Supplementary Information

Cobalt-Catalyzed Highly Enantioselective Hydrogenation of $\alpha,\beta$-Unsaturated Carboxylic Acids

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Supplementary Methods

General information

All the reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under an argon atmosphere or in an argon-filled glove box. Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers without further purification. Anhydrous solvents were purchased from J&K Chemical and degassed by bubbling argon over a period of 30 min. Purification of products was carried out by flash chromatography using silica gel (200-300 mesh). Thin layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. Co(acac)₂ and other metal precursors were purchased from Strem or Alfa.

¹H, ¹³C, ¹⁹F and ³¹P NMR spectra were recorded on a Bruker Avance 400 MHz or a Bruker Avance 600 MHz spectrometer with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm, δ scale) downfield from TMS at 0.00 ppm and referenced to the CDCl₃ at 7.26 ppm for ¹H NMR or 77.0 ppm for ¹³C NMR. Data are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz) and signal area integration in natural numbers. ¹³C NMR and ³¹P NMR analyses were recorded with ¹H decoupling. Enantiomeric excess values were determined with Agilent 1290 or 1260 Series HPLC instrument on a chiral stationary phase. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Rudolph Autopol I polarimeter at 589 nm.
Asymmetric hydrogenation of 2,3-disubstituted acrylic acids

Method A (for 1a-o).

In an argon-filled glovebox, Co(acac)₂ (0.010 M in iPrOH, 0.10 mL, 0.001 mmol) and (S,S)-Ph-BPE (0.010 M in THF, 0.10 mL, 0.001 mmol) were stirred in a vial at room temperature for 10 min. Then zinc dust (0.65 mg, 0.01 mmol) and iPrOH (0.50 mL) were added and the mixture was stirred for 15 min. After that, substrate (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H₂. The reaction was then stirred under H₂ (40 atm) at room temperature for 24 h. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.

Method B (for 1p-u).

In an argon-filled glovebox, CoCl₂ (0.025 M in THF, 0.2 mL, 0.005 mmol) and (S,S)-Ph-BPE (2.53 mg, 0.005 mmol) in MeOH (0.2 mL) were stirred in a vial at room temperature for 10 min. Then zinc dust (0.65 mg, 0.01 mmol) and MeOH (0.2 mL) were added and the mixture was stirred for 15 min. After that, substrate (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H₂. The reaction was then stirred under H₂ (60 atm) at 50 °C for 72 h. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.
Supplementary Table 1. Cobalt precursors screening\textsuperscript{[a]}

| entry | cobalt            | conv. [%]\textsuperscript{[b]} | ee [%]\textsuperscript{[c]} |
|-------|-------------------|---------------------------------|-----------------------------|
| 1     | Co(BF\textsubscript{4})\textsubscript{2}·6H\textsubscript{2}O | ND                             | --                          |
| 2     | Co(II) stearate   | 23                             | --                          |
| 3     | Co(II) oxalate    | ND                             | --                          |
| 4     | CoCl\textsubscript{2} | ND                            | --                          |
| 5     | Co(acac)\textsubscript{2} | 70                           | 94                          |
| 6     | Co(OAc)\textsubscript{2}·4H\textsubscript{2}O | 57                             | 87                          |

\textsuperscript{[a]} Reaction conditions: 1 (0.1 mmol), [Co] (5 mol%), (S,S)-Ph-BPE (5 mol%) in MeOH (0.4 mL) under 60 atm H\textsubscript{2} pressure at 50 °C for 24 h. [b] Determined by \textsuperscript{1}H NMR. [c] Determined by HPLC analysis.
**Supplementary Table 2. Ligand screening**

| Ligand Structure | Reaction Conditions | Conversion | ee Value |
|------------------|---------------------|------------|----------|
| 1a               | Co(acac)$_2$ (5 mol%), Ligand (5 mol%) in MeOH, 60 atm H$_2$, 50 °C, 24 h | 70% yield, 94% ee |          |
| E2               | R = Me, 0% yield    |            |          |
| E3               | R = iPr, 0% yield   |            |          |
| E4               | R = Me, 9% yield, 70% ee |          |          |
| E5               | R = iPr, 56% yield, 66% ee |          |          |
| E6               | (S)-Binapine, 63% yield, 30% ee |          |          |
| E7               | (S,S)-Binaphane, 0% yield |          |          |
| E8               | (Rc,Sp)-DuanPhos, 0% yield |          |          |
| E9               | (S)-SDP, 0% yield |            |          |
| E10              | R = Ph, 0% yield |            |          |
| E11              | R = 4-MeO-Ph, 0% yield |          |          |
| E12              | R = 4-MeO-3,5-Me$_2$-Ph, 0% yield |          |          |
| E13              | (S)-QuinoxP, 0% yield |          |          |
| E14              | (R)-(S)-Josiphos, 0% yield |          |          |
| E15              | R = Ph, 0% yield |            |          |
| E16              | R = 3,5- tBu-4-MeO-Ph, 0% yield |          |          |
| E17              | (S)-MeO-BIPHEP, 0% yield |          |          |
| E18              | R = Ph, 0% yield |            |          |
| E19              | R = 3,5-Me$_2$-Ph, 0% yield |          |          |
| E20              | (R)-BenzP, 0% yield |            |          |

[a] Reaction conditions: 1 (0.1 mmol), Co(acac)$_2$ (5 mol%), Ligand (5 mol%) in MeOH (0.4 mL) under 60 atm H$_2$ pressure at 50 °C for 24 h. Conversions were determined by $^1$H NMR and ee values were determined by HPLC analysis.
### Supplementary Table 3. Solvent screening[^a]

| entry | solvent   | conv. [%][^b] | ee [%][^c] |
|-------|-----------|---------------|------------|
| 1     | MeOH      | 70            | 94         |
| 2     | tBuOH     | 88            | 87         |
| 3     | iPrOH     | >98           | 93         |
| 4     | TFE       | >98           | 84         |
| 5     | DME       | 7             | 43         |
| 6     | toluene   | 15            | 86         |
| 7     | CH₃CN     | 58            | 64         |
| 8     | THF       | ND            | --         |
| 9     | 1,4-Dioxane | ND       | --         |
| 10    | Et₂O      | ND            | --         |

[^a]: Reaction conditions: 1 (0.1 mmol), Co(acac)₂ (5 mol%), (S,S)-Ph-BPE (5 mol%) in solvent (0.6 mL) under 60 atm H₂ pressure at 50 °C for 24 h. [^b] Determined by ^1^H NMR. [^c] Determined by HPLC analysis.

### Supplementary Table 4. Additive screening[^a]

| entry | additive | conv. [%][^b] | ee [%][^c] |
|-------|----------|---------------|------------|
| 1     | Zn       | >98           | 97         |
| 2     | Mn       | >98           | 96         |
| 3     | LiO^Bu   | 36            | 95         |
| 4     | NaO^Bu   | 48            | 95         |
| 5     | KO^Bu    | 55            | 93         |
| 6     | Cs₂CO₃   | 7             | 88         |
| 7     | NaOH     | 57            | 93         |
| 8     | none     | 61            | 93         |

[^a]: Reaction conditions: 1 (0.1 mmol), Co(acac)₂ (1 mol%), (S,S)-Ph-BPE (1 mol%), additive (10 mol%) in iPrOH (0.6 mL) under 60 atm H₂ pressure at 50 °C for 24 h. [^b] Determined by ^1^H NMR. [^c] Determined by HPLC analysis.
**Supplementary Table 5. Pressure and temperature screening**[^a]

| entry | H$_2$ [atm] | T [°C] | conv. [%][[^b]] | ee [%][[^c]] |
|-------|-------------|--------|----------------|-------------|
| 1     | 60          | 80     | >98            | 95.6        |
| 2     | 60          | 30     | >98            | 96.9        |
| 3     | 60          | rt     | >98            | 97.4        |
| 4     | 18          | rt     | 97             | 97.3        |
| 5     | 25          | rt     | >98            | 97.2        |
| 6     | 30          | rt     | >98            | 96.9        |
| 7     | 40          | rt     | >98            | 97.3        |

[^a]: Reaction conditions: 1 (0.1 mmol), Co(acac)$_2$ (1 mol%), (S,S)-Ph-BPE (1 mol%), Zn (10 mol%) in iPrOH (0.6 mL) for 24 h. [^b]: Determined by $^1$H NMR. [^c]: Determined by HPLC analysis.

**Characterization data of compound 2**

(R)-2,3-diphenylpropanoic acid (2a).[^1] White solid, 99% yield, 97% ee, [α]$_D^{25} = -77.62$ (c = 0.84, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.29 – 7.25 (m, 4H), 7.24 – 7.10 (m, 4H), 7.09 – 7.04 (m, 2H), 3.82 (t, $J = 7.7$ Hz, 1H), 3.37 (dd, $J = 13.8$, 8.4 Hz, 1H), 2.99 (dd, $J = 13.8$, 7.0 Hz, 1H). $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 179.2, 138.7, 137.9, 128.9, 128.7, 128.3, 128.1, 127.6, 126.4, 53.5, 39.2. The enantiomeric excess of 2a was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 210 nm, $t_R = 19.9$ min (major), 29.6 min (minor).

(S)-2-methyl-3-phenylpropanoic acid (2b).[^2] Colorless oil, 99% yield, 96% ee, [α]$_D^{25} = +12.13$ (c = 0.78, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) δ 7.30 (t, $J = 7.3$ Hz,
2H), 7.25 – 7.16 (m, 3H), 3.09 (dd, J = 13.4, 6.3 Hz, 1H), 2.88 – 2.75 (m, 1H), 2.68 (dd, J = 13.4, 8.0 Hz, 1H), 1.19 (d, J = 6.9 Hz, 3H). \(^{13}\)C NMR (101 MHz, Chloroform-d) \(\delta\) 182.3, 139.0, 129.0, 128.4, 126.4, 41.3, 39.3, 16.5. The enantiomeric excess of 2b was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \(\lambda = 210\) nm, \(t_R\) = 9.5 min (minor), 10.5 min (major).

(S)-2-methyl-3-(p-tolyl)propanoic acid (2c).\(^3\) Colorless oil, 99% yield, 97% ee, \([\alpha]_D^{25} = +49.23\) (c = 0.39, CHCl\(_3\)). \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.13 – 7.06 (m, 4H), 3.04 (dd, J = 13.4, 6.3 Hz, 1H), 2.74 (dt, J = 13.7, 6.9 Hz, 1H), 2.64 (dd, J = 13.4, 8.0 Hz, 1H), 2.33 (s, 3H), 1.18 (d, J = 6.9 Hz, 3H). \(^{13}\)C NMR (101 MHz, Chloroform-d) \(\delta\) 182.4, 135.9, 129.1, 128.9, 41.3, 38.9, 21.0, 16.4. The enantiomeric excess of 2c was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \(\lambda = 220\) nm, \(t_R\) = 12.8 min (minor), 13.9 min (major).

(S)-3-(4-methoxyphenyl)-2-methylpropanoic acid (2d).\(^4\) Colorless oil, 93% yield, 99% ee, \([\alpha]_D^{25} = +20.44\) (c = 0.91, CHCl\(_3\)). \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.10 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.01 (dd, J = 13.4, 6.4 Hz, 1H), 2.72 (h, J = 6.8 Hz, 1H), 2.62 (dd, J = 13.4, 7.9 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H). \(^{13}\)C NMR (101 MHz, Chloroform-d) \(\delta\) 182.3, 158.1, 131.1, 129.9, 113.8, 55.2, 41.4, 38.4, 16.4. The enantiomeric excess of 2d was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \(\lambda = 220\) nm, \(t_R\) = 29.0 min (minor), 30.7 min (major).
(S)-3-[(1,1'-biphenyl)-4-yl]-2-methylpropanoic acid (2e). White solid, 98% yield, 94% ee, \([\alpha]_D^{25} = +7.09\) (c = 1.03, CHCl₃). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.60 – 7.55 (m, 2H), 7.52 (d, \(J = 8.1\) Hz, 2H), 7.42 (t, \(J = 7.6\) Hz, 2H), 7.33 (t, \(J = 7.3\) Hz, 1H), 7.26 (d, \(J = 8.2\) Hz, 2H), 3.12 (dd, \(J = 13.4, 6.3\) Hz, 1H), 2.81 (h, \(J = 6.8\) Hz, 1H), 2.72 (dd, \(J = 13.4, 8.0\) Hz, 1H), 1.22 (d, \(J = 6.9\) Hz, 3H). \(^{13}\)C NMR (151 MHz, Chloroform-\(d\)) \(\delta\) 182.2, 140.9, 139.3, 138.1, 129.4, 128.7, 127.1, 127.0, 41.2, 38.9, 16.5. HRMS calculated [M-H]⁻ for C₁₆H₁₅O₂ = 239.1078, found: 239.1073. The enantiomeric excess of 2e was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \(\lambda = 210\) nm, \(t_R = 30.5\) min (minor), 31.8 min (major).

(S)-3-(4-fluorophenyl)-2-methylpropanoic acid (2f). Colorless oil, 92% yield, 96% ee, \([\alpha]_D^{25} = +13.90\) (c = 0.59, CHCl₃). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.14 (dd, \(J = 8.4, 5.5\) Hz, 2H), 6.97 (t, \(J = 8.7\) Hz, 2H), 3.02 (dd, \(J = 13.3, 6.4\) Hz, 1H), 2.79 – 2.70 (m, 1H), 2.66 (dd, \(J = 13.3, 7.6\) Hz, 1H), 1.18 (d, \(J = 6.7\) Hz, 3H). \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 182.1, 161.6 (d, \(J = 244.6\) Hz), 134.6 (d, \(J = 3.5\) Hz), 130.4 (d, \(J = 7.9\) Hz), 115.2 (d, \(J = 21.1\) Hz), 41.4, 38.5, 16.5. \(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) \(\delta\) -116.7. The enantiomeric excess of 2f was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \(\lambda = 210\) nm, \(t_R = 10.7\) min (minor), 12.1 min (major).

(S)-3-(4-chlorophenyl)-2-methylpropanoic acid (2g). Colorless oil, 95% yield, 95% ee, \([\alpha]_D^{25} = +14.20\) (c = 0.69, CHCl₃). \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 7.25 (d, \(J = 7.3\) Hz, 2H), 7.12 (d, \(J = 8.1\) Hz, 2H), 3.02 (dd, \(J = 13.6, 6.8\) Hz, 1H), 2.73 (p, \(J =
7.1 Hz, 1H), 2.66 (dd, J = 13.6, 7.6 Hz, 1H), 1.18 (d, J = 6.9 Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-d) δ 181.9, 137.4, 132.3, 130.3, 128.6, 41.3, 38.6, 16.6. The enantiomeric excess of 2g was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 220 nm, tR = 10.1 min (minor), 10.5 min (major).

[S]-3-(4-bromophenyl)-2-methylpropanoic acid (2h). Colorless oil, 91% yield, 93% ee, [α]D$^{25}$ = +16.88 (c = 0.96, CHCl3). $^1$H NMR (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 3.01 (dd, J = 13.4, 6.7 Hz, 1H), 2.74 (h, J = 6.9 Hz, 1H), 2.64 (dd, J = 13.5, 7.6 Hz, 1H), 1.18 (d, J = 6.9 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 182.0, 137.9, 131.5, 130.7, 120.3, 41.1, 38.6, 16.5. The enantiomeric excess of 2h was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 98/2, flow rate = 0.5 mL/min, uv-vis detection at λ = 230 nm, tR = 19.4 min (minor), 20.2 min (major).

(S)-2-methyl-3-(4-(trifluoromethyl)phenyl)propanoic acid (2i). Colorless oil, 87% yield, 87% ee, [α]D$^{25}$ = +7.16 (c = 0.95, CHCl3). $^1$H NMR (400 MHz, Chloroform-d) δ 7.55 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.12 (dd, J = 12.6, 5.9 Hz, 1H), 2.85 – 2.70 (m, 2H), 1.21 (d, J = 6.7 Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-d) δ 181.7, 143.1, 129.3, 128.9 (q, J = 32.3 Hz), 125.4 (q, J = 3.9 Hz), 124.2 (q, J = 271.8 Hz), 40.9, 38.9, 16.6. $^{19}$F NMR (376 MHz, Chloroform-d) δ -62.4. The enantiomeric excess of 2c was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 98/2, flow rate = 0.5 mL/min, uv-vis detection at λ = 220 nm, tR = 13.0 min (minor), 13.6 min (major).
(S)-3-(3-methoxyphenyl)-2-methylpropanoic acid (2j). Colorless oil, 89% yield, 94% ee, $[\alpha]_D^{25} = +5.53$ (c = 0.85, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.21 (t, $J = 7.8$ Hz, 1H), 6.82 – 6.72 (m, 3H), 3.79 (s, 3H), 3.06 (dd, $J = 13.5$, 6.4 Hz, 1H), 2.77 (h, $J = 6.8$ Hz, 1H), 2.65 (dd, $J = 13.5$, 8.1 Hz, 1H), 1.19 (d, $J = 6.9$ Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 182.2, 159.6, 140.6, 129.4, 121.4, 114.7, 111.8, 55.1, 41.1, 39.3, 16.5. The enantiomeric excess of 2j was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at $\lambda = 220$ nm, $t_R = 15.1$ min (minor), 18.5 min (major).

(S)-3-(2-methoxyphenyl)-2-methylpropanoic acid (2k). Colorless oil, 97% yield, 97% ee, $[\alpha]_D^{25} = +27.62$ (c = 0.21, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.24 – 7.18 (m, 1H), 7.16 – 7.10 (m, 1H), 6.91 – 6.81 (m, 2H), 3.81 (s, 3H), 3.05 (dd, $J = 13.2$, 6.7 Hz, 1H), 2.86 (h, $J = 6.6$ Hz, 1H), 2.71 (dd, $J = 13.2$, 7.6 Hz, 1H), 1.16 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-$d$) $\delta$ 182.8, 159.6, 140.6, 129.4, 121.4, 114.7, 111.8, 55.1, 41.1, 39.3, 34.2, 16.7. The enantiomeric excess of 2k was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at $\lambda = 220$ nm, $t_R = 10.0$ min (minor), 11.1 min (major).

(S)-3-(2-bromophenyl)-2-methylpropanoic acid (2l). Colorless oil, 92% yield, 92% ee, $[\alpha]_D^{25} = +14.94$ (c = 0.79, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.55 (d, $J = 7.9$ Hz, 1H), 7.23 (d, $J = 4.5$ Hz, 2H), 7.09 (dt, $J = 8.0$, 4.5 Hz, 1H), 3.19 (dd, $J = 13.5$, 6.9 Hz, 1H), 2.93 (h, $J = 6.8$ Hz, 1H), 2.82 (dd, $J = 13.5$, 7.6 Hz, 1H), 1.23 (d, $J = 6.9$ Hz, 1H).
= 7.0 Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-$d$) $\delta$ 182.0, 138.4, 132.9, 131.3, 128.2, 127.3, 124.7, 39.4, 39.3, 16.7. The enantiomeric excess of 2l was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at $\lambda = 220$ nm, $t_R = 8.7$ min (minor), 9.2 min (major).

![Chemical Structure](attachment:chemical_structure.png)

**[(S)-2-methyl-3-((thiophen-2-yl)propanoic acid (2m).]** Colorless oil, 90% yield, 97% ee, $[\alpha]_D^{25} = +5.19$ (c = 0.77, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.15 (dd, $J = 5.1$, 1.2 Hz, 1H), 6.93 (dd, $J = 5.1$, 3.4 Hz, 1H), 6.86 – 6.81 (m, 1H), 3.26 (dd, $J = 14.7$, 6.6 Hz, 1H), 2.94 (dd, $J = 14.7$, 7.4 Hz, 1H), 2.80 (h, $J = 7.0$ Hz, 1H), 1.24 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-$d$) $\delta$ 181.9, 141.3, 126.8, 125.7, 123.9, 41.6, 33.2, 16.6. The enantiomeric excess of 2m was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at $\lambda = 230$ nm, $t_R = 11.5$ min (minor), 14.0 min (major).

![Chemical Structure](attachment:chemical_structure.png)

**[(R)-2-(4-methoxybenzyl)-3-methylbutanoic acid (2n).]** White solid, 92% yield, 85% ee, $[\alpha]_D^{25} = +36.60$ (c = 1.06, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.09 (d, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 3.77 (s, 3H), 2.83 – 2.77 (m, 2H), 2.44 (dt, $J = 9.1$, 6.3 Hz, 1H), 1.95 (h, $J = 6.8$ Hz, 1H), 1.03 (dd, $J = 11.5$, 6.8 Hz, 6H). $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 181.0, 158.0, 131.6, 129.7, 113.8, 55.2, 54.6, 34.5, 30.3, 20.3, 20.0. The enantiomeric excess of 2n was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at $\lambda = 210$ nm, $t_R = 16.2$ min (major), 18.6 min (minor).
(R)-1-(tert-butoxycarbonylpiperidine-3-carboxylic acid (2o). White solid, 87% yield, 93% ee, $\left[\alpha\right]_D^{25} = -5.22$ (c = 0.69, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 4.12 (brs, $J = 7.1$ Hz, 1H), 3.88 (dt, $J = 13.3$, 4.1 Hz, 1H), 3.03 (brs, 1H), 2.85 (ddd, $J = 13.7$, 10.9, 3.0 Hz, 1H), 2.48 (tt, $J = 10.1$, 3.9 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.77 – 1.58 (m, 2H), 1.45 (s, 9H). $^{13}$C NMR (151 MHz, Chloroform-$d$) $\delta$ 178.8, 154.7, 79.9, 45.6, 43.8, 41.1, 28.4, 27.2, 24.1. The enantiomeric excess of 2o was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at $\lambda = 210$ nm, $t_R = 15.8$ min (minor), 16.6 min (major).

(S)-2-phenoxbutanoic acid (2p). White solid, 80% yield, 93% ee, $\left[\alpha\right]_D^{25} = -15.57$ (c = 0.61, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.80 (brs, 1H), 7.34 – 7.20 (m, 2H), 6.98 (t, $J = 7.3$ Hz, 1H), 6.88 (d, $J = 7.9$ Hz, 2H), 4.57 (t, $J = 6.0$ Hz, 1H), 2.06 – 1.90 (m, 2H), 1.07 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 177.3, 157.6, 129.6, 121.8, 115.2, 25.9, 9.6. The enantiomeric excess of 2p was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 1.0 mL/min, uv-vis detection at $\lambda = 220$ nm, $t_R = 12.1$ min (minor), 16.5 min (major).

(S)-2-(p-tolloyloxy)butanoic acid (2q). White solid, 97% yield, 93% ee, $\left[\alpha\right]_D^{25} = -22.50$ (c = 0.88, CHCl$_3$). $^1$H NMR (600 MHz, Chloroform-$d$) $\delta$ 7.07 (d, $J = 7.9$ Hz, 2H), 6.80 (d, $J = 8.1$ Hz, 2H), 4.54 (t, $J = 6.1$ Hz, 1H), 2.28 (s, 3H), 1.98 (q, $J = 7.8$ Hz, 2H), 1.07 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (150 MHz, Chloroform-$d$) $\delta$ 174.9, 156.9, 129.4, 121.8, 115.4, 25.9, 25.8, 9.6. The enantiomeric excess of 2q was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 1.0 mL/min, uv-vis detection at $\lambda = 230$ nm, $t_R = 11.0$ min (minor), 16.5 min (major).
1.07 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-$d$) $\delta$ 177.3, 155.5, 131.2, 130.0, 115.2, 77.5, 25.9, 20.5, 9.5. The enantiomeric excess of 2q was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 1.0 mL/min, uv-vis detection at $\lambda = 220$ nm, $t_R = 8.5$ min (major), 9.4 min (minor).

(S)-2-(4-methoxyphenoxy)butanoic acid (2r).$^9$ White solid, 92% yield, 95% ee, $[\alpha]_D^{25} = -35.87$ (c = 0.92, CHCl$_3$). $^1$H NMR (600 MHz, Chloroform-$d$) $\delta$ 8.43 (brs, 1H), 6.98 – 6.62 (m, 4H), 4.51 (t, $J = 5.4$ Hz, 1H), 3.76 (s, 3H), 2.00 (dq, $J = 14.3$, 6.8 Hz, 2H), 1.10 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (151 MHz, Chloroform-$d$) $\delta$ 177.2, 154.6, 151.7, 116.6, 114.7, 78.3, 55.7, 26.0, 9.5. The enantiomeric excess of 2r was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at $\lambda = 230$ nm, $t_R = 20.5$ min (major), 22.7 min (minor).

(S)-2-(4-(tert-butyl)phenoxy)butanoic acid (2s).$^9$ White solid, 93% yield, 93% ee, $[\alpha]_D^{25} = -25.56$ (c = 0.63, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.74 (brs, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 6.84 (d, $J = 8.3$ Hz, 2H), 4.56 (t, $J = 5.6$ Hz, 1H), 2.08 – 1.91 (m, 2H), 1.29 (s, 9H), 1.09 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 177.3, 155.3, 144.6, 126.4, 114.7, 77.4, 34.1, 31.4, 26.0, 9.6. The enantiomeric excess of 2s was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 99/1, flow rate = 0.5 mL/min, uv-vis detection at $\lambda = 220$ nm, $t_R = 26.4$ min (major), 29.6 min (minor).
(S)-2-(4-chlorophenoxy)butanoic acid (2t). White solid, 95% yield, 91% ee, [α]D\textsubscript{25} = -31.43 (c = 0.28, CHCl\textsubscript{3}). \textsuperscript{1}H NMR (600 MHz, Chloroform-d) δ 8.89 (brs, 1H), 7.26 – 7.21 (m, 2H), 6.83 (d, J = 8.9 Hz, 2H), 4.60 – 4.52 (m, 1H), 2.02 (dh, J = 14.3, 7.0 Hz, 2H), 1.10 (t, J = 7.4 Hz, 3H). \textsuperscript{13}C NMR (151 MHz, Chloroform-d) δ 177.0, 156.2, 129.5, 126.8, 116.5, 77.4, 26.0, 9.5. The enantiomeric excess of 2t was determined by HPLC analysis after esterification with TMSCHN\textsubscript{2} on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 99/1, flow rate = 0.5 mL/min, uv-vis detection at λ = 230 nm, t\textsubscript{R} = 22.4 min (minor), 37.3 min (major).

(S)-2-methoxy-3-phenylpropanoic acid (2u). Colorless oil, 89% yield, 99% ee, [α]D\textsubscript{25} = -20.00 (c = 0.51, CHCl\textsubscript{3}). \textsuperscript{1}H NMR (400 MHz, Chloroform-d) δ 8.21 (brs, J = 95.3 Hz, 1H), 7.33 – 7.21 (m, 5H), 4.02 (dd, J = 8.0, 4.2 Hz, 1H), 3.38 (s, 3H), 3.14 (dd, J = 14.2, 4.2 Hz, 1H), 3.02 (dd, J = 14.2, 8.1 Hz, 1H). \textsuperscript{13}C NMR (101 MHz, Chloroform-d) δ 176.5, 136.6, 129.3, 128.4, 126.8, 81.3, 58.6, 38.6. The enantiomeric excess of 2u was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 1.0 mL/min, uv-vis detection at λ = 210 nm, t\textsubscript{R} = 14.8 min (minor), 24.3 min (major).
Asymmetric hydrogenation of α-substituted acrylic acids

Method C (for 3a-i).

In an argon-filled glovebox, CoCl$_2$ (0.025 M in THF, 0.2 mL, 0.005 mmol) and (S,S)-Ph-BPE (2.53 mg, 0.005 mmol) in HFIP (0.2 mL) were stirred in a vial at room temperature for 10 min. Then zinc dust (0.65 mg, 0.01 mmol) and HFIP (0.2 mL) were added and the mixture was stirred for 15 min. After that, substrate (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H$_2$. The reaction was then stirred under H$_2$ (60 atm) at 50 °C for 48 h. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.

Supplementary Table 6. Solvent screening of 3a$^a$

| entry | solvent         | conv. [%]$^b$ | ee [%]$^c$ |
|-------|-----------------|---------------|------------|
| 1     | MeOH            | 98            | 73         |
| 2     | iPrOH           | 21            | 81         |
| 3     | tBuOH           | 22            | 84         |
| 4     | TFE             | >98           | 82         |
| 5     | EtOH            | 69            | 76         |
| 6     | nPrOH           | 15            | 50         |
| 7     | nBuOH           | <5            | 61         |
| 8     | iBuOH           | <5            | 48         |
| 9     | 2-methoxyethanol| ND            | --         |
| 10    | HFIP            | >98           | 98         |

[a] Reaction conditions: 3a (0.1 mmol), CoCl$_2$ (5 mol%), (S,S)-Ph-BPE (5 mol%) in solvent (0.4 mL) under 60 atm H$_2$ pressure at 50 °C for 48 h. [b] Determined by $^1$H NMR. [c] Determined by HPLC analysis.
Characterization data of compound 4

(R)-2-phenylpropanoic acid (4a). Yellowish solid, 90% yield, 98% ee, [α]_D^{25} = -24.04 (c = 0.47, CHCl_3). ^1H NMR (400 MHz, Chloroform-d) δ 10.83 (brs, 1H), 7.35 – 7.22 (m, 5H), 3.72 (q, J = 7.2 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H). ^13C NMR (151 MHz, Chloroform-d) δ 180.9, 139.7, 128.6, 127.6, 127.4, 45.4, 18.1. The enantiomeric excess of 4a was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 210 nm, t_R = 12.3 min (major), 13.7 min (minor).

(R)-2-(p-tolyl)propanoic acid (4b). Colorless oil, 98% yield, >99% ee, [α]_D^{25} = -26.91 (c = 0.81, CHCl_3). ^1H NMR (400 MHz, Chloroform-d) δ 7.21 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 3.70 (q, J = 7.2 Hz, 1H), 2.34 (s, 3H), 1.49 (d, J = 7.1 Hz, 3H). ^13C NMR (101 MHz, Chloroform-d) δ 180.8, 137.0, 136.8, 129.3, 127.4, 44.9, 21.0, 18.1. The enantiomeric excess of 4b was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 210 nm, t_R = 12.7 min (major), 14.4 min (minor).

(R)-2-(4-methoxyphenyl)propanoic acid (4c). White solid, 89% yield, >99% ee, [α]_D^{25} = -50.33 (c = 0.61, CHCl_3). ^1H NMR (400 MHz, Chloroform-d) δ 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.68 (q, J = 7.2 Hz, 1H), 1.48 (d, J = 7.2 Hz, 3H). ^13C NMR (101 MHz, Chloroform-d) δ 180.7, 158.8, 131.9, 128.6, 114.0, 55.2, 44.5, 18.1. The enantiomeric excess of 4c was determined by HPLC analysis on
Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 220 nm, \( t_R = 19.4 \) min (major), 21.5 min (minor).

(R)-2-(4-fluorophenyl)propanoic acid (4d). Yellowish oil, 96% yield, >99% ee, \([\alpha]_D^{25} = -33.47 \quad (c = 0.75, \text{CHCl}_3)\). ¹H NMR (400 MHz, Chloroform-\(d\)) \( \delta \) 7.26 (t, \( J = 4.3 \) Hz, 2H), 7.00 (t, \( J = 8.6 \) Hz, 2H), 3.69 (q, \( J = 7.0 \) Hz, 1H), 1.47 (d, \( J = 7.1 \) Hz, 3H). ¹³C NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 180.3, 162.0 (d, \( J = 245.8 \) Hz), 135.6 (d, \( J = 3.0 \) Hz), 129.1 (d, \( J = 8.0 \) Hz), 115.5 (d, \( J = 21.7 \) Hz), 44.7, 18.2. ¹⁹F NMR (376 MHz, Chloroform-\(d\)) \( \delta \) -115.35. The enantiomeric excess of 4d was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \( \lambda = 210 \) nm, \( t_R = 16.3 \) min (major), 21.5 min (minor).

(R)-2-(3-methoxyphenyl)propanoic acid (4e). Colorless oil, 95% yield, 97% ee, \([\alpha]_D^{25} = -45.47 \quad (c = 0.53, \text{CHCl}_3)\). ¹H NMR (600 MHz, Chloroform-\(d\)) \( \delta \) 7.26 – 7.23 (m, 1H), 6.92 – 6.86 (m, 2H), 6.81 (dd, \( J = 8.2, 2.2 \) Hz, 1H), 3.80 (s, 3H), 3.73 – 3.69 (m, 1H), 1.50 (d, \( J = 7.2 \) Hz, 3H). ¹³C NMR (151 MHz, Chloroform-\(d\)) \( \delta \) 180.3, 159.7, 141.2, 129.6, 112.0, 113.4, 112.7, 55.2, 45.3, 18.0. The enantiomeric excess of 4e was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \( \lambda = 220 \) nm, \( t_R = 16.6 \) min (major), 20.3 min (minor).

(R)-2-(2-methoxyphenyl)propanoic acid (4f). White solid, 94% yield, 98% ee, \([\alpha]_D^{25} \)
\( \delta_{25} = -61.92 \) (c = 0.73, CHCl\(_3\)). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta 7.24 \) (ddd, \( J = 7.3, 4.0, 1.4 \) Hz, 2H), 6.94 (t, \( J = 7.1 \) Hz, 1H), 6.87 (d, \( J = 8.3 \) Hz, 1H), 4.07 (q, \( J = 7.2 \) Hz, 1H), 3.82 (s, 3H), 1.47 (d, \( J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 180.7, 156.7, 128.8, 128.3, 128.0, 120.8, 110.7, 55.5, 39.1, 16.8. The enantiomeric excess of \( 4f \) was determined by HPLC analysis on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \( \lambda = 220 \) nm, \( t_R = 15.9 \) min (minor), 18.8 min (major).

(R)-2-(o-tolyl)propanoic acid (4g). \(^{13}\) Colorless oil, 89% yield, 90% ee, \([\alpha]_D^{25} = -57.27\) (c = 0.63, CHCl\(_3\)). \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \( \delta 7.28 \) (d, \( J = 7.2 \) Hz, 1H), 7.22 – 7.14 (m, 3H), 3.98 (q, \( J = 7.2 \) Hz, 1H), 2.37 (s, 3H), 1.48 (d, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (151 MHz, Chloroform-\(d\)) \( \delta \) 180.6, 138.4, 135.9, 130.5, 127.1, 126.5, 126.4, 41.2, 19.6, 17.6. The enantiomeric excess of \( 4g \) was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \( \lambda = 210 \) nm, \( t_R = 16.4 \) min (major), 20.8 min (minor).

(R)-2-(naphthalen-2-yl)propanoic acid (4h). \(^{13}\) White solid, 99% yield, 96% ee, \([\alpha]_D^{25} = -32.5\) (c = 0.60, CHCl\(_3\)). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \( \delta 7.85 – 7.74 \) (m, 4H), 7.51 – 7.42 (m, 3H), 3.91 (q, \( J = 7.0 \) Hz, 1H), 1.60 (d, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (151 MHz, Chloroform-\(d\)) \( \delta \) 180.4, 137.2, 133.4, 132.7, 128.4, 127.8, 127.6, 126.3, 126.2, 125.9, 125.7, 45.5, 18.1. The enantiomeric excess of \( 4h \) was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at \( \lambda = 230 \) nm, \( t_R = 41.5 \) min (minor), 44.5 min (major).
**[(R)-2-phenylpropanoic acid (4i)](https://doi.org/10.1021/acs.orglett.9b03526)**. Yellowish oil, 94% yield, 80% ee, [α]_D^{25} = -16.22 (c = 0.74, CHCl₃). ¹H NMR (400 MHz, Chloroform-d) δ 7.29 (t, J = 7.3 Hz, 2H), 7.21 (dd, J = 15.7, 7.2 Hz, 3H), 3.09 (dd, J = 13.4, 6.3 Hz, 1H), 2.78 (q, J = 7.1 Hz, 1H), 2.67 (dd, J = 13.3, 8.0 Hz, 1H), 1.18 (d, J = 6.8 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 182.3, 139.0, 129.0, 128.4, 126.4, 41.4, 39.1, 16.5. The enantiomeric excess of 4i was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 210 nm, t_r = 11.1 min (major), 12.6 min (minor).
Details of applications

Procedure for asymmetric hydrogenation of 1v.

In an argon-filled glovebox, CoCl$_2$ (0.005 M in THF, 0.2 mL, 0.001 mmol) and (R,R)-Ph-BPE (0.51 mg, 0.001 mmol) in MeOH (0.2 mL) were stirred in a vial at room temperature for 10 min. Then zinc dust (0.65 mg, 0.01 mmol), MeOH (0.2 mL) were added and the mixture was stirred for 15 min. After that, substrate 1v (0.1 mmol) and THF (0.6 mL) were added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H$_2$. The reaction was then stirred under H$_2$ (60 atm) at 50 °C for 48 h. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.

\[\text{(S)-3-(2,4-dimethoxyphenyl)-2-(4-methoxyphenyl)propanoic acid (2v).}^{1}\]

White solid, 90% yield, 94% ee, [α]$_D^{25}$ = +76.53 (c = 0.95, CHCl$_3$). $^1$H NMR (400 MHz, Chloroform-d) δ 7.22 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.40 (d, J = 2.1 Hz, 1H), 6.29 (dd, J = 8.2, 2.2 Hz, 1H), 3.88 (t, J = 7.3 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.76 (s, 3H), 3.26 (dd, J = 13.6, 8.4 Hz, 1H), 2.94 (dd, J = 13.6, 6.7 Hz, 1H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 179.4, 159.5, 158.7, 158.4, 131.0, 130.9, 129.1, 119.4, 113.9, 103.6, 98.3, 55.2, 55.2, 55.2, 50.5, 33.9. The enantiomeric excess of 2v was determined by HPLC analysis on Chiralpak OD-3 column after esterification with TMSCHN$_2$. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 210 nm, t$_R$ = 11.5 min (minor), 14.8 min (major).
Procedure for asymmetric hydrogenation of 1x.

In an argon-filled glovebox, CoCl$_2$ (0.005 M in THF, 0.2 mL, 0.001 mmol) and $(R,R)$-Ph-BPE (0.51 mg, 0.001 mmol) in $i$BuOH (0.2 mL) were stirred in a vial at room temperature for 10 min. Then zinc dust (0.65 mg, 0.01 mmol), $i$BuOH (0.2 mL) were added and the mixture was stirred for 15 min. After that, substrate 1x (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H$_2$. The reaction was then stirred under H$_2$ (60 atm) at 50 $^\circ$C for 72 h. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.

Supplementary Table 7. Solvent screening of 1x$^{[a]}$

| entry | solvent          | conv. [%]$^{[b]}$ | $dr$ [%]$^{[c]}$ |
|-------|------------------|-------------------|-----------------|
| 1     | MeOH             | $>98$             | 9.0/1           |
| 2     | $i$PrOH          | $>98$             | 11.3/1          |
| 3     | TFE              | $>98$             | 14.4/1          |
| 4     | $i$BuOH          | 97                | 4.1/1           |
| 5     | EtOH             | $>98$             | 9.3/1           |
| 6     | nPrOH            | $>98$             | 10.5/1          |
| 7     | nBuOH            | $>98$             | 10.7/1          |
| 8     | $i$BuOH          | $>98$             | 17.0/1          |
| 9     | 2-Methoxyethanol | $>98$             | 10.0/1          |
| 10    | HFIP             | 98                | 12.0/1          |

$^{[a]}$ Reaction conditions: 1x (0.1 mmol), CoCl$_2$ (5 mol%), $(R,R)$-Ph-BPE (5 mol%) in solvent (0.4 mL) under 60 atm H$_2$ pressure at 50 $^\circ$C for 40 h. $^{[b]}$ Determined by $^1$H NMR. $^{[c]}$ Determined by HPLC analysis.
**2(R,4S)-5-([1,1'-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2-methylpentanoic acid (2x).** White solid, 97% yield, 17/1 dr, [α]D25 = +1.49 (c = 0.94, CHCl3). 1H NMR (600 MHz, Chloroform-d) δ 7.57 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 9.0 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.7 Hz, 1H), 7.26 – 7.22 (m, 2H), 6.33 (d, J = 9.5 Hz, 0.5H), 4.56 (d, J = 9.1 Hz, 0.5H), 4.09 – 3.88 (m, 1H), 2.95 – 2.45 (m, 2H), 2.70-2.55 (m, 1H), 1.84 (t, J = 11.3 Hz, 0.5H), 1.54 – 1.45 (m, 0.5H), 1.40 (s, 5H), 1.29 (s, 5H), 1.20 (d, J = 6.9 Hz, 3H). 13C NMR (151 MHz, Chloroform-d) δ 180.8, 179.4, 157.1, 156.4, 141.1, 140.8, 139.5, 139.2, 139.2, 137.7, 136.3, 129.8, 128.7, 127.2, 127.0, 127.0, 80.3, 80.2, 68.1, 50.8, 49.7, 42.1, 41.1, 39.5, 38.2, 36.5, 36.2, 31.5, 30.1, 29.7, 28.3, 28.0, 17.8, 15.9. HRMS calculated [M-H]- for C23H28NO4 = 382.2024, found: 382.2022. The enantiomeric excess of 2x was determined by HPLC analysis on Chiralpak AS-3 column. Conditions: hexane/isopropanol = 92/8, flow rate = 0.9 mL/min, uv-vis detection at λ = 210 nm, tR = 11.2 min (major), 13.8 min (minor).

**Procedure for asymmetric hydrogenation of 1w, 3j.**

In an argon-filled glovebox, CoCl2 (0.025 M in THF, 0.2 mL, 0.005 mmol) and (R,R)-Ph-BPE (2.53 mg, 0.005 mmol) in MeOH (0.2 mL) were stirred in a vial at room temperature for 10 min. Then zinc dust (0.65 mg, 0.01 mmol) and MeOH (0.2 mL) were added and the mixture was stirred for 15 min. After that, substrate (0.1 mmol) and HFIP (0.2 mL) were added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H2. The reaction was then stirred under H2 (60 atm) at 50 °C. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.
(R)-2-(benzyloxy)-3-(4-fluorophenyl)propanoic acid (2w). White solid, 95% yield, >99% ee, [α]_D^{25} = +23.97 (c = 0.58, CHCl₃). ^1H NMR (400 MHz, Chloroform-d) δ 7.31 – 7.25 (m, 3H), 7.22 – 7.12 (m, 4H), 6.97 (t, J = 8.7 Hz, 2H), 4.67 (d, J = 11.7 Hz, 1H), 4.40 (d, J = 11.7 Hz, 1H), 4.14 (dd, J = 8.2, 3.9 Hz, 1H), 3.20 – 2.93 (m, 2H). ^13C NMR (101 MHz, Chloroform-d) δ 187.9, 161.9 (d, J = 245.0 Hz), 136.6, 132.3 (d, J = 3.0 Hz), 131.0 (d, J = 8.0 Hz), 128.5, 128.1, 127.9, 115.2 (d, J = 21.3 Hz), 78.5, 72.8, 38.0. ^19F NMR (565 MHz, Chloroform-d) δ -116.17. The enantiomeric excess of 2w was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 210 nm, t_R = 22.6 min (major), 28.2 min (minor).

(R)-2-(6-methoxynaphthalen-2-yl)propanoic acid (4j). White solid, 87% yield, 97% ee, [α]_D^{25} = -17.34 (c = 0.56, CHCl₃). ^1H NMR (400 MHz, Chloroform-d) δ 7.70 (d, J = 9.6 Hz, 3H), 7.41 (dd, J = 8.5, 1.7 Hz, 1H), 7.16 – 7.08 (m, 2H), 3.91 (s, 3H), 3.90 – 3.83 (m, 1H), 1.58 (d, J = 7.1 Hz, 3H). ^13C NMR (101 MHz, Chloroform-d) δ 180.4, 157.6, 134.9, 133.8, 129.3, 128.8, 127.2, 126.2, 126.1, 119.0, 105.5, 55.3, 45.3, 18.1. The enantiomeric excess of 4j was determined by HPLC analysis on Chiralpak OJ-3 column. Conditions: hexane/isopropanol = 97/3, flow rate = 0.8 mL/min, uv-vis detection at λ = 230 nm, t_R = 83.0 min (minor), 97.2 min (major).

Procedure for asymmetric hydrogenation of 3k.

In an argon-filled glovebox, CoCl₂ (0.005 M in THF, 0.2 mL, 0.001 mmol) and (R,R)-Ph-BPE (0.51 mg, 0.001 mmol) in HFIP (0.2 mL) were stirred in a vial at room temperature for 10 min. Then zinc dust (0.65 mg, 0.01 mmol) and HFIP (0.2 mL) were added and the mixture was stirred for 15 min. After that, substrate (0.1 mmol) was
added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H₂. The reaction was then stirred under H₂ (60 atm) at 50 °C for 72 h. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.

![Structure](image-url)

(R)-2-(4-isobutylphenyl)propanoic acid (4k). White solid, 89% yield, 99% ee, [α]_D^{25} = -3.46 (c = 1.04, CHCl₃). ¹H NMR (400 MHz, Chloroform-d) δ 7.22 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 3.71 (q, J = 7.1 Hz, 1H), 2.45 (d, J = 7.2 Hz, 2H), 1.84 (dp, J = 13.6, 6.8 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H), 0.90 (d, J = 6.6 Hz, 6H). ¹³C NMR (101 MHz, Chloroform-d) δ 180.6, 140.8, 137.0, 129.4, 127.3, 45.0, 44.9, 30.2, 22.4, 18.1. The enantiomeric excess of 4k was determined by HPLC analysis after esterification with TMSCHN₂ on Chiralpak AD-3 column. Conditions: hexane/isopropanol = 99/1, flow rate = 0.5 mL/min, uv-vis detection at λ = 220 nm, t_R = 8.0 min (minor), 8.3 min (major).

**Procedure for asymmetric hydrogenation of 5.**

In an argon-filled glovebox, CoCl₂ (0.025 M in THF, 1.0 mL, 0.025 mmol) and (S,S)-Ph-BPE (12.7 mg, 0.025 mmol) in MeOH (1.0 mL) were stirred in a vial at room temperature for 10 min. Then zinc dust (16.4 mg, 0.25 mmol) was added and the mixture was stirred for 15 min. After that, substrate 5 (5 mmol), MeOH (11.0 mL) and HFIP (1.0 mL) were added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H₂. The reaction was then stirred under H₂ (30 atm) at 50 °C for 72 h. The hydrogen gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The ee values were determined by HPLC with a chiral column.
(R)-Dihydroartemisinic acid (6).\(^{11}\) White solid, 98% yield, 97/3 dr, \([\alpha]_D^{25} = -8.84\) (c = 0.85, CHCl\(_3\)). \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 5.12 (s, 1H), 2.53 – 2.46 (m, 2H), 1.97 – 1.87 (m, 2H), 1.84 – 1.77 (m, 1H), 1.66 – 1.51 (m, 6H), 1.47 – 1.38 (m, 2H), 1.28 – 1.24 (m, 1H), 1.19 (d, \(J = 6.9\) Hz, 3H), 1.16 – 1.07 (m, 1H), 0.96 (qd, \(J = 12.9, 2.9\) Hz, 1H), 0.87 (d, \(J = 6.5\) Hz, 3H). \(^{13}\)C NMR (151 MHz, Chloroform-\(d\)) \(\delta\) 183.6, 136.0, 119.3, 43.6, 42.2, 41.7, 36.3, 35.2, 27.6, 27.4, 26.6, 25.7, 23.8, 19.7, 15.1. The diastereomeric ratio of compound 6 was determined by HPLC analysis with Agilent Poroshell 120, EC-C18 (2.7um) column. Conditions: gradient elution with ACN /H\(_2\)O (with 1.0% FA) (0-1 Min: ACN/H\(_2\)O=20/80; 1-35 Min: ACN/H\(_2\)O= 99/1 to 20/80; 35-40 Min: ACN/H\(_2\)O=20/80), flow rate = 0.5 mL/min, uv-vis detection at 210 nm, \(t_R = 32.2\) min (major), 32.7 min (minor).
**Supplementary Note 1**

**Control experiments**

To provide insight into the possible catalyst activation mode and the mechanism of the asymmetric hydrogenation of α,β-unsaturated carboxylic acids, several control and catalytic experiments were conducted. Only starting material was observed suggesting that no reaction occurred for the corresponding ethyl ester 1b’ under standard conditions. Moreover, no hydrogenation product was observed when 1 mol% of CH₃COOH or 1b was added to the reaction mixture as external carboxylic acid.

**Supplementary Figure 1.** Control experiments. (a): the asymmetric hydrogenation of ethyl ester 1b’ under standard condition; (b): with 1 mol% CH₃COOH as additives; (c) with 1 mol% of 1b as additives.
Supplementary Note 2

Deuterium-Labeling experiment

Hydrogenation of 1b in isopropanol-d$_8$ and/or CH$_3$COOD.

The reactions using isopropanol-d$_8$ as solvent were conducted, and no deuteration was observed with or without Zn as activator. Addition of CH$_3$CO$_2$D (5 eq) as additive could not produce the deuterated product either, indicating that protonation of the Co-alkyl intermediate was probably not involved in the current reaction (Supplementary Figure 2 and 3). HRMS calculated [2b-H]$^-$ for C$_{10}$H$_{11}$O$_2$ = 163.0765, found 163.0755.
Supplementary Figure 2. Deuterium-labeling experiment in the presence of Zn and the corresponding HR-MS spectrums. (a): in isopropanol-$d_8$; (b): with 5 eq. CH$_3$COOD as additives; (c) with 5 eq. CH$_3$COOD as additives in isopropanol-$d_8$. 
Supplementary Figure 3. Deuterium-labeling experiment in the absence of Zn and the corresponding HR-MS spectrums. (a): in isopropanol-$d_8$; (b): with 5 eq. CH$_3$COOD as additives; (c) with 5 eq. CH$_3$COOD as additives in isopropanol-$d_8$. 
**Hydrogenation of 1b with D$_2$.**

In an argon-filled glovebox, Co(acac)$_2$ (0.050 M in iPrOH, 0.10 mL, 0.005 mmol) and (S,S)-Ph-BPE (0.050 M in THF, 0.10 mL, 0.005 mmol) were stirred in a vial at room temperature for 10 min. Then zinc dust (3.3 mg, 0.05 mmol) and iPrOH (0.50 mL) were added and the mixture was stirred for 15 min. After that, 1b (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with D$_2$. The reaction was then stirred under D$_2$ (40 atm) at room temperature for 48 h. The gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. The deuterium-labeling experiment using D$_2$ gas indicates H$_2$ as the hydrogen donor. HRMS calculated $^{[2b-d_2]}$-H$^+$ for C$_{10}$H$_9$D$_2$O$_2^{-} = 165.0890$, found 165.0877.

**Supplementary Figure 4.** HR-MS of Deuterium-Labeling Experiment of 1b with D$_2$.

$^{[2b-d_2]}$ White solid, 94% yield, $^{1}$H NMR (600 MHz, Chloroform-$d$) $\delta$ 7.29 (t, $J = 7.4$ Hz, 2H), 7.21 (dd, $J = 23.0$, 7.4 Hz, 3H), 2.66 (s, 1H), 1.18 (s, 3H).
Supplementary Figure 5. $^1$H NMR (600 MHz, CDCl$_3$) of 2b-$d_2$

Hydrogenation of 1b with H$_2$/D$_2$ in the presence of Zn.

In an argon-filled glovebox, Co(acac)$_2$ (0.050 M in iPrOH, 0.10 mL, 0.005 mmol) and (S,S)-Ph-BPE (0.050 M in THF, 0.10 mL, 0.005 mmol) were stirred in a vial at room temperature for 10 min. Then zinc dust (3.3 mg, 0.05 mmol) and iPrOH (0.50 mL) were added and the mixture was stirred for 15 min. After that, 1b (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H$_2$. The reaction was then stirred under H$_2$/D$_2$ (40 atm) at room temperature for 48 h. The gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. HRMS calculated [2b-H]$^-$ for C$_{10}$H$_{11}$O$_2^-$ = 163.0765, found 163.0752. HRMS calculated {2b-$d_1$}-H$^-$ for C$_{10}$H$_{10}$DO$_2^-$ = 164.0827, found 164.0815. HRMS calculated {2b-$d_2$}-H$^-$ for C$_{10}$H$_9$D$_2$O$_2^-$ = 165.0890, found 165.0877.
Supplementary Figure 6. The reaction of 1b with H2/D2 in the presence of Zn.

**Hydrogenation of 1b with H2/D2 in the absence of Zn.**

In an argon-filled glovebox, Co(acac)2 (0.050 M in iPrOH, 0.10 mL, 0.005 mmol) and (S,S)-Ph-BPE (0.050 M in THF, 0.10 mL, 0.005 mmol) were stirred in a vial at room temperature for 10 min. After that, 1b (0.1 mmol) and iPrOH (0.50 mL) were added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H2. The reaction was then stirred under H2/D2 (60 atm) at 50 °C for 72 h. The gas was released slowly and carefully. The resulting solution was concentrated in vacuum and the residue was purified by chromatography on silica gel. HRMS calculated [2b-H]− for C10H11O2− = 163.0765, found 163.0753. HRMS calculated {2b-d1}-H}− for C10H10DO2− = 164.0827, found 164.0816. HRMS calculated {2b-d2}-H}− for C10H9D2O2− = 165.0890, found 165.0878.
Supplementary Figure 7. The reaction of 1b with H₂/D₂ in the absence of Zn.
Supplementary Note 3

EPR experiments

Procedures for EPR experiments.

(1) In an argon-filled glovebox, Co(acac)$_2$ (1.3 mg, 0.005 mmol), (S,S)-Ph-BPE (2.53 mg, 0.005 mmol) and THF (1 mL) were stirred in a vial at room temperature for 10 min. The reaction mixture (0.2 mL) and THF (0.2 mL) were added to a quartz tube. The quartz tube was then glassed in liquid helium and subjected to X-band EPR analysis (Supplementary Figure 9).

(2) In an argon-filled glovebox, Co(acac)$_2$ (1.3 mg, 0.005 mmol), (S,S)-Ph-BPE (2.53 mg, 0.005 mmol) and toluene (1 mL) were stirred in a vial at room temperature for 10 min. After that, 1b (1.6 mg, 0.01 mmol) was added to the reaction mixture and stirred for 10 min. The reaction mixture (0.2 mL) and toluene (0.2 mL) were added to a quartz tube. The quartz tube was then glassed in liquid nitrogen and subjected to X-band EPR analysis (Supplementary Figure 10).

(3) In an argon-filled glovebox, Co(acac)$_2$ (0.050 M in iPrOH, 0.10 mL, 0.005 mmol) and (S,S)-Ph-BPE (0.050 M in THF, 0.10 mL, 0.005 mmol) were stirred in a vial at room temperature for 10 min. Then zinc dust (3.3 mg, 0.05 mmol) and iPrOH (0.50 mL) were added and the mixture was stirred for 15 min. After that, 1b (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H$_2$. The reaction was then stirred under H$_2$ (40 atm) at room temperature for 30 min. The gas was released slowly and carefully. The solvent was removed under vacuum and the autoclave was then transformed to glovebox. The residue was dissolved in toluene (1 mL) and filtrated through celite to remove the Zn. After that the filtrate (0.2 mL) and toluene (0.2 mL) were added to a quartz tube. The quartz tube was then glassed in liquid nitrogen and subjected to X-band EPR analysis (Supplementary Figure 11).

(4) In an argon-filled glovebox, Co(acac)$_2$ (0.050 M in iPrOH, 0.10 mL, 0.005 mmol)
and (S,S)-Ph-BPE (0.050 M in THF, 0.10 mL, 0.005 mmol) were stirred in a vial at room temperature for 10 min. After that, 1b (0.1 mmol) was added to the reaction mixture. The vial was subsequently transferred into an autoclave and purged by three cycles of pressurization/venting with H₂. The reaction was then stirred under H₂ (60 atm) at 50 °C for 30 min. The gas was released slowly and carefully. The solvent was removed under vacuum and the autoclave was then transformed to glovebox. The residue was dissolved in toluene (1 mL). The solution (0.2 mL) and toluene (0.2 mL) were added to a quartz tube. The quartz tube was then glassed in liquid nitrogen and subjected to X-band EPR analysis (Supplementary Figure 12).

(5) In an argon-filled glovebox, bis(2-ethylhexanoate)cobalt (2.7 mg, 0.005 mmol, 65 wt. % in mineral spirits), (S,S)-Ph-BPE (2.56 mg, 0.005 mmol) and THF (1 mL) were stirred in a vial at room temperature for 10 min. The reaction mixture (0.2 mL) and THF (0.2 mL) were added to a quartz tube. The quartz tube was then glassed in liquid helium and subjected to X-band EPR analysis (Supplementary Figure 13).

The EPR spectrum of Co(acac)₂, Co(acac)₂+BPE and Co(acac)₂+BPE+substrate were recorded, and the EPR signal changed greatly after the addition of BPE and the substrate. The spectrum of Co(acac)₂+BPE+substrate [Co(BPE)(O₂CR)₂] was very similar to that of BPE+Cobalt(II)(2-ethylhexanoate)₂, indicating that coordination of BPE to Co(acac)₂ and substitution of acac by the substrate probably happened. The reaction mixture in the presence of H₂ after 30 min was also monitored with EPR, and the EPR spectra were very similar to that of [Co(BPE)(O₂CR)₂], indicating that the formation of Co(BPE)(O₂CR)₂ species during hydrogenation reaction and which was probably an off-cycle resting state in the current reaction.
Supplementary Figure 8. EPR spectrum of Co(acac)$_2$ in THF glass at 4.8 K. Field strength window = 500-4500 G. Frequency = 9.374998 GHz; modulation frequency = 100 kHz; modulation amplitude = 5 G; microwave power = 0.04 mW.

Supplementary Figure 9. EPR spectrum of (1) in THF glass at 4.8 K. Field strength window = 500-4500 G. Frequency = 9.373563 GHz; modulation frequency = 100 kHz; modulation amplitude = 5 G; microwave power = 0.006 mW.
Supplementary Figure 10. EPR spectrum of (2) in toluene glass at 100 K. (a): Field strength window = 500-4500 G; (b): Field strength window = 2600-3700 G. Frequency = 9.301772 GHz; modulation frequency = 100 kHz; modulation amplitude = 4 G; microwave power = 2.0 mW.

Supplementary Figure 11. EPR spectrum of (3) in toluene glass at 100 K. (a): Field strength window = 500-4500 G; (b): Field strength window = 2600-3700 G. Frequency = 9.301210 GHz; modulation frequency = 100 kHz; modulation amplitude = 4 G; microwave power = 2.0 mW.
Supplementary Figure 12. EPR spectrum of (4) in toluene glass at 100 K. (a): Field strength window = 500-4500 G; (b): Field strength window = 2600-3700 G. Frequency = 9.303780 GHz; modulation frequency = 100 kHz; modulation amplitude = 4 G; microwave power = 2.0 mW.

Supplementary Figure 13. EPR spectrum of (5) in THF glass at 4.8 K. (a): Field strength window = 500-4500 G; (b): Field strength window = 2600-3700 G. Frequency = 9.373040 GHz; modulation frequency = 100 kHz; modulation amplitude = 5 G; microwave power = 0.025 mW.
Supplementary Note 4

Plausible mechanism

Based on experimental observations, the plausible mechanism was proposed in Supplementary Figure 14. The key catalytic intermediate E could be generated through two pathways. In the absence of Zn, complex E can be generated through carboxy group mediated H₂ heterolytic process. Coordination of Co(acac)₂ with (S,S)-Ph-BPE generates Co(II) complex A, which then undergoes ligand exchange with more acidic substrate 1b to produce complex B, complex B and B’ are in equilibrium with each other. Heterolysis of H₂ by complex B’ produces the key catalytic species E via transition state C. However, E may be produced through protonation of dihydride complex D with 1b when employing one-electron reductant. The key intermediate E then enters the catalytic cycle (Figure S12, left). Intramolecular migratory insertion of complex E produces five-membered intermediate F. Coordination of H₂ to F forms complex G, which undergoes subsequent sigma-bond metathesis to give complex H. The ligand exchange of intermediate H with unsaturated carboxylate substrate releases the hydrogenation product 2b and regenerates the cobalt hydride complex D. Chirik and coworkers reported an alternative mechanism which involved the migratory insertion of the dihydride complex and the subsequent reductive elimination as key step (Figure S12, right). The cobalt dihydride species D generated in situ first underwent migratory insertion to form cobalt-alkyl intermediate I and the product was produced after subsequent reductive elimination. The cobalt(0) species J then underwent H₂ oxidative addition and regenerated the cobalt dihydride species D.
Supplementary Figure 14. Plausible mechanism. (a): the activation of pre-catalyst in the absence of Zn; (b) the activation of pre-catalyst in the presence of Zn; (c) plausible catalytic cycle.
Supplementary Figures

Supplementary Figure 15. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2a

Supplementary Figure 16. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2a
Supplementary Figure 17. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2b

Supplementary Figure 18. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2b
Supplementary Figure 19. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2c

Supplementary Figure 20. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2c
**Supplementary Figure 21.** $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2d

**Supplementary Figure 22.** $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2d
Supplementary Figure 23. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2e

Supplementary Figure 24. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2e
Supplementary Figure 25. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2f

Supplementary Figure 26. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2f
Supplementary Figure 27. $^{19}$F NMR (376 MHz, CDCl$_3$) spectrum of 2f

Supplementary Figure 28. $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 2g
Supplementary Figure 29. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2g

Supplementary Figure 30. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2h
Supplementary Figure 31. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2h

Supplementary Figure 32. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2i
Supplementary Figure 33. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2i

Supplementary Figure 34. $^{19}$F NMR (376 MHz, CDCl$_3$) spectrum of 2i
Supplementary Figure 35. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2j

Supplementary Figure 36. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2j
Supplementary Figure 37. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2k

Supplementary Figure 38. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2k
Supplementary Figure 39. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2l

Supplementary Figure 40. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2l
Supplementary Figure 41. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2m

Supplementary Figure 42. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2m
Supplementary Figure 43. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2n

Supplementary Figure 44. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2n
Supplementary Figure 45. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2o

Supplementary Figure 46. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2o
Supplementary Figure 47. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2p

Supplementary Figure 48. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2p
Supplementary Figure 49. $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 2q

Supplementary Figure 50. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2q
Supplementary Figure 51. $^1\text{H}$ NMR (600 MHz, CDCl$_3$) spectrum of 2r

Supplementary Figure 52. $^{13}\text{C}$ NMR (151 MHz, CDCl$_3$) spectrum of 2r
Supplementary Figure 53. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2s

Supplementary Figure 54. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2s
Supplementary Figure 55. $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 2t

Supplementary Figure 56. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2t
Supplementary Figure 57. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2u

Supplementary Figure 58. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2u
Supplementary Figure 59. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4a

Supplementary Figure 60. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 4a
Supplementary Figure 61. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4b

Supplementary Figure 62. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 4b
Supplementary Figure 63. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4c

Supplementary Figure 64. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 4c
Supplementary Figure 65. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4d

Supplementary Figure 66. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 4d
Supplementary Figure 67. $^{19}$F NMR (376 MHz, CDCl$_3$) spectrum of 4d

Supplementary Figure 68. $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 4e
Supplementary Figure 69. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 4e

Supplementary Figure 70. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4f
Supplementary Figure 71. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 4f

Supplementary Figure 72. $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 4g
Supplementary Figure 7. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 4g

Supplementary Figure 74. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4h
Supplementary Figure 7. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 4h

Supplementary Figure 76. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4i
Supplementary Figure 77. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 4i

Supplementary Figure 78. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2v
Supplementary Figure 79. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2v

Supplementary Figure 80. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 2w
Supplementary Figure 81. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 2w

Supplementary Figure 82. $^{19}$F NMR (565 MHz, CDCl$_3$) spectrum of 2w
Supplementary Figure 83. $^1$H NMR (600 MHz, CDCl$_3$) spectrum of 2x

Supplementary Figure 84. $^{13}$C NMR (151 MHz, CDCl$_3$) spectrum of 2x
Supplementary Figure 85. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4j

Supplementary Figure 86. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 4j
Supplementary Figure 87. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 4k

Supplementary Figure 88. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 4k
Supplementary Figure 89. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of 6

Supplementary Figure 90. $^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of 6
Supplementary Figure 91. HPLC spectrum of rac-2a
Supplementary Figure 92. HPLC spectrum of 2a
Supplementary Figure 93. HPLC spectrum of rac-2b
Supplementary Figure 94. HPLC spectrum of 2b
Supplementary Figure 95. HPLC spectrum of rac-2c
Supplementary Figure 96. HPLC spectrum of 2c
Supplementary Figure 97. HPLC spectrum of rac-2d
Supplementary Figure 98. HPLC spectrum of 2d
Supplementary Figure 99. HPLC spectrum of rac-2e
Supplementary Figure 100. HPLC spectrum of 2e
Supplementary Figure 101. HPLC spectrum of rac-2f
Supplementary Figure 102. HPLC spectrum of 2f
Supplementary Figure 103. HPLC spectrum of rac-2g
Supplementary Figure 104. HPLC spectrum of 2g
Supplementary Figure 105. HPLC spectrum of rac-2h
Supplementary Figure 106. HPLC spectrum of 2h
Supplementary Figure 107. HPLC spectrum of rac-2i
Supplementary Figure 108. HPLC spectrum of rac-2i
Supplementary Figure 109. HPLC spectrum of rac-2j
Supplementary Figure 110. HPLC spectrum of 2j
Supplementary Figure 111. HPLC spectrum of rac-2k
Supplementary Figure 112. HPLC spectrum of 2k
Supplementary Figure 113. HPLC spectrum of rac-2l
Supplementary Figure 114. HPLC spectrum of 2l
Supplementary Figure 115. HPLC spectrum of rac-2m
Supplementary Figure 116. HPLC spectrum of 2m
Supplementary Figure 117. HPLC spectrum of rac-2n
Supplementary Figure 118. HPLC spectrum of 2n
Supplementary Figure 119. HPLC spectrum of rac-2o
Supplementary Figure 120. HPLC spectrum of 2o
Supplementary Figure 121. HPLC spectrum of rac-2p
Supplementary Figure 122. HPLC spectrum of 2p
Supplementary Figure 123. HPLC spectrum of rac-2q
Supplementary Figure 124. HPLC spectrum of rac-2q
Supplementary Figure 125. HPLC spectrum of rac-2r
Supplementary Figure 126. HPLC spectrum of 2r
Supplementary Figure 127. HPLC spectrum of rac-2s
Supplementary Figure 128. HPLC spectrum of 2s
Supplementary Figure 129. HPLC spectrum of rac-2t
Supplementary Figure 130. HPLC spectrum of 2t
Supplementary Figure 131. HPLC spectrum of rac-2u
Supplementary Figure 132. HPLC spectrum of 2u
Supplementary Figure 133. HPLC spectrum of rac-4a
Supplementary Figure 134. HPLC spectrum of 4a
Supplementary Figure 135. HPLC spectrum of rac-4b
**Supplementary Figure 136.** HPLC spectrum of 4b
Supplementary Figure 137. HPLC spectrum of rac-4c
Supplementary Figure 138. HPLC spectrum of 4c
Supplementary Figure 139. HPLC spectrum of rac-4d
Supplementary Figure 140. HPLC spectrum of 4d
Supplementary Figure 141. HPLC spectrum of rac-4e
Supplementary Figure 142. HPLC spectrum of 4e
Supplementary Figure 143. HPLC spectrum of rac-4f
Supplementary Figure 144. HPLC spectrum of 4f
Supplementary Figure 145. HPLC spectrum of rac-4g
Supplementary Figure 146. HPLC spectrum of 4g
Supplementary Figure 147. HPLC spectrum of rac-4h
Supplementary Figure 148. HPLC spectrum of 4h
Supplementary Figure 149. HPLC spectrum of rac-4i
Supplementary Figure 150. HPLC spectrum of 4i
Supplementary Figure 151. HPLC spectrum of rac-2v
Supplementary Figure 152. HPLC spectrum of 2v
Supplementary Figure 153. HPLC spectrum of rac-2w
Supplementary Figure 154. HPLC spectrum of 2w
Supplementary Figure 155. HPLC spectrum of rac-2x
Supplementary Figure 156. HPLC spectrum of 2x
Supplementary Figure 157. HPLC spectrum of rac-4j
Supplementary Figure 158. HPLC spectrum of 4j
Supplementary Figure 159. HPLC spectrum of rac-4k
Supplementary Figure 160. HPLC spectrum of 4k
Supplementary Figure 161. HPLC spectrum of rac-6
Supplementary Figure 162. HPLC spectrum of 6
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