Enantioselective Morita–Baylis–Hillman Reaction Promoted by
L-Threonine-Derived Phosphine–Thiourea Catalysts

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A. General Information

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. Toluene, THF and diethyl ether were dried and distilled from sodium benzophenone ketyl prior to use. CHCl₃ and CH₂Cl₂ were distilled from CaH₂ prior to use. Dioxane was dried and distilled from Na prior to use. All the solvents used in reactions involving phosphorous-containing compounds were degassed by N₂. ¹H and ¹³C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL- T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL- T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separations were performed on Merck 60 (0.040- 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis.

The absolute configuration of 12a was assigned by comparing its specific rotation with that of known compound reported in the literature.¹ The configurations of other MBH adducts were assigned by analogy.

B. Preparation of the Catalysts

(S)-tert-Butyl 1-(diphenylphosphino)-3-methylbutan-2-ylcarbamate 2

To a solution of (S)-1-(diphenylphosphino)-3-methylbutan-2-amine (150 mg, 0.55 mmol) and Et₂N (153 μL, 1.10 mmol) in CH₂Cl₂ (5 mL) under N₂ was added (Boc)₂O (143 mg, 0.66 mmol). The reaction mixture was stirred at room temperature for 2 hrs, solvent was then removed under reduced pressure, and the residue was directly purified by column chromatography on silica gel (hexane/ethyl acetate = 15:1 to 10: 1) to afford catalyst 2 as a white solid (171 mg, 84% yield).
Preparation of serine-derived dipeptidic phosphinothiourea catalyst 3a

\[
\begin{align*}
\text{BocHN} & \quad \text{CO}_2\text{H} \quad \text{+} \quad \text{BnNH}_2 \\
\text{CSCl}_2, \text{NaHCO}_3 & \quad \text{CH}_2\text{Cl}_2, 0^\circ \text{C} \to \text{rt} \\
\text{BnHN} & \quad \text{CO} \quad \text{NCS} \quad \text{3a-1} \\
& \quad \text{BnHN} \quad \text{NH} \quad \text{BnHN} \quad \text{NH} \\
\text{Ph}_2\text{PN} & \quad \text{NH}_2 \\
& \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
\text{BnHN} & \quad \text{NH} \quad \text{S} \quad \text{N} \quad \text{N} \quad \text{PPh}_2 \quad \text{3a}
\end{align*}
\]

(5)-N-Benzyl-4-((5)-1-(diphenylphosphino)-3-methylbutan-2-ylamino)-2-isopropyl-4-thioxobutanamide 3a

To a solution of isothiocyanate 3a-1\(^2\) (82 mg, 0.33 mmol) in CH\(_2\)Cl\(_2\) (1 mL) under N\(_2\) was added (S)-1 (diphenylphosphino)-3-methylbutan-2-amine (81.4 mg, 0.3 mmol). The mixture was stirred at room temperature for 24 h, the solvent was then removed under reduced pressure, and the residue was directly subjected to column chromatographic separation on silica gel (hexane/ethyl acetate =15:1 to 8:1) to afford catalyst 3a as a white solid (135 mg, 79% yield).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.40 (m, 4H), 7.31-7.24 (m, 11H), 6.84 (br, 1H), 4.81 (s, 1H), 4.46-4.42 (m, 3H), 2.40-2.36 (m, 1H), 2.28-2.13 (m, 1H), 2.07 (s, 1H), 2.03-1.98 (m, 1H), 0.98-0.89 (m, 6H), 0.83(s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 137.3, 132.8 (dd), 128.6, 128.4 (d), 127.4, 64.1, 57.6 (d), 43.5, 31.9 (d), 30.9, 19.4, 18.8, 18.1; \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) -23.1; HRMS (ESI) m/z calcd for C\(_{30}\)H\(_{35}\)N\(_5\)OPS [M+H]\(^+\) = 520.2551, found = 520.2550.

(5)-N,N-Dibenzyl-4-((5)-1-(diphenylphosphino)-3-methylbutan-2-ylamino)-2-isopropyl-4-thioxobutanamide 3b

\[
\begin{align*}
\text{Bn}_2\text{N} & \quad \text{CO} \quad \text{NCS} \quad \text{3b-1} \\
& \quad \text{Ph}_2\text{PN} \quad \text{NH}_2 \\
& \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
\text{Bn}_2\text{N} & \quad \text{NH} \quad \text{S} \quad \text{N} \quad \text{N} \quad \text{PPh}_2 \quad \text{3b}
\end{align*}
\]

Catalyst 3b was prepared from N-Boc-L-Valine, following the same procedure described for the synthesis of 3a.
A white solid (67% yield); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.71 (br, 1H), 7.41-7.27 (m, 18H), 7.25 (d, $J = 5.1$ Hz, 2H), 5.80 (br, 1H), 4.72 (s, 4H), 4.38 (d, $J = 13.8$ Hz, 1H), 2.38-2.35 (m, 1H), 2.34-2.22 (m, 2H), 2.14-1.97 (m, 1H), 0.98 (d, $J = 6.3$ Hz, 3H), 0.88 (d, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 5.7$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 138.9, 136.3 (d), 132.9 (dd), 132.8, 128.6 (d), 128.3 (d), 127.9 (d), 127.4, 57.3 (d), 50.5, 47.9, 31.9 (dd), 19.6 (d), 18.8, 17.9; $^{31}$P NMR (202 MHz, CDCl$_3$) δ -23.4; HRMS (ESI) m/z calcd for C$_{37}$H$_{45}$N$_3$OPS [M+H]$^+ = 610.3021$, found = 610.3023.

**Typical procedure for preparation of catalysts 4a-4j**

![Reaction Scheme]

To a solution of (S)-1-(diphenylphosphino)-3-methylbutan-2-amine$^3$ (81 mg, 0.30 mmol) in CH$_2$Cl$_2$ (2 mL) under N$_2$ was added isothiocyanate (1.1 eq., 0.33 mmol), and the reaction mixture was stirred at room temperature for 24 hrs. Solvent was then removed under reduced pressure, and the residue was directly subjected to column chromatographic separation on silica gel (hexane/ethyl acetate = 12:1 to 8:1) to afford catalyst 4a-4j as a white solid (71-95% yield).

**(S)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-phenylthiourea 4a**

![Molecule Structure]

A white solid (86% yield); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.05 (br, 1H), 7.42-7.16 (m, 13H), 7.00 (d, $J = 10.3$ Hz, 2H), 5.92 (d, $J = 11.4$ Hz, 1H), 4.50 (br, 1H), 2.36-2.30 (m, 1H), 2.24-2.17 (m, 1H), 2.09-2.00 (m, 1H), 0.80 (d, $J = 9.0$ Hz, 3H), 0.75 (d, $J = 9.0$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 180.1, 135.9, 132.9 (d), 132.7 (d), 130.1, 128.5 (dd), 127.1, 125.2, 58.5 (d), 31.7 (d), 31.2 (d), 18.8, 17.9; $^{31}$P NMR (121 MHz, CDCl$_3$) δ -23.9; HRMS (ESI) m/z calcd for C$_{24}$H$_{28}$N$_2$PS [M+H]$^+ = 407.1711$, found = 407.1711.

**(S)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-(diphenylphosphino)-3-methylbutan-2-yl)thiourea 4b**

![Molecule Structure]

A white solid (86% yield); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.23 (br, 1H), 7.66 (d, $J = 12.6$ Hz, 3H), 7.44 (t, $J = 2.9$ Hz, 4H), 7.42-7.29 (m, 6H), 6.22 (br, 1H), 4.62 (br, 1H), 2.54-2.52 (m, 1H), 2.51-2.49 (m, 1H), 2.34-2.16 (m, 1H), 0.95
(t, J = 7.8 Hz, 6H); $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ -23.2; HRMS (ESI) m/z calcd for C$_{26}$H$_{28}$F$_6$N$_2$PS [M+H]$^+$ = 543.1459, found = 543.1459. The characterization data were in agreement with the values reported in the literature.$^4$

\(\text{(S)-1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea 4c}\)

A white solid (81% yield); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.59 (br, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.47-7.41 (m, 4H), 7.31(d, J = 3.8 Hz, 6H), 7.22 (d, J = 7.6 Hz, 2H), 6.19 (br, 1H), 4.64 (br, 1H), 2.50-2.46 (m, 1H), 2.32-2.27 (m, 1H), 2.19-2.15 (m, 1H), 0.91 (t, J = 7.3 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.6, 139.8, 137.9, 132.8 (d), 132.6, 128.8 (d), 128.5 (dd), 127.9, 127.7, 128.2, 126.9, 124.8, 123.6, 122.7, 58.7 (d), 31.9, 30.8 (d), 18.5 (d); $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ -24.1; HRMS (ESI) m/z calcd for C$_{25}$H$_{27}$F$_3$N$_2$PS [M+H]$^+$ = 475.1585, found = 475.1582.

\(\text{(S)-1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(4-nitrophenyl)thiourea 4d}\)

A white solid (86% yield); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.76 (br, 1H), 8.14-8.11 (m, 2H), 7.46-7.30 (m, 12H), 6.49 (br, 1H), 4.62 (br, 1H), 2.55-2.53 (m, 1H), 2.50-2.48 (m, 1H), 2.35-2.15 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 179.4, 143.9, 143.3, 138.0 (d), 137.4, 132.7 (d), 128.8 (dd), 125.3, 122.1, 58.6 (d), 32.0, 30.7, 18.5; $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ -23.7; HRMS (ESI) m/z calcd for C$_{24}$H$_{27}$N$_3$O$_2$PS [M+H]$^+$ = 452.1562, found = 452.1560.

\(\text{(S)-1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(4-methoxyphenyl)thiourea 4e}\)

A white solid (75% yield); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.60 (br, 1H), 7.48-7.41 (m, 4H), 7.36-7.31 (m, 6H), 7.00-6.96 (m, 2H), 6.89-6.84 (m, 2H), 5.78 (d, J = 8.2 Hz, 1H), 4.55 (br, 1H), 3.80 (s, 3H), 2.44-2.37 (m, 1H), 2.29-2.21 (m, 1H), 2.16-2.05 (m, 1H), 0.86 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 180.7, 158.8, 132.9 (d), 132.6 (d), 128.6, 128.3 (dd), 127.68, 115.1, 58.3 (d), 55.4, 31.7 (d), 31.2 (d), 18.8, 17.9, $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ -24.1; HRMS (ESI) m/z calcd for C$_{25}$H$_{30}$N$_2$O$_3$PS [M+H]$^+$ = 437.1816, found = 437.1811.
A white solid (91% yield); $^1$H NMR (300 MHz, CDCl₃) δ 8.05 (br, 1H), 7.46-7.40 (m, 4H), 7.32-7.31 (m, 6H), 7.04 (d, J = 6.8 Hz, 4H), 5.83 (d, J = 5.9 Hz, 1H), 4.57 (br, 1H), 2.47-2.44 (m, 1H), 2.42-2.40 (m, 1H), 2.28-2.04 (m, 1H), 0.86 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl₃) δ 180.3, 162.9, 159.6, 138.1, 132.9 (d), 132.6 (d), 131.8, 128.7, 128.5 (dd), 127.7, 127.6, 117.0, 116.7, 58.44(d), 31.8 (d), 31.1 (d), 18.7, 18.1; $^{31}$P NMR (121 MHz, CDCl₃) δ -24.3; HRMS (ESI) m/z calcd for C$_{24}$H$_{27}$BrN$_2$PS [M+H]$^+$ = 425.1617, found = 425.1624.

(S)-1-(4-Chlorophenyl)-3-(1-diphenylphosphino)-3-methylbutan-2-yl)thiourea 4g

A white solid (81% yield); $^1$H NMR (500 MHz, CDCl₃) δ 8.20 (br, 1H), 7.46-7.41 (m, 4H), 7.32-7.29 (m, 7H), 7.02 (d, J = 8.2 Hz, 2H), 5.95 (br, 1H), 4.60 (br, 1H), 2.47-2.45 (m, 1H), 2.44-2.42 (m, 1H), 2.28-2.11 (m, 1H), 0.88 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) δ 179.9, 138.2 (d), 132.8 (d), 132.5 (dd), 130.1, 128.8 (d), 128.5 (d), 126.5, 58.5 (d), 31.8 (d), 31.0 (d), 18.7, 18.2; $^{31}$P NMR (202 MHz, CDCl₃) δ -24.2; HRMS (ESI) m/z calcd for C$_{24}$H$_{27}$ClN$_2$PS [M+H]$^+$ = 441.1321, found = 441.1322.

(S)-1-(4-Bromophenyl)-3-(1-diphenylphosphino)-3-methylbutan-2-yl)thiourea 4h

A white solid (75% yield); $^1$H NMR (500 MHz, CDCl₃) δ 8.07 (br, 1H), 7.41-7.36 (m, 6H), 7.27-7.25 (m, 6H), 6.90 (d, J = 8.2 Hz, 2H), 5.90 (br, 1H), 4.54 (br, 1H), 2.42-2.38 (m, 1H), 2.23-2.18 (m, 1H), 2.10-2.07 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) δ 179.9, 138.2 (d), 135.1, 132.8 (dd), 128.8 (d), 128.5 (d), 126.5, 120.2, 58.6 (d), 31.85 (d), 30.9 (d), 18.7, 18.3; $^{31}$P NMR (202 MHz, CDCl₃) δ -24.2; HRMS (ESI) m/z calcd for C$_{24}$H$_{27}$BrN$_2$PS [M+H]$^+$ = 485.0816, found = 485.0815.

(S)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(3-fluorophenyl)thiourea 4i
A white solid (79% yield); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.05 (br, 1H), 7.41-7.34 (m, 4H), 7.33-7.17 (m, 7H), 6.88-6.74 (m, 3H), 6.02 (d, \(J = 11.6\) Hz, 1H), 4.52 (br, 1H), 2.40-2.38 (m, 1H), 2.36-2.34 (m, 1H), 2.23-2.02 (m, 1H), 0.86 (d, \(J = 2.9\) Hz, 3H), 0.82 (d, \(J = 2.9\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 179.7, 164.8, 161.5, 138.1 (d), 137.8 (d), 132.8 (dd), 131.1 (d), 128.7, 128.5 (dd), 119.9 (d), 113.5 (d), 111.8 (d), 58.6 (d), 31.8 (d), 31.0 (d), 18.7, 18.2; \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\) -24.1; HRMS m/z calcd for C\(_{26}\)H\(_{27}\)FN\(_2\)PS [M+H]\(^+\) = 425.1617, found = 425.1621.

(5)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(2-fluorophenyl)thiourea 4j

A white solid (82% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.63 (br, 1H), 7.49-7.40 (m, 4H), 7.33-7.21 (m, 8H), 7.16-7.10 (m, 2H), 6.05 (br, 1H), 4.60 (br, 1H), 2.42-2.39 (m, 1H), 2.38-2.32 (m, 1H), 2.31-2.13 (m, 1H), 0.90 (d, \(J = 7.0\) Hz, 3H), 0.86 (d, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 180.3, 156.9, 154.9, 138.0 (d), 132.8 (d), 132.7 (d), 128.7, 128.4 (dd), 128.1 (d), 126.7, 124.9, 116.8 (d), 58.6 (d), 31.6, 31.1 (d), 18.7, 17.9; \(^{31}\)P NMR (202 MHz, CDCl\(_3\)) \(\delta\) -24.1; HRMS (ESI) m/z calcd for C\(_{26}\)H\(_{27}\)FN\(_2\)PS [M+H]\(^+\) = 425.1617, found = 425.1617.

C. Analytical Data and HPLC Chromatogram of MBH products

(R)-Methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate 12a

A yellow solid; \([\alpha]\)^\(27\) \(_D\) = -83.4 (c 1.00, MeOH), (lit.\(^1\): \([\alpha]\)^\(25\) \(_D\) = -86.6 (c 0.54, MeOH)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.20 (d, \(J = 8.8\) Hz, 2H), 7.57 (d, \(J = 8.8\) Hz, 2H), 6.39 (s, 1H), 5.87 (s, 1H), 5.29 (d, \(J = 5.1\) Hz, 1H), 3.74 (s, 3H), 3.32 (d, \(J = 5.7\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.4, 148.6, 147.5, 140.9, 127.3, 127.2, 123.6, 72.75, 52.19; HRMS (ESI) m/z calcd for C\(_{11}\)H\(_{13}\)NO\(_5\) [M+H]\(^+\) = 238.0715, found = 238.0705; the ee value was 87%, \(t_r\) (minor) = 25.2 min, \(t_r\) (major) = 33.6 min (Chiralcel IC-H, \(\lambda = 254\) nm, 10% iPrOH/hexanes, flow rate = 0.5 mL/min).
Racemic **12a**

Enantiomerically enriched **12a**

**(R)-Methyl 2-(hydroxy(3-nitrophenyl)methyl)acrylate 12b**

![Chemogram](image1)

A yellow solid; 
$[\alpha]_{D}^{27} = -2.7$ (c 0.85, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.13-8.15 (m, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 6.41 (s, 1H), 5.90 (s, 1H), 5.64 (d, $J = 5.1$ Hz, 1H), 3.74 (s, 3H), 3.32 (d, $J = 5.7$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.4, 148.4, 143.6, 140.9, 132.6, 129.3, 127.2, 122.8, 121.5, 72.6, 52.2; HRMS (ESI) m/z calcd for C$_{11}$H$_{12}$NO$_5$ [M+H]$^+$ = 238.0715, found = 238.0706; The ee value was 85%, $t_R$ (minor) = 13.4 min, $t_R$ (major) = 16.1 min (Chiralcel IC-H, $\lambda = 254$ nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

**(R)-Methyl 2-(hydroxy(2-nitrophenyl)methyl)acrylate 12c**

![Chemogram](image2)

A yellow solid; 
$[\alpha]_{D}^{27} = -16.9$ (c 0.80, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.95 (dd, $J = 1.3$ Hz, 8.2 Hz, 1H), 7.74-7.76 (m, 1H), 7.64 (d, $J = 7.3$ Hz, 1H), 7.44-7.48 (m, 1H), 6.36 (s, 1H), 6.12 (s, 1H), 5.73 (s, 1H), 3.73 (s, 3H), 3.43 (br, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.4, 148.3, 140.7, 136.1, 133.4, 128.9, 128.7, 126.5, 124.6, 67.7, 52.1;
HRMS (ESI) m/z calcld for C_{11}H_{12}NO_{5} [M+H]^+ = 238.0715, found = 238.0712; The ee value was 69%, t_{R} (minor) = 14.4 min, t_{R} (major) = 16.9 min (Chiralcel OD-H, \( \lambda = 254 \) nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

(R)-Methyl 2-((4-cyanophenyl)(hydroxy)methyl)acrylate 12d

A colorless oil; \([\alpha]^{27}_D = -4.4 \ (c 0.85, \text{CHCl}_3)\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \( \delta \ 7.63 \ (d, J = 8.2 \ \text{Hz}, 2\ H), \ 7.51 \ (d, J = 8.2 \ \text{Hz}, 2\ H), \ 6.37 \ (s, 1\ H), \ 5.85 \ (s, 1\ H), \ 5.58 \ (d, J = 4.4 \ \text{Hz}, 1\ H), \ 3.73 \ (s, 3\ H), \ 3.29 \ (d, J = 5.7 \ \text{Hz}, 1\ H); \ ^{13}^C\) NMR (125 MHz, CDCl\(_3\)) \( \delta \ 166.4, \ 146.6, \ 141.0, \ 132.2, \ 127.2, \ 127.1, \ 118.7, \ 111.6, \ 72.8, \ 52.1; \) HRMS (ESI) m/z calcld for C\(_{12}\)H\(_{12}\)NO\(_3\) [M+H]^+ = 218.0817, found = 218.0816; The ee value was 87%, t_{R} (minor) = 16.3 min, t_{R} (major) = 22.0 min (Chiralcel IC-H, \( \lambda = 254 \) nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

(R)-Methyl 2-((3-cyanophenyl)(hydroxy)methyl)acrylate 12e
A colorless; [α]$^D_27$ = +11.5 (c 0.87, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.69 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 6.39 (s, 1H), 5.86 (s, 1H), 5.56 (d, J = 5.7 Hz, 1H), 3.74 (s, 3H), 3.28 (d, J = 6.3 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.4, 142.9, 141.1, 131.4, 131.0, 129.1, 127.0, 118.7, 112.5, 72.5, 52.1; HRMS (ESI) m/z calcd for C$_{12}$H$_{12}$NO$_3$ [M+H]$^+$ = 218.0817, found = 218.0824; The ee value was 85%, t$_R$ (minor) = 17.1 min, t$_R$ (major) = 24.4 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

(R)-Methyl 2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)acrylate 12f

A colorless; [α]$^D_27$ = -4.3 (c 0.71, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.60 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 6.36 (s, 1H), 5.84 (s, 1H), 5.59 (d, J = 5.7 Hz, 1H), 3.73 (s, 3H), 3.27 (br, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.5, 145.3, 141.4, 129.9 (q), 126.8, 126.8, 125.4 (q), 125.2, 123.0, 72.9, 52.1; HRMS (ESI) m/z calcd for C$_{12}$H$_{12}$F$_3$O$_3$ [M+H]$^+$ = 261.0714, found = 261.0717; The ee value was 87%, t$_R$ (minor) = 12.9 min, t$_R$ (major) = 20.4 min (Chiralcel IC-H, λ = 254 nm, 5% iPrOH/hexanes, flow rate = 0.5 mL/min).
(R)-Methyl 2-((3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)acrylate 12g

A colorless oil; [α]$_D^{27}$ = 20.9 (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 (s, 2H), 7.80 (s, 1H), 6.24 (s, 1H), 5.88 (s, 1H), 5.65 (s, 1H), 3.76 (s, 3H), 3.34 (br, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.3, 144.0, 140.8, 132.1, 131.6, 127.5, 126.8, 124.4, 122.2, 121.8, 121.7, 72.5, 52.3; HRMS (ESI) m/z calcd for C$_{13}$H$_{11}$F$_6$O$_3$ [M+H]$^+$ = 329.0612, found = 329.0620; The ee value was 84%, t$_R$ (minor) = 12.7 min, t$_R$ (major) = 10.7 min (Chiralcel OD-H, λ = 254 nm, 5% iPrOH/hexanes, flow rate = 0.5 mL/min).

(Racemic 12g)

Enantiomerically enriched 12g

(R)-Methyl 2-((4-chloro-3-nitrophenyl)(hydroxy)methyl)acrylate 12h

A colorless oil; [α]$_D^{27}$ = -7.7 (c 1.10, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.89 (d, J = 1.9 Hz, 1H), 7.49-7.55 (m, 2H), 6.39 (s, 1H), 5.91 (s, 1H), 5.56 (s, 1H), 3.74 (s, 3H), 3.43 (br, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.2, 147.8, 142.1, 140.7, 131.7, 131.1, 127.3, 126.0, 123.6, 71.9, 52.2; HRMS (ESI) m/z calcd for C$_{11}$H$_{11}$ClNO$_5$ [M+H]$^+$ = 272.0326, found = 272.0329; The ee value was 85%, t$_R$ (minor) = 19.0 min, t$_R$ (major) = 23.4 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 0.5 mL/min).

(Racemic 12h)

Enantiomerically enriched 12h
(R)-Methyl 2-([(4-fluorophenyl)(hydroxy)methyl]acrylate 12i

A colorless oil; [α]$_{D}^{27}$ = -20.0 (c 0.50, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.33-7.36 (m, 2H), 7.02 (t, J = 8.8 Hz, 2H), 6.33 (s, 1H), 5.82 (s, 1H), 5.54 (d, J = 5.1 Hz, 1H), 3.73 (s, 3H), 3.06 (d, J = 5.1 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.7, 163.3, 161.4, 141.9, 137.0 (d), 128.3 (d), 126.1, 115.3 (d), 72.6, 52.9; HRMS (ESI) m/z calcd for C$_{11}$H$_{12}$FO$_3$ [M+H]$^+$ = 211.0770, found = 211.0772; The ee value was 81%, $t_R$ (minor) = 13.9 min, $t_R$ (major) = 24.2 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 0.5 mL/min).

(R)-Methyl 2-([(4-chlorophenyl)(hydroxy)methyl]acrylate 12j

A colorless oil; [α]$_{D}^{27}$ = -22.4 (c 1.31, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.30 (m, 4H), 6.32 (s, 1H), 5.83 (s, 1H), 5.51 (d, J = 5.0 Hz, 1H), 3.71 (s, 3H), 3.23 (d, J = 5.1 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.6, 141.6, 139.8, 133.5, 128.5, 127.9, 126.2, 72.5, 51.9; (ESI) m/z calcd for C$_{11}$H$_{12}$ClO$_3$ [M+H]$^+$ = 227.0475, found = 227.0480; The ee value was 84%, $t_R$ (minor) = 13.6 min, $t_R$ (major) = 21.0 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 0.5 mL/min).
(R)-Methyl 2-((3-chlorophenyl)(hydroxy)methyl)acrylate 12k

A colorless oil; [α] 270 = -6.6 (c 0.63, CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.55 (dd, J = 1.9 Hz, 7.6 Hz, 1H), 7.22-7.36 (m, 3H), 6.33 (s, 1H), 5.98 (s, 1H), 5.58 (s, 1H), 3.77 (s, 3H), 3.33 (br, 1H); 13C NMR (125 MHz, CDCl3) δ 166.9, 140.6, 138.2, 132.8, 129.4, 129.0, 128.1, 126.9, 69.3, 52.1; HRMS (ESI) m/z calcd for C11H11ClO3 [M+H]+ = 227.0475, found = 227.0476; The ee value was 82%, tR (minor) = 20.5 min, tR (major) = 31.1 min (Chiralcel IC-H, λ = 254 nm, 5% iPrOH/hexanes, flow rate = 0.5 mL/min).

(R)-Methyl 2-((4-bromophenyl)(hydroxy)methyl)acrylate 12l

A colorless oil; [α] 270 = +7.9 (c 1.0, CHCl3); 1H NMR (500 MHz, CDCl3) δ 7.84 (d, J = 8.2 Hz, 2H), 7.45 (dd, J = 2.6 Hz, 8.9 Hz, 2H), 6.33 (s, 1H), 5.82 (s, 1H), 5.49 (d, J = 5.1 Hz, 1H), 3.71 (s, 3H), 3.22 (d, J = 5.1 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ 166.5, 141.6, 140.3, 131.5, 128.3, 126.3, 121.7, 72.6, 51.9; (ESI) m/z calcd for C11H12BrO3 [M+H]+ = 270.9970, found = 270.9961; The ee value was 83%, tR (minor) = 14.2 min, tR (major) = 21.8 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 0.5 mL/min).
**(R)-Methyl 2-((3-bromophenyl)(hydroxy)methyl)acrylate 12m**

A colorless oil; [α]<sub>27</sub><sup>0</sup> = -14.9 (c 0.80, CHCl₃); <sup>1</sup>H NMR (500 MHz, CDCl₃) δ 7.52 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 8.2 Hz, 1H), 6.35 (s, 1H), 5.84 (s, 1H), 5.50 (s, 1H), 3.73 (s, 3H), 3.22 (br, 1H); <sup>13</sup>C NMR (125 MHz, CDCl₃) δ 166.5, 143.6, 141.4, 130.8, 129.9, 129.6, 126.6, 125.2, 122.5, 72.6, 52.0; HRMS (ESI) m/z calcd for C₁₁H₁₂BrO₃ [M+H]<sup>+</sup> = 270.9949, found = 270.9952; The ee value was 84%, t<sub>r</sub> (minor) = 14.6 min, t<sub>r</sub> (major) = 20.7 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 0.5 mL/min).

**(R)-Methyl 2-(hydroxy(phenyl)methyl)acrylate 12n**

A colorless oil; [α]<sub>27</sub><sup>0</sup> = -94.3 (c 0.42, MeOH), (lit.⁵ [α]<sub>28</sub><sup>0</sup> = -109.3 (c, 0.54, MeOH)); <sup>1</sup>H NMR (500 MHz, CDCl₃) δ 7.32-7.38 (m, 4H), 7.26-7.29 (m, 1H), 6.33 (s, 1H), 5.84 (s, 1H), 5.56 (s, 1H), 3.71 (s, 3H), 3.15 (br, 1H); <sup>13</sup>C NMR (125 MHz, CDCl₃) δ 166.8, 142.0, 141.3, 128.4, 127.8, 126.6, 126.1, 73.2, 51.9; HRMS (ESI) m/z calcd for C₁₁H₁₃O₃ [M+H]<sup>+</sup> = 193.0865, found = 193.0866; The ee value was 80%, t<sub>r</sub> (minor) = 14.8 min, t<sub>r</sub> (major) = 29.1 min (Chiralcel IC-H, λ = 254 nm, 5% iPrOH/hexanes, flow rate = 1.0 mL/min).
(R)-Methyl 2-(hydroxy(p-tolyl)methyl)acrylate 12o

A colorless oil; [α]_D^27 = -57.4 (c 0.52, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.26 (d, J = 6.6 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.33 (s, 1H), 5.85 (d, J = 1.3 Hz, 1H), 5.53 (s, 1H), 3.71 (s, 3H), 2.99 (br, 1H), 2.34 (s, 1H); ^13C NMR (125 MHz, CDCl_3) δ 166.7, 142.1, 138.3, 137.5, 129.1, 126.5, 125.8, 73.0, 51.9, 21.1; HRMS (ESI) m/z calcd for C_{12}H_{15}O_3 [M+H]^+ = 207.1021, found = 207.1022; The ee value was 76%, t_R (minor) = 21.6 min, t_R (major) = 37.5 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 0.5 mL/min).

(R)-Methyl 2-(hydroxy(m-tolyl)methyl)acrylate 12p

A colorless oil; [α]_D^27 = -46.7 (c 0.45, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.15-7.26 (m, 3H), 7.10 (d, J = 6.9 Hz, 2H), 6.34 (s, 1H), 5.85 (s, 1H), 5.53 (s, 1H), 3.72 (s, 3H), 3.05 (br, 1H), 2.35 (s, 1H); ^13C NMR (125 MHz, CDCl_3) δ 166.7, 141.9, 141.2, 138.0, 128.5, 128.3, 127.2, 125.9, 123.6, 73.2, 51.9, 21.4; HRMS (ESI) m/z calcd for C_{12}H_{15}O_3 [M+H]^+ = 207.1021, found = 207.1015; The ee value was 77%, t_R (minor) = 9.9 min, t_R (major) = 17.3 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).
(R)-Methyl 2-(hydroxy(naphthalen-2-yl)methyl)acrylate 12q

A white solid; [α]_D^27 = -12.6 (c 0.43, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.82-7.86 (m, 4H), 7.48 (d, J = 7.6 Hz, 3H), 6.38 (s, 1H), 5.88 (s, 1H), 5.75 (d, J = 3.2 Hz, 1H), 3.72 (s, 3H), 3.15 (d, J = 5.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 166.8, 141.9, 138.6, 133.2, 133.0, 128.2, 128.1, 127.6, 126.4, 126.1, 126.0, 125.5, 124.6, 73.4, 52.9; HRMS (ESI) m/z calcd for C₁₅H₁₅O₃ [M+H]⁺ = 243.1021, found = 243.1021; the ee value was 90%, tᵣ (minor) = 13.0 min, tᵣ (major) = 18.6 min (Chiralcel IC-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

(R)-Methyl 2-(hydroxy(pyridin-3-yl)methyl)acrylate 12r

A colorless oil; [α]_D^27 = -44.5 (c 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.49 (s, 1H), 8.41 (d, J = 4.4 Hz, 1H), 7.71-7.73 (m, 1H), 7.23-7.26 (m, 1H), 6.37 (s, 1H), 5.95 (s, 1H), 5.59 (m, 1H), 3.70 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.3, 148.6, 148.3, 141.6, 134.5, 126.2, 123.4, 70.7, 51.9; HRMS (ESI) m/z calcd for C₁₀H₁₂NO₃ [M+H]⁺ = 194.0817, found = 194.0813; the ee value was 84%, tᵣ (minor) = 12.0 min, tᵣ (major) = 19.2 min (Chiralcel IC-H, λ = 254 nm, 30% iPrOH/hexanes, flow rate = 1.0 mL/min).
(S)-Methyl 2-(hydroxy(thiophen-2-yl)methyl)acrylate 12s

A colorless oil; [$\alpha$]$^D_{27} = +46.7$ (c 0.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.24-7.26 (m, 1H), 6.94 (m, 2H), 6.35 (s, 1H), 5.95 (s, 1H), 5.76 (d, $J = 6.3$ Hz, 1H), 3.74 (s, 3H), 3.44 (br, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.5, 145.7, 141.3, 126.8, 126.1, 125.2, 124.7, 69.6, 51.9; HRMS (ESI) m/z calcd for C$_9$H$_{11}$O$_3$S [M+H]$^+$ = 199.0429, found = 199.0427; The ee value was 70%, $t_R$ (minor) = 11.6 min, $t_R$ (major) = 17.1 min (Chiralcel IC-H, $\lambda = 254$ nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

References

D. NMR Spectra of the Catalyst and the Products

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\begin{align*}
\text{zfr-valine-Boc} & \\
\end{align*}
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\begin{align*}
\text{zfr-646} & \\
\end{align*}
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**Processing Parameters**
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$^{13}$C AMX500 hxy-440

4h

$^{31}$p AMX500 hxy-440

4h
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wyq-142B 1H normal range AC300

wyq-142B 13C Standard AC300
$^3$P AC300 hxy-LTBPS

![Chemical structure of compound 5c](image)

$^1$H normal range AC300 hxy-327

![Chemical structure of compound 5d](image)
1H AMX500 hxy-487

13C AMX500 hxy-487
1H AMX500 hxy-499

13C AMX500 hxy-499