Catalytic Asymmetric Intramolecular α -Alkylation of Aldehydes

Supporting Information

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Substrate Syntheses:

Acetal **A**. Sodium (100 mmol, 2.3 g) was dissolved in dry ethanol (70 mL) and the solution was heated to 80°C. Diethylmalonate (90 mmol, 13.6 mL) was added and the mixture was stirred for further 30 min. After the addition of 2-bromo-1,1-dimethoxyethane (120 mmol, 14 mL) the mixture was refluxed for 36 h. The mixture was allowed to cool down to rt and the solvent was removed in vacuo. Dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO_4), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **A** (14.2 g, 57.6 mmol, 64%).

Acetal **A**: Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 1.17 (t, $J = 7.0$ Hz, 6H); 2.14 (m, 2H); 3.23 (s, 6H); 3.40 (t, $J = 4.6$ Hz, 1H); 4.10 (q, $J = 7.0$ Hz, 4H); 4.35 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 13.6, 31.3, 47.2, 52.6, 61.0, 102.2, 168.6.

Acetal **B**. To acetal **A** (3 g, 12 mmol) in dry THF (60 mL) was added sodium hydride (0.32 g, 13.2 mmol) at 0°C and the mixture was allowed to warm to rt until gas evolution ceased. After addition of 1,3-diiodo-propane (24 mmol, 2.7 mL) the mixture was refluxed for 24 h. Additional 1,3-diiodo-propane (1 mL) was added and the mixture was refluxed for further 12 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO_4), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **B** (3.6 g, 72%).

 Acetal **B**: Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, *J* = 6.9 Hz, 6H); 1.66 (m, 2H); 1.97 (m, 2H); 2.14 (d, *J* = 5.5 Hz, 2H); 3.08 (t, *J* = 6.6 Hz, 2H); 3.22 (s, 3H); 4.10 (q, *J* = 6.9 Hz, 4H); 4.35 (t, *J* = 5.5 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 5.5, 13.7, 27.9, 33.4, 35.4, 53.1, 54.4, 61.0, 101.5, 171.4.

Aldehyde **9**. To acetal **B** (2 g, 4.8 mmol) in acetone (7 mL) and water (7 mL) was added *p*-toluene-sulfonic acid (0.72 mmol, 0.12 g) and the mixture was refluxed for 2 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaHCO₃-solution, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give aldehyde **9** (1.4 g, 81%).

 Aldehyde **9**: Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.19 (t, *J* = 7.1 Hz, 6H); 1.73 (m, 2H); 2.00 (m, 2H); 2.88 (s, 2H); 3.08 (t, *J* = 6.7 Hz, 2H); 4.10 (q, *J* = 7.1 Hz, 4H); 9.66 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 4.8, 13.6, 28.3, 34.5, 46.1, 53.9, 61.6, 169.7, 198.2.

Acetal **C**. To acetal **A** (3 g, 12 mmol) in dry THF (60 mL) was added sodium hydride (0.32 g, 13.2 mmol) at 0°C and the mixture was allowed to warm to room temperature until gas evolution ceased. After addition of 1,3-diiodo-propane (24 mmol, 2.7 mL) the mixture was refluxed for 24 h. Additional 1,3-diiodo-propane (1 mL) was added and the mixture was refluxed for further 12 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **C** (3.4 g, 77%).

 Acetal **C**: Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, *J* = 7.0 Hz, 6H); 1.65 (m, 2H); 1.96 (m, 2H); 2.13 (d, *J* = 5.5 Hz, 2H); 3.21 (s, 6H); 3.32 (t, *J* = 5.4 Hz, 2H); 4.04 (q, *J* = 7.0 Hz, 4H); 4.35 (t, *J* = 5.3 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 14.0, 27.2, 31.5, 33.1, 36.2, 53.2, 54.1, 61.3, 101.9, 171.8.

Aldehyde 11. To acetal **C** (3 g, 8.1 mmol) in acetone (12 mL) and water (12 mL) was added *p*-toluene-sulfonic acid (1.2 mmol, 0.2 g) and the mixture was refluxed for 2 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaHCO₃-solution, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give aldehyde **11** (2.3 g, 88%).

Acetal D. To acetal **A** (1.2 g, 5 mmol) in dry THF (40 mL) was added sodium hydride (0.13 g, 5.5 mmol) at 0°C and the mixture was allowed to warm to room temperature until gas evolution ceased. After addition of *p*-toluenesulfonic acid 3-iodo-propyl ester (7.9 mmol, 2.7 g) the mixture was refluxed for 36 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **D** (1.6 g, 69%).

Aldehyde 12. To acetal **D** (1.5 g, 3.3 mmol) in acetone (5 mL) and water (5 mL) was added *p*-toluene-sulfonic acid (0.72 mmol, 0.12 g) the mixture was refluxed for 2 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaHCO₃-solution, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give aldehyde **12** (0.9 g, 66%).

Acetal **E**. Dibenzylmalonate (30 mmol, 8.5 g) was dissolved in dry toluene (70 mL) and potassium (30 mmol, 1.2 g) was added at 0°C. The mixture was stirred for 3h at rt and then refluxed for 2 h. The mixture was cooled to rt and 2-bromo-1,1-dimethoxy-ethane (60 mmol, 7 mL) was added before the mixture was refluxed for 36 h. The mixture was allowed to cool down to rt. Dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO_4), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **E** (5.7 g, 15.3 mmol, 51%).

Acetal **F**. To acetal **E** (12 mmol, 4.4 g) in dry THF (60 mL) was added sodium hydride (0.32 g, 13.2 mmol) at 0°C and the mixture was allowed to warm to room temperature until gas evolution ceased. After addition of 1,3-diiodo-propane (24 mmol, 2.7 mL) the mixture was refluxed for 24 h. Additional 1,3-diiodo-propane (1 mL) was added and the mixture was refluxed for further 12 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO_4), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **F** (3.9 g, 7.2 mmol, 60%).

Aldehyde 13. To acetal **F** (2 g, 3.7 mmol) in acetone (5 mL) and water (5 mL) was added *p*-toluene-sulfonic acid (0.56 mmol, 0.1 g) and the mixture was refluxed for 2 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaHCO₃-solution, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give aldehyde **13** (1.2 g, 2.4 mmol, 65%).

Acetal G. Sodium (46 mmol, 1.1 g) was dissolved in dry ethanol (35 mL) and the solution was heated to 80°C. Diethylmalonate (45 mmol, 6.8 mL) was added and the mixture was stirred for further 30 min. After the addition of 3-bromo-1,1-dimethoxypropane (49 mmol, 9 g) the mixture was refluxed for 36 h. The mixture was allowed to cool down to rt and the solvent was removed in vacuo. Dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **G** (5.9 g, 22.5 mmol, 49%).

Acetal H. To acetal **G** (2.8 g, 10.6 mmol) in dry THF (40 mL) was added sodium hydride (0.33 g, 13.7 mmol) at 0°C and the mixture was allowed to warm to room temperature until gas evolution ceased. After the addition of 1,2-dibromo-ethane (22 mmol, 2.0 mL) the mixture was refluxed for 24 h. Additional 1,2-dibromo-ethane (1 mL) was added and the mixture was refluxed for further 12 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried

(MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **H** (2 g, 51%).

Aldehyde **15**. To acetal **H** (2 g, 5.4 mmol) in acetone (5 mL) and water (5 mL) was added *p*-toluene-sulfonic acid (0.81 mmol, 0.14 g) and the mixture was refluxed for 2 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaHCO₃-solution, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give aldehyde **15** (1.2 g, 3.7 mmol, 68%).

Acetal **I**. A solution of triethylamine (150 mmol, 20 mL) and 2,2-dimethoxy-ethylamine (50 mmol, 5.5 g) in dry dichloromethane (100 mL) was cooled to 0°C and *p*-toluenesulfonyl chloride (50 mmol, 9.5 g) was added to the solution. After 24 h dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (25% ethyl acetate/hexane) to give acetal **I** (10.6 g, 41 mmol, 82%).

Acetal **J**. To acetal **I** (4 g, 15.4 mmol) in dry THF (90 mL) was added sodium hydride (0.4 g, 16.7 mmol) at 0°C and the mixture was allowed to warm to rt until gas evolution

ceased. After the addition of 1,3-diiodo-propane (30 mmol, 3.4 mL) the mixture was refluxed for 24 h. Additional 1,3-diiodo-propane (1 mL) was added and the mixture was refluxed for further 12 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (25% ethyl acetate/hexane) to give acetal **H** (3.0 g, 10 mmol, 65%).

 Acetal **J**: Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.08 (m, 2H); 2.35 (s, 3H); 3.12 (m, 4H); 3.14 (m, 2H); 3.32 (s, 6H); 4.43 (m, 1H); 7.23 (d, *J* = 8.0 Hz, 2H); 7.64 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 2.5, 14.2, 21.5, 32.4, 51.0, 51.2, 55.1, 104.4, 127.2, 129.8, 137.3, 143.5.

Aldehyde **17**. To acetal **J** (2.8 g, 9.4 mmol) in acetone (30 mL) was added an aqueous solution of HCl (4 N) and the mixture was stirred for 48 h. Dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaHCO₃-solution, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (25% ethyl acetate/hexane) to give aldehyde **17** (1.9 g, 5.0 mmol, 53%).

 Aldehyde **17**: Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 2.04 (m, 2H); 2.44 (s, 3H); 3.18 (t, *J* = 6.9 Hz, 2H); 3.25 (t, *J* = 6.8 Hz, 2H); 3.89 (s, 2H); 7.33 (d, *J* = 8.2 Hz, 2H); 7.69 (d, *J* = 8.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 0.4, 20.5, 31.4, 49.5, 57.0, 126.5, 129.0, 134.8, 143.1, 196.3.

Acetal **K**. To acetal **A** (3 g, 12 mmol) in dry THF (60 mL) was added sodium hydride (0.32 g, 13.2 mmol) at 0°C and the mixture was allowed to warm to room temperature until gas evolution ceased. After the addition of diiodomethane (24 mmol, 2.0 mL) the mixture was refluxed for 24 h. Additional 1,3-diiodo-propane (1 mL) was added and the mixture was refluxed for further 12 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give acetal **K** (2.3 g, 6.3 mmol, 52%).

Aldehyde **19**. To acetal **K** (2 g, 5.5 mmol) in acetone (6 mL) and water (6 mL) was added *p*-toluene-sulfonic acid (0.72 mmol, 0.12 g) and the mixture was refluxed for 2 h. After the mixture was allowed to cool down to rt dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaHCO₃-solution, dried (MgSO₄), filtered, and concentrated. The residue was purified on a silica gel column (5% ethyl acetate/hexane) to give aldehyde **9** (1.1 g, 3.0 mmol, 55%).

Asymmetric α-Alkylations:

Procedure [1]. Reactions in chloroform. A solution of the aldehyde (0.5 mmol) in dry chloroform (2.5 mL) was added to the catalyst ((*S*)- or (*R*)-α-methylproline, 5-20 mol%) and the mixture was cooled to -30°C. After the addition of triethylamine (0.5 mmol, 70 μL) the mixture was stirred for 24-48 h. The mixture was filtered and concentrated. The residue was purified on a silica gel column (20% ethyl acetate/hexane) to give the pure aldehyde.

The synthesis of the racemic compounds was performed according to procedure [1] at room temperature with (*rac*)-proline (25 mol%).

Procedure [2]. Reactions in mesitylene. A solution of the aldehyde (0.5 mmol) in dry mesitylene (2.5 mL) was added to the catalyst ((*S*)- or (*R*)- α-methylproline, 20 mol%) and the mixture was cooled to -15°C. After the addition of triethylamine (0.5 mmol, 70 μL) the mixture was stirred for 216 h. The mixture was filtered and concentrated. The residue was purified on a silica gel column (20% ethyl acetate/hexane) to give the aldehyde.

Enantiomeric Excess-Determination:

(2-Oxo-propyl)-phosphonic acid diethyl ester (2 mmol, 0.3 mL) was added to lithium hydroxide monohydrate (0.5 mmol, 21 mg) in THF (3 mL) and the mixture was stirred for 30 min. After the addition of the reaction mixtures from procedures [1] or [2] the resulting mixture was stirred for further 30 min. The resulting enone was isolated through preparative TLC and analyzed by chiral stationary phase HPLC.

10

Aldehyde **10**: Colorless oil (111 mg, 0.46 mmol, 92%, from iodide **9**), (109 mg, 0.45 mmol, 90%, from bromide **11** / 24 mg, 0.1 mmol, 20% from tosylate **12**). HRMS (ESI) calcd for MNa^+ 265.1052, found 265.1053. HPLC (enone derivative, Chiralpak AS-RH, 78% H_2O 22% CH_3CN) t_r (S) = 108.8 min, t_r (R) = 122.6 min, ee = 95% (from iodide **9**); ee = 94% (from bromide **11**); ee = 91% (from tosylate **12**). ^1H NMR (400 MHz, CDCl_3) δ 1.22 (m, 6H); 1.71-1.79 (m, 2H); 1.98-2.04 (m, 2H); 2.22-2.25 (m, 1H); 2.36-2.39 (m, 1H); 3.26 (t, J = 7.9 Hz, 1H); 4.16-4.21 (m, 2H); 4.22-4.28 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 22.7, 25.1, 34.6, 57.5, 62.0, 62.6, 170.1, 171.1, 200.0.

14

Aldehyde **14**: Yellow oil (172 mg, 0.47 mmol, 94%). HRMS (ESI) calcd for MNa^+ 389.1365, found 389.1364. HPLC (enone derivative, Chiralpak AS-RH, 60% H_2O 40% CH_3CN) t_r (S) = 73.5 min, t_r (R) = 79.8 min, ee = 95%. ^1H NMR (400 MHz, CDCl_3) δ 1.60-1.67 (m, 2H); 1.89-1.95 (m, 2H); 2.18-2.23 (m, 1H); 2.29-2.32 (m, 1H); 3.20 (t, J = 7.8 Hz, 1H); 4.96-5.07 (m, 4H); 7.13-7.28 (m, 10H); 9.65 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 21.6, 24.1, 33.6, 56.5, 61.6, 66.6, 127.4, 127.5, 127.6, 134.1, 168.8, 169.7, 198.8.

16

Aldehyde **16**: Colorless oil (111 mg, 0.46 mmol, 92%, procedure [2] / 112 mg, 0.47 mmol, 93%, procedure [1]). HRMS (CI, isobutane) calcd for MH^+ 243.1233, found 243.1230. HPLC (enone derivative, Chiralpak AD-RH, 65% H_2O 35% CH_3CN) t_r (S) = 21.2 min, t_r (R) = 23.0 min, ee = 96%, procedure [2] / 84%, procedure [1]. ^1H NMR (400 MHz, CDCl_3) δ 1.18 (m, 6H); 1.88-1.94 (m, 2H); 2.18 (m, 2H); 2.36-2.44 (m, 2H); 2.84 (m, 1H); 4.08-4.15 (m, 4H); 9.57 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 13.6, 25.2, 33.3, 50.4, 59.9, 61.3, 171.1, 201.7.

Aldehyde **17** (0.5 mmol, 191 mg) in dry chloroform (2.5 mL) was added to the catalyst (α -methylproline, 15 mol%) and the mixture was cooled to -30°C . After the addition of triethylamine (0.5 mmol, 70 μL) the mixture was stirred for 24 h. The mixture was then poured to NaBH_4 (0.5 mmol, 19 mg) in methanol (2.5 mL) and stirred for further 1h. Dichloromethane and water were added and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NH_4Cl -solution, dried (MgSO_4), filtered, and concentrated. The residue was purified on a silica gel column (10% ethyl acetate/hexane) to give the alcohol **18a**.

18a

Alcohol **18a**: Colorless solid (66 mg, 0.26 mmol, 52%). HRMS (ESI) calcd for MNa^+ 278.0827, found 278.0825. HPLC (Chiralpak AD-RH, 65% H_2O 35% CH_3CN) t_r (S) = 21.2 min, t_r (R) = 23.0 min, ee = 91%. $[\alpha]_D^{25} = -78.9^\circ$ (c = 1.0, MeOH); Literature: $[\alpha]_D = -89.4^\circ$ (c = 1,

MeOH). ^1H NMR (400 MHz, CDCl_3) δ 1.39 (m, 1H); 1.63 (m, 2H); 1.71 (m, 1H); 2.40 (s, 1H); 2.37 (s, 3H); 3.22 (m, 2H); 3.39 (m, 1H); 3.58 (m, 2H); 7.26 (d, $J = 8.2$ Hz, 2H); 7.66 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 19.4, 22.1, 26.8, 47.9, 59.7, 63.7, 125.5, 127.7, 131.8, 141.7.

20

195.3.

Aldehyde **20**. Colorless oil (75 mg, 0.35 mmol, 70%, procedure [2]). HRMS (CI, isobutane) calcd for MH^+ 215.0920, found 215.0916. HPLC (enone derivatized, Chiralpak AS-RH, 78% H_2O 22% CH_3CN) t_r (S) = 41.5 min, t_r (R) = 47.3 min, $ee = 86\%$. ^1H NMR (400 MHz, CDCl_3) δ 1.21 (t, $J = 6.9$ Hz, 6H); 1.74 (m, 1H); 2.00 (m, 1H); 2.66 (m, 1H); 4.11-4.21 (m, 4H); 9.24 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 12.9, 18.2, 33.8, 61.2, 164.9, 166.9,

NMR-Spectra of the Substrates:

-S16-

19

NMR-Spectra and HPLC-Traces of the Alkylation Products: