Catalytic Asymmetric Friedel-Crafts Alkylation of α,β-Unsaturated Carbonyl Compounds.
Enantioselective Addition of Aromatic C-H Bonds to Alkenes

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General Methodes. All reactions were carried out under an atmosphere of N₂ using anhydrous solvent and flame-dried glassware. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Purification of the products, when necessary, was carried out by flash chromatography (FC) using Merck silica gel 60 (230-400 mesh). TLC was performed using Merck silica gel 60 F₂₅⁴ plates and visualized with blue stain. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ¹H NMR and ¹³C NMR spectra were recorded at 400 and 100 MHz respectively, using CDCl₃ as the solvent, and are reported in ppm downfield from TMS (δ=0) for ¹H NMR and relative to the central CDCl₃ resonance (δ=77.0) for ¹³C NMR. The enantiomeric excess (ee) of the products were determined by HPLC or GC. For the ee determination with HPLC either Daciel Chiralcel OD-R, OJ,
OB, OD or Daicel Chiralpak AD columns were used, whereas for the GC-FID an Astec G-TA column was used.

**Materials.** Ligands, metals, indoles 1a-1e, 2-methyl-furan 1f and 1,3-dimethoxy-benzene 1g were obtained from commercial sources. Enone 2a\(^1\) and oxo-(triphenyl-\(\lambda^5\)-phosphanylidene)-propionic acid ethyl ester\(^2\) were synthesized according to literature procedures.

**(E)-2-Oxo-pent-3-enoic acid ethyl ester (2b)** In a 5 mL flask were added the Wittig-reagent oxo-(triphenyl-\(\lambda^5\)-phosphanylidene)-propionic acid ethyl ester (1.13 g, 3.0 mmol), acetaldehyde (1.0 mL, 18 mmol) and 3 mL CH\(_2\)Cl\(_2\). The flask was closed with a stopper and the mixture was stirred at room temperature for 6 d. The solvent was evaporated and the product was isolated in 35\% yield as a pale yellow oil by FC (silica gel, Et\(_2\)O:pentane, 1:9). \(^1\)H NMR \(\delta\) 1.38 (t, \(J=7.4, 3\)H), 2.00 (dd, \(J=6.8, 2.0\) Hz, 3H), 4.35 (q, \(J=7.4, 2\)H), 6.67 (dq, \(J=15.6, 2.0\) Hz, 1H), 7.20 (dq, \(J=15.6, 6.8\) Hz, 1H); \(^{13}\)C NMR \(\delta\) 14.1, 19.0, 62.3, 127, 150.3, 162.5, 183.5; mass (TOF ES\(^+-\)): m/z 165 (M+Na); HRMS calc. for C\(_7\)H\(_{10}\)NaO\(_3\) 165.0528, found 165.0518.

**(E)-5-BenzylOxy-2-oxo-pent-3-enoic acid ethyl ester (2c)** In a 5 mL flask were added the Wittig-reagent oxo-(triphenyl-\(\lambda^5\)-phosphanylidene)-propionic acid ethyl ester (752 mg, 2.0 mmol), benzyloxyacetaldehyde (425 \(\mu\)L, 3.0 mmol) and 2 mL CH\(_2\)Cl\(_2\). The flask was closed with a stopper and the mixture
was stirred at room temperature for 3 d. The solvent was evaporated and the product was isolated as a pale yellow oil in 56% yield by FC (silica gel, Et₂O:pentane, 1:6). ¹H NMR δ 1.38 (t, J=7.0 Hz, 3H), 4.27 (dd, J=3.9, 2.0 Hz, 2H), 4.36 (q, J=7.0 Hz, 2H), 4.60 (s, 2H), 6.98 (dt, J=16.0, 2.0 Hz, 1H), 7.20 (dt, J=16.0, 3.9 Hz, 1H), 7.30-7.39 (m, 5H); ¹³C NMR δ 14.0, 62.4, 68.7, 72.9, 123.8, 127.9, 128.5, 137.3, 149.3, 161.9, 183.0; mass (TOF ES⁺): m/z 271 (M+Na)⁺; HRMS calc. for C₁₄H₁₆NaO₄ 271.0946, found 271.0952.

(E)-4-(4-Chloro-phenyl)-2-oxo-but-3-enoic acid methyl ester (2d) In a 500 mL 3-necked roundbottom flask was added pyruvic acid (17.6 g, 0.2 mol), p-chlorobenzaldehyde (28.1 g, 0.2 mol) and 15 mL MeOH. The mixture was place in an ice bath and under stirring was added a solution of KOH (16.8 g, 0.3 mol) in 50 mL MeOH. The first 2/3 of the base was added slowly and the reaction temperature was kept below 25°C. The ice bath was then removed and the rest of the base was added quickly. Yellow preceipitate were formed at once. The temperature was kept at 30°C for 1 h and then at 0°C overnight. The yellow crystals were filtered off and washed twice with cold MeOH and once with Et₂O. The crystals were air dried to afford 34.3 g of the crude potassium salt.

30 mL acetylchlorid was added 200 mL MeOH at 0°C to generate HCl. The potassium salt was added and the mixture stirred for 15 min before the ice bath was removed. After 2
h the mixture is refluxed overnight. The reaction mixture was evaporated and the yellow solid was extracted with 75 mL H$_2$O and two times 75 mL CH$_2$Cl$_2$. The combined organic phases are washed with 75 mL saturated Na$_2$CO$_3$ and then 75 mL H$_2$O. The organic phase was dried with MgSO$_4$ and evaporated. The yellow crystals were recrystallized in abs. EtOH to give the pure enone in 29% overall yield. Mp=116-125°C; $^1$H NMR $\delta$ 3.94 (s, 3H), 7.34 (d, $J$=16.0 Hz, 1H), 7.40 (d, $J$=8.8 Hz, 2H), 7.57 (d, $J$=8.8 Hz, 2H), 7.82 (d, $J$=16.0 Hz, 1H); $^{13}$C NMR $\delta$ 53.1, 120.7, 129.4, 130.2, 132.4, 137.7, 147.0, 162.3, 182.0; mass (TOF ES$^+$): m/z 247 (M+Na)$^+$; HRMS calc. for C$_{11}$H$_9$ClNaO$_3$ 247.0138, found 247.0143.

**General Procedure I:**

**Enantioselective Addition of Indoles to \( \beta,\gamma \)-Unsaturated \( \alpha\alpha \)-Ketoesters Catalyzed by \((S)-4a\):** To a flame dried Schlenk tube were added Cu(OTf)$_2$ (14.46 mg, 0.04 mmol) and the ligand 2,2'-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] (S)-4 (12.96 mg, 0.044 mmol) under a stream of N$_2$. The mixture was dried under vacuum for 1-2 h, the anhydrous solvent (2.0 mL) was added, and the resulting suspension was stirred vigorously for 1-2 h. The catalyst is green and heterogeneous in Et$_2$O whereas it is homogeneous in all other solvents used. To the catalyst in solution was added first the enone 1a (0.8 mmol). The solution was stirred at room temperature for 15 min, then cooled to the desired reaction temperature where the appropriate indole 2 (0.8 mmol) was added. The solution was
then stirred at the temperature and the time given in the tables. Pentane (1.0 mL) was added to the reaction mixture. The heterogeneous mixture was filtered through a 40 mm plug of silica gel. The silica was washed with 5-10 mL of 60% pentane in Et₂O followed by 5-10 mL of CH₂Cl₂ and the combined fractions was evaporated. The crude product 3a-i exist both in its keto and enol form, however this equilibrium shifts towards the keto form in MeOH at room temperature. The keto form of 3a-i was purified by FC. In many cases the last purification is not necessary as the reaction is very clean.

**General Procedure II:**

**Enantioselective Addition of 2-methyl-furan to β,γ-Unsaturated α-Ketoesters Catalyzed by (S)-4a:** To a flame dried Schlenk tube were added Cu(OTf)₂ (36.1 mg, 0.100 mmol) and the 2,2'-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] (S)-4 (30.9 mg, 0.105 mmol). The two solids were stirred under vacuum for 1-2 h and the chosen anhydrous solvent was added (2 mL). The green catalyst was then stirred for 0.5-1 h before use. The catalyst was at all times kept under an N₂ atmosphere. The enone 2 (1.00 mmol) was added at room temperature and the Schlenk tube was then moved to the desired reaction temperature. The 2-methyl-furan (1.10-1.33 eq) was added and the reaction stirred until full conversion. The reaction was quenched through a silica plug using CH₂Cl₂ as eluent. After evaporation the crude product was purified by FC. However,
often the FC was not necessary due to the purity of the crude product.

**General Procedure III:**

**Enantioselective Addition of 1,3-dimethoxybenzene to β,γ-Unsaturated α-Ketoesters Catalyzed by (S)-4b:** To a flame dried Schlenk tube were added CuBr₂ (22.3 mg, 0.100 mmol), AgSbF₆ (68.7 mg, 0.200 mmol) and the 2,2'-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] (S)-4 (30.9 mg, 0.105 mmol). The Schlenk tube was covered with aluminum foil to protect the solids from light. The solids were stirred under vacuum for 1-2 h and anhydrous CH₂Cl₂ was added (2.0 mL). The catalyst mixture was then stirred overnight. The green heterogen solution was filtered through Hyflo to remove AgBr before use. The catalyst was at all times kept under an N₂ atmosphere. The enone 2 (1.00 mmol) is added at room temperature and the Schlenk tube was then cooled to the desired reaction temperature. The 1,3-dimethoxy-benzene (3 eq) was added and the reaction stirred until full conversion. The reaction was quenched through a silica plug using CH₂Cl₂ as eluent. After evaporation the crude product was purified by FC.

(-)-(4R)-4-(1H-Indol-3-yl)-2-oxo-4-phenyl-butyric acid methyl ester (3a). According to general procedure I indole 1a (235.0 mg, 2.0 mmol) was reacted with enone 2a (380.2 mg, 2 mmol) in Et₂O (4 mL) at -78°C with 2 mol% catalyst. Full conversion was obtained after 64 h during which the
reaction was allowed to warm up to -30°C. The reaction was quenched with H₂O and extracted three times with Et₂O. The organic layer was dried and the solvent evaporated. Purification by FC on silica gel (Et₂O:pentane, 30:70) gave 3a as a white solid in 77% yield and with 99.5% ee detected by HPLC using a Chiralcel OD-R column (MeOH, flow rate=0.5 mL/min) \( t_r = 8.9 \) min. (minor), \( t_r = 10.1 \) min (major); mp=98°C; [\( \alpha \)]\(_{D}^{23.9}\) =-23.9° (c=0.0100 g/mL, CHCl₃); \(^1\)H NMR \( \delta \) 3.60 (dd, \( J=16.8, 7.6 \) Hz, 1H), 3.69 (dd, \( J=16.8, 7.6 \) Hz, 1H), 3.77 (s, 3H), 4.93 (t, \( J=7.6 \) Hz, 1H), 7.01-7.44 (m, 10H), 8.00 (s, br, 1H); \(^13\)C NMR \( \delta \) 37.7, 45.6, 52.9, 111.1, 118.3, 119.4, 119.5, 121.4, 122.3, 126.4, 126.6, 127.7, 128.5, 136.5, 143.1, 161.3, 192.6; mass (TOF ES⁺): m/z 330 (M+Na)⁺; HRMS calc. for C₁₉H₁₇NNaO₃ 330.1106, found 330.1108.

\((-\)-(4R)-4-(1-Methyl-indol-3-yl)-2-oxo-4-phenyl-butyric acid methyl ester (3b).\) According to general procedure I indole 1b (102.2 µL, 0.8 mmol) was reacted with enone 2a (152.1 mg, 0.8 mmol) in Et₂O (2 mL) at -78°C with 5 mol% catalyst. Full conversion was obtained after 48 h where the reaction was allowed to warm up to -30°C. Purification with a silica plug gave pure 3b as a white solid in 98% yield and with 96% ee detected by HPLC using a Chiralcel OD-R column (MeOH, flow rate=0.5 mL/min) \( t_r = 10.5 \) min (minor), \( t_r = 11.8 \) min (major); mp=100°C; [\( \alpha \)]\(_{D}^{26.6}\) =-26.6° (c=0.0100 g/mL, CHCl₃); \(^1\)H NMR \( \delta \) 3.60 (dd, \( J=17.2, 8.0 \) Hz, 1H), 3.68 (dd, \( J=17.2, 8.0 \) Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 4.93
(+)-(4R)-4-(5-Methoxy-1H-indol-3-yl)-2-oxo-4-phenyl-butyric acid methyl ester (3c). According to general procedure I indole 1c (117.74 mg, 0.8 mmol) was reacted with enone 2a (152.1 mg, 0.8 mmol) in Et₂O (2 mL) at -78°C with 5 mol% catalyst. Full conversion was obtained after 1 h. Purification with a silica plug gave 3c as a dark yellow semicrystalline oil in 95% yield and with 99.5% ee detected by HPLC using a Chiralcel OD column (hexane:i-PrOH 85:15, flow rate=0.5 mL/min) \( t_r = 13.1 \) min (minor), \( t_r = 15.6 \) min (major); \([\alpha]_{D}^{\text{rt}} = +5.2^\circ \) (c=0.0100 g/mL, CHCl₃); \(^1\text{H} \text{NMR} \delta 3.54 \) (dd, \( J=16.8, 8.0 \) Hz, 1H), 3.62 (dd, \( J=16.8, 8.0 \) Hz, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 4.82 (t, \( J=8.0. \) Hz, 1H), 6.75-7.29 (m, 9H), 7.92 (s, br, 1H); \(^{13}\text{C} \text{NMR} \delta 37.6, 45.5, 52.9, 55.7, 101.2, 111.8, 112.2, 117.9, 122.2, 126.6, 126.7, 127.7, 128.5, 131.6, 143.1, 153.8, 161.2, 192.6; mass (TOF ES\(^+\)): \( m/z 392 \) (M+Na+MeOH\(^+\)); HRMS calc. for C\(_{21}\)H\(_{23}\)NNaO\(_5\) 392.1474, found 392.1476.

(−)-(4R)-4-(6-Chloro-1H-indol-3-yl)-2-oxo-4-phenyl-butyric acid methyl ester (3d). According to general procedure I indole 1d (60.6 mg, 0.4 mmol) was reacted with enone 2a (76.0 mg, 0.4 mmol) in Et₂O (2 mL) at -20°C with 10 mol%
catalyst. Full conversion was obtained after 16 h where the reaction was allowed to warm up to 0°C. Purification by FC on silica gel (Et₂O:pentane, 30:70) gave 3d as a white solid in 69% yield and with 97% ee detected by HPLC using a Chiralcel OD column (hexane:i-PrOH 85:15, flow rate=0.5 mL/min) tᵣ=15.4 min (major), tᵣ=19.6 min (minor); mp=158°C; [α]ᵣₑD=−18.5° (c=0.0100 g/mL, CHCl₃); ¹H NMR δ 3.50 (dd, J=16.8, 7.2 Hz, 1H), 3.59 (dd, J=16.8, 7.2 Hz, 1H), 3.71 (s, 3H), 4.80 (t, J=7.2 Hz, 1H), 6.89–7.23 (m, 9H), 7.95 (s, br, 1H); ¹³C NMR δ 37.5, 45.5, 53.0, 111.1, 118.5, 120.3, 120.3, 122.0, 125.0, 126.7, 127.7, 128.3, 128.6, 136.9, 142.9, 161.2, 192.4; mass (TOF ES⁺): m/z 397 (M+Na+MeOH)⁺; HRMS calc. for C₂₀H₂₀ClNNaO₄ 396.0979, found 396.0983.

(−)-(1R)-3-(3-Methoxycarbonyl-3-oxo-1-phenyl-propyl)-1H-indole-6-carboxylic acid methyl ester (3e). According to general procedure I indole 1e (70.0 mg, 0.4 mmol) was reacted with enone 2a (76.0 mg, 0.4 mmol) in Et₂O (2 mL) at −20°C with 10 mol% catalyst. Full conversion was obtained after 16 h where the reaction was allowed to warm up to 0°C. Purification with a silica plug gave 3e as a pale yellow solid in 82% yield and with 94% ee detected by HPLC using a Chiralcel OD-R column (MeOH, flow rate=0.3 mL/min) tᵣ=16.3 min (minor), tᵣ=18.0 min (major); mp=180°C; [α]ᵣₑD=−2.9° (c=0.0100 g/mL, CHCl₃); ¹H NMR δ 3.54 (dd, J=17.2, 7.6 Hz, 1H), 3.62 (dd, J=17.2, 7.6 Hz, 1H), 3.71 (s, 3H), 3.84 (s, 3H) 4.85 (t, J=7.6 Hz, 1H), 7.12–7.25 (m,
6H), 7.35 (d, J=8.0 Hz, 1H), 7.63 (d, J=8.0, 1H), 8.01 (s, 1H) 8.30 (s, br, 1H); \(^{13}\text{C}\) NMR \(\delta 37.5, 45.5, 52.0, 53.0, 113.5, 118.7, 119.0, 120.6, 124.0, 124.8, 126.8, 127.7, 128.6, 129.9, 135.8, 142.8, 161.2, 168.0, 192.4;\) mass (TOF ES\(^{+}\)): \(m/z\) 388 (M+Na)\(^{+}\); HRMS calc. for C\(_{21}\)H\(_{19}\)NNaO\(_5\) 388.1161, found 388.1158.

\((-\)-(4\text{R})-4-(1H-Indol-3-yl)-2-oxo-pentanoic acid ethyl ester (3f).\) According to general procedure I indole 1a (94.0, 0.8 mmol) was reacted with enone 2b (113.7 mg, 0.8 mmol) in Et\(_2\)O (2 mL) at \(-78^\circ\text{C}\) with 5 mol\% catalyst. Full conversion was obtained after 16 h. Purification with a silica plug gave 3f as a yellow oil in 96\% yield and with 95\% ee detected by HPLC using a Chiralcel OB column (hexane:i-PrOH 98:2, flow rate=0.5 mL/min) \(t_\text{r}=26.1\) min (major), \(t_\text{r}=33.1\) min (minor); \([\alpha]_\text{D}^20\text{}=\text{1.7}^\circ\) (c=0.0100 g/mL, CHCl\(_3\)); \(^{1}\text{H}\) NMR \(\delta 1.30\) (t, \(J=7.6\) Hz, 3H), 1.44 (d, \(J=6.8\) Hz, 3H), 3.12 (dd, \(J=16.8, 8.4\) Hz, 1H), 3.36 (dd, \(J=16.8, 6.0\) Hz, 1H), 3.71 (m, 1H), 4.23 (q, \(J=6.8\) Hz, 2H), 7.02 (s, 1H), 7.13 (t, \(J=6.8\) Hz, 1H), 7.18 (t, \(J=6.8\) Hz, 1H), 7.36 (d, \(J=8.0\) Hz, 1H), 7.67 (d, \(J=7.2\) Hz, 1H) 7.95 (s, br, 1H); \(^{13}\text{C}\) NMR \(\delta 13.8, 20.9, 26.6, 46.8, 62.4, 111.2, 119.0, 119.3, 120.1, 120.4, 122.0, 126.1, 136.4, 161.1, 194.1;\) mass (TOF ES\(^{+}\)): \(m/z\) 300 (M+Na+H\(_2\)O)\(^{+}\); HRMS calc. for C\(_{15}\)H\(_{19}\)NNaO\(_4\) 300.1212, found 300.1200.

\((-\)-(4\text{R})-4-(5-Methoxy-1H-indol-3-yl)-2-oxo-pentanoic acid ethyl ester (3g).\) According to general procedure I indole
1c (117.7, 0.8 mmol) was reacted with enone 2b (113.7 mg, 0.8 mmol) in Et₂O (2 mL) at -78°C with 5 mol% catalyst. Full conversion was obtained after 1 h. Purification with a silica plug gave 3g as a yellow oil in 95% yield and with >99.5% ee detected by HPLC using a Chiralcel OJ column (hexane:i-PrOH 85:15, flow rate=0.5 mL/min) \( t_r = 26.5 \) min (minor), \( t_r = 37.2 \) min (major); \([\alpha]^{\text{RT}}_D = -10.4^\circ \) (c=0.0100 g/mL, CHCl₃); \(^1\)H NMR \( \delta 1.29 \) (t, \( J=7.6 \) Hz, 3H), \( 1.41 \) (d, \( J=6.8 \) Hz, 3H), \( 3.09 \) (dd, \( J=16.8, 8.0 \) Hz, 1H), \( 3.33 \) (dd, \( J=16.8, 6.0 \) Hz, 1H), \( 3.65 \) (m, 1H), \( 3.88 \) (s, 3H), \( 4.23 \) (q, \( J=7.2 \) Hz, 2H), \( 6.86 \) (dd, \( J=9.2, 2.4 \) Hz, 1H), \( 6.98 \) (d, \( J=2.8 \) Hz, 1H), \( 7.09 \) (d, \( J=2.4 \) Hz, 1H), \( 7.23 \) (d, \( J=9.2 \) Hz, 1H), \( 7.89 \) (s, br, 1H); \(^{13}\)C NMR \( \delta 13.9, 20.9, 26.5, 46.8, 56.0, 62.4, 101.0, 111.9, 112.2, 120.1, 121.1, 126.5, 131.6, 153.9, 161.1, 194.1; \) mass (TOF ES\(^+\)): \( m/z \) 330 (M+Na+H₂O\(^+\)); HRMS calc. for C₁₆H₂₁NNaO₅ 330.1317, found 330.1320.

(+)-(4R)-5-Benzylxylo-4-(6-chloro-1H-indol-3-yl)-2-oxo-pentanoic acid ethyl ester (3h). According to general procedure I indole 1d (60.6 mg, 0.4 mmol) was reacted with enone 2c (99.3 mg, 0.4 mmol) in Et₂O (2 mL) at -20°C with 10 mol% catalyst. Full conversion was obtained after 16 h where the reaction was allowed to warm up to 0°C. Purification by FC on silica gel (Et₂O:pentane, 30:70) gave 3i as a red semicrystaline solid in 70% yield and with 80% ee detected by HPLC using a Chiralpak AD column (hexane:i-PrOH 90:10, flow rate=0.5 mL/min) \( t_r = 47.3 \) min (minor), \( t_r = 50.8 \) min (major); \([\alpha]^{\text{RT}}_D = +14.7^\circ \) (c=0.0100 g/mL, CHCl₃);
(+)-(4R)-5-Benzylxyloxy-4-(5-methoxy-1H-indol-3-yl)-2-oxo-pentanoic acid ethyl ester (3i). According to general procedure I indole 1c (58.9, 0.4 mmol) was reacted with enone 2c (99.3 mg, 0.4 mmol) in Et₂O (2 mL) at -78°C with 5 mol% catalyst. Full conversion was obtained after 1 h. Purification with a silica plug gave 3i as a yellow oil in 98% yield and with 95% ee detected by HPLC using a Chiralcel OJ column (hexane:i-PrOH 85:15, flow rate=0.5 mL/min) tᵣ=45.2 min (minor), tᵣ=51.0 min (major); [α]ᵣ₊D=+23.0° (c=0.0100 g/mL, CHCl₃); ¹H NMR δ 1.26 (t, J=6.8 Hz, 3H), 3.19 (dd, J=15.6, 6.4 Hz, 1H), 3.43 (dd, J=15.6, 8.4 Hz, 1H), 3.63 (t, J=9.2 Hz, 1H), 3.81 (dd, J=9.2, 4.4 Hz, 1H), 3.86 (s, 3H), 3.97 (m, 1H), 4.19 (m, 2H), 4.50 (s, 2H), 6.86 (dd, J=9.6, 2.4 Hz, 1H), 7.03 (d, J=2.4 Hz, 1H), 7.09 (d, J=2.4 Hz, 1H), 7.23-7.36 (m, 6H), 7.93 (s, br, 1H); ¹³C NMR δ 13.9, 34.0, 42.8, 55.9, 62.2, 72.9, 73.5, 100.7, 111.9, 112.5, 115.3, 122.0, 126.8
mass (TOF ES\(^+\)): m/z 436 (M+Na+H\(_2\)O\(^+\)); HRMS calc. for C\(_{23}\)H\(_{27}\)NNaO\(_6\) 436.1736, found 436.1738.

(-)-(4\(R\))-4-(5-Methyl-furan-2-yl)-2-oxo-4-phenyl-butyric acid methyl ester (3j). According to general procedure II 2-methyl-furan 1\(f\) (120 \(\mu\)L, 1.33 mmol) was reacted with enone 2\(a\) (190.2 mg, 1.00 mmol) in Et\(_2\)O (2 mL) at 0°C using 10 mol\% catalyst. The reaction was quenched after 2 d and evaporation of the solvent gave 3\(j\) as a pale yellow oil in 99% yield and 88% ee detected by HPLC using a Chiralcel OD column (hexane:i-PrOH 85:15, flow rate=0.5 mL/min) \(t\_e=11.7\) min (minor), \(t\_e=13.8\) min (major); \([\alpha]\)\text{rt} D = -37.0° (c=0.0102 g/mL, CH\(_2\)Cl\(_2\)); \(^1\)H NMR \(\delta\) 2.21 (s, 3H), 3.41 (dd, \(J=17.6, 7.5\) Hz, 1H), 3.64 (dd, \(J=17.6, 7.5\) Hz, 1H), 3.64 (dd, \(J=17.6, 7.5\) Hz, 1H), 4.60 (t, \(J=7.5\) Hz, 1H), 5.83-5.84 (m, 1H), 5.86-5.87 (m, 1H), 7.23-7.33 (m, 5H); \(^{13}\)C NMR \(\delta\) 13.8, 40.1, 44.5, 53.3, 106.3, 107.0, 127.3, 128.1, 128.9, 141.3, 151.6, 154.1, 161.3, 191.9; mass (TOF ES\(^+\)): m/z 295 (M+Na\(^+\)); HRMS calc. for C\(_{16}\)H\(_{16}\)NaO\(_4\) 295.0946, found 295.0949.

(+)-(4\(R\))-4-(5-Methyl-furan-2-yl)-2-oxo-pentanoic acid ethyl ester (3k). According to general procedure II 2-methyl-furan 1\(f\) (50 \(\mu\)L, 0.55 mmol) was reacted with enone 2\(b\) (71.1 mg, 0.50 mmol) in Et\(_2\)O (2 mL) at 0°C using 10 mol\% catalyst. The reaction was quenched after 1 d. Evaporation of the solvent gave 3\(k\) as a pale yellow oil in 94% yield and 88% ee detected by GC using a Astec G-TA column at
115°C isotherm; \([\alpha]^{rt}_D (Hg(436nm))=+5.6^\circ\) (c=0.0104 g/mL, CH\(_2\)Cl\(_2\)); \(^1^H\) NMR \(\delta\) 1.28 (d, \(J=6.6\) Hz, 3H), 1.36 (t, \(J=7.0\) Hz, 3H), 2.23 (s, 3H), 2.93 (dd, \(J=17.3, 7.6\) Hz, 1H), 3.22 (dd, \(J=17.3, 6.2\) Hz, 1H), 3.37-3.45 (m, 1H), 4.30 (q, \(J=7.0\) Hz, 2H), 5.82-5.83 (m, 1H), 5.86-5.87 (m, 1H); \(^{13^C}\) NMR \(\delta\) 13.7, 14.2, 19.0, 28.9, 45.3, 62.7, 105.0, 106.0, 150.9, 156.5, 161.2, 193.4; mass (TOF ES\(^+\)): m/z 247 (M+Na\(^+\); HRMS calc. for C\(_{12}\)H\(_{16}\)NaO\(_4\) 247.0946, found 247.0948.

\((+)-(4^R)-5\)-Benzyloxy-4-(5-methyl-furan-2-yl)-2-oxo-pentanoic acid ethyl ester (3l). According to general procedure II 2-methyl-furan 1f (60 \(\mu\)L, 0.67 mmol) was reacted with enone 2c (124.1 mg, 0.50 mmol) in Et\(_2\)O (2 mL) at 0\(^\circ\)C using 10 mol% catalyst. The reaction was quenched after 1 d. Evaporation of the solvent gave 3l as a pale yellow oil in 90% yield and 80% ee detected by HPLC using a Chiralpak AD column (hexane:i-PrOH 95:5, flow rate=0.5 mL/min) \(t_R=12.5\) min (minor), \(t_R=13.5\) min (major); \([\alpha]^{rt}_D=+8.4^\circ\) (c=0.0100 g/mL, CH\(_2\)Cl\(_2\)); \(^1^H\) NMR \(\delta\) 1.29 (t, \(J=7.2\) Hz, 3H), 2.22 (s, 3H), 3.11 (dd, \(J=16.0, 6.0\) Hz, 1H), 3.26 (dd, \(J=16.0, 6.8\) Hz, 1H), 3.50-3.56 (m, 1H), 3.68-3.73 (m, 2H), 4.21 (q, \(J=7.2\) Hz, 1H), 4.22 (q, \(J=7.2\) Hz, 1H), 4.45 (s, 2H), 5.83-5.84 (m, 1H), 5.94-5.95 (m, 1H), 7.25-7.35 (m, 5H); \(^{13^C}\) NMR \(\delta\) 13.7, 14.2, 36.2, 40.9, 62.5, 72.0, 73.1, 106.2, 106.7, 127.9, 128.6, 138.1, 151.3, 152.3, 161.0, 192.6; mass (TOF ES\(^+\)): m/z 353 (M+Na\(^+\); HRMS calc. for C\(_{19}\)H\(_{22}\)NaO\(_5\) 353.1365, found 353.1371.
(−)-(4R)-4-(4-Chloro-phenyl)-4-(5-methyl-furan-2-yl)-2-oxo-butyric acid methyl ester (3m). According to general procedure II 2-methyl-furan 1f (100 µL, 1.11 mmol) was reacted with enone 2d (224.6 mg, 1.00 mmol) in Et₂O (2 mL) at 0°C using 10 mol% catalyst. The reaction was quenched after 18 h. Purification by FC (silica gel, EtOAc:pentane 1:9) gave 3m as a pale yellow oil in 89.5% yield and 79% ee detected by HPLC using a Chiralcel OB column (hexane:i-PrOH 80:20, flow rate=0.5 mL/min) $t_r=32$ min (minor), $t_r=44$ min (major); $[\alpha]_{D}^\text{rt}=-47.1^\circ$ (c=0.0103 g/mL, CH₂Cl₂); $^1$H NMR δ 2.21 (s, 3H), 3.40 (dd, $J=18.0$, 7.2 Hz, 1H), 3.61 (dd, $J=18.0$, 7.2 Hz, 1H), 3.84 (s, 3H), 4.57 (t, $J=7.2$ Hz, 1H), 5.83-5.87 (m, 2H), 7.20-7.28 (m, 4H); $^{13}$C NMR δ 13.7, 39.4, 44.3, 53.3, 106.3, 107.1, 129.5, 133.1, 139.9, 151.8, 153.6, 161.2, 191.6; mass (TOF ES$^+$): m/z 329 (M+Na)$^+$; HRMS calc. for C₁₆H₁₅ClNaO₄ 329.0557, found 329.0616.

(+)-(4R)-4-(2,4-Dimethoxy-phenyl)-2-oxo-pentanoic acid ethyl ester (3n). According to general procedure III 1,3-dimethoxy-benzene 1g (200 µL, 1.5 mmol) was reacted with enone 2b (71.1 mg, 0.50 mmol) in CH₂Cl₂ (2 mL) at 0°C using 10 mol% catalyst. The reaction was quenched after 2 h. Purification by FC (silica gel, Et₂O:pentane, 1:5) gave 3o as a clear oil in 65% yield and 89% ee detected by HPLC using a Chiralpak AD column (hexane:i-PrOH 95:5, flow rate=0.5 mL/min) $t_r=14.5$ min (minor), $t_r=18.0$ min (major); $[\alpha]_{D}^\text{rt}(\text{Hg}(436nm))=+9.0^\circ$ (c=0.0091 g/mL, CH₂Cl₂); $^1$H NMR δ 1.28 (d, $J=7.0$ Hz, 3H), 1.34 (t, $J=7.1$ Hz, 3H), 3.01 (dd,
(+)-(4R)-4-(2,4-Dimethoxy-phenyl)-2-oxo-4-phenyl-butyric acid methyl ester (3o). According to general procedure III 1,3-dimethoxy-benzene 1g (400 µL, 3.0 mmol) was reacted with enone 2a (190.2 mg, 1.0 mmol) in CH₂Cl₂ (2 mL) at -78°C using 10 mol% catalyst. The reaction temperature was raised to -60°C to permit stirring. The reaction was quenched after 28 h. Purification by FC (silica gel, Et₂O:pentane, 3:7) gave 3n as a colorless thick oil in 68% yield and 60% ee detected by HPLC using a Chiralpak AD column (hexane:i-PrOH 95:5, flow rate=0.5 mL/min) tᵣ=23.8 min (minor), tᵣ=26.6 min (major); [α]ᵣ$_D$=+15.0° (c=0.0102 g/mL, CH₂Cl₂); $^1$H NMR δ 3.46 (dd, J=16.8, 7.6 Hz, 1H), 3.61 (dd, J=16.8, 7.6 Hz, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 4.93 (t, J=7.6 Hz, 1H), 6.37-6.41 (m, 2H), 6.95 (d, J=8.6 Hz, 1H), 7.13-7.19 (m, 1H), 7.21-7.29 (m, 4H); $^{13}$C NMR δ 38.6, 44.5, 52.8, 55.2, 98.6, 104.0, 123.9, 126.2, 127.8, 128.3, 128.5, 143.0, 157.5, 159.5, 161.2, 192.4; mass (TOF ES⁺): m/z 351 (M+Na)⁺; HRMS calc. for C$_{19}$H$_{20}$NaO$_5$ 351.1208, found 351.1205.
Crystal structure analysis of 3d: \( \text{C}_{19}\text{H}_{16}\text{ClNO}_3 \), colorless prisms, 0.55*0.25*0.20mm\(^3\), orthorhombic, space group \( \text{P}2_1\text{P}2_1\text{P}_2_1 \), \( a=9.5974(4) \), \( b=12.4442(5) \), \( c=14.4731(6) \) Å, \( V=1728.6(1)\text{Å}^3 \), \( Z=4 \), \( \rho_{\text{calc}}=1.309\text{Mg} \cdot \text{m}^{-3} \), MoKa radiation (\( \lambda=0.71073\text{Å} \)), \( 2\theta_{\text{max}}=27.5^\circ \), \( T=295\text{K} \), \( \gamma=0.236\text{mm}^{-1} \), no correction for absorption. Area detector data collected on a Siemens SMART CCD diffractometer, nearly full sphere of reflections; data integration, correction for Lorentz and polarization effects and averaging with SMART, SAINT, and XPREP software.\(^{[3]}\) There were 18837 reflections, giving 4004 independent, of which 2645 with \( I>3\text{sig}(I) \) were used for the refinement. Structure solved by direct methods (SIR97)\(^{[4]}\) refined by full matrix least squares on \( F \),\(^{[5]}\) 283 parameters, hydrogen atoms refined with isotropic temperature parameters, all other atoms anisotropic, \( R=0.042 \), \( wR=0.047 \), max. residual electron density \( \Delta\rho_{\text{max}}=0.33\text{e} \cdot \text{Å}^{-3} \). The absolute configuration was determined by using the anomalous scattering from chlorine by refinement of the Rogers parameter.\(^{[6]}\) The result was 0.85(15), which unambiguously established the chirality, as it is shown in Figure 1.\(^{[7]}\) Crystallographic data for the structure reported in this paper has been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149312. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
References


