Supporting information for
“Organocatalytic Regioselective Michael Additions of Cyclic Enones via Asymmetric Phase Transfer Catalysis.”
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Experimental Section

General methods. The $^1$H NMR and $^{13}$C NMR spectra were recorded at 200 MHz and 50 MHz respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for $^1$H NMR and for $^{13}$C NMR relative to the central CDCl$_3$ resonance ($\delta = 77.5$). Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). The enantiomeric excess (ee) of the products was determined by HPLC (CHIRALPAK IB or whelk O1 (R,R) columns, see below for the single compounds) or CSP-GC using a GC-FID 5890 Hewlett-Packard series II. Chiral column: MEGA (diacetyl $\tau$-butylsilyl $\beta$-CAX 30%) 25m x 0.25 mm; head column pressure: 100 kPa, gas carrier He, isotherm at 180°C.

Materials. Analytical grade solvents were used as received. All commercially available reagents were used as received. Compounds 1, 4, 5, 7, 8, 10, 3a, 3b, 3c, 3d, 3e are commercially available and were used as received. These compounds were prepared according to standard literature procedures (reaction of cinchonine with the corresponding commercially available benzyl bromides in refluxing toluene and precipitation of the ammonium salt upon addition of ether): 3f, 3g, 3h, 3i. A new procedure has been used for catalysts: 3j, 3k, 3l, 3m, 3n, 3o. Compound 10 has been prepared according to standard literature procedure.

General procedure for the enantioselective dimerization of enones catalyzed by 3a-o. Catalysts 3a-o (0.065 mmoles, 12.5 mol%, see table 1) and enones 1, 4, 5, 7, 8 were placed in a test tube and toluene (4 mL) was added. After 5 minutes, a solution of 50% KOH (2 mL) was added dropwise taking care that the temperature of the reaction mixture did not exceed 30 C. The resulting biphasic mixture was stirred at rt for 24 h. In the case of enone 1, no starting material could be detected after 6 h with most of the catalysts employed. The organic layer was separated and directly purified by FC on silica gel (petrol ether, then petrol ether: ether 50: 50). The resulting dimerization products 2, 6, 9 were analyzed to determine ee by CSP-GC or HPLC.
Yields and ee: see table 1. ee was determined by CSP-GC using a chiral MEGA (diacetyl t-butyldisilyl β-CAX 30%) 25m x 0.25 mm column: isotherm 180 °C for 16 min; 2: $\tau_{\text{minor}} = 15.0$ min, $\tau_{\text{major}} = 15.4$ min; (employing catalyst 3a, 47%ee). The spectral data for this compound were identical to that reported in the literature. [see ref. 7b in the manuscript] 

$[\alpha]_{D}^\text{rt} = -3$ (sample with 47% ee, prepared using general procedure at rt and employing as the catalyst 3a, benzyl cinchoninium chloride); (c= 0.0035 g/ 1 mL, CH$_2$Cl$_2$)

Yield: 80% with catalyst 3n and 75% with catalyst 3o;

$^1$H NMR $\delta$ (CDCl$_3$) 6.42 (t, 1H, J 6.4 Hz), 2.90 – 2.80 (m, 1H), 2.59 – 2.29 (m 6H), 1.95 – 1.38 (m, 12H).

$^{13}$C NMR (CDCl$_3$) 213.54, 204.61, 148.38, 139.50, 49.86, 43.69, 42.69, 38.18, 37.34, 29.35, 27.18, 24.78, 24.26, 21.37.

$[\alpha]_{D}^\text{rt} = +18$ (sample with -73% ee, prepared using general procedure at rt and employing as the catalyst 3o, 3,5,4-trimethoxybenzyl cinchonidinium bromide); (c= 0.0035 g/ 1 mL, CH$_2$Cl$_2$)

HRMS calc. C$_{14}$H$_{20}$O$_2$ $^+$: 220.1463; found: 220.1464.
Yields and ee: see table 2. ee was determined by CSP-GC using a chiral MEGA (diacetyl t-butyldimethyl β-CAX 30%) 25m x 0.25 mm column: isotherm 180 °C for 30 min; 9: \[ \tau_{major} = 23.0 \text{ min, } \tau_{minor} = 25.9 \text{ min} \] (employing catalyst 3a, 47%ee).

\(^1\)H NMR \( \delta \) (CDCl3) \( 5.95 \) (t, 1H, J 1.6 Hz), \( 2.40 – 2.23 \) (m, 4H), \( 1.97 – 1.91 \) (m, 2H), \( 1.45 – 1.04 \) (m, 3H) 1.20 (s, 3H).

\(^13\)C NMR (CDCl3) 218.04, 209.75, 179.89, 129.87, 53.04, 52.62, 44.37, 41.49, 36.75, 35.89, 32.27, 26.89.

\([\alpha]\) \( ^{\text{D}} \) = -6.5 (sample with 47% ee prepared using general procedure at rt and employing as the catalyst 3a, benzyl cinchonidinium chloride); (c= 0.0046 g/ 1 mL, CH2Cl2)

HRMS calc. C\(_{12}\)H\(_{16}\)O\(_2\)\(^+\): 192.1150; found: 192.1152.

Procedure for the addition of 2-cyclohexenone 1 to 10:

Catalyst 3n or 3o (0.065 mmoles, 12.5 mol%), enones 10 (0.52 mmol, 1eq.) and 1 (0.52 mmol, 1eq.) were placed in a test tube and toluene (4 mL) was added. After 5 minutes, a solution of 50% KOH (2 mL) was added dropwise taking care that the temperature of the reaction mixture did not exceed 30 °C. More 2-cyclohexenone (0.52 mmol, 1eq.) was added twice after 5 and 10 hours. The resulting biphasic mixture was stirred at rt for 24 h. The organic layer was separated and directly purified by FC on silica gel (petrol ether, then petrol ether: ether 50: 50). The resulting products 11 was analyzed to determine ee. 1.20 And 1.15 eq. of 2 were isolated as well employing catalyst 3n or 3o, respectively.

The ee was determined by HPLC using Chiralpak IB column (hexane/i-PrOH 90:10); flow rate 0.75 mL/min; 11: \( \tau_{major} = 8.0 \) min; \( \tau_{minor} = 8.8 \) min. (employing catalyst 3n, 47%ee); 11: \( \tau_{minor} = 8.0 \) min; \( \tau_{major} = 8.8 \) min. (employing catalyst 3m, 65%ee);

Yield: 95% with catalysts 3n and 94% with catalysts 3m.

\(^1\)H NMR \( \delta \) (CDCl3) 7.28 – 7.13 (m, 5H), 6.76 (t, 1H, J 4.2 Hz), 4.54 (t,1H J 5.9Hz), 2.45 – 2.35 (m 4H), 2.02 (d, 2H, J 5.9Hz), 1.13-1.08 (m, 2H), 1.10 (s, 9H).

\(^13\)C NMR (CDCl3) 212.91, 197.98, 145.02, 142.77, 141.66, 128.06 (2C), 127.78 (2C), 126.04, 43.89, 40.81, 39.90, 38.70, 26.10 (3C), 25.98, 22.56.

\([\alpha]\) \( ^{\text{D}} \) = -22 (sample with 47% ee, prepared using general procedure at rt and employing as the catalyst 3n, 3,5,4-tribenzyloxybenzyl cinchoninium bromide) (c= 0.0305 g/ 1 mL, CH2Cl2)

Determination of absolute configuration:

The absolute configuration of 2 has been determined by correlation with known compound 12, according to the scheme below:

\[
\text{KOH}_{\text{aq}}, \text{Toluene} \quad \text{rt,}
\]

1. \( \text{RuCl}_3, \ \text{NaIO}_4, \ \text{CH}_3\text{CN, H}_2\text{O, CCl}_4 \ \text{rt, 12h}\)
2. \( \text{K}_2\text{CO}_3, \text{MeI, DMSO, rt, 12h}\)

Overall Y=30%

12: \([\alpha]_{\text{D}}^{560} = -24 \ (c= 0.059 \ \text{g/ mL, EtOH}) \ [\text{ref 6}]\)
12: \([\alpha]_{\text{D}}^{\text{rt}} = -2 \ (c= 0.059 \ \text{g/ mL, EtOH}) \ [\text{ref 6}]\)

Since compound 12 has been reported to have negative rotation by several authors\(^6\) we assigned the absolute configuration to our product to be (\(R\)).

Catalyst 3i:

Yield: 72%;

\( ^1\text{H NMR} \ \delta \ (\text{MeOD}) \ 8.85 \ (d, \ 1H, \ J \ 4.6 \ Hz), \ 8.25 - 8.20 \ (m, \ 1H), \ 8.04 - 7.99 \ (m, \ 1H), \ 7.87 \ (d, \ 1H, \ J \ 4.6 \ Hz), \ 7.80 - 7.70 \ (m, \ 2H), \ 7.43 - 7.35 \ (m, \ 1H), \ 7.25 - 7.17 \ (m, \ 2H), \ 7.04 - 7.02 \ (m, \ 1H), \ 6.52 \ (s, \ 1H), \ 6.05 - 5.88 \ (m, \ 1H), \ 5.22 \ (d, \ 1H, \ J \ 6.0 \ Hz), \ 5.14 \ (m, \ 1H), \ 5.03 \ (m, \ 2H), \ 4.37 - 4.25 \ (m, \ 1H), \ 3.97 - 3.79 \ (m, \ 6H), \ 3.64 \ (dd, \ 1H, \ J \ 11.4, \ 11.6 \ Hz), \ 3.1 \ (m, \ 1H), \ 2.60 - 2.31 \ (m, \ 2H), \ 1.84 - 1.71 \ (m, \ 3H), \ 1.11 - 0.80 \ (m, \ 1H). \)

\( ^{13}\text{C NMR} \ \delta \ (\text{DMSO}) \ 159.11, \ 149.95, \ 149.86, \ 147.36, \ 144.79, \ 136.86, \ 129.66, \ 129.44, \ 129.08, \ 127.15, \ 125.72, \ 124.09, \ 123.95, \ 119.84, \ 119.28, \ 116.72, \ 115.39, \ 66.81, \ 64.26, \ 61.56, \ 55.87, \ 55.27, \ 53.66, \ 36.44, \ 26.10, \ 22.80, \ 20.60. \)

\([\alpha]_{\text{D}}^{\text{rt}} = +139 \ ( c= 0.042 \ \text{g/ mL, CH}_3\text{OH})\)

HRMS calc. \( \text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_2^+ \): 415.2386; found: 415.2360.
Catalyst 3g:

![Catalyst 3g](image)

Yield: 76%;

**$^{1}$H NMR** δ (DMSO) 8.88 (d, 1H, J 4.37 Hz), 8.37 (d, 1H, J 8.03 Hz), 8.00 (d, 1H, J 8.03 Hz), 7.75 – 7.40 (m, 5H), 6.81 (d, 1H, J 3.1Hz), 6.41 (s, 1H), 5.98 - 5.80 (m, 1H), 5.24 – 5.00 (m, 4H), 4.15 – 3.89 (m, 3H), 3.40 – 3.35 (m, 1H), 3.15-3.00 (m, 1H), 2.58-2.45 (m, 1H), 2.21- 2.09 (m, 1H), 1.75-1.66 (m, 3H), 0.97 – 0.82 (m, 1H).

**$^{13}$C NMR** (DMSO) 159.09, 149.83, 147.34, 144.77, 136.84, 129.62, 129.41,129.02, 127.13, 125.71, 124.07, 123.92, 119.82, 119.25, 116.70, 115.36, 66.82, 64.26, 61.53, 55.86, 55.25, 53.64, 36.44, 26.09, 22.84, 20.60.

$[\alpha]_{D}^{\text{rt}} = + 135$ (c= 0.046 g/1 mL, CH$_3$OH)

**HRMS** calc. C$_{26}$H$_{26}$F$_{3}$N$_{2}$O$: 439.1992; found: 439.1962.

**General procedure for the Preparation of catalysts 3k-o:**

**CAUTION:** alkoxy substituted benzyl bromides are unstable in basic solutions and if solvent is removed. They are very lachrymatory and their preparation must be done in fume hood. This procedure allows using directly the toluene solution of the corresponding bromides.

Either piperonyl alcohol, (for catalysts 3k) 3,4 dibenzyloxy alcohol,$^7$ (for catalysts 3l) or 3,4,5,-trimethoxybenzyl alcohol,$^8$ (for catalysts 3m and 3o) or 3,4,5-tribenzyloxybenzyl alcohol$^9$ (for catalysts 3n) (1 mmol) was placed in a flask, dissolved in 10 mL of toluene and 5 mL of HBr were added dropwise at rt. The reaction mixture was stirred for 0.5 h and the organic layer separated and added in a separate flask to cinchonine (for catalysts 3k-n) or cinchonidine (for catalysts 3o) (0.7 mmol). 4 mL of DMF was added in the preparation of catalysts 3k-o. The suspension was refluxed for 5 hours. After a TLC check showed that all cinchonine reacted, the reaction was cooled at rt, diethyl ether was added to precipitate the ammonium salts. The precipitate was filtered, washed twice with a 1:1 mixture ether: petrol ether to remove DMF, toluene and traces of benzyl bromides dried and used.
Catalyst 3k:

Yield: 85%;

$^1$H NMR $\delta$ (MeOD) 8.86 (d, 1H, J 4.3 Hz), 8.25 - 8.20 (m, 1H), 8.05 – 8.00 (m, 1H), 7.87 (d, 1H, J 4.5 Hz), 7.81 – 7.70 (m, 2H), 7.14 – 7.09 (m, 2H), 6.93 (d, 1H, J 7.1 Hz), 6.51 (s, 1H), 6.02 – 5.88 (m, 4H), 5.25 (d, 1H, J 6.0 Hz), 5.15 (d, 1H, J 1.6 Hz), 4.89 (m, 2H), 4.32 – 4.28 (m, 1H), 3.94 – 3.71 (m, 2H), 3.61 (dd, 1H, J=12.4, 12.6 Hz), 3.12 - 2.96 (m, 1H), 2.61 – 2.31 (m, 2H), 1.86 – 1.71 (m, 3H), 1.04 – 0.81 (m, 1H).

$^{13}$C NMR (DMSO) 149.85, 148.47, 148.11, 147.33, 144.88, 136.92, 129.42, 129.09, 128.04, 127.15, 124.10, 123.91, 120.91, 119.83, 116.71, 113.22, 118.26, 101.49, 66.72, 64.29, 61.60, 55.60, 53.36, 36.46, 26.16, 22.82, 20.57.

$[\alpha]_D^{19}$ = + 99 (c= 0.047 g/ 7 mL, CH$_3$OH)

HRMS calc. C$_{27}$H$_{29}$N$_2$O$_3$$^+$: 429.2173; found: 429.2175.

Catalyst 3l:

Yield: 80%;

$^1$H NMR $\delta$ (CDCl$_3$) 8.79 (d, 1H, J 4.5 Hz), 8.22 - 8.17 (m, 1H), 7.81 (d, 1H, J 4.5 Hz), 7.60 (d, 2H, J 7.0 Hz), 7.49 – 7.44 (m, 1H), 7.41 – 7.29 (m, 8H), 7.22 – 7.11 (m, 2H), 6.96 – 6.91 (m, 1H), 6.83 – 6.73 (m, 1H), 6.56 (m, 2H), 6.40 (m, 1H), 5.96 – 5.68 (m, 2H), 5.31 – 5.02 (m, 8H), 4.28 – 4.17 (m, 1H), 4.07 – 3.17 (m, 1H), 3.79 – 3.67 (m, 1H), 3.10 – 2.99 (m, 1H), 2.13 – 1.92 (m, 3H), 1.50 – 1.34 (m, 2H), 0.79 – 0.59 (m, 1H).

$^{13}$C NMR (CDCl$_3$) 149.79, 149.21, 147.10, 146.82, 144.33, 137.11, 136.90, 135.37, 129.27, 128.37 (3C), 128.20 (2C), 128.08, 127.67 (2C), 127.46, 127.16 (3C), 127.05, 126.83, 123.32, 123.14,
119.50, 119.06, 117.79, 112.97, 70.43, 69.86, 66.30, 65.44, 61.27, 55.78, 53.17, 37.81, 27.09, 23.67, 21.60.

\[ \alpha_{\text{rt}} \] D = +83 (c= 0.049 g/1.5 mL, CH₃OH)

HRMS calc. C₄₀H₄¹N₂O₃⁺: 597.3117; found: 597.3114.

Catalyst 3m:

Yield: 95 %;

\(^1\)H NMR δ (CDCl₃) 8.86 (d, 1H, J 4.7 Hz), 8.34 (d, 1H, J 6.3 Hz), 7.98 – 7.95 (m, 1H), 7.76 (d, 1H, J 7.2 Hz), 7.18 – 7.10 (m, 2H), 6.98 (m, 2H), 6.79 (s, 1H), 6.46 (s, 1H), 6.04 – 5.77 (m, 2H), 5.33 – 5.16 (m, 2H), 4.16 – 3.99 (m, 2H), 3.87 (m, 12H), 3.53 – 3.42 (m, 1H), 2.42 – 2.28 (m, 1H), 1.80 – 1.67 (m, 3H), 0.76 – 0.62 (m, 1H).

\(^{13}\)C NMR (CDCl₃) 152.57 (2C), 149.12, 146.72, 144.11, 138.84, 135.17, 129.14, 128.24, 127.15, 123.17, 122.99, 121.57 (2C), 119.39, 117.85, 110.83, 66.61, 65.20, 61.86, 60.26, 56.27 (3C), 53.64, 37.82, 26.82, 25.54, 21.36.

\[ \alpha_{\text{rt}} \] D = +121 (c= 0.023 g/1 mL, CHCl₃)

HRMS calc. C₂₉H₃₅N₂O₄⁺: 475.2591; found: 475.2599.

Catalyst 3o:

Yield: 95 %;

\(^1\)H NMR δ (CDCl₃) 8.84 (d, 1H, J 4.5 Hz), 8.10 – 8.06 (m, 1H), 7.80 (d, 1H, J 4.6 Hz), 7.76 – 7.71 (m, 1H), 7.06 (m, 2H), 6.51 (m, 2H), 5.63 (m, 2H), 5.43 – 5.35 (m, 1H), 5.27 – 5.19 (m, 1H), 4.96 – 4.90 (m, 1H), 4.02 – 3.94 (m, 2H), 3.86 (m, 12H), 3.79 - 3.64 (m, 2H), 3.25 – 3.20 (m, 1H), 2.58 – 2.46 (m, 1H), 1.99 – 1.88 (m, 3H), 1.13 – 1.00 (m, 1H).
$^{13}$C NMR (CDCl$_3$): 152.85 (2C), 149.33, 147.14, 144.42, 139.12, 136.11, 129.52, 128.66, 127.50, 123.50, 122.82, 121.80, 119.66, 117.62, 67.33, 64.53, 62.70, 60.44, 56.52 (3C), 50.70, 37.79, 26.33, 24.98, 21.97.

$[\alpha]_{	ext{D}}^{19}$ = -120 (c = 0.016 g/1 mL, CHCl$_3$)

HRMS calc. C$_{29}$H$_{35}$N$_2$O$_4$+: 475.2591; found: 475.2570.

Catalyst 3n:

Yield: 75 %;

$^1$H NMR δ (CDCl$_3$) 8.87 (d, 1H, J 4.5 Hz), 8.28 - 8.23 (m, 1H), 7.92 (d, 1H, J 4.5 Hz), 7.61 – 7.50 (m, 6H), 7.33 – 7.18 (m, 13H), 7.08 – 7.03 (m, 2H), 6.79 – 6.76 (m, 1H), 6.46 (s,1H), 6.06 (d, 1H, J 11.4 Hz), 5.91 – 5.74 (m, 1H), 5.31 – 5.01 (m, 10H), 4.33 – 4.23 (m, 1H), 4.09 – 4.00 (m, 1H), 3.71 – 3.60 (m, 1H), 3.14 (1H, J 11.8 Hz), 2.17 – 1.98 (m, 1H), 1.59 – 1.30 (m, 3H), 0.72 – 0.59 (m, 1H).

$^{13}$C NMR (CDCl$_3$) 151.72 (2C), 148.79, 146.21, 145.16, 139.44, 138.08, 136.85, 135.37, 128.96, 128.55, 128.28 (4C), 128.09 (2C), 128.00(2C), 127.77(4C), 127.73, 127.65 (2C), 127.42 (2C), 123.39, 123.14, 121.48, 119.64, 118.05, 112.92, 74.85, 70.39 (2C), 66.67, 65.59, 61.80, 56.15, 53.51, 37.91, 27.10, 23.87, 21.77.

$[\alpha]_{	ext{D}}^{19}$ = +100 (c= 0.0115 g/1 mL, CH$_3$OH)

HRMS calc. C$_{47}$H$_{47}$N$_2$O$_4$+: 703.3536; found: 703.3541.

References

Copies of NMR Spectra: