SUPPORTING INFORMATION

A simple asymmetric organocatalytic approach to optically active cyclohexenones

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**General Methods.** The $^1$H and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts ($\delta$) for $^1$H and $^{13}$C are given in ppm relative to residual signals of the solvents (CHCl$_3$). Coupling constants (J) are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Chromatography was carried out by flash chromatography (FC) using Merck silica gel 60 (230-400 mesh) according to the method of Still et al.$^1$ Optical rotations were measured on a Perkin-Elmer 241 polarimeter and they are reported as follows: $[\alpha]_D^n$ (c in g per 100 mL, solvent).

**Materials.** Commercial grade reagents and aldehydes were used without further purification; catalyst 4 was prepared according to literature procedure.$^2$

**Determination of Absolute Configuration.** The absolute configurations of the optically active compounds 3a,d,e and 9 were determined on the basis of the measured optical rotations that were compared with literature values. All other absolute configurations were assigned by analogy.

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Experimental Procedures and Characterizations

**General Procedure for the Organocatalytic Asymmetric Michael Reaction.** In an ordinary vial equipped with a magnetic stirring bar, β-ketoester 1 (0.25 mmol) was added to a mixture of catalyst 4 (0.025 mmol, 10 mol%) and α,β-unsaturated aldehyde 2 (0.37 mmol) in the aqueous solution (0.5 mL). The stirring was maintained at room temperature until complete consumption of the β-ketoester. The crude reaction mixture was directly charged on silica gel and subjected to FC.

**General Procedure for the Organocatalytic Asymmetric Synthesis of Cyclohexenones 3a-i.** In an ordinary vial equipped with a magnetic stirring bar, β-ketoester 1 (0.25 mmol) was added to a mixture of catalyst 4 (0.025 mmol, 10 mol%), α,β-unsaturated aldehyde 2 (0.37 mmol). The stirring was maintained at room temperature until complete consumption of the β-ketoester. After addition of toluene (1 mL) and p-TSA (0.05 mmol, 20 mol%), the reaction was stirred at 80 °C for 16 h. The crude reaction mixture was directly charged on silica gel and subjected to FC.

**(R)-**tert-Butyl-2-acetyl-5-oxo-3-phenylpentanoate 5a. The title compound was isolated after FC (CH$_2$Cl$_2$/Et$_2$O: 99/1). The ee was determined on the relative compound 7. HRMS: C$_{18}$H$_{26}$NaO$_5$ – [M+Na$^+$+MeOH] calcld.: 345.1678, found: 345.1665. δ$_H$ (400 MHz; CDCl$_3$) (dr 6/1, major diasteromer) 1.13 (s, 9H), 2.26 (s, 3H), 2.72 (m, 2H), 3.81 (d, $J = 10.8$, 1H), 3.95 (ddd, $J = 10.8$, 9.08, 4.66, 1H), 7.41-7.13 (m, 5H), 9.58 (t, $J = 1.65$, 1H); δ$_C$ (100 MHz; CDCl$_3$) 27.3, 29.5, 38.9, 48.2, 66.4, 82.2, 127.3, 128.4, 128.6, 140.2, 166.6, 200.5, 202.1.

**(R)-**5-Oxo-3-phenylhexanal 7. The title compound was isolated after treatment of 5a (0.25 mmol) with 50% TFA in CH$_2$Cl$_2$ (0.5 mL). After 1 h reaction time the crude mixture was quenched with H$_2$O and extracted with CH$_2$Cl$_2$. Filtration on a silica pad afforded the pure product. The ee was determined by GC analysis on a Astec G-TA chiral stationary phase ($T_1 = 70 ^\circ C$; $T_2 = 165 ^\circ C$, rate = 10 °C/min; $T_3 = 165 ^\circ C$; $\tau_R = 16.5$ min, $\tau_S = 16.6$ min). $[\alpha]_D^{11}$ = -12.9 (c = 1.0, CH$_2$Cl$_2$, 94% ee). Spectroscopic data are in accordance with literature values.$^3$

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(R)-5-Methyl-cyclohex-2-enone 3a. The title compound was obtained following the general procedure and isolated after FC (CH$_2$Cl$_2$/Et$_2$O: 99/1) in 93% yield and 80% ee. [α]$_D^{\text{rt}}$ = -74.6 (c = 0.5, CHCl$_3$, 80% ee), lit.$^4$ [α]$_D^{\text{rt}}$ = -91.0 (c = 0.8, CHCl$_3$). The ee was determined by GC analysis on an Astec G-TA chiral stationary phase (T$_1$ = 60 °C; T$_2$ = 70 °C, rate = 2 °C/min; T$_3$ = 90 °C, rate = 1 °C/min; $\tau$$_R$ = 20.7 min, $\tau$$_S$ = 21.6 min). Spectroscopic data are in accordance with literature values.$^5$

(R)-5-Ethyl-cyclohex-2-enone 3b. The title compound was obtained following the general procedure and isolated after FC (CH$_2$Cl$_2$/Et$_2$O: 99/1) in 98% yield and 94% ee. [α]$_D^{\text{rt}}$ = -43.1 (c = 0.1, CHCl$_3$, 94% ee). The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T$_1$ = 70 °C; T$_2$ = 200 °C, rate = 10 °C/min; $\tau$$_R$ = 6.8 min, $\tau$$_S$ = 6.9 min). Spectroscopic data are in accordance with literature values.$^6$

(R)-5-iso-Propyl-cyclohex-2-enone 3c. The title compound was obtained following the general procedure and isolated after FC (CH$_2$Cl$_2$/Et$_2$O: 99/1) in 56% yield and 96% ee. [α]$_D^{\text{rt}}$ = -33.0 (c = 0.1, CHCl$_3$, 96% ee). The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T$_1$ = 70 °C; T$_2$ = 200 °C, rate = 10 °C/min; $\tau$$_R$ = 7.8 min, $\tau$$_S$ = 7.9 min). δ$_H$ (400 MHz; CDCl$_3$) 0.92 (d, J = 2.0, 3H), 0.94 (d, J = 2.0, 3H), 1.60 (m, 1H), 1.94-1.84 (m, 1H), 2.08-2.20 (m, 2H), 2.44-2.36 (m, 1H), 2.49-2.53 (m, 1H), 6.02 (m, 1H), 7.00 (ddd, J = 10.0, 6.0, 2.4, 1H); δ$_C$ (100 MHz; CDCl$_3$) 19.4, 19.5, 29.6, 32.0, 41.5, 41.9, 129.5, 150.5, 200.7.

(R)-5-Butyl-cyclohex-2-enone 3d. The title compound was obtained following the general procedure and isolated after FC (CH$_2$Cl$_2$/Et$_2$O: 99/1) in 69% yield and 92% ee. [α]$_D^{\text{rt}}$ = -44.9 (c = 0.5, CHCl$_3$, 92% ee), lit.$^7$ [α]$_D^{\text{rt}}$ = -51.2 (c = 1.4,

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CHCl₃. The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T₁ = 70 °C; T₂ = 120 °C, rate = 5 °C/min; T₃ = 136 °C, rate = 2 °C/min; τᵣ = 15.8 min, τₛ = 15.9 min). Spectroscopic data are in accordance with literature values.⁸

(R)-5-Phenylcyclohex-2-enone 3e. The title compound was obtained following the general procedure and isolated after FC (hexane/Et₂O: 80/20) in 63% yield and 94% ee. The ee was determined on the parent compound 7. [α]ᵣ⁰D = -39.5 (c = 1.0, CHCl₃, 94% ee), lit.⁹ [α]ᵣ⁰D = -43.0 (c = 1.25, CHCl₃). Spectroscopic data are in accordance with literature values.¹⁰

(R)-5-(4-Fluorophenyl)cyclohex-2-enone 3f. The title compound was obtained following the general procedure and isolated after FC (hexane/AcOEt: 85/15) in 65% yield and 95% ee. The ee was determined by HPLC analysis on 2 Daicel Chiralpak AD columns in a row (hexane/i-PrOH: 95/5, flow 0.8 mL/min; τₛ = 24.1 min, τᵣ = 25.0 min). [α]ᵣ⁰D = -29.1 (c = 1.0, CHCl₃, 95% ee). HRMS: C₁₂H₁₁FNaO - [M+Na⁺] calcd.: 213.0692, found: 213.0692. δH (400 MHz; CDCl₃) 2.40-2.75 (m, 4H), 3.27-3.39 (m, 1H), 6.12 (dd, J = 10.1, 2.75, 1H), 7.15-7.23 (m, 2H), 6.97-7.07 (m, 3H); δC (100 MHz; CDCl₃) 33.7, 40.2, 44.9, 115.5 (d, J = 21.3), 128.1 (d, J = 8.3), 129.8, 138.8 149.3, 161.6 (d, J = 246.9), 198.9.

(R)-5-m-Tolylcyclohex-2-enone 3g. The title compound was obtained following the general procedure and isolated after FC (hexane/AcOEt: 90/10) in 72% yield and 94% ee. The ee was determined by HPLC analysis on 2 Daicel Chiralpak AD columns in a row (hexane/i-ProOH: 98/2, flow 0.5 mL/min; τᵣ = 29.7 min, τₛ = 30.7 min). [α]ᵣ⁰D = -34.2 (c = 0.5, CH₂Cl₂, 94% ee). HRMS: C₁₃H₁₄NaO - [M+Na⁺] calcd.: 209.0942, found: 209.0947. δH (400 MHz; CDCl₃) 2.36 (s, 3H), 2.46-2.82 (m, 4H), 3.26-3.37 (m, 1H), 6.05-6.24 (m, 1H), 7.00-7.13 (m, 4H), 7.24 (t, J = 7.07, 1H); δC (100 MHz; CDCl₃) 21.4. 33.7, 40.9, 44.9, 123.6, 127.4, 127.8, 128.6, 129.7, 134.3, 143.1, 149.6, 199.3.

**Supplementary Material (ESI) for Chemical Communications**

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(R)-5-Ethyl-2-methyl-cyclohex-2-enone 3h. The title compound was obtained following the general procedure and isolated after FC (hexane/Et$_2$O: 80/20) in 82% yield and 91% ee. [$\alpha$]$_{D}^{20}$ = -66.0 (c = 0.1, CHCl$_3$). The ee was determined by HPLC analysis on a Daicel Chiralpak AD column at 0 °C (hexane/i-PrOH: 99/1, flow 0.5 mL/min; $\tau_R$ = 14.5 min, $\tau_S$ = 16.3 min). $\delta$H (400 MHz; CDCl$_3$) 0.91 (t, $J$ = 7.2, 3H), 1.37 (m, 2H), 1.70 (s, 3H), 1.77-2.14 (m, 3H), 2.24-2.32 (m, 1H), 2.56 (m, 1H), 6.71 (dd, $J$ = 2.6, 1.4 Hz, 1H); $\delta$C (100 MHz; CDCl$_3$) 11.0, 15.8, 28.5, 32.2, 37.3, 44.3, 135.5, 145.0, 200.42.

(R)-2,5-Diethylcyclohex-2-enone 3i. The title compound was obtained following the general procedure isolating the intermediate Michael adduct; the title compound was purified by FC (Et$_2$O/pentane: 1/10) in 74% overall yield and 89% ee. The ee was determined by GC analysis on an Astec G-TA chiral stationary phase (T$_1$ = 70 °C; T$_2$ = 100 °C, rate = 10 °C/min; T$_3$ = 100 °C, time = 8 min; T$_4$ = 180 °C, rate = 10 °C/min; $\tau_R$ = 14.2 min, $\tau_S$ = 14.4 min). [$\alpha$]$_{D}^{20}$ = -10.1 (c = 1.0, CHCl$_3$, 89% ee). HRMS: C$_{10}$H$_{16}$NaO - [M+Na$^+$] calcd.: 175.1099, found: 175.1093. $\delta$H (400 MHz; CDCl$_3$) 0.91 (t, $J$ = 7.46, 3H), 1.00 (t, $J$ = 7.46, 3H), 1.33-1.47 (m, 2H), 1.88-2.15 (m, 3H), 2.14-2.27 (m, 2H), 2.37-2.48 (m, 1H), 2.49-2.59 (m, 1H), 6.62-6.72 (m, 1H); $\delta$C (100 MHz; CDCl$_3$) 11.1, 12.8, 22.2, 28.6, 32.2, 37.2, 44.6, 140.9, 143.3, 199.9.

Synthesis of (2S,4S)-1-benzyl-2-methyl-4-phenylpiperidine 9. In an ordinary vial equipped with a magnetic stirring bar, $\beta$-ketoester 1a (0.25 mmol) was added to a mixture of catalyst 4 (0.025 mmol, 10 mol%) and $\alpha,\beta$-unsaturated aldehyde 2 (0.37 mmol). After 5 h CH$_2$Cl$_2$ (0.5 mL) and TFA (0.5 mL) were added and the stirring was maintained for 1 h. The reaction was quenched with NaHCO$_3$, extracted with AcOEt, dried over MgSO$_4$ and evaporated. The crude reaction mixture was transferred to an ordinary vial equipped with a magnetic stirring bar and MeOH, NaBH$_3$CN (0.75 mmol, 3 equiv.) and benzylamine (1M in MeOH, pH $\approx$6-7; 0.37 mmol, 1.5 equiv.) were added. After 5 min NaBH$_3$CN (0.125 mmol, 0.5 equiv.) was added and the stirring was maintained for 20 h until GC/MS showed the reaction to be complete. The reaction was quenched with NH$_4$Cl, extracted with AcOEt, dried over MgSO$_4$ and...
evaporated. The title compound was purified by FC (hexane/AcOEt: 90/10) in 46% overall yield, dr >20:1 and 94% ee. The ee was determined on the parent compound 7. \([\alpha]_{\text{D}}^1 = -57.2 \ (c = 1.0, \text{CH}_2\text{Cl}_2, \ 94\% \text{ ee})\). HRMS: C_{19}H_{24}N - [M+H^+] calcd.: 266.1909, found: 266.1919. \(\delta_{\text{H}}\) (400 MHz; CDCl\(_3\)) 1.29 (d, J = 6.1, 3H), 1.52-1.91 (m, 4H), 2.08 (dt, J = 11.6, 3.4, 1H), 2.31-2.46 (m, 1H), 2.51-2.68 (m, 1H), 2.95 (td, J = 11.6, 3.4, 1H), 3.21 (d, J = 13.3, 1H), 4.18 (d, J = 13.3, 1H), 7.45-7.14 (m, 10H); \(\delta_{\text{C}}\) (100 MHz; CDCl\(_3\)) 21.4, 33.3, 42.9, 43.0, 53.2, 57.1, 58.1, 126.0, 126.7, 126.8, 128.1, 128.3, 129.2, 139.1, 146.4.

**Determination of relative configuration of the compound 9.** (2S,4S)-1-benzyl-2-methyl-4-phenylpiperidine 9 (0.12 mmol) was subjected to hydrogenation on 10% Pd/C, in i-PrOH (2 mL) and catalytic amount of AcOH under an atmosphere of 70 psi H\(_2\), for 30 h. The reaction was filtered, washed with K\(_2\)CO\(_3\) (aq.), dried over MgSO\(_4\) and evaporated. Toluene (0.8 mL) and HCl (37% aq, 0.18 mmol, 1.5 equiv.) were added. The stirring was maintained at rt for 0.5 h and then the solution was kept at 5 °C for 6 h without stirring. The precipitate was filtered off and washed with cold toluene. Comparison of the spectroscopic data with literature values\(^{11}\) gave the cis-relative configuration.