Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION

A simple asymmetric organocatalytic approach to optically active cyclohexenones

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Contents

General Methods……p 2

Materials……..……p 2

Determination of Absolute Configuration……p 2

Experimental Procedures and Characterizations……p 3

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) 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: $[\alpha]^{rt}_{D}$ (*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]

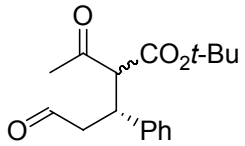
Determination of Absolute Configuration. The absolute configurations of the optically active compounds **3a**,**d**,**e** and **9** were determined on the basis of the measured optical rotations that were compared with literature values. All other absolute configurations were assigned by analogy.

[1] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[2] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794.

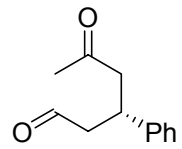
Experimental Procedures and Characterizations

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-unsatured 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-unsatured 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.

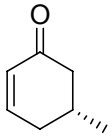


(*R*)-*tert*-Butyl-2-acetyl-5-oxo-3-phenylpentanoate 5a. The title compound was isolated after FC (CH_2Cl_2/Et_2O: 99/1). The ee was determined on the relative compound **7**. HRMS: $C_{18}H_{26}NaO_5$ – [M+Na^++MeOH] calcd.: 345.1678, found: 345.1665. δ_H (400 MHz; $CDCl_3$) (dr 6/1, major diasteromer) 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.

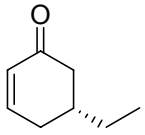


(*R*)-5-Oxo-3-phenylhexanal 7. The title compound was isolated after treatment of **5a** (0.25 mmol) with 50% TFA in CH_2Cl_2 (0.5 mL). After 1 h reaction time the crude mixture was quenched with H_2O and extracted with CH_2Cl_2. Filtration on a silica pad afforded the pure product. The ee was determined by GC analysis on a Astec G-TA chiral stationary phase (T_1 = 70 °C; T_2 = 165 °C, rate = 10 °C/min; T_3 = 165 °C; τ_R = 16.5 min, τ_S = 16.6 min). $[\alpha]^{rt}_D$ = -12.9 (c = 1.0, CH_2Cl_2, 94% ee). Spectroscopic data are in accordance with literature values.[3]

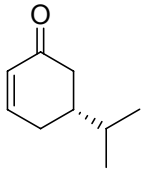
[3] G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993,** *115,* 830.



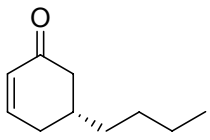
(*R*)-5-Methyl-cyclohex-2-enone 3a. The title compound was obtained following the general procedure and isolated after FC (CH_2Cl_2/Et_2O: 99/1) in 93% yield and 80% ee. $[\alpha]^{rt}_D$ = -74.6 (c = 0.5, $CHCl_3$, 80% ee), lit.[4] $[\alpha]^{rt}_D$ = -91.0 (c = 0.8, $CHCl_3$). The ee was determined 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; τ_R = 20.7 min, τ_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_2Cl_2/Et_2O: 99/1) in 98% yield and 94% ee. $[\alpha]^{rt}_D$ = -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; τ_R = 6.8 min, τ_S = 6.9 min). Spectroscopic data are in accordance with literature values.[6]



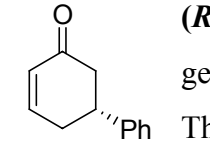
(*R*)-5-*iso*-Propyl-cyclohex-2-enone 3c. The title compound was obtained following the general procedure and isolated after FC (CH_2Cl_2/Et_2O: 99/1) in 56% yield and 96% ee. $[\alpha]^{rt}_D$ = -33.0 (c = 0.1, $CHCl_3$, 96% ee). The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T_1 = 70 °C; T_2 = 200 °C, rate = 10 °C/min; τ_R = 7.8 min, τ_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.



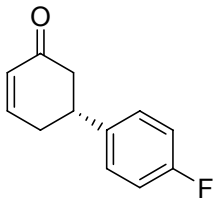
(*R*)-5-Butyl-cyclohex-2-enone 3d. The title compound was obtained following the general procedure and isolated after FC (CH_2Cl_2/Et_2O: 99/1) in 69% yield and 92% ee. $[\alpha]^{rt}_D$ = -44.9 (c = 0.5, $CHCl_3$, 92% ee), lit.[7] $[\alpha]^{rt}_D$ = -51.2 (c = 1.4,

[4] E. Friedrich, W. Lutz, *Angew. Chem.* **1977**, 426.
[5] I. Fleming, P. Maiti, C. Ramarao**,** *Org. Biomol. Chem.* **2003**, *1*, 3989.
[6] C. Böner, M. Dennis, E. Sinn, S. Woodward, *Eur. J. Org. Chem*. **2001**, 2435.
[7] M. Asoaka, K. Takenouchi, H. Takei, *Chem. Lett.* **1988**, 921

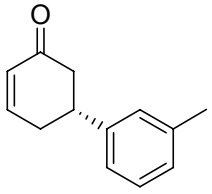
$CHCl_3$). The ee was determined by GC analysis on a Chromopak CP-Chirasil Dex CB-column (T_1 = 70 °C; T_2 = 120 °C, rate = 5 °C/min; T_3 = 136 °C, rate = 2 °C/min; τ_R = 15.8 min, τ_S = 15.9 min). Spectroscopic data are in accordance with literature values.[8]



(*R*)-5-Phenylcyclohex-2-enone 3e. The title compound was obtained following the general procedure and isolated after FC (hexane/Et_2O: 80/20) in 63% yield and 94% ee. The ee was determined on the parent compound **7**. $[\alpha]^{rt}_D$ = -39.5 (c = 1.0, $CHCl_3$, 94% ee), lit.[9] $[\alpha]^{rt}_D$ = -43.0 (c = 1.25, $CHCl_3$). Spectroscopic data are in accordance with literature values.[10]

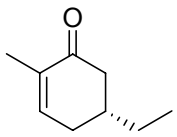


(*R*)-5-(4-Fluorophenyl)cyclohex-2-enone 3f. The title compound was obtained following the general procedure and isolated after FC (hexane/AcOEt: 85/15) in 65% yield and 95% ee. The ee was determined by HPLC analysis on 2 Daicel Chiralpak AD columns in a row (hexane/*i*-PrOH: 95/5, flow 0.8 mL/min; τ_S = 24.1 min, τ_R = 25.0 min). $[\alpha]^{rt}_D$ = -29.1 (c = 1.0, $CHCl_3$, 95% ee). HRMS: $C_{12}H_{11}FNaO$ - $[M+Na^+]$ calcd.: 213.0692, found: 213.0680. δ_H (400 MHz; $CDCl_3$) 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); δ_C (100 MHz; $CDCl_3$) 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.

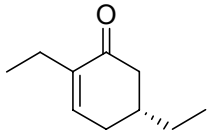


(*R*)-5-*m*-Tolylcyclohex-2-enone 3g. The title compound was obtained following the general procedure and isolated after FC (hexane/AcOEt: 90/10) in 72% yield and 94% ee. The ee was determined by HPLC analysis on 2 Daicel Chiralpak AD columns in a row (hexane/*i*-PrOH: 98/2, flow 0.5 mL/min; τ_R = 29.7 min, τ_S = 30.7 min). $[\alpha]^{rt}_D$ = -34.2 (c = 0.5, CH_2Cl_2, 94% ee). HRMS: $C_{13}H_{14}NaO$ - $[M+Na^+]$ calcd.: 209.0942, found: 209.0947. δ_H (400 MHz; $CDCl_3$) 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); δ_C (100 MHz; $CDCl_3$) 21.4, 33.7, 40.9, 44.9, 123.6, 127.4, 127.7, 128.6, 129.7, 138.3, 143.1, 149.6, 199.3.

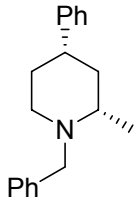
[8] G. Hareau, M. Koiwa, S, Hikichi, F. Sato, *J. Am. Chem. Soc*. **1999**, *121*, 3640.
[9] M. Moriya, T. Kamikubo, K. Ogasawara, *Synthesis* **1995**, *2*, 187.
[10] A. P. Rutherford, C. S. Gibb, R. C. Hartley, J. M. Goodman, *J. Chem. Soc. Perkin Trans. 1* **2001**, *9*, 1051.



(*R*)-5-Ethyl-2-methyl-cyclohex-2-enone 3h. The title compound was obtained following the general procedure and isolated after FC (hexane/Et_2O: 80/20) in 82% yield and 91% ee. $[\alpha]^{rt}_D$ = -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; τ_R = 14.5 min, τ_S = 16.3 min). δ_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); δ_C (100 MHz; $CDCl_3$) 11.0, 15.8, 28.5, 32.2, 37.3, 44.3, 135.5, 145.0, 200.42.

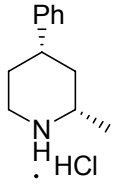


(*R*)-2,5-Diethylcyclohex-2-enone 3i. The title compound was obtained following the general procedure isolating the intermediate Michael adduct; the title compound was purified by FC (Et_2O/pentane: 1/10) in 74% overall yield and 89% ee. The ee was determined by GC analysis on an Astec G-TA chiral stationary 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; τ_R = 14.2 min, τ_S = 14.4 min). $[\alpha]^{rt}_D$ = -10.1 (c = 1.0, $CHCl_3$, 89% ee). HRMS: $C_{10}H_{16}NaO$ - $[M+Na^+]$ calcd.: 175.1099, found: 175.1093. δ_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); δ_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, β-ketoester **1a** (0.25 mmol) was added to a mixture of catalyst **4** (0.025 mmol, 10 mol%) and α,β-unsatured aldehyde **2** (0.37 mmol). After 5 h CH_2Cl_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, $NaBH_3CN$ (0.75 mmol, 3 equiv.) and benzylamine (1M in MeOH, pH ≈6-7; 0.37 mmol, 1.5 equiv.) were added. After 5 min $NaBH_3CN$ (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_4Cl, 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**. $[\alpha]^{rt}_D$ = -57.2 (c = 1.0, CH_2Cl_2, 94% ee). HRMS: $C_{19}H_{24}N$ - $[M+H^+]$ calcd.: 266.1909, found: 266.1919. δ_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); δ_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_2CO_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.

[11] M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005,** *127,* 1313.