Catalytic Asymmetric Hydrolysis: Asymmetric Hydrolytic Protonation of Enol Esters Catalyzed by Phase-Transfer Catalysts

Yamamoto, Eiji
Department of Chemistry, Kyushu University

Nagai, Ayano
Department of Chemistry, Kyushu University

Hamasaki, Akiyuki
Department of Chemistry, Kyushu University

Tokunaga, Makoto
Department of Chemistry, Kyushu University

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Asymmetric Ester Hydrolysis: Catalytic Asymmetric Protonation of Enolesters Catalyzed by Phase Transfer Catalysts

Eiji Yamamoto, Ayano Nagai, Akiyuki Hamasaki, Makoto Tokunaga*
Department of Chemistry, Graduate School of Science, Kyushu University, Fukuoka 812-8581, Japan
E-mail: mtok@chem.kyushu-uiv.jp

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1. General.

Unless otherwise stated, all the reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry solvents. Commercial reagents were used as received. $^1$H and $^{13}$C NMR spectra were recorded on a JEOL spectrometer ECS-400, ECS-600 and AL-400. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ap = apparent, sex =sextet, sep = septet), integration, coupling constant (Hz) and assignment. The enantiomeric excesses were determined by GC or HPLC analysis employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the appropriate racemic mixtures. GC analysis was carried out using Agilent GC 6850 series II equipped with InertCap CHIRAMIX Column (length 30 m, i.D. 0.25 mm, df. 0.25 μm) from GL Sciences Inc. and CHIRASIL-DEX CB (length 25 m, i.D. 0.25 mm, df. 0.25 μm) from Varian using helium as a carrier gas. GC yields were determined by employing HP-1 (length 30 m, i.D. 0.320 mm, df. 0.25 μm) or HP-INNOWAX (length 30 m, i.D. 0.320 mm, df. 0.25 μm) column from Agilent Technologies using helium as a carrier gas. FAB-MS analysis was performed with an Ultrahigh Performance Mass Spectrometer JMS-HX110A in Institute for Materials Chemistry and Engineering (IMCE). HPLC analysis was performed on a JASCO LC-2000 Plus Series equipped with a variable wavelength detector using chiral stationary columns (Chiracel AD-H, 0.46 cm x 25 cm) from Daicel. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Chromatography was performed on silica-gel (Kanto Chemicals, Silica gel 60N, spherical, neutral; particle size 40–100 μm). Abbreviations; Bn = benzyl, conversion = conv, enantiomeric excess = ee, eq = equiv, er = enantiomer ratio, DMAP = N,N-dimethylaminopyridine, MTPACl = Methoxy-1-(trifluoromethyl)phenylacetyl chloride, piv = pivaloyl, product = pro, RT = room temperature, substrate = sub.


CDCl₃, CD₃OD and C₆D₆ were used as solvents for NMR analyses. Chloroform was purified prior to use following the guidelines of Perrin and Armarego. Pyridine (anhydrous), CH₂Cl₂ (anhydrous) and THF (anhydrous, stabilizer free) were used as anhydrous solvents. N-9-anthracenylmethyl-cinchonidinium chloride (1a, Sigma-Aldrich), N-benzylcinchonidinium chloride (1d, TOKYO CHEMICAL INDUSTRY CO., LTD.), N-benzylcinchoninium chloride (1e, TOKYO CHEMICAL INDUSTRY CO., LTD.) and cinchonidine (Wako Pure Chemical Industries, Ltd.) were used as received. All other chemical reagents were used in commercial grade. Catalyst 1b, 1c, 2-isopropyl-cycloheptanone (3h), 2-allyl-4,4-dimethyl-cyclohexanone and 2-cycloheptylidene-1,1-dimethylhydrazine were prepared according to the reported procedures.

3. Preparation and Characterization of enolesters

3-1. Synthesis of 2-substituted ketones

4,4-dimethyl-2-propylcyclohexanone (3d)

2-allyl-4,4-dimethylcyclohexanone (570 mg, 3.43 mmol, 1 equiv) in 1-butanol (3.43 mL) was placed in a glass tube with a magnetic stirring bar. RuCl₂(PPh₃)₃ (16.4 mg, 0.017 mmol, 0.5 mol%) was added and the tube was placed in an autoclave. Hydrogen was introduced into the autoclave at a pressure of 2 MPa after hydrogen replacement, then stirred for 11 h at 30 °C. The resultant solution was purified by silica-gel column chromatography (Hexane : Et₂O = 10:1) to give 3d (566 mg, 3.36 mmol, 98%) as yellow oil. $^1$H NMR (400 MHz, CDCl₃): δ = 2.44 (td, J = 6.4, 14.2 Hz, 1 H), 2.36 (dt, J = 6.0, 6.0 Hz, 1 H), 2.22 (dt, J = 3.2, 14.2 Hz, 1 H), 1.80-1.55 (m, 4 H), 1.34-1.22 (m, 3 H), 1.19 (s, 3 H), 1.06 (tq, 6.9, 6.9 Hz, 1 H), 0.99 (s, 3 H), 0.87 (t, J = 7.4 Hz, 3 H). $^{13}$C NMR (100 MHz, CDCl₃): δ = 214.1, 46.8, 45.8, 40.2, 38.6, 31.6, 31.2, 30.9, 24.7, 20.3, 14.3. Anal. Calcd (%) for C₁₁H₂₂O: C, 78.51; H, 11.98. Found: C, 78.24; H, 11.98.
2-propylcycloheptanone \(^{(3f)}\)

BuLi (1.67 M in hexane, 5.25 mmol, 3.14 mL, 1.05 equiv) was added dropwise to a stirred solution of 2-cycloheptylidene-1,1-dimethylhydrazine (771 mg, 5.0 mmol, 1 equiv) in THF (anhydrous, 20 mL) at \(-5^\circ C\) under a nitrogen atmosphere and stirred for 1 h. After that, propyl iodide (893 mg, 512 \(\mu\)L, 5.25 mmol, 1.05 equiv) was added dropwise to the solution, and then the resulting solution was allowed to warm to RT and stirred for 4 h. Distilled water was added to the resultant solution and cooled to 0 \(^\circ C\). Then the solution was acidified with 1N HCl aq to reach pH 1-2 (The mixture was homogenized by adding THF and methanol). After stirring at 45 \(^\circ C\) for another 2 h, the solution was extracted with diethylether. The organic extracts were combined, dried over Na\(_2\)SO\(_4\) and concentrated. The resultant crude product was purified by silica-gel chromatography (hexane:Et\(_2\)O = 20:1) to give \(3f\) (560 mg, 3.63 mmol, 73\%) as pale yellow oil. \(^{13}\)C NMR was in agreement with the literature. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.54-2.34\) (m, 3 H), 1.89-1.76 (m, 4 H), 1.68-1.48 (m, 2H), 1.40-1.17 (m, 6 H), 0.86 (t, \(J = 7.4\) Hz, 3 H). Anal. Calcd (%) for C\(_{10}\)H\(_{18}\)O: C, 77.87; H, 11.76. Found: C, 78.01; H, 11.83.

2-butylcycloheptanone \(^{(3g)}\)

BuLi (1.67 M in hexane, 5.25 mmol, 3.14 mL, 1.05 equiv) was added dropwise to a stirred solution of 2-cycloheptylidene-1,1-dimethylhydrazine (771 mg, 5.0 mmol, 1 equiv) in THF (anhydrous, 20 mL) at \(-5^\circ C\) under a nitrogen atmosphere and stirred for 1 h. After that, butyl bromide (719 mg, 564 \(\mu\)L, 5.25 mmol, 1.05 equiv) was added dropwise to the solution, and then the resulting solution was allowed to warm to RT and stirred for 4 h. Distilled water was added to the resultant solution and cooled to 0 \(^\circ C\). Then the solution was acidified with 1N HCl aq to reach pH 1-2 (The mixture was homogenized by adding THF and methanol). After stirring at 45 \(^\circ C\) for another 2 h, the solution was extracted with diethylether. The organic extracts were combined, dried over Na\(_2\)SO\(_4\) and concentrated. The resultant crude product was purified by silica-gel chromatography (hexane:Et\(_2\)O = 20:1) to give \(3g\) (643 mg, 3.82 mmol, 77\%) as pale yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.53-2.32\) (m, 3 H), 1.90-1.77 (m, 4 H), 1.68-1.50 (m, 2H), 1.38-1.14 (m, 8 H), 0.86 (t, \(J = 6.9\) Hz, 3 H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 216.9, 52.5, 42.7, 32.2, 31.3, 29.7, 29.5, 28.5, 24.8, 20.5, 14.2\). Anal. Calcd (%) for C\(_{11}\)H\(_{20}\)O: C, 78.77; H, 11.76. Found: C, 78.01; H, 11.83.

3-2. Synthesis of enolesters

**Procedures:** A typical experimental procedure for the preparation of enolesters is described below. Aqueous HClO\(_4\) solution (60\%, 106.8 \(\mu\)L, 5 mol\%) was added to a mixture of 2-propylcyclohexanone \(3c\) (2.80 g, 20 mmol, 1 equiv) and chloroacetic acid anhydride (6.84 g, 40 mmol, 2 equiv) in CCl\(_4\) (12 mL) and CH\(_2\)Cl\(_2\) (12 mL) under air. The reaction mixture was stirred for 14 h at 30 \(^\circ C\). Then, Et\(_2\)O (50 mL) and saturated NaHCO\(_3\) aq (50 mL) were added to the reaction mixture and stirred for a few minutes. After that, the organic layer was separated and the aqueous layer was extracted with Et\(_2\)O (50 mL \(\times\) 3). Organic layers were combined and dried with Na\(_2\)SO\(_4\) followed by evaporation. The resultant crude product was purified by silica-gel column chromatography (Et\(_2\)O/Hexane) to give \(2c\) (3.73 g, 17.2 mmol, 86\%) as pale yellow oil.
2-ethylcyclohex-1-en-1-yl 2-chloroacetate (2b)

85% yield, yellow oil (4 equiv of 2-chloroacetic anhydride was used.)

\[\delta = 4.12 \text{ (s, 2 H), 2.15-2.12 (m, 4 H), 1.93 (q, J = 7.9 Hz, 2 H), 1.74-1.66 (m, 2 H), 1.65-1.57 (m, 2 H), 0.92 (t, J = 7.8 Hz, 3 H).}\]

\[^{13}\text{C NMR (400 MHz, CDCl}_3\):} \delta = 165.7, 141.4, 126.7, 40.9, 27.3, 26.9, 23.2, 23.1, 22.4, 12.0.\]


2-propylcyclohex-1-en-1-yl 2-chloroacetate (2c)

86% yield, yellow oil (2 equiv of chloroacetic anhydride was used.)

\[\delta = 4.11 \text{ (s, 2 H), 2.18-2.08 (m, 2 H), 2.08-2.00 (m, 2 H), 1.89 (t, 7.4 Hz, 2 H), 1.74-1.66 (m, 2 H), 1.66-1.56 (m, 2 H), 1.36 (sex, 6.0 Hz, 2 H), 0.85 (t, 7.4Hz, 3 H).}^{13}\text{C NMR (100 MHz, CDCl}_3\):} \delta = 165.7, 142.2, 125.2, 40.9, 32.1, 27.8, 26.9, 23.1, 22.4, 20.5, 14.1.\]

Anal. Calcd (%) for C\(_{11}\)H\(_{17}\)ClO\(_2\): C, 60.97; H, 7.91. Found: C, 61.25; H, 8.00.

4,4-dimethyl-2-propylcyclohex-1-en-1-yl 2-chloroacetate (2d)

94 %yield, pale yellow oil (3 equiv of 2-chloroacetic anhydride was used.)

\[\delta = 4.12 \text{ (s, 2 H), 2.18-2.11(m, 2 H), 1.90-1.80 (m, 4 H), 1.49-1.42 (m, 2 H), 1.39-1.28 (m, 2 H), 0.97-0.92 (m, 6 H), 0.88-0.80 (m, 3 H).}^{13}\text{C NMR (100 MHz, CDCl}_3\):} \delta = 165.8, 141.2, 123.9, 41.8, 40.9, 35.6, 32.1, 29.4, 27.9 (2 carbons), 24.5, 20.4, 14.0.\]

Anal. Calcd (%) for C\(_{13}\)H\(_{21}\)ClO\(_2\): C, 63.79; H, 8.65. Found: C, 64.06; H, 8.79.

[1,1’-bi(cyclohexan)]-1-en-2-yl 2-chloroacetate (2e)

82% yield, yellow oil (2 equiv of chloroacetic anhydride was used.)

\[\delta = 4.11 \text{ (s, 2 H), 2.34-2.27 (m, 1 H), 2.13-2.10 (m, 2 H), 2.03-2.00 (m, 2 H), 1.73-1.55 (m, 7 H), 1.46-1.40 (m, 2 H), 1.29-1.03 (m, 5 H).}^{13}\text{C NMR (100 MHz, CDCl}_3\):} \delta = 165.8, 140.8, 129.7, 41.0, 38.1, 30.3 (2 carbons), 27.0, 26.6 (2 carbons), 26.2, 23.8, 22.9, 22.5.\]


2-propycyclohept-1-en-1-yl 2-chloroacetate (2f)

84% yield, pale yellow oil (4 equiv of chloroacetic anhydride was used.)

\[\delta = 4.09 \text{ (s, 2 H), 2.30-2.28 (m, 2 H), 2.11-2.08 (m, 2 H), 1.92 (t, J = 7.3 Hz, 2 H), 1.72-1.50 (m, 6 H), 1.34 (tq, 7.4 Hz, 7.4 Hz, 2 H), 0.84 (t, 7.3 Hz, 3 H).}^{13}\text{C NMR (100 MHz, CDCl}_3\):} \delta = 165.9, 146.6, 129.9, 40.9, 34.5, 33.0, 31.5, 31.1, 26.4, 25.3, 20.5, 14.0.\]

2-butylcyclohept-1-en-1-yl 2-chloroacetate (2g)

85% yield, pale yellow oil (4 equiv of chloroacetic anhydride was used.)

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 4.10 \text{ (s, 2 H), 2.33-2.27 (m, 2 H), 2.13-2.07 (m, 2 H), 1.95-1.88 (m, 2 H), 1.73-1.65 (m, 2 H), 1.65-1.57 (m, 2 H), 1.57-1.49 (m, 2 H). 1.34-1.29 (m, 4 H), 0.90-0.83 (t, 6.9 Hz, 3 H)} \]

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 166.0, 146.3, 130.2, 40.9, 33.0, 32.1, 31.5, 31.1, 29.5, 26.4, 25.3, 22.6, 14.1$. Anal. Calcd (%) for C$_{13}$H$_{21}$ClO$_2$: C, 63.79; H, 8.65. Found: C, 64.04; H, 8.62.

2-isopropylcyclohept-1-en-1-yl 2-chloroacetate (2h)

56% yield, yellow oil (2 equiv of chloroacetic anhydride was used.)

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 4.12 \text{ (s, 2 H), 2.69 (sep, 6.9 Hz, 1 H), 2.32-2.24 (m, 2H), 2.08-2.01 (m, 2 H), 1.75-1.65 (m, 2H), 1.65-1.55 (m, 2 H), 1.55-1.45 (m, 2 H). 0.88 (d, 6.9 Hz, 6 H).} \]

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 165.9, 144.9, 134.8, 40.9, 33.2, 32.0, 28.2, 26.9, 25.2, 25.1$. Anal. Calcd (%) for C$_{12}$H$_{19}$ClO$_2$: C, 62.58; H, 8.28.

2-cyclohexylcyclohept-1-en-1-yl 2-chloroacetate (2i)

66% yield, yellow oil (2 equiv of chloroacetic anhydride was used.)

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 4.11 \text{ (s, 2 H), 2.30-2.27 (m, 3 H), 2.09-2.06 (m, 2 H), 1.73-1.58 (m, 7 H), 1.50-1.03 (m, 5 H).} \]

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 166.0, 145.3, 134.5, 40.9, 39.4, 33.2, 32.0, 29.9 (2 carbons)$, 26.8, 26.37(2 carbons), 26.35, 26.1, 25.3. Anal. Calcd (%) for C$_{15}$H$_{23}$ClO$_2$: C, 66.53; H, 8.56. Found: C, 66.70; H, 8.59.

2-benzylcyclohept-1-en-1-yl 2-chloroacetate (2j)

96% yield, pale yellow oil (5 equiv of chloroacetic anhydride was used.)

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.30-7.23 (m, 2 H), 7.22-7.13 (m, 3 H), 4.11(s, 2 H), 3.30 (s, 2 H), 2.39 (m, 2 H), 2.06-2.01 (m, 2 H), 1.72-1.62 (m, 4 H) 1.45-1.36 (m, 2 H).} \]

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 166.1, 147.5, 138.9, 129.0 (2 carbons)$, 128.6, 128.5 (2 carbons), 126.3, 140.9, 38.2, 33.1, 31.3, 30.8, 26.3, 25.2. Anal. Calcd (%) for C$_{16}$H$_{19}$ClO$_2$: C, 68.93; H, 6.87. Found: C, 69.06; H, 6.89.

2-(4-methylpentyl)cyclohex-1-en-1-yl 2-chloroacetate (2k)

96% yield, pale yellow oil (4 equiv of chloroacetic anhydride was used)

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 4.10 (s, 2 H), 2.16-2.09 (m, 2 H), 2.11-2.07 (m, 2 H), 1.90 (t, J = 7.8 Hz, 2 H), 1.75-1.65 (m, 2 H), 1.65-1.56 (m, 2 H), 1.50 (sep, 6.4 Hz, 1 H), 1.36-1.27 (m, 2 H), 1.15-1.07 (m, 2 H), 0.84 (d, 6.4 Hz, 6 H).} \]

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 165.7, 142.0, 125.5, 40.9, 38.9, 30.3, 27.88, 27.85, 26.9, 25.1, 23.1, 22.7 (2 carbons), 22.4$. Anal. Calcd (%) for C$_{14}$H$_{23}$ClO$_2$: C, 64.98; H, 8.96. Found: C, 61.12; H, 7.89.
4. General procedure for asymmetric hydrolysis of enolesters catalyzed by PTC

Procedures: A typical experimental procedure for asymmetric hydrolysis of enolesters is described below. A round-bottomed screw cap tube (φ13x100 mm) equipped with a magnetic stir bar is charged N-9-anthracenylmethyl cinchonidinium chloride (6.1 mg, 0.01 mmol, 10 mol%) and CHCl₃ / Mesitylene (267 μL / 133 μL) solution under air, followed by the addition of 2-chloroethanol (6.7 μL, 0.10 mmol, 1 equiv) and 50 % KOH aq (100 μL). Then, the mixture was stirred at – 40 °C for 10 min followed by the addition of enolester 2c (21.6 mg, 0.10 mmol, 1 equiv). The efficiency of agitation has an effect on the yield and enantioselectivity. The reaction mixture was stirred for 13 h at – 40 °C. Then, the reaction mixture was immediately passed through a thin pad of silica-gel and the resultant crude product was purified by silica-gel column chromatography to give (R)-3c (13.9 mg, 99% yield, 92 : 8 er) followed by Chiral GC analysis (Conditions: InertCap CHIRAMIX, length 30 m, i. D. 0.25 mm, df. 0.25 μm; Detector: FID; Temperature: injector 200 °C, detector 240 °C, oven 40-180 °C, program 3 °C/min, t_major = 34.7 min, t_minor = 35.6 min). In case of 1 or 2 mmol-scale and 5 mmol-scale reaction, a 20-mL Schlenk flask and a 50-mL recovery flask were used for an alternative reaction container respectively.

5. Preliminary results of asymmetric hydrolysis of the acetyl enolate (2a).

Procedures: To the stirred solution of 1a (6.1 mg, 0.1 mmol, 10 mol%) and solid KOH (85% purity, 9.9 mg, 0.15 mmol, 1.5 equiv) was added 2a (18.2 mg, 0.1 mmol, 1 equiv) at RT. After the 1-14 h, the reaction mixture was directly passed through a short silica-gel pad. Resultant solution was analyzed by GC (according to general procedure for asymmetric hydrolysis of enolesters catalyzed by PTC.). Obtained preliminary results are shown below.

Table S1 Preliminary results of asymmetric hydrolysis

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>solvent</th>
<th>yield (%)</th>
<th>er</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>toluene</td>
<td>20</td>
<td>70:30</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>toluene</td>
<td>65</td>
<td>64:36</td>
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<tr>
<td>3</td>
<td>1</td>
<td>CHCl₃</td>
<td>10</td>
<td>79:21</td>
</tr>
</tbody>
</table>

a) GC yield. b) Less than 1% of EtOH was contained in the solvent.
6-1. Effects of alcohols

**Procedures:** N-9-anthracenylmethyl cinchonidinium chloride (6.1 mg, 0.01 mmol, 10 mol%) was added to the CHCl₃ (400 μL) under air, followed by the addition of an alcohol (0.05 mmol, 0.5 equiv) and 50% KOH aq (200 μL). Then, the mixture was stirred for 10 min at –40 °C followed by the addition of enolester 2c (21.6 mg, 0.10 mmol, 1 equiv). The reaction mixture was stirred for 1 h at –40 °C. Then, the reaction mixture was immediately passed through a thin pad of silica-gel. Resultant solution was analyzed by GC (according to general procedure for asymmetric hydrolysis of enolesters catalyzed by PTC.). Obtained results are shown below.

Table S1 Preliminary results of asymmetric hydrolysis

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>yield (%)&lt;sup&gt;a)&lt;/sup&gt;</th>
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<td>1</td>
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<td>30</td>
<td>85:15</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>64</td>
<td>85:15</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>66</td>
<td>87:13</td>
</tr>
<tr>
<td>4</td>
<td>PhCH₂</td>
<td>44</td>
<td>84:16</td>
</tr>
<tr>
<td>5</td>
<td>t-BuCH</td>
<td>2</td>
<td>76:24</td>
</tr>
</tbody>
</table>

<sup>a)</sup> GC yield.

6-2. Confirmation of mass balance of reaction products

Asymmetric hydrolysis of 3c was performed according to the general procedures. After 19.5 h, 1 N HCl aq (2 mL) was added to the reaction mixture in order to neutralize KOH aq in the solution. After that, internal standard (diglyme) was added to the solution. The resultant mixture was homogenized by addition of MeOH followed by GC analysis.

Table S3. Analysis of reaction products

<table>
<thead>
<tr>
<th>components</th>
<th>yield (%)&lt;sup&gt;a)&lt;/sup&gt;</th>
<th>components</th>
<th>yield (%)&lt;sup&gt;a)&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>0</td>
<td>99</td>
<td>Substrate</td>
<td>0</td>
</tr>
<tr>
<td>99</td>
<td>88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a)</sup> GC yield.

6-3. Asymmetric hydrolysis of enolesters with the in situ generated stoichiometric Q⁺OH⁻ reagent.

**Reaction in homogenous system (CHCl₃):** N-9-anthracenylmethyl cinchonidinium chloride (61 mg, 0.10 mmol, 1 equiv) in MeOH solution in 1-neck recovery flask (50 mL) was passed through a column filled with an anion exchange resin (Amberlyst A-26 OH form, 233 mg, 10 meq). MeOH of the eluate was distilled away under reduced pressure at 0 °C. The resultant dried residue was dissolved with CHCl₃ (0.5 mL) and repeatedly dried in vacuo for 15 min at 0 °C. Then, chloroform (1 mL) was added to the dried residue. The mixture was cooled down to –40 °C and stirred for 5 min. An enolester 2c (21.7 mg,
0.10 mmol, 1 equiv) was added to the solution and stirred for 4 h at the same temperature. After that, the reaction mixture was immediately passed through thin pad of silica-gel and an internal standard (tridecane) was added to the eluate. Then, the resultant mixture was analyzed by GC (\((R)-3c\), 99%, 89:11 er).

**Reaction in biphasic system (CHCl\textsubscript{3}/H\textsubscript{2}O):** N-9-anthracenylmethyl cinchonidinium chloride (61 mg, 0.10 mmol, 1 equiv) in MeOH solution was passed through a column filled with an anion exchange resin (Amberlyst A-26 OH form, 233 mg, 10 meq). MeOH of the eluate was distilled away under reduced pressure at 0 °C. The resultant dried residue in 1-neck recovery flask (50 mL) was dissolved with CHCl\textsubscript{3} (0.5 mL) and the solution was transferred to a screw vial using MeOH as a solvent. Solvents were removed under reduced pressure at 0 °C. The resultant dried residue was dissolved with CHCl\textsubscript{3} (0.5 mL) and removed repeatedly. Then the dried residue was further dried in vacuo for 15 min at 0 °C. Then, CHCl\textsubscript{3} (400 μL) and distilled water (100 μL) was added to the residue. The mixture was stirred for 2 min at 25 °C. An enolester 2c (21.7 mg, 0.10 mmol, 1 equiv) was added to the solution and stirred for 4 h at the same temperature. After that, the reaction mixture was immediately passed through thin pad of silica-gel and an internal standard (tridecane) was added to the eluate. Then, the resultant mixture was analyzed by GC. (\((R)-3c\) (77%, 77:23 er).

6-4. Asymmetric hydrolysis of enolesters with the in situ generated stoichiometric Q\textsuperscript{+}CF\textsubscript{3}CH\textsubscript{2}O\textsuperscript{-} reagent. N-9-anthracenylmethyl cinchonidinium chloride (61 mg, 0.10 mmol, 1 equiv) in MeOH solution was passed through a column filled with an anion exchange resin (Amberlyst A-26 OH form, 233 mg, 10 meq). 2,2,2-Trifluoroethanol (125 mg, 1.25 mmol, 5 equiv) was added to the elution and stirred for 15 min at RT. The solvent was removed under reduced pressure, then added CHCl\textsubscript{3} and the solution was transferred to a screw vial. Solvents were removed by evaporation and dried in vacuo for 6 h. To the resultant solid was added CHCl\textsubscript{3} (400 μL), distilled water (100 μL). Then the mixture was stirred for 2 min at 25 °C. An enolester 2c (21.7 mg, 0.1 mmol, 1 equiv) was added to the solution and stirred for 4 h at the same temperature. After that, the reaction mixture was immediately passed through thin pad of silica-gel and an internal standard (tridecane) was added to the eluate. Then, the resultant mixture was analyzed by GC. (\((R)-3c\) (55%, 69:31 er).

6-5. Preparation method for a sample of NOE experiment of N-9-anthracenylmethyl cinchonidinium 2,2,2-trifluoroethanoxide. N-9-anthracenylmethyl cinchonidinium chloride (130 mg, 0.25 mmol, 1 equiv) in MeOH solution was passed through a column filled with an anion exchange resin, Amberlyst A-26 OH form (10 meq). 2, 2, 2-Trifluoroethanol (125 mg, 1.25 mmol, 90 μL, 5 equiv) was added to the eluate and stirred for 15 min. The solvent was removed under reduced pressure, then added CDCl\textsubscript{3} (0.5 mL) and removed the solvent again. After that, CDCl\textsubscript{3} (1.0 mL) was added to the residue and 600 μL of the solution was transferred to a NMR tube. D\textsubscript{2}O (50 μL) was added to the sample. After that, it was subjected to two freeze-pump-thaw cycles followed by keeping in refrigerator for 12 h. Then, NMR experiments were performed.\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): 8 = 8.79 (d, J = 8.9 Hz, 1 H, H\textsubscript{10}), 8.64 (d, J = 3.4 Hz, 1 H, H\textsubscript{1}), 8.61 (d, J = 8.3 Hz, 1 H, H\textsubscript{3}), 8.39 (d, J = 8.9 Hz, 1 H, H\textsubscript{29}), 8.14 (s, 1 H, H\textsubscript{2}), 7.95 (d, J = 3.4 Hz, 1 H, H\textsubscript{2}), 7.75 (d, 8.2 Hz, 1 H, H\textsubscript{22}), 7.70 (d, J = 8.2 Hz, 1 H, H\textsubscript{20}), 7.47 (d, J = 8.3 Hz, 1 H, H\textsubscript{8}), 7.40-7.28 (m, 3 H, H\textsubscript{20} + H\textsubscript{21} + H\textsubscript{28}), 7.28-7.23 (m, 1 H, H\textsubscript{27}), 7.06 (t, J = 6.8 Hz, 1 H, H\textsubscript{6}), 6.99-6.94 (m, 1 H, H\textsubscript{7}), 6.98 (s, 1 H, H\textsubscript{10}), 6.46 (d, J = 13.7 Hz, 1 H, H\textsubscript{16b}), 6.41 (d, J = 13.7 Hz, 1 H, H\textsubscript{16a}), 5.36 (ddd, J = 6.6, 11.0, 17.2 Hz, 1 H, H\textsubscript{3}), 5.01 (d, J = 17.2 Hz, 1 H, H\textsubscript{3}), (d, J = 11.0 Hz, 1 H, H\textsubscript{3}), 4.76-4.66 (m, 1 H, H\textsubscript{15b}), 4.76-4.66 (m, 1 H, H\textsubscript{15b}), 4.49-4.43 (m, 1 H, H\textsubscript{11}), 4.05-3.93 (m, 3.1H, H\textsubscript{35} + excess), 3.92-3.83 (m, 1 H, H\textsubscript{32b}), 2.61 (t, J = 12.4 Hz, H\textsubscript{32b}), 2.65-2.57 (m, 1 H, H\textsubscript{22a}), 2.40-2.31 (m, 1 H, H\textsubscript{22a}), 1.66-1.61 (m, 1 H, H\textsubscript{21}), 1.90-1.72 (m, 2 H, H\textsubscript{14b} + H\textsubscript{12b}), 1.66-1.61 (m, 1 H, H\textsubscript{13}), 1.11-1.02 (m, 1 H, H\textsubscript{14a}), 0.95-0.87 (m, 1 H, H\textsubscript{12a}).
$^1$H and 2D-NOESY chart

Green: negative, Red: positive
6-6. Kinetic resolution of an aryl ester bearing binaphthyl backbone

6-6-1. Synthesis of the catalyst and substrate
Synthesis of 1-bromomethyl-2,3,4,5-tetraphenyl benzene (8)

To a stirred solution of tetraphenyl cyclopentadienone (3.85 g, 10 mmol, 1 equiv) in toluene (10 mL) was added propargyl bromide (3.01 mL, 40 mmol, 4 equiv). After stirring for 8 h at 110 °C the reaction mixture was allowed to cool down to RT. Resultant white precipitate was filtrated and washed with hexane to give 8 (4.36 g, 9.1 mmol, 91%) as white solid. 1H NMR (600 MHz, CDCl₃); δ = 7.64 (s, 1 H), 7.20-7.11 (m, 10 H), 6.92-6.88 (m, 3 H), 6.86-6.81 (m, 2 H), 6.76-6.72(m, 2 H), 4.40 (s, 2 H). 13C NMR (150 MHz, CDCl₃); δ = 142.2, 141.5, 141.4, 140.9, 140.6, 139.8, 139.6, 138.7, 135.1, 131.5, 131.4(2 carbons), 131.2 (2 carbons), 129.3 (2 carbons), 127.9 (2 carbons), 127.6 (2 carbons), 127.0 (2 carbons), 126.8, 126.7 (2 carbons), 126.5, 125.8, 125.6, 32.8. Anal. Calcd (%) for C₃₁H₂₃Br: C, 78.32; H, 4.88. Found: C, 78.29; H, 4.86.

Synthesis of catalyst 1g

A stirred solution of quinine (1 mmol, 324 mg, 1 equiv) in DMF:EtOH:CHCl₃ (9:7.5:1, 200 μL) solution was added 1-bromomethyl-2,3,4,5-tetraphenyl benzene 8 (1 mmol, 475 mg, 1 equiv). The mixture was allowed to warm up to 100 °C. After 2 h, the reaction mixture was cooled to RT. The resultant solution was evaporated and purified by Silica-gel column chromatography to give 1g (344 mg, 0.43 mmol, 43%) as pale pink powder. 1H NMR (400 MHz, CD₃OD) δ = 8.73-8.67 (m, 1 H), 7.97 (d, J = 9.2 Hz, 1 H), 8.00-7.95 (m, 2 H), 7.77 (d, J = 4.6 Hz, 1H) 7.48 (dd, J = 2.3, 9.6 Hz, 1 H), 7.31-7.20 (m, 8 H), 6.91-6.71 (m, 12 H), 6.49 (s, 1 H), 5.63-5.52 (m, 1H), 5.59 (d, J = 12.4 Hz, 1 H), 4.96-4.84 (m, 3 H), 4.05 (s, 3 H), 3.95-3.85 (m, 1 H), 3.78 (t, J = 11.4 Hz, 1 H), 3.64-3.55 (m, 1 H), 3.55-3.44 (m, 1 H), 3.28 (s, 1 H), 3.04-2.94 (m, 1 H), 2.76 (s, 1 H), 2.16-2.24 (m, 2 H), 1.98 (s, 1 H), 1.95-1.84 (m, 1 H), 1.31-1.20 (m, 1 H). 13C NMR (100 MHz, CDCl₃); δ = 158.7, 146.9, 144.5, 144.0, 143.6, 143.3, 143.1, 141.7, 140.8, 139.6, 139.2, 138.6, 137.5, 135.6, 131.6, 131.4, 131.04, 131.00, 130.94, 130.6, 129.7, 128.1, 128.0, 127.6, 127.1, 126.8, 126.6, 125.9, 125.6, 124.4, 121.4, 120.2, 115.8, 101.4, 68.4, 64.9, 61.8, 61.1, 55.4, 53.5, 51.6, 37.6, 26.3, 24.5, 21.2. HRMS (FAB+) m/z calculated for C₅₁H₄₇N₂O₂: 719.3632 found 719.3641 [M-Br]

Synthesis of 2'-acetoxy-[1,1'-binaphthalen]-2-yl pivalate (7)

To a mixture of 2'-hydroxy-[1,1'-binaphthalen]-2-yl pivalate (1.14 g, 4.0 mmol) and acetyl chloride (310 μL, 4.4 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (610 μL, 4.4 mmol) at 0 °C and the mixture was stirred at RT for 20 h. The reaction was quenched by adding HCl (1N, 30 mL) and extracted with AcOEt. The resulting extracts were washed with brine, and dried, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography to give 6 (1.63 g, 3.96 mmol, 99%) as white solid. 1H NMR (600 MHz, CDCl₃); δ = 7.99-7.95 (m, 1 H), 7.93-7.89 (m, 1 H), 7.46-7.37 (m, 4 H), 7.31-7.22 (m, 6 H), 1.76 (s, 3 H), 0.76 (s, 9 H). 13C-NMR (100 MHz, CDCl₃); δ = 176.6, 169.2, 147.0, 146.9, 133.5, 133.4, 131.6, 129.5, 129.4, 128.1, 128.0, 127.6, 127.1, 126.8, 126.6, 125.9, 125.6, 124.4, 121.4, 120.2, 115.8, 101.4, 68.4, 64.9, 61.8, 61.1, 55.4, 53.5, 51.6, 37.6, 26.3, 24.5, 21.2. HRMS (FAB+) m/z calculated for C₂₇H₂₄O₄: 426.1823 found 426.1824 [M+H]

6-6-2. Asymmetric hydrolysis of the acetate ester

Asymmetric hydrolsis of the acetate ester

A mixture of the catalyst 1g (0.01 mmol, 10 mol%) and 1N K₂CO₃ aq (200 μL, 0.2 mmol, 2 equiv) in toluene (200 μL) was stirred at 20 °C. After 20 min, the rac-7 (0.1 mmol, 1 equiv) was added and the mixture was stirred at the same temperature. Silica-gel column chromatography (Hexane: CHCl₃: Et₂O = 20:6.5:1) was carried out to give (S)-8 (15% yield, 78:22 er) and (R)-7 (80% yield, 43.5:56.5 er); HPLC analysis: CHIRALPAK AD-H (+), hexane/2-propanol = 20/1, flow rate = 1.0 mL/min, 25 °C, 7: t_major = 7.9 min, t_minor = 17.4 min, 8: t_major = 10.6 min, t_minor = 16.5 min)(S)-7; [α]D²⁵ = + 35.1, (c 0.5, CHCl₃), (R)-8; [α]D²⁵ = - 3.63, (c 1.0, CHCl₃). k_rel = 4.1 (The k_rel value was calculated from ee_sub and ee_pro with equations as follows.: conv = ee_sub/(ee_sub+ee_pro), k_rel = ln[(1 – conv (1 + ee_pro)) / ln(1 – conv (1 – ee_pro))])

Synthesis of 2'-acetoxy-[1,1'-binaphthalen]-2-yl pivalate (7)
Recovered substrate (S)-7

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\text{H NMR (600 MHz, CDCl}\text{3)} \delta = 7.99-7.95 (m, 1 H), 7.93-7.89 (m, 1 H), 7.46-7.37 (m, 4 H), 7.31-7.22 (m, 6 H), 1.76 (s, 3 H), 0.76 (s, 9 H). 13C-NMR (100 MHz, CDCl3) \delta = 176.6, 169.2, 147.0, 146.9, 133.5, 133.4, 131.6, 131.5, 129.5, 129.4, 128.1, 128.0, 126.8 (2 carbons), 126.2, 126.1, 125.8, 125.7, 123.7, 123.6, 122.0, 121.9, 38.8, 26.5 (3 carbons), 20.6. elemental analysis calcd (%) for C27H24O3: C 78.62, H 5.86; found: C 78.60, H 5.86.
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Product (R)-8

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\text{H NMR (600 MHz, CDCl}\text{3)} \delta = 8.06 (d, J = 6.0 Hz, 1 H), 7.97 (d, J = 5.5 Hz, 1 H), 7.87 (d, J = 6.0 Hz, 1 H), 7.81 (d, J = 5.5 Hz, 1 H), 7.50 (t, J = 5.5 Hz, 1 H), 7.39-7.28 (m, 5H), 7.26-7.21 (m, 1 H), 7.05 (d, J = 5.5 Hz, 1 H), 5.14 (s, 1 H), 0.78 (s, 9 H). 13C-NMR (150 MHz, CDCl3) \delta = 177.9, 151.8, 148.4, 133.7, 133.6, 132.3, 130.8, 130.4, 129.1, 128.4, 128.0, 127.5, 126.7, 126.3, 125.7, 124.6, 123.6, 123.1, 121.9, 118.3, 114.3, 38.8, 26.5(3 carbons). elemental analysis calcd (%) for C25H23O3: C, 81.06; H, 5.99; found: C, 81.11, H, 5.99.
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HPLC chart of rac-7

HPLC chart of rac-8

HPLC chart of recovered substrate (S)-7 and product (R)-8
7. Formal synthesis of the biologically-active natural product
7-1. Synthesis of catalyst 1f

Synthesis of amine 9
To the stirred solution of (–)-cinchonidine (883 mg, 3 mmol, 1 equiv) in dry Et₂O (15 mL) at –25 °C was added tBuLi (1.57M in pentane, 5.73 mL, 9 mmol, 3 equiv) in one portion and stirred for 10 min. Then, the reaction mixture was allowed to warm up to RT and stirred for another 1 h. Reaction was monitored by TLC analysis (toluene:MeOH:Et₃N = 10:1:1, tBu adducts turn blue under the UV irradiation). AcOH was added to quench the residual basic reagents in cool bath, then EtOAc (30 mL) and H₂O (30 mL) was added followed by the addition of I₂ until strong brown color persists. After that, Na₂S₂O₃ aq was added to quench residual I₂. The reaction mixture was extracted with EtOAc. The organic layer was dried with Na₂SO₄ and evaporated. The crude mixture was purified by silica-gel column chromatography (toluene:MeOH:Et₃N = 20:1:1) to give the product 9 (704 mg, 1.92 mmol, 64%) as white solid. Analytical sample was prepared by the PTLC purification (CH₂Cl₂:MeOH = 4:1)

1H NMR (400 MHz, CDCl₃): δ = 8.07 (d, J = 8.2 Hz, 1 H), 7.90 (d, J = 8.7 Hz, 1 H), 7.72, (s, 1 H), 7.63 (t, J = 7.8 Hz, 1H), 7.39 (t, J =7.4 Hz, 1H), 5.71 (ddd, J=7.8, 10.1, 17.4 Hz, 1 H), 5.66 (s, 1 H), 4.93 (d, J = 17.4 Hz, 1 H), 4.88 (d, J = 10.1 Hz, 1 H), 3.53-3.43 (m, 1 H), 3.12-3.00 (m, 2 H), 2.70-2.59 (m, 2 H), 2.29-2.20 (m, 1 H), 1.80-1.65 (m, 4 H), 1.50-1.40 (m, 11 H). 13C NMR (150 MHz, CDCl₃): δ = 169.0, 148.3, 147.7, 142.0, 130.4, 128.7, 125.9, 123.9, 122.6, 115.2, 114.4, 72.4, 60.3, 57.2, 43.4, 40.1, 38.3, 30.2 (3 carbons), 28.1, 27.7, 21.4. FABMS m/z calculated for C₂₃H₃₀N₂O: 351.24 found 351.29 [M+H] Anal. Calcd (%) for C₂₃H₃₀N₂O: C, 78.82; H, 8.63; N, 7.99 Found: C, 78.38; H, 8.63, N; 7.89.

Synthesis of 1f
To the stirred solution of amine 9 (73 mg, 0.2 mmol, 1 equiv) in CHCl₃-THF (1:1) was added 9-bromomethylanthracene (57 mg, 0.21 mmol, 1.05 equiv) followed by concentration with nitrogen gas stream down to a volume 0.2 mL. The mixture was stirred at 80 °C for 10 min. Then, the solution was allowed to cool down to RT. After that, resultant precipitate was dissolved with CHCl₃. To the solution was added Et₂O dropwise to solidify the product. The resulting solid was filtrated and washed with Et₂O to give the product (118 mg, 0.19 mmol, 95%) as pale yellow powder. Analytical sample was prepared by the PTLC purification (EtOAc:MeOH = 4:1)

1H NMR (600 MHz, CDCl₃): δ = 8.81 (d, J = 8.9 Hz, 1 H), 8.68 (s, 1 H), 8.60-8.54 (m, 1 H), 8.54-8.48 (m, 1 H), 8.16-8.09 (m, 1 H), 7.82-7.70 (m, 4 H), 7.60-7.52 (m, 2 H), 7.01 (s, 1 H), 6.36 (d, J = 13.7 Hz, 1 H), 5.86 (d, J = 13.7 Hz, 1 H), 5.66 (ddd, J=7.6, 9.6, 17.2 Hz, 1 H), 5.00 (d, J = 17.2 Hz, 1 H), 4.92 (d, J = 9.6 Hz, 1 H), 4.66-4.59 (m, 1 H), 4.48-4.40 (m, 1 H), 3.90-3.84 (m, 1 H), 3.13 (t, J = 11.7 Hz, 1 H), 2.76-2.66 (m, 1 H), 2.36 (br s, 1 H), 2.24-2.14 (m, 1 H), 2.12-2.00 (m, 1 H), 1.87 (s, 1 H), 1.66-1.20 (s, 9 H), 1.45-1.37 (m, 1 H), 1.35-1.20 (m, 1 H). 13C NMR (150 MHz, CDCl₃): δ = 169.0, 148.3, 147.7, 145.1, 137.5, 137.5, 133.4, 133.3, 132.3, 131.60, 131.55, 129.8, 129.7, 129.6, 129.2, 127.93, 127.88, 126.9, 125.2, 124.5, 123.9, 123.1, 122.7, 118.0, 117.0, 116.3, 78.2, 68.6, 66.2, 62.3, 55.4, 51.9, 38.3, 38.0, 29.2 (3 carbons), 26.0, 24.9, 21.8. FABMS m/z calculated for C₃₈H₄₁N₂O⁺ 541.32 found 541.38 [M].
Synthesis of (R)-3k from cyclohexanone (4)

To a stirred solution of cyclohexanone (4.91 g, 50 mmol, 1 equiv) and N, N-dimethyl hydrazine (3.16 g, 52.5 mmol, 1.05 equiv) in toluene (40 mL) was added trifluoroacetic acid (80 mg, 0.7 mmol, 1.4 mol%). The mixture was refluxed for 5 h. After that, the resulting solution was cooled to RT. Then, distilled water was added to the solution and extracted with Et₂O. The organic layer was dried over Na₂SO₄. The solution was evaporated and purified by distillation under reduced pressure to give colorless oil (yield of 7: 6.13 g, 43.7 mmol, 87%) laced with toluene (molar ratio = 10 : 1). This was used without further purification. BuLi (1.67 M in hexane, 10.5 mmol, 6.30 mL, 1.0 equiv) was added dropwise to a stirred solution of 7 (1.47 g, 10.5 mmol, 1 equiv) in THF (anhydrous, 20 mL) at –5 °C under a nitrogen atmosphere and stirred for 1 h. After that, 1-bromo-4-methylpentane (1.733 g, 10.5 mmol, 1 equiv) was added dropwise to the solution, and then the resulting solution was allowed to warm to RT and stirred for 5 h. The resultant solution was added water and cooled to 0 °C. Then the solution was acidified with concentrated HCl aq to reach pH = 1-2. After stirring at 45 °C for another 3 h, the solution was extracted with Et₂O. The organic extracts were combined, dried over Na₂SO₄, and concentrated to give yellow oil. Silica-gel column chromatography of the crude residue by eluting with diethylether/hexane (1:30-1:20) afforded 3k (1.76 g, 9.66 mmol, 92%) as a colorless oil and ¹H NMR was in agreement with the literature. ¹H NMR (400 MHz, CDCl₃): δ = 2.40-2.32 (m, 1 H), 2.32-2.18 (m, 2H), 2.13-2.04 (m, 1 H), 2.04-1.92 (m, 1 H), 1.88-1.79 (m, 1 H), 1.79-1.57 (m, 3 H), 1.51 (sep, J = 6.4 Hz, 1 H), 1.42-1.31 (m, 1H), 1.31-1.08 (m, 5 H), 0.84 (d, J = 6.9 Hz, 6 H). ¹³C NMR (100 MHz, CDCl₃): δ = 213.8, 50.9, 42.1, 39.1, 33.9, 29.7, 28.1, 27.9, 25.0, 24.9, 22.71, 22.66. Anal. Calcd (%) for C₁₂H₂₂O: C, 79.06; H, 12.16. Found: C, 79.03; H, 12.12.

2k was synthesized according to the general method (pale yellow oil, 96% yield). Asymmetric hydrolysis of 2k was performed according to the general method of Asymmetric hydrolysis of enolesters (cat. 1f was used in place of cat. 1a). (R)-(+)-2-(4-Methylpentyl)cycloheptanone was obtained in 96% yield and 92: 8 er as a colorless oil.

8. Derivatization of ketones to the corresponding alcohol and Mosher’s esters
General procedure: reduction of ketones

A typical experimental procedure for the reduction of ketones is described below. To the stirred solution of a ketone (0.01 mmol, 1 equiv) in absolute EtOH (0.5 mL) was added NaBH₄ (9.5 mg, 0.25 mmol, 2.5 equiv) followed by stirring at RT for 24-48 h. The reaction mixture was monitored by TLC. After the substrate was completely converted, the reaction mixture was quenched with water and 1N HCl aq. The resultant solution was extracted with Et₂O (x 3). After that, the organic layer was combined and dried over Na₂SO₄. The crude product was concentrated and purified by silica-gel chromatography to give the corresponding alcohol.

2-propyl-cycloheptanol (10f)¹³

0.0758 mmol (11.7 mg) of 2-propylcyclohepanone 3f (Table 2, entry 5) was used. The product (diastereomeric mixture) was obtained as colorless oil (11.5 mg, 0.0736 mmol, 97%). ¹H NMR (600 MHz, CDCl₃): δ = 3.94-3.89 (m, 0.66 H), 3.49-3.44 (m, 0.34 H), 1.80-1.15 (m, 16 H), 0.93-0.86 (m, 3H). ¹³C NMR (150 MHz, CDCl₃): major isomer, δ = 73.4, 44.2, 35.6, 35.2, 28.3, 27.2, 26.8, 22.0, 21.0, 14.5. minor isomer, δ = 73.4, 47.2, 36.8, 36.5, 29.1, 28.7, 26.9, 22.3, 20.2, 14.6.

2-butyl-cycloheptanol (10g)⁹,¹⁴

0.097 mmol (16.3 mg) of 2-butylcycloheptanone 3g (Table 2, entry 6) was used. The product (diastereomixture) was obtained as colorless oil (0.0916 mmol, 15.6 mg, 94%). ¹H NMR (600 MHz, CDCl₃): δ = 3.94-3.89 (m, 0.7 H), 3.71-3.20 (m, 0.3 H), 1.80-1.10 (m, 18 H), 0.95-0.80 (m, 3 H). ¹³C NMR (150 MHz, CDCl₃): major isomer, δ = 73.4, 44.5, 35.6, 32.6, 30.2, 28.3, 27.2, 26.85, 23.1, 22.0, 14.2. minor isomer, δ = 73.4, 47.4, 36.5, 34.2, 29.4, 29.1, 28.8, 26.91, 23.2, 22.3, 14.2.

2-isopropyl-cycloheptanol(10h)¹⁵

0.097 mmol (15 mg) of 2-isopropylcycloheptanone 3h (Table 2, entry 7) was used. The product was obtained as colorless oil in 93% yield (major isomer: 10.8 mg, 0.0691 mmol, 71%, minor isomer: 3.3 mg, 0.0211 mmol, 22%). ¹H NMR of major isomer (600 MHz, CDCl₃): δ = 4.13-4.09 (m, 1 H), 1.76-1.67 (m, 3 H), 1.67-1.49 (m, 5 H), 1.48-1.35 (m, 3 H), 1.19-1.13 (m, 2 H), 0.95 (t, J = 5.5 Hz, 6 H). ¹³C NMR of major isomer (100 MHz, CDCl₃): δ = 71.5, 50.2, 36.9, 31.4, 28.2, 27.9, 24.1, 22.2, 21.1. Anal. Calcd (%) for C₁₀H₂₀O: C, 76.86; H, 12.90. Found: C, 76.44; H, 12.64.

Mosher’s esterification

(2R)-2-propylcycloheptyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (11f)

To the stirred solution of an alcohol (0.0644 mmol, 1 equiv) in dry CH₂Cl₂ (0.5 mL) was added (R)-MTPACl (32.5 mg, 0.129 mmol, 2.0 equiv), dry pyridine (20.4 mg, 0.258 mmol, 4 equiv) and N,N-dimethyl aminopyridine (1 mg, 4 μmol, 6 mol%) followed by stirring at RT for 48 h. The reaction mixture was monitored by TLC. After the substrate was completely converted, the reaction mixture was diluted with Et₂O. The crude was washed with saturated CuSO₄ aq and extracted with Et₂O (x3). The resultant solution was was concentrated and purified by silica-gel chromatography (Hexane/Et₂O = 50:1-40:1) to give the corresponding ester (93%) as colorless oil. ¹H NMR (600 MHz, CDCl₃): δ = 7.56-7.49 (m, 2 H), 7.41-7.35 (m, 3 H), 5.32-5.29 (m, 0.335 H), 5.29-5.24 (m, 0.335 H), 4.96-4.88 (m, 0.33 H), 3.57-3.50 (m, 3 H), 1.95-1.00 (m, 15 H), 0.90-0.71 (m, 3 H).
To the stirred solution of an alcohol (0.059 mmol, 1 equiv) in dry CH$_2$Cl$_2$ (0.5 mL) was added ($R$)-MTPA-Cl (29.8 mg, 0.118 mmol, 2.0 equiv), dry pyridine (18.7 mg, 0.16 mmol, 4 equiv) and $N,N$-dimethyl aminopyridine (1 mg, 4 μmol, 7 mol%) followed by stirring at RT for 48 h. The reaction mixture was monitored by TLC. After the substrate was completely converted, the reaction mixture was diluted with Et$_2$O. The crude was washed with saturated CuSO$_4$ aq and extracted with Et$_2$O (x3). The resultant solution was concentrated and purified by silica-gel chromatography (Hexane/Et$_2$O = 50:1-40:1) to give the corresponding ester (99%) as inhomogeneous colorless oil. $^1$H NMR (600 MHz, C$_6$D$_6$): $\delta$ = 7.71-7.63 (m, 2 H), 7.08-7.01 (m, 2 H), 7.01-6.95 (m, 1 H), 5.28-5.22 (m, 0.72 H), 4.96-4.93 (m, 0.14 H), 4.92-4.88 (m, 0.14 H), 3.43-3.39 (m, 3 H), 1.83-0.74 (m, 20 H).

9. Analysis of hydrolyzed products

The product ([(S)-(+)-2-ethyl-cyclohexanone]) was obtained as a colorless oil and 87:13 er. $^1$H and $^{13}$C NMR were in agreement with the literature. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.40-1.90 (m, 5 H), 1.90-1.54 (m, 4 H), 1.44-1.29 (m, 1 H), 1.29-1.15 (m, 1 H), 0.86 (t, $J$ = 7.3 Hz, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 213.6, 52.4, 42.1, 33.5, 28.1, 24.9, 22.5, 11.8. Anal. Calcld (%) for C$_8$H$_{14}$O: C, 76.14; H, 11.18. Found: C, 76.30; H, 11.21. Enantiomeric ratio (er) was determined by GC with a CHIRASIL-DEX CB column (conditions, starting temperature: 60 $^\circ$C [hold 10 min.], rate of temperature increase: 2 $^\circ$C/min up to 120 $^\circ$C), $t_r$ (major) = 27.6 min., $t_r$ (minor) = 28.3 min. $\alpha_D^{25.6} = + 36.1$, (c 0.5, CHCl$_3$) The absolute configuration was established by comparison of the optical rotation to the literature value for (R)-(−)-2-ethylcyclohexanone: $\alpha_D^{25} = -23.6$ (c 4.31, MeOH).

The product ([(S)-(+)-2-propylcyclohexanone]) was obtained as a pale yellow oil and 92:8 er. $^1$H and $^{13}$C NMR were in agreement with the literature. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.39-2.31 (m, 1 H), 2.31-2.20 (m, 2 H), 2.12-1.92 (m, 2 H), 1.86-1.56 (m, 4 H), 1.42-1.08 (m, 4 H), 0.87 (t, $J$ = 6.9 Hz, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 213.7, 50.6, 42.0, 33.9, 31.7, 28.1, 24.9, 20.4, 14.3. Anal. Calcld (%) for C$_9$H$_{16}$O: C, 77.09; H, 11.50. Found: C, 77.01; H, 11.50. Enantiomeric ratio (er) was determined by GC with a InertCap CHIRAMIX Column (conditions, starting temperature: 40 $^\circ$C [hold 0 min.], rate of temperature increase: 3 $^\circ$C/min up to 120 $^\circ$C [hold 15 min.], $t_r$ (major) = 37.5 min., $t_r$ (minor) = 38.7 min. $\alpha_D^{22.5} = +33.5$, (c 1.0, CHCl$_3$) The absolute configuration was established by comparison of the
optical rotation to the literature value for \((R)-(\cdash)-2\text{-propylcyclohexanone: } [\alpha]_D^{25} = -25.7 \text{ (c 0.82, MeOH)}^{20}.

The product\(^7\) \((+)-4,4\text{-dimethyl-2-propylcyclohexanone)} was obtained as a pale yellow oil and \(92:8\) er. \(\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3): \delta = 2.44 (\text{td, } J = 6.4, 14.2 \text{ Hz, 1 H}), 2.36 (\text{dt, } J = 6.0, 6.0 \text{ Hz, 1 H}), 2.22 (\text{dt, } J = 3.2, 14.2 \text{ Hz, 1 H}), 1.80-1.55 (\text{m, 4 H}), 1.34-1.22 (\text{m, 3 H}), 1.19 (\text{s, 3 H}), 1.06 (\text{tq, } J = 6.9, 6.9 \text{ Hz, 1 H}), 0.99 (\text{s, 3 H}), 0.87 (\text{t, } J = 7.4 \text{ Hz, 3 H}). \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3): \delta = 214.1, 46.8, 45.8, 40.2, 38.6, 31.6, 31.2, 30.9, 24.7, 20.3, 14.3. \text{Anal. Calcd (\% for C}_{11}\text{H}_{20}\text{O: C, 78.51; H, 11.98. Found: C, 78.24; H, 11.98. Enantiomeric ratio (er) was determined by GC with a InertCap CHIRAMIX Column (conditions, starting temperature: 40 °C [hold 0 min.], rate of temperature increase: 3 °C/min up to 120 °C [hold 15 min.]), } t_\text{m} (\text{major}) = 42.9 \text{ min.}, t_\text{m} (\text{minor}) = 44.1 \text{ min. } [\alpha]_D^{25.9} = +26.6, (\text{c 1.0, CHCl}_3)

The product\(^7\) \((\cdash)-4,4\text{-dimethyl-2-propylcyclohexanone)} was obtained as a pale yellow oil and \(92:8\) er. \(\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3): \delta = 2.44 (\text{td, } J = 6.4, 14.2 \text{ Hz, 1 H}), 2.36 (\text{dt, } J = 6.0, 6.0 \text{ Hz, 1 H}), 2.22 (\text{dt, } J = 3.2, 14.2 \text{ Hz, 1 H}), 1.80-1.55 (\text{m, 4 H}), 1.34-1.22 (\text{m, 3 H}), 1.19 (\text{s, 3 H}), 1.06 (\text{tq, } J = 6.9, 6.9 \text{ Hz, 1 H}), 0.99 (\text{s, 3 H}), 0.87 (\text{t, } J = 7.4 \text{ Hz, 3 H}). \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3): \delta = 214.1, 46.8, 45.8, 40.2, 38.6, 31.6, 31.2, 30.9, 24.7, 20.3, 14.3. \text{Anal. Calcd (\% for C}_{11}\text{H}_{20}\text{O: C, 78.51; H, 11.98. Found: C, 78.24; H, 11.98. Enantiomeric ratio (er) was determined by GC with a InertCap CHIRAMIX Column (conditions, starting temperature: 40 °C [hold 0 min.], rate of temperature increase: 3 °C/min up to 120 °C [hold 15 min.]), } t_\text{m} (\text{major}) = 42.9 \text{ min.}, t_\text{m} (\text{minor}) = 44.1 \text{ min. } [\alpha]_D^{25.9} = +26.6, (\text{c 1.0, CHCl}_3)

The product\((+)-\cdash-2\text{-cyclohexylcyclohexanone)} was obtained as a colorless oil and \(87:13\) er and \(\text{\textsuperscript{1}H and } \text{\textsuperscript{13}C NMR were in agreement with the literature}^{12}. \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3): \delta = 2.39-2.29 (\text{m, 1 H}), 2.28-2.18 (\text{m, 1 H}), 2.11-2.01 (\text{m, 1 H}), 1.98-1.45 (\text{m, 12 H}), 1.33-1.18 (\text{m, 2 H}), 1.16-0.80 (\text{m, 3 H}). \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3): \delta = 213.8, 56.6, 41.9, 36.1, 31.6, 29.42, 29.37, 29.0, 26.6, 26.5, 24.0. \text{Anal. Calcd (\% for C}_{12}\text{H}_{20}\text{O: C, 79.94; H, 11.18. Found: C, 79.78; H, 11.27. Enantiomeric ratio (er) was determined by GC with a CHIRASIL-DEX CB column (conditions, starting temperature: 40 °C [hold 1 min.], rate of temperature increase: 2 °C/min up to 160 °C), } t_\text{m} (\text{minor}) = 55.1 \text{ min.}, t_\text{m} (\text{major}) = 55.3 \text{ min. } [\alpha]_D^{24.8} = +46.1, (\text{c 1.0, CHCl}_3)\) The absolute configuration was established by comparison of the
optical rotation to the literature value for (S)-(–)-2-cyclohexylcyclohexanone: \([\alpha]^D_{24.3} = -38.1 \text{ (c 1.58, MeOH)}\).

The product (2-(+)-propylcycloheptanone) was obtained as a pale yellow oil and 94.5: 5.5 er and \(^{13}\)C NMR was in agreement with the literature. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.54-2.34 \text{ (m, 3 H)}, 1.89-1.76 \text{ (m, 4 H)}, 1.68-1.48 \text{ (m, 2H)}, 1.40-1.17 \text{ (m, 6 H)}, 0.86 \text{ (t, } J = 7.4 \text{ Hz, 3 H)}\). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 216.8, 52.3, 42.7, 34.6, 31.3, 29.7, 28.5, 24.8, 20.5, 14.2\). Anal. Calcd (%) for C\(_{10}\)H\(_{18}\)O: C, 77.87; H, 11.76. Found: C, 78.01; H, 11.83. \([\alpha]^D_{25.3} = +49.7 \text{ (c 1.0, CHCl}_3\text{)}\). Enantiomeric ratio (er) was determined by \(^1\)H NMR after the product was reduced and esterified to the corresponding mosher’s ester (600 MHz, C\(_6\)D\(_6\), major isomer: \(\delta = 5.33-5.29 \text{ ppm}, \text{ minor isomer: } \delta = 5.29-5.25 \text{ ppm}\)).

The product (2-(+)-butylcycloheptanone) was obtained as a pale yellow oil and 95: 5 er. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.53-2.32 \text{ (m, 3 H)}, 1.90-1.77 \text{ (m, 4 H)}, 1.68-1.50 \text{ (m, 2H)}, 1.38-1.14 \text{ (m, 8 H)}, 0.86 \text{ (t, } J = 6.9 \text{ Hz, 3 H)}\). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 216.9, 52.5, 42.7, 32.2, 31.3, 29.7, 29.5, 28.5, 24.8, 22.9, 14.1\). Anal. Calcd (%) (%) for C\(_{11}\)H\(_{20}\)O: C, 78.51; H, 11.98. Found: C, 78.44; H, 11.96. \([\alpha]^D_{25.3} = +49.7 \text{ (c 1.0, CHCl}_3\text{)}\). Enantiomeric ratio (er) was determined by \(^1\)H NMR after the product was reduced and esterified to the corresponding mosher’s ester (600 MHz, C\(_6\)D\(_6\), major isomer: \(\delta = 4.97-4.92 \text{ ppm}, \text{ minor isomer: } \delta = 4.92-4.87 \text{ ppm}\)).
The product ((R)-(+)-2-benzylcycloheptanone) was obtained as a colorless oil and 89.5: 10.5 er and $^1$H NMR was in agreement with the literature.\(^2\) $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.29-7.22 (m, 2 H), 7.21-7.11 (m, 3 H), 3.06 (dd, $J$ = 6.0, 13.8 Hz, 1 H), 2.86-2.75 (m, 1 H), 2.54 (dd, $J$ = 8.7, 13.8 Hz, 1 H), 2.48-2.40 (m, 2H), 1.90-1.70 (m, 4 H), 1.68-1.54 (m, 1 H), 1.38-1.22 (m, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 215.7, 140.1, 129.2, 128.4, 126.1, 53.7, 43.3, 38.0, 30.4, 29.4, 28.7, 24.3. Anal. Calcd (%) for C$_{14}$H$_{18}$O: C, 83.12; H, 8.97. Found: C, 82.87; H, 8.88. Enantiomeric ratio (er) was determined by HPLC with a Chiracel AD-H column (conditions, Hexane : EtOH = 100 : 1, flow rate = 1 mL / min, 25 °C), $t_r$ (minor) = 8.9 min., $t_r$ (major) = 9.7 min. $[\alpha]_D^{26.7} = + 54.1$, (c 1.0, CHCl$_3$) The absolute configuration was established by comparison of the optical rotation to the literature value for (R)-(+-)2-benzylcyclohexanone: $[\alpha]_D = + 41.4$ (c = 5, MeOH, 88% ee).\(^1\)

The product ((+)-isopropylcycloheptanone) was obtained as a pale yellow oil and 95: 5 er, and $^1$H and $^{13}$C NMR was in agreement with the literature.\(^4\) $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.49 (td, $J$ = 3.2, 12.8 Hz, 1 H), 2.40-2.30 (m, 1 H), 2.19-2.10 (m, 1 H), 2.00-1.80 (m, 5 H), 1.60-1.42 (m, 1 H), 1.42-1.12 (m, 3 H), 0.87 (dd, $J$ = 6.4, 12.8 Hz, 6 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 217.2, 59.8, 42.9, 30.6, 30.1, 28.2, 27.8,25.5, 21.1, 19.6. Anal. Calcd (%) for C$_{10}$H$_{18}$O: C, 77.87; H, 11.76. Found: C, 77.81; H, 11.89. Enantiomeric ratio (er) was determined by GC with a CHIRASIL-DEX CB column (conditions, starting temperature: 60 °C [hold 10 min.], rate of temperature increase: 2 °C/min up to 120 °C) after the product was reduced to the corresponding alcohol (major isomer). $t_r$ (major) = 48.2 min., $t_r$ (minor) = 48.4 min. $[\alpha]_D^{30.0} = + 95.5$, (c 1.0, CHCl$_3$).
The product ((}),(+))-2-cyclohexylcycloheptanone) was obtained as a colorless oil and 94:6 er, and $^{13}$C NMR was in agreement with the literature. $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta = 2.52$ (dt, $J = 3.2, 12.4$ Hz, 1 H), 2.35-2.28 (m, 1 H), 2.21-2.14 (m, 1 H), 1.98-1.79 (m, 4 H), 1.75-1.40 (m, 7 H), 1.40-1.07 (m, 6 H), 1.17-0.84 (m, 2 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 217.4, 59.3, 42.8, 40.7, 31.4, 30.2, 30.0, 27.9, 27.8, 26.47, 26.44, 25.8$. Anal. Calcd (%) for C$_{13}$H$_{22}$O: C, 79.94; H, 11.18. Found: C, 79.98; H, 11.25. Enantiomeric ratio (er) was determined by GC with a CHIRASIL-DEX CB column (conditions, starting temperature: 60 °C [hold 1 min.], rate of temperature increase: 1 °C/min up to 160 °C). $t_r$(major) = 85.3 min., $t_r$(minor) = 85.6 min. $[\alpha]_D^{25.8} = +78.3$, (c 1.0, CHCl$_3$) The absolute configuration was established by comparison of the optical rotation to the literature value for ((})-(+))-2-cyclohexylcycloheptanone: $[\alpha]_D^{20} = +87.3$ (c 0.284, CH$_2$Cl$_2$). The product ((})-(+)-2-(4-methylpentyl)cycloheptanone) was obtained as a colorless oil and 92:8 er, and $^{1}$H NMR was in agreement with the literature. $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta = 2.40-2.32$ (m, 1 H), 2.32-2.18 (m, 2H), 2.13-2.04 (m, 1 H), 2.04-1.92 (m, 1 H), 1.88-1.79 (m, 1 H), 1.79-1.57 (m, 3 H), 1.51 (sep, $J = 6.4$, Hz, 1 H) 1.42-1.31 (m, 1 H), 1.31-1.08 (m, 5 H), 0.84 (d, $J = 6.9$ Hz, 6 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 213.8, 50.9, 42.1, 39.1, 33.9, 29.7, 28.1, 27.9, 25.0, 24.9, 22.71, 22.66$. Anal. Calcd (%) for C$_{12}$H$_{22}$O: C, 79.06; H, 12.16. Found: C, 79.03; H, 12.12. Enantiomeric ratio (er) was determined by GC with a CHIRASIL-DEX CB column (conditions, starting temperature: 60 °C [hold 10 min.], rate of temperature increase: 2 °C/min up to 120 °C). $t_r$(major) = 51.1 min., $t_r$(minor) =...
52.0 min. \([\alpha]_D^{24.4} = +20.1\), (c 1.0, CHCl3). The absolute configuration was established by comparison of the optical rotation to the literature value for \((R)-(-)-2-(4\text{-Methylpentyl})\text{cycloheptanone}: [\alpha]_D^{20} = +18.4\) (c 3.75, EtOH)\(^{12}\).

10. Reactivity of enolesters bearing chloroacetyl group and PNP amino acid esters

The pKa values of products (alcohols and acids) are described below (Fig. S1). The pKa value of cyclohexenol is 4.55 point larger than \(p\)-nitrophenol, although chloroacetic acid is more acidic than \(N\)-benzoylglycine by 0.75 point. Therefore, enolesters bearing chloroacetyl group seem to be less reactive compared to PNP esters derived from \(N\)-benzoyl aminoacids.

\[
\begin{align*}
\text{Cl} & \quad \text{O} & \quad \text{O} & \quad \text{C} & \quad \text{H} & \quad \text{C} \\
\text{Cl} & \quad \text{O} & \quad \text{OH} & \quad + & \quad \text{HO} & \quad \text{C} \\
pKa = 2.86^{(23)} & \quad pKa = 11.70^{(24)}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{O} & \quad \text{N} & \quad \text{O} & \quad \text{C} & \quad \text{H} & \quad \text{C} \\
\text{Ph} & \quad \text{N} & \quad \text{H} & \quad \text{O} & \quad \text{C} & \quad \text{H} & \quad \text{NO}_2 \\
pKa = 3.61^{(25)} & \quad pKa = 7.15^{(26)}
\end{align*}
\]

Fig. S1 Comparison of pKa values between product acids and alcohols (in water)

11. References
Figures represent the positions of carbons.
Overall picture of HMQC (compound 9)
Expanded figure 1 of HMQC (compound 9)
Expanded figure 2 of HMQC (compound 9)
Expanded figure 3 of HMQC (compound 9)
Overall picture of HMBC (compound 9)
Expanded figure 2 of HMBC (compound 9)
Expanded figure 3 of HMBC (compound 9)
Expanded figure 4 of HMBC (compound 9)
Expanded figure 5 of HMBC (compound 9)
Expanded figure 6 of HMBC (compound 9)