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Pd(DPEPhos)Cl_2-catalyzed Negishi cross-couplings for the formation of biaryl and diarylmethane phloroglucinol adducts

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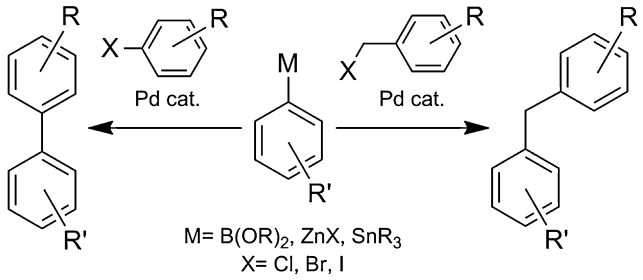
ABSTRACT

Several functionalized biaryls and diarylmethanes containing the phloroglucinol subunit were synthesized in 55–85% yields using Negishi cross-couplings of 2,4,6-trimethoxyphenylzinc chloride with aryl and benzyl halides in the presence of catalytic quantities of Pd(DPEPhos)Cl_2. These simple to prepare couplings were generally complete in 1–24 h depending on the halide, and were applicable to aryl and benzyl halides containing both electron-donating and electron-withdrawing groups.

1. Introduction

Biaryls and diarylmethanes continue to be seen as fundamental motifs in organic synthesis,[1] industrial processes[1a,2] and medicinal chemistry.[3] Given their significance, the synthesis of such compounds has received great attention.[1,4] The palladium-catalyzed cross-coupling of aryl or benzyl halides with arylmetallic species has become an increasingly important and popular method for the synthesis of these structural motifs (Scheme 1). The Suzuki method,[5] involving the use of arylboronic acids and/or boronate esters, is perhaps the most popular method and has been widely used for both biaryl[6] and diarylmethane[7] syntheses. Stille[8] and Negishi[9] protocols have also been applied to the formation of both substructures. More recently, numerous syntheses of diarylmethanes involving the coupling of aryl halides with benzyl halides using zinc powder/dust in the presence of palladium or cobalt catalysts have been reported.[10] However, no literature method for the convenient synthesis of both biaryls and diarylmethanes was identified. As such, a single method for both structural arrays was targeted for further development.



Scheme 1. Palladium-catalyzed cross-couplings of arylorganometallic derivatives with aryl and benzyl halides.

Of particular interest was the synthesis of biaryl and diarylmethane derivatives containing the 1,3,5-trimethoxyphenyl (TMP) subunit. This subunit is a useful protected precursor to phloroglucinol **1** (Fig. 1), a commonly occurring unit in many natural products,[11] including tannins or proanthocyanidins.[12] One subgroup of such proanthocyanidins are the C8-substituted catechin derivatives **2** (Fig. 1). Access to substituted catechins has received increased attention over the last decade in order to gain some insight into structure–activity relationships of these compounds.[13] In particular, the biological properties of these molecules, which include antioxidant[14] and anticancer[15] activities, have been of great interest in this field of study.

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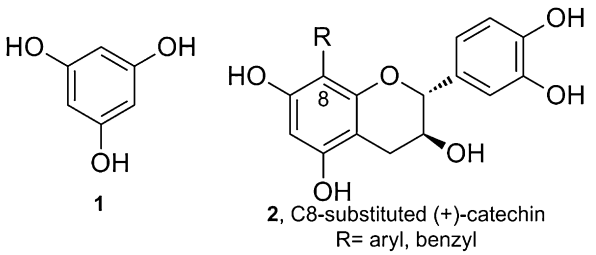
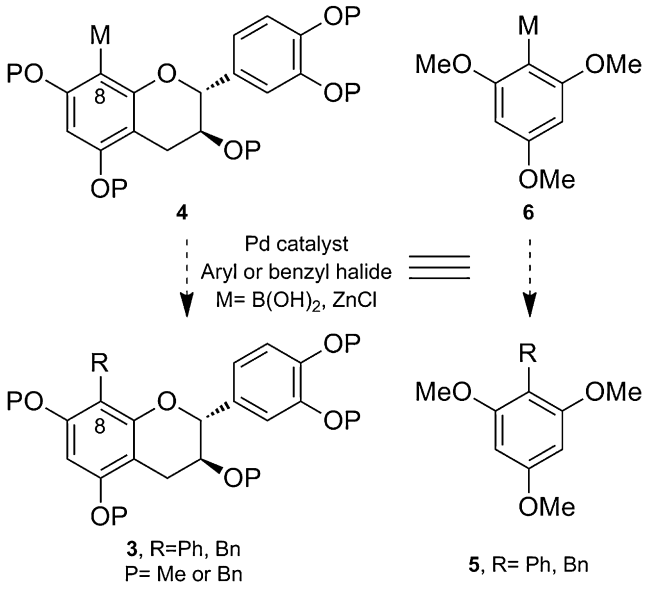


Fig. 1. Phloroglucinol 1 and C8-substituted (+)-catechin 2.

Access to a variety of protected C8-phenyl- and C8-benzyl-substituted catechin derivatives **3** using a C8-metallated moiety **4** in Pd-catalyzed cross-coupling procedures presented an interesting pathway towards the synthesis of these compounds. Given the complexity of the catechin derivative, cross-couplings of the 1,3,5-trimethoxyphenyl subunit were screened as a model system to establish the potential of such a pathway (Scheme 2). Accordingly, the synthesis of phenyl- and benzyl-substituted trimethoxybenzenes **5** was targeted through the development of suitable cross-couplings of metallated 2,4,6-trimethoxyphenyl derivatives **6** with aryl and benzyl halides.



Scheme 2. Pd-catalyzed cross-coupling pathway to C8-susbtituted catechins **3** from C8-metallated catechins **4** and the synthesis of model trimethoxyphenyl adducts **5**.

2. Results and discussion

To test the initial scope of the designed synthetic pathway, 1,3,5-trimethoxybenzene (**7**) or its mono-brominated analogue **8**[16] were converted to either boronic acid **9a** (M=B(OH)$_2$) or organozinc **9b** (M=ZnCl). The formation of diarylmethane **10** was then attempted through the coupling of these organometallics with benzyl bromide (BnBr) in the presence of Pd(PPh$_3$)$_2$Cl$_2$ (Scheme 3).

2.1. Attempted Suzuki couplings of boronic acid 9a with benzyl bromide

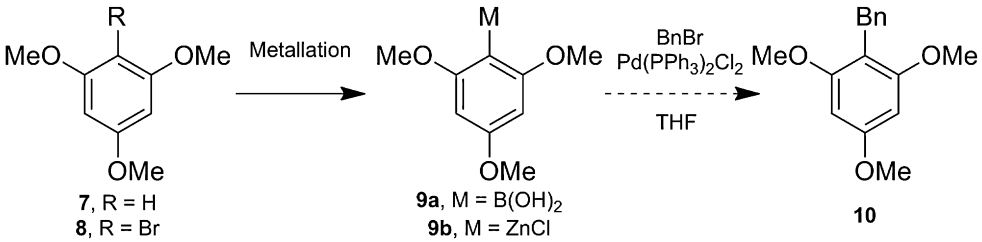
As a well-utilized coupling method, Suzuki cross-couplings involving boronic acid **9a** were attempted first. Initially, boronic acid **9a** was synthesized from **7** using a modification to the method reported by Chaumeil et al.[17] Directed *ortho*-lithiation of **7** using *n*-BuLi furnished an organolithium intermediate, which was then treated with excess B(OMe)$_3$. Aqueous quenching of the resulting boronate salt provided the desired boronic acid **9a**, which was readily purified by crystallization (Scheme 4). Reaction scale for this transformation was very important; using ca. 1 g or fewer of **7**, yields of **9a** were typically 20–30%. Increasing the reaction scale resulted in much higher conversions to the point where **9a** was consistently obtained in 70–75% yields after purification when conducting the reaction with 10–15 g of **7**.

With **9a** available, Pd(PPh$_3$)Cl$_2$-mediated Suzuki couplings to benzyl bromide were attempted using either NaOH or K$_2$CO$_3$ as the base in aqueous, and anhydrous, THF (Scheme 4). Under the aqueous conditions, the desired diarylmethane **10** was obtained in very poor yields (10–20%) following isolation by silica chromatography. The major compound recovered for these couplings was **7**, presumably formed from protonolysis of **9a**. In the case of the anhydrous couplings, no product was detected by ^{1}H NMR analysis of crude reaction mixtures. In these cases, only benzyl bromide and **7** were recovered after aqueous quenching.

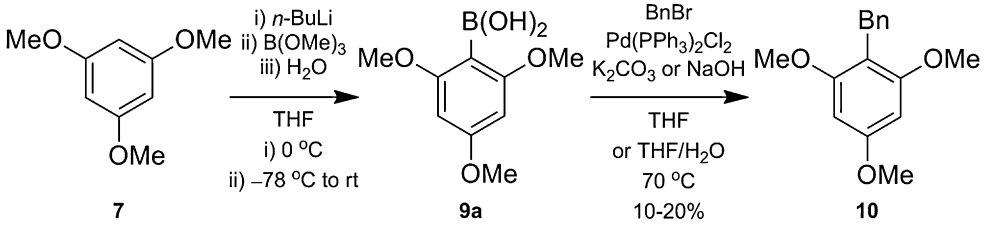
The reasons for the poor Suzuki coupling results were not entirely clear. As protonolysis of **9a** to **7** was identified as the major reaction pathway under both aqueous and anhydrous conditions, it was likely that the boronic acid was the problematic coupling partner. Both K$_2$CO$_3$ and NaOH showed poor solubility in anhydrous THF, so in these cases there may not have been any base available in solution to activate boronic acid **9a**. This activation step has been reported to be crucial in successful transmetallation of boronic acids to a Pd catalyst.[18] If **9a** could not be activated by the base or if there was minimal activation, then the coupling to benzyl bromide would not proceed. In the aqueous base couplings, boronic acid **9a** may have deboronated under the aqueous conditions to provide **7** at a faster rate than the transmetallation of the activated boronic acid to the Pd catalyst. As a result, **7** formed as the major product of the coupling and only a small proportion of the desired diarylmethane **10** was produced.

2.2. Development of Negishi cross-coupling system utilizing organozinc 9b

Given the poor compatibility of boronic acid **9a** under the basic and/or aqueous conditions and subsequent poor Suzuki coupling results, the organozinc derivative of trimethoxybenzene **9b** was investigated as the organometallic coupling partner. Formation of



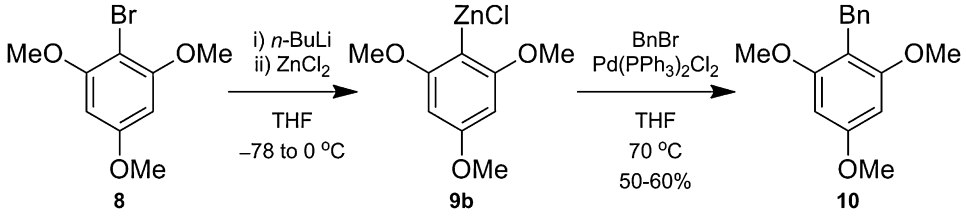
Scheme 3. Proposed synthetic method for diarylmethane **10** from organometallics **9a** or **9b**.



Scheme 4. Synthesis of boronic acid **9a** and attempted Suzuki couplings to benzyl bromide.

organozinc **9b** was achieved using a low temperature lithium–halogen exchange of bromide **8** using *n*-BuLi in THF, followed by addition of anhydrous $ZnCl_2$ as a solution in THF.[19] The presumably formed organozinc species was then immediately coupled to benzyl bromide in the presence of precatalyst $Pd(PPh_3)_2Cl_2$ (Scheme 5).[20]

a yellow suspension upon addition to the reaction mixture; heating to approximately 30 °C was required to ensure complete dissolution of the catalyst. Interestingly, no distinguishable differences between the reactivity of benzyl chloride and benzyl bromide were observed. Both halides showed similar coupling yields and reaction times using either $Pd(PPh_3)_2Cl_2$ or $Pd(DPEPhos)Cl_2$ as the pre-



Scheme 5. Formation of organozinc **9b** and its Pd-catalyzed coupling to benzyl bromide.

Using these conditions, the desired diarylmethane **10** was consistently isolated in 50–60% yield when organozinc **9b** was employed in slight excess (1.5 mol equiv) with stirring for 16–20 h at 70 °C in the presence of 1 mol % of the precatalyst.

It is worthwhile to note at this point that generation of the intermediate organolithium species prior to addition of $ZnCl_2$ could also have been achieved through directed *ortho*-lithiation of **7** as used for the synthesis of boronic **9a**. In the case of organozinc **9b** formation, this transformation was typically carried out using approximately 1.5 mmol of **8**. At this scale, coupling yields using organozinc **9b** derived from directed *ortho*-lithiation of **7** varied widely. In contrast, the organolithium derived from lithium–halogen exchange of bromide **8** reacted smoothly upon addition of $ZnCl_2$, and the presumably formed organozinc **9b** coupled to benzyl bromide to provide highly consistent yields of diarylmethane **10**.

Table 1
Catalyst screening for the Negishi cross-coupling of **9b** with BnBr or BnCl

Entry	Catalyst	Loading (mol %)	Electrophile	Temp (°C)	Time (h)	Yield[a] (%)
1	$Pd(PPh_3)_2Cl_2$	1	BnBr	70	20	60
2	$Pd(PPh_3)_2Cl_2$	1	BnCl	70	20	61
3	$Pd(PPh_3)_4$	4	BnBr	70	24	55
4	$Pd(DPEPhos)Cl_2$[b]	1	BnBr	70	1.5	84
5	$Pd(DPEPhos)Cl_2$	1	BnCl	70	1.5	85
6	$Pd(DPEPhos)Cl_2$	5	BnCl	20	48	19
7	$Pd(dba)_2$/DPEPhos[c]	5	BnBr	70	2.5	64
8	$Pd(dppf)Cl_2 \cdot CH_2 \cdot Cl_2$[d]	3	BnBr	70	48	52

[a] Isolated yield after silica gel purification.
[b] DPEPhos=bis(*o*-diphenylphosphinophenyl) ether.
[c] dba=dibenzylideneacetone.
[d] dppf=1,1′-bis(diphenylphosphino)ferrocene.

2.3. Catalyst screening for the developed Negishi coupling method

In an effort to improve the isolated yield of diarylmethane **10**, numerous Pd(0) catalysts and their Pd(II) precatalyst analogues were employed at various loadings and temperatures using either benzyl bromide or benzyl chloride (BnCl) as the electrophilic partners in the developed Negishi cross-coupling (Table 1). Reactions were carried out in THF, monitored by TLC for the consumption of the halide and were stopped after a maximum of 48 h.

It was found that the bidentate ligand precatalyst $Pd(DPEPhos)Cl_2$[21] was by far the most effective Pd reagent employed in the transformation, showing relatively higher yields (84–85%), faster coupling rates and requiring only low catalyst loading (ca. 1 mol %) at 70 °C (entries 4 and 5) compared to other catalytic systems attempted. The effect of temperature for this catalyst was also examined. When the coupling was carried out at 20 °C (entry 6) diarylmethane **10** was produced in very poor yield (19%) despite the use of higher catalyst loading (5 mol %) and a longer reaction time. This low coupling yield was attributed to the poor catalyst solubility at 20 °C, apparent because the catalyst remained as

catalyst (compare entries 1 with 2 and 4 with 5). Comparison of the results of entry 1 with entry 3 and entry 4 with entry 7, clearly show that Pd(II) precatalysts were more effective than their Pd(0) counterparts for this coupling procedure.

Notably, bibenzyl **11** (Fig. 2) was formed as a homocoupling byproduct in approximately 10% yields (with respect to the halide) when $Pd(PPh_3)_2Cl_2$ was employed as the precatalyst in the coupling reaction. In contrast, this byproduct was not detected when the coupling was carried out using $Pd(DPEPhos)Cl_2$. This accounted for the higher observed coupling yields obtained using $Pd(DPEPhos)Cl_2$ versus $Pd(PPh_3)_2Cl_2$. In the $Pd(DPEPhos)Cl_2$-catalyzed couplings the halide was not being consumed in this homocoupling side reaction,

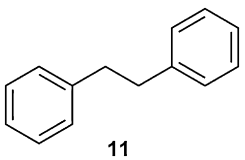


Fig. 2. Bibenzyl **11**, obtained as a byproduct in the $Pd(PPh_3)_2Cl_2$-catalyzed cross-couplings.

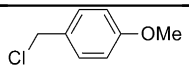
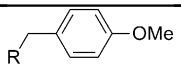
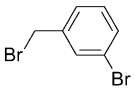
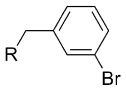
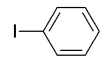
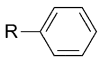
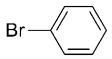
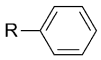
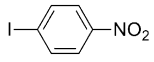
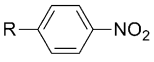
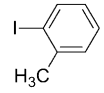
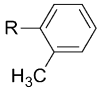
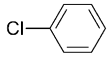
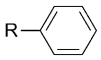
so a greater quantity of halide was available to participate in the cross-coupling with organozinc **9b**.

The coupling was also attempted using another bidentate ligand precatalyst, Pd(dppf)Cl_2.CH_2Cl_2 (entry 8) at 70 °C. The coupling using this catalyst was very sluggish, with TLC analysis showing benzyl bromide was still present even after 48 h, and 52% was the highest coupling yield obtained using this catalyst. It was noted that this catalyst did not appear to dissolve completely in the reaction mixture. This provided some explanation for the sluggish reaction rate as the actual catalyst loading present in solution was likely much lower than that added to the reaction mixture (3 mol %).

2.4. Extension of Negishi coupling system to other electrophiles

In order to further investigate the scope of this methodology, the optimized Pd(DPEPhos)Cl_2-catalyzed coupling procedure was expanded to the coupling of organozinc **9b** with numerous benzyl and aryl halides containing a variety of functional groups to furnish substituted diarylmethanes and biaryls containing the 1,3,5-trimethoxyphenyl subunit (Table 2).

Table 2
Pd(DPEPhos)Cl_2-mediated cross-couplings of **9b** with benzyl and aryl halides

Entry	Halide	Rxn time[a] (h)	Product[b]	Yield[c] (%)
1	 **12a**	4	 **13a**	68
2	 **12b**	3[d]	 **13b**	55
3	 **12c**	5	 **13c**	81
4	 **12d**	24	 **13c**	77
5	 **12e**	4	 **13d**	80
6	 **12f**	6	 **13e**	74
7	 **12g**	48	 **13c**	0

[a] Reaction conditions: halide (1 equiv), **9b** (1.5 equiv), THF, Pd(DPEPhos)Cl_2 (~1 mol %), 70 °C. Reactions were monitored by TLC for consumption of halide.
[b] R=2,4,6-trimethoxyphenyl.
[c] Isolated yields following silica chromatography.
[d] Conducted at 40 °C.

A variety of cross-coupling products were constructed in acceptable to very good yields using low precatalyst loading (ca. 1 mol %) in reasonable reaction times. Entries 1 and 2 show benzyl bromides and chlorides containing either electron donating or electron withdrawing substituents can be coupled to organozinc **9b** using the developed catalytic system. In order to establish the selectivity of cross-couplings of benzyl bromides in comparison with aryl bromides, the reactivity of bromide **12b** in the coupling system was explored (entry 2). Reduction of the reaction temperature to 40 °C resulted in the selective coupling of the benzylic bromide (at 70 °C, mixtures of aryl, benzyl and bis coupled products were obtained). This strongly suggested under these reaction conditions, oxidative addition of the Pd catalyst into the benzyl carbon–bromine bond was much faster in comparison to the aryl bromide. The reduced reaction temperature resulted in a decreased coupling yield compared to that obtained for the couplings of other benzyl halides. The 55% isolated yield of diarylmethane **13b**, however, was acceptable when the difficult nature of the coupling was taken into consideration. Furthermore, this selective coupling provides opportunities for iterative syntheses of larger and more elaborate motifs, as the remaining aryl bromide could be coupled to other organometallic reagents in a subsequent step.

Aryl halides **12c**–**f** (entries 3–6) also readily coupled to organozinc **9b** under the conditions developed to provide the corresponding biaryls **13c**–**e**. Notably, biaryl **13c** was obtained in comparable yields using either iodobenzene **12c** (entry 3) or bromobenzene **12d** (entry 4) as the coupling electrophile. A much longer reaction time was required, however, to achieve complete coupling of **12d**. Additionally, chlorobenzene **12g** could not be coupled under the developed conditions (entry 7). This suggested that the nature of the aryl halide (Cl, Br or I) played an important role in the rate of the coupling reaction, which contrasted to the earlier results observed for the coupling rates of benzyl halides. The coupling system was also extended to incorporate aryl iodides containing either electron withdrawing (entry 5) or electron donating (entry 6) substituents. Comparison of the coupling yields and times of these aryl iodides suggested that the yield was not greatly affected by the substituent, but the coupling rate increased slightly in the presence of the strongly electron withdrawing nitro group. The synthesis of biaryls **13c** and **13e** also supported the experimental and theoretical results reported recently by Liu et al.[22] This report concluded that the best results for synthesis of *ortho*-substituted biaryls using Negishi methods requires the coupling of a more *ortho*-substituted arylzinc species with a less substituted aryl iodide. This was indeed the case for biaryls **13c** and **13e**, which were synthesized in good yield (81% and 74%, respectively) through the coupling of the more substituted organozinc **9b** with the less substituted iodides **12c** and **12f**.

3. Conclusions

In summary, various biaryls and diarylmethanes containing the highly electron rich 1,3,5-trimethoxyphenyl subunit were synthesized in moderate to very good yields utilizing a single, easy to prepare and conduct Pd(DPEPhos)Cl_2-catalyzed Negishi coupling protocol. Importantly, this method was applicable to the coupling of both benzyl and aryl halides containing electron withdrawing and electron donating substituents. To the best of our knowledge, this is the first report of a single method, that is, conveniently applicable to both biaryl and diarylmethane synthesis. Extension of these methods to other aromatic and aliphatic electrophiles is currently underway in order to access additional products containing the phloroglucinol subunit. The application of similar Pd-catalyzed coupling procedures towards the synthesis of C8-subsituted catechin derivatives is also under investigation.

4. Experimental

4.1. General methods

4.1.1. Materials. Commercial reagents were purchased from Sigma–Aldrich and used without further purification unless noted. THF was distilled from sodium/benzophenone ketyl under an atmosphere of nitrogen prior to use. All Pd catalysts other than Pd(DPEPhos)Cl_2 were purchased from Sigma–Aldrich, used as received and stored under nitrogen in fridge at 4 °C between uses. *N*-Bromosuccinimide (NBS) was recrystallised from hot water prior to use. *n*-BuLi was used as received as a solution in hexanes and titrated according to the method of Suffert[23] either prior to use or on a weekly basis when in regular use. 1-Bromo-2,4,6-trimethoxybenzene (**8**) was prepared according to the literature procedure of Mondal et al.[16]

4.1.2. Experimental procedures. All reactions were conducted using anhydrous solvents under an argon atmosphere and performed in oven dried round bottom or vial flasks fitted with a rubber suba seal unless stated. Organic solutions were concentrated via rotary evaporation under reduced pressure. Thin layer chromatography (TLC) was performed using the indicated solvent systems on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized via exposure to a UV lamp (λ=254 nm) and developed by dipping in a $KMnO_4$ solution followed by brief heating using a heat gun. Silica gel chromatography was conducted using E. Merck silica gel (230–400 mesh).

4.1.3. Spectral and structural analysis. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. ^1H NMR (400 MHz) chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protonium in the NMR solvent ($CHCl_3$, δ=7.26). Data are reported as the following: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad, app=apparent), coupling constant *J* hertz (Hz), and integration. ^{13}C NMR chemical shifts (100 MHz) are reported in ppm downfield from tetramethylsilane and referenced to the carbon resonances in the NMR solvent ($CDCl_3$, δ=77.0). High resolution mass spectra (HRMS) were performed at the Monash University Mass Spectrometry Unit and were recorded using a Bruker 4.7 T FTMS Ultra High Resolution spectrometer using Electrospray Ionisation (ESI). Melting points were recorded using a Reichert hot stage apparatus and are uncorrected. FTIR spectra were recorded using a Lambda Scientific FTIR-7600 instrument in ATR mode using a solid sample. FTIR absorbances are reported as wavenumbers (cm^{-1}).

4.2. 2,4,6-Trimethoxyphenylboronic acid (9a)

The title compound was prepared using an adapted procedure for the same compound reported by Chaumeil et al.[17] To a stirring solution of 1,3,5-trimethoxybenzene **7** (11.3 g, 67.2 mmol) in THF (200 mL) at 0 °C, *n*-BuLi (45 mL, 1.60 M, 72.0 mmol) was added dropwise over 10 min. The resulting white suspension was stirred at this temperature for 2 h and then cooled to −78 °C. $B(OMe)_3$ (15.0 mL, 135 mmol) in THF (15 mL) was added dropwise over 1 h and the resulting mixture was stirred at −78 °C for 1 h before being allowed to slowly warm in the cold bath to room temperature overnight. The resulting cloudy, white mixture was cooled to 0 °C and water (100 mL) was added dropwise with stirring over 30 min. The mixture was poured into water (200 mL) and CH_2Cl_2 (300 mL) and stirred vigorously for 15 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4×50 mL), and the combined organics were dried (Na_2SO_4), filtered and concentrated to provide a white powdery solid. The solid was dissolved in minimal boiling $CHCl_3$ and a roughly equal portion of hot Et_2O was added. The mixture was cooled to room temperature and placed in a −20 °C freezer overnight to allow crystallization of the product. The resulting white crystals were isolated by suction, washed with cold Et_2O (10 mL) and allowed to dry to provide 10.1 g (71%) of the desired boronic acid **9a**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.14 (s, 2H), 3.87 (s, 6H), 3.83 (s, 3H). NMR data for the synthesized compound corresponded to those reported for the title compound by Chaumeil et al.[17]

4.3. 1,3,5-Trimethoxy-(2-phenylmethyl)benzene (10). General procedure for the coupling of boronic acid 9a with benzyl bromide

A 25 mL round bottom flask was charged with **9a** (ca. 320 mg, 1.51 mmol), either anhydrous NaOH or K_2CO_3 (ca. 3 mmol) and Pd(PPh_3)$_2Cl_2$ (1 mol %). THF (10 mL) was then added and the mixture was stirred until the boronic acid and catalyst dissolved. The resulting mixture was degassed with an Argon sparge for 30 min. Neat BnBr (120 μL, 1 mmol) was added via syringe, followed by water (2 mL) for the aqueous reactions. The resulting mixtures were stirred for 24 h at 70 °C, then cooled to room temperature and quenched by the addition of satd aq NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (2×20 mL) and the combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. The title product **10** was obtained in ~10% isolated yield using aqueous K_2CO_3 as the base and ~20% using aqueous NaOH as the base. In both cases the product was isolated as a white, powdery solid following silica gel chromatography (CH_2Cl_2/hexanes, 1:1) of the crude mixtures. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.07 (m, 5H), 6.15 (s, 2H), 3.93 (s, 2H), 3.80 (s, 3H), 3.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 159.1, 142.5, 128.6, 128.1, 125.4, 110.6, 90.9, 55.9, 55.5, 28.5. Mp 93–94 °C (lit. Mp 93–95 °C). NMR and mp data for the synthesized compound corresponded to those reported by Katritzky et al.[24] for the title compound.

4.4. 1,3,5-Trimethoxy-(2-phenylmethyl)benzene (10). Table 1: representative procedure for the Pd(PPh_3)$_2Cl_2$-catalyzed cross-coupling of 9b with benzyl bromide

To a stirring solution of 1-bromo-2,4,6-trimethoxybenzene **8** (0.32 g, 1.29 mmol) in anhydrous THF (4 mL) at −78 °C, *n*-BuLi (1.00 mL, 1.40 M, 1.40 mmol) was added dropwise over 1 min and stirring was continued until a white precipitate formed (ca. 10–15 min). To this mixture, a solution of $ZnCl_2$ (1.40 mL, 1.00 M in THF, 1.40 mmol), was added dropwise and the resulting clear, colourless solution was stirred at −78 °C for 15 min and then slowly warmed to 0 °C over 30 min. Neat BnBr (100 μL, 0.84 mmol) was added at 0 °C, followed immediately by solid Pd(PPh_3)$_2Cl_2$ (6 mg, 1 mol %) and the resulting mixture was warmed to 70 °C and stirred for 20 h. The mixture was cooled to room temperature and dilute HCl (2 M, 10 mL) was added, followed by CH_2Cl_2 (20 mL) and the mixture was rapidly stirred for 10 min. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the yellow residue by silica gel chromatography (CH_2Cl_2/hexanes 1:1) provided 131 mg (60%) of the title compound as a white powdery solid.

4.5. [Bis(*o*-diphenylphosphinophenyl)ether]palladium(II) chloride (Pd(DPEPhos)Cl_2)

The title compound was prepared using an adapted procedure as reported by Kranenburg et al.[25] A suspension of bis(triphenylphosphino)palladium(II) chloride (Pd(PPh_3)$_2Cl_2$, 0.32 g, 0.46 mmol) and bis(*o*-diphenylphosphinophenyl)ether (DPEPhos, 0.30 g, 0.56 mmol)

in THF (20 mL) was stirred at room temperature for 24 h. The THF was removed in vacuo and the remaining solids were filtered by suction, and washed with several portions of Et_2O. The residual solid was collected and dried in vacuo to afford 0.31 g (95%) of the desired product as a dull yellow solid. The catalyst was used without further purification and stored in fridge at 4 °C under nitrogen between uses.

4.6. 1,3,5-Trimethoxy-2-[(4-methoxyphenyl)methyl]benzene (13a, Table 2, entry 1). Representative procedure for Table 2 couplings

To a stirring solution of 1-bromo-2,4,6-trimethoxybenzene **8** (0.29 g, 1.17 mmol) in anhydrous THF (4 mL) at −78 °C, *n*-BuLi (1.00 mL, 1.25 M, 1.25 mmol) was added dropwise over 1 min and stirring was continued until a white precipitate formed (ca. 10–15 min). To this mixture, a solution of $ZnCl_2$ (1.20 mL, 1.00 M in THF, 1.20 mmol), was added dropwise and the resulting clear, colourless solution was stirred at −78 °C for 15 min and then slowly warmed to 0 °C over 30 min. Neat 4-methoxy-benzyl chloride (**12a**, 110 μL, 0.81 mmol) was added at 0 °C, followed immediately by solid Pd(DPEPhos)Cl_2 (7 mg, 1 mol %) and the resulting mixture was warmed to 70 °C and stirred for 4 h. The mixture was cooled to room temperature and dilute HCl (2 M, 10 mL) was added, followed by CH_2Cl_2 (20 mL) and the mixture was rapidly stirred for 10 min. The phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the yellow residue by silica gel chromatography (CH_2Cl_2/hexanes 1:1) provided 160 mg (68%) of the title compound as a white powdery solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J=8.8 Hz, 2H), 6.76 (d, J=8.8 Hz, 2H), 6.15 (s, 2H), 3.88 (s, 2H), 3.80 (s, 3H), 3.79 (s, 6H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.0, 157.6, 134.7, 129.5, 113.6, 111.0, 90.9, 55.9, 55.5, 55.4, 27.6. Mp 73–77 °C (lit. Mp 77–78 °C). NMR and mp data for the synthesized compound corresponded to those reported by Hofmann et al.[26] for the title compound.

4.7. 1,3,5-Trimethoxy-2-[(3-bromophenyl)methyl]benzene (13b, Table 2, entry 2)

The title compound was prepared by the general Table 2 procedure using **12b** as the halide, except 40 °C was used as the reaction temperature rather than 70 °C. Purification by silica gel chromatography (CH_2Cl_2/hexanes, 1:1) afforded the product (55%) as a white, powdery solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.26–7.07 (m, 3H), 6.16 (s, 2H), 3.91 (s, 2H), 3.81 (s, 3H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.0, 144.9, 131.7, 129.6, 128.5, 127.3, 122.2, 109.6, 90.9, 55.9, 55.5, 28.7. HRMS (ESI): calculated for $C_{16}H_{17}{}^{79}BrO_3$, $[M+H]^+$=337.0434, found 337.0437. Mp 72–75 °C. FTIR (solid): 3005, 2937, 2839, 1596, 1468, 1455, 1415, 1207, 1190, 1149, 1121, 1059, 1040, 819, 776, 691, 671, 521 cm^{-1}.

4.8. 2,4,6-Trimethoxybiphenyl (13c, Table 2, entries 3 and 4)

The title compound was prepared by the general Table 2 procedure using either **12c** or **12d** as the halide. Purification by silica gel chromatography (EtOAc/hexanes, 1:9) afforded the product (81% from **12c**, 77% from **12d**) as a white, powdery solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.24 (m, 5H), 6.22 (s, 2H), 3.85 (s, 3H), 3.70 (s, 6H). Mp 152–154 °C (lit. Mp 152 °C). NMR and mp data for the synthesized compound using both electrophiles matched those reported by Becht et al.[27] for the title compound.

4.9. 2,4,6-Trimethoxy-4′-nitrobiphenyl (13d, Table 2, entry 5)

The title compound was prepared by the general Table 2 procedure using **12e** as the halide. Purification by silica gel chromatography (EtOAc/hexanes, 1:9) afforded the product (80%) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J=9.0 Hz, 2H), 7.50 (d, J=9.0 Hz, 2H), 6.23 (s, 2H), 3.86 (s, 3H), 3.72 (s, 6H). Mp 167–169 °C (lit. Mp 170 °C). NMR and mp data for the prepared compound corresponded to those reported by Abramovitch et al.[28] for the title compound.

4.10. 2,4,6-Trimethoxy-2′-methylbiphenyl (13e, Table 2, entry 6)

The title compound was prepared by the general Table 2 procedure using **12f** as the halide. Purification by silica gel chromatography (EtOAc/hexanes, 1:9) afforded the product (74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.15 (m, 4H), 6.27 (s 2H), 3.91 (s, 3H), 3.73 (s, 6H), 2.12 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 158.5, 138.0, 134.4, 131.5, 129.7, 127.2, 125.4, 112.1, 91.0, 56.0, 55.5, 20.0. HRMS (ESI): calculated for $C_{16}H_{18}O_3$, $[M+H]^+$=259.1329, found 259.1336. Mp 91–93 °C. FTIR (solid): 3017, 2956, 2936, 2846, 1607, 1585, 1456, 1410, 1338, 1223, 1207, 1153, 1124, 1058, 1003, 807, 768, 731 cm^{-1}.

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Supplementary data

Characterization data, ^{1}H and ^{13}C NMR and HRMS for new compounds **13b** and **13e** are available. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.030. These data include MOL files and InChIKeys of the most important compounds described in this article.

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