Active Site Design in a Chemzyme: Development of a Highly Asymmetric and Remarkable Temperature Independent Catalyst for the Imino Aldol Reaction

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Experimental procedures and spectral data for all new compounds.

Melting points were determined on a Hoover Unimelt apparatus and are uncorrected. IR spectra were taken on a Nicolet 20SX FTIR. $^1$H and $^{13}$C NMR spectra were recorded on a Brucker 400 MHz or a Brucker 500 MHz or a Varian 300 MHz instrument in CDCl$_3$ unless otherwise noted. CDCl$_3$ was used as internal standard for both $^1$H NMR ($\delta = 7.24$) and $^{13}$C NMR ($\delta = 77.0$). Low-resolution mass spectra were recorded on a Finnigan 1015 mass spectrometer. Elemental analyses were done by Galbraith Laboratories in Knoxville, TN.

HPLC were carried out using a waters M-45 Solvent Delivery System equipped with Waters Model U6K Universal Liquid Chromatograph Injector, a Waters Model 440 Absorbance detector, a Spectra-Physics Chromjet Integrator. Chiral HPLC data were obtained with a Daicel Chiralcel OD, a Daicel Chiralpak AD, and a Daicel Chiralpak AS column from Chiral technologies, Inc. Column chromatography was performed with Merck silica gel grade 60, 230-400 mesh. All reactions were carried out under argon atmosphere in dried glassware. All solvents were purified according to standard procedures. Ketene silyl acetal were prepared according to the procedure reported by Ireland et al.$^{[1]}$. 6,6’-DibromoBINOL was synthesized according to the procedure reported by Ding$^{[2]}$ and resolved according to the procedure reported by Cai.$^{[3]}$

A typical experimental procedure for the synthesis of aldimines: The appropriate aldehyde and aminophenol were dissolved in benzene and 50 mg of ZnCl$_2$ was added to the reaction. The resultant solution was refluxed with a Dean-Stark trap for 4 h, and then cooled to room
temperature. The ZnCl$_2$ was filtered off and the filtrate was concentrated to give the crude product. The crude aldimines were recrystallized from ethanol to give the pure products.

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\text{N-Benzylidene-2-aminophenol 1.}^{[4]} \text{ yellow crystal; } ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 6.90 \text{ (dt, } J = 7.6, 1.2 \text{ Hz, 1H), 7.01 (dd, } J = 8.1, 1.3 \text{ Hz, 1H), 7.19 (dt, } J = 8.1, 1.3 \text{ Hz, 1H), 7.30 (dd, } J = 8.0, 1.4 \text{ Hz, 1H), 7.47 \sim 7.50 \text{ (m, 3H), 7.90 \sim 7.92 \text{ (m, 2H), 8.69 (s, 1H).}}
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\text{N-Benzylidene-2-amino-6-methylphenol 11.} \text{ } ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 2.30 \text{ (s, 3H), 6.80 (t, } J = 7.6 \text{ Hz, 1H), 7.05 (d, } J = 7.9 \text{ Hz, 1H), 7.46 \sim 7.49 \text{ (m, 3H), 7.89 \sim 7.92 \text{ (m, 2H), 8.68 (s, 1H).}}
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\text{N-Benzylidene-2-amino-5-methylphenol 12.} \text{ yellow crystal; } R_f = 0.48 \text{ (9/1 hexanes/ethyl acetate); mp } 95 - 97 \degree \text{C (ethanol); } ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 2.34 \text{ (s, 3H), 6.72 (d, } J = 8.1 \text{ Hz, 1H), 6.86 (s, 1H), 7.21 (d, } J = 8.1 \text{ Hz, 1H), 7.31 (br, 1H), 7.43 - 7.48 \text{ (m, 3H), 7.87 - 7.91 \text{ (m, 2H), 8.65 (s, 1H); } ^{13}\text{C NMR (400 MHz, CDCl}_3\text{): } \delta = 21.3, 115.5, 115.6, 120.9, 128.7, 128.9, 131.5, 132.9, 136.1, 139.5, 152.4, 155.8; MS (El) } m/z \text{ (relative intensity): 211 (70), 210 (45), 134 (100), 107 (13),}
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104 (21), 77 (52); Anal. Calcd. for C\textsubscript{14}H\textsubscript{13}NO: C, 79.59; H, 6.20; N, 6.36. Found: C, 79.50; H, 6.29; N, 6.62.

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\begin{align*}
\text{N-Benzylidene-2-amino-4-methylphenol} & \text{ 13.} & \text{yellow crystal; } R_t = 0.41 \text{ (9/1 hexanes/ethyl acetate); } ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 2.33 \text{ (s, } 3\text{H), 6.93 (d, } J = 8.2 \text{ Hz, } 1\text{H), 7.02 (d, } J = 8.7 \text{ Hz, } 1\text{H), 7.11 (s, } 1\text{H), 7.13 (br, } 1\text{H), 7.45 - 7.50 \text{ (m, } 3\text{H), 7.88 - 7.93 \text{ (m, } 2\text{H), 8.65 (s, } 1\text{H); } ^1\text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 20.7, 114.8, 116.4, 128.87, 128.94, 129.4, 129.6, 131.7, 135.2, 136.0, 150.3, 156.9.}
\end{align*}
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\begin{align*}
\text{N-Benzylidene-2-amino-3-methylphenol} & \text{ 14.} & \text{pale yellow powder; } R_t = 0.43 \text{ (9/1 hexanes/ethyl acetate); mp 115 - 117 \textdegree C (ethanol); } ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 2.32 \text{ (s, } 3\text{H), 6.32 (br, } 1\text{H), 6.78 (d, } J = 7.6 \text{ Hz, } 1\text{H), 6.85 (d, } J = 7.9 \text{ Hz, } 1\text{H), 7.01(dd, } J = 7.9, 7.6 \text{ Hz, } 1\text{H), 7.45 - 7.55 \text{ (m, } 3\text{H), 7.89 (d, } J = 7.4 \text{ Hz, } 2\text{H), 8.49 (s, } 1\text{H); } ^1\text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 18.6, 112.6, 122.9, 126.3, 128.0, 128.8, 129.0, 132.1, 135.7, 137.2, 150.0, 164.7; \text{ MS (EI) } m/z \text{ (relative intensity): } 211 (100), 210 (63), 134 (90), 107 (14), 104 (25), 77 (97); \text{ Anal. Calcd. for C}_{14}\text{H}_{13}\text{NO: C, 79.59; H, 6.20; N, 6.36. Found: C, 79.43; H, 6.16; N, 6.56.}
\end{align*}
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**N-Benzylidene-2-amino-4,6-dimethylphenol 15a.** yellow crystal; \( R_f = 0.50 \) (9/1 hexanes/ethyl acetate); mp 60 - 61 °C (ethanol); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 2.28 \) (s, 6H), 6.88 (s, 1H), 6.97 (s, 1H), 7.24 (s, 1H), 7.45 - 7.49 (m, 3H), 7.88 - 7.92 (m, 2H), 8.66 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 15.5, 20.6, 113.6, 124.1, 128.5, 128.8, 128.9, 130.9, 131.5, 134.5, 136.1, 148.6, 156.5 \); IR (neat): \( \nu = 3400\text{b}, 1625\text{m}, 1576\text{m}, 1486\text{s}, 1238\text{w} \text{cm}^{-1} \); MS (El) \( m/z \) (relative intensity): 225 (79), 224 (55), 148 (100), 121 (8), 104 (10), 91 (33), 77 (29); Anal. Calcd. for C\(_{15}\)H\(_{15}\)NO: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.92; H, 6.64; N, 6.22.

![Image](16.png)

**N-Benzylidene-2-amino-4-chlorophenol 16.**\(^{[5]}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 6.93 \) (d, \( J = 8.6 \) Hz, 1H), 7.26 (d, \( J = 2.4 \) Hz, 1H), 7.46 - 7.53 (m, 3H), 7.88 - 7.90 (m, 2H), 8.62 (s, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 116.0, 116.2, 125.0, 128.5, 128.9, 129.0, 132.1, 135.4, 136.2, 150.9, 158.3 \).

![Image](15b.png)

**N-(4¢-Chloro-benzylidene)-2-amino-4,6-dimethylphenol 15b.** yellow crystal; \( R = 0.43 \) (9/1 hexanes/ethyl acetate); mp 112 - 4 °C (ethanol); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.28 \) (s, 6H), 6.89 (s, 1H), 6.94 (s, 1H), 7.18 (s, 1H), 7.42 (d, \( J = 8.2 \) Hz, 2H), 7.80 (d, \( J = 8.0 \) Hz, 2H), 8.58 (s, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 15.6, 20.7, 113.5, 124.1, 128.4, 129.0, 129.7, 131.1, 134.0, 134.4, 137.3, 148.5, 154.7 \); MS (El) \( m/z \) (relative intensity): 261 (31, \(^{37}\)Cl [M’]), 260 (47, \(^{37}\)Cl), 259 (74, \(^{35}\)Cl), 258 (81, \(^{35}\)Cl), 149 (34), 148 (100), 91 (48), 77 (55); Anal. Calcd. for C\(_{15}\)H\(_{14}\)ClNO: C, 69.36; H, 5.43; N, 5.39. Found: C, 69.05; H, 5.47; N, 5.32.
**N-(4′-methoxy-benzylidene)-2-amino-4,6-dimethylphenol 15c.** yellow crystal; \( R = 0.32 \) (9/1 hexanes/ethyl acetate); mp 57 - 9 °C (ethanol); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.255 \text{ (s, 3H), 2.262 \text{ (s, 3H), 3.86 \text{ (s, 3H), 6.84 \text{ (s, 1H), 6.92 \text{ (s, 1H), 6.96 \text{ (d, } J = 6.9 \text{ Hz, 2H), 7.21 \text{ (s, 1H), 7.83 \text{ (d, } J = 6.9 \text{ Hz, 2H), 8.57 \text{ (s, 1H);}}) \text{ } 13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 15.6, 20.8, 55.4, 113.5, 114.2, 123.7, 128.3, 129.0, 130.2, 130.4, 134.8, 148.2, 155.9, 162.3; MS (EI) m/z (relative intensity): 256 (18), 255 (91) [M\(^+\)], 254 (100), 148 (67), 121 (39), 91 (37), 77 (38); Anal. Calcd. for C\(_{16}\)H\(_{17}\)NO\(_2\): C, 75.27; H, 6.71; N, 5.49. Found: C, 74.67; H, 6.84; N, 5.44.

**N-(3′,4′-dimethoxy-benzylidene)-2-amino-4,6-dimethylphenol 15d.** yellow crystal; \( R = 0.13 \) (9/1 hexanes/ethyl acetate); mp 124 - 5 °C (ethanol); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.25 \text{ (s, 3H), 2.26 \text{ (s, 3H), 3.93 \text{ (s, 3H), 3.94 \text{ (s, 3H), 6.84 - 6.93 \text{ (m, 3H), 7.20 \text{ (s, 1H), 7.32 \text{ (dd, } J = 1.6, 8.3 \text{ Hz, 1H), 7.53 \text{ (s, 1H), 8.54 \text{ (s, 1H);}}) \text{ } 13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 15.6, 20.7, 55.8, 55.9, 108.8, 110.5, 113.7, 123.7, 124.2, 128.3, 129.2, 130.2, 134.9, 148.0, 149.3, 152.1, 156.3; MS (EI) m/z (relative intensity): 286 (23), 285 (100) [M\(^+\)], 284 (82), 151 (24), 148 (69), 138 (23), 91 (25), 77 (27); Anal. Calcd. for C\(_{17}\)H\(_{19}\)NO\(_3\): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.14; H, 6.81; N, 4.85.
**N-(1′-Naphthylmethylene)-2-amino-4,6-dimethylphenol 15e.** yellow crystal; \( R_f = 0.36 \) (9/1 hexanes/ethyl acetate); mp 125 - 6 °C (ethanol); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.30 \) (s, 3H), 2.32 (s, 3H), 6.91 (s, 1H), 7.03 (s, 1H), 7.19 (s, 1H), 7.53 - 7.64 (m, 3H), 7.90 - 7.98 (m, 2H), 8.15 (d, \( J = 7.1 \) Hz, 1H), 8.86 (d, \( J = 8.5 \) Hz, 1H), 9.33 (s, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 15.6, 20.8, 113.6, 123.5, 124.0, 125.3, 126.2, 127.4, 128.5, 128.9, 129.0, 130.8, 131.3, 131.4, 132.0, 133.8, 135.4, 148.3, 155.8; MS (El) \text{m/z (relative intensity): 276 (24), 275 (100) [M^+], 274 (90), 148 (72), 128 (35), 91 (25), 77 (27); Anal. Calcd. for C\(_{19}\)H\(_{17}\)NO: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.57; H, 6.22; N, 5.00.**

**A typical experimental procedure for the reaction of aldimine with silyl ketene acetals.**

To VAPOL (0.11 mmol) and Zr(O-i-Pr)\(_4\)/iPrOH (0.05 mmol) in toluene (0.9 mL) was added 1-methylimidazole (0.06 mmol) in toluene (0.1 mL) at room temperature. The mixture was stirred for 1 h at the same temperature. An aldimine (0.25 mmol in 1 mL) toluene solution was added to the catalyst and the mixture was stirred for an additional 5 min. Then the silyl ketene acetal (0.3 mmol) was added. The mixture was stirred for 15 h at room temperature. Aqueous NaHCO\(_3\) was added to quench the reaction. The mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 10 mL). The combined organic layer was concentrated to give the crude product.

The crude product was treated with THF and aqueous1N HCl (10:1) at 0 °C for 30 min. Then the reaction was quenched with aqueous NaHCO\(_3\) and extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine and concentrated. The desired product was obtained by chromatography on silica gel. The optical purity was determined by chiral HPLC analysis.

The experimental details for individual reactions (temperatures, concentration, yields, % ee, etc.) can be found in Tables I – IV in the manuscript.

\(^1\)H NMR Investigation of the Catalyst.
A sample of the catalyst was prepared at room temperature in d$_8$-toluene from one equivalent of zirconium tetra-tert-butoxide and two equivalents of the VAPOL ligand and two equivalents of N-methylimidazole. The spectrum was recorded after stirring for 2 hours and was unchanged after 1 and 5 days. The same spectrum was obtained with zirconium tetra-iso-propoxide. On the basis of these spectra, the catalyst structure is tentatively assigned as structure 6 with an additional N-methylimidazole coordinated to the zirconium. Figures 1A and 1B (pages 19-20) show the $^1$H NMR spectra of the catalyst and Figures 2 (page 21) and 3 (page 22) show the $^1$H NMR spectra of VAPOL and N-methylimidazole, respectively. The bay proton of the VAPOL ligand is shifted downfield in the catalyst (from 9.91 to 11.45 ppm) whereas all of the protons of N-methylimidazole are shifted upfield. The presence of a single bay proton indicates a C$_2$-symmetrical species.

![Structure 6]

**Methyl 3-(2-hydroxy-phenylamino)-3-phenyl-2,2-dimethyl-propionate 3.** The spectral data for this compound are the same as those previously reported for this compound.$^{[7]}$ $^1$H NMR (400 MHz, CDCl$_3$): δ = 1.20 (s, 3H), 1.23 (s, 3H), 3.67 (s, 3H), 4.53 (brs, 1H), 4.85 (brs, 1H), 5.39 (s, 3H), 6.37 (dd, $J = 7.8$, 1.1 Hz, 1H), 6.52 (dt, $J = 7.0$, 1.2 Hz, 1H), 6.59 (dt, $J = 7.8$, 1.1 Hz, 1H), 6.70 (d, $J = 7.6$ Hz, 1H), 7.20 - 7.27 (m, 5H). The major isomer obtained from the reaction with the S-VAPOL ligand is different in absolute configuration than that observed for the reaction with the S-dibromoBINOL ligand as judged by the retention times obtained by chiral HPLC (Daicel Chiralpak AD, Hexanes/i-PrOH = 9/1, flow rate 1.0 mL/min): $R_t = 9.56$ min (major enantiomer), $R_t = 12.71$ min (minor enantiomer).
Methyl 3-(2-hydroxy-3-methylphenylamino)-3-phenyl-2,2-dimethyl-propionate 17. \(R_f = 0.29\) (8/2 hexanes/ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.27\) (s, 6H), 2.24 (s, 3H), 3.74 (s, 3H), 4.58 (br, 1H), 4.82 (s, 1H), 5.41 (br, 1H), 6.34 (br, 1H), 6.53 - 6.59 (m, 3H), 7.25 - 7.33 (m, 5H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 15.7, 19.9, 24.5, 47.4, 52.2, 65.0, 113.3, 120.3, 120.7, 122.6, 127.4, 127.9, 128.4, 135.0, 139.0, 143.4, 177.6\); HPLC (Daicel Chiralcel OD, hexanes/i-PrOH = 95/5, flow rate = 1.0 mL/min): \(R_t = 8.9\) min (minor enantiomer), \(R_t = 10.3\) min (major enantiomer), (S-VAPOL as ligand).

Methyl 3-(2-hydroxy-4-methylphenylamino)-3-phenyl-2,2-dimethyl-propionate 18. yellow solid; \(R_f = 0.27\) (8/2 hexanes/ethyl acetate); mp 134-136 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.19\) (s, 3H), 1.20 (s, 3H), 2.11 (br, 3H), 3.69 (s, 3H), 4.49 (br, 2H), 5.64 (br, 1H), 6.31 (br, 1H), 6.38 (br, 1H), 6.54 (br, 1H), 7.19 - 7.27 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 19.6, 20.6\) (br), 24.5, 47.4 (br), 52.3, 65.2 (br), 115.5 (br), 121.0 (br), 127.4, 127.9, 128.5, 129.0, 132.4 (br), 139.0 (br), 145.4 (br), 178.0 (one peak missing); IR (neat): \(\nu = 3415\)br, 2951br, 1708s, 1622m, 1530s, 1284s, 1139s cm\(^{-1}\); MS (El) m/z (relative intensity): 313 (5), 213 (16), 212 (100), 134 (9), 117 (4), 91 (11), 77 (12); Anal. Calcd. for C\(_{19}\)H\(_{23}\)NO\(_3\): C, 72.80; H, 7.40; N, 4.47. Found: C,72.96; H, 7.55; N, 4.47; HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 9/1, flow rate = 1.0 mL/min): \(R_t = 10.1\) min (major enantiomer), \(R_t = 23.2\) min (minor enantiomer), (S-VAPOL as ligand).
Methyl 3-(2-hydroxy-5-methylphenylamino)-3-phenyl-2,2-dimethyl-propionate 19. \( R_f = 0.3 \) (8/2 hexanes/ethyl acetate); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 1.20 \) (s, 3H), 1.23 (s, 3H), 2.06 (s, 3H), 3.68 (s, 3H), 4.57 (s, 1H), 4.91 (br, 1H), 5.35 (br, 1H), 6.22 (s, 1H), 6.31 (d, \( J = 6.6 \) Hz, 1H), 6.57 (d, \( J = 6.6 \) Hz, 1H), 7.18 - 7.29 (m, 5H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 20.0, 20.8, 47.3, 52.2, 64.4, 114.2, 114.8, 118.2, 127.5, 128.0, 128.4, 130.5, 135.5, 139.2, 142.0, 177.9; \) MS (EI) \( m/z \) (relative intensity): 313 (4), 213 (16), 212 (100), 134 (22), 132 (12), 117(13), 105 (10), 91 (40), 77 (44); Anal. Calcd. for C\(_{19}\)H\(_{23}\)NO\(_3\): C, 72.80; H, 7.40; N, 4.47. Found: C,72.42; H, 7.39; N, 4.38.

HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 9/1, flow rate = 1.0 mL/min): \( R_t = 7.6 \) min (major enantiomer), \( R_t = 13.6 \) min (minor enantiomer), (S-VAPOL as ligand).

Methyl 3-(2-hydroxy-6-methylphenylamino)-3-phenyl-2,2-dimethyl-propionate 20. grey solid; \( R_f = 0.28 \) (8/2 hexanes/ethyl acetate); mp 135 - 138 \( ^\circ \)C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 1.15 \) (s, 3H), 1.29 (s, 3H), 2.11 (s, 3H), 3.72 (s, 3H), 3.91 (br, 1H), 4.68 (s, 1H), 6.47 (dd, \( J = 6.7, 2.3 \) Hz, 1H), 6.63 - 6.68 (m, 2H), 6.80 (br, 1H), 7.15 - 7.25 (m, 5H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 18.5, 19.0, 25.3, 47.6, 52.3, 66.5, 113.7, 122.5, 122.9, 127.7, 127.8, 128.9, 130.2, 132.5, 139.3, 149.8, 179.0; \) IR (neat): \( \nu = 3722 \)br, 2974m, 1709s, 1588m, 1491s, 1461s, 1277s, 1138s cm\(^{-1}\); MS (EI) \( m/z \) (relative intensity): 313 (3), 213 (17), 212 (100), 134 (29), 132 (8), 117(22), 105 (12), 91 (72), 77 (55); Anal. Calcd. for C\(_{19}\)H\(_{23}\)NO\(_3\): C, 72.80; H, 7.40; N, 4.47. Found: C,72.93; H, 7.47; N, 4.43. HPLC
(Daicel Chiralpak AD, hexanes/i-PrOH = 9/1, flow rate = 0.9 mL/min): $R_t = 7.3$ min (major enantiomer), $R_t = 8.6$ min (minor enantiomer), (S-VAPOL as ligand).

Methyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-phenyl-2,2-dimethyl-propionate 21a.

white solid; $R_t = 0.33$ (8/2 hexanes/ethyl acetate); mp 145 - 146 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.20 (s, 3H), 1.21 (s, 3H), 2.02 (s, 3H), 2.14 (s, 3H), 3.68 (s, 3H), 4.52 (s, 1H), 4.77 (br, 1H), 4.97 (s, 1H), 6.10 (s, 1H), 6.27 (s, 1H), 7.16-7.28 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 15.6, 19.9, 20.8, 24.3, 47.4, 52.1, 64.8, 113.7, 121.0, 122.4, 127.4, 127.9, 128.4, 129.7, 135.0, 139.1, 140.8, 177.7;

MS (EI) $m/z$ (relative intensity): 327 (9) [M$^+$], 227 (18), 226 (100), 148 (8), 136 (5), 131(2), 91 (12), 77 (5); Anal. Calcd. for C$_{20}$H$_{25}$NO$_3$: C, 73.37; H, 7.69; N, 4.28. Found: C,71.19; H, 7.63; N, 4.09 (failed);

HPLC (Daicel Chiralpak AS, hexanes/i-PrOH = 9/1, flow rate = 1.0 mL/min): $R_t = 4.9$ min (major enantiomer), $R_t = 5.5$ min (minor enantiomer), (R-VAPOL as ligand).

Methyl 3-(2-hydroxy-5-chlorophenylamino)-3-phenyl-2,2-dimethylpropionate 22.

$R_t = 0.28$ (8/2, hexanes/ethylacetate): $^1$H NMR (300 MHz, CD$_3$OD): $\delta =$ 1.16 (s, 3 H), 1.25 (s, 3 H), 3.66 (s, 3 H), 4.53 (s, 1H), 4.89 (s, 2 H), 6.22 (d, $J =$ 2.4 Hz, 1 H), 6.33 (dd, $J =$ 8.3, 2.4 Hz, 1 H), 6.54 (d, $J =$ 8.3 Hz, 1 H), 7.20 - 7.30 (m, 5 H); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta =$ 21.1, 24.7, 48.3, 52.6, 65.3, 112.4, 114.8, 116.9, 125.7, 128.7, 129.0, 129.5, 138.6, 140.3, 144.5, 178.4. HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 9/1, flow rate 1.0 mL/min): $R_t = 7.15$ min (major enantiomer), $R_t = 12.00$ min (minor enantiomer), (S-VAPOL as ligand).
Methyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-(4-chlorophenyl)-propionate 21b.  
white solid; Rf = 0.33 (8/2 hexanes/ethyl acetate); mp 129 - 131 °C; 1H NMR (500 MHz, CDCl₃): δ = 1.23 (s, 3H), 1.26 (s, 3H), 2.09 (s, 3H), 2.19 (s, 3H), 3.72 (s, 3H), 4.55 (s, 1H), 4.69 (br, 2H), 6.10 (s, 1H), 6.33 (s, 1H), 7.25-7.30 (m, 4H); 13C NMR (125 MHz, CDCl₃): δ = 15.6, 20.2, 20.9, 24.2, 47.2, 52.2, 64.2, 113.0, 120.9, 122.4, 128.1, 129.6, 129.8, 133.1, 134.8, 137.8, 140.4, 177.2; HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 2/98, flow rate = 1.0 mL/min): R₁ = 21.9 min (minor enantiomer), R₂ = 25.1 min (major enantiomer), (R-VAPOL as ligand).

Methyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-(4-methoxyphenyl)-2,2-dimethyl-propionate 21c.  white solid; Rf = 0.21 (8/2 hexanes/ethyl acetate); mp 128 - 129 °C; 1H NMR (300 MHz, CDCl₃): δ = 1.17 (s, 3H), 1.18 (s, 3H), 2.02 (s, 3H), 2.13 (s, 3H), 3.67 (s, 3H), 3.75 (s, 3H), 4.45 (s, 1H), 4.65 (br, 1H), 4.89 (s, 1H), 6.09 (s, 1H), 6.27 (s, 1H), 6.79 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H); 13C NMR (75 MHz, CDCl₃): δ = 15.7, 20.0, 21.0, 24.4, 47.5, 52.1, 55.1, 64.2, 113.2, 113.6, 120.8, 122.2, 129.2, 129.5, 131.0, 134.9, 140.7, 158.6, 177.6; LRMS (El) m/z (relative intensity): 358 (1), 357 (6) [M⁺], 257 (35), 256 (100), 221 (21), 151 (28), 148(26), 121 (41), 91 (17), 77 (15), 73 (36); HRMS (El) Calcd for C₂₁H₂₇NO₄ 357.1940, found 357.1940 (8.7); IR (neat): ν = 3426, 1717, 1608,
Methyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-(3,4-dimethoxyphenyl)-2,2-dimethyl-propionate 21d. white solid; \( R_f = 0.22 \) (7/3 hexanes/ethyl acetate); mp 125 - 127 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.19 \) (s, 3H), 1.20 (s, 3H), 2.03 (s, 3H), 2.14 (s, 3H), 3.67 (s, 3H), 3.83 (s, 6H), 4.44 (br, 1H), 4.67 (br, 1H), 4.88 (s, 1H), 6.12 (s, 1H), 6.28 (s, 1H), 6.74 – 6.83 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 15.6, 20.2, 20.9, 24.3, 47.5, 52.1, 55.6, 55.7, 64.6, 110.4, 111.3, 113.2, 120.5, 120.6, 122.4, 129.5, 131.6, 135.2, 140.5, 148.0, 148.2, 177.5; LRMS (El) \( m/z \) (relative intensity): 388 (2), 387 (8) [M\(^+\)], 287 (46), 286 (100), 251 (42), 192 (13), 191 (36), 181 (37), 151 (28), 148(42), 121 (11), 91 (22), 77 (19), 73 (54); HRMS (El) Calcd for C\(_{22}\)H\(_{29}\)NO\(_5\) 387.2046, found 387.2046 (100); IR (neat): \( \nu = 3430, 2951, 2838, 1719, 1601, 1514, 1464, 1261, 1204, 1142, 1026, 735 \text{ cm}^{-1}; \) HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 9/1, flow rate = 1.0 mL/min): \( R_t = 9.3 \) min (minor enantiomer), \( R_t = 10.9 \) min (major enantiomer), (\( R \)-VAPOL as ligand).

Methyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-(1-naphthyl)-2,2-dimethyl-propionate 21e. white solid; \( R_f = 0.27 \) (8/2 hexanes/ethyl acetate); mp 139 - 140 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.19 \) (s, 3H), 1.26 (s, 3H), 1.88 (s, 3H), 2.13 (s, 3H), 3.70 (s, 3H), 4.98 (s, 1H), 5.06 (br, 1H), 5.61 (s, 1H), 6.05 (s, 1H), 6.22 (s, 1H), 7.41 - 7.60 (m, 4H), 7.74 (d, \( J = 8.2 \) Hz, 1H), 7.85 (dd, \( J = 1.1, 8.2 \) Hz, 1H), 6.1 (d, \( J = 8.2 \) Hz, 1H), 6.28 (s, 1H), 6.74 – 6.83 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 15.6, 20.2, 20.9, 24.3, 47.5, 52.1, 55.6, 55.7, 64.6, 110.4, 111.3, 113.2, 120.5, 120.6, 122.4, 129.5, 131.6, 135.2, 140.5, 148.0, 148.2, 177.5; LRMS (El) \( m/z \) (relative intensity): 388 (2), 387 (8) [M\(^+\)], 287 (46), 286 (100), 251 (42), 192 (13), 191 (36), 181 (37), 151 (28), 148(42), 121 (11), 91 (22), 77 (19), 73 (54); HRMS (El) Calcd for C\(_{22}\)H\(_{29}\)NO\(_5\) 387.2046, found 387.2046 (100); IR (neat): \( \nu = 3430, 2951, 2838, 1719, 1601, 1514, 1464, 1261, 1204, 1142, 1026, 735 \text{ cm}^{-1}; \) HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 9/1, flow rate = 1.0 mL/min): \( R_t = 9.3 \) min (minor enantiomer), \( R_t = 10.9 \) min (major enantiomer), (\( R \)-VAPOL as ligand).
Hz, 1H), 8.39 (d, J = 8.8 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 15.6, 19.9, 20.8, 25.2, 48.5, 52.2, 57.9, 113.0, 120.6, 122.2, 125.0, 125.2, 125.8, 127.9, 129.0, 129.7, 132.8, 133.5, 135.1, 135.7, 140.4, 177.6; LRMS (EI) $m/z$ (relative intensity): 378 (3), 377 (13) [$M^+$], 277 (57), 276 (100), 181 (57), 141 (52), 128(19), 91 (17), 73 (23); HRMS (EI) Calcd for C$_{24}$H$_{27}$NO$_3$ 377.1998, found 377.1998 (100); IR (neat): $\nu$ = 3426, 2363, 2336, 1717, 1599, 1512, 1458, 1437, 1261, 1197, 1149, 1132, 799, 779, 667 cm$^{-1}$; HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 95/5, flow rate = 1.0 mL/min): $R_t$ = 11.0 min (minor enantiomer), $R_t$ = 13.8 min (major enantiomer), (R-VAPOL as ligand).

**tert-Butyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-phenyl-propionthioate 23a.** white solid; $R_t$ = 0.32 (9/1 hexanes/ethyl acetate); mp 90 - 92 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.41 (s, 9H), 2.05 (s, 3H), 2.17 (s, 3H), 2.85 (dd, $J$ = 4.9, 14.8 Hz, 1H), 2.96 (dd, $J$ = 8.8, 15.1 Hz, 1H), 4.17 (s, 1H), 4.68 (dd, $J$ = 4.9, 8.8 Hz, 1H), 5.36 (s, 1H), 6.17 (s, 1H), 6.39 (s, 1H), 7.27 – 7.30 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 15.8, 20.9, 29.6, 48.5, 51.7, 56.7, 115.0, 122.2, 122.7, 126.3, 127.2, 128.5, 129.3, 134.2, 141.8, 141.9, 198.6; LRMS (EI) $m/z$ (relative intensity): 358 (7), 357 (24) [$M^+$], 226 (54), 148(36), 138 (12), 137 (100), 136 (61), 131 (63), 108 (22), 91 (47), 77 (50), 57 (97); HRMS (EI) Calcd for C$_{21}$H$_{27}$NO$_2$S 357.1763, found 357.1760 (18); IR (neat): $\nu$ = 3412, 2963, 2922, 1670, 1601, 1514, 1454, 1353, 1196, 1149, 730 cm$^{-1}$; HPLC (Daicel Chiralpak AD, hexanes/i-PrOH = 9/1, flow rate = 1.0 mL/min): $R_t$ = 11.7 min (major enantiomer), $R_t$ = 15.5 min (minor enantiomer), (R-VAPOL as ligand).
**tert-Butyl 3-(2-hydroxy-3,5-dimethylphenylamino)-3-(1-naphthyl)-propionthioate 23e.**

white solid; $R_t = 0.31$ (8/2 hexanes/ethyl acetate); mp 122 - 124 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 1.45 (s, 9H), 2.00 (s, 3H), 2.21 (s, 3H), 2.95 (dd, $J =$ 9.3, 14.8 Hz, 1H), 3.12 (dd, $J =$ 4.1, 14.8 Hz, 1H), 4.74 (br, 1H), 5.09 (br, 1H), 5.64 (dd, $J =$ 4.1, 9.3 Hz, 1H), 6.13 (s, 1H), 6.35 (s, 1H), 7.38 – 7.65 (m, 4H), 7.76 (d, $J =$ 8.2 Hz, 1H), 7.90 (dd, $J =$ 1.4, 8.2 Hz, 1H), 8.23 (d, $J =$ 8.4 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 15.8, 20.9, 29.7, 48.6, 51.2, 52.3, 113.3, 121.1, 122.3, 122.4, 123.1, 125.4, 125.5, 126.3, 127.8, 129.0, 129.8, 130.4, 133.9, 134.8, 137.1, 140.7, 198.4; LRMS (EI) $m/z$ (relative intensity): 407 (3) [M$^+$], 317 (16), 275 (37), 274 (32), 182 (18), 181 (100), 153 (33), 152 (34), 148(24), 138 (12), 137 (47), 91 (13), 77 (14), 57 (73); HRMS (EI) Calcd for C$_{25}$H$_{29}$NO$_2$S 407.1919, found 407.1915 (5.5); IR (neat): $\nu =$ 3414, 2963, 2920, 2361, 1670, 1599, 1512, 1456, 1363, 1194, 1149, 777 cm$^{-1}$; HPLC (Daicel Chiralpak AD, hexanes/i-ProOH = 9/1, flow rate = 1.0 mL/min): $R_t =$ 12.9 min (major enantiomer), $R_r =$ 16.5 min (minor enantiomer), (R-VAPOL as ligand).

**A typical experimental procedure for the removal of N-protecting group:** A solution of cerium ammonium nitrate (163 mg, 0.3 mmol) in water (0.95 mL) was added dropwisely to a solution of imino aldol adducts (0.1 mmol) in acetonitrile (2 mL) at 0 °C. After stirring for 1 h, another portion of cerium ammonium nitrate (109 mg, 0.2 mmol) in 1N HNO$_3$ (0.3 mL) was added and the mixture was stirred for an additional 2.5 h at room temperature. The mixture was then diluted with water (8 mL) and neutralized to pH 8 to 9. The aqueous layer was extracted with ethyl acetate (3 X 5 mL). The combined organic layers were washed with sat. aqueous NaHSO$_3$, 10% Na$_2$SO$_3$, brine and dried over MgSO$_4$. Removal of solvent under vacuo and further purified by flash chromatography on silica gel gave desired products as yellow oils. Removal of color staffs by acid extraction gave final products as colorless oils.
Methyl 3-amino-3-phenyl-2,2-dimethyl-propionate 25a.\[8\] colorless oil (prepared from compound 21a with 98.5% ee); R\(_f\) = 0.18 (1/1 hexanes/ethyl acetate); \([\alpha]_D^{20} = +34.2\) (c = 0.33 in 1N HCl); \(^1\)H NMR (300 MHz, CDCl\(_3\)):\(\delta = 1.06\) (s, 3H), 1.12 (s, 3H), 1.62 (br, 2H), 3.67 (s, 3H), 4.21 (s, 1H), 7.22 – 7.28 (m, 5H); \(^13\)C NMR (75 MHz, CDCl\(_3\)):\(\delta = 19.3, 23.6, 47.8, 51.8, 61.9, 127.3, 127.8, 128.1, 141.9, 177.8\); LRMS (El) m/z (relative intensity): 208 (7) [M\(^+\) + 1], 147 (25), 146 (86), 132 (19), 131 (18), 115 (25), 107 (54), 105 (100), 104 (71), 91 (57), 79 (93), 78 (51), 77 (86); HRMS (FAB) Calcd for C\(_{12}\)H\(_{18}\)NO\(_2\) [M\(^+\) + 1] 208.1338, found 208.1342 (100); IR (neat): \(\nu = 3030, 2982, 2951, 1734, 1664, 1421, 1454, 1263, 1132, 706\) cm\(^{-1}\).

Methyl 3-amino-3-(4-chloro-phenyl)-2,2-dimethyl-propionate 25b. colorless oil (prepared from compound 21b with 95.4% ee); R\(_f\) = 0.20 (1/1 hexanes/ethyl acetate); \([\alpha]_D^{20} = +33.0\) (c = 0.60 in 1N HCl); \(^1\)H NMR (300 MHz, CDCl\(_3\)):\(\delta = 1.04\) (s, 3H), 1.10 (s, 3H), 1.55 (br, 2H), 3.65 (s, 3H), 4.19 (s, 1H), 7.18 (d, \(J = 8.6\) Hz, 2H), 7.25 (d, \(J = 8.6\) Hz, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)):\(\delta = 19.5, 23.4, 47.7, 51.9, 61.3, 127.8, 129.3, 132.9, 140.2, 177.4\); LRMS (El) m/z (relative intensity): 142 (76, \(^37\)Cl), 140 (100, \(^35\)Cl), 77 (67); IR (neat): \(\nu = 3391, 2990, 2947, 1720, 1684, 1489, 1437, 1261, 1145, 831\) cm\(^{-1}\).
Methyl 3-amino-3-(4-methoxy-phenyl)-2,2-dimethyl-propionate 25c. Colorless oil (prepared from compound 21c with 99.8% ee); Rf = 0.18 (3/7 hexanes/ethyl acetate); [α]D²⁰ = +33.6 (c = 0.36 in 1N HCl); ¹H NMR (300 MHz, CDCl₃): δ = 1.03 (s, 3H), 1.10 (s, 3H), 1.57 (br, 2H), 3.66 (s, 3H), 3.76 (s, 3H), 4.16 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 19.3, 23.5, 47.8, 51.8, 55.2, 61.2, 113.1, 129.0, 133.9, 158.7, 177.9; LRMS (EI) m/z (relative intensity): 238 (1) [M⁺], 137 (49), 136 (100), 135 (78), 134 (43), 121 (35), 109 (85), 94 (65), 93 (67), 77 (52); IR (neat): ν = 2978, 2951, 2837, 1732, 1610, 1512, 1466, 1250, 1132, 835 cm⁻¹.

Methyl 3-amino-3-(3,4-dimethoxy-phenyl)-2,2-dimethyl-propionate 25d. Colorless oil (prepared from compound 21d with 96.4% ee); Rf = 0.14 (3/7 hexanes/ethyl acetate); [α]D²⁰ = +32.2 (c = 0.43 in 1N HCl); ¹H NMR (300 MHz, CDCl₃): δ = 1.06 (s, 3H), 1.13 (s, 3H), 1.57 (br, 2H), 3.67 (s, 3H), 3.849 (s, 3H), 3.853 (s, 3H), 4.18 (s, 1H), 6.80 (m, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 19.6, 23.5, 47.8, 51.8, 55.9, 55.9, 61.6, 110.3, 111.2, 120.3, 134.4, 148.16, 148.24, 177.9; LRMS (EI) m/z (relative intensity): 252 (1), 251 (7), 206 (22), 178 (11), 167 (55), 165 (100), 164 (17), 151 (31), 150 (50), 139 (83), 124 (87), 122 (49), 121 (36); IR (neat): ν = 2949, 2835, 2361, 1734, 1516, 1466, 1201, 1140, 1028 cm⁻¹.

Methyl 3-amino-3-(1-naphthyl)-2,2-dimethyl-propionate 25e. Colorless oil (prepared from compound 21e with 93.0% ee); Rf = 0.21 (1/1 hexanes/ethyl acetate); [α]D²⁰ = +33.4 (c = 0.38 in 1N HCl); ¹H NMR (300 MHz, CDCl₃): δ = 1.04 (s, 3H), 1.24 (s, 3H), 1.72 (br, 2H), 3.67 (s, 3H), 5.31 (s, 1H), 7.42 - 7.52 (m, 3H), 7.62 (dd, J = 1.4, 7.1 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.82 (dd, J = 1.1, 7.7 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 19.2, 24.4, 48.7, 51.9, 54.6, 123.6,
tert-Butyl 3-amino-3-(1-naphthyl)-propionthioate 24e.  colorless oil (prepared from compound 23e with 91% ee); $R_f = 0.11$ (1/1 hexanes/ethyl acetate); $[\alpha]_D^{20} = +10.5 (c = 0.11$ in 1N HCl); $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.47$ (s, 9H), 1.84 (br, 2H), 2.87 (dd, $J = 9.9, 15.4$ Hz, 1H), 2.98 (dd, $J = 3.0, 15.4$ Hz, 1H), 5.28 (br, 1H), 7.43 – 7.56 (m, 3H), 7.67 (d, $J = 7.1$ Hz, 1H), 7.75 (d, $J = 8.2$ Hz, 1H), 7.86 (d, $J = 9.6, 1$H), 8.14 (d, $J = 8.5$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 29.8, 48.4, 53.3, 122.55, 122.56, 125.4, 125.5, 126.2, 127.7, 128.9, 130.2, 133.7, 199.2 (two carbons not located due to overlap); LRMS (EI) $m/z$ (relative intensity): 287 (2) [M$^+$], 270 (36), 230 (37), 210 (19), 196 (22), 181 (17), 168 (10), 157 (22), 156 (100), 129 (36), 84 (55), 57 (73); IR (neat): $\nu = 2961, 2361, 2336, 1676, 1558, 1506, 1456, 1363, 777$ cm$^{-1}$.

References: