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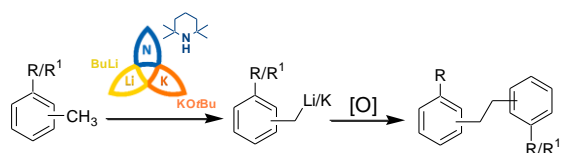
Homo- and Hetero-Oxidative Coupling of Benzyl Anions

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TOC Graphical Abstract



Abstract

The regioselective benzylic metalation of substituted toluenes using BuLi/KO*t*Bu/TMP(H) (LiNK metalation conditions) with subsequent *in situ* oxidative C-C coupling has been developed for the facile generation of 1,2-diarylethanes. A range of oxidants can be used for the oxidative coupling step, with 1,2-dibromoethane proving optimal. Heterocouplings can be achieved starting from a mixture of two different toluenes with a bias towards cross coupling achievable by using a two-fold excess of one toluene starting material. The utility of this approach is illustrated by the synthesis of several biologically active natural products. A distinct advantage is that the synthetic steps typically required to pre-activate the coupling substrates are eliminated and no transition metal is required to facilitate the C-C bond formation.

Introduction

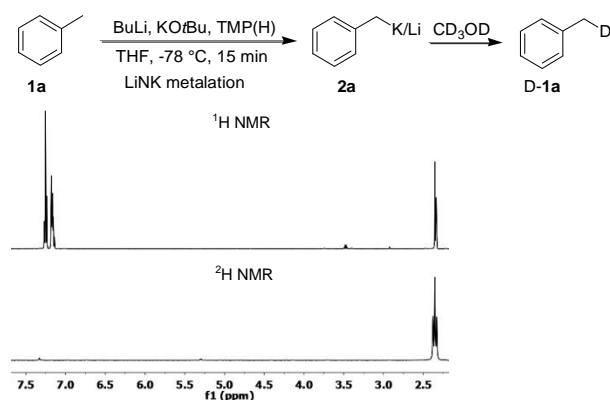
The repertoire of carbon-carbon bond formation reactions utilizing oxidative coupling, while limited, continues to expand.¹ As might be expected, the majority of these transformations are transition metal catalyzed but some transition metal free variants have been accomplished. Recent examples include the coupling of Grignard reagents using TEMPO or 3,3',5,5'-tetra-*t*-butyldiphenylquinone as oxidants.² As oxidative C-C coupling requires the combining of two carbon nucleophiles, this approach would have enhanced synthetic efficiency if the nucleophiles could be generated *via* a direct C-H deprotonation of readily available inexpensive starting substrates and the oxidative coupling could be achieved without a transition metal.

We have recently described use of the reagent triad BuLi/KO*t*Bu/TMP(H) (LiNK metalation) to *in situ* generate a mixed Li/K metal TMP amide as a general method for benzylic metalations with excellent selectivity.³ We now report the use of this benzylic metalation strategy in tandem with an *in situ* oxidative coupling for Csp³-Csp³ bond formation.⁴ Oxidative homo-coupling of benzyl anions has previously been noted, but it has remained relatively unexplored as a synthetic procedure.⁵

Results and Discussion

Prior to this study, we first established the regioselectivity of LiNK metalation of toluene by its treatment with 1.2 equiv. of BuLi/KO*t*Bu/TMP(H) in THF at -78 °C and quenching with CD₃OD (Scheme 1). ¹H and ²H NMR analysis of the product showed that deuterium (73% D) was solely incorporated into the benzylic position with no aryl deuterium observed, confirming that organometallic **2a** could be selectively generated (Scheme 1). The apparent simplicity of this metalation belies the fact achieving this deprotonation with complete selectivity without the use of an excess of toluene at elevated temperatures can be challenging.⁶ The ability of LiNK metalation conditions to provide routine low temperature access to the thermodynamically favored benzyl anion prompted us to combine this with a tandem oxidative C-C bond forming strategy.

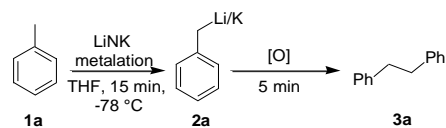
Scheme 1. Selective benzylic metalation of toluene



Having established our metalation approach could selectively provide **2a**, a variety of oxidants were examined to achieve its homo-coupling to 1,2-diphenylethane **3a** (Table 1). Encouragingly, treatment of **2a** at $-78\text{ }^{\circ}\text{C}$ for 5 minutes with oxygen, ceric ammonium nitrate (CAN) or iodine all gave the coupled product **3a** in 62, 35, and 47% yields respectively (Table 1, entries 1-3). The inexpensive oxidant 1,2-dibromoethane proved optimal giving a product yield of 71% (entry 4).⁷ In this case oxidative coupling occurred immediately upon addition of dibromoethane based upon the disappearance of the characteristic organometallic color. Interestingly, when TEMPO was used as oxidant at $-78\text{ }^{\circ}\text{C}$ and the reaction worked up after 5 minutes, only a trace of **3a** was observed. Yet, upon warming the reaction to rt for 2 h, coupling product was efficiently formed in a 58% yield. In comparison, benzyl magnesium chloride was also examined for its ability to oxidatively couple with dibromoethane. No reaction was found to occur at $-78\text{ }^{\circ}\text{C}$ yet upon reaction for 2 h at rt a 81% yield of **3a** was obtained (entries 7, 8). This shows a general ability of benzylic organometallics to undergo transition metal free oxidative couplings with the enhanced low temperature reactivity of **2a** versus the Grignard attributable to the more ionic character of **2a**. While the exact mechanism of the dibromoethane mediated coupling of **2a** is as of yet unknown, two general possibilities could be envisaged. The first being the one electron oxidation of **2a** by dibromoethane with subsequent dimerization to **3a**. Alternatively bromination of **2a** by dibromoethane could form benzyl bromide which could generate **3a** by *in situ* reaction with unreacted **2a**. As oxygen is capable of oxidizing **2a** to produce **3a** this mechanism could be

viable with dibromoethane as it is a known oxidant. But to illustrate that bromination/coupling pathway could also be in operation treatment of **2a** with benzylbromide did also produce **3a**.

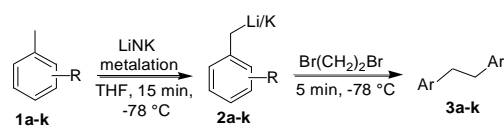
Table 1. LiNK metalation and oxidative coupling of toluene



entry	substrate	oxidant	temp / °C	3a yield % ^a
1	1a	O ₂	-78	62
2	1a	CAN	-78	35
3	1a	I ₂	-78	47
4	1a	Br(CH ₂) ₂ Br	-78	71
5	1a	TEMPO	-78	trace
6	1a	TEMPO	rt / 2 h	58
7	PhCH ₂ MgCl	Br(CH ₂) ₂ Br	-78	0
8	PhCH ₂ MgCl	Br(CH ₂) ₂ Br	rt / 2 h	81 ^b

^a yield refers to isolated product. ^b The possibility of Grignard bromination with Br(CH₂)₂Br with *in situ* coupling of PhCH₂Br and PhCH₂MgBr also exists.

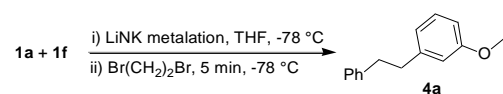
The generality of this metalation/coupling method was next examined for a series of substituted toluene derivatives. The reaction sequence proved very general and tolerant of fluoro, amino, carboxy, ether and amido functional groups in *ortho*, *meta* and *para* positions relative to the methyl group (Table 2, entries 1-8). Di and tri-substituted toluenes and xylenes were also successfully dimerized in good yields (entries 9-10). Of particular note is the hexa-methoxylated natural product brittonin A **3k** which can be synthesized with 69% yield in a single step (Table 2, entry 11).⁸

Table 2. Homo-oxidative coupling of substituted toluenes

entry	subst.	R	product	yield (%) ^a
1	1a	H	3a	71
2	1b	2-F	3b	78
3	1c	2-NMe ₂	3c	58
4	1d	2-CO ₂ H	3d	53
5	1e	2-OMe	3e	63
6	1f	3-OMe	3f	68
7	1g	3-OMOM	3g	46
8	1h	4-CONiPr	3h	83
9	1i	3,5-(OMe) ₂	3i	80 ^b
10	1j	2-OMe-4-Me	3j	88
11	1k	3,4,5-(OMe) ₃	3k	69

^a yield refers to isolated product. ^b substrate added to a premixed solution of BuLi/KOtBu/TMP(H).

In an effort to optimize conditions for hetero-couplings, toluene **1a** and 3-methylanisole **1f** were used as test substrates (Table 3). It was found that metalation and oxidative coupling of a 1:1 ratio of each substrate gave a 24% yield of hetero-dimer **4a** following chromatographic separation from the two homo-dimers **3a** (25%) and **3f** (19%). This yield could be improved to 41% if a 2:1 ratio of **1a**:**1f** was used and a comparable yield was obtained if the ratio was reversed with an excess of **1f** employed (Table 3, entries 2 and 3).

Table 3. Hetero-oxidative coupling of toluenes

entry	substrates	equiv. 1a:1f	product	yield (%) ^a
1	1a/1f	1 : 1	4a	24
2	1a/1f	2 : 1	4a	41
3	1a/1f	1 : 2	4a	39

^a yield refers to isolated product based on limiting reagent.

While complete selectivity for **4a** was not achieved, this single step approach from the simplest toluene starting materials remains favorable if alternative multi-step routes are considered. For example, alternative multi-step approaches to **4a** would require synthesis of suitably functionalized starting substrates such as; benzyl phosphonium ylide and aryl aldehyde for Wittig olefination followed by alkene reduction.⁹ This approach requires five individual reactions from toluene starting materials and the use of a transition metal catalyst (i.e. oxidation of one toluene substrate to its aromatic aldehyde, bromination of the other toluene substrate to its benzyl bromide, conversion to its phosphonium salt, Wittig olefination and alkene reduction) versus one for the hetero-oxidative coupling with no transition metal required. Other alternative multi-step approaches include the Pd catalyzed coupling of 2-phenylethyltrifluoroborate and arylbromide and arylzinc chloride and triphenylethanyl indium.^{10,11}

1,2-Diarylethane (bibenzyl) is a particularly common natural product scaffold isolated from numerous plants such as liverwort and orchids.¹² Use of these plants has a long history in traditional medicine and ongoing analysis of individual extracted bibenzyls has shown diverse biological activities including antifungal, antimicrobial, antioxidant, anti-proliferative and multidrug resistance reversal properties. Typical substituent patterns for this natural product class include varying degrees of methoxy or phenolic substituents on the aromatic rings. Exploiting our cross-coupling approach, it was possible to synthesize numerous examples of these natural products in a single synthetic operation (Table 4).

Compound **4b** was synthesized in a 43% yield from toluene and 3-OMOM-toluene **1g**. Acidic deprotection to 3-phenethylphenol **4c** was readily achieved providing the phenolic substituted

natural product **4c**.¹³ Oxidative cross-coupling of toluene was equally successful with 3,5-dimethoxytoluene and 3,4,5-trimethoxytoluene, to give natural products **4d** and **4e** (entries 3, 4).¹⁴ Similarly, the tri- and tetra-methoxy substituted bibenzyls **4f** (batatasin III dimethylether) and **4g** (aloifol I dimethylether) were obtained in 58 and 52% yields from 3-methoxytoluene with **1i** and **1k** respectively.¹⁵

Table 4. Synthesis of ether and phenolic substituted 1,2-diarylethane (bibenzyl) natural products

Reaction scheme: $\text{ArCH}_3 + \text{Ar}^1\text{CH}_3 \xrightarrow[\text{ii) Br(CH}_2)_2\text{Br, 5 min, -78 }^\circ\text{C}]{\text{i) LiNK metalation, THF, -78 }^\circ\text{C}}$ **4a-4g**

entry	subst.	equiv. ratio	R / R ¹	prod.	yield (%) ^a
1	1a/1f	2 : 1	H/3-OMe	4a	41
2	1a/1g	2 : 1	H/3-OMOM	4b^b	43
3	1a/1i	2 : 1	H/3,5-(OMe) ₂	4d^c	40
4	1a/1k	2 : 1	H/3,4,5-(OMe) ₃	4e	46
5	1f/1i	2 : 1	3-OMe/3,5-(OMe) ₂	4f^c	58
6	1f/1k	2 : 1	3-OMe/3,4,5-(OMe) ₃	4g	52

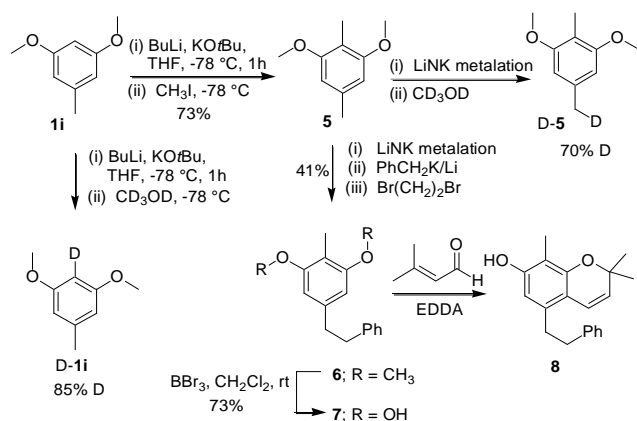
^a yield refers to isolated product based on limiting reagent. ^b OMOM deprotected to **4c** (R / R¹ = H/3-OH) with HCl/MeOH in 83% yield.

^c substrate added to a premixed solution of BuLi/KO*t*Bu/TMP(H).

The synthesis of stilbostemin M **6**, stilbostemin B **7** and bauhinol D **8** from 1,3-dimethoxy-5-methylbenzene **1i** provided an illustration of how the complementary metalation selectivity achievable with classic super-base conditions of BuLi/KO*t*Bu¹⁶ and LiNK (BuLi/KO*t*Bu/TMP(H)) can be exploited for targeted synthesis (Scheme 2). As described above the benzylic metalation of **1i** under LiNK conditions could be used for synthesis of natural product **4d** (Table 4, entry 3). In contrast, selective kinetic metalation of **1i** at the C-2 aryl position (between the two methoxy groups) with BuLi/KO*t*Bu was confirmed by deuteration and exploited for the synthesis of 1,3-dimethoxy-2,5-dimethylbenzene **5** by reaction with methyl iodide (Scheme 2). Substrate **5** presents an elevated selectivity challenge for a LiNK metalation as it contains two non-equivalent methyl groups with oxidative coupling at the 5-methyl required for the natural product syntheses. As we have previously shown, it could be anticipated, based

upon relative CH acidities of both methyl groups, that this could be achieved.^{3a} The desired 5-methyl selectivity was confirmed by ²H NMR product analysis following LiNK metalation and treatment with CD₃OD, with the spectrum showing one triplet corresponding to D-**5** and no aryl deuteration (Scheme 2, supporting information). With the desired regioselective metalation established, oxidative cross-coupling of **5** with toluene gave stilbostemin M in a 41% yield. Demethylation of **6** with BBr₃ gave the corresponding diphenol natural product **7**, stilbostemin B, which has been shown to be a biologically active isolate from the roots of *Stemona japonica* and *Stemona tuberosa* and has numerous cited uses in Chinese medicine.¹⁷ In addition to being natural products in themselves, the bibenzyls we have described are common intermediates in the synthesis of prenyl and pyranyl, furan and glycoside substituted analogues.¹⁸ For example, conversion of **7** into bauhinol D **8** by ethylenediaminediacetate (EDDA) catalyzed reaction with 3-methyl-2-butenal has recently been shown.¹⁹

Scheme 2. Synthesis of stilbostemin M **6**, stilbostemin B **7** and bauhinol D **8**.



Conclusion

In summary, regioselective benzylic metalation with BuLi/KOtBu/TMP(H) can be used in conjunction with 1,2-dibromoethane mediated oxidative coupling to allow direct access to the bibenzyl scaffold. This one-pot synthetic operation from toluene starting materials allows easy access to this biologically important natural product class without requiring additional synthetic steps to pre-activate the coupling partners or the use of a transition metal catalyst. A distinct advantage is that the synthetic steps typically required to pre-activate the coupling toluene

substrates are eliminated thereby dramatically reducing the number of synthetic step. Further synthetic applications utilizing LiNK metalation are under development and will be reported in due course.

Experimental

General Methods. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique. All solvents were purified and degassed before use. Unless it is specified, all reagents were used as received without further purifications. TMP was distilled from CaH_2 prior to use and THF was obtained from a solvent purification system. BuLi was purchased as a 2.5 M solution in hexanes. KO t Bu was purchased as a 1 M solution in THF. The exact concentration of the organolithium solution was determined by titration with diphenylacetic acid in THF prior to use.²⁰

*Deuteriomethylbenzene (D-1a).*²¹ A solution of toluene **1a** (1.00 mL, 9.38 mmol) in THF (5 mL) at -78°C was treated dropwise with BuLi (2.50 M, 4.50 mL, 11.20 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 11.20 mL, 11.20 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (1.60 mL, 9.38 mmol). The reaction mixture was stirred for 1 h at -78°C and CD_3OD (0.60 mL) added. The reaction mixture was allowed to warm to room temperature and portioned between diethyl ether (30 mL) and water (30 mL). The organic layer was washed several times with water, and the combined organic extracts were dried over magnesium sulphate and distilled with a fractionating column. The fraction boiling between 110 and 115 $^\circ\text{C}$ was collected to give **D-1a** as a colorless oil (73% D incorporation). ^1H NMR (500 MHz, CDCl_3): δ 7.29-7.22 (m, 2H), 7.21-7.12 (m, 3H), 2.37-2.30 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 137.8, 129.0, 128.2, 127.3, 125.3, 21.1 (t, $J = 19.1$ Hz). ^2H NMR (92.07 MHz, CH_2Cl_2): δ 2.35 (t, $J = 2.2$ Hz).

2-Deuterio-1,3-dimethoxy-5-methylbenzene (D-1i). A solution of 3,5-dimethoxytoluene **1i** (121 mg, 0.80 mmol) in THF (10 mL) at -78°C was treated dropwise with BuLi (2.50 M in hexanes, 0.35 mL, 0.88 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 0.88 mL, 0.88 mmol) was added dropwise, and the reaction mixture was stirred for 1 h at -78°C . Then CD_3OD (0.20 mL) was added, and the reaction mixture was stirred at -78°C for an additional time of 5 min. The reaction mixture was warmed to room temperature and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL),

dried over sodium sulphate and concentrated to dryness to give **D-1i** as a colorless oil (105 mg, 86%, 85% D incorporation). ¹H NMR (500 MHz, CDCl₃): δ 6.33 (s, 2H), 3.77 (s, 6H), 2.30 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 159.7, 139.2, 106.1, 96.5 (bs), 54.2, 20.8. ²H NMR (92.07 MHz, CH₂Cl₂): δ 6.28 (s). HRMS [M]⁺: 153.0900, C₉H₁₁DO₂ requires 153.0900.

5-(Deuteriomethyl)-1,3-dimethoxy-2-methylbenzene (D-5). A solution of 1,3-dimethoxy-2,5-dimethylbenzene **5** (75 mg, 0.45 mmol) in THF (10 mL) at -78 °C was treated dropwise with BuLi (2.50 M in hexanes, 0.20 mL, 0.50 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 0.50 mL, 0.50 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (76 μL, 0.45 mmol). The reaction mixture was stirred for 15 min at -78 °C and CD₃OD (0.20 mL) added and stirred for a further 5 min. The reaction mixture was warmed to room temperature and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness to give **D-5** as a colorless solid (65 mg, 86%, 70% D incorporation, mp. 48-49 °C). ¹H NMR (500 MHz, CDCl₃): δ 6.36 (s, 2H), 3.80 (s, 6H), 2.33-2.29 (m, 2H), 2.05 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 158.2, 136.2, 136.1, 111.4, 104.5, 55.7, 21.6 (t, *J* = 19.4 Hz), 7.8. ²H NMR (92.07 MHz, CH₂Cl₂): δ 2.31 (t, *J* = 2.2 Hz). HRMS [M]⁺: 167.1055, C₁₀H₁₃DO₂ requires 167.1057.

General procedure for the optimization of homocoupling reaction. A solution of toluene **1a** (46 mg, 0.50 mmol) in THF (15 mL) at -78 °C was treated dropwise with BuLi (2.37 M, 0.25 mL, 0.60 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 0.60 mL, 0.60 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (84 μL, 0.50 mmol). The reaction mixture was stirred for 15 min at -78 °C, oxidant added and stirred for a further 5 min. The reaction mixture was warmed to room temperature and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 92:8 cyclohexane:diethyl ether gave 1,2-diphenylethane **3a** as a colorless solid (*R_f* = 0.80).

O₂ (bubbling): 28 mg, 62%.

Ceric ammonium nitrate: (822 mg, 1.50 mmol). 16 mg, 35%.

Iodine: (380 mg, 1.50 mmol). 21 mg, 47%.

1,2-Dibromoethane: (0.13 mL, 1.50 mmol). 32 mg, 71%.

TEMPO: (158 mg, 1.00 mmol). After the addition of TEMPO the reaction mixture was stirred for 2 h at room temperature. 26 mg, 58%.

Coupling reaction of benzylmagnesium chloride.

1,2-Diphenylethane (3a). Benzyl chloride (60 mg, 0.47 mmol) was added dropwise to a stirred suspension of magnesium powder (12 mg, 0.50 mmol) in dry THF (4 mL), and the reaction mixture was refluxed under nitrogen. After 30 min the resulting Grignard reagent was cooled down to room temperature, and 1,2-dibromoethane (0.13 mL, 1.50 mmol) was added. The reaction mixture was stirred for 2 h, then quenched with water and extracted with diethyl ether (2 x 10 mL). The combined organic layer was dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 92:8 cyclohexane:diethyl ether gave 1,2-diphenylethane **3a** as a colorless solid (35 mg, 81%).

Coupling reaction of 2a with benzyl bromide.

1,2-Diphenylethane (3a). A solution of toluene **1a** (92 mg, 1.00 mmol) in THF (15 mL) at -78°C was treated dropwise with BuLi (2.37 M, 0.51 mL, 1.20 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.20 mL, 1.20 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.00 mmol). The reaction mixture was stirred for 15 min at -78°C , benzyl bromide added (0.12 mL, 1.00 mmol) and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 92:8 cyclohexane:diethyl ether gave 1,2-diphenylethane **3a** ($R_f = 0.80$, 135 mg) contaminated by benzyl bromide.

1,2-Diphenylethane (3a).²² A solution of toluene **1a** (46 mg, 0.50 mmol) in THF (15 mL) at -78°C was treated dropwise with BuLi (2.37 M, 0.25 mL, 0.60 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 0.60 mL, 0.60 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (84 μL , 0.50 mmol). The reaction mixture was stirred for 15 min at -78°C , 1,2-dibromoethane added (0.13 mL, 1.50 mmol) and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 92:8 cyclohexane:diethyl ether gave 1,2-diphenylethane **3a** as a colorless solid ($R_f = 0.80$, 32 mg, 71%). mp. 50-51 $^{\circ}\text{C}$, lit. mp. 51-53 $^{\circ}\text{C}$.^{22b} ^1H NMR (500 MHz, CDCl_3): δ 7.29-7.23 (m, 4H),

7.20-7.15 (m, 6H), 2.91 (s, 4H). ^{13}C NMR (125 MHz, CDCl_3): δ 141.8, 128.5, 128.3, 125.9, 37.9. HRMS $[\text{M}]^+$: 182.1092, $\text{C}_{14}\text{H}_{14}$ requires 182.1096.

1,2-Bis(2-fluorophenyl)ethane (3b).²³ A solution of 2-fluorotoluene **1b** (165 mg, 1.50 mmol) in THF (15 mL) at -78 °C was treated dropwise with BuLi (2.37 M, 0.76 mL, 1.80 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.80 mL, 1.80 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.37 mL, 4.50 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 90:10 cyclohexane:diethyl ether gave **3b** as a colorless solid (R_f = 0.80, 128 mg, 78%, mp. 40-41 °C lit. mp. 40-41 °C).^{23b} ^1H NMR (500 MHz, CDCl_3): δ 7.21-7.09 (m, 4H), 7.04-6.98 (m, 4H), 2.94 (s, 4H). ^{13}C NMR (125 MHz, CDCl_3): δ 161.2 (d, J = 244.9 Hz), 130.7 (d, J = 5.0 Hz), 128.3 (dd, J = 18.8, 15.0 Hz), 127.7 (d, J = 8.1 Hz), 123.8 (d, J = 3.6 Hz), 115.2 (d, J = 22.1 Hz), 29.7-29.6 (m). HRMS $[\text{M}]^+$: 218.0912, $\text{C}_{14}\text{H}_{12}\text{F}_2$ requires 218.0907.

2,2'-(Ethane-1,2-diyl)bis(N,N-dimethylaniline) (3c). A solution of *N,N*-dimethyl-*o*-toluidine **1c** (203 mg, 1.50 mmol) in THF (15 mL) at -78 °C was treated dropwise with BuLi (2.37 M, 0.76 mL, 1.8 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.80 mL, 1.80 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.37 mL, 4.50 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with water (3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 80:20 cyclohexane:diethyl ether (0.5% Et_3N) gave **3c** as a colorless solid (R_f = 0.60, 116 mg, 58%, mp. 53-54 °C). ^1H NMR (500 MHz, CDCl_3): δ 7.28 (d, J = 7.5 Hz, 2H), 7.17 (t, J = 7.5 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 7.02 (t, J = 7.4 Hz, 2H), 3.03 (s, 4H), 2.68 (s, 12H). ^{13}C NMR (125 MHz, CDCl_3): δ 152.9, 137.4, 129.8, 126.6, 123.4, 119.6, 45.2, 31.9. HRMS $[\text{M}]^+$: 268.1937, $\text{C}_{18}\text{H}_{24}\text{N}_2$ requires 268.1939. Analysis calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.49; H, 8.86; N, 10.17.

2,2'-(Ethane-1,2-diyl)dibenzoic acid (3d).²⁴ A solution of *o*-toluic acid **1d** (272 mg, 2.00 mmol) in THF (18 mL) at -78 °C was treated dropwise with BuLi (2.30 M, 1.74 mL, 4.00 mmol) and

stirred for 5 min. KO^tBu (1.0 M in THF, 4.00 mL, 4.00 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.34 mL, 2.00 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.52 mL, 6.00 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Trituration from diethyl ether with cooling gave **3d** as a pale yellow solid (144 mg, 53%, mp. 228-229 °C, lit. mp. 229-231 °C).^{24b} ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.86 (bs, 2H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.45 (td, *J* = 7.5, 1.1 Hz, 2H), 7.31-7.24 (m, 4H), 3.19 (s, 4H). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.2, 143.2, 132.1, 131.0, 130.9, 130.7, 126.5, 36.0. HRMS [M+Na]⁺: 293.0796, C₁₆H₁₄O₄Na requires 293.0790.

1,2-Bis(2-methoxyphenyl)ethane (3e).²⁵ A solution of 2-methylanisole **1e** (122 mg, 1.00 mmol) in THF (15 mL) at -78 °C was treated dropwise with BuLi (2.50 M, 0.48 mL, 1.20 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.20 mL, 1.20 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.00 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.26 mL, 3.00 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 98:2 cyclohexane:diethyl ether gave **3e** as a colorless solid (*R*_f = 0.70, 76 mg, 63%, mp. 78-79 °C, lit. mp. 81-82 °C).²⁵ ¹H NMR (500 MHz, CDCl₃): δ 7.16 (t, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.90-6.78 (m, 4H), 3.80 (s, 6H), 2.89 (s, 4H). ¹³C NMR (125 MHz, CDCl₃): δ 156.5, 129.8, 128.7, 125.9, 119.3, 109.2, 54.3, 29.4. HRMS [M]⁺: 242.1298, C₁₆H₁₈O₂ requires 242.1307.

1,2-Bis(3-methoxyphenyl)ethane (3f).²⁶ A solution of 3-methylanisole **1f** (122 mg, 1.00 mmol) in THF (15 mL) at -78 °C was treated dropwise with BuLi (2.50 M, 0.48 mL, 1.20 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.20 mL, 1.20 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.00 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.26 mL, 3.00 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 96:4 cyclohexane:diethyl ether gave **3f** as a colorless oil (*R*_f = 0.60, 82 mg, 68%). ¹H NMR (500

MHz, CDCl₃): δ 7.19 (t, J = 7.7 Hz, 2H), 6.79-6.71 (m, 6H), 3.77 (s, 6H), 2.89 (s, 4H). ¹³C NMR (125 MHz, CDCl₃): δ 159.6, 143.4, 129.3, 120.9, 114.2, 111.3, 55.1, 37.8. HRMS [M+H]⁺: 243.1377, C₁₆H₁₉O₂ requires 243.1385.

1,2-Bis(3-(methoxymethoxy)phenyl)ethane (**3g**). A solution of 1-methoxymethoxy-3-methylbenzene **1g** (250 mg, 1.64 mmol) in THF (20 mL) at -78 °C was treated dropwise with BuLi (2.40 M, 0.82 mL, 1.97 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.97 mL, 1.97 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.28 mL, 1.64 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.42 mL, 4.92 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (30 mL), washed with 2 M HCl (3 x 10 mL), dried over sodium sulfate and concentrated to dryness. Purification by alumina gel chromatography eluting with 99:1 cyclohexane:ethyl acetate gave **3g** as a colorless oil (R_f = 0.60, 115 mg, 46%). ¹H NMR (400 MHz, CDCl₃): δ 7.22-7.18 (m, 2H), 6.89-6.84 (m, 6H), 5.16 (s, 4H), 3.48 (s, 6H), 2.90 (s, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 157.34, 143.39, 129.30, 122.07, 116.44, 113.78, 94.50, 55.95, 37.73. HRMS [M]⁺: 302.1519, C₁₈H₂₂O₄ requires 302.1518.

4,4'-(Ethane-1,2-diyl)bis(N,N-diisopropylbenzamide) (**3h**). A solution of *N,N*-diisopropyl-4-methylbenzamide **1h** (219 mg, 1.00 mmol) in THF (15 mL) at -78 °C was treated dropwise with BuLi (2.50 M, 0.48 mL, 1.20 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.20 mL, 1.20 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.00 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.26 mL, 3.00 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with 2 M HCl (3 x 10 mL), dried over sodium sulfate and concentrated to dryness. Purification by silica gel chromatography eluting with 15:85 cyclohexane:diethyl ether gave **3h** as a colorless solid (R_f = 0.60, 96 mg, 88%, mp. 144-145 °C). ¹H NMR (500 MHz, CDCl₃): δ 7.23 (d, 4H, J =7.9 Hz), 7.17 (d, 4H, J =7.9 Hz), 3.69 (bs, 4H), 2.93 (s, 4H), 1.33 (bs, 24H). ¹³C NMR (125 MHz, CDCl₃): δ 171.1, 142.1, 136.7, 128.4, 125.8, 37.4, 20.8. (Note: *i*Pr tertiary C not observed). HRMS [M+H]⁺: 437.3188, C₂₈H₄₁N₂O₂ requires 437.3168. Analysis calcd for C₂₈H₄₀N₂O₂: C, 77.02; H, 9.23; N, 6.42. Found: C, 76.73; H, 9.34; N, 6.30.

1,2-Bis(3,5-dimethoxyphenyl)ethane (3i).²⁷ A solution of 2,2,6,6-tetramethylpiperidine (0.22 mL, 1.31 mmol) in THF (10 mL) at $-78\text{ }^{\circ}\text{C}$ was treated dropwise with BuLi (2.35 M, 0.67 mL, 1.57 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.57 mL, 1.57 mmol) was added dropwise and stirred for 5 min. A solution of 3,5-dimethoxytoluene **1i** (200 mg, 1.31 mmol) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise to the reaction mixture and stirred for 15 min at $-78\text{ }^{\circ}\text{C}$. Then 1,2-dibromoethane (0.34 mL, 3.93 mmol) was added and the mixture was stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (30 mL), washed with 2 M HCl (3 x 10 mL), dried over sodium sulfate and concentrated to dryness to give **3i** as a colorless solid (160 mg, 80%, mp. $96\text{-}97\text{ }^{\circ}\text{C}$, lit. mp. $99\text{-}100\text{ }^{\circ}\text{C}$).^{27b} ^1H NMR (400 MHz, CDCl_3): δ 6.36-6.35 (m, 4H), 6.33-6.32 (m, 2H), 3.77 (s, 12H), 2.85 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 160.7, 144.1, 106.5, 98.0, 55.3, 38.0. HRMS $[\text{M}+\text{H}]^+$: 303.1600, $\text{C}_{18}\text{H}_{23}\text{O}_4$ requires 303.1596.

1,2-Bis(3-methoxy-4-methylphenyl)ethane (3j). A solution of 2,5-dimethylanisole **1j** (209 mg, 1.50 mmol) in THF (15 mL) at $-78\text{ }^{\circ}\text{C}$ was treated dropwise with BuLi (2.50 M in hexanes, 0.72 mL, 1.80 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.80 mL, 1.80 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.26 mL, 1.50 mmol). The reaction mixture was stirred for 15 min at $-78\text{ }^{\circ}\text{C}$, 1,2-dibromoethane (0.37 mL, 4.50 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (30 mL), washed with 2 M HCl (3 x 10 mL), dried over sodium sulfate and concentrated to dryness. Purification by silica gel chromatography eluting with 98:2 cyclohexane:EtOAc gave **3j** as a colorless solid ($R_f = 0.50$, 178 mg, 88%, mp. $70\text{-}71\text{ }^{\circ}\text{C}$). ^1H NMR (500 MHz, CDCl_3): δ 7.03 (d, $J = 7.5\text{ Hz}$, 2H), 6.71 (d, $J = 7.5\text{ Hz}$, 2H), 6.62 (s, 2H), 3.78 (s, 6H), 2.88 (s, 4H), 2.18 (s, 6H). ^{13}C NMR (125 MHz, CDCl_3): δ 157.6, 140.7, 130.4, 124.0, 120.1, 110.4, 55.2, 38.1, 15.8. HRMS $[\text{M}+\text{H}]^+$: 271.1708, $\text{C}_{18}\text{H}_{23}\text{O}_2$ requires 271.1698. Analysis calcd for $\text{C}_{18}\text{H}_{22}\text{O}_2$: C, 79.96; H, 8.20. Found: C, 79.68; H, 8.27.

1,2-Bis(3,4,5-trimethoxyphenyl)ethane (3k) (brittonin A).²⁸ A solution of 3,4,5-trimethoxytoluene **1k** (182 mg, 1.00 mmol) in THF (15 mL) at $-78\text{ }^{\circ}\text{C}$ was treated dropwise with BuLi (2.50 M in hexanes, 0.48 mL, 1.20 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.20 mL, 1.20 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.00 mmol). The reaction mixture was stirred for 15 min at $-78\text{ }^{\circ}\text{C}$, 1,2-dibromoethane (0.26 mL, 3.00 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt

and the solvent removed under reduced pressure. The residue was dissolved in diethyl ether (30 mL), washed with 2 M HCl (3 x 10 mL), dried over sodium sulfate and concentrated to dryness. Triturating from diethyl ether with cooling gave **3k** as a colorless solid (125 mg, 69%, mp. 138-139 °C, lit. mp. 138-139 °C).^{28b} ¹H NMR (500 MHz, CDCl₃): 6.36 (s, 4H), 3.82 (s, 18H), 2.85 (s, 4H). ¹³C NMR (125 MHz, CDCl₃): δ 153.0, 137.3, 136.3, 105.6, 60.8, 56.1, 38.4. HRMS [M+Na]⁺: 385.1637, C₂₀H₂₆O₆Na requires 385.1627.

General procedure for the optimization of heterocoupling reaction. A solution of toluene **1a** and 3-methylanisole **1f** in THF (20 mL) at -78 °C was treated dropwise with BuLi (2.37 M) and stirred for 5 min. KO^tBu (1.0 M in THF) was added dropwise followed by 2,2,6,6-tetramethylpiperidine. The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.22 mL, 5.00 equiv.) added and stirred for a further 5 min. The reaction mixture was warmed to room temperature and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 96:4 cyclohexane:diethyl ether gave 1-methoxy-3-phenethylbenzene **4a** as a colorless oil (R_f = 0.60).

Tabulated results:

entry	1a (mg, mmol)	1f (mg, mmol)	Li:K:TMP (eq.)	4a (mg, mmol, yield%)	3a (mg, mmol)	3f (mg, mmol)
1	46, 0.50	61, 0.50	2.2 : 2.2 : 2	26, 0.121, 24%	21, 0.115	23, 0.094
2	92, 1.00	61, 0.50	3.3 : 3.3 : 3	43, 0.202, 41%	72, 0.395	23, 0.095
3	46, 0.50	122, 1.00	3.3 : 3.3 : 3	41, 0.195, 39%	25, 0.139	60, 0.248

*1-Methoxy-3-phenethylbenzene (4a).*¹¹ A solution of 3-methylanisole **1f** (61 mg, 0.50 mmol) and toluene **1a** (92 mg, 1.00 mmol) in THF (20 mL) at -78 °C was treated dropwise with BuLi (2.37 M, 0.69 mL, 1.65 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.65 mL, 1.65 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.22 mL, 2.50 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by

silica gel chromatography eluting with 96:4 cyclohexane:diethyl ether gave 1-methoxy-3-phenethylbenzene **4a** as a colorless oil ($R_f = 0.60$, 43 mg, 41%). ^1H NMR (500 MHz, CDCl_3): δ 7.29-7.25 (m, 2H), 7.21-7.16 (m, 4H), 6.80-6.70 (m, 3H), 3.77 (s, 3H), 2.95-2.86 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3): δ 159.6, 143.4, 141.7, 129.3, 128.4, 128.3, 125.9, 120.9, 114.2, 111.3, 55.1, 37.9, 37.8. HRMS $[\text{M}]^+$: 212.1209, $\text{C}_{15}\text{H}_{16}\text{O}$ requires 212.1201.

1-(Methoxymethoxy)-3-phenethylbenzene (4b).²⁹ A solution of 1-(methoxymethoxy)-3-methylbenzene **1g** (76 mg, 0.50 mmol) and toluene **1a** (92 mg, 1.00 mmol) in THF (20 mL) at $-78\text{ }^\circ\text{C}$ was treated dropwise with BuLi (2.50 M, 0.66 mL, 1.65 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.65 mL, 1.65 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol). The reaction mixture was stirred for 15 min at $-78\text{ }^\circ\text{C}$, 1,2-dibromoethane (0.22 mL, 2.50 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 94:6 cyclohexane:diethyl ether (0.25% Et $_3$ N) gave **4b** as a colorless oil ($R_f = 0.60$, 53 mg, 43%). ^1H NMR (500 MHz, CDCl_3): δ 7.30-7.26 (m, 2H), 7.22-7.17 (m, 4H), 6.90-6.82 (m, 3H), 5.15 (s, 2H), 3.48 (s, 3H), 2.95-2.87 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3): δ 157.3, 143.5, 141.7, 129.3, 128.4, 128.3, 125.9, 122.1, 116.4, 113.7, 94.5, 55.9, 37.9, 37.8. HRMS $[\text{M}+\text{Na}]^+$: 265.1204, $\text{C}_{16}\text{H}_{18}\text{O}_2\text{Na}$ requires 265.1204.

3-Phenethylphenol (4c).¹³ A solution of 1-(methoxymethoxy)-3-phenethylbenzene **4b** (52 mg, 0.22 mmol) in methanol (15 mL) was treated dropwise with conc. HCl (0.50 mL) and stirred overnight at reflux. The reaction mixture was cooled to rt, extracted into ethyl acetate (3 x 30 mL) and washed with water. The combined organic material was dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 80:20 cyclohexane:ethyl acetate gave **4c** as a white solid ($R_f = 0.50$, 36 mg, 83%, mp. 74-75 $^\circ\text{C}$, lit. mp. 75-76 $^\circ\text{C}$).¹³ ^1H NMR (500 MHz, CDCl_3): δ 7.28 (t, $J = 7.4\text{ Hz}$, 2H), 7.21-7.12 (m, 4H), 6.76 (d, $J = 7.4\text{ Hz}$, 1H), 6.68-6.63 (m, 2H), 4.70 (s, 1H), 2.94-2.84 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3): δ 155.5, 143.7, 141.6, 129.5, 128.4, 128.3, 125.9, 121.0, 115.4, 112.8, 37.7, 37.6. HRMS $[\text{M}]^+$: 198.1060, $\text{C}_{14}\text{H}_{14}\text{O}$ requires 198.1045.

1,3-Dimethoxy-5-phenethylbenzene (4d).³⁰ A solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol) in THF (20 mL) at $-78\text{ }^\circ\text{C}$ was treated dropwise with BuLi (2.37 M, 0.69 mL,

1.65 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.65 mL, 1.65 mmol) was added dropwise and stirred for 5 min. A solution of 3,5-dimethoxytoluene **1i** (76 mg, 0.50 mmol) and toluene **1a** (92 mg, 1.00 mmol) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise to the reaction mixture and stirred for 15 min at $-78\text{ }^{\circ}\text{C}$. Then 1,2-dibromoethane (0.22 mL, 2.50 mmol) was added and the mixture was stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 96:4 cyclohexane:diethyl ether gave **4d** as a colorless oil ($R_f = 0.40$, 49 mg, 40%). ¹H NMR (500 MHz, CDCl₃): δ 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 6.36-6.29 (m, 3H), 3.75 (s, 6H), 2.94-2.83 (m, 4H). ¹³C NMR (125 MHz, CDCl₃): δ 160.7, 144.2, 141.7, 128.4, 128.3, 125.9, 106.5, 98.0, 55.2, 38.2, 37.6. HRMS [M+H]⁺: 243.1397, C₁₆H₁₉O₂ requires 243.1385.

1,2,3-Trimethoxy-5-phenethylbenzene (4e).³¹ A solution of 3,4,5-trimethoxytoluene **1k** (91 mg, 0.50 mmol) and toluene **1a** (92 mg, 1.00 mmol) in THF (20 mL) at $-78\text{ }^{\circ}\text{C}$ was treated dropwise with BuLi (2.50 M, 0.66 mL, 1.65 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.65 mL, 1.65 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol). The reaction mixture was stirred for 15 min at $-78\text{ }^{\circ}\text{C}$, 1,2-dibromoethane (0.22 mL, 2.50 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 80:20 cyclohexane:diethyl ether gave **4e** as a colorless oil ($R_f = 0.50$, 63 mg, 46%). ¹H NMR (500 MHz, CDCl₃): δ 7.28 (t, $J = 7.4\text{ Hz}$, 2H), 7.21-7.15 (m, 3H), 6.36 (s, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 2.94-2.84 (m, 4H). ¹³C NMR (125 MHz, CDCl₃): δ 153.0, 141.6, 137.4, 136.3, 128.5, 128.3, 125.9, 105.5, 60.8, 56.1, 38.3, 37.9. HRMS [M+H]⁺: 273.1484, C₁₇H₂₁O₃ requires 273.1491.

1,3-Dimethoxy-5-(3-methoxyphenethyl)benzene (4f) (batatasin III dimethyl ether).¹⁵ A solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol) in THF (20 mL) at $-78\text{ }^{\circ}\text{C}$ was treated dropwise with BuLi (2.35 M, 0.70 mL, 1.65 mmol) and stirred for 5 min. KO^tBu (1.0 M in THF, 1.65 mL, 1.65 mmol) was added dropwise and stirred for 5 min. A solution of 3,5-dimethoxytoluene **1i** (76 mg, 0.50 mmol) and 3-methylanisole **1f** (122 mg, 1.00 mmol) in THF (5 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise to the reaction mixture and stirred for 15 min at $-78\text{ }^{\circ}\text{C}$.

Then 1,2-dibromoethane (0.22 mL, 2.50 mmol) was added and the mixture was stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 85:15 pentane:diethyl ether gave **4f** as a pale yellow solid ($R_f = 0.60$, 79 mg, 58%, mp. 41-42 °C). ^1H NMR (500 MHz, CDCl_3): δ 7.19 (td, $J = 7.9, 1.9$ Hz, 1H), 6.80-6.72 (m, 3H), 6.36-6.30 (m, 3H), 3.77 (s, 3H), 3.75 (s, 6H), 2.91-2.82 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3): δ 160.8, 159.7, 144.1, 143.3, 129.3, 120.8, 114.2, 111.3, 106.5, 98.0, 55.2, 55.1, 38.1, 37.7. HRMS $[\text{M}+\text{H}]^+$: 273.1501, $\text{C}_{17}\text{H}_{21}\text{O}_3$ requires 273.1491.

1,2,3-Trimethoxy-5-(3-methoxyphenethyl)benzene (4g) (aloifol I dimethyl ether).³² A solution of 3,4,5-trimethoxytoluene **1k** (91 mg, 0.50 mmol) and 3-methylanisole **1f** (122 mg, 1.00 mmol) in THF (20 mL) at -78 °C was treated dropwise with BuLi (2.50 M, 0.66 mL, 1.65 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.65 mL, 1.65 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol). The reaction mixture was stirred for 15 min at -78 °C, 1,2-dibromoethane (0.22 mL, 2.50 mmol) added and stirred for a further 5 min. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 70:30 cyclohexane:diethyl ether gave **4g** as a colorless oil ($R_f = 0.40$, 79 mg, 52%). ^1H NMR (500 MHz, CDCl_3): δ 7.20 (t, $J = 7.8$ Hz, 1H), 6.80-6.71 (m, 3H), 6.37 (s, 2H), 3.82 (s, 3H), 3.82 (s, 6H), 3.78 (s, 3H), 2.91-2.83 (m, 4H). ^{13}C NMR (125 MHz, CDCl_3): δ 159.6, 153.0, 143.2, 137.4, 136.3, 129.3, 120.9, 114.3, 111.3, 105.5, 60.8, 56.1, 55.1, 38.2, 38.0. HRMS $[\text{M}+\text{Na}]^+$: 325.1409, $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}$ requires 325.1416.

1,3-Dimethoxy-2,5-dimethylbenzene (5).³³ A solution of 3,5-dimethoxytoluene **1i** (228 mg, 1.50 mmol) in THF (20 mL) at -78 °C was treated dropwise with BuLi (2.50 M, 0.66 mL, 1.65 mmol) and stirred for 5 min. KO t Bu (1.0 M in THF, 1.65 mL, 1.65 mmol) was added dropwise, and the reaction mixture was stirred for 1 h at -78 °C. Methyl iodide (0.10 mL, 1.65 mmol) was added, and the reaction mixture was stirred at -78 °C for 30 min. The reaction was quenched with HCl (2 M, 20 mL), warmed to rt and extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with a saturated solution of sodium thiosulphate (2 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel

chromatography eluting with 20:1 cyclohexane:diethyl ether gave **5** as a colorless solid ($R_f = 0.70$, 181 mg, 73%, mp. 47-48 °C lit. mp. 49-50 °C).^{33b} ^1H NMR (500 MHz, CDCl_3): δ 6.36 (s, 2H), 3.80 (s, 6H), 2.33 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 158.2, 136.1, 111.4, 104.5, 55.7, 21.9, 7.8. HRMS $[\text{M}+\text{H}]^+$: 167.1069, $\text{C}_{10}\text{H}_{15}\text{O}_2$ requires 167.1072.

1,3-Dimethoxy-2-methyl-5-phenethylbenzene (6) (stilbostemin M).³⁴ Solution A. A solution of 1,3-dimethoxy-2,5-dimethylbenzene **5** (83 mg, 0.50 mmol) in THF (10 mL) at -78 °C was treated dropwise with BuLi (2.50 M in hexanes, 0.42 mL, 1.05 mmol) and stirred for 5 min. KOtBu (1.0 M in THF, 1.05 mL, 1.05 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (84 μL , 0.50 mmol). The reaction mixture was stirred for 15 min at -78 °C. Solution B. A solution of toluene **1a** (92 mg, 1.00 mmol) in THF (10 mL) at -78 °C was treated dropwise with BuLi (2.50 M, 0.44 mL, 1.10 mmol) and stirred for 5 min. KOtBu (1.0 M in THF, 1.10 mL, 1.10 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.00 mmol). The reaction mixture was stirred for 15 min at -78 °C and transferred *via* cannula into the solution of metalated 1,3-dimethoxy-2,5-dimethylbenzene (Solution A). The resulting mixture was immediately quenched with 1,2-dibromoethane (0.22 mL, 2.50 mmol) and stirred for a further 5 min at -78 °C. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Diethyl ether (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 98:2 pentane:diethyl ether gave **6** as a colorless solid ($R_f = 0.50$, 52 mg, 41%, mp. 77-78 °C, lit. mp. 77-79 °C).³⁴ ^1H NMR (500 MHz, CDCl_3): δ 7.30-7.26 (m, 2H), 7.22-7.16 (m, 3H), 6.34 (s, 2H), 3.77 (s, 6H), 2.95-2.85 (m, 4H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 157.2, 140.8, 139.2, 127.5, 127.3, 124.9, 111.0, 102.9, 54.7, 37.4, 37.0, 6.9. HRMS $[\text{M}+\text{H}]^+$: 257.1531, $\text{C}_{17}\text{H}_{21}\text{O}_2$ requires 257.1542.

2-Methyl-5-phenethylbenzene-1,3-diol (7) (stilbostemin B).³⁵ A solution of 1,3-dimethoxy-2-methyl-5-phenethylbenzene **6** (30 mg, 0.12 mmol) in dichloromethane (10 mL) at -78 °C was treated dropwise with BBr_3 (1.0 M in dichloromethane, 0.70 mL, 0.70 mmol). The reaction mixture was warmed to rt and stirred for 3.5 hours. The reaction was then poured into a saturated solution of sodium bicarbonate (10 mL) and stirred vigorously for 30 min. The product was extracted with CH_2Cl_2 , washed with a saturated solution of sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 1:1 cyclohexane:ethyl acetate gave **7** as a

colorless solid ($R_f = 0.70$, 20 mg, 73%, mp. 152-153 °C, lit. mp. 153-154 °C).^{35b} ^1H NMR (500 MHz, CD_3OD): δ 7.22 (t, $J = 7.5$ Hz, 2H), 7.17-7.10 (m, 3H), 6.17 (s, 2H), 4.81 (s, 2H), 2.86-2.66 (m, 4H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ 157.1, 143.3, 141.2, 129.4, 129.2, 126.7, 109.6, 107.8, 39.0, 38.9, 8.3. HRMS $[\text{M}+\text{H}]^+$: 229.1228, $\text{C}_{15}\text{H}_{17}\text{O}_2$ requires 229.1229.

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Supporting Information Available All ^1H , ^2H and ^{13}C NMR spectra. This material is available free of charge via the Internet

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