Giving substance to the Losanitsch series

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Supporting Information

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Experimental Section

Materials and Methods: Anhydrous Me₂SO was purchased from Aldrich and stored under an atmosphere of argon. CDCl₃, CD₂Cl₂, and C₇D₈ were purchased from Aldrich and used without further purification. All other reagents and solvents were purchased from commercial sources and were used without further purification, unless indicated otherwise. All reactions were carried out under an atmosphere of N₂ in flame-dried flasks using anhydrous solvents, unless indicated otherwise. Thin-layer chromatography (TLC) was carried out using glass or aluminum plates, precoated with silica-gel 60 containing fluorescent indicator (Whatman LK6F). The plates were inspected by UV light (254 nm) and/or KMnO₄ stain. Column chromatography was carried out employing the flash technique using silica-gel 60F (230-400 mesh). ¹H and ¹³C NMR spectra were recorded on a Bruker ARX500 (500 MHz) spectrometer. VT-NMR Spectra were recorder on a Bruker Avance 600 MHz spectrometer, which was temperature-calibrated using neat ethylene glycol or MeOH. The chemical shifts (δ) for ¹H spectra, given in ppm, are referenced to the residual proton signal of the deuterated solvent. The chemical shifts (δ) for ¹³C spectra are referenced relative to the signal from the carbon of the deuterated solvent. High-resolution mass spectra were measured on a Finnigan LCQ iontrap mass spectrometer (HR-ESI).

General Synthetic Procedures

Suzuki-Miyaura Cross-Couplings: The aryl halide (1.00 equiv), the boronic acid pinacol ester (1.10 equiv per halide), CsF (3.00 equiv per halide) and (dppf)PdCl₂ (5 mol % per halide) were dissolved in a degassed *p*-dioxane / H₂O mixture (2 : 1 v/v, 0.12 M based on the aryl halide). The resulting mixture was heated under reflux overnight. It was then cooled to rt and the products were purified using techniques outlined with specific measures for the individual reactions discussed in the section on synthetic procedures.

Synthetic Procedures



2: Methyl 4-bromo-3-methylbenzoate (1) (5.00 g, 21.8 mmol, 1.0 equiv) and bis(pinacolato)diboron (6.10 g, 24.0 mmol, 1.1 equiv) were dissolved in anhydrous degassed Me₂SO (80 mL). KOAc (6.42 g, 65.4 mmol, 3.0 equiv) and PdCl₂(dppf) (890 mg, 1.09 mmol, 5 mol%) were added and the reaction mixture was heated to 80 °C overnight, before being cooled to rt and extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with

CH₂Cl₂. The combined organic phases were washed with H₂O, dried (MgSO₄), concentrated and subjected to column chromatography (SiO₂: hexanes:EtOAc = 5:1) to give compound **2** as a colorless oil (5.84 g, 21.2 mmol, 97%). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 7.81 (m, 3H), 3.91 (s, 3H), 2.57 (s, 3H), 1.35 (s, 12H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.4, 144.9, 135.8, 131.8, 130.5, 125.6, 83.9, 52.1, 24.9, 22.1 ppm. HRMS (ESI): *m/z* calcd for C₁₅H₂₂BO₄ [*M* + H]⁺ 277.1608; found 277.1611.



3: Following the General Coupling Procedure, **2** (1.42 g, 5.14 mmol, 1.0 equiv) and 1,4dibromo-2,5-dimethylbenzene (**5**) ((6.79 g, 25.7 mmol, 5.0 equiv) were dissolved in a degassed mixture of dioxane (500 mL) and H₂O (200 mL) at 80 °C before CsF (2.34 g, 15.4 mmol, 3.0 equiv) and PdCl₂(dppf) (210 mg, 0.260 mmol, 5 mol%) were added. After completion of the reaction, the mixture was cooled to rt, before being extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with CH₂Cl₂. The combined organic phases were washed with brine, dried (MgSO₄) and concentrated. The crude product was subjected to column chromatography (SiO₂: hexanes:EtOAc = 10:1) to give the product **3** as a colorless oil (973 mg, 2.93 mmol, 57%). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 7.97 (s, 1H), 7.97 (s, 1H), 7.91 (dd, J = 7.9, 1.3 Hz, 1H), 7.91 (dd, J = 7.9, 1.3 Hz, 1H), 7.48 (s, 1H), 7.48 (s, 1H), 7.16 (d, J = 7.9 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 6.97 (s, 1H), 6.97 (s, 1H), 3.96 (s, 3H), 3.96 (s, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 2.12 (s, 3H), 2.12 (s, 3H), 1.99 (s, 3H), 1.99 (s, 3H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.2, 145.4, 139.8, 136.2, 135.05, 134.85, 133.5, 131.09, 130.98, 129.40, 129.23, 126.9, 123.8, 52.2, 22.4, 19.8, 19.0 ppm. HRMS (ESI): *m/z* calcd for C₁₇H₁₈Br₂ [*M* + H]⁺ 333.0485; found 333.0479.



4: Compound 3 (900 mg, 2.70 mmol, 1.0 equiv) and bis(pinacolato)diboron (754 mg, 2.97 mmol, 1.1 equiv) were dissolved in anhydrous degassed Me₂SO (11 mL). KOAc (795 mg, 8.10 mmol, 3.0 equiv) and PdCl₂(dppf) (110 mg, 0.135 mmol, 5 mol%) were added and the

reaction mixture was heated to 80 °C overnight, before being cooled to rt and extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with CH₂Cl₂. The combined organic phases were washed with H₂O, dried (MgSO₄), concentrated and subjected to column chromatography (SiO₂: hexanes:EtOAc = 5:1) to give compound **4** as a colorless oil (880 mg, 2.38 mmol, 88%). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 7.97 (s, 1H), 7.91 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.70 (s, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.92 (s, 1H), 3.96 (s, 3H), 2.55 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H), 1.39 (s, 12H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.3, 146.6, 143.2, 142.1, 137.4, 136.1, 131.6, 131.0, 130.2, 129.3, 128.9, 126.8, 83.5, 52.1, 34.7, 25.0, 21.7, 19.8, 19.0 ppm. HRMS (ESI): *m/z* calcd for C₂₃H₃₀BO₄ [*M* + H]⁺ 380.2268; found 380.2263.



2-mer: Following the General Coupling Procedure, **1** (830 mg, 3.01 mmol, 1.0 equiv) and **2** (690 mg, 3.01 mmol, 1.0 equiv) were reacted in a degassed 2:1 dioxane/H₂O mixture (90 mL) with CsF (1.37 g, 9.03 mmol, 3.0 equiv) and PdCl₂(dppf) (123 mg, 0.150 mmol, 5 mol%) for 15 h. The reaction mixture was cooled to rt before being extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and concentrated. The crude product was absorbed on silica-gel and subjected to column chromatography (SiO₂: hexanes:EtOAc = 5:1) to give the **2-mer** as a colorless solid (502 mg, 1.68 mmol, 56%). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 7.99 (s, 2H), 7.93 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 3.97 (s, 6H), 2.10 (s, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.1, 145.5, 135.9, 131.2, 129.5, 129.0, 127.0, 52.2, 19.7 ppm. HRMS (ESI): *m/z* calcd for C₁₈H₁₉O₄ [*M* + H]⁺ 299.1278; found 299.1288.



3-mer: Following the General Coupling Procedure, **2** (2.00 g, 7.24 mmol, 2.3 equiv) and 1,4diiodo-2,5-dimethyl benzene (**6**) (1.13 g, 3.15 mmol, 1.0 equiv) were reacted in a degassed 2:1 dioxane/H₂O mixture (150 mL) with CsF (2.87 g, 18.9 mmol, 3.0 equiv) and PdCl₂(dppf) (260 mg, 0.315 mmol, 5 mol%) for 15 h. The reaction mixture was cooled to rt before being extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and concentrated. The crude product was absorbed on silica-gel and subjected to column chromatography (SiO₂: hexanes:EtOAc = 9:1) to give the **3-mer** as a colorless solid (904 mg, 2.25 mmol, 71%). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 8.00 (s, 2H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.11 (m, 1H), 7.00 (d, *J* = 6.9 Hz, 2H), 3.97 (s, 6H), 2.19 (m, *J* = 5.9 Hz, 3H), 2.12 (m, *J* = 6.8 Hz, 3H), 2.05-2.04 (m, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.31, 167.30, 146.44, 146.38, 145.5, 139.90, 139.86, 136.44, 136.35, 135.9, 132.62, 132.53, 131.19, 131.03, 130.3, 129.66, 129.57, 129.45, 129.02, 129.00, 128.96, 127.01, 126.89, 126.84, 52.2, 19.94, 19.80, 19.72, 19.2 ppm. HRMS (ESI): *m/z* calcd for C₂₆H₂₇O₄ [*M* + H]⁺ 403.1904; found 403.1903.



4-mer: Following the General Coupling Procedure, **2** (2.00 g, 7.24 mmol, 2.3 equiv) and **7** (1.46 g, 3.15 mmol, 1.0 equiv) were reacted in a degassed 2:1 dioxane/H₂O mixture (150 mL) with CsF (2.87 g, 18.9 mmol, 3.0 equiv) and PdCl₂(dppf) (260 mg, 0.315 mmol, 5 mol%) for 15 h. The reaction mixture was cooled to rt, before being extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and concentrated. The crude product was absorbed on silica-gel and subjected to column chromatography (SiO₂: hexanes:EtOAc = 9:1) to give the **4-mer** as a colorless solid (940 mg, 1.86 mmol, 59%). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 8.01 (s, 2H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.30 (m, 2H), 7.11-7.09 (m, 2H), 7.01 (d, *J* = 7.1 Hz, 2H), 3.98 (s, 6H), 2.21 (m, *J* = 6.8 Hz, 6H), 2.12 (m, *J* = 6.1 Hz, 6H), 2.05 (m, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.3, 146.71, 146.63, 140.71, 140.66, 140.61, 139.43, 139.40, 139.38, 139.34, 136.49, 136.44, 133.14, 133.04, 132.95, 132.39, 132.34, 132.29, 132.24, 131.19, 131.00, 130.91, 130.85, 130.1, 129.75, 129.65, 129.02, 128.91, 128.88, 126.86, 126.81, 52.1, 19.98, 19.84, 19.48, 19.47, 19.32, 19.28, 19.24 ppm. HRMS (ESI): *m/z* calcd for C₃₄H₃₅O₄ [*M*+H]⁺ 507.2530; found 507.2539.



5-mer: Following the General Coupling Procedure, **4** (290 mg, 0.763 mmol, 2.2 equiv) and 1,4diiodo-2,5-dimethyl benzene (**6**) (124 mg, 0.347 mmol, 1.0 equiv) were reacted in a degassed 2:1 dioxane/H₂O mixture (24 mL) with CsF (316 mg, 2.08 mmol, 3.0 equiv) and PdCl₂(dppf)

(28.0 mg, 0.035 mmol, 5 mol%) for 15 h. The reaction mixture was cooled to rt before being extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and concentrated. The crude product was absorbed on silica-gel and subjected to column chromatography (SiO₂: CH₂Cl₂:hexanes = 1:1 \rightarrow 1:0) to give the **5-mer** as a colorless solid (170 mg, 0.278 mmol, 80%). ¹H NMR (500 MHz, C₇D₈, 25 °C): δ = 8.16 (m, 2H), 8.08-8.04 (m, 2H), 7.16 (m, 4H), 7.11 (m, 2H), 6.98 (m, 2H), 3.63 (m, 6H), 2.19 (m, 6H), 2.15 (m, 6H), 2.08 (m, 6H), 2.02 (m, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.4, 146.77, 146.70, 140.93, 140.88, 140.82, 140.17, 140.14, 139.29, 139.27, 136.52, 136.46, 133.20, 133.14, 133.09, 133.03, 132.90, 132.86, 132.81, 132.79, 132.77, 132.75, 132.71, 132.67, 132.32, 132.29, 132.21, 132.18, 131.00, 130.93, 130.74, 130.67, 130.1, 129.77, 129.67, 128.88, 128.85, 126.85, 126.80, 52.1, 19.98, 19.84, 19.50, 19.46, 19.35, 19.29, 19.24 ppm. HRMS (ESI): *m/z* calcd for C₄₂H₄₃O₄ [*M* + H]⁺ 611.3156; found 611.3160.



6-mer: Following the General Coupling Procedure, **4** (290 mg, 0.763 mmol, 2.2 equiv) and **7** (160 mg, 0.347 mmol, 1.0 equiv) were reacted in a degassed 2:1 dioxane/H₂O mixture (24 mL) with CsF (316 mg, 2.08 mmol, 3.0 equiv) and PdCl₂(dppf) (28.0 mg, 0.035 mmol, 5 mol%) for 15 h. The reaction mixture was cooled to rt, before being extracted with CH₂Cl₂ and H₂O. The aqueous phase was washed twice with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and concentrated. The crude product was absorbed on silica-gel and subjected to column chromatography (SiO₂: CH₂Cl₂:hexanes = 1:1 → 1:0) to give the **6-mer** as a colorless solid (196 mg, 0.274 mmol, 79%). ¹H NMR (500 MHz, C₇D₈, 25 °C): δ = 8.48 (m, 2H), 8.38 (m, 2H), 7.54-7.48 (m, 6H), 7.43 (m, 2H), 7.31 (m, 2H), 3.96 (m, 6H), 2.54-2.51 (m, 12H), 2.48-2.47 (m, 6H), 2.40 (m, 6H), 2.35-2.33 (m, 6H) ppm. ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 167.4, 146.79, 146.71, 140.93, 140.88, 140.40, 140.35, 140.12, 140.07, 139.30, 139.27, 139.25, 136.52, 136.47, 133.2, 132.86, 132.80, 132.75, 132.72, 132.31, 132.29, 132.20, 132.17, 130.95, 130.93, 130.84, 130.74, 130.71, 130.63, 130.0, 129.77, 129.68, 128.88, 128.85, 126.85, 126.80, 52.1, 19.98, 19.84, 19.51, 19.50, 19.35, 19.29, 19.24 ppm. HRMS (ESI): *m/z* calcd for C₅₀H₅₁O₄ [*M* + H]⁺ 715.3782; found 715.3791.

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Figure S1: VT ¹H NMR Spectra of the **5-mers** recorded in C_7D_8 at 600 MHz. The mixture of isomers was allowed to equilibrate at every temperature for 15 minutes before the spectra were recorded at 10 degree intervals. The temperature was calibrated with neat ethylene glycol and methanol. A total of 32 heterotopic methyl peaks are expected for all the isomers. They could not all be resolved at low temperature at highfield.

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Figure S2: VT ¹H NMR Spectra of the **6-mers** recorded in C_7D_8 at 600 MHz. The mixture of isomers was allowed to equilibrate at every temperature for 15 minutes before the spectra were recorded at 10 degree intervals. The temperature was calibrated with neat ethylene glycol and methanol. A total of 80 heterotopic methyl peaks are expected for all the isomers. They could not all be resolved at low temperature at highfield.