Asymmetric Copper-Catalyzed Carbozincation of Cyclopropenes en route to the Formation of Diastereo- and Enantiomerically Enriched Polysubstituted Cyclopropanes

Authors: Daniel S. Müller and Ilan Marek

The Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry, and The Lise Meitner-Minerva Center for Computational Quantum Chemistry, Technion-Israel Institute of Technology, Technion City, Haifa 32000, Israel

Table of contents

1 General experimental details S2
2 Optimization reactions S3
3 Substrate Synthesis S5
4 Cu-catalyzed enantioselective carbozincation of cyclopropenes S6
5 References S24
6 NMR spectra S25
1 General experimental details

Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of argon. TMSCl was purified by distillation under a nitrogen atmosphere over CaH₂. Methyl vinyl ketone was purified by vacuum distillation. Ether and THF were dried from Pure-Solv® Purification System (Innovative Technology©). All other commercially obtained reagents were used as received. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde, phosphomolybdic acid, or potassium permanganate. Column chromatography was performed using Fluka silica gel 60 Å (40–63μm, 230–400 mesh). ¹H NMR spectra were recorded on Bruker spectrometers (AVIII400) and are reported relative to deuterated solvent signals. Chemical shifts are reported in parts per million (ppm) with respect to the residual solvent signal CDCl₃ (¹H NMR: δ = 7.26; ¹³C NMR: δ = 77.16). Peak multiplicities are reported as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, app = apparent. High-resolution mass spectra (HRMS) were obtained by the mass spectrometry facility at the Technion. Reactions were monitored by gas chromatography spectrometry (GC) using an Agilent Technologies 7820A GC with an Agilent Technologies 19091J-413 (30 m × 0.3 mm) column or (GC-MS) Thermo Scientific™ Ion Trap GC/MS: ITQ™ 900 with a Varian Factor Four Capillary column (VF-5 ms, 30 m × 0.25 mm). HPLC chromatograms were recorded using Agilent© 1100 Series line. Following chiral columns were tested: CHIRAL PAK® AD-H (0.46 cm Φ × 25 cm), CHIRALCEL® OD (0.46 cm Φ × 25 cm) and CHIRALCEL® IA column (0.46 cm Φ × 25 cm). Enantiomeric excesses were determined by chiral-GC: Varian 3900 with J&W Scientific Cycldodex B (30 m × 0.32 mm) or FS-Lipodex E (25 m × 0.25 mm). Temperature programs for chiral GC are described as follows: initial temperature (°C)-initial time (min)—temperature gradient (°C/min)—final temperature (°C). Optical rotations were measured on a SCHMIDT and HAENSCH© Unipol L1000 polarimeter with [α]D values reported in degrees; concentration (c) is in g/100 mL. Racemic samples were obtained by carrying out the reaction under conditions indicated for the optically enriched cyclopropane 3a using a 1:1 mixture of (R)- and (S)-DTBM-SEPHOS (5.5 mol%, each) and Cu(CH₃CN)₄PF₆(10 mol%).
2 Optimization reactions

Table S1: Initial screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>CuX</th>
<th>Ligand</th>
<th>Conv.</th>
<th>d.r.</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>CuI</td>
<td>TPP</td>
<td>&lt; 20%</td>
<td>n.d.</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>Et₂O</td>
<td>CuI</td>
<td>DPEPHOS</td>
<td>&lt; 20%</td>
<td>n.d.</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>CuI</td>
<td>(R)-BINAP</td>
<td>&lt; 20%</td>
<td>n.d.</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>CuI</td>
<td>--</td>
<td>100%</td>
<td>4:1</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>Et₂O</td>
<td>Cu(CH₃CN)₄PF₆</td>
<td>TPP</td>
<td>100%</td>
<td>1.7 : 1</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>Et₂O</td>
<td>Cu(CH₃CN)₄PF₆</td>
<td>DPEPHOS</td>
<td>&lt; 20%</td>
<td>n.d.</td>
<td>--</td>
</tr>
<tr>
<td>7</td>
<td>Et₂O</td>
<td>Cu(CH₃CN)₄PF₆</td>
<td>(R)-BINAP</td>
<td>68%</td>
<td>1 : 1.7</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>Et₂O</td>
<td>CuTC</td>
<td>TPP</td>
<td>100%</td>
<td>1.7 : 1</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>Et₂O</td>
<td>CuTC</td>
<td>DPEPHOS</td>
<td>&lt; 20%</td>
<td>n.d.</td>
<td>--</td>
</tr>
<tr>
<td>10</td>
<td>Et₂O</td>
<td>CuTC</td>
<td>(R)-BINAP</td>
<td>100%</td>
<td>15 : 1</td>
<td>84:16</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>CuTC</td>
<td>(R)-BINAP</td>
<td>100%</td>
<td>20:1</td>
<td>81:19</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>CuTC</td>
<td>--</td>
<td>100%</td>
<td>4:1</td>
<td>--</td>
</tr>
<tr>
<td>13</td>
<td>Et₂O</td>
<td>CuTC</td>
<td>--</td>
<td>100%</td>
<td>3:1</td>
<td>--</td>
</tr>
<tr>
<td>14</td>
<td>Et₂O</td>
<td>CuTC</td>
<td>Josiphos</td>
<td>&lt; 20%</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>15</td>
<td>Et₂O</td>
<td>CuTC</td>
<td>Trost-Ligand</td>
<td>&lt; 20%</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>16</td>
<td>Et₂O</td>
<td>CuTC</td>
<td>Feringa-Ligand</td>
<td>100%</td>
<td>1.6 : 1.0</td>
<td>74:26</td>
</tr>
<tr>
<td>17</td>
<td>THF</td>
<td>CuTC</td>
<td>Feringa-Ligand</td>
<td>100%</td>
<td>5:1</td>
<td>58:42</td>
</tr>
</tbody>
</table>

[a] Ligand, copper salt and solvent were stirred for 1h at rt then cyclopropene was added followed by Et₂Zn. In all cases 10-50% dimer side-product was observed. [b] Estimated by GC-MS. [c] Determined by chiral GC with Cyclodex-B as stationary phase.
Table S2: Screening of copper salt

Table S3: Screening of solvents

Note: Even though ethyl acetate gave slightly better results compared to diethyl ether we continued our investigations with diethyl ether. Dry diethyl ether was available from the solvent system which was not the case for ethyl acetate.
3 Substrate synthesis

The substrates were prepared as shown in table S4. The procedures described in the references were followed.

![Chemical structure](image)

In some cases the olefin was commercially available.

Table S4: Substrate synthesis

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Structure</th>
<th>Reference for synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td><img src="image" alt="Structure" /></td>
<td>W. M. Sherrill, R. Kim, M. Rubin, <em>Tetrahedron</em> 2008, 64, 8610–8617.</td>
</tr>
<tr>
<td>1c</td>
<td><img src="image" alt="Structure" /></td>
<td>W. M. Sherrill, R. Kim, M. Rubin, <em>Tetrahedron</em> 2008, 64, 8610–8617.</td>
</tr>
</tbody>
</table>
4 Cu-catalyzed enantioselective carbozincation of cyclopropenes

((1R,2R)-2-ethyl-1-methylcyclopropyl)benzene (3a)

General procedure GP1.

Cu(CH$_3$CN)$_4$PF$_6$ (11.2 mg, 0.03 mmol, 3 mol%) and (R)-DTBM-SEGPHOS® (38.9 mg, 0.033 mmol, 3.3 mol%) were dissolved in THF (4.0 mL) under argon atmosphere. After stirring the pale pink solution for 1 h at rt the mixture was cooled to 0 °C and the cyclopropene substrate 1a (2.0 mL, 130.2 mg, 1.0 mmol, 1.0 eq.; 0.5 M solution in pentane) was added. After 5 min Et$_2$Zn (1.2 mL, 1.2 mmol, 1.2 eq., 1.0 M solution in hexanes) was added dropwise at the wall of the flask. After 3 h at 0 °C the reaction mixture was quenched with HCl (1.0 M; 5.0 mL) and diluted with Et$_2$O (10 mL). The organic phase was separated and the aqueous phase extracted with Et$_2$O (10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes) to obtain 3a as a colorless oil (136 mg, 0.85 mmol, 85% yield). R$_f$ = 0.79 (Hexanes; stained with phosphomolybdic acid).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.27 – 7.19 (m, 4H), 7.14 – 7.08 (m, 1H), 1.54 – 1.41 (m, 2H), 1.35 (s, 3H), 1.04 (t, J = 7.3 Hz, 3H), 1.01 (d, J = 4.3 Hz, 1H), 0.99 – 0.89 (m, 1H), 0.34 (dd, J = 5.4, 4.6 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 149.1, 128.3, 127.1, 125.4, 28.4, 24.3, 23.0, 20.7, 20.3, 14.6. Spectral data consistent with reported data.[1] GC analysis (Cyclodex-B; 60-1-70-0.4-82-180; $t_R1 = 34.1$ min, $t_R2 = 34.9$ min) indicated 93:7 er. [α]$_D^{20} = -23.1$ (c = 0.48, CHCl$_3$).
((1R,2S,3S)-2-ethyl-3-iodo-1-methylcyclopropyl)benzene (3b)

To cyclopropyl zinc reagent (1.0 mmol; prepared according to general procedure GP1) was added iodine (914 mg, 3.6 mmol, 3.6 eq.) at 0 °C. The reaction was stirred for 4 h at this temperature and then quenched with sat. aqueous solution of Na$_2$S$_2$O$_3$ (10 mL) and diluted with Et$_2$O (10 mL). The organic phase was separated and the aqueous phase extracted with Et$_2$O (10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes) to obtain 3b as a pale pink oil (277 mg, 0.97 mmol, 97% yield). R$_f$ = 0.64 (Hexanes; stained with phosphomolybdic acid).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.22 – 7.14 (m, 4H), 7.13 – 7.07 (m, 1H), 3.07 (d, $J$ = 8.2 Hz, 1H), 1.50 – 1.32 (m, 2H), 1.30 (s, 3H), 1.01 (t, $J$ = 7.4 Hz, 3H), 0.99 – 0.93 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.9, 128.6, 127.3, 126.4, 28.7, 27.4, 23.6, 22.3, 13.1, 12.3.

HRMS (TOF-MS ES$^+$): [M+H]$^+$, calculated for C$_{12}$H$_{16}$I: 287.0297; found 287.0289. \([\alpha]_D^{20} = +52.1\ (c = 0.51, \text{CHCl}_3).\)

Note: The enantiomeric ratio of 3b could not be determined by chiral HPLC or GC (see chemical materials and methods). Therefore, the same enantiomeric ratio as for 3a was assigned. For proof that transmetalation does not change the enantiomeric ratio see compounds 3j, 3k, 3s and 3t.
((1S,2R,3S)-2-ethyl-1-methyl-3-styrylcyclopropyl)benzene (3c)

To cyclopropyl zinc reagent (0.6 mmol; prepared according to general procedure GP1) was added (E)-(2-bromovinyl)benzene\(^2\) (193 \(\mu\)L, 274 mg, 1.5 mmol, 2.5 eq.) and a solution of \(\text{Pd(OAc)}_2\) (4.0 mg, 0.018 mmol, 0.03 eq.) and SPhos (14.8 mg, 0.036 mmol, 0.06 eq.) in THF (0.5 mL) at 0 \(^\circ\)C. Stirring was continued for 16 h during which the cooling bath slowly warmed to 20 \(^\circ\)C. The reaction mixture was treated with HCl (1 M, 5 mL) and extracted with Et\(_2\)O (3 \(\times\) 15 mL). The combined organic phases were dried over Na\(_2\)SO\(_4\) and the reduced in vacuo. The oily residue was purified by flash chromatography (hexanes) to obtain 3c as a colorless oil (145 mg, 0.55 mmol, 92% yield). \(R_f = 0.35\) (Hexanes; UV detection).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41 – 7.35 (m, 2H), 7.35 – 7.28 (m, 6H), 7.24 – 7.16 (m, 2H), 6.63 (d, \(J = 15.7\) Hz, 1H), 6.17 (dd, \(J = 15.7, 9.7\) Hz, 1H), 1.98 (t, \(J = 9.4\) Hz, 1H), 1.69 – 1.61 (m, 2H), 1.45 (dd, \(J = 7.6, 9.5\) Hz, 1H), 1.42 (s, 3H), 1.11 (t, \(J = 7.3\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 149.7, 138.1, 131.6, 128.7, 128.5, 127.5, 127.2, 126.8, 125.9, 125.8, 32.8, 31.8, 30.9, 18.5, 16.4, 14.4. HRMS (APCI): \([\text{M+H}]^+\), calculated for C\(_{20}\)H\(_{23}\): 263.1794; found 263.1783.

Note: The enantiomeric ratio of 3c could not be determined by HPLC or GC with the chiral columns tested (see chemical materials and methods). Therefore, the same enantiomeric ratio as for 3a was assigned.

((1S,2S,3R)-2-allyl-3-ethyl-1-methylcyclopropyl)benzene (3d)

To cyclopropyl zinc reagent (1.0 mmol; prepared according to general procedure GP1) was added CuCN-2LiCl (0.5M in THF; 0.96 mL, 0.48 mmol, 0.48 eq.) at \(-40\) \(^\circ\)C. After 5 min allyl bromide (243 \(\mu\)L, 338 mg, 2.8 mmol, 2.8 eq.) was added. After stirring for 1 h at \(-40\) \(^\circ\)C the reaction was slowly warmed to rt and continued to stir for 4 h. The reaction mixture was treated with HCl (1 M, 5 mL) and extracted with Et\(_2\)O (3 \(\times\) 10 mL). The combined organic phases were dried over Na\(_2\)SO\(_4\) and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes to hexanes: EtOAc = 30:1) to obtain 3d as a colorless oil (182 mg, 0.91 mmol, 91% yield). \(R_f = 0.82\) (Hexanes; stained with KMnO\(_4\)).
**1H NMR** (400 MHz, CDCl₃) δ 7.27 – 7.22 (m, 4H), 7.16 – 7.09 (m, 1H), 6.01 – 5.89 (m, 1H), 5.11 (dd, J = 17.1, 1.7 Hz, 1H), 5.00 (dd, J = 10.2, 1.6 Hz, 1H), 2.25 – 2.11 (m, 2H), 1.55 – 1.37 (m, 2H), 1.26 (s, 3H), 1.18 – 1.10 (dt, J = 8.0 Hz, J = 7.4 Hz), 1.27 – 1.20 (m, 4H). **13C NMR** (101 MHz, CDCl₃) δ 150.5, 138.6, 128.3, 127.5, 125.5, 114.6, 29.1, 28.7, 26.4, 26.3, 17.7, 15.3, 14.6. **HRMS** (TOF-MS ES⁺): [M+H]⁺, calculated for C₁₅H₂₁: 201.1643; found 201.1629.

Note: The enantiomeric ratio of 3d could not be determined by HPLC or GC with the chiral columns tested (see chemical materials and methods). Therefore, the same enantiomeric ratio as for 3a was assigned.

**Ethyl 2-(((1S,2S,3R)-3-ethyl-2-methyl-2-phenylcyclopropyl)methyl)acrylate (3e)**

To cyclopropyl zinc reagent (1.0 mmol; prepared according to general procedure GP1) was added CuCN 2LiCl (0.5M in THF; 0.96 mL, 0.48 mmol, 0.48 eq.) at -40 °C. After 5 min the ethyl 2-(bromomethyl)acrylate (389 µL, 540 mg, 2.8 mmol, 2.8 eq.) was added. After stirring for 1 h at -40 °C the reaction was slowly warmed to rt and continued to stir for 4 h. The reaction was quenched with sat. aqueous solution of NH₄Cl (10 mL) and diluted with Et₂O (10 mL). The organic phase was separated and the aqueous phase extracted with Et₂O (10 mL). The combined organic phases were dried over Na₂SO₄ and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes to hexanes: EtOAc = 30:1) and dried under high vacuum [¹] to obtain 3e as a colorless oil (264 mg, 0.97 mmol, 97% yield). Rₐ = 0.57 (Hexanes: EtOAc = 10:1; stained with KMnO₄).

**1H NMR** (400 MHz, CDCl₃) δ 7.20 – 7.13 (m, 4H), 7.07 – 7.01 (m, 1H), 6.13 (d, J = 1.0 Hz, 1H), 5.59 (d, J = 1.5 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.38 (dd, J = 7.2, 1.0 Hz, 2H), 1.50 – 1.26 (m, 2H), 1.21 (t, J = 9.0, 3H), 1.18 (s, 3H), 1.17 – 1.13 (m, 1H), 1.06 – 1.00 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). **13C NMR** (101 MHz, CDCl₃) δ 167.5, 150.0, 141.0, 128.3, 127.1, 125.5, 124.4, 60.7, 29.2, 26.4, 26.1, 25.5, 17.6, 15.0, 14.5, 14.3. **HRMS** (TOF-MS ES⁺): [M+H]⁺, calculated for C₁₈H₂₄O₂: 273.1855; found 273.1816. [α]D = +14.5 (c = 0.48, CHCl₃).
Note: The enantiomeric ratio of 3e could not be determined by HPLC or GC with the chiral columns tested (see chemical materials and methods). Therefore the same enantiomeric ratio as for 3a was assigned.

[1] This was done in order to remove a side product which was generated by addition of EtZnR to ethyl 2-(bromomethyl)acrylate. \( R_f = 0.50 \) (Hexanes: EtOAc = 1:1).

---

### 4-(((1S,2S,3R)-3-ethyl-2-methyl-2-phenylcyclopropyl)butan-2-one (3f)

**General procedure GP2:**

\[
\text{Cu(CH}_3\text{CN)}_4\text{PF}_6 \ (11.2 \ mg, \ 0.03 \ mmol, \ 3 \ mol\%) \text{ and } (R)-\text{DTBMSEGPHOS}^\circledR \ (38.9 \ mg, \ 0.033 \ mmol, \ 3.3 \ mol\%) \text{ were dissolved in THF (4.0 mL) under argon atmosphere. After stirring the pale pink solution for 1 h at rt the mixture was cooled to 0 °C and the cyclopropene substrate (130.2 mg, 1.0 mmol, 1.0 eq.) was added as a 0.5 M solution in pentane. After 5 min Et}_2\text{Zn (1.0 M solution in hexanes; 1.2 mL, 1.2 mmol, 1.2 eq.) was added dropwise at the wall of the flask over 1 min. After the reaction was stirred for 3 h at 0 °C the reaction vessel was cooled to −40 °C and CuCN}^2\text{LiCl (0.5 M in THF; 5.3 mL, 2.64 mmol, 2.6 eq.) was added followed by TMSCl (675 μL, 574 mg, 5.3 mmol, 5.3 eq.) and methyl vinyl ketone (240 μL, 201 mg, 2.88 mmol, 2.9 eq.). After stirring for 1 h at −40 °C the reaction was slowly warmed over 5 h to rt and stirring was continued for 4 h at rt. The reaction was quenched with HCl (1 M, 5 mL) and stirred for 20 min at rt. Then NH}_4\text{OH was added until the pH was ~9. The blue reaction mixture was extracted with Et}_2\text{O (3 × 10 mL) and the combined ethereal phases washed with dist. H}_2\text{O (2 × 10 mL), dried over Na}_2\text{SO}_4 \text{ and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3f as a colorless oil (189 mg, 0.82 mmol, 82% yield).} \]

\( R_f = 0.24 \) (Hexanes: EtOAc = 20:1; stained with anisaldehyde).

**1H NMR** (400 MHz, CDCl\(_3\)) \( \delta 7.20 – 7.10 \) (m, 4H), 7.05 (d, \( J = 6.9 \) Hz, 1H), 2.48 (t, \( J = 7.7 \) Hz, 2H), 2.06 (s, 3H), 1.70 – 1.52 (m, 2H), 1.45 – 1.25 (m, 2H), 1.16 (s, 3H), 0.97 (t, \( J = 7.3 \) Hz, 3H), 0.94 – 0.88 (m, 2 H). **13C NMR** (101 MHz, CDCl\(_3\)) \( \delta 208.7, 150.2, 128.2, 127.4, 125.4, 44.2, 30.0, 29.1, 26.4 \) (2C's), 18.8, 17.4, 15.2, 14.5. **HRMS** (TOF-MS ES\(^+\)): [M+H]\(^+\), calculated for C\(_{16}\)H\(_{22}\)O: 231.1749; found 231.1724. HPLC analysis (CHIRALCEL OD, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, \( t_{R1} = 6.5 \) min, \( t_{R2} = 7.4 \) min) indicated 93:7 er. \([\alpha]_D^{20} = +19.3\ (c = 0.48, \text{CHCl}_3)\).
4-((1S,2S,3R)-2,3-dimethyl-2-phencylcyclopropyl)butan-2-one (3g)

General procedure GP3:

CuTC (9.5 mg, 0.038 mmol, 5.0 mol%) and (R)-DTBM-SEGPHOS® (48.3 mg, 0.041 mmol, 5.5 mol%) were dissolved in Et₂O (3.0 mL) under argon atmosphere. After stirring the solution for 1 h at rt the mixture was cooled to −78 °C and the cyclopropene substrate (1.5 mL, 99.1 mg, 0.75 mmol, 1.0 eq.; 0.5 M solution in pentane) was added. After 5 min Et₂Zn (0.9 mL, 0.9 mmol, 1.2 eq.; 1.0 M solution in heptanes) was added dropwise at the wall of the flask. The reaction was stirred for 3 h at −78 °C then warmed to −40 °C over 1 h. CuCN·2LiCl (0.5 M in THF; 4.0 mL, 1.99 mmol, 2.64 eq.) was added followed by TMSCl (506 µL, 430 mg, 4.0 mmol, 5.3 eq.) and methyl vinyl ketone (180 µL, 151 mg, 2.16 mmol, 2.9 eq.). After stirring for 1 h at −40 °C the reaction was slowly warmed over 5 h to rt and stirring was continued for 4 h at rt. The reaction was quenched with HCl (1 M, 5 mL) and stirred for 20 min at rt. Then NH₄OH was added until the pH was ~9. The blue reaction mixture was extracted with Et₂O (3 × 10 mL) and the combined ethereal phases washed with dist. H₂O (2 × 10 mL), dried over Na₂SO₄ and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3g as a colorless oil (82 mg, 0.38 mmol, 51% yield). Rₚ = 0.18 (Hexanes: EtOAc = 20:1; stained with anisaldehyde).

**1H NMR** (400 MHz, CDCl₃) δ 7.23 – 7.11 (m, 4H), 7.10 – 7.03 (m, 1H), 2.49 (t, J = 7.3 Hz, 2H), 2.10 (s, 3H), 1.62 (dt, J = 7.8, 7.5 Hz, 2H), 1.16 (s, 3H), 1.12 – 1.05 (m, 1H), 1.01 (d, J = 6.2 Hz, 3H), 0.95 – 0.86 (m, 1H). **13C NMR** (101 MHz, CDCl₃) δ 208.9, 150.1, 128.3, 127.1, 125.4, 44.0, 30.0, 26.5, 25.9, 21.0, 18.6, 14.8, 8.3. **HRMS** (TOF-MS ES⁺): [M+H]⁺, calculated for C₁₅H₂₁O: 217.1587; found 217.1586. HPLC analysis (CHIRALCEL OD, 1%
IPA: 99% hexanes, 1.0 mL/min, 254 nm, \( t_{R1} = 6.88 \text{ min}, t_{R2} = 7.68 \text{ min} \) indicated 88:12 er. \([\alpha]_{D}^{20} = +15.2 \) (c = 0.58, CHCl₃).

4-((1S,2S,3R)-3-butyl-2-methyl-2-phenylcyclopropyl)butan-2-one (3h)

3h was prepared according to general procedure GP2 on 0.4 mmol scale. A 1.0 M commercial solution of of \( n \)Bu₂Zn in heptanes was used. The oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3h as a colorless oil (55 mg, 0.21 mmol, 53% yield). \( R_f = 0.19 \) (Hexanes: EtOAc = 20:1; stained with anisaldehyde).

\(^1\)H NMR (400 MHz, CDCl₃) \( \delta 7.31 – 7.21 \) (m, 4H), 7.18 – 7.12 (m, 1H), 2.59 (t, \( J = 7.7 \) Hz, 2H), 2.19 (s, 3H), 1.79 – 1.65 (m, 2H), 1.49 – 1.33 (m, 6H), 1.26 (s, 3H), 1.09 – 0.98 (m, 2H), 0.94 (t, \( J = 7.0 \) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta 209.1, 150.3, 128.4, 127.5, 125.6, 44.3, 32.6, 30.2, 27.4, 26.5, 26.4, 24.0, 23.0, 19.0, 15.4, 14.3. \) HRMS (TOF-MS ES\(^{+}\)): [M+H]\(^{+}\), calculated for C\(_{18}\)H\(_{27}\)O: 259.2056; found 259.2050. HPLC analysis (CHIRALCEL OD, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, \( t_{R1} = 5.8 \text{ min}, t_{R2} = 6.4 \text{ min} \) indicated 86:14 er \([\alpha]_{D}^{20} = +8.4 \) (c = 0.40, CHCl₃).
3i was prepared according to the general procedure GP3 on a 1.0 mmol scale. A 1.0 M commercial solution of of commercially available \( \text{Ph}_2\text{Zn} \) in THF was used. Flash chromatography (hexanes) of the crude product afforded \( \text{3i} \) as a colorless oil (148 mg, 0.85 mmol, 85% yield) and as a 93:7 mixture of diastereomers. \( R_f = 0.52 \) (minor) and 0.57 (major); (hexanes; stained with phosphomolybdic acid). By column chromatographic purification a diastereomerically pure sample was obtained.

\[ ^1\text{H NMR} \text{ (400 MHz, CDCl}_3; \text{ major diastereomer) } \delta 7.40 - 7.26 \text{ (m, 8H), 7.24 - 7.16 \text{ (m, 2H), 2.40 \text{ (dd, } J = 8.5, 6.7 \text{ Hz, 1H), 1.44 \text{ (dd, } J = 8.7, 5.1 \text{ Hz, 1H), 1.25 - 7.16 \text{ (m, 1H), 1.11 \text{ (s, 3H).}} } ^{13}\text{C NMR} \text{ (101 MHz, CDCl}_3; \delta 148.0, 139.2, 129.3, 128.5, 128.2, 127.0, 126.1, 125.9, 31.5, 27.1, 21.1, 18.8. Spectral data consistent with reported data.} \]

HPLC analysis (CHIRALCEL OD, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, \( t_{R1} = 6.5 \text{ min, } t_{R2} = 7.4 \text{ min} \)) indicated 82:18 er. [\( \alpha \)\text{D}]\text{20} = -118.9 (c = 0.51, CHCl\text{3}). Lit.\(^{[4]}\) [\( \alpha \)\text{D}]\text{20} = -156.5 (c = 1.08, CHCl\text{3}; 95:5 er).
1-chloro-4-((1R,2R)-2-ethyl-1-methylcyclopropyl)benzene (3j)

Cyclopropane 3j was prepared according to general procedure GP1 (1.0 mmol scale). The catalyst loading was 5.0 mol% (unoptimized conditions). After standard work-up the oily residue was purified by flash chromatography (hexanes) to obtain 3j as a colorless oil (185 mg, 0.95 mmol, 95% yield). R_f = 0.85 (Hexanes; stained with phosphomolybdic acid). ^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.25 (m, 2H), 7.22 – 7.19 (m, 2H), 1.61 – 1.46 (m, 2H), 1.40 (s, 3H), 1.11 (t, J = 7.4 Hz, 3H), 1.06 (dd, J = 8.9, 4.4 Hz, 1H), 1.01 – 0.93 (m, 1H), 0.44 – 0.41 (m, 1H).

^13C NMR (101 MHz, CDCl_3) δ 147.7, 131.1, 128.6, 128.3, 128.5, 128.3, 128.5, 23.8, 23.0, 20.7, 20.2, 14.6.

HRMS (TOF-MS ES^+): [M+H]^+, calculated for C_{12}H_{16}Cl: 195.0941; found 195.0945. GC analysis (Cyclodex-B; 80-1-120; t_R1 = 37.5 min, t_R2 = 38.2 min) indicated 91:9 er. [α]_D^{20} = −21.3 (c = 0.84, CHCl_3).
Ketone 3k was prepared according to general procedure GP2 (1.0 mmol scale). The catalyst loading was 5.0 mol% (unoptimized conditions). After standard work-up the oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3k as a colorless oil (174 mg, 0.66 mmol, 66% yield). R_f = 0.21 (Hexanes: EtOAc = 20:1; stained with anisaldehyde). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.23 – 7.19 (m, 2H), 7.16 – 7.11 (m, 2H), 2.56 (t, $J = 7.6$ Hz, 2H), 2.17 (s, 3H), 1.78 – 1.62 (m, 2H), 1.54 – 1.32 (m, 2H), 1.22 (s, 3H), 1.05 (t, $J = 7.3$ Hz, 3H), 1.00 – 0.92 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 208.8, 148.8, 131.1, 128.9, 128.4, 44.1, 30.1, 29.3, 26.6, 26.0, 18.4, 17.4, 15.1, 14.5. HRMS (TOF-MS ES$^+$): [M+H]$^+$, calculated for C$_{16}$H$_{22}$OCl: 265.1359; found 265.1350. HPLC analysis (CHIRALCEL AD-H, 0.5% IPA: 99.5% hexanes, 1.0 mL/min, 254 nm, $t_{R1} = 7.0$ min, $t_{R2} = 8.0$ min) indicated 91:9 er. [$\alpha$]$_D^{20} = +18.7$ (c = 0.42, CHCl$_3$).

Cu(CH$_3$CN)$_4$PF$_6$ (3.8 mg, 0.01 mmol, 1.0 mol%) and (R)-DTBMS-SEGPHOS® (13.0 mg, 0.011 mmol, 1.1 mol%) were dissolved in THF (4.0 mL) under argon atmosphere. After stirring the pale pink solution for 1 h at rt the mixture was cooled to 0 °C and the cyclopropene substrate (2.0 mL, 165 mg, 1.0 mmol, 1.0 eq.) was added as a 0.5 M solution in pentane. After 5 min Et$_2$Zn (1.0 M solution in hexanes; 1.2 mL, 1.2 mmol, 1.2 eq.) was added dropwise at the wall of the flask over 1 min. After stirring the solution for 4 h
at 0 °C a solution of Pd(OAc)$_2$ (10.0 mg, 0.04 mmol, 0.04 eq.) and SPhos (33 mg, 0.08 mmol, 0.08 eq.) in THF (1.0 mL) was added at rt followed by 4-bromoacetophenone (498 mg, 2.5 mmol, 2.5 eq.). Stirring at rt was continued for 16 h. Then the reaction mixture was treated with HCl (1 M, 5 mL) and extracted with Et$_2$O (3 × 15 mL). The combined organic phases were dried over Na$_2$SO$_4$ and reduced in vacuo. The oily residue was heated to 250 °C at 1 mbar to remove 1-(4-ethylphenyl)ethanone and then purified by flash chromatography (hexanes / ethyl acetate = 20:1) to obtain 3s as a colorless viscous oil (235 mg, 0.75 mmol, 75% yield).

H NMR (400 MHz, CDCl$_3$) δ 7.93 (d, $J$ = 8.2 Hz, 2H), 7.38 (apd, $J$ = 8.0 Hz, 2H), 7.34 – 7.27 (m, 4H), 2.60 (s, 3H), 2.41 (d, $J$ = 9.4 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.49 – 1.39 (m, 1H), 1.28 – 1.21 (m, 1H), 1.19 (s, 3H), 1.14 (t, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 197.9, 147.8, 143.6, 135.3, 131.7, 131.1, 129.1, 128.6, 128.4, 31.8, 31.1, 28.5, 26.6, 19.5, 17.6, 14.6. $R_f$ = 0.53 (Hexanes: EtOAc = 10:1; stained with anisaldehyde). HRMS (APCI): [M+H]$^+$, calculated for C$_{20}$H$_{22}$ClO: 313.1354; found 313.1360. HPLC analysis (CHIRALCEL OD, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, $t_{R1}$ = 7.9 min, $t_{R2}$ = 8.9 min) indicated 91:9 er. [α]$_D^{20}$ = +166.9 (c = 0.60, CHCl$_3$).

4-((1R,2S,3R)-2-(4-chlorophenyl)-3-ethyl-2-methylcyclopropyl)benzaldehyde (3t) Cu(CH$_3$CN)$_4$PF$_6$ (3.8 mg, 0.01 mmol, 0.5 mol%) and (R)-DTBMS-SEGPHOS$^\circledR$ (13.0 mg, 0.011 mmol, 0.55 mol%) were dissolved in THF (8.0 mL) under argon atmosphere. After stirring the pale pink solution for 1 h at rt the mixture was cooled to 0 °C and the cyclopropene substrate (4.0 mL, 329.3 mg, 2.0 mmol, 1.0 eq.) was added as a 0.5 M solution in pentane. After 5 min Et$_2$Zn (1.0 M solution in hexanes; 2.4 mL, 2.4 mmol, 1.2 eq.) was added dropwise.
at the wall of the flask over 1 min. After stirring the solution for 5 h at 0 °C a solution of Pd(OAc)$_2$ (20.0 mg, 0.08 mmol, 0.04 eq.) and SPhos (66 mg, 0.16 mmol, 0.08 eq.) in THF (2.0 mL) was added at rt followed by 4-Bromobenzaldehyde (925 mg, 5.0 mmol, 2.5 eq.). Stirring at rt was continued for 16 h. Then the reaction mixture was treated with HCl (1 M, 5 mL) and extracted with Et$_2$O (3 × 15 mL). The combined organic phases were dried over Na$_2$SO$_4$ and reduced in vacuo. The oily residue was heated to 250 °C at 1 mbar to remove 4-ethylbenzaldehyde and then purified by flash chromatography (hexanes / ethyl acetate = 20:1) to obtain 3t as a colorless oil (523 mg, 1.75 mmol, 88% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.00 (s, 1H), 7.85 (apd, $J = 8.1$ Hz, 2H), 7.46 (apd, $J = 7.9$ Hz, 2H), 7.35 – 7.27 (m, 4H), 2.43 (d, $J = 9.4$ Hz, 1H), 1.84 – 1.72 (m, 1H), 1.52 – 1.72 (m, 1H), 1.30 – 1.21 (m, 1H), 1.19 (s, 3H), 1.15 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 192.1, 147.7, 145.3, 113.7, 131.5, 129.8, 129.1, 128.7, 32.0, 31.2, 28.7, 19.5, 17.7, 14.6. HRMS (APCI): [M+H]$^+$, calculated for C$_{19}$H$_{20}$ClO: 299.1197; found 299.1261. $R_f = 0.54$ (Hexanes: EtOAc = 10:1; stained with KMnO$_4$). HPLC analysis (CHIRALCEL AD-H, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, $t_R1 = 7.9$ min, $t_R2 = 10.0$ min) indicated 91:9 er. $[\alpha]_D^{20} = +178.4$ (c = 0.84, CHCl$_3$).

Ketone 3a was prepared according to general procedure GP2 (1.0 mmol scale). The catalyst loading was 5.0 mol% (unoptimized conditions). After standard work-up the oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3l as a colorless oil (146 mg, 0.56 mmol, 56% yield). $R_f = 0.21$ (Hexanes: EtOAc = 20:1; stained with anisaldehyde). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.17 – 7.13 (m, 2H), 6.85 – 6.79 (m, 2H), 3.78 (s, 3H), 2.58...
(t, J = 7.7 Hz, 2H), 2.18 (s, 3H), 1.83 – 1.62 (m, 2H), 1.54 – 1.33 (m, 2H), 1.22 (s, 3H), 1.06 (t, J = 7.3 Hz, 3H), 1.01 – 0.91 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 209.0, 157.5, 142.7, 128.6, 113.7, 55.3, 44.3, 30.0, 28.9, 26.3, 25.9, 18.9, 17.5, 15.6, 14.1. HRMS (TOF-MS ES⁺): [M+H]+, calculated for C17H25O2: 261.1855; found 261.1850. HPLC analysis (CHIRALCEL OD, 0.5% IPA: 99.5% hexanes, 1.0 mL/min, 254 nm, tR1 = 9.5 min, tR2 = 10.2 min) indicated 90:10 er. [α]D20 = +18.9 (c = 0.88, CHCl3).

**4-((1S,2S,3R)-3-ethyl-2-isopropyl-2-phenylcyclopropyl)butan-2-one (3m)**

Ketone 3m was prepared according to general procedure GP2 (1.0 mmol scale). The catalyst loading was 5.0 mol% (unoptimized conditions). After standard work-up the oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3m as a colorless oil (167 mg, 0.65 mmol, 65% yield). Rf = 0.32 (Hexanes: EtOAc = 20:1; stained with anisaldehyde).

1H NMR (400 MHz, CDCl3) δ 1H NMR (400 MHz, CDCl3) δ 7.25 – 7.23 (m, 4H), 7.19 – 7.14 (m, 1H), 2.62 (t, J = 7.4 Hz, 2H), 2.21 – 2.14 (m, 3H), 2.04 – 1.89 (m, 1H), 1.78 – 1.70 (m, 1H), 1.69 – 1.59 (m, 2H), 1.48 – 1.35 (m, 1H), 1.11 (t, J = 7.4 Hz, 3H), 0.99 – 0.91 (m, 2H), 0.85 (m, 6H). 13C NMR (101 MHz, CDCl3) δ 208.9, 145.4, 131.8, 127.3, 125.8, 44.7, 37.2, 30.1, 28.8, 26.7, 26.1, 20.8, 20.6, 18.1, 16.7, 15.2. HRMS (TOF-MS ES⁺): [M+H]+, calculated for C18H27O: 259.2062; found 259.2060. HPLC analysis (CHIRALCEL OD, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, tR1 = 6.0 min, tR2 = 8.0 min) indicated 99.7:0.3 er. [α]D20 = +16.9 (c = 1.08, CHCl3).
4-((1S,2R,3S)-2-ethyl-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-3-yl)butan-2-one (3n)

Ketone 3n was prepared according to general procedure GP2 (1.0 mmol scale). The catalyst loading was 5.0 mol% (unoptimized conditions). After standard work-up the oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3n as a colorless viscous oil (165 mg, 0.64 mmol, 64% yield). Rf = 0.25 (Hexanes: EtOAc = 20:1; stained with anisaldehyde).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.16 – 7.10 (m, 1H), 7.09 – 7.03 (m, 2H), 6.72 (d, $J$ = 7.9 Hz, 1H), 2.88 (t, $J$ = 6.2 Hz, 2H), 2.57 (dd, $J$ = 9.7, 5.7 Hz, 2H), 2.17 (s, 3H), 1.92 – 1.82 (m, 2H), 1.79 – 1.69 (m, 4H), 1.58 – 1.40 (m, 2H), 1.19 – 1.10 (m, 2H), 1.05 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 208.7, 143.8, 137.0, 128.6, 126.2, 124.3, 121.7, 44.1, 34.2, 31.4, 31.0, 30.0, 23.6, 22.8, 18.4, 17.3, 14.6. Rf = 0.25 (Hexanes: EtOAc = 20:1; stained with anisaldehyde).

HRMS (TOF-MS ES$^+$): [M+H]$^+$, calculated for C$_{18}$H$_{24}$O: 257.19055 found 257.19049. HPLC analysis (CHIRALCEL OD, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, $t_{R1}$ = 7.0 min, $t_{R2}$ = 10.5 min) indicated 94:6 er. $[\alpha]_D^{20} = +41.1$ (c = 0.59, CHCl$_3$).
((1S,2R)-2-ethyl-1-methylcyclopropyl)methyl)benzene (3o)

CuTC (9.5 mg, 0.05 mmol, 5.0 mol%) and (R)-DTBM-SEGPHOS® (64.9 mg, 0.055 mmol, 5.5 mol%) were dissolved in Et₂O (3.0 mL) under argon atmosphere. After stirring the solution for 1 h at rt the mixture was cooled to -78 °C and the cyclopropene substrate (2.0 mL, 130.2 mg, 1.0 mmol, 1.0 eq.) was added as a 0.5 M solution in pentane.

After 5 min Et₂Zn (1.0 M solution in hexanes; 1.2 mL, 1.2 mmol, 1.2 eq.) was added dropwise at the wall of the flask. The reaction was stirred for 3 h at -78 °C then over 3 h warmed to 0 °C. The reaction mixture was quenched with HCl (1.0 M; 5.0 mL) and diluted with Et₂O (10 mL). The organic phase was separated and the aqueous phase extracted with Et₂O (2 ×10 mL). The combined organic phases were dried over Na₂SO₄ and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes) to obtain 3o as a colorless oil (148 mg, 0.85 mmol, 85% yield) and a 4:1 mixture of unassigned diastereomers. R<sub>r</sub> = 0.80 (Hexanes; stained with phosphomolybdic acid).

<sup>1</sup>H NMR (400 MHz, CDCl₃; mixture of diastereomers) δ 7.22 – 7.06 (m), 2.62 (d, J = 14.5 Hz; major), 2.52 – 2.46 (m), 2.39 (d, J = 14.0 Hz, minor), 1.61 – 1.48 (m), 1.30 – 1.16 (m), 0.95 (t, J = 7.3 Hz; major), 0.90 – 0.85 (m, 1H), 0.84 (s; major), 0.65 – 0.57 (m; minor), 0.55 – 0.46 (m), 0.39 (dd, J = 8.4, 4.2 Hz, major), 0.11 (t, J = 4.8 Hz; major), -0.12 (t, J = 4.8 Hz; minor). <sup>13</sup>C NMR (101 MHz, CDCl₃; mixture of diastereomers) δ 141.3 (major), 141.0 (minor), 129.38 (minor), 129.35 (major), 128.2 (major), 128.1 (minor), 126.0 (minor), 125.8 (major), 47.4 (minor), 39.9 (major), 27.3 (major), 25.7 (minor), 25.0 (major), 25.0 (minor), 23.4 (major), 23.0 (minor), 20.6 (major), 19.2 (major), 18.6 (minor), 17.5 (minor), 14.6 (major), 14.6 (minor). HRMS (TOF-MS ES⁺): [M+H]<sup>+</sup>, calculated for C₁₃H₁₈: 175.1487; found 175.1476.

Note: The enantiomeric ratio of 3o could not be determined by HPLC or GC with the chiral columns tested (see chemical materials and methods). Therefore, the same enantiomeric ratio as for 3p was assigned.
4-((1S,2S,3R)-2-benzyl-3-ethyl-2-methylcyclopropyl)butan-2-one (3p)

CuTC (9.5 mg, 0.038 mmol, 5 mol%) and (R)-DTBM-SEGPHOS® (48.3 mg, 0.041 mmol, 5.5 mol%) were dissolved in Et₂O (3.0 mL) under argon atmosphere. After stirring the pale pink solution for 1 h at rt the mixture was cooled to −78 °C and the cyclopropene substrate (108.2 mg, 0.75 mmol, 1.0 eq.) was added as a 0.5 M solution in pentane. After 5 min Et₂Zn (1.0 M solution in hexanes; 0.9 mL, 0.9 mmol, 1.2 eq.) was added dropwise at the wall of the flask over 1 min. After the reaction was stirred for 3 h at -78 °C and 1 h at 0 °C the reaction vessel was cooled to -40 °C and CuCN·2LiCl (0.5M in THF; 4.0 mL, 2.0 mmol, 2.7 eq.) was added followed by TMSCl (506 µL, 430 mg, 3.96 mmol, 5.3 eq.) and methyl vinyl ketone (180 µL, 151 mg, 2.16 mmol, 2.9 eq.). After stirring for 1 h at - 40 °C the reaction was slowly warmed over 5 h to rt and stirring was continued for 4 h at rt. The reaction was quenched with HCl (1 M, 5 mL) and stirred for 20 min at rt. Then NH₄OH was added until the pH was ~9. The reaction mixture was extracted with Et₂O (3 × 10 mL) and the combined ethereal phases washed with dist. H₂O (2 × 10 mL), dried over Na₂SO₄ and reduced in vacuo. The oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1) to obtain 3p as a colorless oil (124 mg, 0.51 mmol, 68% yield). Rf = 0.25 (Hexanes: EtOAc = 20:1; stained with anisaldehyde).

¹H NMR (400 MHz, CDCl₃; mixture of diastereomers) δ ¹H NMR (400 MHz, CDCl₃) δ 7.23 – 7.18 (m), 7.17 – 7.07 (m), 2.59 (d, J = 1.6 Hz; major), 2.46 (t, J = 7.6 Hz; major), 2.37 – 2.29 (m, minor), 2.09 (s, major), 2.04 (s, minor), 1.78 – 1.66 (m, 1H), 1.60 – 1.41 (m, 1H), 1.34 – 1.16 (m, 1H), 0.95 (t, J = 7.3 Hz; major), 0.87 (s; major), 0.86 – 0.83 (m, minor), 0.76 (s, minor), 0.63 – 0.58 (m, minor), 0.53 – 0.46 (m, major). ¹³C NMR (101 MHz, CDCl₃; mixture of diastereomers) δ 209.3 (minor), 209.2 (major), 140.9 (minor), 140.5 (major), 129.5 (major), 129.3 (minor), 128.2 (major), 128.1 (minor), 126.0 (minor), 125.8 (major), 49.0 (minor), 44.6 (major), 44.2 (minor), 35.2 (major), 30.2 (major), 30.1 (minor), 29.4 (major), 27.8 (minor), 27.1 (major), 26.6 (major), 24.8 (minor), 22.6 (minor), 21.6 (major), 19.4 (major), 18.9 (minor), 18.1 (major), 17.6 (minor), 15.0 (major), 14.6 (minor), 12.2 (minor).

HRMS (TOF-MS ES⁺):[M+H]⁺, calculated for C₁₇H₂₅O: 245.1900; found 245.1896. HPLC analysis analysis (CHIRALCEL OD, 1% IPA: 99% hexanes, 1.0 mL/min, 254 nm, tᵣ₁ = 7.63 min, tᵣ₂ = 8.93 min) indicated 99.3:0.7 er. Note: First peak in HPLC trace belongs to the minor diastereomer. We were unable to find conditions to efficiently separate the enantiomers of the minor diastereomer.
Ketone 3q was prepared according to general procedure GP2 (0.5 mmol scale). The catalyst loading was 5.0 mol% (optimized). A prolonged reaction time of 8 h at 0 °C was necessary to achieve full conversion for the carbozincation. After standard work-up the oily residue was purified by flash chromatography (hexanes: EtOAc = 20:1 to 10:1) to obtain 3q as a colorless viscous oil (68 mg, 0.23 mmol, 47% yield). $R_f = 0.32$ (Hexanes: EtOAc = 10:1; stained with anisaldehyde).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28 – 7.22 (m, 4H), 7.19 – 7.09 (m, 3H), 7.08 – 6.98 (m, 3H), 2.67 – 2.51 (m, 2H), 2.09 (s, 3H), 1.94 – 1.81 (m, 1H), 1.64 – 1.52 (m, 1H), 1.45 – 1.25 (m, 3H), 1.22 – 1.11 (m, 1H), 1.08 (t, $J = 6.5$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 208.6, 149.1, 139.5, 131.7, 128.6, 128.3, 127.2, 126.5, 125.5, 44.2, 37.5, 32.0, 30.1, 29.3, 20.9, 19.7, 14.9. HRMS TOF-MS ES+: [M+H]$^+$, calculated for C$_{21}$H$_{25}$O: 293.1900; found 293.1898. HPLC analysis (CHIRALCEL OD, 0.5% IPA: 99.5% hexanes, 1.0 mL/min, 254 nm, $t_{R1} = 12.3$ min, $t_{R2} = 15.3$ min) indicated 90:10 er. $[\alpha]_D^{20} = -6.6$ (c = 0.36, CHCl$_3$).
1-(4-((1R,2S,3R)-2-tert-butyl-3-ethyl-2-methylcyclopropyl)phenyl)ethanone (3r)

CuTC (11.4 mg, 0.06 mmol, 10.0 mol%) and (R)-DTBM-SEGPHOS® (77.9 mg, 0.066 mmol, 11.0 mol%) were dissolved in Et₂O (2.5 mL) under argon atmosphere. After stirring the solution for 1 h at rt the mixture was cooled to −78 °C and cyclopropene 1h (1.0 mL, 55.1 mg, 0.6 mmol, 1.0 eq; 0.6 M solution in pentane) was added. After 5 min Et₂Zn (1.0 M solution in hexanes; 0.72 mL, 1.2 mmol, 1.2 eq.) was added dropwise at the wall of the flask. The reaction was stirred for 3 h at −78 °C then was warmed to 0 °C over 3 h (GC-analysis showed 30% conversion after 3 h at −78 °C). To the in situ generated cyclopropylzinc was added a solution of Pd(OAc)₂ (5.4 mg, 0.024 mmol, 0.04 eq.) and SPhos (32.9 mg, 0.048 mmol, 0.08 eq.) in THF (1.0 mL) followed by 4-bromoacetophenone (298 mg, 1.5 mmol, 2.5 eq.). Stirring at rt was continued for 16 h. Then the reaction mixture was treated with HCl (1 M, 5 mL) and extracted with Et₂O (3 × 15 mL). The combined organic phases were dried over Na₂SO₄ and reduced in vacuo. The oily residue purified by flash chromatography (hexanes / ethyl acetate = 50:1 to 30:1) to obtain 3r as a pale yellow oil (124 mg, 0.48 mmol, 80% yield). Rₚ = 0.45 (Hexanes: EtOAc = 10:1; stained with phosphomolybdic acid).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (appd, J = 8.3 Hz, 2H), 7.22 (appd, J = 7.8 Hz, 2H), 2.56 (s, 3H), 2.04 (d, J = 9.2 Hz, 1H), 1.70 – 1.59 (m, 1H), 1.19 – 1.12 (m, 1H), 1.11 – 1.01 (m, 1H), 1.00 – 0.96 (m, 3H), 0.95 (s, 9H), 0.77 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 198.0, 145.6, 134.7, 131.3, 128.2, 33.0, 30.6, 27.1, 26.9, 26.6, 25.9, 19.6, 14.8, 11.8. HRMS (APCI): [M+H]+, calculated for C₁₈H₂₇O: 259.2056; found 259.2063. HPLC analysis (CHIRALCEL...
OD, 0.5% IPA: 99.5% hexanes, 1.0 mL/min, 254 nm, $t_{R1} = 5.9$ min, $t_{R2} = 6.2$ min) indicated
96:4 er. $[\alpha]_D^{20} = +30.7$ (c = 0.76, CHCl$_3$).

5 References

NMR Spectra
mixture of diastereomers
mixture of diastereomers
NOE's

COSY Signals are shown in blue.
NOESY Signals are shown in red.