Supporting Information
for
Multivalent polyglycerol supported imidazolidin-4-one organocatalysts for enantioselective Friedel–Crafts alkylations

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Experimental procedures, analytical data, copies of NMR spectra and GC reports

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1. General methods

Commercial reagents were used as received. All reactions were carried out under magnetic stirring and were monitored by TLC analysis on 0.20 mm silica gel plates (Macherey-Nagel G/UV254). Column chromatography was carried out on silica gel 60 M (0.04–0.063 mm) Macherey-Nagel. Dialysis was performed in benzoylated cellulose tubes from Sigma-Aldrich (D7884-10FT, width: 32 mm, molecular weight cut-off (MWCO) 2000 g·mol⁻¹). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. ¹H NMR and ¹³C NMR spectra were recorded on Bruker (ECP 400, AC 500, AV 700) or JEOL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to CDCl₃ (¹H: δ = 7.24 ppm; ¹³C: δ = 77.23 ppm), DMSO-d₆ (¹H: δ = 2.50 ppm; ¹³C: δ = 39.51 ppm) or acetone-d₆ (¹H: δ = 2.05 ppm; ¹³C: δ = 29.92 ppm). Integrals are in accordance with assignments, coupling constants are given in Hz. For detailed peak assignments 2D spectra were recorded where necessary (COSY, DEPT, HSQC, HMQC, HMBC and NOESY). IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR System spectrophotometer JASCO FT/IR–4100. HRMS analyses were performed on a Varian Inc. Ionspec QFT-7 (ESI-TOF, 4 μL/min, 1.0 bar, 4 kV). Optical rotation measurements were performed on a P-2000 polarimeter from Jasco in a 1 dm optical-path length cell with the frequency of the NaD line measured at the temperature and concentration (in g/100 mL) indicated. The enantiomeric excess was determined by chiral GC: Agilent 6850 Series II GC System equipped with Hydrodex-β-TBDAc column or Agilent 7890B equipped with Lipodex E column, the standards were prepared using racemic 5-benzyl-2,2,3-trimethylimidazolidin-4-one as catalyst.
2. Experimental procedures

General procedure for the synthesis of compound 10

(S)-5-(4′-Hydroxylbenzyl)-2,2,3-trimethylimidazolidin-4-one (10). To an ethanolic solution of MeNH₂ (8.0 M in EtOH; 69 mL, 550 mmol, 5.0 equiv) (S)-tyrosine methyl ester hydrochloride (9, 25.5 g, 110 mmol, 1.0 equiv) was added and the solution was stirred for 20 h at 25 °C. After completion of the reaction the organic solvents were removed under reduced pressure, the residue was re-suspended in THF and again concentrated. To remove excess MeNH₂ the THF addition–removal cycle was repeated several times. The white solid thus obtained was used in the next step without further purification. The crude product and p-toluenesulfonic acid (209 mg, 1.10 mmol, 0.01 equiv) were dissolved in mixture of anhyd. MeOH (200 mL) and anhyd. acetone (40 mL) and the mixture was refluxed for 18 h. After completion, the reaction mixture was cooled to room temp., all solvents were removed under reduced pressure, and the so-obtained residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH 20:1) to yield 10 (20.4 g, 79%).

¹H-NMR (CDCl₃, 700 MHz):  δ = 6.99 (d, J = 8.5 Hz, 2H; Ar-H), 6.72 (d, J = 8.5 Hz, 2H; Ar-H), 3.75 (t, J = 5.3 Hz, 1H; CH), 2.98 (d, J = 5.4 Hz, 2H; Bn-H), 2.72 (s, 3H; N-Me), 1.25 (s, 3H; Me), 1.14 ppm (s, 3H; Me);

¹³C-NMR (CDCl₃, 175 MHz):  δ = 173.9, 155.9, 130.7, 127.3, 115.9, 76.1, 59.4, 35.8, 27.1, 25.5, 25.1 ppm.
Synthesis of compound 5

(S)-5-(p-(Hex-5'-yn-1'-yloxy)benzyl)-2,2,3-trimethylimidazolidin-4-one (5). NaH (60% in mineral oil; 282 mg, 7.02 mmol, 1.1 equiv) was added to solution of 10 (1.50 g, 6.40 mmol, 1 equiv) in anhyd. DMF (5 mL) at 0 °C. After 30 min of stirring at 0 °C, TBAI (23.0 mg, 0.06 mmol, 0.01 equiv) and 6-chloro-1-hexyne (1.01 mL, 8.32 mmol, 1.3 equiv) were added to the reaction and the mixture was allowed to warm to 25 °C and stirred for an additional 16 h. After this time, MeOH (1 mL) and H₂O (5 mL) were added and the mixture was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/EtOH/EtOAc 10:2:1) to yield 5 (1.78 g, 88%) as white solid. m.p.: 45–47 °C; \( R_f = 0.14 \) (pentane/EtOH/EtOAc 10:2:1); [α]D²⁴ = −69.7 (c = 0.94 in CHCl₃); ¹H-NMR (CDCl₃, 700 MHz): δ = 7.10 (d, \( J = 8.7 \) Hz, 2H; Ar-H), 6.79 (d, \( J = 8.7 \) Hz, 2H; Ar-H), 3.93 (t, \( J = 6.3 \) Hz, 2H; H-1’), 3.72 (dd, \( J = 5.9, 5.0 \) Hz, 1H; H-5), 3.04–2.96 (AB system, \( J = 14.4, 6.3 \) Hz, 2H; Bn-H), 2.72 (s, 3H; N-Me), 2.24 (td, \( J = 7.1, 2.7 \) Hz, 2H; H-4’), 1.95 (t, \( J = 2.7 \) Hz, 1H; H-6’), 1.89–1.85 (m, 2H; H-2’), 1.71–1.66 (m, 2H; H-3’), 1.24 (s, 3H; Me), 1.14 ppm (s, 3H; Me); ¹³C-NMR (CDCl₃, 175 MHz): δ = 173.4 (C-4), 157.9 (Ar-C), 130.5 (2Ar-CH), 128.8 (Ar-C), 114.6 (2Ar-CH), 84.1 (C≡CH), 75.5 (C-2), 68.7 (C≡CH), 67.2 (C-’), 59.3 (C-5), 36.1 (Bn-C), 28.3 (C-’), 27.2 (N-Me), 25.2 (2xMe), 25.0 (C-3’), 18.1 ppm (C-4’); IR (CDCl₃): \( \tilde{\nu} = 3304, 3286, 2974, 2943, 2871, 1688, 1612, 1580, 1511, 1474, 1428, 1398, 1368, 1244, 1178, 1148,
1054, 1032, 822 cm\(^{-1}\); HRMS (ESI): m/z: calcd for C\(_{19}\)H\(_{26}\)N\(_2\)O\(_2\)+H\(^+\): 315.2067; found: 315.2075 [M+H\(^+\)].

**Synthesis of hPG-OH** \(^1\)

Hyperbranched polyglycerol (hPG) \(1\) with \(M_n= 9.000\) g/mol\(^{-1}\) (loading OH = 13.5 mmol/g, PDI = 1.87) was synthesized by a one-step ring opening anionic polymerization (ROAP) method, according to the earlier reported methods.\(^2\) 1,1,1-Tris(hydroxymethyl)propane (TMP) was used as the starter in ROAP. Azide functionalized hPG were synthesized according to previously reported procedures.\(^3-4\)

**Synthesis of hPG-OMs** \(2a-c \(^3-4\)

**General procedure:** Mesylation of hyperbranched polyglycerol \(1\) was carried out under an inert gas atmosphere and exclusion of moisture. In a two-necked 1 L flask, hyperbranched polyglycerol \(1\) (13.51 mmol OH-groups) was dissolved in anhyd. pyridine (60 mL). The resulting solution was stirred at 25 °C for 10 min and then cooled to 0 °C in an ice bath. A solution of methanesulfonyl chloride (1.2 equiv, with respect to functionalization degree) in anhyd. pyridine (20 mL) was added dropwise to the reaction mixture and stirring at 25 °C was continued for 16 h. The reaction mixture was then filtered and the solvent was removed under reduced pressure.

The degrees of functionalization were confirmed by \(^1\)H NMR of the crude products correlating the \(CH_3\)-Ms with polyglycerol backbone protons.
hPG-OMs (>95%), 2a

Reaction conditions were as described above, using 1 (1.0 g). The crude product was washed with cold H₂O (3 × 10 mL), further dissolved and dialyzed in acetone for 72 h to give pure 2a (1.52 g, 76% yield). ¹H-NMR (DMSO-d₆, 400 MHz): δ = 5.09–4.86 (functionalized secondary PG-groups), 4.58–4.35 (functionalized primary PG-groups), 4.05–3.45 (PG backbone), 3.27–3.11 (br s; Ms), 1.49–1.39 (m; CCH₂CH₃ of starter), 0.91 ppm (t; CCH₂CH₃ of starter).

hPG-OMs (57%), 2b

Reaction conditions were as described above, using 1 (1.0 g). The crude product was dissolved in an acetone/H₂O mixture (1:1 v/v) and dialyzed in the same mixture for 72 h to give pure 2b (1.31, 82% yield). ¹H-NMR (acetone-d₆, 400 MHz): δ = 5.08–4.85 (functionalized secondary PG-groups), 4.42–4.17 (functionalized primary PG-groups), 4.05–3.75 (PG backbone), 3.25–3.12 (br s; Ms), 1.42–1.34 (m; CCH₂CH₃ of starter), 0.87 ppm (t; CCH₂CH₃ of starter).

hPG-OMs (30%), 2c

Reaction conditions were as described above, using 1 (1.0 g). The crude product was dissolved in a MeOH/H₂O mixture (1:1 v/v) and dialyzed in the same mixture for 72 h to give pure 2c (1.12, 87% yield). ¹H-NMR (DMSO-d₆, 400 MHz): δ = 5.11–4.81 (functionalized secondary PG-groups), 4.30–4.21 (functionalized primary PG-groups), 4.15–3.45 (PG backbone), 3.27 (br s; Ms), 1.43–1.31 (m, CCH₂CH₃ of starter), 0.90 ppm (t, CCH₂CH₃ of starter).
Synthesis of hPG-N\textsubscript{3} 3a–c\textsuperscript{3,4}

**General procedure:** To a homogeneous mixture of O-mesylpolyglycerol 2a–c (1 equiv) in DMF (15 mL), NaN\textsubscript{3} (3 equiv) was added and the resulting suspension was heated at 65 °C for 72 h. After completion of the reaction, the mixture was cooled to room temp. and filtered through Celite\textsuperscript{®} to remove excess NaN\textsubscript{3}. The filtrate was concentrated under reduced pressure at a temperature below 40 °C and handled with a plastic spatula to avoid a potentially explosive degradation of the polyazide.

**hPG-N\textsubscript{3} (95%), 3a**

Reaction conditions were as described above, using 2a (1.52 g). The crude product was dissolved in CHCl\textsubscript{3} and extracted four times with H\textsubscript{2}O. The organic phase was dried over anhyd. MgSO\textsubscript{4}. To remove traces of DMF from the crude product an additional dialysis in a MeOH/CHCl\textsubscript{3} mixture (1:1 v/v) was performed to give pure 3a (0.72 g, 72% yield). $^1$H-NMR (CDCl\textsubscript{3}, 400 MHz): $\delta$ = 4.04–3.35 (m; PG backbone), 1.45–1.33 (m; C\textsubscript{6}H\textsubscript{3}CH\textsubscript{3} of starter), 0.85 ppm (t; CCH\textsubscript{2}CH\textsubscript{3}, of starter); $^{13}$C-NMR (CDCl\textsubscript{3}, 400 MHz): $\delta$ = 76.4–51.5 (PG backbone), 25.7 (C\textsubscript{6}H\textsubscript{3}CH\textsubscript{3} of starter), 8.8 ppm (CCH\textsubscript{2}CH\textsubscript{3} of starter); IR: $\bar{\nu}$ = 2871, 2091 (N\textsubscript{3}), 1447, 1345, 1267, 1174, 1099, 927 cm$^{-1}$.

**hPG-N\textsubscript{3} (57%), 3b**

Reaction conditions were as described above, using 2b (1.31 g). The crude product was dissolved in acetone/H\textsubscript{2}O mixture (1:1 v/v) and dialyzed in the same mixture for 72 h to give pure 3b (0.78 g, 81% yield). $^1$H-NMR (CDCl\textsubscript{3}, 400 MHz): $\delta$ = 4.02–3.34 (m; PG backbone), 1.38–1.27 (m; C\textsubscript{6}H\textsubscript{3}CH\textsubscript{3} of starter), 0.79 (t; CCH\textsubscript{2}CH\textsubscript{3}, of starter);
$^{13}$C-NMR ($\text{CDCl}_3$, 100 MHz): $\delta = 77.7$–53.9 (PG backbone), 25.7 (CCH$_2$CH$_3$ of starter), 8.0 (CCH$_2$CH$_3$ of starter) ppm; IR: $\tilde{\nu} = 3398, 2871, 2096$ (N$_3$), 1769, 1636, 1453, 1455, 1270, 1077, 991, 929 cm$^{-1}$.

**hPG-N$_3$ (30%), 3c**

Reaction conditions were as described above, using 2c (1.12 g). The residue was purified by dialysis in H$_2$O for 48 h to give pure 3c (0.78 g, 86% yield). $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta = 4.05$–3.35 (m; PG backbone), 1.35–1.29 (m; CCH$_2$CH$_3$ of starter), 0.77 ppm (t; CCH$_2$CH$_3$ of starter); $^{13}$C-NMR (DMSO-$d_6$, 100 MHz): $\delta = 78.5$–54.0 (PG backbone), 24.1 (CCH$_2$CH$_3$ of starter), 10.4 ppm (CCH$_2$CH$_3$ of starter); IR: $\tilde{\nu} = 3382, 2871, 2359, 2341, 2098$ (N$_3$), 2035, 1771, 1635, 1558, 1455, 1272, 1078, 932, 869, 671 cm$^{-1}$.

**Synthesis of hPG-cat. 4a–c$^5$**

![hPG.png]

**General procedure:** hPG-azide 3a–c (1.0 equiv) and alkyne 5 (2.0 equiv) were dissolved in a THF/H$_2$O mixture (3:1 v/v; 4 mL) and the resulting solution was degassed for 10 min. Sodium ascorbate (2.0 equiv) in H$_2$O (100 mg/mL) and CuSO$_4$·5H$_2$O (0.2 equiv) in H$_2$O (100 mg/mL) were mixed and the resulting solution was added dropwise to the solution of hPG-azide 3a–c and alkyne 5. The reaction mixture was stirred at 25 °C for app. 48 h and the progress of the reaction was monitored by infrared (IR) spectroscopy. After completion of the
reaction, the mixture was diluted with CHCl₃ and the resulting solution was washed with sat. aq. EDTA solution (2 × 10 mL), followed by water (2 × 10 mL), and dried over anhyd. Na₂SO₄. The compounds were further purified by dialysis MeOH/CHCl₃ mixture (1:1 v/v) 24 h, and then MeOH and CHCl₃, respectively, for 12 h each.

The degrees of functionalization were confirmed by ¹H NMR correlating the aromatic protons with polyglycerol backbone protons.

**hPG-Cat (95%), 4a**

Reaction conditions and purification methods were as described above, using 3a (100 mg) to give pure 4a (296 mg, 71% yield). ¹H-NMR (CDCl₃, 700 MHz): δ = 7.64–7.36 (m, 1H; triazole), 7.13–7.04 (m, 2H; Ar-H), 6.80–6.70 (m, 2H; Ar-H), 5.37–4.70 (functionalized secondary PG-groups), 4.67–4.38 (functionalized primary PG-groups), 4.31–3.15 (PG backbone), 3.92–3.84 (m, 2H; CH₂O-Ar), 3.74–3.65 (br s, 1H; HNCHCON[CH₃]), 3.07–2.98 (m, 1H; Bn-H), 2.97–2.88 (m, 1H; Bn-H), 2.76–2.63 (m, 5H; N-CH₃, triazole-CH₂⁻), 1.84–1.62 (m, 4H; [CH₂]₂⁻), 1.25 (s, 3H; Me), 1.17 ppm (s, 3H; Me); ¹³C-NMR (CDCl₃, 175 MHz): δ = 173.5 (C=O), 157.8 (C-Ar), 147.7 (C₅-triazole), 130.5 (C-Ar), 129.1 (C-Ar), 122.0 (C-Ar), 114.5 (C-Ar), 75.6 (NC[CH₃]₂N), 72.9–68.6 (PG backbone), 67.4 (CH₂O-Ar), 59.4, 36.2, 29.0–28.7, 27.3, 26.1–25.9, 25.2 (2xMe), 24.3 ppm; IR: ʋ = 2929, 1682 (CONHCH₃), 1611, 1510, 1429, 1399, 1243, 1177, 1112, 811, 752 cm⁻¹.
hPG-Cat (57%), 4b

Reaction conditions and purification methods were as described above, using 3b (100 mg) to give pure 4b (121 mg, 40% yield). $^1$H-NMR (CDCl$_3$, 700 MHz): $\delta$ = 7.57–7.40 (m, 1H; triazole), 7.09–7.07 (m, 2H; Ar-H), 6.75 (m, 2H; Ar-H), 5.18–4.68 (functionalized secondary PG-groups), 4.49–4.24 (functionalized primary PG-groups), 4.20–3.25 (PG backbone), 3.90–3.82 (m, 2H; CH$_2$OAr), 3.74–3.65 (br s, 1H; NHCHCON[CH$_3$]), 3.02–3.00 (m, 1H; Bn-H), 2.94–2.88 (m, 1H; Bn-H), 2.71–2.62 (m, 5H; N-CH$_3$, triazol-CH$_2$-), 1.76–1.67 (m, 4H; [CH$_2$]$_2$), 1.22 (s, 3H; Me), 1.14 ppm (s, 3H; Me); $^{13}$C NMR (CDCl$_3$, 175 MHz): $\delta$ = 173.5 (C=O), 157.9 (C-Ar), 147.6 (C$_5$-triazole), 130.6 (C-Ar), 129.1–128.9 (C-Ar), 122.8–122.6 (C$_4$-triazole), 114.6 (C-Ar), 75.6 (N[C(CH$_3$)]$_2$N), 72.9–68.6 (PG backbone), 67.5 (CH$_2$OAr), 59.3, 36.2, 28.8, 27.2, 25.9, 25.2 (2xMe), 24.2 ppm; IR: $\tilde{\nu}$ = 3312, 2924, 1679 (CONHCH$_3$), 1611, 1510, 1428, 1398, 1388, 1296, 1241, 1176, 1110, 807, 664 cm$^{-1}$.

hPG-Cat (30%), 4c

Reaction conditions and purification methods were as described above, using 3c (100 mg) to give pure 4c (64.0 mg, 35% yield). $^1$H-NMR (CDCl$_3$, 700 MHz): $\delta$ = 7.61–7.41 (m, 1H; triazole), 7.14–7.08 (m, 2H; Ar-H), 6.81–6.72 (m, 2H; Ar-H), 5.00–4.60 (functionalized secondary PG-groups), 4.44–4.32 (functionalized primary PG-groups), 4.28–3.15 (PG backbone), 3.87–3.80 (m, 2H; CH$_2$O-Ar), 3.03–3.01 (m, 1H; Bn-H), 3.76–3.67 (br s, 1H; NHCHCON[CH$_3$]), 2.94–2.89 (m, 1H; Bn-H), 2.76–2.63 (m, 5H; N-Me, triazol-CH$_2$-), 1.84–1.70 (m, 4H; [CH$_2$]$_2$), 1.27 (s, 3H; Me), 1.15 ppm (s, 3H; Me); $^{13}$C-NMR (CDCl$_3$, 175 MHz): $\delta$ = 173.6 (C=O), 157.9 (C-Ar), 147.6 (C$_5$-triazole), 130.6 (C-Ar), 129.0–128.9 (C-Ar), 122.9–122.6 (C$_4$-Triazole), 114.6 (C-Ar), 75.6 (N[C(CH$_3$)]$_2$N), 72.0–68.6 (PG backbone), 67.5 (CH$_2$OAr), 59.3, 36.2, 28.8, 27.2, 25.9, 25.2 (2xMe), 24.2 ppm; IR: $\tilde{\nu}$ = 3312, 2924, 1679 (CONHCH$_3$), 1611, 1510, 1428, 1398, 1388, 1296, 1241, 1176, 1110, 807, 664 cm$^{-1}$.
75.6 ($\text{NC(CH}_3)_2\text{N}$), 72.9–68.6 (PG backbone), 67.5 (CH$_2$OAr), 59.3, 36.2, 28.8, 27.2, 25.9, 25.2 (2xMe), 24.2 ppm; IR: $\tilde{\nu}$ = 3357, 2869, 1675 (CONHCH$_3$), 1611, 1431, 1400, 1242, 1177, 1077, 808, 664 cm$^{-1}$.

**Synthesis of compound 6**

![Compound 6](image)

$[^G1]-\text{N}_3$ was synthesized according to the earlier reported methods.$^6$

**Synthesis of compound 7**

![Compound 7](image)

To a homogeneous solution of alkyne 5 (100 mg, 0.32 mmol, 1.0 equiv) and $[^G1]-\text{N}_3$ 6 (120 mg, 0.35 mmol, 1.1 equiv) in a THF/H$_2$O mixture (3:1 v/v; 4 mL), DIPEA (4.00 mg, 0.032 mmol, 0.1 equiv) was added. Stock solutions (100 mg/mL in H$_2$O) of sodium ascorbate (13.0 mg, 0.064 mmol, 0.2 equiv) and CuSO$_4$•5H$_2$O (8.00 mg, 0.032 mmol, 0.1 equiv) were added simultaneously to the reaction mixture which was further stirred at 25 °C for 12 h. After completion of the reaction, the resulting residue was diluted with H$_2$O and
extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed consecutively with sat. aq EDTA solution (2 × 10 mL) and H₂O (3 × 10 mL), dried over anhyd. Na₂SO₄, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (CH₂Cl₂/MeOH 20:1) to give pure 7 as a mixture of diastereoisomers (150 mg, 70% yield).

¹H-NMR (CD₃OD, 500 MHz): δ = 7.88–7.79 (m, 1H; triazole), 7.17–7.12 (m, 2H; Ar-H), 6.86–6.82 (m, 2H; Ar-H), 4.96–4.93 (m, 1H), 4.21–4.13 (m, 2H), 4.12–4.02 (m, 1H), 3.98–3.88 (m, 7H), 3.74 (dd, J = 7.8, 4.1 Hz, 1H), 3.64–3.58 (m, 2H), 3.54–3.43 (m, 4H), 3.03 (dd, J = 14.3, 4.2 Hz, 1H; Bn-H), 2.85 (dd, J = 14.3, 7.3 Hz, 1H; Bn-H), 2.78 (d, J = 7.0 Hz, 2H; triazole-CH₂), 2.75 (s, 3H; N-CH₃), 1.88–1.75 (m, 4H; -CH₂-), 1.36 (s, 3H; OC(CH₃)₂), 1.31–1.29 (m, 6H; OC(CH₃)₂), 1.23 (s, 3H; Me), 1.13 ppm (s, 3H; Me); ¹³C-NMR (CD₃OD, 125 MHz): δ = 174.2, 158.2, 147.2, 130.2, 129.2, 121.9, 114.3, 109.2 (2C), 76.1, 74.7 (2C), 71.9, 71.6, 70.1, 70.0, 69.9, 67.3, 66.0, 59.6, 35.8, 28.5, 25.8, 25.7, 25.6, 24.7, 24.3 (2C), 24.2, 23.5 ppm; IR: ν = 2982, 2932, 2870, 1685 (CONHCH₃), 1611, 1581, 1550, 1510, 1473, 1455, 1427, 1397, 1380, 1369, 1241, 1177, 1145, 1111, 1078, 953, 838, 731 cm⁻¹; HRMS (ESI) calcd for C₃₄H₄₅N₅O₈⁺H⁺: 660.3967; found 660.3970 [M+H]⁺, 682.3748 [M+Na]⁺.
Ion exchange resin Dowex 50W (500 mg) was added to 7 (100 mg, 0.15 mmol) dissolved in MeOH (4 mL), and the mixture heated to reflux for 12 h. After cooling, Dowex 50W was filtered off and washed with a 6% solution of NH₃ in MeOH. The filtrate was concentrated under reduced pressure to yield 8 as a mixture of diastereoisomers (80.0 mg, 95% yield).

^1H-NMR (CD₃OD, 700 MHz): δ = 7.93–7.81 (m, 1H; triazole), 7.19–7.14 (m, 2H; Ar-H), 6.87 (dd, J = 8.8, 2.6 Hz, 2H; Ar-H), 5.00–4.94 (m, 1H), 4.66–4.48 (m, 1H), 4.04–3.88 (m, 4H), 3.82–3.42 (m, 12H), 3.05 (dd, J = 14.4, 4.2 Hz, 1H; Bn-H), 2.88 (dd, J = 14.4, 7.2 Hz, 1H; Bn-H), 2.77 (m, 5H), 1.95–1.77 (m, 4H), 1.29 (s, 3H; Me), 1.23 ppm (s, 3H; Me); ^13C-NMR (CD₃OD, 125 MHz): δ = 174.1, 158.1, 158.1, 147.4, 147.2, 130.2, 130.2, 129.1, 123.4, 123.3, 121.9, 121.9, 121.9, 115.0, 114.3, 77.7 (2C), 77.6 (2C), 76.1, 72.6 (2C), 72.4, 72.3, 71.3 (2C), 71.0 (2C), 70.8 (2C), 70.7, 70.0 (2C), 69.9 (2C), 67.2 (2C), 62.9 (3C), 62.8 (2C), 60.9 (3C), 60.1, 59.5, 51.4, 50.7, 50.6, 35.8, 35.6, 31.4, 28.7, 28.5, 28.4 (2C), 25.7, 25.6, 24.7, 24.6 (2C), 24.2, 23.5, 22.3, 13.0 ppm; IR: v = 3339 (OH), 2928, 2870, 1736, 1657 (CO-NH-CH₃), 1611, 1580, 1549, 1510, 1444, 1404, 1298, 1241, 1177, 1111, 1024, 953, 820, 659 cm⁻¹; HRMS (ESI) calcd for C₂₈H₄₅N₅O₈+H⁺: 580.3341; found: 580.3404 [M+H]^+, 602.318 [M+Na]^+. 
General procedure for the synthesis of 16

5-Benzyl-2,2,3-trimethylimidazolidin-4-one (16). Reaction conditions and work-up were as described above (Section 2 Supporting Information File 1, page S3), using (S)-phenylalanine methyl ester hydrochloride (1.08 g, 5.03 mmol, 1.0 equiv). The so-obtained crude product was purified by column chromatography on silica gel (EtOAc) to give pure 16 (790 mg, 72%).

$^1$H-NMR (CDCl$_3$, 500 MHz): $\delta = 7.24–7.14$ (m, 5H), 3.72 (dd, $J = 6.8$, 4.5 Hz, 1H), 3.07 (dd, $J = 14.2$, 4.5 Hz, 1H), 2.94 (dd, $J = 14.2$, 6.8 Hz, 1H), 2.68 (s, 1H), 1.19 (s, 3H), 1.09 ppm (s, 3H); $^{13}$C-NMR (CDCl$_3$, 125 MHz): $\delta = 173.4$, 137.2, 129.5, 128.6, 126.8, 75.5, 59.3, 37.4, 27.3, 25.4, 25.2 ppm.

Synthesis of trans-p-methoxy-cinnamaldehyde (14c)

trans-p-Methoxy-cinnamaldehyde (14c). KOt-Bu (824 mg, 7.34 mmol, 2.0 equiv) was added to a suspension of (1,3-dioxan-2-ylmethyl)triphenylphosphonium bromide (3.47 g, 8.08 mmol, 2.2 equiv) in anhyd. THF (30 mL) at 0 °C and the mixture was stirred for 30 min at this temp. A solution of p-anisaldehyde (500 mg, 3.67 mmol, 1.0 equiv) in anhyd. THF (7 mL) was then slowly added, and the mixture was stirred for
1 h at 25 °C and then heated at reflux for an additional 24 h. Then, the reaction mixture was quenched by the addition of aq oxalic acid (8 g in 100 mL of H₂O) and stirred at 25 °C for an additional 16 h. Afterwards, the mixture was extracted with Et₂O (2 × 50 mL), the combined organic layers were washed consecutively with sat. aq NaHCO₃ (80 mL) and H₂O (80 mL), dried over anhyd. Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (pentane/EtOAc 7:1) afforded pure trans-p-methoxy-cinnamaldehyde (14c) as a yellow solid (595 mg, 83%).

¹H-NMR (CDCl₃, 400 MHz): δ = 9.62 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 15.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.58 (dd, J = 15.8, 7.8 Hz, 1H), 3.83 ppm (s, 3H); ¹³C-NMR (CDCl₃, 175 MHz): δ = 193.7, 162.2, 152.7, 130.4, 126.8, 126.5, 114.6, 55.5 ppm.

3. General procedure for the Friedel–Crafts alkylation

A solution of the catalyst 4a–c or 8 or 16 (x mol %) in the solvent indicated was treated with aq TFA (5 M; x mol %). The mixture was stirred at room temp. for 10 minutes, then the aldehyde 12 or 14a–e (0.25 mmol, 1.0 equiv) was added at the desired temperature T. After 5 minutes of stirring, N-methylpyrrole (11, 111 μL, 1.25 mmol, 5.0 equiv) was added and the reaction was stirred at the same temperature T. Et₂O (3 mL) was added to the mixture and the catalyst was removed by filtration, washed several time with Et₂O, then recovered with CH₂Cl₂ and dried in vacuo for future use. The organic phase was concentrated under reduced pressure and the so-obtained residue was purified by silica gel chromatography (pentane/Et₂O) to afford the corresponding products.
4. Friedel–Crafts alkylation products

Synthesis of compound 13

(R)-3-(1-Methyl-1H-pyrrol-2-yl)butanal (15a).

(S)-3-(1-Methyl-1H-pyrrol-2-yl)-3-phenylpropanal (13). Reaction conditions and work-up were as described above, using commercially available trans-cinnamaldehyde (12, 31.5 µL) and N-methylpyrrole (11). Purification by column chromatography on silica gel (pentane/Et₂O 7:1) gave 13 (46.2 mg, 87%).

\[ \text{H-NMR (CDCl}_3, 400 \text{ MHz): } \delta = 9.74 (t, J = 0.8 \text{ Hz, } 1H), 7.30–7.13 (m, 5H), 6.55 (t, J = 2.0 \text{ Hz, } 1H), 6.12–6.09 (m, 2H), 4.56 (t, J = 7.5 \text{ Hz, } 1H), 3.31 (s, 3H), 3.15 (ddd, J = 17.2, 8.4, 2.0 \text{ Hz, } 1H), 2.95 ppm (ddd, J = 17.2, 6.8, 1.6 Hz, 1H); \text{C-NMR (CDCl}_3, 175 \text{ MHz): } \delta = 200.9, 142.5, 133.1, 128.8, 127.7, 126.8, 122.5, 106.7, 106.6, 50.1, 37.7, 33.9 ppm. 

The enantiomeric excess was determined by chiral GC on a Hydrodex-β-TBDAc column (120 °C isotherm, 1.1 mL/min He): S isomer \( t_r = 185.45 \text{ min} \) and \( R \) isomer \( t_r = 191.51 \text{ min} \). The absolute configuration was determined by reduction to the corresponding alcohol and comparison of the optical specific rotation with reported data.

Synthesis of compound 15a

(R)-3-(1-Methyl-1H-pyrrol-2-yl)butanal (15a). Reaction conditions and work-up were as described above, using commercially available predominantly trans-
crotonaldehyde (14a, 20.4 μL) and N-methylpyrrole (11). Purification by column chromatography on silica gel (pentane/Et₂O 9:1) gave 15a (32.5 mg, 86%). ¹H-NMR (CDCl₃, 400 MHz): δ = 9.74 (t, J = 1.7 Hz, 1H), 6.53 (t, J = 2.2 Hz, 1H), 6.05 (t, J = 3.2 Hz, 1H), 5.88 (dd, J = 3.6, 2.0 Hz, 1H), 3.59 (s, 3H), 3.38 (q, J = 7.2 Hz, 1H), 2.79 (ddd, J = 17.2, 6.2, 1.5 Hz, 1H), 2.64 (ddd, J = 17.2, 7.9, 1.8 Hz, 1H), 1.27 ppm (d, J = 6.9 Hz, 3H); ¹³C-NMR (CDCl₃, 175 MHz): δ = 201.7, 136.6, 121.6, 106.8, 104.2, 50.6, 33.6, 25.4, 21.4 ppm. The enantiomeric excess was determined by chiral GC on a Hydrodex-β-TBDAc column (130 °C isotherm, 1.1 mL/min He): S isomer tᵣ = 11.00 min and R isomer tᵣ = 11.48 min. The absolute configuration was determined by reduction to the corresponding alcohol and comparison of the optical specific rotation with reported data.⁹

**Synthesis of compound 15b**

(R)-3-(1-Methyl-1H-pyrrol-2-yl)hexanal (15b).¹⁰ Reaction conditions and work-up were as described above, using commercially available trans-2-hexenal (14b, 29.1 μL) and N-methylpyrrole (11). Purification by column chromatography on silica gel (pentane/Et₂O 8:1) gave 15b (37.2 mg, 83%). ¹H-NMR (CDCl₃, 400 MHz): δ = 9.69 (t, J = 1.6 Hz, 1H), 6.50 (dd, J = 2.4, 1.6 Hz, 1H), 6.06 (t, J = 3.2 Hz, 1H), 5.87 (dd, J = 3.2, 1.6 Hz, 1H), 3.58 (s, 3H), 3.27 (q, J = 6.8 Hz, 1H), 2.73 (ddd, J = 17.2, 7.6, 1.6 Hz, 1H), 2.69 (ddd, J = 17.2, 6.8, 2.0 Hz, 1H), 1.61–1.55 (m, 2H), 1.30–1.22 (m, 2H), 0.87 ppm (t, J = 7.3 Hz, 3H); ¹³C-NMR (CDCl₃, 175 MHz): δ = 202.1, 136.6, 121.2, 106.8, 104.8, 49.6, 38.6, 33.8, 30.5, 20.2, 14.0 ppm. The enantiomeric excess was
determined by chiral GC on a Hydrodex-β-TBDAc column (90 °C isotherm, 1.1 mL/min He): $R$ isomer $t_r = 111.97$ min and $S$ isomer $t_r = 114.95$ min. The absolute configuration was determined by reduction to the corresponding alcohol and comparison of the optical specific rotation with reported data.\textsuperscript{10}

**Synthesis of compound 15c**

\[\begin{align*}
\text{OMe} & \quad \text{Me} \\
\text{N} & \quad \text{H} \\
\text{O} & \quad \text{Me}
\end{align*}\]

\((S)-3-(4\text{-}\text{Methoxyphenyl})\text{-}3\text{-}(1\text{-}\text{methyl}\text{-}1H\text{-}\text{pyrrol-2-yl})\text{propanal} \ (15c)\).\textsuperscript{10} Reaction conditions and work-up were as described above, using \textit{trans-\textit{p}-methoxy-cinnamaldehyde} (14c, 40.5 mg) and \textit{N}-methylpyrrole (11). Purification by column chromatography on silica gel (pentane/Et\textsubscript{2}O 6:1) gave 15c (48.6 mg, 80%). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 700 MHz): $\delta = 9.76$ (t, $J = 1.8$ Hz, 1H), 7.07 (d, $J = 8.7$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 6.57 (t, $J = 2.1$ Hz, 1H), 6.12 (dd, $J = 3.5$, 2.8 Hz, 1H), 6.09–6.08 (m, 1H), 4.53 (t, $J = 7.5$ Hz, 1H), 3.79 (s, 3H), 3.33 (s, 3H), 3.14 (ddd, $J = 17.1$, 7.9, 2.1 Hz, 1H), 2.95 ppm (ddd, $J = 17.1$, 7.9, 2.1 Hz, 1H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 175 MHz): $\delta = 201.3$, 158.3, 134.4, 133.5, 128.7, 122.5, 114.1, 106.5, 106.4, 55.3, 50.2, 36.8, 34.0 ppm. The enantiomeric excess was determined by chiral GC on a Lipodex E column (150 °C isotherm, 1.1 mL/min He): $R$ isomer $t_r = 116.11$ min and $S$ isomer $t_r = 120.75$ min.
Synthesis of compound 15d

(S)-3-(4-Chlorophenyl)-3-(1-methyl-1H-pyrrol-2-yl)propanal (15d). Reaction conditions and work-up were as described above, using commercially available trans-p-chloro-cinnamaldehyde (14d, 43.4 mg) and N-methylpyrrole (11). Purification by column chromatography on silica gel (pentane/Et₂O 4:1) gave 15d (53.4 mg, 86%). \(^{1}\)H-NMR (CDCl₃, 700 MHz): δ = 9.73 (br t, 1H), 7.28–7.26 (m, 2H), 7.11–7.10 (m, 2H), 6.58 (br t, 1H), 6.13–6.10 (m, 2H), 4.57 (t, J = 7.5 Hz, 1H), 3.33 (s, 3H), 3.17 (ddd, J = 17.4, 7.9, 1.5 Hz, 1H), 2.95 ppm (ddd, J = 17.3, 7.1, 1.3 Hz, 1H); \(^{13}\)C-NMR (CDCl₃, 175 MHz): δ = 200.3, 141.1, 132.7, 132.5, 129.1, 129.0 122.7, 106.7, 50.0, 36.9, 33.8 ppm. The enantiomeric excess was determined by chiral GC on a Hydrodex-β-TBDAc column (160 °C isotherm, 1.1 mL/min He): S isomer tᵣ = 74.69 min and R isomer tᵣ = 79.00 min. The absolute configuration was determined by comparison of the optical specific rotation of the aldehyde with reported data.\(^{1}\)
Synthesis of compound 15e

(S)-3-(1-Methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl)propanal,  (15e).\textsuperscript{10}  Reaction conditions and work-up were as described above, using commercially available trans-p-nitro-cinnamaldehyde (14e, 44.3 mg) and N-methylpyrrole (11). Purification by column chromatography on silica gel (pentane/Et\textsubscript{2}O 5:1) gave 15e (64.2 mg, 99\%).\textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta = 9.75\) (br t, 1H), 8.13 (d, \(J = 8.7\) Hz, 2H), 7.33 (d, \(J = 8.7\) Hz, 2H), 6.57 (t, \(J = 2.2\) Hz, 1H), 6.12 (d, \(J = 2.3\) Hz, 2H), 4.69 (t, \(J = 7.3\) Hz, 1H), 3.31 (s, 3H), 3.24 (dd, \(J = 17.7, 7.5, 1.3\) Hz, 1H), 3.01 ppm (ddd, \(J = 17.3, 6.9, 0.8\) Hz, 1H); \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 125 MHz): \(\delta = 199.6, 150.3, 146.9, 131.9, 128.9, 124.2, 123.1, 107.1, 48.8, 37.0, 34.0\) ppm. The enantiomeric excess was determined by chiral GC on a Hydrodex-\(\beta\)-TBDAc column (140 °C to 200 °C, gradient 1 °C/min, 1.1 mL/min He): S isomer \(t_r = 113.36\) min and R isomer \(t_r = 116.67\) min. The absolute configuration was determined by comparison of the optical specific rotation of the aldehyde with reported data.\textsuperscript{10}
5. Spectra of compounds

$^1$H and $^{13}$C-NMR of compound 5
Crude $^1$H-NMR of hPG-OMs 2c

FT-IR of hPG-N$_3$ 3a
FT-IR of hPG-N₃ 3b

FT-IR of hPG-N₃ 3c
$^{1}H, ^{13}C$-NMR and FT-IR of compound 4a
$^1$H, $^{13}$C-NMR and FT-IR of compound 4b
$^1$H, $^{13}$C-NMR and FT-IR of compound 4c
$^1$H and $^{13}$C-NMR of compound 7
$^1$H and $^{13}$C-NMR of compound 8
Friedel–Crafts alkylation products

$^1$H and $^{13}$C-NMR of compound 13
$^1$H and $^{13}$C-NMR of compound 15a
$^{1}H$ and $^{13}C$-NMR of compound 15b
$^1$H and $^{13}$C-NMR of compound 15c
$^1$H and $^{13}$C-NMR of compound 15d
$^1\text{H}$ and $^{13}\text{C}$-NMR of compound 15e
6. GC reports

Racemic 13.

Sample Info: Hydrogen-5-Diacetate
120 °C 200 min
1.1 mL/min He
50:1 split, 5 µL injection
racemic

----------------------------------------------

| Peak RetTime Type Width | Area   | Height | Area % |
|------------------------|--------|--------|--------|
| #  | [min] | [min]   | [pA*s] | [pA]  |
| 1  | 185.456 MM | 1.7632 | 656.13544 | 6.20205 | 50.27559 |
| 2  | 191.506 MM | 1.6850 | 648.94202 | 6.41878 | 49.72441 |

Enantioenriched 13 (optimized conditions: Table 4, entry 4).

----------------------------------------------

| Peak RetTime Type Width | Area   | Height | Area % |
|------------------------|--------|--------|--------|
| #  | [min] | [min]   | [pA*s] | [pA]  |
| 1  | 186.368 MM | 1.9155 | 1037.09875 | 9.02356 | 84.80318 |
| 2  | 191.076 MM | 1.4762 | 185.84918 | 2.09825 | 15.19682 |
Racemic 15a.

Enantioenriched 15a.
Racemic 15b.

Sample Info : Hydrogen-S-TMEDA
90 °C
1.1 mL/min He
50:1 split
racemic nPr

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Enantioenriched 15b.

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Racemic 15c.

Enantioenriched 15c.
Racemic 15d.

Sample Info: Hydrogen-8-TBDAc
140 °C
1.1 mL/min He
50:1 split
racemic

Enantioenriched 15d.

Peak RetTime Type Width Area Height Area
# [min] [min] [pA*s] [pA] %
1 74.689 MM 0.8409 1714.01038 33.97167 50.14686
2 78.999 MM 0.7999 1703.97095 35.50229 49.85314

Peak RetTime Type Width Area Height Area
# [min] [min] [pA*s] [pA] %
1 75.325 MM 1.1146 3665.77295 54.81347 85.28955
2 78.647 MM 0.6337 632.25977 16.62761 14.71045
Racemic 15e.

Sample Info:
- Temperature: 140 °C to 200 °C, 1 °C/min
- Injection rate: 1.1 ml/min
- Split ratio: 50:1
- Type: racemic

Enantioenriched 15e.

Sample Info:
- Temperature: 140 °C to 200 °C, 1 °C/min
- Injection rate: 1.1 ml/min
- Split ratio: 50:1
- Type: racemic

Peak RetTime Width Area Height Area %

1 113.359 MM 0.6509 3841.62915 96.36903 49.93319
2 116.674 MM 0.6930 3851.90869 92.63337 50.06681

Peak RetTime Width Area Height Area %

1 0.165 BV 0.0111 7.023994e-1 9.02892e-2 0.02670
2 113.262 MM 0.6214 2338.9106 62.72633 88.84003
3 117.058 MM 0.5343 293.05025 9.14316 11.1336
7. References

1) Zhang, Y.; Zhao, L.; Lee, S. S.; Ying, J. Y. Adv. Synth. Catal. 2006, 348, 2027–2032.
   doi: 10.1002/adsc.200600240

2) Sunder, A.; Mülhaupt, R.; Haag, R.; Frey, H. Adv. Mater. 2000, 12, 235–239.
   doi: 10.1002/(SICI)1521-4095(200002)12:3<235::AID-ADMA235>3.0.CO;2-Y

3) Roller, S.; Zhou, H; Haag, R. Molec. Divers. 2005, 9, 305–316.
   doi: 10.1007/s11030-005-8117-y

4) Paez, J. I.; Brunetti, V.; Strumia, M. C.; Becherer, T.; Solomun, T.; Miguel, J.; Hermanns, C. F.; Calderón, M.; Haag, R. J. Mater. Chem. 2012, 22, 19488–19497.
   doi: 10.1039/c2jm32486e

5) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; K. B. Sharpless, Angew. Chem. Int. Ed. 2002, 41, 2596–2599.
   doi: 10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4

6) Wyszogrodzka, M.; Haag, R. Chem. Eur. J. 2008, 14, 9202–9214.
   doi: 10.1002/chem.200800892

7) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. J. Am. Chem. Soc. 2000, 122, 4243–4244.
   doi: 10.1021/ja000092s

8) Sonoda, Y.; Goto, M.; Tsuzuki, S.; Tamaoki, N. J. Phys. Chem. A 2006, 110, 13379–13387.
   doi: 10.1021/jp064937j

9) Paras, N. A.; MacMillan, D. W. C. J. Am. Chem. Soc. 2001, 123, 4370–4371.
   doi: 10.1021/ja015717g
10) Riente, P.; Yadav, J.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 3668–3671.
doi: 10.1021/ol301515d