Supplementary Material for Organic & Biomolecular Chemistry

Diastereoselective Intramolecular SmI_2/H_2O/Amine Mediated Couplings

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ELECTRONIC SUPPLEMENTARY INFORMATION

General synthesis of substrates 1-7, 9-10 and 12-13

2-Iodophenol (3.3 g, 15 mmol) was added to a suspension of K_2CO_3 (6.2 g, 45 mmol) in DMF (50 ml) stirred under nitrogen atmosphere. Allyl bromide (1.6 ml, 18 mmol) was added slowly by syringe and the mixture was stirred over night. Water (50 ml) was added and the solution was extracted with n-hexane (4×50 ml). The combined organic layer was washed with water (3×50 ml), 10% KOH (2×50 ml), $Na_2S_2O_3$ (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered and concentrated. Distillation under vacuum gave **1** as colourless oil (90-100% yield).

1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, 2H), 5.30 (d, 1H), 5.50 (d, 2H), 6.06 (m, 1H), 6.68 (t, 1H), 6.79 (d, 1H), 7.24 (t, 1H), 7.76 (d, 1H). MS (EI): *m/z* 260 (M^+), 130, 102.

2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (m, 2H), 4.06 (t, 2H), 5.13 (d, 1H), 5.21 (d, 1H), 5.97 (m, 1H), 6.71 (t, 1H), 6.80 (d, 1H), 7.27 (t, 1H), 7.77 (d, 1H). MS (EI): *m/z* 274(M^+), 246, 220, 142, 113.

3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (m, 2H), 2.32 (q, 2H), 4.02 (t, 2H), 5.0 (d, 1H), 5.10 (d, 1H), 5.85 (m, 1H), 6.68 (t, 1H), 6.90 (d, 1H), 7.30 (t, 1H), 7.75 (d, 1H). MS (EI): *m/z* 288 (M^+), 220, 161, 119, 92.

4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, 2H), 5.30 (d, 1H), 5.40 (d, 1H), 6.02 (m, 1H), 6.85 (d, 1H), 7.0 (t, 1H), 7.29 (d, 2H). MS (EI): *m/z* 260 (M^+), 245, 220, 191, 133, 105.

5: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (d, 3H), 4.54 (d, 2H), 5.75 (m, 1H), 5.92 (m, 1H), 6.71 (t, 1H), 6.82 (d, 1H), 7.27 (t, 1H), 7.78 (d, 1H). MS (EI): *m/z* 274 (M^+), 248, 220, 130, 91.

6: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 4.50 (s, 2H), 5.03 (s, 1H), 5.21 (s, 1H), 6.72 (t, 1H), 6.81 (d, 1H), 7.28 (t, 1H), 7.78 (d, 1H). MS (EI): *m/z* 274 (M^+), 260, 220, 147, 91.

7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 1H), 4.77 (s, 2H), 6.76 (t, 1H), 7.00 (d, 1H), 7.30 (t, 1H), 7.79 (d, 1H). MS (EI): *m/z* 258 (M^+), 219, 191, 131, 103.

9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, 2H), 5.35 (d, 1H), 5.52 (d, 1H), 6.02 (m, 1H), 6.98 (d, 1H), 7.17 (t, 1H), 8.00 (d, 1H). MS (EI): *m/z* 262 (M^++1), 131, 102.

10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (m, 2H), 4.07 (t, 2H), 5.20 (m, 2H), 5.95 (m, 1H), 6.98 (d, 1H), 7.18 (t, 1H), 8.00 (d, 1H). MS (EI): *m/z* 276 (M^+), 145, 129, 114.

12: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 1H), 1.95 (m, 3H), 2.07 (m, 1H), 2.16 (m, 1H), 4.81 (s, 1H), 5.92 (d, 1H), 5.99 (m, 1H), 6.71 (t, 1H), 6.89 (d, 1H), 7.29 (t, 1H), 7.78 (d, 1H). MS (EI): *m/z* 300 (M^+), 285, 145, 80.

13: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 1H), 1.95 (m, 3H), 2.07 (m, 1H), 2.16 (m, 1H), 4.79 (s, 1H), 5.86 (d, 1H), 6.02 (m, 1H), 7.05 (d, 1H), 7.16 (t, 1H), 7.98 (d, 1H). MS (EI): *m/z* 302 (M^+), 176, 96, 81.

Synthesis of substrate 8

2-Iodophenol (2.86 g, 13 mmol), *p*-toluenesulfonate-3-butyn-1-ol (3.09 g, 13.8 mmol) and KOH (0.77 g, 13.8 mmol) was refluxed in dry THF (200 ml) under nitrogen atmosphere for 48 hours. The mixture was cooled and poured into an extraction funnel containing water/CH_2Cl_2 (100 ml), shaken and separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 ml) and the combined organic phase was washed with water (3×60 ml), 10% KOH (2×60 ml) and brine (60 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The remaining yellowish liquid was purified through silica by flash chromatography with ethyl acetate:hexane (1:5) leaving **8** as yellowish crystals (0.87 g, 25%).

8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 1H), 2.75 (t, 2H), 4.15 (t, 2H), 6.72 (t, 1H), 6.82 (d, 1H), 7.30 (t, 1H), 7.78 (d, 1H). MS (EI): *m/z* 272 (M^+), 220, 144, 115.

Synthesis of substrate 11

N-Benzyloxycarbonyl-2-iodo-aniline (1.59 g, 4.5 mmol) was dissolved in dry THF (50 ml) and the mixture was cooled to 0 °C. Sodium hydride (60%, 0.20 g, 5.0 mmol) was added in portions. When the gas evolution had ceased, the ice bath was removed and the suspension was stirred at room temperature for 30 min. The mixture was then recooled to 0 °C and allyl bromide (0.47 ml, 5.4 mmol) was added. The reaction mixture was allowed to reach room temperature overnight. The reaction was carefully quenched by addition of water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×50 ml) and the organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified through silica by flash chromatography with ethyl acetate:hexane (1:20) leaving **11** as colourless oil (0.82 g, 46%).

11: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 2H), 6.80 (t, 1H), 7.02 (s, 1H), 7.40 (m, 6H), 7.77 (d, 1H), 8.07 (d, 1H). MS (EI): *m/z* 394 (M^++1), 286, 267, 130, 91.

Synthesis of substrates 14-15

14-15: 5-Iodovanillin (2.0 g, 7.2 mmol) was added to a suspension of K_2CO_3 (3.0 g, 21.6 mmol) in DMF (40 ml) stirred under nitrogen atmosphere. Racemic 3-bromocyclohexene (1.54 g, 8.6 mmol) was added slowly by syringe and the mixture was stirred over night. Water (50 ml) was added and the solution was extracted with n-hexane (4×50 ml). The combined organic layer was washed with water (3×50 ml), 10% KOH (2×50 ml), $Na_2S_2O_3$ (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered and concentrated, which yielded 1-(cyclohex-2-enyloxy)-5-iodovanillin as colourless oil (95% yield).

14: 1-(cyclohex-2-enyloxy)-5-iodovanillin (1.0 g, 2.8 mmol) was dissolved in EtOH (50 ml) and treated with $NaBH_4$ (0.21 g, 5.6 mmol) followed by stirring at room temperature for 1 hour. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated, which yielded **14** as colourless oil (100% yield).

15: 1-(cyclohex-2-enyloxy)-5-iodovanillin (1.0 g, 2.8 mmol, 1 equiv.) and isopropyl amine (0.95 ml, 11.2 mmol, 4 equiv.) were dissolved in benzene (120 ml), followed by reflux with Dean-Stark trap over night. Excess isopropyl amine and benzene were finally

evaporated leaving the corresponding imine in quantitative yield. The imine was dissolved in EtOH (50 ml) and treated with $NaBH_4$ (0.21 g, 5.6 mmol, 2 equiv.) followed by stirring at room temperature for 1 hour. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated, which yielded **15** as slightly yellow oil (100% yield).

14: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (m, 1H), 1.81 (m, 1H), 2.03 (m, 3H), 2.16 (m, 1H), 3.86 (s, 3H), 4.61 (s, 2H), 4.77 (s, 1H), 5.31 (s, -OH), 5.93 (s, 2H), 6.92 (s, 1H), 7.36 (s, 1H). MS (EI): *m/z* 360 (M^+), 260, 231, 218, 207, 179.

15: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, 6H), 1.60 (m, 1H), 1.80 (m, 1H), 2.01 (m, 3H), 2.13 (m, 1H), 2.85 (m, 1H), 3.68 (s, 2H), 3.84 (s, 3H), 4.73 (s, 1H), 5.92 (s, 2H), 6.87 (s, 1H), 7.32 (s, 1H). MS (EI): *m/z* 402(M^++1), 331, 320, 263, 215, 161.

Synthesis of substrate 16

5-Iodovanillin (2.0 g, 7.2 mmol, 1 equiv.) was dissolved in MeOH/DMF (30/30 ml) and then BF_3×DEE (0.44 g, 3.1 mmol, 0.44 equiv.) and 1,2-ethanedithiol (0.75 g, 7.9 mmol, 1.1 equiv.) were added. After 1 hour at room temperature the reaction was quenched by addition of HCl (1M, 100 ml) followed by extraction with diethylether (DEE). Evaporation yielded the 1,3-dithiane of 5-iodovanillin as a white powder, which was recrystallized in n-hexan:DEE. The 1,3-dithiane (dithioketal) was treated with 3-bromocyclohexene, as previously described for substrates **14-15**, leaving **16** as a slightly yellow oil (90% overall yield).

16: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (m, 1H), 1.82 (m, 1H), 2.02 (m, 3H), 2.14 (m, 1H), 3.35 (m, 2H), 3.50 (m, 2H), 3.86 (s, 3H), 4.76 (s, 1H), 5.55 (s, (1H), 5.93 (s, 2H), 7.08 (s, 1H), 7.51 (s, 1H). MS (EI): *m/z* 434 (M^+), 309, 246, 197.

General procedure for SmI_2/H_2O/amine mediated reaction

In a standard procedure, 2.5-10 ml of SmI_2 in THF (2.5 equiv., 0.1 M) was added to a dry Schlenk tube, containing a magnetic stirrer bar and fitted with a septum, inside a glove box under nitrogen atmosphere. The ligand (7.5 equiv. R_3N) and the substrate (1 equiv.) were added under stirring. To this mixture the proton donor, i.e. H_2O (6.25 equiv.), was

added slowly at 20.0 °C. The reaction is finished in a less than a minute. To 0.2 ml of the quenched solution was added diethyl ether (1 ml) and HCl (0.1 ml, 0.12 M), or KOH (10%) for products containing nitrogen, to remove the inorganic salts and finally saturated $Na_2S_2O_3$ (5 dr.) to remove excess iodine. The clear organic layer was transferred to a vial and analysed on the GC and GC/MS. Evaporated samples were also analysed on ^{1}H NMR, and COSY or NOESY when considered necessary.

Large scale (2 mmol)

SmI_2 in THF (50 ml, 5 mmol, 2.5 equiv., 0.1 M) was added to a dry round bottomed flask, containing a magnetic stirrer bar and fitted with a septum, inside a glove box under nitrogen atmosphere. Triethyl amine (15 mmol, 7.5 equiv.) and the substrate **1** (0.52 g, 2 mmol, 1 equiv.) were added under stirring. H_2O (15 mmol, 7.5 equiv.) was then added slowly at room temperature. The reaction was finished in less than one minute. The reaction mixture was diluted with diethyl ether (100 ml) and washed with HCl (2*50 ml, 0.1 M), saturated $Na_2S_2O_3$ (2*50 ml) and finally brine (50 ml). The organic phase was dried over $MgSO_4$, filtered and evaporated yielding the product as oil (0.26 g, 97% yield).

Gas Chromatography

The products were separated on a chiral stationary phase GC column: CP Chirasil-Dex CB column (∅ = 0.25 mm, length = 25 m) using helium as carrier gas at a flow rate of 2 ml/min. The injector temperature was 225 °C. The column temperature program started at 100 °C for 10 minutes, increased to 200 °C during 10 minutes and was finally left at 200 °C for another 5 minutes. The detector temperature was 250 °C (FID).

The products were also separated on GC/MS using a CP-Sil 8 CB Low Bleed column (∅ = 25 mm, length = 30 m), using helium as carrier gas at a flow rate of 1 ml/min. The standard method included an injector temperature of 225 °C, and a column temperature at initially 70 °C for 4 min, followed by heating to 250 °C (10 °C/min) for 10 min. The detector temperature was 250 °C (FID).

^{1}H NMR and MS for products from SmI_2/H_2O/amine mediated reaction

1a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, 3H), 3.55 (m, 1H), 4.08 (t, 1H), 4.70 (t, 1H), 6.80 (d, 1H), 6.88 (t, 1H), 7.13 (t, 1H), 7.17 (d, 1H). MS (EI): *m/z* 134 (M^+), 119, 105, 91, 77.

2a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, 3H), 1.72 (m, 1H), 2.09 (m, 1H), 2.95 (m, 1H), 4.18 (m, 2H), 6.8-7.3 (m, 4H). MS (EI): *m/z* 148 (M^+), 133, 119, 105, 91, 77

2b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (m, 2H), 4.02 (t, 2H), 5.14 (m, 2H), 5.91 (m, 1H), 6.8-7.3 (m, 5H). MS (EI): *m/z* 148 (M^+), 133, 119, 105, 91, 77.

3b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 2H), 2.26 (q, 2H), 3.98 (t, 2H), 5.03 (m, 2H), 5.87 (m, 1H), 6.93 (m, 3H), 7.29 (t, 2H). MS (EI): *m/z* 162 (M^+), 121, 94, 77, 69.

4a (=1b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (d, 2H), 5.30 (d, 1H), 5.42 (d, 2H), 6.08 (m, 1H), 6.95 (m, 3H), 7.28 (m, 2H). MS (EI): *m/z* 134 (M^+), 119, 102, 87.

5a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, 3H), 1.60 (m, 1H), 1.80 (m, 1H), 3.38 (m, 1H), 4.21 (t, 1H), 4.63 (t, 1H), 6.80 (d, 1H), 6.85 (t, 1H), 7.10 (t, 1H), 7.15 (d, 1H). MS (EI): *m/z* 148 (M^+), 119, 91.

6a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 6H), 4.24 (s, 2H), 6.9 (m, 1H), 7.11 (d, 2H), 7.26 (1H). MS (EI): *m/z* 148 (M^+), 133, 105.

6b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 4.42 (s, 2H), 4.99 (s, 1H), 5.10 (s, 1H), 6.94 (m, 3H), 7.26 (m, 2H). MS (EI): *m/z* 148 (M^+), 133, 102.

7a=1a

7b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 1H), 4.71 (s, 2H), 7.00 (m, 3H), 7.32 (t, 2H). MS (EI): *m/z* 131 (M^+), 103, 77.

8a=2a

8b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 1H), 2.69 (t, 2H), 4.1 (t, 2H), 6.8-7.25 (m, 5H). MS (EI): *m/z* 146 (M^+), 131, 118, 107, 94.

9a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, 3H), 3.55 (m, 1H), 4.17 (t, 1H), 4.78 (t, 1H), 7.01 (d, 2H), 8.05 (t, 1H). MS (EI): *m/z* 135 (M^+), 120, 106, 92, 77.

10a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (d, 3H), 1.86 (m, 1H), 2.21 (m, 1H), 4.21 (m, 2H), 7.05 (t, 1H), 7.21 (d, 1H), 8.16 (d, 1H). MS (EI): *m/z* 149 (M^+), 134, 120, 106, 93, 78.

10b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (q, 2H), 4.07 (t, 2H), 5.16 (m, 2H), 5.90 (m, 1H), 7.03 (t, 1H), 7.21 (d, 1H), 8.22 (d, 1H), 8.32 (s, 1H). MS (EI): *m/z* 149 (M^+), 134, 121, 108, 95, 78.

11a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3H), 4.14 (t, 1H), 4.19 (m, 2H), 5.05 (s, 2H), 6.9-7.8 (m, 4H). MS (EI): *m/z* 267 (M^+), 224, 208, 130, 90

11b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (m, 1H), 3.50 (m, 1H), 5.03 (s, 2H), 5.16 (m, 2H), 5.83 (m, 1H), 6.9-7.8 (m, 5H). MS (EI): *m/z* 267 (M^+), 223, 131, 91, 89.

12a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 8H), 3.20 (m, 1H), 4.69 (m, 1H), 6.8-7.3 (m, 4H). MS (EI): *m/z* 174 (M^+), 159, 145, 131, 115, 102, 89.

12b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3-2.1 (m, 6H), 4.82 (s, 1H), 5.90 (m, 1H), 5.99 (m, 1H), 6.8-7.3 (m, 5H). MS (EI): *m/z* 174 (M^+), 145, 117, 94.

13a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.0 (m, 8H), 3.25 (m, 1H), 4.79 (m, 1H), 7.05 (m, 2H), 8.03 (d, 1H). MS (EI): *m/z* 175 (M^+), 160, 146, 132, 104.

13b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3-2.0 (m, 6H), 4.8 (s, 1H), 5.9 (m, 2H), 7.0 (m, 2H), 8.0-8.2 (m, 2H). MS (EI): *m/z* 175 (M^+), 161, 147, 96, 81.

14a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 8H), 3.19 (q, 1H), 3.90 (s, 3H), 4.62 (s, 2H), 4.75 (q, 1H), 6.80 (s, 2H). MS (EI): *m/z* 235 (M^++1), 218, 204, 179, 135.

14b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3-2.1 (m, 6H), 3.89 (s, 3H), 4.63 (s, 2H), 4.79 (s, 1H), 5.95 (m, 2H), 6.9 (m, 3H). MS (EI): *m/z* 234 (M^+), 154, 137, 121, 79.

15a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 8H), 2.91 (m, 1H), 3.13 (q, 1H), 3.75 (s, 2H), 3.90 (s, 3H), 4.69 (q, 1H), 6.77 (s, 2H). MS (EI): *m/z* 275 (M^+), 243, 212.

15b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3-2.1 (m, 6H), 2.90 (m, 1H), 3.75 (s, 2H), 3.90 (s, 3H), 4.75 (s, 1H), 5.90 (m, 2H), 6.88 (2H). MS (EI): *m/z* 275 (M^+), 218, 195, 181, 137.

16a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 8H), 3.15 (q, 1H), 3.35 (m, 2H), 3.50 (m, 2H), 3.84 (s, 3H), 4.75 (s, 1H), 5.65 (s, 1H), 6.99 (s, 2H). MS (EI): *m/z* 309 (M^+), 279, 245, 194.

16a′: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 8H), 2.65 (s, 4H), 3.15 (q, 1H), 3.70 (s, 3H), 3.85 (s, 2H), 4.75 (q, 1H), 6.75 (1H), 6.98 (s, 1H). MS (EI): *m/z* 311 (M^+), 218, 150.

16a″ (desulf.): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9-2.1 (m, 8H), 2.30 (s, 3H), 2.90 (q, 1H), 3.87 (s, 3H), 4.67 (q, 1H), 6.57 (s, 1H), 6.61 (s, 1H). MS (EI): *m/z* 218 (M^+), 203, 174, 156.