Synthesis of 5-Substituted Resorcinol Derivatives Via Cross-Coupling Reactions

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Suzuki and Stille cross-coupling reactions were utilized in the synthesis of 5-substituted 1,3-dimethoxybenzene and 5-substituted resorcinol derivatives. The substituted resorcinol derivatives were obtained in only three steps from inexpensive reagents. 1,3-Dimethoxybenzoic acid and 1-chloro-3,5-dimethoxybenzene were transformed into 1-iodo-, 1-bromo-, 1-trimethyltin-3,5-dimethoxybenzene and 3,5-dimethoxyphenyl boronic acid. 5-Allyl-1,3-dimethoxybenzene and 3,5-dimethoxybiphenyl derivatives were obtained via cross coupling reactions under mild conditions. HI, BBr_3 and AlI_3 were used to demethylate these dimethoxybenzenes into their resorcinol derivatives.

Introduction

5-Substituted resorcinol derivatives are interesting biologically active compounds, possessing fungicidal and bacteriocidal activities[1]. They have antileukemic properties[2][3] and cleave DNA in the presence of Cu(II) and O_2[4]. Furthermore they are important building blocks in the synthesis of cannabis derivatives[5]. However, the accessibility of this type of compounds is rather poor. Only few starting compounds are available and those being available are rather expensive. There are many possible ways to synthesize these compounds but all have disadvantages. The oldest one, the construction of the aromatic ring[6][7][8][9][10] is not compatible with many functional groups. Another synthetic route is the Sandmeyer reaction on 3,5-dimethoxyaniline, followed by introduction of a halide[11][12] or other substituents[13]. The drawback of this synthetic pathway is that 1,3-dimethoxyaniline is expensive and the yields are only moderate. Routes starting from commercially available 1,3-dimethoxybenzene or resorcinol derivatives have also been published; methyl 3,5-dihydroxybenzoate[3], 3,5-dimethoxybenzaldehyde[4][14] and 3,5-dimethoxybenzylic alcohol[15] have been used. The reactions with these compounds all result in the formation of alkyl or vinyl substituted resorcinol derivatives in moderate to good yields. Only recently Fürstner et. al.[16] published an elegant synthesis of 5-alkylresorcinols. 3,5-Dimethoxyphenol was treated with triflic anhydride after which 3,5-dimethoxyphenyltriflate was obtained. Subsequent reactions with several boranes yielded 5-alkyl substituted resorcinol derivatives in good yields.

In this paper we present simple methods to synthesize 5-substituted resorcinol derivatives. We used 1-chloro-3,5-dimethoxybenzene (**4**) and 1,3-dimethoxy benzoic acid as starting compounds. 1-Iodo- (**5**), 1-bromo- (**3**), 1-trimethyltin-3,5-dimethoxybenzene (**6**) and 3,5-dimethoxyphenyl boronic acid (**11**) were synthesized, which are all versatile compounds that can be used in further reactions. Via these routes both electrophilic and nucleophilic 5-substituted 1,3-dimethoxybenzenes are readily available, which can react to form a wide range of substituted products. 5-Aryl and 5-allyl substituted 1,3-dimethoxybenzene derivatives are examples that can be obtained via the Stille and Suzuki cross-coupling reactions under mild conditions. These cross-coupling reactions are tolerant to functional groups like aldehydes, carboxylic acids, esters, nitriles and alkenes. The introduction of protective groups can be avoided when these cross-coupling reactions are used.

An additional problem in the synthesis of 5-substituted resorcinols is the demethylation reaction, the final step in the synthesis of these products. Several reagents are used in literature like MeMgI, HI, AlI_3, $SiMe_3I$, NaCN, LiI, 9-iodoborabicyclo[3.3.1]nonane (9-iodo-9-BBN) and BBr_3[4][5][11][12][16][17][18][19] but it is difficult to select a proper demethylating agent. These reagents are highly reactive towards other groups and therefore not always applicable. Finally demethylation of 1,3-dimethoxybenzene derivatives is more difficult than that of other methoxybenzenes[17]. Therefore we investigated several demethylating reagents and selected the optimal reagent.

Results and Discussion

3,5-Dimethoxybenzoic acid was converted into 3,5-dimethoxybenzoyl chloride (**1**) with $SOCl_2$ under standard conditions, affording a quantitative yield[20]. The reaction with PCl_5 did not result in the desired product as the reagent was too aggressive, a black tar was formed. Subsequently 1-bromo-3,5-dimethoxybenzene (**3**) was synthesized from **1** using the "Barton" procedure[21] (see Scheme 1). In this reaction, ester **2** is formed in situ and undergoes decarboxylative halogenation in $CBrCl_3$ resulting in the formation of **3** in 60% yield. The excess of $CBrCl_3$ was recycled and after distillation it was reused at least three times in

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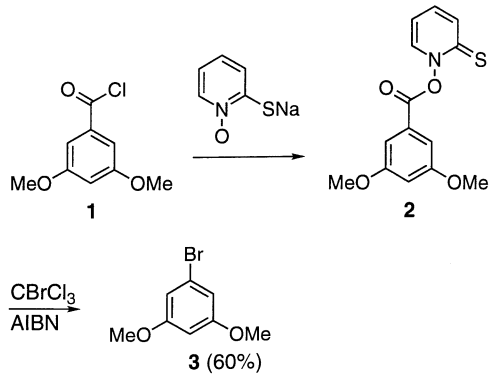
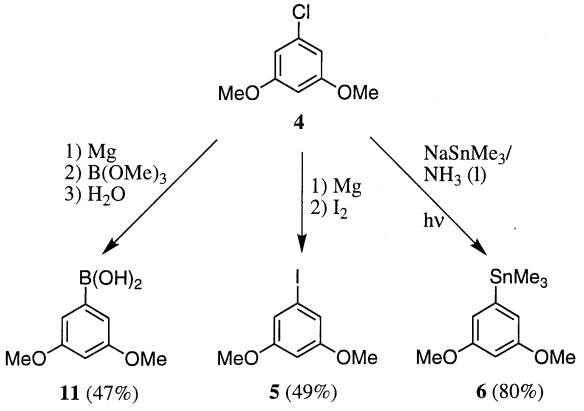
Scheme 1. Conversion of 3,5-dimethoxybenzoyl chloride (**1**) into 5-bromo-1,3-dimethoxybenzene (**3**) via the "Barton" procedure



this reaction. This is an elegant and fast route, competitive with the one used by Dean et. al.[11], which also starts from **1**. Their route involves the reaction of benzoylchloride (**1**) with ammonia yielding the amide. Via a Hofmann rearrangement and a Sandmeyer reaction bromide **3** was obtained in an overall yield of 41%.

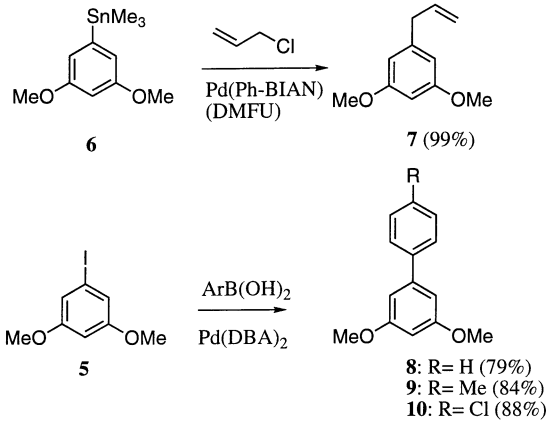
The other starting compound used in the synthesis of the substituted resorcinol derivatives, 1-chloro-3,5-dimethoxybenzene (**4**) is shown in Scheme 2. The reaction of iodine with the Grignard reagent, obtained from **4** and magnesium, yielded 1-iodo-3,5-dimethoxybenzene (**5**). A small disadvantage of this route is the troublesome and not always reproducible formation of the Grignard reagent. Activated Mg was prepared in several ways and, applied in the synthesis of the Grignard of **4**. Mg dust, a mixture of Mg/$C_2H_4Br_2$ and $MgCl_2$/K/KI[22] were tried, but the use of neither of these reagents resulted in completion of the reaction. Typical yields of this Grignard reaction are ≈ 50% after work up. 1,1′,3,3′-Tetramethoxybiphenyl was formed as a side product in this reaction. Large amounts of unreacted **4** could be removed by distillation.

Scheme 2. Conversion of 1-chloro-3,5-dimethoxybenzene (**4**) into 1-iodo- (**5**), 1-trimethyltin-1,3-dimethoxybenzene (**6**) and 3,5-dimethoxyphenyl boronic acid



The palladium catalyzed reaction of 1-iodo-3,5-dimethoxybenzene (**5**) with three different aryl boronic acids, under phosphine-free reaction conditions, afforded the 1,3-dimethoxy substituted biphenyls **8**–**10** (see Scheme 3). Compounds **8**–**10** are formed in high yields using this "Suzuki reaction"[23][24]. 1,3-Dimethoxybiphenyl (**8**) had already been prepared from 3,5-dimethoxyaniline[13]. After diazotation and reaction with benzene the aniline was converted into **8** in a yield comparable to ours. The route used in this paper, however, opens a way to more diverse products. It should be noted that the reaction of **5** with *p*-chlorophenyl boronic acid reached completion within 6 h, precipitated palladium black indicated the end of the reaction. The chlorine moiety reduces the electron density on the aromatic ring, which makes this particular substrate more reactive. The reactions with phenyl- and *p*-tolyl boronic acid needed prolonged reaction times. Products **8**–**10** can also be prepared via the reverse reaction of 3,5-dimethoxyphenyl boronic acid (**11**) with aromatic iodides. Similar yields were observed when this procedure was used. Again the Grignard formation was troublesome in the synthesis of **11** itself, but the yield of **11** can be compared with that of **5** which was also obtained from the Grignard of **4**.

Scheme 3. Palladium catalyzed cross-coupling reactions with substituted 3,5-dimethoxybenzene derivatives



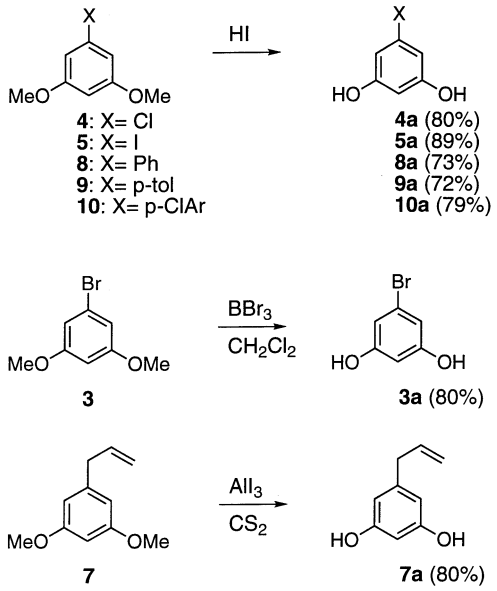
Another versatile starting compound in the synthesis of substituted 1,3-dimethoxybenzene derivatives is 1-trimethyltin-3,5-dimethoxybenzene (**6**). Aryltin compounds react with both alkyl and aryl halides, in "Stille type" reactions, giving access to a wide range of products. A route published by Yammal et. al.[25][26] was chosen to prepare compound **6** (see Scheme 2). The introduction of the $SnMe_3$ group on the aromatic ring was accomplished via a reaction of $NaSnMe_3$ with **4**. This is a light-induced radical reaction that proceeds extremely well with chloroarenes. Bromo- or iodoarenes give the reduced compound (1,3-dimethoxybenzene). We increased the scale of the reaction up to 80 mmol, a 25 fold increase compared to the published[25] values for similar compounds. The obtained yield (80%) was high compared to that of the Grignard reaction. This reaction was also highly reproducible and the only side product in this reaction was 1,3-dimethoxybenzene, which could be easily removed by distillation.

Compound **6** reacted with allylchloride in a "Stille type" reaction, forming 5-allyl-1,3-dimethoxybenzene (**7**) in quantitative yield (see Scheme 3). A Pd^0 compound with

Ph-BIAN [bis(phenylimino) acenaphtene] and DMFU (dimethyl fumarate) as ligands is the catalyst in this reaction. Only a small catalytic amount (0.1 mol%) was needed and no side products were formed. This catalyst is preferred to the $(PPh_3)_4Pd$ catalyst because it is about 17 times as fast[27] under these conditions. Side reactions like group exchange with phenyl groups of triphenylphosphine[28] are avoided when this ligand is used. The reaction of the Grignard of **4** with allyl bromide[19] proved unsuccessful in our case. Neither distillation nor column chromatography was successful in removing unreacted **4** from the product mixture. The overall yield is now increased up to 80% starting from **4**.

HI, BBr_3[17][18] and AlI_3[19] were selected as the appropriate demethylation reagents (see Scheme 4). Reagents like $SiMe_3I$, NaCN and LiI proved unsuccessful for these substrates. The use of MeMgI[4][15] was avoided because of the high reactivity towards other groups.

Scheme 4. Demethylation of substituted 3,5-dimethoxybenzene derivatives



We used HI to demethylate the 1,3-dimethoxybenzenes **4, 5, 8−10**. The reactions of **5**, **8−10** proceeded smoothly, after 3 h. of reflux good yields of resorcinol derivatives **5a**, **8a−10a** (average 80%) were obtained. This is in contrast to the reaction of **4** with HI, which gave large amounts of 5-iodoresorcinol (**5a**) and traces of resorcinol via halogen exchange. Therefore the reaction time was reduced to 90 minutes after which no side products could be detected. We have tried to optimize the reaction conditions as to make 1-chloro-3,5-dimethoxybenzene (**4**) react to 5-iodoresorcinol (**5a**) in one step. However, next to 5-chlororesorcinol (**4a**), resorcinol is the dominant product at higher conversions. The separation of **5a** and **4a** could not be accomplished and we did not succeed in obtaining pure **5a** from this reaction. The same halogen exchange was found monitoring the reaction of 1-bromo-3,5-dimethoxybenzene (**3**) with HI since after 15 min **5a** was already observed in ≈ 30% yield (estimation from GC-MS). Both Hodgson[12] and Dean [11] have used this demethylation reagent in the synthesis of **3a** and **4a,** but they made no mention of halogen exchange. Several batches of HI from different suppliers were tested but this unexpected side reaction turned out to be very persistent. To avoid this side reaction, BBr_3 was used as demethylation agent to convert **3** into **3a** in 80% yield. HI was not used to demethylate 5-allyl-1,3-dimethoxybenzene (**7**), because of its high reactivity towards double bonds. Again BBr_3 was used, but in this instance addition of HBr to the double bond occurred in yields up to 30% . Fürstner et. al.[16] also found side reactions when BBr_3 was used for demethylating substrates that contain double bonds. They reported that haloboration takes place whereas in our case addition of HBr was found. We added $(i\text{Pr})_2\text{NEt}$ to this reaction mixture to trap the acid and indeed addition of HBr was prevented. However, only low yields (< 10%) could be isolated when this combination of reagents was used. Therefore we used AlI_3 as demethylating agent[19]. The major disadvantage of this route is the use of CS_2 as solvent. After reaction the product contains sulphur contaminations that are difficult to remove. In our modified procedure the product is treated with PBu_3 after reaction. Column chromatography to remove the phosphorus compounds is sufficient and now a pure and odourless compound is obtained. Recently 9-iodo-9-BBN was used in the demethylation of resorcinol derivatives[16]. It proved a mild and successful demethylation agent but it is rather expensive compared to AlI_3.

In conclusion we can state that new methods have been applied successfully to the synthesis of 5-substituted resorcinol derivatives. The presented 1,3-dimethoxybenzene derivatives are now readily available and react with both nucleophilic and electrophilic substrates to form the desired products in high yields. The methods presented are translated easily to the synthesis of biologically active analogues, which opens up new areas in that field of research.

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Experimental Section

General: NMR: ^{1}H NMR (300.13 MHz) and ^{13}C NMR (75.48 MHz) were measured on Bruker AMX 300 and DRX 300 machines. The solvent used is $CDCl_3$, unless stated otherwise, with TMS as external reference. − IR spectra were measured on a Nicolet 510m FT-IR spectrophotometer. − GC-MS measurements were done on a Hewlett-Packard GC, equipped with a DB-5MS column; length 12 m; inner diameter 0.2 mm; film thickness 0.33 μm. − Melting points were determined on a Gallenkamp MFB-595 melting point apparatus, the values are uncorrected. − Column chromatography was performed with silica gel 60, 70−230 mesh ASTM (Merck). − Analytical TLC was performed on TLC aluminium foil, silica gel 60 F_{254} (Merck). − Elemental analyses were performed in our own laboratory on an Elementar Vario EL apparatus (Foss Electric). − Irradiation experiments were performed with a Philips HPK 125W high pressure Hg lamp.

Chemicals: THF was distilled from sodium/benzophenone, DMF and CH_2Cl_2 from CaH_2 and petroleum ether, boiling range 60−80°C (= PE) was distilled before use. AIBN, 5-chloro-1,3-dimethoxybenzene, dimethoxybenzoic acid, were purchased from Acros Chimica, phenyl boronic acid, trimethyltin chloride, BBr_3 in CH_2Cl_2 from Aldrich, $CBrCl_3$ and 2-mercaptopyridine *N*-oxide sodium salt from Merck. *p*-Tolyl boronic acid, *p*-chlorophenyl boronic acid[29], $Pd(DBA)_2$[30] (DBA = dibenzylidene acetone) and Pd(Ph-BIAN)(DMFU)[31] were prepared according to literature procedures.

3,5-Dimethoxybenzoyl Chloride (**1**)[20]: A flask adapted with a $CaCl_2$ drying tube, containing a suspension of 10 g of 3,5-dimethoxybenzoic acid (55 mmol), 6 ml of thionyl chloride (82.5 mmol) and a drop of DMF was refluxed for 18 h. The excess of thionyl chloride was removed in vacuo and a yellow oil was obtained. The oil was distilled under reduced pressure (b.p. 110°C/0.5 Torr) yielding 21.5 g (99%) of a colorless oil, which solidified after two days. − ^{1}H NMR ([D$_6$]acetone): δ = 6.48 (d, 2 H, ^4J = 2.1 Hz), 6.41 (t, 1 H, ^4J = 2.1 Hz). − ^{13}C NMR ([D$_6$]acetone): δ = 168.49 (*C*OCl), 162.1 (*C*−O), 135.6 (*C*−Cl), 109.8, 108.5, 56.4 (O−*C*H$_3$).

1-Bromo-3,5-dimethoxybenzene (**3**)[21]**:** A mixture of 3 g of **1** (15.1 mmol) and 370 mg of AIBN [2,2′-azobis(2-methylpropionitrile)] (2.3 mmol) in 30 ml of $CBrCl_3$ was added in 45 min to a refluxing suspension of 2.5 g of 2-mercaptopyridine *N*-oxide sodium salt (15.5 mmol) in 30 ml of $CBrCl_3$. The suspension was refluxed until the yellow color had disappeared (5−15 min). The suspension was cooled to room temp. and the $CBrCl_3$ was removed in vacuo. The residue was purified by column chromatography using silica gel (eluent 30%, PE/CH_2Cl_2). Yield 2 g (60%) of a white solid, m.p. 66.5−66.8°C (ref.[11] 66°C). − IR (KBr): $\tilde{\nu}$ = 3080−2936 (w) cm^{-1}, 1581, 1471, 1452, 1428, 1300, 1201, 1160, 1036. − ^{1}H NMR: δ = 6.66 (d, 2 H, ^4J = 2.2 Hz), 6.38 (t, 1 H, ^4J = 2.3 Hz), 3.78 (s, 6 H, O−C*H*$_3$). − ^{13}C NMR: δ = 161.5 (*C*−O), 123.2 (*C*-Br), 110.1 , 100.0 , 55.8 (O−*C*H$_3$). − MS; *m/z*: 216, 218 [M$^+$]. − $C_8H_9BrO_2$ (217.1): calcd. C 44.27, H 4.18; found C 44.61, H 4.25.

1-Iodo-3,5-dimethoxybenzene (**5**): Magnesium flakes 3.7 g (154 mmol) were brought into a flame dried flask, followed by addition of 20 g of **4** (116 mmol) dissolved in 30 ml of THF. The suspension was refluxed for 36 h and the suspension was cooled on an ice bath. Subsequently 19.2 g of iodine dissolved in 60 ml of THF was added dropwise while stirring the viscous slurry vigorously. After 2 h the solution was treated with 50 ml of 1 M of HCl and 40 ml of diethyl ether, the organic layer was separated and washed twice with 1 M of a sodium thiosulfate solution. After drying with $MgSO_4$ the yellow solution was evaporated and the remaining solid was purified by column chromatography using silica gel (eluent 10%, EtOAc/PE). Yield 15 g (49%) of a white solid, m.p. 74.3−74.6°C. − IR (KBr): $\tilde{\nu}$ = 3069−2834 (w) cm^{-1}, 1576, 1471, 1450, 1424, 1294, 1198, 1162, 1032. − ^{1}H NMR: δ = 6.85 (d, 2 H, ^4J = 2.3 Hz), 6.40 (t, 1 H, ^4J = 2.3 Hz), 3.75 (s, 6 H, O−C*H*$_3$). − ^{13}C NMR: δ = 160.8 (*C*−O), 115.9, 100.4 , 94.0 (*C*−I), 55.3 (O−*C*H$_3$). − MS; *m/z*: 264 [M$^+$]. − $C_8H_9IO_2$ (264.1): calcd. C 36.38, H 3.43; found C 36.60, H 3.46.

3,5-Dimethoxybiphenyl (**8**)[32]: A mixture of 1 g of **5** (3.8 mmol), 0.5 g of phenyl boronic acid (4.1 mmol) and 1.3 g of K_2CO_3 (9.5 mmol) dissolved in 10 ml of acetone and 5 ml of water was frozen with liquid nitrogen, evacuated and refilled with Ar. This procedure was repeated and followed by addition of 10 mg of $Pd(DBA)_2$ (0.015 mmol). The evacuation procedure was repeated once more and the mixture was refluxed for 18 h. The reaction mixture was cooled to room temp., filtered and the acetone removed in vacuo. After addition of 20 ml of CH_2Cl_2 the organic layer was washed twice with 10 ml of demineralized water. The organic layer was evacuated and the resulting off white oil purified by column chromatography on silica gel (eluent: 40%, PE/CH_2Cl_2). Yield 0.64 g (79%) of a white solid, m.p. 62.4−62.6°C (ref.[13] 61−62°C). − IR (KBr): $\tilde{\nu}$ = 3150−2820 (w) cm^{-1}, 1595, 1574, 1416, 1216, 1154, 1067, 1025. − ^{1}H NMR: δ = 7.62 (d, 2 H, ^3J = 6.9 Hz), 7.44 (m, 3H), 6.78 (d, 2 H, ^4J = 2.2 Hz), 6.52 (t, 1 H, ^4J = 2.2 Hz), 3.88 (s, 6 H, O−C*H*$_3$). − ^{13}C NMR: δ = 160.9 (*C*−O), 143.3 (*C*−C), 141.0 (*C*−C), 128.5, 127.4, 127.0, 105.3, 99.1, 55.2 (O−*C*H$_3$). − MS; *m/z*: 214 [M$^+$], 185. − $C_{14}H_{14}O_2$ (214.3): calcd. C 78.47, H 6.59; found C 78.00, H 6.32.

1-(4′-Methylphenyl)-3,5-dimethoxybenzene (**9**): The same conditions as for **8** were used, with the following amounts: 3 g of **5** (11.36 mmol), 1.67 g of *p*-tolyl boronic acid (12.27 mmol), 3.9 g of K_2CO_3 (28.4 mmol) and 26 mg of $Pd(DBA)_2$ (0.045 mmol). Yield 2.2 g (84.5%) of a white solid, m.p. 57.3−57.5°C. − IR (KBr): $\tilde{\nu}$ = 3160−2780 (w) cm^{-1}, 1604, 1592, 1569, 1452, 1204, 1196, 1161, 1150, 1065, 1034. − ^{1}H NMR: δ = 7.49 (d, 2 H, ^3J = 8.0 Hz), 7.25 (d, 2 H, ^3J = 8.0 Hz), 6.73 (d, 2 H, ^4J = 2.2 Hz), 6.46 (t, 1 H, ^4J = 2.2 Hz), 3.86 (s, 6 H, O−C*H*$_3$), 2.41 (s, 3 H, C*H*$_3$). − ^{13}C NMR: δ = 161.4 (*C*−O), 144.9 (*C*−C), 138.7 (*C*−C), 137.8 (*C*−C), 129.8, 127.4, 105.7, 99.4, 55.8 (O−*C*H$_3$), 21.5 (*C*H$_3$). − MS; *m/z*: 228 [M$^+$], 199. − $C_{15}H_{16}O_2$ (228.3): calcd. C 78.92, H 7.06; found C 78.30, H 6.78.

1-(4′-Chlorophenyl)-3,5-dimethoxybenzene (**10**): The same conditions as for **8** were used, with the following amounts: 3 g of **5** (11.36 mmol), 1.92 g of *p*-chlorophenyl boronic acid (12.27 mmol), 3.9 g of K_2CO_3 (28.4 mmol) and 26 mg of $Pd(DBA)_2$ (0.045 mmol). When palladium black was observed (6 h), the reaction mixture was cooled to room temp. and worked up. Yield 2.5 g (88%) of a white solid, m.p. 64.6−64.8°C. − IR (KBr): $\tilde{\nu}$ = 3072−2823 (w) cm^{-1}, 1596, 1566, 1425, 1391, 1209, 1193, 1154, 1061. − ^{1}H NMR: δ = 7.50 (d, 2 H, ^3J = 8.55 Hz), 7.40 (d, 2 H, ^3J = 8.55 Hz), 6.68 (d, 2 H, ^4J = 2.2 Hz), 6.48 (t, 1 H, ^4J = 2.2 Hz), 3.85 (s, 6 H, O−C*H*$_3$). − ^{13}C NMR: δ = 161.5 (*C*−O), 141.0 (*C*−C), 140.0 (*C*−C), 135.0 (*C*−Cl), 129.3, 128.8, 105.7, 99.8, 55.8 (O−*C*H$_3$). − MS; *m/z*: 248, 246 [M$^+$]. − $C_{14}H_{13}ClO_2$ (248.7): calcd. C 67.61, H 5.27; found C 67.40, H 5.04.

1-Trimethyltin-3,5-dimethoxybenzene (**6**)[26]: To a cooled (−60°C) solution of 15 g of trimethyltin chloride (75.6 mmol) in 1.5 l of liquid NH_3, addition of Na was continued (≈ 2.1 equiv.) until the blue color remained. Subsequently 12.3 g of **4** (71.3 mmol) was added and the solution was allowed to warm to −33°C. The flask was equipped with a dry ice cooler and the suspension was irradiated for 4 h with a high pressure mercury lamp. When the reaction reached completion 1−2 ml of MeI was added upon which the yellow color disappeared. Subsequently 75 ml of H_2O and 75 ml of THF were added and the solution was allowed to warm to room temp. overnight under a gentle stream of N_2. Diethyl ether (100 ml) and 50 ml of H_2O were added, the water layer was washed twice with 50 ml of diethyl ether, the collected organic layers were washed twice with 50 ml of H_2O, dried with $MgSO_4$ and evaporated to dryness. Yield after distillation 17 g (80%) of a colorless oil, b.p. 100°C/0.5 Torr. − IR ($CDCl_3$): $\tilde{\nu}$ = 3075−2913 (w) cm^{-1}, 1582, 1452, 1409, 1325, 1281, 1204, 1157, 1063, 1044. − ^{1}H NMR: δ = 6.65 (d, 2 H, ^4J = 2.4 Hz, $^3J_{Sn-H}$ = 48 Hz), 6.42 (t, 1 H, ^4J = 2.4 Hz), 3.82 (s, 6 H, O−C*H*$_3$), 0.31 (s, 9 H, SnC*H*$_3$, $^3J_{Sn-H}$ = 54 Hz). − ^{13}C NMR: δ = 161.4 [*C*−O, ^3J(^{117}Sn−C) = 63 Hz, ^{3}J(^{119}Sn−C) = 66 Hz], 145.8 [*C*-Sn, ^1J(^{117}Sn−C) = 430 Hz, ^1J(^{119}Sn−C) = 454 Hz], 114.4 [^2J(^{117}Sn-C) = 35 Hz, ^2J(^{119}Sn-C) = 42 Hz], 101.6, 56.6 (O−*C*H$_3$), −5.7 [Sn*C*H$_3$, ^1J(^{117}Sn−C) = 351 Hz, ^1J(^{119}Sn−C) = 363 Hz]. − MS; *m/z*: 302 (M$^+$, w), 287 (M$^+$ -

15, s). − $C_{11}H_{18}O_2Sn$ (301): calcd. C 43.90, H 6.13; found C 44.05, H 6.01.

3,5-Dimethoxyphenyl Boronic Acid (**11**): A mixture of 2 g of Mg and 5 g (29.5 mmol) of **4** in 10 ml of THF was refluxed for 24 h. The brown slurry was cooled to room temp., diluted with 20 ml of THF, filtered and added to a cooled (−78°C) solution of 5 ml of $B(OMe)_3$ (44.3 mmol) in 40 ml of THF. The grey suspension was allowed to warm to room temp. overnight. The reaction mixture was poured onto 20 ml of 1 M of HCl and 50 ml of diethyl ether. After separation the water layer was washed with 30 ml of diethyl ether and the collected organic layers were washed twice with 25 ml of 1 M of NaOH. After washing twice with 10 ml of CH_2Cl_2, the water layer was acidified with conc. HCl and extracted twice with 25 ml of CH_2Cl_2. The organic fraction was dried with $MgSO_4$ and evaporated to dryness. Yield 2.4 g (45%) of a white solid , m.p. 200.7−201.7°C. − IR (KBr): $\tilde{\nu}$ = 3284 (m, OH) cm^{-1}, 3010−2840 (w), 1589, 1448, 1422, 1364, 1336, 1202, 1158, 1060, 1041. − ^1H NMR ([D$_6$]acetone): δ = 7.28 (s, O−*H*), 7.15 (d, 2 H, ^4J = 2.3 Hz), 6.64 (t, 1 H, ^4J = 2.3 Hz), 3.88 (s, 6 H, O−CH_3). − ^{13}C NMR ([D$_6$]DMSO): δ = 161.1 and 161.0 (*C*−O), 142.6 and 137.4 (*C*−B), 112.6 and 111.9, 103.4 and 102.5, 56.0 (O−*C*H$_3$). − $C_8H_{11}BO_4$ (182.0): C 52.80, H 6.09; found C 53.15, H 6.13.

5-Allyl-1,3-dimethoxybenzene (**7**)[27]**:** A mixture of 17 g of **6** (56 mmol), 7 ml of allyl chloride (90 mmol) and 25 mg of Pd(PhBIAN)(DMFU) (0.043 mmol) in 120 ml of dry DMF was heated overnight at 50°C. The solution was cooled to room temp. and poured onto a mixture of 150 ml of H_2O and 100 ml of hexane. The water layer was washed twice with 50 ml of hexane and the collected hexane layers were washed three times with 50 ml of H_2O. The organic layer was dried with $MgSO_4$, evaporated and distilled. Yield 8 g (99%) of a colorless oil b.p. 68°C/0.25 Torr. − IR (neat): $\tilde{\nu}$ = 3079−2837 (w) cm^{-1}, 1608, 1589, 1462, 1430, 1346, 1323, 1295, 1207. − ^1H NMR: δ = 6.37 (d, 2 H, ^4J = 2.1 Hz), 6.33 (d, 1 H, ^4J = 2.1 Hz), 5.95 (m, 1 H, *H*−Ol), 5.1 (m, 2 H, *H*−Ol), 3.79 (s, 6 H, O−CH_3), 3.34 (d, 2 H, CH_2, ^3J = 6.7 Hz). − ^{13}C NMR: δ = 161.1 (*C*−O), 142.7 (*C*−C), 137.3, 116.2 (Ol*C*H$_2$), 106.9, 98.4, 55.6 (O−*C*H$_3$), 40.7 (*C*H$_2$). − MS; *m*/*z*: 178 [M$^+$].

5-Bromoresorcinol (**3a**): A solution of 2 g of **3** (9.2 mmol) dissolved in 25 ml of dry CH_2Cl_2 was cooled to −78°C. Hereafter 19 mmol of BBr_3 (19 ml of a 1 M solution in CH_2Cl_2) was added and the reaction mixture was allowed to warm to room temp. overnight. The brown solution was cooled on ice and 50 ml of water was slowly added. The two layers were separated and the water layer was washed twice with 40 ml of CH_2Cl_2. The collected organic layers were washed once with 30 ml of 1 M solution of sodium thiosulfate and once with 50 ml of water, dried with $MgSO_4$ and evaporated to dryness. After purification via column chromatography using silica gel (eluent 40%, EtOAc/PE) the residue was crystallized from $CHCl_3$ yielding 1.4 g (78%) of a grey-brown light sensitive solid[12], m.p. 85−86.4°C (ref.[12] 87°C). − IR (KBr): $\tilde{\nu}$ = 3620 (m, OH) cm^{-1}, 3268 (br, OH), 1599, 1473, 1297, 1197, 1154. − ^1H NMR ([D$_6$]acetone): δ = 8.63 (s, 2 H, *H*−O), 6.53 (d, 2 H, ^4J = 2.1 Hz), 6.33 (t, 1 H, ^4J = 2.1 Hz). − ^{13}C NMR ([D$_6$]acetone): δ = 160.2 (*C*−O), 123.1 (*C*−Br), 111.0, 102.7. − MS; *m*/*z*: 188, 190 [M$^+$]. − $C_6H_5BrO_2$ (189): calcd. C 38.13, H 2.67; found C 37.76, H 3.32.

5-Chlororesorcinol (**4a**): A solution of 11 g of **4** (66.7 mmol) and 80 ml (57 w%) of HI (623 mmol) was refluxed for 90 min. The solution was cooled to room temp. and diluted with 100 ml water and 100 ml of diethyl ether was added. The organic layer was separated and subsequently washed twice with 10 ml of 1 M of sodium thiosulfate and once with 50 ml of brine. After drying with $MgSO_4$ the solvent was evaporated. The residue was crystallized from benzene/hexane yielding 7.7 g (80%) of a yellow solid, m.p. 112−114°C (ref.[12] 117°C). − IR (KBr): $\tilde{\nu}$ = 3626 (w, OH) cm^{-1}, 3272 (br, OH),1605, 1491, 1473, 1300, 1196, 1153, 1094. − ^1H NMR ([D$_6$]acetone): δ = 8.74 (s, 2 H, *H*−O), 6.48 (d, 2 H, ^4J = 2.1 Hz), 6.41 (t, 1 H, ^4J = 2.1 Hz). − ^{13}C NMR ([D$_6$]acetone): δ = 164.2 (*C*−O), 139.4 (*C*−Cl), 112.1, 106.4. − MS; *m*/*z*: 144, 146 [M$^+$].

5-Iodoresorcinol (**5a**): A solution of 2.5 g of **5** (9.5 mmol) and 12 ml (57 w%) of HI (90 mmol) was refluxed for 3 h. The dark brown solution was cooled to room temp. and diluted with 20 ml water, followed by addition of 20 ml of diethyl ether. The organic layer was separated and washed twice with 10 ml of 1 M of sodium thiosulfate and once with 10 ml of demineralized water. After drying with $MgSO_4$ the solvent was evaporated yielding 2 g of a white solid (89%), m.p. 84.6−85°C (ref.[12] 92.3°C). − IR (KBr): $\tilde{\nu}$ = 3589 (m, OH) cm^{-1}, 3239 (br, OH), 1610, 1586, 1480, 1473, 1344, 1165. − ^1H NMR ([D$_6$]acetone): δ = 8.62 (s, 2 H, *H*−O), 6.83 (d, 2 H, ^4J = 2.2 Hz), 6.44 (t, 1 H, ^4J = 2.2 Hz). − ^{13}C NMR ([D$_6$]acetone): δ = 160.1 (*C*−O), 117.6, 103.9, 95.2 (*C*−I)**.** − MS; *m*/*z*: 236 [M$^+$]. − C6H5IO2·0.5 H_2O (236.0): calcd. C 29.41, H 2.47; found: C 29.25, H 2.74.

5-Phenylresorcinol (**8a**): The same procedure as for **5a** was used, with 0.86 g (4 mmol) of **8** and 5 ml of HI (40 mmol). After workup the yellow oil was purified by column chromatography using silica gel (eluent 40%, EtOAc/PE). Yield 0.54 g (73%) of a white solid, m.p. 157°C (ref.[7] 157°C). − IR (KBr): $\tilde{\nu}$ = 3308 (br, OH) cm^{-1}, 1624, 1603, 1339, 1201, 1158, 1148, 1000. − ^1H NMR: δ = 8.35 (s, 2 H, *H*−O), 7.56 (d, 2 H, ^3J = 7.2 Hz), 7.41 (t, 2 H, ^3J = 7.05 Hz), 7.31 (t, 1 H, ^3J = 7.2 Hz), 6.65 (br, 2 H), 6.40 (br, 1 H). − ^{13}C NMR: δ = 159.9 (*C*−O), 144.1 (*C*−C), 142.1 (*C*−C), 129.6, 128.2, 127.6, 106.5, 102.6. − MS; *m*/*z*: 286 [M$^+$]. − $C_{12}H_{10}O_2$ (186.2): calcd. C 77.40 , H 5.41; found C 77.34, H 5.44.

5-(4′-Methylphenyl)resorcinol (**9a**): The same procedure as for **5a** was used, with 0.91 g (4 mmol) of **9** and 5 ml of HI (40 mmol). After workup the yellow oil was purified by column chromatography using silica gel (eluent 40%, EtOAc/PE). Yield 0.58 g (72%) of a white solid, m.p. 163.2−164°C. − IR (KBr): $\tilde{\nu}$ = 3360 (br, OH) cm^{-1}, 1631, 1611, 1482, 1259, 1162, 1010, 1002. − ^1H NMR: δ = 8.28 (s, 2 H, *H*−O), 7.44 (d, 2 H, ^3J = 6.82 Hz), 7.21 (d, 2 H, ^3J = 6.82 Hz), 6.61 (br, 2 H), 6.35 (br, 1 H), 2.33 (s, 1 H, CH_3). − ^{13}C NMR: δ = 159.8 (*C*−O), 144.1 (*C*−C), 139.3 (*C*−C), 137.8 (*C*−C), 130.3, 127.5, 106.3, 102.4, 21.1 (*C*H$_3$). − MS; *m*/*z*: 214 [M$^+$]. − $C_{13}H_{12}O_2$ (202.1): calcd. C 77.98, H 6.04; found C 77.74, H 6.12.

5-(4′-Chlorophenyl)resorcinol (**10a**): The same procedure as for **5a** was used, with 1.0 g (4 mmol) of **10** and 5 ml of HI (40 mmol). After workup the yellow oil was purified by column chromatography using silica gel (eluent 40%, EtOAc/PE). Yield 0.7 g (79%) of a white solid, m.p. 151.9−152.3°C. − IR (KBr): $\tilde{\nu}$ = 3265 (br, OH) cm^{-1}, 1625, 1605, 1481, 1473, 1165, 1153, 1004. − ^1H NMR: δ = 8.38 (s, 2 H, *H*−O), 7.57 (d, 2 H, ^3J = 6.42 Hz), 7.41 (d, 2 H, ^3J = 6.42 Hz), 6.59 (br, 2 H), 6.39 (br, 1 H). − ^{13}C NMR: δ = 160.0 (*C*−O), 142.8 (*C*−C), 140.9 (*C*−C), 133.7 (*C*−Cl), 129.7, 129.3, 106.4, 103.0. − MS; *m*/*z*: 224, 222 [M$^+$]. − $C_{12}H_9ClO_2 \cdot 0.5\ H_2O$ (220.7): calcd. C 62.76, H 4.39; found C 62.78, H 4.49.

5-Allylresorcinol (**7a**): A mixture of 5.6 g of aluminium (210 mmol) and 42 g of iodine (168 mmol) in 400 ml of carbon disulphide was heated at reflux for 2 h. The brown reaction mixture was cooled on an ice bath and 10 g of **7** (56 mmol) in 20 ml of carbon disulphide was slowly added. The reaction mixture was refluxed overnight and then cooled on an ice bath, 100 ml of ice water was added and the mixture was stirred for 30 min. After addition of

100 ml of water, the two layers were separated and the water layer was washed twice with 75 ml of diethyl ether. The organic layers were collected and washed respectively with 50 ml of a 1 M sodium thiosulfate solution and twice with 50 ml of water. The organic layer was dried with $MgSO_4$ and evaporated to dryness. The brown oil was dissolved in 20 ml of THF and 2 ml of PBu_3 was added. After refluxing overnight and evaporation the product was purified by column chromatography on silica gel (eluent 30%, EtOAc/PE 60−80). Yield 6.8 g (81%) of a yellow colorless oil. − IR (neat): $\tilde{\nu}$ = 3326 (br, OH) cm^{-1}, 2979−2907 (w), 1605, 1477, 1453, 1154, 1000. − ^{1}H NMR: δ = 6.26 (d, 2 H, ^4J = 2 Hz), 6.21 (t, 1 H, ^4J = 2 Hz), 5.81 (m, 1 H, *H*CCH$_2$), 5.0 (d, 1 H, *H*HCCH, J = 5 Hz), 5.0 (s, 1 H, H*H*CCH), 3.17 (d, 2 H, C*H*$_2$, ^3J = 6.8 Hz). − ^{13}C NMR: δ = 159.9 (*C*−O), 143.5 (*C*−C), 137.0, 116.4 (*C*H$_2$), 108.6, 101.0, 40.2 (*C*H$_2$). − MS; *m*/*z*: 150 [M$^+$].

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