Note

Synthetic Studies Toward Bazzanin K: Regioselective and Chemoselective Three-Component Suzuki Coupling

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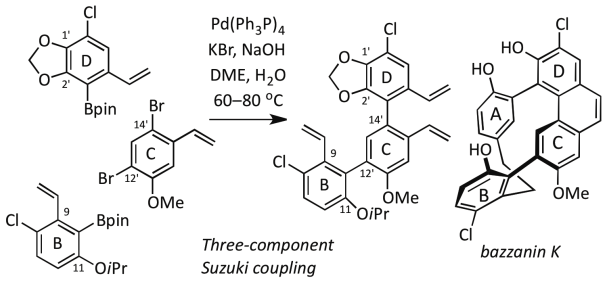
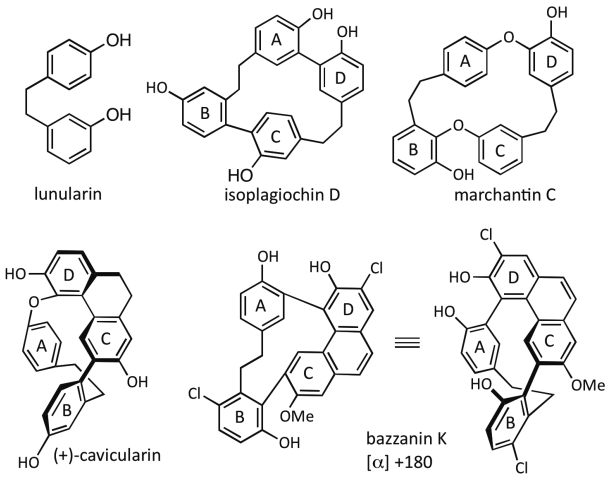


Abstract: The terphenyl substructure of the chiral cyclophane natural product bazzanin K was constructed. The key step involved sequential Suzuki couplings of a non-symmetric dibromobenzene, which can be performed as a two-step process or as a one-pot three-component coupling. The key step represented a regioselective coupling of a dibromobenzene, as well as a chemoselective coupling of phenyl bromides in the presence of phenyl chlorides. Terphenyl intermediates displayed atropdiastereoisomerism, and they were converted to a single phenanthrene target by way of ring-closing metathesis.

The macrocyclic bis(bibenzyl) (MBB) natural products are a family of several dozen dimeric molecules produced by liverworts (Figure 1).[1] Various members of the family have interesting biological activities including anti-tumor, antimicrobial, and antiviral activities.[2]

Figure 1. MBB Natural Products.

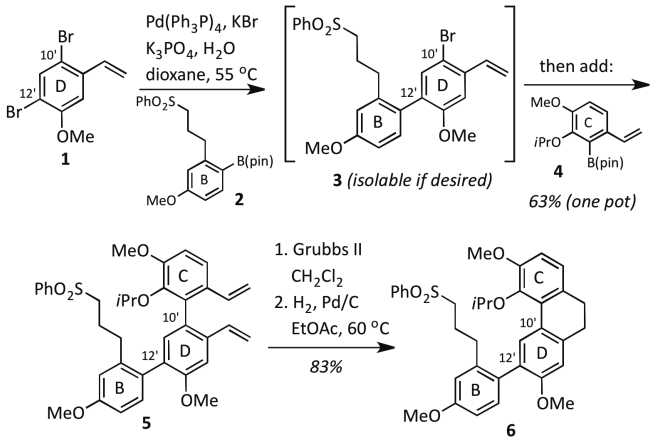


The MBB natural products are biosynthesized from two equivalents of lunularin by oxidative phenolic couplings.[3] The two lunularin substructures can be joined by either C–C bonds (e.g., isoplagiochin D),[4] by C–O bonds (e.g., marchantin C),[5] or by one of each linkage type. MBB family members display a wide range of linkage regiochemistry resulting from the phenolic radical couplings.[1] Additional oxidation of the MBB scaffold is very common, usually in the form of additional benzene hydroxylation or unsaturation of the ethylene tethers.[1] Particularly interesting MBB structures arise from additional ring-forming oxidations, such as cavicularin[6] and bazzanin K (Figure 1, bottom).[7] These molecules are quite strained; the crystal structure of cavicularin reveals that the A-ring exists in a non-planar boat-like conformation.[6]

Our interest in MBB natural products arises from the structural and conformational properties of these more highly oxidized congeners. Specifically, the strained molecular architectures lead to conformations with restricted bond rotations, and they can display molecular chirality. Cavicularin exists as a non-racemic chiral molecule that is conformationally stable up to approximately 180 ºC.[8] Bazzanin K was isolated as an optically active sample.[7] Assuming the sample was pure, this indicates that it is both chiral and conformationally stable as a non-racemic sample at room temperature. However, its conformational stability has not been confirmed[9] or investigated at elevated temperatures. Strained macrocyclic molecules are not trivial to prepare, especially as non-racemic compounds, and these structures represent formidable challenges for synthetic chemists.

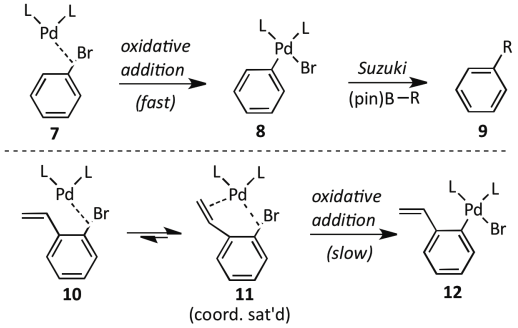
We previously synthesized cavicularin using a key Suzuki reaction (or Suzuki–Miyaura reaction) cascade to build the dihydrophenanthrene portion of the molecule (Scheme 1).[10] It was discovered that a regioselective Suzuki coupling of **1** and **2** occurs at the C12' bromide (cavicularin numbering) to give **3**. The C10' bromide, which is proximal to the vinyl group, is kinetically deactivated, and the regioselectivity for the bromide distal to the alkene is high (>10:1).[11] A subsequent second Suzuki reaction occurs at the C10' bromide of **3** with boronic ester **4** to give **5**. It was also found that this sequence could be performed as a three-component Suzuki coupling of **1**, **2**, and **4** to give terphenyl **5** by sequential addition of the boronic esters (as shown in Scheme 1). Terphenyl **5** was advanced by ring-closing metathesis to give a phenanthrene, which was then hydrogenated to give dihydrophenanthrene **6**.

Scheme 1. Suzuki Cascade for Cavicularin.



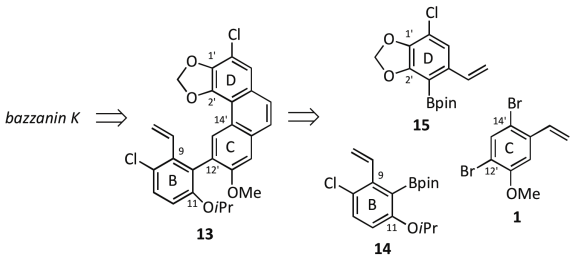
Investigations into the regioselective Suzuki coupling of dibromobenzenes suggest that the kinetic selectivity occurs during oxidative addition (Scheme 2).[11] Complexes involving Pd(0) and a C–Br bond (**7**) undergo oxidative addition with relatively fast rates to give Pd(II) intermediates (**8**), which proceed via the familiar Suzuki mechanism to give coupled products **9**. However, when the σ-bond complex is flanked by an adjacent alkene (**10**), further coordination can occur to render the Pd(0) coordinatively saturated (**11**), prohibiting oxidative addition. This coordinative saturation lowers the concentration of the available starting material for the oxidative addition step (**10**), and in turn, lowers the rate of oxidative addition to give **12**.

Scheme 2. Alkenes as Regiocontrol Elements in Oxidative Addition.



It was anticipated that the regiochemical directing effect of alkenes could be used to access the structurally more complicated target bazzanin K (Scheme 3). Application in a bazzanin K synthesis would demonstrate that this control element could be used in structurally complicated systems. Retrosynthetic simplification of the natural product leads to intermediate phenanthrene **13**. The terphenyl substructure of **13** would be prepared using Suzuki couplings of **1**, **14**, and **15** subject to the regiochemical control model discussed above.[12]

Scheme 3. Retrosynthetic Analysis of Bazzanin K.



The key Suzuki strategy envisioned for bazzanin K represented a process with more potential complications than our previous work. First, both boronic esters (**14** and **15**) are α,α-disubstituted, which would lead to more sterically congested products than we prepared in our cavicularin synthesis. Second, both boronic esters contain resident chlorides, and the desired couplings require chemoselectivity with respect to the different halogens. It is well known that bromides undergo Suzuki reactions in the presence of chlorides;[13] however, it should be noted that the presence of chloride also complicates the synthesis of the boronic esters themselves, as they are commonly prepared from halide starting materials.[14]

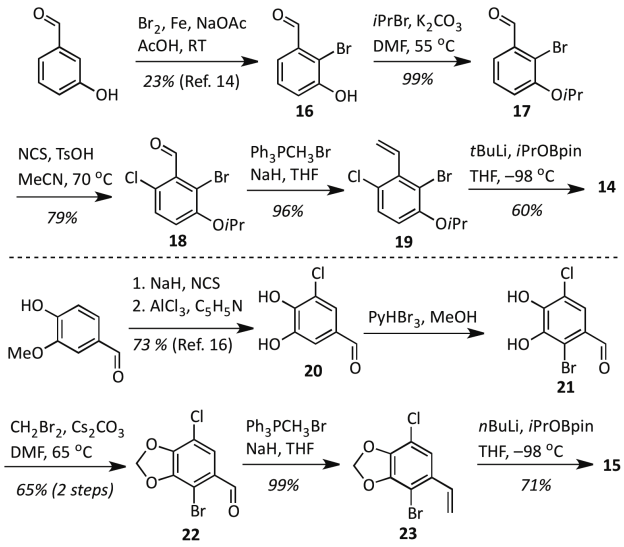
At first glance, boronic ester coupling partners **14** and **15** appear to be simple building block molecules; however, they are deceptively challenging to construct.

Regioselective syntheses of tetra- and penta-substituted benzenes are far from trivial. Moreover, **14** and **15** have multiple carbon, oxygen, and halogen substituents, and synthetic approaches to these coupling partners must balance the reactivity of the resident substituents, but also introduce new substituents with control of regiochemistry.

We planned on installing the boronic ester from the corresponding bromide.[14] Since we would perform halogenation reactions that would likely not be compatible with alkenes, we also decided to introduce the styrenes late in the synthesis through olefinations of the corresponding aldehydes. The aldehyde functional group would also provide a key regiochemical control element in the substitution reactions, and many benzaldehydes are readily available. With the above considerations in mind, we began our synthesis of bazzanin K.

Our studies commenced with 3-hydroxybenzaldehyde, which underwent regioselective bromination to give **16** following literature precedent (Scheme 4).[15] The phenol was protected as the isopropyl ether (**17**) using standard conditions.[16] Regioselective chlorination was directed by the isopropyl ether to give intermediate **18**. Wittig olefination produced styrene **19**. Intermediate **19** underwent chemoselective halogen-boron exchange with the bromide at low temperature to give coupling partner **14**. Chemical yields on this final step were substantially lower if the reaction was performed at –78 ºC.

Scheme 4. Preparation of Boronic Ester Coupling Partners.

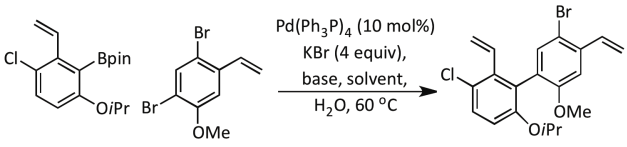


Boronic ester **15** was prepared using a similar strategy. Following literature precedent, vanillin was regioselectively chlorinated and dealkylated to give benzaldehyde **20**.[17] Bromination yielded **21** with the desired regiochemistry. Protection of the catechol produced intermediate **22**. Olefination of benzaldehyde **22** gave styrene **23**. Chemoselective bromine-boron exchange at low temperature completed the preparation of coupling partner **15**.

With the key coupling partners in hand, the sequential Suzuki couplings were investigated. We began with dibromide **1** and boronic ester **14** using conditions identified in our cavicularin synthesis (Table 1, entry 1).[10] Gratifyingly, neither the steric hindrance of the boronic ester, the spectator chloride, nor the vinyl group adjacent to the boronic ester prevented a successful and selective coupling reaction. Although the regio- and chemoselectivity of the coupling were high (only one observable coupling product), the chemical yield of **24** was modest. It was found that NaOH was superior to phosphate bases (entry 2). We also found that yields were higher when 1,2-dimethoxyethane (DME) was used as the solvent, rather than 1,4-

dioxane (entry 3). After a brief screen of bases in DME (entries 4–6), we settled on NaOH over phosphate or carbonate bases. Finally, we found that adding 1.4 equivalents of boronic ester **14** in portions gave acceptable yields of **24** (entry 7).

Table 1. Regioselective Chemoselective Suzuki Reaction.



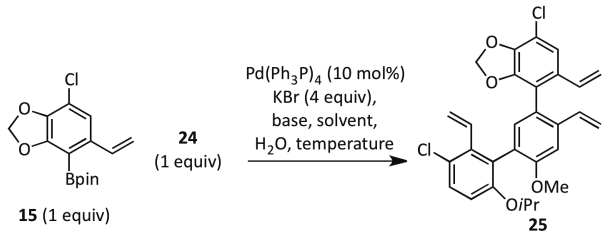
14 (1 equiv) **1** (1 equiv) **24**

entry	base (4 equiv.)	solvent	yield
1	K_3PO_4	1,4-dioxane	*47%*
2	NaOH	1,4-dioxane	*54%*
3	K_3PO_4	DME	*56%*
4	NaOH	DME	*63%*
5	K_2CO_3	DME	*19%*
6	Cs_2CO_3	DME	*30%*
7[a]	NaOH	DME	*65%*

[a] 1.4 equiv. of **14** added portionwise

With biphenyl **24** in hand, we investigated the second Suzuki coupling with boronic ester **15** (Table 2). We started with conditions from the previous Suzuki coupling, and we were pleased to observe a successful coupling to give terphenyl **25** in 36% yield (entry 1). The balance of the material was unreacted starting material and products of dehalogenation or protodeboronation. Increasing the temperature to 80 ºC led to full consumption of the starting material and an increase in chemical yield of **25** to 53% (entry 2). Further increases to the reaction temperature had a deleterious effect on the yield (entry 3). The amount of **15** was increased to 1.5 equivalents and the yield increased to 69% (entry 4). No undesired reactivity of the chloride substituents was observed. We also briefly evaluated different solvents and bases, but the chemical yields of the coupling did not increase (entries 5–6).

Table 2. Chemoselective Suzuki Reaction.

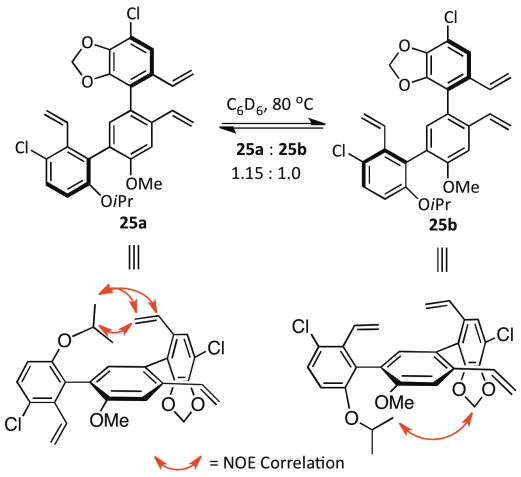


entry	base (4 equiv.)	solvent	temperature	yield
1	NaOH	DME	60 °C	*36%*
2	NaOH	DME	80 °C	*53%*
3	NaOH	DME	85 °C	*43%*
4[a]	NaOH	DME	80 °C	*69%*
5	NaOH	1,4-dioxane	80 °C	*49%*
6	K_3PO_4	DME	80 °C	*64%*

[a] 1.5 equiv. **15**

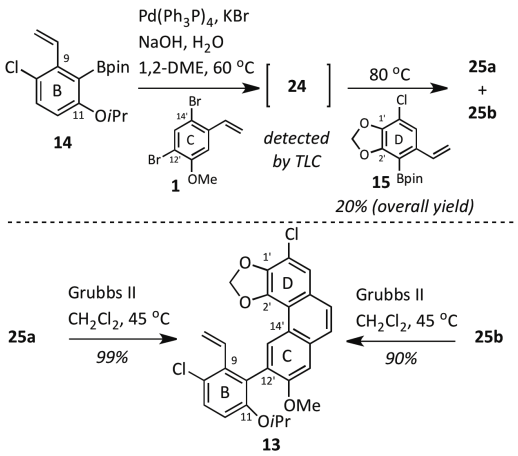
Interestingly, we discovered that **25** exists as two diastereomeric atropisomers (Figure 2). [18] The atropisomers were separated using standard column chromatography. Figure 2 shows two conformations of the terphenyl; key NOE correlations are indicated, which allowed us to tentatively assign each atropdiastereomer. Conformer **25a** showed NOE cross peaks between the isopropyl ether and one of three nearly chemical-shift identical vinyl groups, whereas **25b** showed correlation of the isopropyl group and the benzodioxole methylene protons. The atropisomers appeared conformationally stable at room temperature during the NMR experiments; however, over the course of a few days we observed small amounts of equilibration of the terphenyls. We dissolved purified samples of **25a** and **25b** in C_6D_6 and heated them to 80 ºC. Both diastereomers converged on a 1.15:1 ratio of atropisomers within a few hours at 80 ºC. The modest thermodynamic preference for **25a** is perhaps unsurprising, since there are no obvious steric effects that would destabilize either of the diastereomers.

Figure 2. Atropisomerism in 25.



With the successful sequential Suzuki couplings of **1**, **14**, and **15**, a one-pot three-component coupling was investigated (Scheme 5). Subjection of **14** and **1** to our standard conditions led to formation of **24** as evidenced by TLC. Boronic ester **15** was added, and the reaction mixture was heated to 80 ºC and allowed to proceed for an additional 48 hours. Terphenyls **25a**-**b** were isolated as single regioisomers in modest yield.

Scheme 5. Three-Component Suzuki Coupling and Phenanthrene Synthesis.



We subjected purified atropisomers **25a** and **25b** independently to ring-closing metathesis conditions, and each diastereomer cyclized to the identical phenanthrene (**13**) in nearly quantitative yield.[19] This result further confirms our assignment of **25a-b** as conformational isomers. More conveniently, chemical mixtures of **25a** and **25b** also react to give phenanthrene product **13**. This completed the full BCD-ring substructure of bazzanin K.

In summary, we have developed a chemoselective (Cl vs Br) and regioselective (Br vs Br) Suzuki reaction of two chloride-substituted boronic esters (**14** and **15**) and a non-symmetric dibromobenzene (**1**). The reaction may be performed sequentially, or as a one-pot three-component coupling. The product terphenyl (**25**) exists as two atropdiastereomers that undergo equilibration at 80 ºC. These intermediates are converted into the C12'-phenyl-substituted phenanthrene substructure of the MBB natural product bazzanin K in nearly quantitative yield. Efforts to advance this material to bazzanin K are underway, and synthetic material will be used to study the conformational properties of the natural product.

Experimental Section

General Experimental Details:

All reactions were carried out under an inert Ar atmosphere in oven-dried glassware. External (heated oil or cryogenic solvent) bath temperatures were used to record all reaction temperatures. Flash column chromatography (FCC) was carried out with SiliaFlash P60, 60 Å silica gel. Reactions and column chromatography were

monitored with EMD silica gel 60 F254 plates and visualized with potassium permanganate stain. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and methanol (MeOH) were dried by passage through activated columns. 1,4-Dioxane, 1,2-dimethoxyethane (DME) were dried and distilled over sodium. All other reagents and solvents were used without further purification from commercial sources. Unless otherwise noted, melting points were obtained from material that solidified after chromatography.

Instrumentation: FT-IR spectra were obtained on NaCl plates with a PerkinElmer Spectrum Vision spectrometer. Proton and carbon NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) unless otherwise noted on a Bruker 700 MHz Avance III Spectrometer with carbon-optimized cryoprobe or Bruker 400 MHz DPX-400 spectrometer. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, br = broad, m = multiplet. Melting points were determined with a Cole-Parmer instrument and are uncorrected.

2-Bromo-3-isopropoxybenzaldehyde (17). A solution of 2-bromo-3-hydroxybenzaldehyde (4.15 g, 20.6 mmol, 1.0 eq) and K_2CO_3 (5.70 g, 41.3 mmol, 2.0 eq) in DMF (41.2 mL, 0.5 M) was stirred for five minutes upon which time *i*PrBr (3.80 g, 30.9 mmol, 1.5 eq) was added, and the reaction mixture was heated to 55 °C. After 6 h, the reaction mixture was cooled to rt, quenched with aqueous LiCl solution, and extracted with Et_2O (90 mL×3). The combined organic layers were washed with

aqueous LiCl (40 mL), H_2O (40 mL), and brine (40 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to yield **17** (4.98 g, 99%) as a yellow oil.

Data for **17**: R_f 0.76 (3:1 hexanes:EtOAc); IR (thin film) 3070, 2978, 2933, 2871, 1690, 1567, 1267, 1237, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1 H), 7.50 (d, *J* =8.0 Hz, 1 H), 7.33 (t, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 4.60 (sept, *J* = 6.0 Hz, 1 H), 1.41 (d, *J* = 6.0 Hz, 6 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 192.6, 155.0, 135.0, 128.1, 121.6, 120.5, 119.0, 72.7, 21.9; HRMS (TOF MS ES+) calcd for $C_{10}H_{11}O_2Br$ [M+H]: 241.9942, found 241.9941.

2-Bromo-6-chloro-3-isopropoxybenzaldehyde (18). A solution of **17** (3.06 g, 12.6 mmol, 1.0 eq) and *p*TsOH·H_2O (4.79 g, 25.2 mmol, 2.0 eq) in CH_3CN (50.3 mL, 0.25 M) was stirred for 5 min. *N*-Chlorosuccinimide (0.850 g, 13.2 mmol, 1.05 eq) was added and the reaction mixture was heated to 70 °C. After 7 h, the reaction mixture was cooled to rt and quenched with aqueous $Na_2S_2O_3$ solution (100 mL) and extracted with Et_2O (200 mL×3). The combined organic layers were washed with H_2O (200 mL) and brine (200 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated. Purification by FCC (12:1 hexanes:EtOAc) yielded **18** (2.75 g, 79%) as a white solid.

Data for **18**: mp 48–50 °C; R_f 0.38 (12:1 hexanes:EtOAc); IR (thin film) 3075, 2978, 2932, 2872, 1704, 1557, 1445, 1285, 1108, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1 H), 7.35 (d, *J* = 8.8 Hz, 1 H), 7.00 (d, *J* = 8.8 Hz, 1 H), 4.56 (sept, *J* = 6.0 Hz, 1 H), 1.40 (d, *J* = 6.0 Hz, 6 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 190.7, 154.0,

133.4, 130.3, 126.6, 119.0, 116.7, 73.1, 21.9; HRMS (TOF MS ES+) calcd for $C_{10}H_{11}O_2ClBr$ [M+H]: 276.9631, found 276.9630.

2-Bromo-4-chloro-1-isopropoxy-3-vinylbenzene (19). To a slurry of NaH (4.03 g, 36.0 mmol, 2.0 eq) in THF (180 mL, 0.1 M) was added methyltriphenylphosphonium bromide (14.1 g, 39.6 mmol, 2.2 eq) portionwise at 0 °C. The reaction mixture was stirred for 10 min. A solution of aldehyde **18** (5.00 g, 18.0 mmol, 1.0 eq) in THF (20 mL, 0.9 M) was added dropwise, and the mixture was warmed to rt and stirred for 30 min. Water (50 mL) was added, and the mixture was extracted with EtOAc (50 mL×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by FCC (40:1 hexanes:EtOAc) yielded **19** as a colorless oil (4.74 g, 96%).

Data for **19**: R_f 0.68 (30:1 hexanes:EtOAc); IR (thin film) 2979, 1557, 1446, 1384, 1281 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 1 H), 6.76 (d, *J* = 8.8 Hz, 1 H), 6.65 (dd, *J* = 17.8, 11.6 Hz, 1 H), 5.67 (dd, *J*= 11.6, 1.2 Hz, 1 H), 5.65 (dd, *J* = 17.8, 1.2 Hz, 1 H), 4.52 (sept, *J* = 6.0 Hz, 1 H), 1.38 (d, *J* = 6.1 Hz, 6 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 153.6, 138.2, 133.7, 128.8, 125.0, 122.4, 116.0, 114.6, 72.7, 22.0; HRMS (TOF MS ES+) calcd for $C_{11}H_{13}OClBr$ [M+H]: 274.9838, found 274.9823.

2-(3-Chloro-6-isopropoxy-2-vinylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14). To a solution of bromide **19** (100 mg, 0.36 mmol, 1.0 eq) in THF (3.63 mL,

0.1 M) at –98 °C was added *t*BuLi (0.43 mL, 1.86 M in pentane, 0.80 mmol, 2.2 eq) dropwise. The solution was stirred for 10 min. *i*PrOBPin (0.30 mL, 1.45 mmol, 4.0 eq) was added dropwise, and mixture was stirred for an additional 30 min. The reaction was quenched with water (3 mL) and extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by FCC (30:1 hexanes:EtOAc) afforded **14** (71.4 mg, 60%) as a white solid.

Data for **14**: mp 94–96 °C; R_f 0.50 (30:1 hexanes: EtOAc); IR (thin film) 2978, 1578, 1443, 1326, 1143 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.1 Hz, 1 H), 6.95 (dd, *J* = 17.5, 11.2 Hz, 1 H), 6.69 (d, *J* = 9.1 Hz, 1 H), 5.59 (d, *J* = 17.5 Hz, 1 H), 5.40 (d, *J* = 11.2 Hz, 1 H), 4.51 (sept, *J* = 6.3 Hz, 1 H), 1.35 (s, 12 H), 1.32 (d, *J* = 6.3 Hz, 6 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 159.7, 141.4, 135.9, 130.4, 124.4, 119.7, 112.5, 83.9, 70.5, 24.9, 22.1 (the carbon directly attached to the B atom was not detected, likely due to quadrupolar broadening); HRMS (TOF MS ES+) calcd for $C_{17}H_{25}O_3ClB$ [M+H]: 323.1585, found 323.1601.

4-Bromo-7-chlorobenzo[d][1,3]dioxole-5-carbaldehyde (22). To a solution of aldehyde **20** (7.50 g, 43.5 mmol, 1.0 eq) in MeOH (150 mL, 0.30 M) at 0 °C was added pyridinium tribromide (18.6 g, 116 mmol, 2.7 eq). The reaction mixture was warmed to rt and stirred for 1 h. The solvent was evaporated and the residue was diluted with 1% aqueous H_2SO_4 (150 mL) and EtOAc (150 mL). The aqueous layer was extracted with EtOAc (150 mL×2). The combined organic phases were washed

with saturated $Na_2S_2O_3$ solution (150 mL), dried over $MgSO_4$, filtered, and concentrated. The crude **21** was used directly without further purification.

To a solution of crude **21** from above (1.00 g, 3.97 mmol, 1.0 eq) in DMF (9.92 mL, 0.4 M) was added Cs_2CO_3 (3.22 g, 9.92 mmol, 2.5 eq), and the mixture was stirred at rt for 15 min. CH_2Br_2 (0.31 mL, 4.4 mmol, 1.1 eq) was added dropwise. The reaction mixture was warmed to 65 °C and stirred for 4 h. The mixture was cooled to rt, quenched with H_2O (8 mL), and extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. Purification by FCC (6:1 hexanes:EtOAc) delivered **22** (530 mg, 65% 2 steps) as a white solid.

Data for **22**: mp 164–165 °C; R_f 0.55 (6:1 hexanes:EtOAc); IR (thin film) 1680, 1592, 1453, 1435, 1337, 1260 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.56 (s, 1 H), 6.24 (s, 2H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 188.5, 148.8, 147.5, 128.2, 126.2, 114.4, 103.21,103.19; HRMS (TOF MS ES+) calcd for $C_8H_5O_3ClBr$ [M+H]: 262.9111, found 262.9110.

4-Bromo-7-chloro-5-vinylbenzo[d][1,3]dioxole (23). To a slurry of NaH (168 mg, 60 % dispersion in mineral oil, 4.19 mmol, 1.2 eq) in THF (23.3 mL, 0.15 M) at 0 °C was added methyltriphenylphosphonium bromide (1.50 g, 4.19 mmol, 1.2 eq). The mixture was stirred for 20 min. A solution of aldehyde **22** (920 mg, 3.49 mmol, 1.0 eq) in THF (11.6 mL, 0.3 M) was added dropwise, and the reaction mixture was stirred for 4 h. The reaction was quenched by addition of H_2O (20 mL) and extracted

with EtOAc (20 mL×3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by FCC (6:1 hexanes:EtOAc) yielded **23** (901.8 mg, 99%) as white solid.

Data for **23**: mp 78–80 °C; R_f 0.74 (6:1 hexanes: EtOAc); IR (thin film) 2922, 2851, 1457, 1435, 1247, 1060, 1039, 933 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.09 (s, 1 H), 6.88 (dd, *J* = 17.5, 11.2 Hz, 1 H), 6.13 (s, 2 H), 5.62 (d, *J* = 17.5 Hz, 1 H), 5.32 (d, *J* = 11.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 147.0, 143.6, 133.6, 132.5, 120.2, 116.5, 113.5, 102.3, 100.8; HRMS (TOF MS ES+) calcd for $C_9H_7O_2ClBr$ [M+H]: 260.9318, found 260.9324.

2-(7-Chloro-5-vinylbenzo[d][1,3]dioxol-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15). To a solution of bromide **23** (300 mg, 1.15 mmol, 1.0 eq) in THF (5.7 mL, 0.2 M) at –98 °C was added *n*BuLi (0.570 mL, 2.21 M in hexane, 1.26 mmol, 1.1 eq) dropwise, and the solution was stirred for 10 min. *i*PrOBpin (0.702 mL, 3.44 mmol, 3.0 eq) was added dropwise, and mixture was stirred for an additional 2.5 h. The reaction was quenched with saturated NH_4Cl solution (3 mL) and extracted with EtOAc (6 mL×3). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated. Purification by FCC (10:1 hexanes:EtOAc) gave **15** (251 mg, 71%) as white solid.

Data for **15**: mp 95–97 °C; R_f 0.30 (30:1 hexanes: EtOAc); IR (thin film) 2980, 1608, 1415, 1329, 1131cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ ^1H NMR (700 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 17.2, 10.8 Hz, 1 H), 7.08 (s, 1 H), 6.06 (s, 1 H), 5.54 (dd, *J* = 17.2, 0.8

Hz, 1 H), 5.18 (dd, *J* = 10.8, 0.8 Hz, 1 H), 1.37 (s, 12 H); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$) δ 153.8, 142.8, 138.2, 136.3, 119.5, 116.2, 114.6, 101.7, 84.1, 24.8 (the carbon directly attached to the B atom was not detected, likely due to quadrupolar broadening); HRMS (TOF MS ES+) calcd for $C_{15}H_{19}O_4ClB$: 309.1065, found 309.1071.

5'-Bromo-3-chloro-6-isopropoxy-2'-methoxy-2,4'-divinyl-1,1'-biphenyl (24). A flask containing bromide **1** (18.7 mg, 0.0642 mmol, 1.0 eq), boronic ester **14** (20.7 mg, 0.0642 mmol, 1.0 eq), $Pd(PPh_3)_4$ (7.4 mg, 6.4 μmol, 10 mol%), KBr (30.5 mg, 0.257 mmol, 4.0 eq) and NaOH (10.3 mg, 0.257 mmol, 4.0 eq) was degassed 3 times (evacuation followed by backfill with Ar), then dimethoxyethane (0.64 mL, 0.1 M) and H_2O (0.032 mL, 5% v/v) were added under argon. The mixture was heated to 60 °C for 16 h. Additional boronic ester **14** (4.1 mg, 0.0128 mmol, 0.2 eq) was added to the mixture, and it was stirred at 60 ºC for another 8 h. Additional boronic ester **14** (4.1 mg, 0.0128 mmol, 0.2 eq) was again added to the mixture, and it was stirred at 60 ºC for another 12 h, upon which time TLC indicated consumption of **1**. The reaction mixture was cooled to rt, filtered, and concentrated. Purification by FCC (100:1 hexanes:EtOAc) yielded **24** (16.9 mg, 0.0417 mmol, 65%) as a colorless oil.

Data for **24**: R_f 0.62 (30:1 hexanes:EtOAc); IR (thin film) 2979, 2934, 1447, 1372, 1274, 1115 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 1 H), 7.22 (s, 1 H), 7.08 (dd, *J* = 17.4, 11.0 Hz, 1H), 7.06 (s, 1 H), 6.82 (d, *J* = 8.8 Hz, 1 H), 6.47 (dd, *J* = 17.9, 11.6 Hz, 1H), 5.75 (dd, J = 17.4, 0.84 Hz, 1H), 5.39 (dd, *J* = 11.0, 0.91 Hz, 1

H), 5.24 (dd, *J* = 11.6, 1.5 Hz, 1 H), 5.12 (dd, *J* = 17.9, 1.5 Hz, 1 H), 4.33 (sept, *J* = 6.0 Hz, 1H), 3.75 (s, 3H), 1.15 (d, *J* = 6.0 Hz, 3 H), 1.12 (d, *J* = 6.0 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$) δ 156.5, 154.4, 137.2, 136.8, 136.1, 135.5, 132.9, 129.5, 128.2, 128.1, 124.8, 120.8, 116.1, 114.6, 113.8, 108.4, 71.5, 55.6, 22.0, 21.9; HRMS (TOF MS ES+) calcd for $C_{20}H_{20}O_2ClBr$ [M+H]: 406.0335, found 406.0345.

7-chloro-4-(3'-chloro-6'-isopropoxy-6-methoxy-2',4-divinyl-[1,1'-biphenyl]-3-yl)-5-vinylbenzo[d][1,3]dioxole (25a & 25b). A flask containing bromide **24** (6.0 mg, 0.015 mmol, 1.0 eq), boronic ester **15** (6.8 mg, 0.022 mmol, 1.5 eq), $Pd(PPh_3)_4$ (1.7 mg, 1.5 μmol, 10 mol%), KBr (7.0 mg, 0.059 mmol, 4.0 eq) and NaOH (2.4 mg, 0.059 mmol, 4.0 eq) was degassed 3 times (evacuation followed by backfill with Ar). Dimethoxyethane (0.15 mL, 0.1 M) and H_2O (0.0075 mL, 5% v/v) were added under argon, and the mixture was heated to 80 °C for 14 h upon which time TLC indicated consumption of the bromide. The reaction mixture was cooled to rt, filtered, and concentrated. Purification by FCC (70:1 to 30:1 hexanes:EtOAc) yielded **25a** (2.8 mg, 37%) as a colorless oil and **25b** (2.5 mg, 32%) as a colorless oil.

Data for **25a**: R_f 0.44 (30:1 hexanes: EtOAc); IR (thin film) 2924, 2853, 1454, 1378, 1261, 1115 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 1 H), 7.21 (s, 1 H), 7.16 (s, 1 H), 6.87 (s, 1 H), 6.82 (d, *J* = 8.8 Hz, 1 H), 6.50 (dd, *J* = 17.5, 11.2 Hz, 1H), 6.47 (dd, *J* = 17.5, 11.1 Hz, 1 H), 6.37 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.00 (d, *J* = 1.3 Hz, 1 H), 5.98 (d, *J* = 1.3 Hz, 1H), 5.74 (d, *J* = 17.5 Hz, 1 H), 5.51 (d, *J* = 17.5 Hz, 1 H), 5.23 (dd, *J* = 11.7, 1.5 Hz, 1 H), 5.19 (dd, *J* = 11.0, 0.77 Hz, 1 H), 5.18 (dd, *J* =

17.9, 1.5 Hz, 1 H), 5.03 (dd, *J* = 11.1, 0.84 Hz, 1 H), 4.32 (sept, *J* = 6.1 Hz, 1H), 3.79 (s, 3H), 1.11 (m, 6 H); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$) δ 156.8, 154.4, 146.8, 143.0, 137.1, 136.5, 134.6, 134.5, 133.5, 132.9, 132.5, 129.24, 129.21, 126.3, 124.9, 124.1, 120.6, 119.9, 119.1, 114.9, 114.7, 114.3, 113.2, 106.7, 101.9, 71.4, 55.6, 22.0, 21.9; HRMS (TOF MS ES+) calcd for $C_{29}H_{27}O_4Cl_2$ [M+H]: 509.1286, found 509.1274.

Data for **25b**: R_f 0.33 (30:1 hexanes: EtOAc); IR (thin film) 2926, 1451, 1382, 1241, 1115 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 1 H), 7.20 (s, 1 H), 7.14 (s, 1 H), 6.84 (s, 1 H), 6.82 (d, *J* = 8.8 Hz, 1 H), 6.53 (dd, *J* = 17.8, 11.6 Hz, 1H), 6.48 (dd, *J* = 17.5, 11.1 Hz, 1 H), 6.29 (dd, *J* = 17.5, 11.1 Hz, 1H), 6.01 (d, *J* = 1.3 Hz, 1 H), 5.95 (d, *J* = 1.3 Hz, 1 H), 5.74 (d, *J* = 17.5 Hz, 1 H), 5.49 (dd, *J* = 17.4, 0.91 Hz, 1 H), 5.24 (dd, *J* = 11.6, 1.7 Hz, 1 H), 5.20 (dd, *J* = 11.0, 0.8 Hz, 1 H), 5.08 (dd, *J* = 17.9, 1.6 Hz, 1 H), 5.04 (dd, *J* = 11.0, 0.9 Hz, 1 H), 4.29 (sept, *J* = 6.1 Hz, 1H), 3.81 (s, 3H), 1.10 (d, *J* = 6.0 Hz, 3 H), 1.09 (d, *J* = 6.0 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$) δ 157.0, 154.6, 146.7, 143.0, 137.4, 136.5, 134.7, 134.6, 133.7, 133.3, 132.7, 129.2, 129.1, 126.4, 125.1, 124.1, 120.4, 119.9, 119.2, 115.3, 114.7, 114.5, 113.2, 106.5, 101.8, 71.7, 55.5, 22.0, 21.9; HRMS (TOF MS ES+) calcd for $C_{29}H_{27}O_4Cl_2$ [M+H]: 509.1286, found 509.1262.

One-pot three-component coupling to give 7-chloro-4-(3'-chloro-6'-isopropoxy-6-methoxy-2',4-divinyl-[1,1'-biphenyl]-3-yl)-5-vinylbenzo[d][1,3]dioxole (25). A flask containing bromide **1** (76.9 mg, 0.263 mmol, 1.0 eq), boronic ester **14** (85.0 mg,

0.263 mmol, 1.0 eq), $Pd(PPh_3)_4$ (30.4 mg, 0.0263 mmol, 10 mol%), KBr (125 mg, 1.05 mmol, 4.0 eq) and NaOH (42.1 mg, 1.05 mmol, 4.0 eq) was degassed 3 times (evacuation followed by backfill with Ar). Dimethoxyethane (2.63 mL, 0.1 M) and H_2O (0.132 mL, 5% v/v) were added under argon and the mixture was heated to 60 °C for 16 h. Additional boronic ester **14** (42.4 mg, 0.132 mmol, 0.5 eq) was added portionwise and the reaction was maintained at 60 ºC for another 48 h, upon which time TLC indicated consumption of the bromide. Boronic ester **15** (114 mg, 0.368 mmol, 1.4 eq) was added to the mixture, and it was heated to 80 ºC for an additional 48 h upon which time TLC indicated completion of the reaction. The reaction mixture was cooled to rt, filtered, and concentrated. Purification by FCC (60:1 to 30:1 hexanes:EtOAc) yielded **25a** (12.8 mg, 9.5%) as a colorless oil and **25b** (14.0 mg, 10.5%) as a colorless oil.

4-Chloro-10-(3-chloro-6-isopropoxy-2-vinylphenyl)-9-methoxyphenanthro[3,4-d][1,3]dioxole (13). To a solution of terphenyl **25a** (2.0 mg, 3.9 μmol, 1.0 eq) in CH_2Cl_2 (0.39 mL, 0.01 M) was added Grubbs 2nd generation catalyst (0.1 mg, 0.16 μmol, 4 mol%). The reaction mixture was heated to 45 °C and stirred for 16 h. The mixture was cooled to rt, filtered, and concentrated. Purification by FCC (60:1 hexanes:EtOAc) yielded **13** (1.9 mg, 99%) as a colorless oil.

Data for **13**: R_f 0.28 (30:1 Hexanes: EtOAc); IR (thin film) 2924, 2853, 1509, 1465, 1424, 1284, 1100, 1059 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 7.55 (dd, *J* = 12.2, 9.0 Hz, 2 H), 7.44 (s, 1 H), 7.37 (d, *J* = 8.9 Hz, 1 H), 7.22 (s, 1 H), 6.89 (d, *J* =

8.4 Hz, 1 H), 6.52 (dd, *J* = 17.9, 11.7 Hz, 1 H), 6.250 (d, *J* = 11.2 Hz, 1 H), 6.248 (d, *J* = 11.2 Hz, 1 H), 5.13 (dd, *J* = 11.6, 1.7 Hz, 1 H), 5.08 (dd, *J* = 17.8, 1.6 Hz, 1 H), 4.35 (sept, *J* = 6.1 Hz, 1 H), 3.87 (s, 3 H), 1.09 (d, *J* = 6.1 Hz, 3 H), 1.07 (d, *J* = 6.1 Hz, 3 H); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$) δ 156.4, 154.8, 143.7, 142.0, 137.5, 133.2, 133.1, 130.4, 130.0, 129.2, 128.2, 127.0, 126.3, 125.7, 124.9, 121.6, 121.5, 120.6, 115.5, 114.8, 113.4, 107.1, 102.0, 71.5, 55.5, 22.0, 21.9; HRMS (TOF MS ES+) calcd for $C_{27}H_{23}O_4Cl_2$ [M+H]: 481.0973, found 481.0998.

4-Chloro-10-(3-chloro-6-isopropoxy-2-vinylphenyl)-9-methoxyphenanthro[3,4-d][1,3]dioxole (13). To a solution of terphenyl **25b** (2.0 mg, 3.9 μmol, 1.0 eq) in CH_2Cl_2 (0.39 mL, 0.01 M) was added Grubbs 2nd generation catalyst (0.1 mg, 0.16 μmol, 4 mol%). The reaction mixture was warmed to 45 °C and stirred for 10 h. The mixture was cooled to rt, filtered, and evaporated. Purification by FCC (60:1 hexanes:EtOAc) yielded **13** (1.7 mg, 90%) as a colorless oil.

Equilibration of 25a. A solution of **25a** (2.0 mg, 3.9 μmol, 1.0 eq) in C_6D_6 (0.50 mL, 0.008 M) in an NMR tube was heated to 80 ºC. The NMR tube was cooled and the ratio of **25a**:**25b** was measured by integration of the ^{1}H NMR spectrum at 6 h (**25a**:**25b** = 1.15:1.0), and 16 h (**25a**:**25b** = 1.15:1.0).

Equilibration of 25b. A solution of **25b** (2.0 mg, 3.9 μmol, 1.0 eq) in C_6D_6 (0.50 mL, 0.008 M) in an NMR tube was heated to 80 ºC. The NMR tube was cooled and the ratio of **25a**:**25b** was measured by integration of the ^{1}H NMR spectrum at 20 min

(**25a**:**25b** = 0.9:1.0), 60 min (**25a**:**25b** = 1.12:1.0), 120 min (**25a**:**25b** = 1.15:1.0), 6 h (**25a**:**25b** = 1.15:1.0), and 16 h (**25a**:**25b** = 1.15:1.0).

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

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