyl-3-carboxylate (3ma). *General procedure B*: obtained from **4l** (116 mg, 0.50 mmol), **2a** (1.3 equiv.) and TBAF•3H_2O (4.0 equiv.); yield: 96 mg (0.39 mmol, 78%). Colourless solid, mp 132°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 1H, J =

1.9), 7.97 (dd, 1H, J = 8.4, 2.2), 7.37 – 7.26 (m, 2H), 7.07 (dd, 1H, J = 7.5, 1.1), 7.07 – 7.00 (m, 3H), 6.79 (s, 1H), 6.31 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 157.7, 152.8, 133.7, 131.9, 131.6, 130.3, 124.8, 123.4, 123.2, 122.0, 117.0, 116.9, 52.3; IR (ATR) ν 3363 (m), 1700 (m), 1684 (s), 1253 (s), 1175 (s); HRMS (EI) calcd. for $C_{14}H_{12}O_4^+$ [M^+]: 244.0736, found: 244.0725.

***N*-(2',6-dihydroxybiphenyl-3-yl)acetamide (3na)**. *General procedure B*: obtained from **4n** (150 mg, 0.50 mmol), **2a** (1.3 equiv.) and TBAF•$3H_2O$ (4.0 equiv.); yield: 84 mg (0.35 mmol, 70%). Colourless oil; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.41 – 7.36 (m, 2H), 7.27 – 7.17 (m, 2H), 6.96 – 6.85 (m, 3H), 3.35 (s, 1H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, methanol-d_4) δ 171.5, 155.1, 152.0, 132.6, 132.3, 129.9, 127.8, 127.2, 125.3, 122.5, 121.4, 117.4, 117.3, 23.6; IR (ATR) ν 3263 (w), 1624 (m), 1488 (s), 1223 (s), 755 (s); HRMS (EI) calcd. for $C_{14}H_{13}O_3N^+$ [M^+]: 243.0895, found: 243.0891.

Procedure for catalyst recovery and reuse experiments. In the first run, *ortho*-iodo phenol **1c** (209 mg, 0.75 mmol), *ortho*-phenol boronic acid **2a** (135 mg, 0.98 mmol), K_2CO_3 (415 mg, 3.00 mmol) and Pd/C (10 wt-%, 15 mg, 2 mol %) were suspended in water (7.5 mL). The reaction mixture was immersed in an oil bath preheated to 80°C for 2.5 h. The mixture was then cooled to ambient temperature and filtered through a filter paper, which was subsequently washed with water (10 mL). The separated aqueous layer was carefully acidified by addition of aqueous HCl (1.0 M) and extracted three times with MTBE (50 mL for each extraction). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica, using hexane/MTBE mixtures of increasing polarity as eluent to furnish the product **3ca** (165 mg, 0.68 mmol, 90%) as a colourless solid, which was checked for purity and identity by ^{1}H NMR-spectroscopy. In the following runs, the filter paper impregnated with the catalyst from the first run was added to the aqueous suspension of base and starting materials. The volume

of water, the amounts of all starting materials, the reaction temperature and reaction time were identical to those reported above for the first run. After each run, the product **3ca** was isolated as described for run 1, and identity and purity were checked by ^{1}H NMR spectroscopy. Yield of **3ca** after run 2: 147 mg (0.60 mmol, 80%); after run 3 (started with a delay of 16 h after recovery of the catalyst from run 2): 172 mg (0.71 mmol, 94%); after run 4: 167 mg (0.68 mmol, 91%); after run 5: 174 mg (0.71 mmol, 95%).

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Supporting Information Available statement

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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