Scaleable catalytic asymmetric Strecker syntheses of unnatural α-amino acids

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Supplementary Methods

General Experimental Procedures. Reactions were carried out in oven-dried round-bottomed flasks, unless otherwise noted. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of nitrogen. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science.

Materials. Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, or Lancaster, and used as received with the following exceptions: dichloromethane and toluene were dried by passing through columns of activated alumina. Diisopropylethylamine and triethylamine were distilled from CaH₂ at 760 torr. TMSCN was distilled at 760 Torr and stored in a Schlenk flask at 0 °C.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Varian-Mercury-400 (400 MHz) or Inova-500 (500 MHz) spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl₃: δ 7.26) Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃: δ 77.16). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak, br = broad).
rotations were measured using a 2-mL cell with a 10-cm path length on a Jasco DIP 370 digital polarimeter. The mass spectral data were obtained at the Harvard University mass spectrometry facility. Chiral HPLC analysis was performed using a Shimadzu VP-series instrument.

**Preparation of amido-thiourea catalysts**

(S)-**tert**-butyl 1-(benzhydryl(methyl)amino)-3,3-dimethyl-1-oxobutan-2-yl carbamate:

An oven-dried 50-mL round-bottomed flask was charged with Boc-L-**tert**-leucine (2.78 g, 12.0 mmol, 1.0 equiv), HBTU (5.01 g, 13.2 mmol, 1.1 equiv), and N-(diphenylmethyl)methylamine (3.55 g, 18 mmol, 1.5 equiv). Anhydrous CH$_2$Cl$_2$ (24 mL) and N,N-diisopropylethylamine (4.18 mL, 24 mmol, 2.0 equiv) were added sequentially via syringe. The flask was capped with a plastic stopper, and the reaction mixture was stirred for 3 days at room temperature. The resulting orange mixture was diluted with Et$_2$O (100 mL), washed with 1 N HCl (2 x 100 mL), sat. NaHCO$_3$ (100 mL), and brine (100 mL). The organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure to provide a viscous orange oil. The product was subjected to purification by flash column chromatography on silica gel (gradient elution, 19:1 → 1:1 hexanes/Et$_2$O, 100 g silica gel, 1.2 L solvent) to provide the product as a white foam (4.51 g, 11.0 mmol, 91% yield). $\alpha$$_{D}$$^25$ = –28.2° (c 1.76, CHCl$_3$). The compound exists as a 5:1 mixture of amide rotamers in CDCl$_3$. $^1$H NMR (500 MHz, CDCl$_3$), major rotamer: δ 7.38-7.14 (11H, m), 5.28 (1H, d, $J$ = 10.0 Hz), 4.57 (1H, d, $J$ = 10.0 Hz), 2.97 (3H, s), 1.46, (9H, s), 1.03 (9H, s); minor rotamer: δ 7.38-7.14 (10H, m), 6.77 (1H, s), 5.28 (1H, d, $J$ = 10.0 Hz), 4.72 (1H, d, $J$ = 10.0 Hz), 2.73, (3H, s), 1.44 (9H, s), 0.93 (9H, s). $^{13}$C $^1$H NMR (126 MHz, CDCl$_3$), major rotamer: δ 173.0, 156.2, 139.3, 138.4, 129.4, 128.5, 128.4, 127.9, 127.9.

Catalysts were prepared by a modification of the literature procedure: Reisman, S. E., Doyle, A. G. & Jacobsen, E. N. Enantioselective thiourea-catalyzed additions to oxocarbenium ions. *J. Am. Chem. Soc.* **130**, 7198–7199 (2008). The preparation of catalysts not described herein has been reported previously by Reisman et al.
127.6, 127.1, 79.6, 60.8, 56.7, 35.2, 33.2, 28.3, 26.5; minor rotamer: δ 173.5, 155.5, 139.4, 138.8, 129.0, 128.5, 128.4, 127.7, 127.6, 79.5, 64.6, 56.1, 35.3, 31.3, 28.3, 26.5. IR (cm⁻¹): 3436 (w), 3326 (w), 3062 (w), 3029 (w), 2965 (m), 2871 (w), 1953 (w), 1893 (w), 1810 (w), 1712 (s), 1640 (s), 1496 (s), 1454 (m), 1404 (m), 1366 (m), 1320 (w), 1245 (m), 1172 (s), 1105 (w), 1058 (w), 1005 (w), 974 (w), 922 (w), 870 (w), 734 (w), 702 (m), 608 (w). LRMS (ESI): 433.25 (100%) [M+Na]⁺.

(S)-2-amino-N-benzhydryl-3,3-trimethylbutanamide:

A 200-mL round-bottomed flask containing (R)-tert-butyl 1-(benzhydryl(methyl)amino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (4.51 g, 11.0 mmol, 1 equiv) and a stir bar was purged with N₂. Anhydrous CH₂Cl₂ (55 mL) and triethylamine (3.07 mL, 22.0 mmol, 2 equiv) were added sequentially via syringe. The reaction was cooled to 0 °C in an ice bath, and trimethylsilyl trifluoromethansulfonate (18.8 mL, 110 mmol, 10 equiv) was added dropwise via syringe over 5 min with stirring. The solution was stirred for 1 h at 0 °C. The slightly yellow homogeneous reaction mixture was treated with 100 mL of ice cold saturated aqueous NaHCO₃ in 10-mL portions over 5 min at 0 °C. The mixture was transferred to a 500-mL separatory funnel, and diluted with saturated aqueous NaHCO₃ (100 mL) and CH₂Cl₂ (50 mL). The layers were thoroughly mixed with venting, and the organic layer was removed. The aqueous layer was extracted with CH₂Cl₂ (50 mL). The combined organic layers were dried over Na₂SO₄, decanted into a 500-mL round-bottomed flask, and concentrated in vacuo to provide a viscous yellow residue. The residue was partitioned between CH₂Cl₂ (50 mL) and saturated NaHCO₃ (50 mL). The aqueous layer was extracted with CH₂Cl₂ (30 mL). The organic layers were dried over Na₂SO₄ and filtered through a 2-cm height pad of silica gel on a 5-cm diameter fritted disk funnel, rinsing with CH₂Cl₂ (30 mL). The receiving flask was switched, and the silica gel pad was further eluted with 1:1:0.04 CH₂Cl₂/Et₂O/MeOH (200 mL) to provide the product as a yellow oil in >95% ¹H-NMR purity (2.98 g, 9.60 mmol, 87% yield). The product was used in the next step without further purification. Spectroscopically pure product may be isolated by subjecting the crude product to flash column chromatography on silica gel (gradient elution, 3:1 CH₂Cl₂/Et₂O → 1:1:0.05 CH₂Cl₂/Et₂O/MeOH). The compound exists as a 3.5:1 mixture of amide rotamers in CDCl₃. ¹H NMR (500 MHz, CDCl₃), major rotamer: δ 7.14–7.34
(11H, m), 3.59 (1H, s), 2.88 (3H, s), 1.54 (2H, br s), 1.02 (9H, s); minor rotamer: δ 7.34-7.14 (10H, m), 6.53 (1H, s), 3.47 (1H, s), 2.72 (3H, s), 1.54 (2H, br s), 1.03 (9H, s).

$^{13}$C {$^1$H} NMR (125 MHz, CDCl$_3$), major rotamer: δ 175.4, 139.2, 138.8, 129.1, 128.44, 128.40, 128.3, 127.4, 127.2, 60.4, 58.4, 35.6, 32.9, 26.4; minor rotamer: δ 176.5, 139.6, 139.0, 128.9, 128.8, 128.5, 127.9, 127.82, 127.79, 64.5, 58.5, 34.9, 31.3, 26.6. IR (cm$^{-1}$): 3381 (w), 3307 (w), 3061 (m), 3029 (m), 2955 (s), 2955 (m), 2867 (m), 1955 (w), 1892 (w), 1813 (w), 1768 (w), 1639 (s), 1495 (s), 1479 (m), 1447 (m), 1409 (m), 1364 (m), 1282 (m), 1104 (m), 1079 (m), 1031 (m), 970 (m), 922 (m), 870 (m), 827 (m), 762 (m), 735 (m), 701 (s). LRMS (ESI): 311.2126 (100%), [C$_{20}$H$_{26}$N$_2$O$^+$][H]$^+$.

(S)-N-benzhydryl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-N,3,3-trimethylbutanamide (4e):

\[
\begin{align*}
\begin{array}{c}
\text{Ph} \quad \text{N} \quad \text{H} \\
\text{Ph} \quad \text{N} \quad \text{H} \\
\text{CF}_3 \quad \text{S} \quad \text{N} \\
\end{array}
\end{align*}
\]

A 100-mL round-bottomed flask containing (S)-2-amino-N-benzhydryl-N,3,3-trimethylbutanamide (2.98 g, 9.60 mmol, 1.0 equiv) was charged with anhydrous CH$_2$Cl$_2$ (30 mL). 3,5-Bis(trifluoromethyl)phenylisothiocyanate (1.75 mL, 9.60 mmol, 1.0 equiv) was added in one portion via syringe.  The flask was capped with a plastic stopper, and the reaction mixture was stirred for 2 h at room temperature.  The clear, yellow solution was concentrated using a rotary evaporator.  The residue was subjected to purification by flash column chromatography on silica gel (gradient elution, hexanes $\rightarrow$ 1:1 hexanes/Et$_2$O, 100 g silica gel, 1.5 L solvent).  The product was isolated as a white solid in $\sim$98$\%$ $^1$H-NMR purity (5.14 g, 8.83 mmol, 92$\%$ yield; 74$\%$ yield over three steps).  The compound exists as a 15:1 mixture of amide rotamers in CDCl$_3$.  \[\alpha_{D}^{25} = -83.4^\circ \text{ (c 1.0, CHCl}_3)\].  \(^1\)H NMR (500 MHz, CDCl$_3$), major rotamer: δ 8.26 (1H, br s), 8.92 (1H, br s), 7.69 (2H, s), 7.59 (1H, s), 7.31–7.37 (3H, m), 7.13–7.16 (2H, m), 6.95–7.06 (5H, m), 5.65 (1H, d, $J = 9$ Hz), 3.13 (3H, s), 1.13 (9H, s); selected minor rotamer resonances: δ 2.76 (3H, s), 0.92 (9H, s).

$^{13}$C {$^1$H} NMR, major rotamer: δ 182.5, 174.2, 139.7, 139.0, 137.3, 131.9 (q, $J_{CF} = 34$ Hz), 129.8, 128.8, 128.7, 128.4, 128.2, 127.5, 127.2, 126.3 (m), 123.1 (q, $J_{CF} = 274$ Hz), 119.3 (m), 62.4, 62.3, 36.5, 34.0, 27.6. IR (cm$^{-1}$): 3313 (br m), 2967 (m), 1609 (m), 1529 (m), 1473 (m), 1380 (m), 1276 (s), 1172 (m), 1127 (s), 961 (m), 889 (w), 847 (w), 758 (w), 698 (m), 681 (m). LRMS (ESI): 582.2 (80$\%$) [M+H]$^+$.
Supplementary Figure 1. $^1$H NMR spectrum of 4e.

Supplementary Figure 2. $^{13}$C NMR spectrum of 4e.
(S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-N,N,3,3-tetramethylbutanamide (4a):

A 50-mL round-bottomed flask was charged with (S)-tert-butyl 1-(dimethylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate\(^\text{32}\) (860 mg, 2.0 mmol, 1.0 equiv) and 4 N HCl in dioxane (5.0 mL). The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure and maintained at ~1 torr for 1 h. The resulting white, foamy solid was dissolved in CH\(_2\)Cl\(_2\) (10 mL). Et\(_3\)N (562 μL, 4.0 mmol, 2.0 equiv) and 3,5-bis(trifluoromethyl)phenylisothiocyanate (596 mg, 2.2 mmol, 1.1 equiv) were added sequentially via syringe. The flask was capped with a plastic stopper, and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to purification by flash column chromatography on silica gel (gradient elution, 3:1 hexanes/Et\(_2\)O → 1:1 hexanes/Et\(_2\)O) to provide the product as a white solid (613 mg, 1.43 mmol, 71% yield over two steps). \([\alpha]_D^{25} = -32.8^\circ\) (c 1.0, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 9.06 (1H, s), 7.90 (2H, s), 7.77 (1H, d, \(J = 9\) Hz), 7.56 (1H, s), 5.68 (1H, d, \(J = 9\) Hz), 3.35 (3H, s), 2.97 (3H, s), 1.12 (9 H, s). \(^13\)C\(^{1}\)H NMR (100 MHz, CDCl\(_3\)): δ 181.8, 174.0, 140.3, 131.7 (q, \(J_{C,F} = 33\) Hz), 123.7 (m), 123.3 (q, \(J_{C,F} = 272\) Hz), 118.1 (m), 60.9, 39.1, 36.2, 36.0, 27.2. IR (cm\(^{-1}\)): 3322 (br m), 2972 (m), 1611 (m), 1532 (s), 1474 (m), 1385 (m), 1274 (s), 1174 (m), 1126 (s), 963 (m), 883 (m), 848 (w), 700 (m), 680 (m). LRMS (ESI): 452.1 (60%) [M+Na\(^+\)].

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\(^{32}\) The preparation of (S)-tert-butyl 1-(dimethylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate has been reported: Vachal, P. & Jacobsen, E. N. Structure-based analysis and optimization of a highly enantioselective catalyst for the Strecker reaction J. Am. Chem. Soc. 124, 10012–10014 (2002).
Preparation of imines

Method A: A 250-mL round-bottomed flask was charged with dichloromethane (80 mL), anhydrous Na$_2$SO$_4$ (30 g), aminodiphenylmethane (12 mmol), and aldehyde (12 mmol). The mixture was stirred at room temperature until the aldehyde had been fully consumed, as determined by $^1$H NMR analysis of an aliquot removed from the reaction mixture (1–12 h). The mixture was filtered through a fritted disk funnel, rinsing with dichloromethane (3 x 10 mL). A 3” plug of silica gel was rinsed with 9:1:0.1 hexanes/diethyl ether/triethylamine (100 mL). The reaction mixture was concentrated under reduced pressure, and the crude residue was filtered through the silica gel plug with 9:1 hexanes/diethyl ether as the eluent. The filtrate was concentrated under reduced pressure to provide the imine product (> 90% yield). The imine was used in the next step without further purification.

Method B: A 100-mL round-bottomed flask was charged with toluene (40 mL), aminodiphenylmethane (12 mmol), and aldehyde (12 mmol). A Dean-Stark trap was attached to the flask, and the mixture was stirred at reflux under N$_2$ in an oil bath until the aldehyde was fully consumed, as determined by $^1$H NMR analysis of an aliquot removed from the reaction mixture. A 3” plug of silica gel was rinsed with 9:1:0.1 hexanes/diethyl ether/triethylamine (100 mL). The reaction mixture was concentrated under reduced pressure, and the crude residue was filtered through the silica gel plug with 9:1 hexanes/diethyl ether as the eluent. The filtrate was concentrated under reduced pressure to provide the imine product (> 90% yield). The imine was used in the next step without further purification.

(E)-N-(2,2-dimethylpropylidene)diphenylmethanamine (2a):

Prepared via Method A. Spectroscopic data match previously reported data.$^{33}$

(E)-N-(2-ethyl-2-methylbutylidene)diphenylmethanamine (2b):$^{34}$

$^{33}$Krueger, C. A., Kuntz, K. W., Dzierba, C. D., Wirschun, W. G., Gleason, J. D., Snapper, M. L. & Hoveyda, A. H. Ti-catalyzed enantioselective addition of cyanide to imines. A practical synthesis of optically pure alpha-amino acids. J. Am. Chem. Soc. 121, 4284–4285 (1999).

$^{34}$The preparation of the aldehyde precursor of this imine is described in Section 6.
Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.70 (1H, s), 7.43 (4H, d, $J = 7.5$ Hz), 7.38 (4H, t, $J = 7.8$ Hz), 7.29 (2H, t, $J = 7.3$ Hz), 5.47 (1H, s), 1.52-1.65 (4H, m), 1.16 (3H, s), 0.87 (6H, t, $J = 7.8$ Hz). $^{13}$C$^{'1}$H NMR (125 MHz, CDCl$_3$): $\delta$ 171.2, 144.3, 128.2, 127.5, 126.6, 77.8, 42.5, 30.6, 20.6, 8.4. IR (cm$^{-1}$): 3061 (w), 3026 (w), 2925 (m, br), 2850 (m, br), 1661 (m), 1493 (m), 1449 (m), 1026 (m), 756 (m), 696 (s). LRMS (ESI): 292.2 (100%) [M+H]$^+$.  

(E)-N-(2-methyl-2-phenylpropylidene)diphenylmethanamine (2c):$^{35}$

Prepared via Method B. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.90 (1H, s), 7.44 (4H, d, $J = 8.0$ Hz), 7.27-7.40 (11H, m), 5.49 (1H, s), 1.60 (6H, s). $^{13}$C$^{'1}$H NMR (125 MHz, CDCl$_3$): $\delta$ 169.4, 145.9, 144.1, 128.4, 128.3, 127.5, 126.8, 126.4, 126.3, 77.3, 44.0, 26.1. IR (cm$^{-1}$): 3060 (w), 3026 (w), 2969 (w), 2836 (w), 1660 (m), 1599 (w), 1493 (m), 1448 (m), 1387 (w), 1364 (w), 1028 (m), 762 (m), 696 (s). LRMS (ESI): 314.2 (100%) [M+H]$^+$.  

(E)-N-((1-methylcyclohexyl)methylene)diphenylmethanamine (2d):$^{34}$

Prepared via Method B. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.74 (1H, s), 7.43 (4H, d, $J = 6.5$ Hz), 7.38 (4H, t, $J = 7.5$ Hz), 7.29 (2H, t, $J = 7.3$ Hz), 5.44 (1H, s), 1.89-1.93 (2H, m), 1.49-1.62 (5H, m), 1.38-1.43 (3H, m), 1.13 (3H, s). $^{13}$C$^{'1}$H NMR (125 MHz, CDCl$_3$): $\delta$ 171.6, 144.3, 128.3, 128.1, 127.6, 127.5, 126.7, 77.8, 39.6, 35.6, 26.0, 25.5, 22.5. IR (cm$^{-1}$): 3062 (w), 3026 (w), 2965 (m, br), 2935 (m), 1661 (m), 1599 (w), 1492 (m), 1452 (m), 1382 (m), 1030 (m), 745 (m), 696 (s). LRMS (ESI): 280.2 (100%) [M+H]$^+$.  

$^{35}$ For the preparation of 2-methyl-2-phenylpropanal, see: Dudnik, A. S., Schwier, T. & Gevorgyan, V. Gold-catalyzed double migration-benzannulation cascade toward naphthalenes. Org. Lett. 10, 1465–1468 (2008).
**(E)-N-(1-adamantyl)diphenylmethanamine (2e):**

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\text{ Prepared via Method A. } ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 7.56 (1H, s), 7.31-7.35 (8H, m), 7.22-7.27 (2H, m), 5.34 (1H, s), 2.06 (3H, s), 1.72-1.79 (12H, m). } ^{13}\text{C} \{^1\text{H}\} \text{ NMR (125 MHz, CDCl}_3\text{): } \delta \text{ 171.6, 144.3, 128.3, 127.5, 126.7, 77.5, 39.5, 38.4, 36.8, 28.1. IR (cm}^{-1}\text{): 3024 (w), 2905 (m, br), 2849 (m), 2798 (m), 1661 (m), 1492 (m), 1449 (m), 1053 (m), 750 (m), 699 (s). LRMS (ESI): 330.2 (100%) [M+H]^+.
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**(E)-N-(cyclohexylmethylene)diphenylmethanamine (2f):**

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\text{ Prepared via Method A. } ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 7.65 (1H, d, } J = 5.0 \text{ Hz), 7.23-7.26 (8H, m), 7.15-7.18 (2H, m), 5.27 (1H, s), 2.24-2.27 (1H, m), 1.80-1.83 (2H, m), 1.70 - 1.72 (2H, m), 1.61-1.64 (1H, m), 1.15-1.29 (5H, m). } ^{13}\text{C} \{^1\text{H}\} \text{ NMR (125 MHz, CDCl}_3\text{): } \delta \text{ 169.1, 144.0, 128.3, 127.6, 126.8, 77.9, 43.5, 29.7, 26.0, 25.4. IR (cm}^{-1}\text{): 3060 (w), 3026 (w), 2932 (m), 2852 (m), 1664 (m), 1493 (m), 1448 (m), 1376 (w), 1276 (w), 1016 (w), 890 (w), 759 (m), 745 (s), 697 (s). LRMS (ESI): 278.2 (50%) [M+H]^+.
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**(E)-N-(4-methoxybenzylidene)diphenylmethanamine (2g):**

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\text{ Prepared via Method A. Spectroscopic data match previously reported data.}
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**(E)-N-(4-methylbenzylidene)diphenylmethanamine (2h):**

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\text{ For the preparation of 1-adamantanecarboxaldehyde, see: Augeri, D. J. et. al. Discovery and preclinical profile of Saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J. Med. Chem. 48, 5025–5037 (2005).}
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Prepared via Method A.  $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.47 (1H, s), 7.82 (2H, d, $J = 8.0$ Hz), 7.50 (4H, m), 7.40 (4H, m), 7.31 (4H, m), 5.67 (1H, s), 2.46 (3H, s).  $^{13}$C{${^1}$H} NMR (125 MHz, CDCl$_3$): $\delta$ 160.6, 144.0, 141.0, 133.7, 129.2, 128.4, 128.4, 127.7, 126.9, 77.8, 21.5. IR (cm$^{-1}$): 3081 (w), 3026 (w), 2919 (w), 2851 (w), 1663 (m), 1461 (m), 1274 (m), 1072 (m), 81 (m), 756 (m), 733 (m), 697 (s). LRMS (ESI): 286.2 (100%) [M+H]$^+$. 

[(E)-N-benzylidenediphenylmethanamine (2i):](image)

Prepared via Method A. Spectroscopic data match previously reported data.$^{33}$

[(E)-N-(4-chlorobenzylidene)diphenylmethanamine (2j):](image)

Prepared via Method A. Spectroscopic data match previously reported data.$^{37}$

[(E)-diphenyl-N-(4-(trifluoromethyl)benzylidene)methanamine (2k):](image)

Prepared via Method A.  $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.50 (1H, s), 7.99 (2H, d, $J = 8.0$ Hz), 7.71 (2H, d, $J = 8.0$ Hz), 7.45 (4H, d, $J = 8.0$ Hz), 7.38 (4H, t, $J = 7.8$ Hz), 7.29 (2H, t, $J = 7.5$ Hz), 5.69 (1H, s).  $^{13}$C{${^1}$H} NMR (125 MHz, CDCl$_3$): $\delta$ 160.6, 144.0, 141.0, 133.7, 129.2, 128.4, 128.4, 127.7, 126.9, 77.8, 21.5. IR (cm$^{-1}$): 3081 (w), 3026 (w), 2919 (w), 2851 (w), 1663 (m), 1461 (m), 1274 (m), 1072 (m), 81 (m), 756 (m), 733 (m), 697 (s). LRMS (ESI): 286.2 (100%) [M+H]$^+$. 

$^{37}$ Lautens, M., Tayama, E. & Nguyen, D. Direct vinylogous Mannich-type reactions via ring opening and rearrangement of vinyloxiranes. *Org. Lett.* 6, 345–347 (2004).
MHz, CDCl3): δ 159.3, 143.5, 139.4, 132.3 (q, J_C-F = 32.2 Hz), 128.6, 128.5, 127.6, 127.2, 125.5 (q, J_C-F = 3.6 Hz), 123.9 (q, J_C-F = 271.3 Hz), 78.0. IR (cm⁻¹): 2981 (w), 1637 (w), 1320 (m), 1131 (s), 1064 (m), 834 (m), 739 (m), 695 (s). LRMS (ESI): 340.1 (100%) [M+H]⁺.

*(E)-4-((benzhydrylimino)methyl)benzonitrile (2l):*

![Chemical Structure of 2l](image)

Prepared via Method A. ¹H NMR (500 MHz, CDCl₃): δ 8.48 (1H, s), 7.96 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 8.5 Hz), 7.44-7.46 (4H, m), 7.37-7.42 (4H, m), 7.29-7.32 (2H, m), 5.70 (1H, s). ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 158.9, 143.2, 140.0, 132.3, 128.8, 128.5, 128.3, 127.5, 127.2, 118.5, 114.0, 78.0. IR (cm⁻¹): 3064 (w), 3023 (w), 2874 (w), 2852 (w), 2222 (m), 1634 (m), 1490 (m), 1451 (m), 1378 (m), 1025 (m), 855 (m), 829 (m), 752 (s), 702 (s). LRMS (ESI): 297.1 (30%) [M+H]⁺.

*(E)-N-(4-bromobenzylidene)diphenylmethanamine (2m):*

![Chemical Structure of 2m](image)

Prepared via Method A. ¹H NMR (500 MHz, CDCl₃): δ 8.41 (1H, s), 7.74-7.76 (2H, m), 7.58-7.60 (2H, m), 7.44-7.45 (4H, m), 7.34-7.39 (4H, m), 7.27-7.30 (2H, m), 5.64 (1H, s). ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 159.5, 143.6, 135.2, 131.7, 129.8, 128.4, 127.6, 127.0, 125.1, 77.8. IR (cm⁻¹): 3062 (w), 3023 (w), 2856 (m), 1638 (m), 1567 (m), 1484 (m), 1481 (m), 1068 (m), 1012 (m), 812 (m), 744 (m), 698 (s). LRMS (ESI): 350.1 (60%) [M+H]⁺.

*(E)-N-(2-methoxybenzylidene)diphenylmethanamine (2n):*

![Chemical Structure of 2n](image)
Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.99 (1H, s), 8.26 (1H, dd, $J = 1.8$, 7.8 Hz), 7.48-7.50 (4H, m), 7.38 (4H, t, $J = 7.5$ Hz), 7.27-7.30 (2H, m), 7.06 (1H, d, $J = 7.3$ Hz), 6.96 (1H, d, $J = 8.5$ Hz), 5.67 (1H, s), 3.89 (3H, s). $^{13}$C{$_^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 158.8, 156.6, 144.3, 131.9, 128.3, 127.7, 127.6, 126.8, 124.7, 120.7, 110.9, 78.4, 55.4. IR (cm$^{-1}$): 3079 (w), 3020 (w), 2938 (w), 2837 (w), 1631 (m), 1598 (m), 1487 (m), 1378 (m), 1175 (m), 1080 (m), 775 (s), 739 (s), 697 (s). LRMS (ESI): 302.2 (100%) [M+H]$^+$. 

$(E)$-N-(2-bromobenzylidene)diphenylmethanamine (2o):

Prepared via Method A. Spectroscopic data match previously reported data.$^{33}$

$(E)$-N-(3-bromobenzylidene)diphenylmethanamine (2p):

Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.39 (1H, s), 8.09 (1H, m), 7.73 (1H, dd, $J = 1.3$, 7.8 Hz), 7.56-7.59 (1H, m), 7.44 (4H, d, $J = 7.0$ Hz), 7.37 (4H, t, $J = 7.8$Hz), 7.27-7.32 (3H, m), 5.65 (1H, s). $^{13}$C{$_^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 159.2, 143.5, 138.2, 133.6, 130.9, 130.0, 128.5, 127.6, 127.3, 127.1, 122.8, 77.8. IR (cm$^{-1}$): 3057 (w), 3026 (w), 2839 (m), 1658 (m), 1565 (m), 1492 (m), 1447 (m), 1381 (m), 1210 (m), 1024 (m), 787 (m), 759 (m), 741 (s), 697 (s). LRMS (ESI): 350.1 (60%) [M+H]$^+$. 

$(E)$-N-(furam-2-ylmethylene)diphenylmethanamine (2q):

Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.39 (1H, s), 8.09 (1H, m), 7.73 (1H, dd, $J = 1.3$, 7.8 Hz), 7.56-7.59 (1H, m), 7.44 (4H, d, $J = 7.0$ Hz), 7.37 (4H, t, $J = 7.8$Hz), 7.27-7.32 (3H, m), 5.65 (1H, s). $^{13}$C{$_^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 159.2, 143.5, 138.2, 133.6, 130.9, 130.0, 128.5, 127.6, 127.3, 127.1, 122.8, 77.8. IR (cm$^{-1}$): 3057 (w), 3026 (w), 2839 (m), 1658 (m), 1565 (m), 1492 (m), 1447 (m), 1381 (m), 1210 (m), 1024 (m), 787 (m), 759 (m), 741 (s), 697 (s). LRMS (ESI): 350.1 (60%) [M+H]$^+$. 

doi: 10.1038/nature08484

SUPPLEMENTARY INFORMATION

www.nature.com/nature
Prepared via Method A. Spectroscopic data match previously reported data.38

\((E)\)-N-(furan-3-ylmethylene)diphenylmethanamine (2r):

\[
\begin{align*}
\text{Prepared via Method A. } & 1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 8.36 (1\text{H, s}), 7.74 (1\text{H, s}), 7.44-7.45 (1\text{H, m}), 7.38-7.40 (4\text{H, m}), 7.33-7.36 (4\text{H, m}), 7.24-7.28 (2\text{H, m}), 6.95 (1\text{H, s}), 5.57 (1\text{H, s}). \\
& 13\text{C}\{1\text{H}\} \text{ NMR (125 MHz, CDCl}_3\text{): } \delta 152.5, 145.3, 143.9, 143.7, 128.4, 127.7, 127.0, 125.7, 108.2, 77.9. \text{ IR (cm}^{-1}\text{): } 3082 (w), 3051 (w), 1644 (m), 1511 (m), 1492 (m), 1153 (m), 1076 (m), 1017 (m), 774 (m), 745 (m), 726 (m), 698 (s). \text{ LRMS (ESI): } 262.1 (80\%) [M+H]^+. \\
\end{align*}
\]

\((E)\)-diphenyl-N-(thiophen-2-ylmethylene)methanamine (2s):

\[
\begin{align*}
\text{Prepared via Method A. } & 1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 8.52 (1\text{H, s}), 7.44-7.46 (5\text{H, m}), 7.36-7.40 (5\text{H, m}), 7.28-7.31 (2\text{H, m}), 7.10 (1\text{H, dd, } J = 3.5, 5.0 \text{ Hz}), 5.66 (1\text{H, s}). \\
& 13\text{C}\{1\text{H}\} \text{ NMR (125 MHz, CDCl}_3\text{): } \delta 154.0, 143.6, 142.7, 130.6, 129.1, 128.4, 127.7, 127.3, 127.0, 77.1. \text{ IR (cm}^{-1}\text{): } 3103 (w), 3061 (w), 2848 (w), 2848 (w), 1626 (m), 1491 (m), 1430 (m), 1218 (m), 1022 (m), 758 (m), 748 (m), 699 (s). \text{ LRMS (ESI): } 278.1 (100\%) [M+H]^+. \\
\end{align*}
\]

\((E)\)-N-(cyclohexenylmethylene)diphenylmethanamine (2t):

\[
\begin{align*}
\text{Prepared via Method A. } & 1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 8.52 (1\text{H, s}), 7.44-7.46 (5\text{H, m}), 7.36-7.40 (5\text{H, m}), 7.28-7.31 (2\text{H, m}), 7.10 (1\text{H, dd, } J = 3.5, 5.0 \text{ Hz}), 5.66 (1\text{H, s}). \\
& 13\text{C}\{1\text{H}\} \text{ NMR (125 MHz, CDCl}_3\text{): } \delta 154.0, 143.6, 142.7, 130.6, 129.1, 128.4, 127.7, 127.3, 127.0, 77.1. \text{ IR (cm}^{-1}\text{): } 3103 (w), 3061 (w), 2848 (w), 2848 (w), 1626 (m), 1491 (m), 1430 (m), 1218 (m), 1022 (m), 758 (m), 748 (m), 699 (s). \text{ LRMS (ESI): } 278.1 (100\%) [M+H]^+. \\
\end{align*}
\]

38 Cainelli, G., Giacomini, D., Trer, A. & Boyl, P. P. Efficient transamination under mild conditions: Preparation of primary amine derivatives from carbonyl compounds via imine isomerization with catalytic amounts of potassium tert-butoxide. J. Org. Chem. 61, 5134–5139 (1996).
Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.98 (1H, s), 7.39-7.41 (4H, m), 7.33-7.36 (4H, m), 7.24-7.28 (2H, m), 6.20 (1H, apparent sextet, $J = 1.8$ Hz), 5.46 (1H, s), 2.48-2.50 (2H, m), 2.23-2.26 (2H, m), 1.68-1.74 (4H, m). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 163.9, 144.4, 138.9, 138.4, 128.3, 127.6, 126.7, 77.6, 26.1, 23.9, 22.5, 22.0. IR (cm$^{-1}$): 3069 (w), 3022 (w), 2932 (m br), 2848 (w), 1643 (m), 1627 (m), 1491 (m), 1448 (m), 1376 (m), 1087 (m), 745 (m), 697 (s). LRMS (ESI): 276.2 (100%) [M+H]$^+$. 

$(E)$-$N$-((E)-2-methylpent-2-enylidene)diphenylmethanamine ($2u$):

Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.03 (1H, s), 7.45 (4H, d, $J = 8.0$ Hz), 7.39 (4H, t, $J = 7.8$ Hz), 7.29 (2H, tt, $J = 1.6$, 7.3 Hz), 5.94 (1H, td, $J = 1.6$, 7.5 Hz), 5.52 (1H), 2.33 (2H, p, $J = 7.5$ Hz), 2.05 (3H, s), 1.12 (3H, t, $J = 7.5$ Hz). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 165.2, 144.4, 143.8, 135.7, 128.3, 128.1, 127.6, 127.5, 126.8, 126.7, 77.5, 21.8, 13.4, 11.6. IR (cm$^{-1}$): 3061 (w), 3026 (w), 2966 (w), 2932 (w), 2872 (w), 2872 (w), 1626 (m), 1492 (m), 1451 (m), 1051 (m), 1030 (m), 740 (m), 696 (s). LRMS (ESI): 264.2 (100%) [M+H]$^+$. 

$(E)$-$N$-((E)-3-phenylallylidene)methanamine ($2v$):

Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.24 (1H, d, $J = 8.5$ Hz), 7.52-7.53 (2H, m), 7.36-7.42 (11H, m), 7.27-7.30 (2H, m), 7.13 (1H, dd, $J = 8.8$, 16.3 Hz), 7.01 (1H, d, $J = 16.0$ Hz), 5.54 (1H, s). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 162.8, 143.6, 142.3, 135.7, 129.2, 128.8, 128.4, 128.3, 127.7, 127.2, 127.0, 78.2. IR (cm$^{-1}$): 3080 (w), 3026 (w), 2851 (w), 1630 (m), 1489 (m), 1446 (m), 1151 (m), 997 (m), 964 (m), 742 (s), 692 (s). LRMS (ESI): 298.2 (100%) [M+H]$^+$. 

$(E)$-$N$-((E)-hex-2-enylidene)diphenylmethanamine ($2w$):
Prepared via Method A. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.07 (1H, d, $J = 8.8$ Hz), 7.35-7.41 (8H, m), 7.26-7.30 (2H, m), 6.46 (1H, dd, $J = 8.8$, 15.6 Hz), 6.27 (1H, dt, $J = 6.7$, 15.5 Hz), 5.45 (1H, s), 2.25 (2H, q, $J = 7.1$ Hz), 1.54 (2H, sextet, $J = 7.4$ Hz), 1.00 (3H, t, $J = 7.4$ Hz). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$): $\delta$ 162.9, 146.3, 143.7, 130.7, 128.3, 127.6, 126.8, 78.0, 34.6, 21.6, 13.6. IR (cm$^{-1}$): 3061 (w), 3026 (w), 2959 (w), 2929 (w), 2871 (w), 1652 (m), 1492 (m), 1451 (m), 1028 (m), 989 (m), 961 (m), 741 (s), 697 (s). LRMS (ESI): 264.2 (100%) [M+H]$^+$. 

Hydrocyanation of imines using TMSCN and MeOH

Caution! HCN is produced. The experiment should be executed in a well-ventilated fume hood. A flame-dried 25-mL round-bottomed flask containing a stir bar was charged with imine (1.0 mmol, 1.0 equiv) and (S)-N-benzhydryl-2-(3-(3,5-bis(trifluoromethyl)phenyl) thioureido)-N,3,3-trimethylbutanamide (4e) (11.6 mg, 0.02 mmol, 0.02 equiv). The flask was capped with a virgin rubber septum and flushed with N₂. Toluene (3.75 mL) was added via syringe under N₂, and the mixture was stirred at room temperature until a homogenous solution formed. The flask was then cooled in a dry ice/acetone (−78 °C) bath for 10 min. A stock solution of HCN was prepared as follows: a flame-dried 10-mL round-bottomed flask containing a stir bar was capped with a virgin septum. Toluene (1.25 mL) was added via syringe under N₂, and the flask was cooled in an ice-water bath for 10 min. TMSCN (0.27 mL, 2.0 mmol, 2.0 equiv) was added via syringe. Methanol (0.075 mL, 1.9 mmol, 1.9 equiv) was then added over 90 s with stirring. The stock solution was stirred at 0 °C for 30 min and then added via syringe to reaction mixture over a period of two minutes with stirring. The reaction flask was sealed with Parafilm, transferred to either a −30 °C freezer or 0 °C refrigerator, and aged for 20 h. After 20 h, the reaction flask was transferred to a well-ventilated fume hood, and the reaction mixture was concentrated under reduced pressure (1 torr). The residue was subjected to purification by flash column chromatography with Et₂O/hexanes as the eluent.

α-Aminonitriles that are solids can show enantiomeric enrichment upon crystallization. All solid α-aminonitriles were homogenized using a metal spatula prior to chiral HPLC analysis to ensure that an accurate measurement of enantioselectivity was obtained. Samples that were not mechanically homogenized yielded inconsistent enantiomeric excess values in the chiral HPLC analysis.

(R)-2-(benzhydrylamino)-3,3-dimethylbutanenitrile (3a):

The reaction was run at −30 °C for 20 h without stirring using (E)-N-(2,2-dimethylpropylidene) diphenylmethanamine (251 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-3,3-dimethylbutanenitrile (275 mg, 0.99
mmol, 99% yield) as a clear colorless oil. The enantiomeric excess was determined to be 93% by chiral HPLC analysis (AS-H, 5.0% IPA in hexanes, 1.0 mL/min, 210 nm, \( t_D^{(major)} = 8.7 \text{ min} \), \( t_D^{(minor)} = 6.0 \text{ min} \); \( [\alpha]_D^{24} = +113.0^\circ \) (c = 1.0, CHCl\(_3\) ); lit\(^{39}\) \( [\alpha]_D^{20} = +87.1^\circ \) (c = 1.19, CHCl\(_3\) ), 63% ee, (R)-enantiomer. Spectroscopic data match previously reported data.\(^{33}\)

\((R)-2\)-(benzhydrylamino)-3-ethyl-3-methylpentanenitrile (3b):

\[
\begin{align*}
\text{H} & \quad \text{Ph} \\
\text{H} & \quad \text{Ph} \\
\text{C} & \quad \text{N} \\
\end{align*}
\]

The reaction was run at \(-30^\circ \text{C} \) for 20 h without stirring using \((E)\)-N-(2-ethyl-2-methylbutylidene)diphenylmethanamine (279 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et\(_2\)O) to afford \((R)-2\)-(benzhydrylamino)-3-ethyl-3-methylpentanenitrile (303 mg, 0.99 mmol, 99% yield) as a clear colorless oil. The enantiomeric excess was determined to be 96% by chiral HPLC analysis (AS-H, 5.0% IPA in hexanes, 1.0 mL/min, 210 nm, \( t_D^{(major)} = 8.4 \text{ min} \), \( t_D^{(minor)} = 5.3 \text{ min} \); \( [\alpha]_D^{23} = +124.6^\circ \) (c = 1.0, CHCl\(_3\) ). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.48 \) (2H, d, \( J = 7.0 \text{ Hz} \)), \( 7.45 \) (2H, d, \( J = 7.0 \text{ Hz} \)), \( 7.32 \) (4H, td, \( J = 8.0, 3.0 \text{ Hz} \)), \( 7.22-7.27 \) (2H, m), \( 5.11 \) (1H, s), \( 3.21 \) (1H, d, \( J = 13.5 \text{ Hz} \)), \( 1.80 \) (1H, d, \( J = 13.0 \text{ Hz} \)), \( 1.54 \) (3H, apparent sextet, \( J = 7.4 \text{ Hz} \)), \( 1.41 \) (1H, apparent sextet, \( J = 7.3 \text{ Hz} \)), \( 0.98 \) (3H, s), \( 0.75 \) (6H, apparent td, \( J = 7.5, 2.2 \text{ Hz} \)). \(^{13}\)C\{\(^1\)H\} NMR (125 MHz, CDCl\(_3\)): \( \delta 143.5, 141.3, 128.7, 128.7, 127.8, 127.7, 127.5, 126.9, 119.7, 65.7, 56.1, 39.3, 28.2, 27.4, 20.5, 7.80, 7.59. \) IR (cm\(^{-1}\) ): 3314 (w), 3028 (w), 2967 (m), 2939 (m), 2224 (w), 1493 (m), 1453 (m), 1112 (m), 745 (s), 702 (s).

\((R)-2\)-(benzhydrylamino)-3-methyl-3-phenylbutanenitrile (3c):

\[
\begin{align*}
\text{H} & \quad \text{Ph} \\
\text{H} & \quad \text{Ph} \\
\text{C} & \quad \text{N} \\
\end{align*}
\]

\(^{39}\) Wunnemann, S., Frohlich, R. & Hoppe, D. Asymmetric Strecker reaction of N-benzhydrylimines utilising new tropos biphenyldiol-based ligands. \textit{Eur. J. Org. Chem.} 684–692 (2008).
The reaction was run at –30 °C for 20 h without stirring using \((E)\)-N-(2-methyl-2-phenylpropylidene)diphenylmethanamine (313 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford \((R)\)-2-(benzhydrylamino)-3-methyl-3-phenylbutanenitrile (331 mg, 0.97 mmol, 97% yield) as a white solid. The enantiomeric excess was determined to be 85% by chiral HPLC analysis (OD-H, 1.0% IPA in hexanes, 1.0 mL/min, 220 nm, \(t_\text{R(major)}= 7.8\) min, \(t_\text{R(minor)} = 9.0\) min; \([\alpha]_D^{24} = +81.8°\) (c = 1.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃): \(\delta 7.45-7.47\ (2H, \text{m}), 7.37-7.43\ (4H, \text{m}), 7.28-7.35\ (8H, \text{m}), 7.24-7.26\ (1H, \text{m}), 5.06\ (1H, \text{s}), 3.47\ (1H, \text{d}, J = 12.5 \text{ Hz}), 1.72\ (1H, \text{d}, J = 12.5 \text{ Hz}), 1.68\ (6H, \text{s}). \(^{13}\)C{¹H} NMR (125 MHz, CDCl₃): \(\delta 143.4, 143.3, 141.1, 128.7, 128.6, 128.4, 127.6, 127.4, 127.0, 126.8, 126.5, 119.2, 65.3, 59.2, 40.8, 25.9, 25.0. IR (cm⁻¹): 3348 (w), 3058 (w), 3025 (w), 2975 (w), 2228 (w), 1493 (m), 1452 (m), 1309 (m), 1122 (m), 1032 (m), 889 (w), 768 (s), 745 (s), 702 (s).

\((R)\)-2-(benzhydrylamino)-2-(1-methylcyclohexyl)acetonitrile (3d):

The reaction was run at –30 °C for 20 h without stirring using \((E)\)-N-((1-methylcyclohexyl)methylene)diphenylmethanamine (291 mg, 1.0 mmol, 1.0 equiv). The product subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford \((R)\)-2-(benzhydrylamino)-2-(1-methylcyclohexyl)acetonitrile (315 mg, 0.99 mmol, 99% yield) as a clear colorless oil. The enantiomeric excess was determined to be 95% by chiral HPLC analysis (AD-H, 5.0% IPA in hexanes, 1.0 mL/min, 230 nm, \(t_\text{R(major)}= 5.8\) min, \(t_\text{R(minor)} = 5.2\) min; \([\alpha]_D^{24} = +108.8°\) (c = 1.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃): \(\delta 7.50\ (2H, \text{d}, J = 7.0 \text{ Hz}), 7.45\ (2H, \text{d}, J = 7.0 \text{ Hz}), 7.30-7.35\ (4H, \text{m}), 7.23-7.28\ (2H, \text{m}), 5.12\ (1H, \text{s}), 3.23\ (1H, \text{d}, J = 12.5 \text{ Hz}), 1.80\ (1H, \text{d}, J = 13.0 \text{ Hz}), 1.48-1.55\ (5H, \text{m}), 1.39-1.45\ (6H, \text{m}), 1.22-1.26\ (1H, \text{m}), 1.09\ (3H, \text{s}). \(^{13}\)C{¹H} NMR (125 MHz, CDCl₃): \(\delta 143.5, 141.4, 128.7, 127.7, 127.6, 127.0, 119.4, 65.7, 58.3, 40.3, 36.8, 34.8, 34.2, 25.9, 21.6, 21.4, 20.6. IR (cm⁻¹): 3314 (w), 3028 (w), 2927 (m), 2853 (m), 2224 (w), 1493 (w), 1452 (m), 1104 (m), 1028 (m), 745 (s), 701 (s).

\((R)\)-2-(benzhydrylamino)-2-(1-adamantyl)acetonitrile (3e):
The reaction was run at –30 °C for 20 h without stirring using (E)-N-(1-adamantyl)diphenylmethanamine (330 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-(1-adamantyl)acetonitrile (352 mg, 0.99 mmol, 99% yield) as an off-white solid. The enantiomeric excess was determined to be 93% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, \( t_R \) (major) = 5.4 min, \( t_R \) (minor) = 5.7 min); \([\alpha]_D^{24} = +69.9^\circ \) (c = 1.0, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.51 (2H, d, \( J = 7.5 \) Hz), 7.47 (2H, d, \( J = 7.0 \) Hz), 7.32-7.39 (4H, m), 7.24-7.29 (2H, m), 5.14 (1H, s), 3.03 (1H, s), 2.08 (3H, s), 1.63-1.86 (13H, m). \(^{13}\)C\(^{1}\)H NMR (125 MHz, CDCl₃): \( \delta \) 143.5, 141.3, 128.7, 128.7, 127.6, 127.5, 127.4, 127.0, 119.0, 65.5, 59.5, 38.7, 37.3, 36.6, 36.5, 35.8, 28.1. IR (cm\(^{-1}\)) 3302 (w), 3025 (w), 2912 (m), 2849 (m), 2222 (w), 1493 (w), 1450 (m), 1346 (w), 1029 (w), 895 (w), 743 (s), 700 (s).

(R)-2-(benzhydrylamino)-2-cyclohexylacetonitrile (3f):

The reaction was run at –30 °C for 20 h without stirring using (E)-N-(cyclohexylmethylene)diphenylmethanamine (277 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-cyclohexylacetonitrile (301 mg, 0.99 mmol, 99% yield) as a white solid. The enantiomeric excess was determined to be 74% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 230 nm, \( t_R \) (major) = 6.3 min, \( t_R \) (minor) = 8.0 min); \([\alpha]_D^{23} = +59.9^\circ \) (c = 1.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.50 (2H, d, \( J = 7.0 \) Hz), 7.44 (2H, d, \( J = 7.0 \) Hz), 7.31-7.37 (4H, m), 7.23-7.29 (2H, m), 5.15 (1H, s), 3.25 (1H, d, \( J = 7.0 \) Hz), 2.00 (1H, d, \( J = 12.5 \) Hz), 1.87 (1H, d, \( J = 10.5 \) Hz), 1.79-1.82 (2H, m), 1.69-1.75 (2H, m), 1.11-1.33 (6H, m). \(^{13}\)C\(^{1}\)H NMR (125 MHz, CDCl₃): \( \delta \) 143.3, 141.3, 128.8, 128.7, 127.6, 127.5, 127.3, 127.0, 119.6, 65.5, 54.1, 40.9, 29.6, 29.0, 26.0, 25.7, 25.6. IR (cm\(^{-1}\)) 3329 (w), 3028 (w), 2930 (m), 2845 (m), 2222 (w), 1493 (m), 1450 (m), 1112 (m), 1027 (m), 880 (m), 750 (s), 707 (s), 697 (s).
(R)-2-(benzhydrylamino)-2-(4-methoxyphenyl)acetonitrile (3g):

The reaction was run at –30 °C for 20 h without stirring using (E)-N-(4-methoxybenzylidene)diphenylmethanamine (301 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (7:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-(4-methoxyphenyl)acetonitrile (324 mg, 0.99 mmol, 99% yield) as a white solid. The enantiomeric excess was determined to be 99% by chiral HPLC analysis (S,S-welk, 2.0% IPA in hexanes, 1.0 mL/min, 200 nm, $t_R$(major) = 19.6 min, $t_R$(minor) = 18.4 min); $[\alpha]_D^{24} = +43.0^\circ$ (c = 1.0, CHCl₃); lit⁴⁰ $[\alpha]_D^{24} = \pm38.0^\circ$ (c = 1.0, CHCl₃), 91% ee, (S)-enantiomer. Spectroscopic data match previously reported data.³³

(R)-2-(benzhydrylamino)-2-p-tolylacetonitrile (3h):

The reaction was run at –30 °C for 20 h without stirring using (E)-N-(4-methylbenzylidene)diphenylmethanamine (285 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-p-tolylacetonitrile (307 mg, 0.98 mmol, 98% yield) as a white solid. The enantiomeric excess was determined to be 98% by chiral HPLC analysis (OD-H, 5.0% IPA in hexanes, 1.0 mL/min, 220 nm, $t_R$(major) = 6.7 min, $t_R$(minor) = 7.3 min); $[\alpha]_D^{24} = +52.8^\circ$ (c = 1.0, CHCl₃); lit³⁹ $[\alpha]_D^{20} = \pm41.0^\circ$ (c = 1.13, CHCl₃), 80% ee, (R)-enantiomer. Spectroscopic data matched previously reported data.⁴¹

(R)-2-(benzhydrylamino)-2-phenylacetonitrile (3i):

⁴⁰ Banphavichit, V., Mansawat, W., Bhanthumnavin, W. & Vilaivan, T. A highly enantioselective Strecker reaction catalyzed by titanium-N-salicyl-beta-aminoalcohol complexes. Tetrahedron 60, 10559–10568 (2004).

⁴¹ Jiao, Z., Feng, X., Liu, B., Chen, F., Zhang, G. & Jiang, Y. Enantioselective Strecker reactions between aldimines and trimethylsilyl cyanide promoted by chiral N,N’-dioxides. Eur. J. Org. Chem. 3818–3826 (2003).
The reaction was run at –30 °C for 20 h without stirring using (E)-N-benzylidenediphenylmethanamine (271 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-phenylacetonitrile (293 mg, 0.98 mmol, 98% yield) as a white solid. The enantiomeric excess was determined to be 98% by chiral HPLC analysis (OD-H, 5.0% IPA in hexanes, 1.0 mL/min, 220 nm, \( t_R^{\text{major}} = 7.1 \text{ min}, t_R^{\text{minor}} = 7.9 \text{ min} \); \([\alpha]_D^{24} = +66.1^\circ (c = 1.0, \text{CHCl}_3)\); lit\(^{33}\) \([\alpha]_D^{24} = -64.2^\circ (c = 5.0, \text{CHCl}_3)\), >99% ee, (S)-enantiomer. Spectroscopic data match previously reported data.\(^{33}\)

(R)-2-(benzhydrylamino)-2-(4-chlorophenyl)acetonitrile (3j):

The reaction was run at –30 °C for 20 h without stirring using (E)-N-(4-chlorobenzylidene)diphenylmethanamine (306 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-(4-chlorophenyl)acetonitrile (324 mg, 0.97 mmol, 97% yield) as a white solid. The enantiomeric excess was determined to be 98% ee by chiral HPLC analysis (OD-H, 5.0% IPA in hexanes, 1.0 mL/min, 220 nm, \( t_R^{\text{major}} = 9.6 \text{ min}, t_R^{\text{minor}} = 11.7 \text{ min} \); \([\alpha]_D^{24} = +42.3^\circ (c = 1.0, \text{CHCl}_3)\); lit\(^{39}\) \([\alpha]_D^{20} = +35.1^\circ (c = 1.09, \text{CHCl}_3)\), 84% ee, (R)-enantiomer. Spectroscopic data match previously reported data.\(^{42}\)

(R)-2-(benzhydrylamino)-2-(4-(trifluoromethyl)phenyl)acetonitrile (3k):

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\(^{42}\) Iyer, M. S., Gigstad, K. M., Namdev, N. D. & Lipton, M. Asymmetric catalysis of the Strecker amino acid synthesis by a cyclic dipeptide. *J. Am. Chem. Soc.* **118**, 4910–4911 (1996).
The reaction was run at 0 °C for 20 h with stirring using (E)-diphenyl-N-(4-(trifluoromethyl)benzylidene)methanamine (339 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et2O) to afford (R)-2-(benzhydrylamino)-2-(4-(trifluoromethyl)phenyl)acetonitrile (360 mg, 0.98 mmol, 98% yield) as a white solid. This enantiomeric excess was determined to be 96% by chiral HPLC analysis (OD-H, 5.0% IPA in hexanes, 1.0 mL/min, 220 nm, \( t_R(\text{major}) = 11.5 \text{ min}, t_R(\text{minor}) = 13.3 \text{ min}; [\alpha]_{D}^{24} = +50.3^\circ \text{ (c = 1.0, CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.72 \text{ (4H, s), 7.61 (2H, d, } J = 8.0 \text{ Hz), 7.49 (2H, d, } J = 7.5 \text{ Hz), 7.42 (2H, t, } J = 7.8 \text{ Hz), 7.31-7.36 \text{ (3H, m), 7.25-7.28 \text{ (1H, m), 5.29 (1H, s), 4.69 (1H, d, } J = 9.0 \text{ Hz), 2.23 (1H, d, } J = 8.5 \text{ Hz).} \) \(^{13}\)C\{\(^1\)H\} NMR (125 MHz, CDCl\(_3\)): \( \delta 142.4, 140.7, 138.7, 131.3 \text{ (q, } J_{C-F} = 32.3 \text{ Hz), 129.1, 128.8, 128.1, 127.8, 127.4, 127.0, 125.9 \text{ (q, } J_{C-F} = 2.5 \text{ Hz), 123.7 \text{ (q, } J_{C-F} = 270.0 \text{ Hz), 118.1, 65.6, 51.9.} \) IR (cm\(^{-1}\)): 3297 (m), 3065 (w), 3028 (w), 2842 (w), 2231 (w), 1618 (w), 1453 (m), 1323 (s), 1166 (m), 1125 (s), 1111 (s), 1066 (m), 1017 (m), 922 (m), 749 (m), 699 (s).

\((R)-4-((benzhydrylamino)(cyano)methyl)benzonitrile (3I):\)

\[\text{Ph} \quad \text{Ph} \]
\[\text{HN} \quad \text{CN}\]

The reaction was run at 0 °C for 20 h with stirring using (E)-4-((benzhydrylimino)methyl)benzonitrile (296 mg, 1.0 mmol, 1.0 equiv) and 10 mol% of \((S)-N\)-benzhydryl-2-(3-(3,5-bis(trifluoromethyl)phenylthioureido)-N,3,3-trimethyl butanamide (4e). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et\(_2\)O) to afford (R)-4-((benzhydrylamino) (cyano)methyl)benzonitrile (310 mg, 0.96 mmol, 96% yield) as a white solid. The enantiomeric excess was determined to be 93% by chiral HPLC analysis (OD-H, 5.0% IPA in hexanes, 1.0 mL/min, 230 nm, \( t_R(\text{major}) = 41.1 \text{ min}, t_R(\text{minor}) = 56.4 \text{ min}; [\alpha]_{D}^{24} = +27.3^\circ \text{ (c = 1.0, CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.72 \text{ (4H, s), 7.57 (2H, d, } J = 7.5 \text{ Hz), 7.45 (2H, d, } J = 7.5 \text{ Hz), 7.39 (2H, t, } J = 7.8 \text{ Hz), 7.29-7.34 \text{ (3H, m), 7.23-7.27 \text{ (1H, m), 5.25 (1H, s), 4.67 (1H, br s), 2.25 (1H, br s).} \) \(^{13}\)C\{\(^1\)H\} NMR (125 MHz, CDCl\(_3\)): \( \delta 142.2, 140.5, 139.7, 132.7, 129.1, 128.8, 128.2, 128.0, 127.9, 127.4, 127.0, 118.1, 117.7, 113.1, 56.7, 52.0. \) IR (cm\(^{-1}\)): 3310 (m), 3296 (m), 3025 (w), 2925 (w), 2845 (w), 2232 (m), 1609 (w), 1492 (m), 1453 (m), 1349 (m), 1189 (m), 925 (m), 746 (s), 703 (s).
(R)-2-(benzhydrylamino)-2-(4-bromophenyl)acetonitrile (3m):

The reaction was run at –30 °C for 20 h with stirring using (E)-N-(4-bromobenzylidene)diphenylmethanamine (350 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-(4-bromophenyl)acetonitrile (369 mg, 0.98 mmol, 98% yield) as a white solid. The enantiomeric excess was determined to be 99% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, \( t_R \) (major) = 15.1 min, \( t_R \) (minor) = 18.4 min); \([\alpha]_D^{24} = +29.4^\circ \) (c = 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): \( \delta \) 7.56-7.59 (4H, m), 7.46 (4H, t, \( J = 8.8 \) Hz), 7.41 (2H, t, \( J = 7.5 \) Hz), 7.30-7.35 (3H, m), 7.26 (1H, t, \( J = 7.3 \) Hz), 5.26 (1H, s), 4.58 (1H, d, \( J = 11.5 \) Hz), 2.18 (1H, d, \( J = 12.0 \) Hz). ¹³C{¹H} NMR (125 MHz, CDCl₃): \( \delta \) 142.4, 140.8, 133.8, 132.1, 129.0, 128.8, 128.7, 128.0, 127.7, 127.3, 127.0, 123.1, 118.2, 65.5, 51.7. IR (cm⁻¹): 3303 (m), 3062 (w), 3026 (w), 2836 (w), 2224 (w), 1594 (w), 1488 (m), 1453 (m), 1187 (w), 1100 (m), 920 (m), 819 (m), 745 (s), 698 (s).

(R)-2-(benzhydrylamino)-2-(2-methoxyphenyl)acetonitrile (3n):

The reaction was run at –30 °C for 20 h without stirring using (E)-N-(2-methoxybenzylidene)diphenylmethanamine (301 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (7:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-(2-methoxyphenyl)acetonitrile (318 mg, 0.97 mmol, 97% yield) as a white solid. The enantiomeric excess was determined to be 88% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, \( t_R \) (major) = 11.7 min, \( t_R \) (minor) = 12.8 min); \([\alpha]_D^{23} = +65.3^\circ \) (c = 1.0, CHCl₃); lit⁴⁰ \([\alpha]_D^{24} = -57.0^\circ \) (c = 1.0, CHCl₃), 83% ee, (S)-enantiomer. ¹H NMR (500 MHz, CDCl₃): \( \delta \) 7.56 (2H, d, \( J = 8.0 \) Hz), 7.48 (2H, d, \( J = 8.0 \) Hz), 7.37-7.41 (3H, m), 7.30-7.35 (4H, m), 7.24-7.28 (1H, m), 7.00 (1H, t, \( J = 7.5 \) Hz), 6.97 (1H, d, \( J = 8.5 \) Hz), 5.23 (1H, s), 4.71 (1H, br d, \( J = 6.5 \) Hz), 3.89 (3H, s), 2.60 (1H br s). ¹³C{¹H} NMR (125 MHz,
CDCl₃): δ 157.0, 142.9, 141.4, 130.5, 128.8, 128.7, 128.7, 127.5, 127.4, 127.2, 126.4, 120.9, 119.0, 111.3, 65.3, 55.5, 48.4. IR (cm⁻¹): 3322 (w), 3027 (w), 2975 (w), 2939 (w), 2227 (w), 1600 (m), 1493 (m), 1450 (m), 1248 (m), 1026 (m), 910 (m), 747 (s), 698 (s).

(R)-2-(benzhydrylamino)-2-(2-bromophenyl)acetonitrile (3o):

![Chemical Structure](image)

The reaction was run at 0 °C for 20 h with stirring using (E)-N-(2-bromobenzylidene)diphenylmethanamine (350 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-(2-bromophenyl)acetonitrile (362 mg, 0.96 mmol, 96% yield) as a white solid. This enantiomeric excess was determined to be 97% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 200 nm, tₘₐₗₐₜ (major)= 12.7 min, tₘᵌₙₐₗₐₜ (minor) = 17.8 min; [α]₂₅°D = +130.0° (c = 1.0, CHCl₃); lit [α]₂₄°D = −122° (c = 5.0, CHCl₃), >99% ee, (S)-enantiomer. Spectroscopic data match previously reported data.³³

(R)-2-(benzhydrylamino)-2-(3-bromophenyl)acetonitrile (3p):

![Chemical Structure](image)

The reaction was run at 0 °C for 20 h with stirring using (E)-N-(3-bromobenzylidene)diphenylmethanamine (350 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford (R)-2-(benzhydrylamino)-2-(3-bromophenyl)acetonitrile (365 mg, 0.97 mmol, 97% yield) as a white solid. The enantiomeric excess was determined to be 92% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, tₘₐₜ (major)= 13.0 min, tₘᵌₜ (minor) = 14.6 min; [α]₂₄°D = +37.5° (c = 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 7.74 (1H, s), 7.59 (2H, t, J = 7.5 Hz), 7.50-7.54 (2H, m), 7.47 (2H, d, J = 7.5 Hz), 7.41 (2H, t, J = 7.5 Hz), 7.30-7.35 (4H, m), 7.25-7.28 (1H, m), 5.26 (1H, s), 4.60 (1H, d, J = 12.0 Hz), 2.19 (1H, d, J = 11.5 Hz). ¹³C{¹H} NMR (125 MHz, CDCl₃): δ 142.4, 140.7, 136.9, 132.2, 130.4, 130.3, 129.0, 128.8, 128.0, 127.7,
The reaction was run at –30 °C for 20 h without stirring using \((E)\)-N-(furan-2-ylmethylene)diphenylmethanamine (261 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford \((S)\)-2-(benzhydrylamino)-2-(furan-2-yl)acetonitrile (285 mg, 0.99 mmol, 99% yield) as a white solid. The enantiomeric excess was determined to be 93% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, \(t_R\)(major) = 11.2 min, \(t_R\)(minor) = 13.4 min); \([\alpha]_D^{24} = +32.9^\circ\) (c = 1.0, CHCl₃); lit\(^{40}\) \([\alpha]_D^{21} = -25.0^\circ\) (c = 1.0, CHCl₃), 91% ee, \((R)\)-enantiomer. Spectroscopic data match previously reported data.\(^{40}\)

\((R)\)-2-(benzhydrylamino)-2-(furan-3-yl)acetonitrile (3r):

The reaction was run at –30 °C for 20 h without stirring using \((E)\)-N-(furan-3-ylmethylene)diphenylmethanamine (261 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et₂O) to afford \((R)\)-2-(benzhydrylamino)-2-(furan-3-yl)acetonitrile (282 mg, 0.98 mmol, 98% yield) as a white solid. This enantiomeric excess was determined to be 97% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, \(t_R\)(major) = 11.9 min, \(t_R\)(minor) = 12.7 min); \([\alpha]_D^{24} = +64.6^\circ\) (c = 1.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 7.61 (1H, s), 7.53 (2H, d, \(J = 10.0\) Hz), 7.44 (3H, d, \(J = 9.5\) Hz), 7.22-7.38 (6H, m), 6.54 (1H, s), 5.21 (1H, s), 4.51 (1H, d, \(J = 15.0\) Hz), 2.12 (1H, d, \(J = 15.0\) Hz). \(^1\)\(^3\)C\({}^1\)H NMR (125 MHz, CDCl₃): \(\delta\) 144.0, 142.6, 140.9, 140.4, 129.0, 128.8, 128.0, 127.7, 127.3, 127.0, 120.9, 118.4, 109.2, 65.3, 44.6. IR (cm\(^{-1}\)): 3295 (m), 3135 (w), 1404 (m), 1385 (w), 1372 (w), 1290 (m), 1280 (w), 1277.7, 1273.7, 1270.0, 120.9, 118.4, 109.2, 65.3, 44.6. IR (cm\(^{-1}\)): 3295 (m), 3135 (w), 3061 (w), 2842 (w), 2231 (w), 1596 (w), 1492 (m), 1474 (m), 1451 (m), 1162 (m), 1102 (m), 1025 (m), 902 (m), 874 (s), 807 (m), 744 (s), 699 (s).
(S)-2-(benzhydrylamino)-2-(thiophen-2-yl)acetonitrile (3s):

![Structure diagram](image)

The reaction was run at 0 °C for 20 h with stirring using (E)-diphenyl-N-(thiophen-2-ylmethylene)methanamine (277 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et$_2$O) to afford (S)-2-(benzhydrylamino)-2-(thiophen-2-yl)acetonitrile (294 mg, 0.97 mmol, 97% yield) as a white solid. The enantiomeric excess determined to be 95% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, $t_R$(major)= 10.0 min, $t_R$(minor) = 11.1 min); $[\alpha]_D^{24} = +68.6^\circ$ ($c = 1.0$, CHCl$_3$); lit$^{40}$ $[\alpha]_D^{24} = 76.0^\circ$ ($c = 1.0$, CHCl$_3$), 98% ee, (S)-enantiomer. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.59 (2H, d, $J = 8.0$ Hz), 7.48 (2H, d, $J = 8.0$ Hz), 7.25-7.41 (8H, m), 7.01-7.02 (1H, m), 5.25 (1H, s), 4.79 (1H, d, $J = 12.0$ Hz), 2.40 (1H, d, $J = 12.0$ Hz). $^{13}$C($^1$H) NMR (125 MHz, CDCl$_3$): $\delta$ 142.4, 140.7, 138.2, 129.0, 128.8, 128.0, 127.7, 127.2, 127.0, 126.8, 126.6, 126.0, 118.1, 65.3, 48.1. IR (cm$^{-1}$): 3295 (m), 3104 (w), 3083 (w), 3059 (w), 3023 (w), 2842 (w), 2230 (w), 1491 (m), 1474 (m), 1451 (m), 1188 (m), 1095 (m), 1025 (m), 915 (m), 843 (m), 744 (m), 725 (m), 698 (s).

(R)-2-(benzhydrylamino)-2-cyclohexenylacetonitrile (3t):

The reaction was run at –30 °C for 20 h without stirring using (E)-N-(cyclohexenylmethylene)diphenylmethanamine (263 mg, 1.0 mmol, 1.0 equiv). The product was purified by flash column chromatography (9:1, hexanes:Et$_2$O) to afford (R)-2-(benzhydrylamino)-2-cyclohexenylacetonitrile (298 mg, 0.99 mmol, 99% yield) as a clear colorless oil. The enantiomeric excess was determined to be 95% ee by chiral HPLC analysis (AD-H, 3.0% IPA in hexanes, 1.0 mL/min, 210 nm, $t_R$(major)= 11.2 min, $t_R$(minor) = 20.2 min); $[\alpha]_D^{23} = +65.4^\circ$ ($c = 1.0$, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 (2H, d, $J = 7.0$ Hz), 7.46 (2H, d, $J = 7.5$ Hz), 7.32-7.40 (4H, m), 7.24-7.30 (2H, m), 6.06 (1H, d, $J = 1.5$ Hz), 5.17 (1H, s), 3.89 (1H, d, $J = 8.0$ Hz), 2.37-2.41 (1H, m), 2.08-2.12 (2H, m), 1.97-2.01 (1H, m), 1.86 (1H, d, $J = 9.5$ Hz), 1.71 (2H, p, $J = 6.0$ Hz), 1.62 (2H, apparent sextet, $J = 5.7$ Hz). $^{13}$C($^1$H) NMR (125 MHz, CDCl$_3$): $\delta$ 143.0, 141.3, 131.9, 128.8, 128.0, 128.3, 127.6, 127.5, 127.4, 127.1, 126.8, 118.6, 65.2, 54.2, 25.9, 24.9,
22.4, 21.8. IR (cm\(^{-1}\)):
3313 (w), 3062 (w), 3029 (w), 2928 (m), 2858 (w), 2228 (w), 1493 (m), 1452 (m), 1076 (m),
1028 (m), 896 (m), 843 (m), 745 (s), 701 (s), 678 (s).

(R,E)-2-(benzhydrylamino)-3-methylhex-3-enenitrile (3u):

The reaction was run at –30 °C for 20 h without stirring using (E)-N-((E)-2-methylpent-2-ene
lidene)diphenylmethanamine (263 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purifi-
cation by flash column chromatography (9:1, hexanes:Et\(_2\)O) to afford (R,E)-2-(benzhydrylamino)-3-methylhex-3-enenitrile (286 mg, 0.98 mmol, 98% yield) as a clear colorless oil. The enantiomeric excess was determined to be 91% ee by chiral
HPLC analysis (AD-H, 1.0% IPA in hexanes, 1.0 mL/min, 220 nm, \(t_d\)(major) = 9.4 min, \(t_d\)(minor) = 8.5 min); \([\alpha]_D^{23}\) = +66.9° (c = 1.0, CHCl\(_3\)).

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)):
δ 7.50-7.52 (2H, m), 7.44-7.45 (2H, m), 7.23-7.37 (6H, m), 5.74 (1H, dt, \(J = 1.0, 6.5\) Hz), 5.13 (1H, s), 3.88 (1H, s), 2.08-2.11 (2H, m), 1.86-1.90 (1H, m), 1.80 (3H, s),
0.98-1.02 (3H, m).

\(^{13}\)C\(^{\{1\}}\) NMR (125 MHz, CDCl\(_3\)):
δ 142.9, 141.4, 132.0, 128.8, 128.7, 128.4, 127.7, 127.5,
127.4, 127.1, 118.7, 65.2, 55.2, 21.2, 13.9, 13.6. IR (cm\(^{-1}\)):
3313 (w), 3062 (w), 3028 (w), 2965 (w), 2932 (w), 2873 (w), 2228 (w), 1493 (m), 1453 (m), 1306 (w), 1189 (w), 1080 (w), 911 (w), 864 (w), 745 (s), 699 (s).

(R,E)-2-(benzhydrylamino)-4-phenylbut-3-enenitrile (3v):

The reaction was run at –30 °C for 20 h with stirring (the reaction mixture was heterogenous) using (E)-diphenyl-N-
((E)-3-phenylallylidene)methanamine (297 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purifi-
cation by flash column chromatography (9:1, hexanes:Et\(_2\)O) to afford (R,E)-2-(benzhydrylamino)-4-phenylbut-3-enenitrile (323 mg, 0.99 mmol, 99% yield) as a white solid. The enantiomeric excess was determined to be 95% ee by chiral
HPLC analysis (AD-H, 3.0% IPA in hexanes, 1.0 mL/min, 210 nm, \(t_d\)(major) = 13.2 min, \(t_d\)(minor) = 19.9 min);
\([\alpha]_D^{23}\) = +13.8° (c = 1.0, CHCl\(_3\)).

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)):
δ 7.56 (2H, d, \(J = 8.0\) Hz), 7.49 (2H, d, \(J = 7.5\) Hz),
7.26-7.44 (11H, m), 6.94 (1H, d, \(J = 16.5\) Hz), 6.25 (1H, dd, \(J = 5.0, 16.0\) Hz), 5.25 (1H, br s), 4.26 (1H, br s), 2.03
(1H, br s). $^{13}$C{$^{1}$H} NMR (125 MHz, CDCl$_3$): $\delta$ 143.1, 141.3, 135.6, 134.1, 129.3, 129.1, 129.0, 128.9, 128.2, 128.0, 127.7, 127.4, 127.1, 122.7, 118.6, 65.6, 50.4. IR (cm$^{-1}$): 3304 (m), 3056 (w), 3027 (w), 2235 (w), 1492 (m), 1452 (m), 1312 (w), 1108 (m), 963 (m), 743 (s), 702 (s), 695 (s).

($R,E$)-2-(benzhydrylamino)hept-3-enenitrile (3w):

![Chemical Structure](image)

The reaction was run at $-30 \, ^\circ C$ for 20 h using ($E$)-N-($E$)-hex-2-enylidene diphénylméthamine (263 mg, 1.0 mmol, 1.0 equiv). The product was subjected to purification by flash column chromatography (9:1, hexanes:Et$_2$O) to afford ($R,E$)-2-(benzhydrylamino)hept-3-enenitrile (281 mg, 0.97 mmol, 97% yield, ~95% purity) as a clear colorless oil. The enantiomeric excess was determined to be 73% by chiral HPLC analysis (OD-H, 2.0% IPA in hexanes, 1.0 mL/min, 220 nm, $t_R$ (major) = 7.9 min, $t_R$ (minor) = 12.2 min; $\left[\alpha\right]_D^{23} = +36.2^\circ$ (c = 1.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.49 (2H, d, $J = 6.8$ Hz), 7.43 (2H, d, $J = 7.2$ Hz), 7.20-7.36 (6H, m), 5.99-6.07 (1H, m), 5.51-5.57 (1H, m), 5.16 (1H, s), 4.00-4.04 (1H, m), 2.07 (2H, q, $J = 7.2$ Hz), 1.85 (1H, d, $J = 12.0$ Hz), 1.43 (2H, apparent sextet, $J = 7.6$ Hz), 0.92 (3H, t, $J = 7.4$ Hz). $^{13}$C{$^{1}$H} NMR (125 MHz, CDCl$_3$): $\delta$ 142.9, 141.2, 135.7, 128.9, 128.7, 127.7, 127.6, 127.4, 127.1, 123.4, 118.6, 65.3, 49.9, 34.0, 21.9, 13.6. IR (cm$^{-1}$): 3314 (w), 3062 (w), 3028 (w), 2959 (w), 2930 (w), 2872 (w), 2228 (w), 1599 (w), 1493 (m), 1453 (m), 1305 (w), 1079 (w), 1028 (w), 967 (m), 744 (s), 698 (s).
HPLC chromatograms of racemic and enantiomerically enriched α-aminonitriles

(R)-2-(benzhydrylamino)-3,3-dimethylbutanenitrile (3a):

![HPLC chromatogram of (R)-2-(benzhydrylamino)-3,3-dimethylbutanenitrile](image)

| Peak | Ret. Time | Area       | Height | Area % | Height % |
|------|-----------|------------|--------|--------|----------|
| 1    | 7.419     | 9043986    | 602998 | 49.815 | 60.540   |
| 2    | 10.641    | 9111281    | 391385 | 50.185 | 39.360   |
| Total| 18155267  | 994383     | 100.000 | 100.000 |

(R)-2-(benzhydrylamino)-3-ethyl-3-methylpentanenitrile (3b):

![HPLC chromatogram of (R)-2-(benzhydrylamino)-3-ethyl-3-methylpentanenitrile](image)

| Peak | Ret. Time | Area       | Height | Area % | Height % |
|------|-----------|------------|--------|--------|----------|
| 1    | 5.971     | 376427     | 37773  | 3.494  | 6.267    |
| 2    | 8.747     | 10195884   | 564925 | 96.506 | 93.733   |
| Total| 101772311 | 662698     | 100.000 | 100.000 |

(R)-2-(benzhydrylamino)-3-methyl-3-phenylbutanenitrile (3c):

![HPLC chromatogram of (R)-2-(benzhydrylamino)-3-methyl-3-phenylbutanenitrile](image)

| Peak | Ret. Time | Area       | Height | Area % | Height % |
|------|-----------|------------|--------|--------|----------|
| 1    | 5.317     | 192344     | 20877  | 5.180  | 2.146    |
| 2    | 8.428     | 8770363    | 412284 | 97.854 | 95.180   |
| Total| 8962707   | 433162     | 100.000 | 100.000 |

doi: 10.1038/nature08484
(R)-2-(benzhydrylamino)-2-(1-methylcyclohexyl)acetonitrile (3d):

Racemic (AD-H, 5.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (95% ee)

(R)-2-(benzhydrylamino)-2-(1-adamantyl)acetonitrile (3e):

Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (93% ee)

(R)-2-(benzhydrylamino)-2-cyclohexylacetonitrile (3f):
Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (74% ee)

(R)-2-(benzhydrylamino)-2-(4-methoxyphenyl)acetonitrile (3g):

Racemic (S,S-whelk, 2.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (99% ee)

(R)-2-(benzhydrylamino)-2-p-tolylacetonitrile (3h):

Racemic (OD-H, 5.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (98% ee)
(R)-2-(benzhydrylamino)-2-phenylacetonitrile (3i):

Racemic (OD-H, 5.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (98% ee)

(R)-2-(benzhydrylamino)-2-(4-chlorophenyl)acetonitrile (3j):

Racemic (OD-H, 5.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (98% ee)

(R)-2-(benzhydrylamino)-2-(4-(trifluoromethyl)phenyl)acetonitrile (3k):

Racemic (OD-H, 5.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (98% ee)
Racemic (OD-H, 5.0% IPA in hexanes, 1.0 mL/min)  
Enantiomerically enriched (96% ee)

(R)-4-((benzhydrylamino)(cyano)methyl)benzonitrile (3l):

Racemic (OD-H, 5.0% IPA in hexanes, 1.0 mL/min)  
Enantiomerically enriched (93% ee)

(R)-2-(benzhydrylamino)-2-(4-bromophenyl)acetonitrile (3m):

Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)  
Enantiomerically enriched (99% ee)
(R)-2-(benzhydrylamino)-2-(2-methoxyphenyl)acetonitrile (3n):

Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (88% ee)

(R)-2-(benzhydrylamino)-2-(2-bromophenyl)acetonitrile (3o):

Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)  Enantiomerically enriched (97% ee)

(R)-2-(benzhydrylamino)-2-(3-bromophenyl)acetonitrile (3p):

doi: 10.1038/nature08484
Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)           Enantiomerically enriched (92% ee)

(S)-2-(benzhydrylamino)-2-(furan-2-yl)acetonitrile (3q):

Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)           Enantiomerically enriched (93% ee)

(R)-2-(benzhydrylamino)-2-(furan-3-yl)acetonitrile (3r):

Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min)           Enantiomerically enriched (97% ee)
(S)-2-(benzhydrylamino)-2-(thiophen-2-yl)acetonitrile (3s):

(R)-2-(benzhydrylamino)-2-cyclohexenylacetonitrile (3t):

(R,E)-2-(benzhydrylamino)-3-methylhex-3-enenitrile (3u):
Racemic (AD-H, 1.0% IPA in hexanes, 1.0 mL/min) Enantiomerically enriched (91% ee)

(R,E)-2-(benzhydrylamino)-4-phenylbut-3-enenitrile (3v):

Racemic (AD-H, 3.0% IPA in hexanes, 1.0 mL/min) Enantiomerically enriched (95% ee)

(R,E)-2-(benzhydrylamino)hept-3-enenitrile (3w):

Racemic (OD-H, 2.0% IPA in hexanes, 1.0 mL/min) Enantiomerically enriched (73% ee)
Potassium cyanide-mediated synthesis of amino acids

(R)-Boc-tert-leucine

\[
\begin{align*}
\text{H}_2\text{N} \quad \text{Ph} & \quad \xrightarrow{\text{Na}_2\text{SO}_4, \text{CH}_2\text{Cl}_2, \text{rt, 1 h}} \\
\text{Ph} & \quad \text{H}_3\text{N} \quad \text{Ph}
\end{align*}
\]

Method A: A 100-mL round-bottomed flask containing a stir bar was charged with Na\textsubscript{2}SO\textsubscript{4} (8.0 g) and CH\textsubscript{2}Cl\textsubscript{2} (40 mL). Trimethylacetaldehyde\textsuperscript{43} (7.65 mL, 52 mmol, 1.3 equiv) and aminodiphenylmethane\textsuperscript{44} (6.89 mL, 40 mmol, 1.0 equiv) were added sequentially via syringe while stirring. The flask was capped with a plastic stopper, and the mixture was stirred at room temperature. The mixture became cloudy after 5 min. After stirring for 1 h, the solution was decanted into a 200-mL round-bottomed flask, rinsing with CH\textsubscript{2}Cl\textsubscript{2} (4 x 5 mL) and concentrated to 8–10 mL using a rotary evaporator. The flask was then maintained at 1 torr for 10 min. A 5-cm diameter fritted disk funnel was filled with a 2-cm high layer of silica gel. The funnel was rinsed with a solution of 20:1:0.5 hexanes/Et\textsubscript{2}O/triethylamine (50 mL) under reduced pressure, followed by a solution of 20:1 hexanes/Et\textsubscript{2}O (50 mL). The oil prepared above was dissolved in 20:1 hexanes/Et\textsubscript{2}O (25 mL) and rinsed through the frit into a tared 250-mL round-bottomed flask under reduced pressure, rinsing with 20:1 hexanes/Et\textsubscript{2}O (4 x 25 mL). The mixture was concentrated (30 torr → 1 torr) to provide a clear, pale yellow oil that solidified into a white solid. The solid was broken up into approximately 1-cm diameter pieces using a spatula, and was maintained at 1 torr for another 15 min.

\textsuperscript{43} Technical grade trimethylacetaldehyde (~75%) purchased from Alfa Aesar was used. Identical results have been obtained with reagent grade trimethylacetaldehyde on 10 mmol scale.

\textsuperscript{44} Aminodiphenylmethane was purchased from Aldrich and used as received.
to provide \(N\)-(2,2-dimethyl propylidene)diphenylmethanamine as a white solid in approximately 98% \(^1\)H-NMR purity. The product was used in the next step without further purification. Yield: 9.93 g (39.6 mmol, 99%).

Method B: A 100-mL round-bottomed flask containing a stir bar was charged with \(\text{Na}_2\text{SO}_4\) (8.0 g) and \(\text{CH}_2\text{Cl}_2\) (40 mL). Trimethylacetaldehyde\(^43\) (7.65 mL, 52 mmol, 1.3 equiv) and aminodiphenylmethane\(^45\) (6.89 mL, 40 mmol, 1.0 equiv) were added sequentially via syringe while stirring. The flask was capped with a plastic stopper, and the mixture was stirred at room temperature. The mixture became cloudy after 5 min. After stirring for 1 h, the mixture was decanted into a 200 mL round-bottomed flask, rinsing with \(\text{CH}_2\text{Cl}_2\) (4 x 5 mL), and concentrated to 8–10 mL using a rotary evaporator. The flask was then maintained at 1 torr for 10 min. The resulting pale yellow solid was taken up in \(\text{CH}_2\text{Cl}_2\) (50 mL), transferred to a 250-mL separatory funnel, and washed with \(\text{NaHCO}_3\) (50 mL). The organic layer was dried over \(\text{Na}_2\text{SO}_4\), filtered through a medium porosity fritted disk funnel into a 200-mL round-bottomed flask, and concentrated in vacuo (30 torr \(\rightarrow\) 1 torr) to provide a pale yellow oil that solidified to a white solid within 5 min at 1 torr. The solid was broken up into approximately 1-cm diameter pieces using a spatula, and was maintained at 1 torr for another 15 min to provide \(N\)-(2,2 dimethylpropylidene) diphenylmethanamine as a white solid in approximately 98% \(^1\)H-NMR purity. The product was used in the next step without further purification. Yield: 9.79 g (38.9 mmol, 97%).

This experiment was carried out as described in the Methods section.

The 100-mL round-bottomed flask containing (R)-2-(benzhydrylamino)-3,3-dimethylbutanenitrile was charged with a 2-cm long stir bar. A solution of 40 mL of aqueous HCl/H\(_2\)SO\(_4\) solution was generated as follows: a 50-mL

\(^45\) Aminodiphenylmethane used in Method B was distilled at 760 torr before use.
Erlenmeyer flask was charged with deionized water (20 mL) and cooled in an ice bath for 5 min. Concentrated hydrochloric acid (8 mL) was added over 1 min, followed by concentrated sulfuric acid (12 mL) over 5 min (in 2-mL portions). The flask was swirled gently and was allowed to cool in the ice bath for 5 min. The solution was then added to the flask containing the α-aminonitrile in one portion, and the flask was fitted with a chilled reflux condenser. The flask was placed in an oil bath that was maintained at 120 °C, and reaction mixture was stirred for 44 h.

The reaction mixture was allowed to cool to room temperature and was then cooled for 2 min in an ice bath. Water (25 mL) and Et₂O (25 mL) were carefully added over 2 min, and the entire contents of the flask were poured into a 250-mL separatory funnel. The flask was rinsed with another 25-mL portion of diethyl ether and another 5-mL portion of water, and the mixture was added to the separatory funnel. The organic and aqueous layers were thoroughly mixed, and the aqueous layer was removed. The organic layer was further extracted with water (25 mL), and the combined aqueous layers were cooled for 5 min in an ice bath within a 250-mL Erlenmeyer flask. Aqueous NaOH (4 N) was added in 10–20-mL portions over 5 min with stirring until pH 11 was reached, as determined by pH paper (approximately 120 mL total). The resulting mixture was transferred to a 500-mL separatory funnel and washed with diethyl ether (2 x 50 mL). The aqueous layer was transferred to a 500-mL Erlenmeyer flask containing a 4-cm long stirbar, acidified to pH 9.5–10.5 by addition of solid NaHCO₃ (1 g), and cooled in an ice bath for 3 min with stirring.

Dioxane (100 mL) was added, followed immediately by Boc₂O (22 g, 100 mmol, 2.5 equiv) in one portion. The flask was covered with Parafilm and allowed to warm to room temperature with stirring. The stir-rate was adjusted to ensure thorough mixing of the upper organic layer and the lower aqueous layer, and the mixture was

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46 The cooled reaction mixture is a biphasic oil with a dark brown-orange upper layer and a light orange lower layer.

47 A milky white precipitate formed after 100 mL of 4 N NaOH had been added.

48 The mixture became viscous upon addition of dioxane and partially solidified upon addition of Boc₂O.

49 Upon stirring at room temperature for 30 min, the mixture was viscous but free-flowing.
stirred at that rate for 14 h. Concentrated HCl was then added to the stirring mixture in 1-mL portions over 5 min until pH 2 was reached (10 mL total). The mixture was transferred to a 500-mL separatory funnel and extracted with Et₂O (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, decanted into a 500-mL round-bottomed flask, and concentrated under reduced pressure (30 torr → 1 torr). Benzene was added (2 x 20 mL), and the resulting solution was concentrated under reduced pressure (30 torr → 1 torr) to yield 14–16 g of a pale yellow, cloudy oil. The residue was partitioned between 1 N aqueous NaOH (100 mL) and Et₂O (75 mL) and then transferred to a 250-mL separatory funnel. The round-bottomed flask was rinsed with two 10-mL portions of 1N aqueous NaOH that were added to the separatory funnel. The organic layer was removed, and the aqueous layer was washed with another 75 mL of Et₂O.

The aqueous layer was transferred to a 250-mL Erlenmeyer flask and cooled in an ice bath for 2 min. Aqueous HCl (4 N) was added in 10-mL portions over 5 min until pH 2 was reached (40 mL total). A white precipitate formed after 35 mL of HCl had been added. The aqueous layer was extracted with diethyl ether (3 x 75 mL), and the combined organic layers were dried over Na₂SO₄, decanted into a 500-mL round-bottomed flask, and concentrated under reduced pressure (30 torr → 1 torr) to yield a white foamy solid. Hexanes (20 mL) was added to the flask, and the resulting mixture concentrated under reduced pressure. The process was repeated twice to yield a white powder that was maintained at 1 torr for 2 h. Yield: 7.04–7.51 g (30.4–32.5 mmol, 76–81% yield from aminodiphenylmethane, range of three experiments). The enantiomeric excess was determined to be 85–86 % by HPLC analysis of the benzyl ester (range of three experiments). The crude product was heated in a solution of 230–240 mL 2:1 hexanes/Et₂O (32 mL/g) for ~ 2 min. Complete dissolution did not occur. A 5-cm long stirbar was then added, the flask was capped with a plastic stopper, and the mixture was stirred at 0 °C for 2 h. The mixture was filtered through a medium porosity fritted disk funnel, and the filtrate was concentrated under reduced pressure to yield a white foamy solid. Hexanes (20 mL) was added, and the resulting mixture was concentrated to provide a white solid. Pentane (20 mL) was added, and the resulting mixture was concentrated to provide a white solid that was maintained at 1 torr for 16 h to provide (R)-Boc-tert-leucine as a white solid: 5.76–6.03 g (24.9–26.1 mmol, 62–

50 After 14 h, the pH 7–8 was reached. The reaction may be monitored as follows: A 50 μL aliquot was removed by pipette, transferred to a NMR tube, and diluted with 600 μL D₂O. ¹H-NMR analysis revealed a single resonance at 0.83 ppm, and no other resonances with greater than 5% relative integration between 0.70 and 1.05 ppm.
65% yield from aminodiphenylmethane, range of three experiments).\textsuperscript{51} The enantiomeric excess of the filtrate was determined to be 98–99% by HPLC analysis of the benzyl ester (range of three experiments); mp: 117–120 °C to 118–121 °C.\textsuperscript{52,53} \([\alpha]^{25}_D = -5.3^\circ\) (c 1.5, EtOAc). lit.\textsuperscript{54} \([\alpha]^{25}_D = + 5.8\) (c 0.6, EtOAc, (S)-enantiomer). The compound is a 6:1 mixture of carbamate rotamers in CDCl\textsubscript{3}; resonances corresponding to the minor rotamer are indicated with a * (many resonances for the minor rotamer are indistinguishable from those reported for the major rotamer, and are not reported).\textsuperscript{55,56} 1\textsuperscript{H} NMR (500 MHz, CDCl\textsubscript{3}, 25 °C), \(\delta\) 5.82 (1H, br s)*, 5.07 (1H, d, \(J = 9\) Hz), 4.12 (1H, d, \(J = 9.5\) Hz), 3.90 (1H, br s)*, 1.45 (9H, s), 1.02 (9H, s). 13\textsuperscript{C} NMR (126 MHz, CDCl\textsubscript{3}, 25 °C): \(\delta\) 177.0, 156.8*, 155.8, 81.7*, 80.1, 63.8*, 61.8, 34.6, 34.1*, 28.5, 26.7. IR (cm\textsuperscript{-1}): 3434 (br w), 3309 (w), 3169 (w), 2972 (m), 1740 (m), 1706 (s), 1686 (s), 1640 (s), 1507 (m), 1411 (s), 1368 (m), 1259 (w), 1233 (m), 1211 (w), 1156 (s), 1056 (m), 1008 (m), 650 (m), 777 (w), 690 (m). LRMS (ESI): 254.1 (70%) [M+Na]\textsuperscript{+}.

\textsuperscript{51} The primary impurity detected during optimization of this protocol is tert-butyl carbamate, which presumably originates from ammonia generated during nitrile hydrolysis. Tert-butyl carbamate may be detected by 1\textsuperscript{H}-NMR spectroscopy as a shoulder on the Or-Bu resonance of Boc-tert-leucine. Boc-tert-leucine prepared using the optimized procedure contains no detectable tert-butyl carbamate.

\textsuperscript{52} The enantiomeric excess of the benzyl ester of the precipitate was 23–29%; mp: 160–166 °C (dec.). The enantiomeric excess of the benzyl ester of a sample of commercially available Boc-L-(S)-tert-leucine (Fluka) was >99%; mp 118–122 °C.

\textsuperscript{53} The synthesis was reproduced on 0.10 mol scale using Procedure B to provide 14.4 g (62 mmol, 62% yield from aminodiphenylmethane) of Boc-D-(R)-tert-leucine as a white solid; mp: 117–120 °C. The enantiomeric excess of the product was determined to be 98.5% by HPLC analysis of the benzyl ester.

The 0.10-mol scale synthesis was executed using identical relative amounts of reagents, concentrations, and reaction times, and required a 1-L separatory funnel, round-bottomed flask, and Erlenmeyer flask.

\textsuperscript{54} Jenssen, K., Sewald, K. & Sewald, N. Synthesis of marimastat and a marimastat conjugate for affinity chromatography and surface plasmon resonance studies. Bioconjugate Chem. 15, 594–600 (2004).

\textsuperscript{55} 1\textsuperscript{H} NMR and 13\textsuperscript{C} NMR spectroscopic data for the major rotamer match previously reported data: Vernall, A. J., Steven, B. & Abell, A. D. Cross-metathesis and ring-closing metathesis reactions of amino acid-based substrates. Tetrahedron, 64, 3980–3997 (2008). The rotameric ratio was not established in this case, and spectroscopic data for the minor rotamer were not reported.

\textsuperscript{56} For a discussion on the temperature-, concentration-, and solvent-dependence of rotameric ratios of N-Boc amino acids, see: Marcovici-Mizrahi, D., Gottlieb, H. E., Marks, V. & Nudelman, A. On the stabilization of the syn-rotamer of amino acid carbamate derivatives by hydrogen bonding. J. Org. Chem. 61, 8402–8406 (1996).
Supplementary Figure 3. $^1$H NMR spectrum of (R)-Boc-tert-leucine
Supplementary Figure 4. $^{13}$C NMR spectrum of (R)-Boc-tert-leucine

Preparation of (R)-benzyl 2-(tert-butoxycarbonylamino)-3,3-dimethylbutanoate for chiral HPLC analysis:

A 2-dram vial containing a small stirbar was charged with Boc-tert-leucine (10 mg, 0.04 mmol), CH$_2$Cl$_2$ (1 mL), 4-dimethylaminopyridine (2 mg, 0.02 mmol, 0.5 equiv), benzyl alcohol (20 μL, 0.2 mmol, 5 equiv), and EDC (20 mg, 0.1 mmol, 2.5 equiv). The solution was stirred at room temperature for 3 h, and then diluted with 10 mL of diethyl ether. The mixture was washed with water (2 x 10 mL), saturated aqueous NaHCO$_3$ (10 mL), and brine (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue can be further purified by flash column chromatography on silica gel (7:1 hexanes/Et$_2$O). Both the crude and purified samples were analyzed by chiral HPLC analysis: (AD-H, 1 mL/min, 5% IPA/hexanes, 210 nm): $t_R$(major) = 9.08 min, $t_R$(minor) = 15.80 min.
Chiral HPLC analysis of benzyl 2-(tert-butoxycarbonylamino)-3,3-dimethylbutanoate

Racemic (AD-H, 1 mL/min, 5% IPA/hexanes)

| Peak# | Ret. Time | Area    | Height  | Area % | Height % |
|-------|-----------|---------|---------|--------|----------|
| 1     | 9.079     | 9478425 | 511779  | 49.539 | 64.587   |
| 2     | 15.802    | 9654664 | 280612  | 50.461 | 35.413   |
| Total |           | 19133088| 792391  | 100.000| 100.000  |

Enantiomerically enriched (98.7% ee, purified):

| Peak# | Ret. Time | Area    | Height  | Area % | Height % |
|-------|-----------|---------|---------|--------|----------|
| 1     | 9.166     | 15543130| 812275  | 99.329 | 99.656   |
| 2     | 15.980    | 105033  | 2803    | 0.671  | 0.344    |
| Total |           | 15648163| 815078  | 100.000| 100.000  |

Enantiomerically enriched (98.5% ee, crude):
(R)-2-(tert-butoxycarbonylamino)-2-(1-methylcyclohexyl)acetic acid

A flame-dried 500-mL round-bottomed flask capped with a rubber septum was charged with anhydrous CH$_2$Cl$_2$ (150 mL) via cannula and cyclohexanecarboxaldehyde$^{57}$ (9.09 mL, 75 mmol, 1.0 equiv) via syringe under N$_2$. The flask was cooled in an ice bath for 10 min, the septum was removed, and t-BuOK (10.9 g, 97.5 mmol, 1.3 equiv) was added in one portion with rapid stirring. The septum was replaced, and iodomethane (14.0 mL, 225 mmol, 3.0 equiv) was added in one portion via syringe. The mixture was stirred at 0 °C under N$_2$ for 30 min. The mixture was then allowed to warm to room temperature and stirred an additional 2 h. The resulting pale yellow, heterogeneous mixture was filtered through a 10-cm diameter medium porosity fritted disk funnel, and the cake was washed with CH$_2$Cl$_2$ (3 x 15 mL). The filtrate was washed with brine (50 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was distilled under reduced pressure (1 torr) while maintaining the receiving flask between −20 to −40 °C (bp < 30 °C). The distillate was a clear, colorless oil that contained (1-methyl)cyclohexanecarboxaldehyde and 1.25 equiv CH$_2$Cl$_2$, as determined by $^1$H-NMR analysis: 13.2 g total, ~7.2 g

$^{57}$ Cyclohexanecarboxaldehyde was purchased from Aldrich and filtered through a cotton plug before use. Alternatively, cyclohexanecarboxaldehyde may be distilled from CaH$_2$ at 760 torr.
(1-methyl)cyclohexanecarboxaldehyde (57 mmol, 76% yield). The product was used in the next step without further purification.

A 100-mL round-bottomed flask containing (1-methyl)cyclohexanecarboxaldehyde (57 mmol) was charged with CH₂Cl₂ (20 mL), Na₂SO₄ (10 g), and aminodiphenylmethane (8.83 mL, 51.3 mmol, 0.9 equiv). The flask was capped with a plastic stopper, and the mixture was stirred at room temperature for 14 h. The reaction mixture was filtered through a medium porosity fritted disk funnel, rinsing with CH₂Cl₂ (4 x 10 mL). The filtrate was concentrated under reduced pressure and maintained at 1 torr with stirring for 1 h to provide a slightly cloudy, colorless oil. A 5-cm diameter fritted disk funnel was filled with a 3-cm high layer of silica gel. The funnel was rinsed with a solution of 20:1:0.5 hexanes/diethyl ether/triethylamine (50 mL) under reduced pressure, followed by a solution of 20:1 hexanes/diethyl ether (50 mL). The oil prepared above was dissolved in 20:1 hexanes/diethyl ether (25 mL) and rinsed through the frit into a 250-mL round-bottomed flask under reduced pressure. The silica gel was rinsed with 20:1 hexanes/diethyl ether (4 x 25 mL). The combined mixture was concentrated (30 torr → 1 torr) to provide a clear, colorless oil that was slightly cloudy. The oil was maintained at 1 torr for 1 h with stirring to provide (E)-N-((1-methylcyclohexyl)methylene) diphenylmethanamine as a colorless oil with 95 % ¹H-NMR purity. Yield: 14.3 g (49.0 mmol, 96% from aminodiphenylmethane, 65% from cyclohexanecarboxaldehyde).

Caution! HCN is produced. The experiment should be executed in a well-ventilated fume hood. A 250-mL round-bottomed flask containing a 4-cm long stir bar was charged with KCN (3.26 g, 50 mmol, 2.0 equiv) and toluene (48 mL), capped with a virgin rubber septum, and cooled at 0 °C for 10 min under N₂. AcOH (1.72 mL, 30 mmol, 1.2 equiv), H₂O (2 equiv) and water (4 equiv), toluene (0.4 M), 0 °C, 4.5 h.

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For more details, see the protocol in the literature: Anderson, J. C., Denton, R. M., Hickin, H. G. & Wilson, C. Synthesis of dibenzofuran-1,4-diones using the Dotz benzannulation. *Tetrahedron* 60, 2327–2335 (2004).
equiv) and water (1.80 mL, 100 mmol, 4.0 equiv) were added sequentially via syringe, and the N₂ inlet was removed. The resulting white, heterogeneous mixture was stirred vigorously at 0 °C. After 5 min the upper organic layer had become a clear, colorless solution, and the lower aqueous layer contained a chunky, white precipitate. After stirring for 20 min, the N₂ inlet was restored, and a freshly prepared stock solution of (E)-N-((1-methylcyclohexyl)methylene)diphenylmethanamine (7.29 g, 25 mmol, 1.0 equiv) and 4e (73 mg, 0.125 mmol, 0.0050 equiv) in toluene (15 mL) was added via syringe over 1 min. The flask containing the stock solution was rinsed with additional toluene (2 x 2 mL), and the rinses were added to the reaction mixture. The N₂ inlet was removed, and the mixture was stirred at 0 °C. After 4.5 h, the reaction mixture was allowed to warm to room temperature over 5 min. The septum was removed, and the reaction mixture was treated with 50 mL of a 0.2 g/mL aqueous K₂CO₃ solution. The mixture was transferred to a 250-mL separatory funnel, the reaction flask was rinsed with Et₂O (3 x 5 mL), and the rinses were added to the separatory funnel. The organic and aqueous layers were thoroughly mixed, and the aqueous layer removed. The organic layer was washed with another 50 mL of K₂CO₃ solution and brine (50 mL). The clear, colorless organic layer was dried over Na₂SO₄, decanted into a 500-mL round-bottomed flask, rinsing with Et₂O (3 x 5 mL), and concentrated to a volume of 70 mL using a rotary evaporator. The flask was then charged with a 2-cm long stir bar, placed in a 25 °C water bath, and concentrated to a volume of approximately 10 mL by vacuum transfer into a −78 °C bath. A sample of the clear, colorless liquid residue was analyzed by chiral HPLC analysis (AD-H, 1 mL/min, 5% IPA/hexanes, 220 nm), t_R(minor) = 5.18 min, t_R(major) = 5.81 min., 89–90% ee (range of two experiments). The liquid was transferred to a 200-mL round-bottomed flask, rinsing with CH₂Cl₂ (3 x 4 mL). The solution was concentrated under reduced pressure (~30 torr → 1 torr). The resulting viscous oil was dissolved in CH₂Cl₂ (2 x 20 mL), and the resulting solution concentrated under reduced pressure (~30 torr → 1 torr) to a mass of 8.6–8.7 g. The crude (R)-2-(benzhydrylamino)-2-(1-methylcyclohexyl)acetonitrile was used in the next step without further purification.

59 The aqueous layers were disposed in a waste container that was maintained at basic pH and stored in a fume hood.

60 ¹H-NMR analysis of the clear, colorless oil revealed <20 mol % remaining toluene. Samples that contained more toluene provided slightly lower overall yield in the amino acid synthesis. Removal of toluene from the viscous α-aminonitrile is slow, but addition of CH₂Cl₂ accelerates this process.
The 200-mL round-bottomed flask containing (R)-2-(benzhydrylamino)-3,3-dimethylbutanenitrile was charged with a 4-cm long stirbar. A solution of 60 mL of aqueous 3:1 HCl/H2SO4 solution was generated as follows: a 125-mL Erlenmeyer flask was charged with deionized water (30 mL) and cooled in an ice bath for 5 min. Concentrated hydrochloric acid (7.5 mL) was added over 1 min, followed by concentrated sulfuric acid (22.5 mL) over 5 min (in 2-mL portions). The flask was swirled gently, and was allowed to further cool in the ice bath for 5 min. The solution was then added to the flask containing the α-aminonitrile in one portion, and the flask was fitted with a chilled reflux condenser. The flask was placed in an oil bath that was maintained at 120 °C, and reaction mixture was stirred for 68 h.

The flask was cooled to room temperature to yield a dark brown mixture, and then further cooled for 2 min in an ice bath. Water (50 mL) and diethyl ether (50 mL) were carefully added over 2 min to provide a black upper organic layer and an orange lower aqueous layer. The entire contents of the flask were poured into a 500-mL separatory funnel. The flask was rinsed with another 50-mL portion of diethyl ether and another 50-mL portion of water, and the mixture was added to the separatory funnel. The organic and aqueous layers were thoroughly mixed, and the aqueous layer was removed. The aqueous layer was further washed with diethyl ether (50 mL), and the combined aqueous layers were cooled for 5 min in an ice bath within a 1-L Erlenmeyer flask. Aqueous NaOH (4 N) was added in 10–20-mL portions over 5 min with stirring until pH 10–11 was reached, as determined by pH paper (approximately 190 mL total). The resulting mixture was transferred to a 1-L separatory funnel and washed with diethyl ether (3 x 50 mL). The aqueous layer was transferred to a 1-L Erlenmeyer flask containing a 5-cm long stirbar, acidified to pH 9.5–10.5 by addition of solid NaHCO3 (1 g), and cooled in an ice bath for 3 min with stirring.

Dioxane (100 mL) was added to the mixture prepared above, followed immediately by Boc2O (16.4 g, 75 mmol, 3.0 equiv) in one portion. The flask was covered with Parafilm and allowed to warm to room temperature with

61 The last 30 mL were added in 5-mL portions, and the mixture was thoroughly mixed after each portion had been added. The pH was checked after each addition to ensure that excess NaOH was not added.

62 The first and second ethereal washes were clear, yellow solutions. The third wash was a clear, nearly colorless solution.

63 The mixture became viscous upon addition of dioxane, and partially solidified upon addition of Boc2O.
The stir-rate was adjusted to ensure thorough mixing of the upper organic layer and the lower aqueous layer, and the mixture was stirred at that rate for 14 h. After 14 h, the pH 7 was reached. Concentrated HCl was carefully added to stirring mixture in 1-mL portions over 5 min until pH 2 was reached, as determined using pH paper (10 mL total). The mixture was transferred to a 1-L separatory funnel and extracted with Et<sub>2</sub>O (3 x 100 mL). The aqueous layer was viscous but free-flowing, and the organic layer was a clear, colorless solution. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, decanted into a 500-mL round-bottomed flask, and concentrated under reduced pressure (30 torr → 1 torr). Benzene was added (3 x 20 mL), and the resulting solution concentrated under reduced pressure (30 torr → 1 torr) to yield 12.5 g of a slightly yellow, cloudy oil. The residue was partitioned between 1 N aqueous NaOH (100 mL) and diethyl ether (75 mL) and transferred to a 250-mL separatory funnel. The round-bottomed flask was rinsed with two 10-mL portions of 1N aqueous NaOH that were added to the separatory funnel. The organic layer was removed, and the aqueous layer was washed with another 75 mL diethyl ether.

The aqueous layer was transferred to a 250-mL Erlenmeyer flask and cooled in an ice bath for 2 min. Aqueous HCl (4 N) was added in 10-mL portions over 5 min until pH ~ 2 was reached (40 mL total). A white precipitate formed after 35 mL of HCl solution had been added. The aqueous layer was extracted with diethyl ether (3 x 75 mL), and the combined clear, colorless organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, decanted into a 500-mL round-bottomed flask, and concentrated under reduced pressure (30 torr → 1 torr) to yield a white foamy solid. Benzene (2 x 20 mL) was added to the flask, and the resulting mixture was was concentrated under reduced pressure. The process was repeated with hexanes (4 x 20 mL) to yield a white powder that was maintained at 1 torr for 1 h. Yield: 4.30–4.33 g (15.8–16.0 mmol, 63–64% yield from imine). The enantiomeric excess was determined to be 87–88 % by HPLC analysis of the benzyl ester (range of two experiments).

The crude product was heated in a solution of 170 mL of 3:1 hexanes/Et<sub>2</sub>O for 2 min. Complete dissolution did not occur. A 5-cm long stirbar was then added, the flask was capped with a plastic stopper, and the mixture was stirred at 0 °C for 2h. The mixture was filtered through a medium porosity fritted funnel and the filtrate was concentrated under reduced pressure to yield a white foamy solid. Hexanes (3 x 20 mL) was added, and the resulting mixture was concentrated to provide a white solid. Pentane (20 mL) was added, and the resulting mixture was concentrated to

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64 Upon stirring at room temperature for 30 min, the mixture was viscous but free-flowing.
provide a white solid that was maintained at 1 torr for 6 h to provide \((R)-2-(\text{tert}-\text{butoxycarbonylamino})-2-(1\text{-methylcyclohexyl})\text{acetic acid as a white powder}: 3.43–3.52 \text{ g (12.6–13.0 mmol, 51–52\% yield from imine, range of two experiments)}; \text{mp 127–130 °C to 128–130 °C. The enantiomeric excess of the filtrate was determined to be 98–99 \% by HPLC analysis of the benzyl ester (see below).} \text{ 1H-NMR analysis revealed \~{}1 mass \% residual hexanes/pentane.\textsuperscript{65} \[\alpha\text{D}^{25} = -15.2^\circ \text{ (c 1.5, EtOAc). The compound exists as a 10:1 mixture of carbamate rotamers in CDCl}_3;} \text{ resonances corresponding to the minor rotamer are indicated with a * (resonances that are indistinguishable from those corresponding to the major rotamer are not reported).} \text{ 1H NMR (500 MHz, CDCl}_3, 25 \text{ °C), }\delta \text{ 5.60 (1H, br s)*, 5.04 (1H, d, } J = 9 \text{ Hz), 4.30 (1H, d, } J = 9 \text{ Hz), 4.08 (1H, br s)*, 1.60–1.32 (10H, m), 1.45 (9H, s), 0.95 (3H, s).} \text{ 13C NMR (126 MHz, CDCl}_3, 25 \text{ °C): }\delta \text{ 177.2, 156.7*, 155.8, 81.6*, 80.1, 62.4*, 60.7, 37.2, 36.8*, 34.9, 34.7, 28.5, 26.0, 21.8, 21.7, 20.5. IR (cm}^{-1}\text{): 3432 (w), 3312 (m), 2935 (m), 1737 (m), 1704 (s), 1640 (m), 1502 (m), 1409 (s), 1367 (m), 1231 (m), 1156 (s), 1026 (m), 844 (m), 777 (w), 685 (m). LRMS (ESI): 294.2 (100\%) [M+Na]^{+}.} \text{\textsuperscript{65} The enantiomeric excess of the benzyl ester of the precipitate was 35–36\%.}
Supplementary Figure 5. $^1$H NMR spectrum of (R)-2-(tert-butoxycarbonylamino)-2-(1-methylcyclohexyl)acetic acid
Supplementary Figure 6. $^{13}$C NMR spectrum of (R)-2-(tert-butoxycarbonylamino)-2-(1-methylcyclohexyl)acetic acid

Preparation of (R)-benzyl 2-(tert-butoxycarbonylamino)-2-(1-methylcyclohexyl)acetate for chiral HPLC analysis:

A 2-dram vial containing a small stir bar was charged with (R)-2-(tert-butoxycarbonylamino)-2-(1-methylcyclohexyl)acetic acid (11 mg, 0.04 mmol), CH$_2$Cl$_2$ (1 mL), 4-dimethylaminopyridine (2 mg, 0.02 mmol, 0.5 equiv), benzyl alcohol (20 μL, 0.2 mmol, 5 equiv), and EDC (20 mg, 0.1 mmol, 2.5 equiv). The solution was stirred at room temperature for 3 h, and then diluted with 10 mL Et$_2$O. The mixture was washed with water (2 x 10 mL), saturated aqueous NaHCO$_3$ (10 mL), and brine (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (7:1 hexanes/Et$_2$O).
and analyzed by chiral HPLC analysis: (AS-H, 1 mL/min, 2% IPA/hexanes, 210 nm): \( t_R(\text{minor}) = 6.84 \text{ min} \), 
\( t_R(\text{major}) = 8.13 \text{ min} \).

**Chiral HPLC analysis of Benzyl 2-(tert-butoxycarbonylamino)-2-(1-methylcyclohexyl)acetate**

Racemic (AS-H, 1 mL/min, 2% IPA/hexanes):

| Peak# | Ret. Time | Area       | Height   | Area %  | Height %  |
|-------|-----------|------------|----------|---------|-----------|
| 1     | 6.839     | 11550874   | 783826   | 50.985  | 56.347    |
| 2     | 8.115     | 11104706   | 607239   | 49.015  | 43.653    |
| Total |           | 22655580   | 1391065  | 100.000 | 100.000   |

Enantiomerically enriched (98.7% ee):

| Peak# | Ret. Time | Area     | Height | Area %  | Height %  |
|-------|-----------|----------|--------|---------|-----------|
| 1     | 6.862     | 90881    | 6480   | 0.655   | 0.862     |
| 2     | 8.128     | 13779918 | 744963 | 99.345  | 99.138    |
| Total |           | 13870798 | 751443 | 100.000 | 100.000   |

**(R)-2-(tert-butoxycarbonylamino)-3-ethyl-3-methylpentanoic acid**

![Chemical reaction](image)
An oven-dried 500-mL round-bottomed flask capped with a rubber septum was charged with anhydrous CH$_2$Cl$_2$ (250 mL) and 2-ethylbutyraldehyde$^{66}$ (12.3 mL, 100 mmol, 1.0 equiv) via syringe under N$_2$. The flask was cooled in an ice bath for 10 min, the septum was removed, and t-BuOK (14.6 g, 130 mmol, 1.3 equiv) was added in one portion with rapid stirring. The septum was replaced, and iodomethane (18.7 mL, 300 mmol, 3.0 equiv) was added in one portion via syringe. The mixture was stirred at 0 °C for 30 min. The mixture was then stirred at room temperature for 2 h. The resulting slightly yellow, heterogeneous mixture was filtered through a 10-cm diameter medium porosity fritted disk funnel, and the cake was washed with CH$_2$Cl$_2$ (3 x 15 mL). The filtrate was washed with brine (50 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was distilled under reduced pressure (~1 torr) while maintaining the receiving flask between −20 to −40 °C (bp <30 °C). The distillate (13.5 g) was a clear, colorless oil that contained CH$_2$Cl$_2$ (0.3 equiv) and t-BuOH (0.2 equiv), and was used without further purification. The purity of the compound was assessed by $^1$H NMR spectroscopy (400 MHz, CDCl$_3$): δ 9.42 (1H, s), 5.30 (0.64 H, s, CH$_2$Cl$_2$), 1.58–1.45 (4H, m), 1.27 (1.97H, s, t-BuOH), 0.98 (3H, s), 0.81 (6H, t, $J$ = 8 Hz).

A 100-mL round-bottomed flask containing crude 2-ethyl-2-methylbutanal was charged with CH$_2$Cl$_2$ (20 mL) and Na$_2$SO$_4$ (10 g). Aminodiphenylmethane (8.83 mL, 80 mmol, 0.80 equiv) was added via syringe. The flask was capped with a plastic stopper, and the mixture was stirred at room temperature for 14 h. The reaction mixture was filtered through a medium porosity fritted disk funnel and rinsed with CH$_2$Cl$_2$ (4 x 10 mL). The filtrate was concentrated under reduced pressure and maintained at 1 torr with stirring for 1 h to provide a slightly cloudy, colorless oil. A 5-cm diameter fritted disk funnel was filled with a 3-cm high layer of silica gel. The funnel was rinsed with a solution of 20:1:0.5 hexanes/Et$_2$O/triethylamine (50 mL) under reduced pressure, followed by a solution of 20:1 hexanes/Et$_2$O (50 mL). The oil prepared above was dissolved in 20:1 hexanes/Et$_2$O (25 mL) and rinsed through the frit into a 250-mL round-bottomed flask under reduced pressure, rinsing with 20:1 hexanes/Et$_2$O (4 x 25 mL). The mixture was concentrated under reduced pressure (30 torr → 1 torr) to provide a clear, colorless

$^{66}$ 2-Ethylbutyraldehyde (~92 %) was purchased from Aldrich and used without further purification.
oil that was slightly cloudy. The oil was maintained at 1 torr for 1 h while stirring to provide \((E)\)-N-(2-ethyl-2-methylbutylidene)diphenylmethanamine in 95 % $^1$H-NMR purity.$^{67}$ Yield: 18.7 g (67 mmol, 84% from aminodiphenylmethane, 67% from 2-ethyl-2-butanal).

![Chemical structure](image)

\textit{Caution! HCN is produced. The experiment should be executed in a well-ventilated fume hood.} A 250-mL round-bottomed flask containing a 4-cm long stir bar was charged with KCN (3.26 g, 50 mmol, 2.0 equiv) and toluene (48 mL), capped with a virgin rubber septum, and cooled at 0 °C for 10 min under N$_2$. AcOH (1.72 mL, 1.2 equiv, 30 mmol) and water (1.80 mL, 4.0 equiv, 160 mmol) were added sequentially via syringe, and the N$_2$ inlet was removed. The resulting white, heterogeneous mixture was stirred vigorously at 0 °C. After 5 min the upper organic layer had become a clear, colorless solution, and the lower aqueous layer contained a chunky, white precipitate. After stirring for 20 min, the N$_2$ inlet was restored, and a freshly prepared stock solution of \((E)\)-N-(2-ethyl-2-methylbutylidene)diphenylmethanamine (6.90 g, 25 mmol, 1.0 equiv) and 4e (73 mg, 0.125 mmol, 0.0050 equiv) in toluene (15 mL) was added via syringe over 1 min. The stock solution was rinsed with additional toluene (2 x 2 mL). The N$_2$ inlet was removed, and the mixture was stirred at 0 °C. After an additional 6 h, the reaction mixture was allowed to warm to room temperature for 5 min. The septum was removed, and the reaction mixture was treated with 50 mL of a 0.2 g/mL aqueous K$_2$CO$_3$ solution. The mixture was transferred to a 250-mL separatory funnel, the reaction flask was rinsed with Et$_2$O (3 x 5 mL), and the rinses were added to the separatory funnel. The organic and aqueous layers were thoroughly mixed, and the aqueous layer removed. The organic layer was washed with another 50 mL of K$_2$CO$_3$ solution and brine (50 mL).$^{68}$ The clear, colorless organic layer was dried over Na$_2$SO$_4$, decanted into a 500-mL round-bottomed flask, rinsing with Et$_2$O (3 x 5 mL), and concentrated at ~30 torr to a volume of approximately 70 mL using a rotary evaporator. The flask was then charged with a 2-cm long stir bar, placed in a 25 °C water bath, and concentrated to a volume of 10 mL by vacuum transfer into a –78 °C bath. A

$^{67}$ Characterization data for \((E)\)-N-(2-ethyl-2-methylbutylidene)diphenylmethanamine are provided above.

$^{68}$ The aqueous layers were disposed in a waste container that was maintained at basic pH and stored in a fume hood.
sample of the clear, colorless liquid residue was analyzed by chiral HPLC analysis (AS-H, 1 mL/min, 1% IPA/hexanes, 220 nm): 88% ee. The liquid was transferred to a 200-mL round-bottomed flask, rinsing with CH₂Cl₂ (3 x 4 mL). The solution was concentrated under reduced pressure (~30 torr → 1 torr). The residue was dissolved in CH₂Cl₂ (2 x 20 mL), and the resulting solution concentrated under reduced pressure (~30 torr → 1 torr) to a mass of 8.5 g of a colorless oil (ca. 90% ¹H-NMR purity). The crude (S)-2-(benzhydrylamino)-3-ethyl-3-methylpentanenitrile was used in the next step without further purification. ⁶⁹

The 200-mL round-bottomed flask containing (R)-2-(benzhydrylamino)-3-ethyl-3-methylpentanenitrile was charged with a 4-cm long stirbar. A solution of 60 mL of aqueous HCl/H₂SO₄ solution was generated as follows: a 125-mL Erlenmeyer flask was charged with deionized water (30 mL) and cooled in an ice bath for 5 min. Concentrated hydrochloric acid (7.5 mL) was added over 1 min, followed by concentrated sulfuric acid (22.5 mL) over 5 min (in 2-mL portions). The flask was swirled gently and was allowed to further cool in the ice bath for 5 min. The solution was then added to the flask containing the α-aminonitrile in one portion, and the flask was fitted with a chilled reflux condenser. The flask was placed in an oil bath that was maintained at 120 °C, and reaction mixture was stirred for 68 h.

After 68h, the flask was cooled to room temperature to yield a dark brown mixture that was further cooled in an ice bath for 2 min. Water (50 mL) and diethyl ether (50 mL) were carefully added over 2 min to provide a dark orange organic layer and a light orange lower aqueous layer. The entire contents of the flask were poured into a 500-mL separatory funnel. The flask was rinsed with another 50-mL portion of diethyl ether and another 50-mL portion of water, and the mixture was added to the separatory funnel. The organic and aqueous layers were thoroughly mixed, and the aqueous layer was removed. The organic layer was further washed with diethyl ether (50 mL), and the combined aqueous layers were cooled for 5 min in an ice bath within a 1-L Erlenmeyer flask. Aqueous NaOH (4 N) was added in 10–20-mL portions over 5 min with stirring until pH ~ 12–13 was reached, as determined by pH paper.

⁶⁹ Characterization data for (S)-2-(benzhydrylamino)-3-ethyl-3-methylpentanenitrile are provided above.
The resulting mixture was transferred to a 1-L separatory funnel and washed with diethyl ether (2 x 50 mL). The aqueous layer was transferred to a 1-L Erlenmeyer flask containing a 5-cm long stirbar, acidified to pH 9.5–10.5 by addition of solid NaHCO₃ (1 g), and cooled in an ice bath for 3 min with stirring.

Dioxane (100 mL) was added, followed immediately by Boc₂O (16.4 g) in one portion. The mixture became viscous upon addition of dioxane and partially solidified upon addition of Boc₂O. The flask was covered with Parafilm and allowed to warm to room temperature while stirring. Upon stirring at room temperature for 30 min, the mixture was viscous but free-flowing. The stir-rate was adjusted to ensure thorough mixing of the upper organic layer and the lower aqueous layer, and the mixture was stirred at that rate for 14 h. After 14 h, the pH 7 was reached. Concentrated HCl was carefully added to stirring mixture in 1-mL portions over 5 min until pH 2 was reached, as determined by pH paper (~10 mL total). The mixture was transferred to a 1-L separatory funnel and extracted with Et₂O (3 x 100 mL). The aqueous layer was viscous but free-flowing, and the organic layer was a clear, colorless solution. The combined organic layers were dried over Na₂SO₄, decanted into a 500-mL round-bottomed flask, and concentrated under reduced pressure (30 torr → 1 torr). Benzene was added (3 x 20 mL), and the resulting solution was concentrated under reduced pressure (30 torr → 1 torr) to yield 10 g of viscous yellow solid. The residue was partitioned between 1 N aqueous NaOH (100 mL) and diethyl ether (75 mL) and transferred to a 250-mL separatory funnel. The round-bottomed flask was rinsed with two 10-mL portions of 1N aqueous NaOH that were added to the separatory funnel. The aqueous layer was removed, and the organic layer was washed with 0.5 N NaOH (50 mL).

The aqueous layer was transferred to a 250-mL Erlenmeyer flask and cooled in an ice bath for 2 min. Aqueous HCl (4 N) was added in 10-mL portions over 5 min until pH 2 was reached (40 mL total). A white precipitate formed after 35 mL of HCl solution had been added. The aqueous layer was extracted with diethyl ether (3 x 75 mL), and the combined clear, colorless organic layers were dried over Na₂SO₄, decanted into a 500-mL round-bottomed flask, and concentrated under reduced pressure (~30 torr → 1 torr) to yield 5.5 g of a white foamy solid that was maintained at 1 torr for 30 min.

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70 The last 30 mL were added in 5-mL portions, and the mixture was thoroughly mixed after each portion had been added. The pH was checked after each addition to ensure that excess NaOH was not added.
The foamy solid was dissolved in diethyl ether (150 mL), and t-BuNH₂ (2.5 mL) was added via syringe. A white precipitate formed, the flask was placed in an ice bath, and the mixture was stirred for 45 min. The mixture was filtered through a 10-cm diameter Buchner funnel, rinsing with ice cold Et₂O (3 x 25 mL). The white precipitate was transferred to a 500-mL round-bottomed flask and maintained at 1 torr for 2 h (6.1 g, 18.3 mmol). The product was taken up in THF (100 mL), heated to reflux, and treated with EtOH in 1–2-mL portions until the solid dissolved completely (~15 mL EtOH total). The flask was capped with a plastic stopper and allowed to cool to room temperature for 30 min. The flask was transferred to a 4 °C refrigerator and maintained at that temperature for 16 h. The fluffy white precipitate was isolated by filtration on a 10-cm diameter Buchner funnel, rinsing with ice cold THF (3 x 25 mL). The precipitate was transferred to a 200-mL round-bottomed flask and maintained at 1 torr for 4 h. Yield: 3.96–4.23 g (11.9–12.7 mmol, 48–51% yield from imine). The enantiomeric excess was determined to be 98–99% by HPLC analysis of the benzyl ester (range of two experiments).

The free acid was isolated by partitioning the salt (100 mg) between aqueous 1 N HCl (10 mL) and diethyl ether (10 mL). The organic layer was washed with brine (10 mL), dried over Na₂SO₄, and concentrated in vacuo to provide (R)-2-(tert-butoxycarbonylamino)-3-ethyl-3-methylpentanoic acid as a viscous, colorless oil (> 90% recovery). 

\[ \delta_{25}^{D} = -11.6^\circ \text{ (c 2.0, EtOAc).} \] The compound exists as a 6:1 mixture of rotamers in CDCl₃; resonances corresponding to the minor rotamer are indicated with a * (many resonances for the minor rotamer are indistinguishable from those reported for the major rotamer, and are not reported). ¹H NMR (500 MHz, CDCl₃): δ 5.63 (1H, br s)*, 5.00 (1H, d, J = 9.5 Hz), 4.31 (1H, d, J = 9.0 Hz), 4.08 (1H, br s)*, 1.44 (9H, s), 1.41–1.38 (4H, m), 0.90 (3H, s), 0.88–0.84 (6H, m). ¹³C {¹H} NMR (100 MHz, CDCl₃): δ 177.7, 156.6*, 155.8, 81.6*, 80.1, 60.4*, 58.8, 39.7, 39.3*, 28.5, 28.3, 27.9, 20.3. IR (cm⁻¹): 2971 (m), 1709 (s), 1656 (s), 1503 (m), 1395 (m), 1368 (m), 1244 (w), 1161 (s), 909 (m), 731 (m). LRMS (ESI): 282.2 (100%) [M+Na]⁺.
Supplementary Figure 7. $^1$H NMR spectrum of (R)-2-(tert-butoxycarbonylamino)-3-ethyl-3-methylpentanoic acid
Supplementary Figure 8. $^{13}$C NMR spectrum of ($R$)-2-((tert-butoxycarbonylamino)-3-ethyl-3-methylpentanoic acid.

Preparation of ($R$)-benzyl 2-((tert-butoxycarbonylamino)-3-ethyl-3-methylpentanoate for chiral HPLC analysis

A 2-dram vial containing a small stir bar was charged with ($R$)-2-((tert-butoxycarbonylamino)-3-ethyl-3-methylpentanoic acid (10 mg, 0.04 mmol), CH$_2$Cl$_2$ (1 mL), 4-dimethylaminopyridine (2 mg, 0.02 mmol, 0.5 equiv), benzyl alcohol (20 μL, 0.2 mmol, 5 equiv), and EDC (20 mg, 0.1 mmol, 2.5 equiv). The solution was stirred at room temperature for 3 h, and then diluted with 10 mL Et$_2$O. The mixture was washed with water (2 x 10 mL), saturated aqueous NaHCO$_3$ (10 mL), and brine (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (7:1 hexanes/Et$_2$O).
and analyzed by chiral HPLC analysis: (AD-H, 1 mL/min, 5% IPA/hexanes, 210 nm): $t_R(\text{major}) = 10.42$ min, $t_R(\text{minor}) = 12.87$ min.

**Chiral HPLC analysis of (R)-benzyl 2-(tert-butoxycarbonylamino)-3-ethyl-3-methylpentanoate**

Racemic (AD-H, 1 mL/min, 5% IPA/hexanes):

Enantiomerically enriched (97.9% ee):

| Peak# | Ret. Time | Area   | Height | Area % | Height % |
|-------|-----------|--------|--------|--------|----------|
| 1     | 10.420    | 11489257 | 518734 | 50.150 | 57.352   |
| 2     | 12.872    | 11420473 | 385733 | 49.850 | 42.648   |
| Total |           | 22909730 | 904468 | 100.000| 100.000  |

| Peak# | Ret. Time | Area   | Height | Area % | Height % |
|-------|-----------|--------|--------|--------|----------|
| 1     | 10.802    | 15952163 | 692582 | 98.959 | 99.156   |
| 2     | 13.330    | 167783  | 5893  | 1.041  | 0.844    |
| Total |           | 16119946 | 698475 | 100.000| 100.000  |
Calculation of intermediate in imine hydrocyanation mechanism

Calculations were executed using the Gaussian 03 program\textsuperscript{71} at the B3LYP/6-31G(d) level of density functional theory. The structure shown below is an intermediate on the potential energy surface leading to (R)-3a (left) that directly precedes the C–C bond forming step. The catalyst structure used in this calculation is an analogue of 4e in which the trifluoromethyl groups have been replaced with protons. The structure was characterized by harmonic frequency calculation and shown to have no imaginary frequencies.

\textbf{Supplementary Table 1.} Coordinates of calculated intermediate in imine hydrocyanation mechanism

\begin{verbatim}
N   -3.62351300  -1.60701800  -0.98824600  
H   -3.62272100  -0.61778900  -1.27926500  
C   -2.41733300  -2.21975000  -1.16298300  
N   -1.52241500  -1.38473100  -1.77411600  
H   -1.80668000  -0.40561900  -1.87265300  
S   -2.01081400  -3.80420000  -0.69691900  
N   -0.43640600   2.28657000   0.49130900  
C   -1.28193600   2.52103900   1.42578000  
H   -0.21638600   1.31250200   0.20453700  
C   -2.65801500   2.28041200  -1.80540000  
N   -3.01824600   1.17097400  -1.62777900  
C    0.17974500   3.31507400  -0.40898700  
H   -0.27226700   3.06698400  -1.37646300  
\end{verbatim}

\textsuperscript{71} Gaussian 03, Revision E.01, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Montgomery, Jr., J. A., Vreven, T., Kudin, K. N., Burant, J. C., Millam, J. M., Iyengar, S. S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G. A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J. E., Hratchian, H. P., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Ayala, P. Y., Morokuma, K., Voth, G. A., Salvador, P., Dannenberg, J. J., Zakrzewski, V. G., Dapprich, S., Daniels, A. D., Strain, M. C., Farkas, O., Malick, D. K., Rabuck, A. D., Raghavachari, K., Foresman, J. B., Ortiz, J. V., Cui, Q., Baboul, A. G., Clifford, S., Cioslowski, J., Stefanov, B. B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R. L., Fox, D. J., Keith, T., Al-Laham, M. A., Peng, C. Y., Nanayakkara, A., Challacombe, M., Gill, P. M. W., Johnson, B., Chen, W., Wong, M. W., Gonzalez, C., & Pople, J. A., Gaussian, Inc., Wallingford CT, 2004.
|    | x       | y       | z       |
|----|---------|---------|---------|
| C  | -0.148548 | -1.729230 | -2.079643 |
| H  | -0.126265 | -2.812751 | -2.174376 |
| C  | 0.304969  | -1.144346 | -3.467883 |
| C  | 0.753909  | -1.281821 | -0.907058 |
| O  | 0.638407  | -0.129740 | -0.449271 |
| N  | 1.674542  | -2.146027 | -0.398777 |
| C  | 1.800164  | -3.554068 | -0.796133 |
| H  | 2.279896  | -4.097936 | 0.018412  |
| H  | 0.813793  | -3.995201 | -0.950816 |
| H  | 2.417548  | -3.669117 | -1.692655 |
| C  | 2.591173  | -1.647226 | 0.654793  |
| H  | 2.479516  | -0.561122 | 0.609890  |
| H  | -1.490674 | 3.571116  | 1.622404  |
| C  | 1.684207  | 3.109451  | -0.481795 |
| C  | 2.337141  | 3.386093  | -1.689468 |
| C  | 2.444530  | 2.709274  | 0.623530  |
| C  | 3.723330  | 3.271803  | -1.789399 |
| H  | 1.755028  | 3.693640  | -2.553446 |
| C  | 1.684207  | 3.109451  | -0.481795 |
| C  | 2.337141  | 3.386093  | -1.689468 |
| C  | 2.444530  | 2.709274  | 0.623530  |
| C  | 3.723330  | 3.271803  | -1.789399 |
| H  | 4.409730  | 2.276592  | 1.389084  |
| C  | 5.555931  | 2.784182  | -0.757946 |
| C  | -0.242534  | 4.737756  | -0.053965 |
| C  | -1.427689  | 5.242993  | -0.612766 |
| C  | 0.513955  | 5.547474  | 0.804396  |
| C  | -1.842206  | 6.541402  | -0.313202 |
| H  | -2.019723  | 4.594875  | -1.258138 |
| C  | 0.918040  | 6.843853  | 1.102794  |
| C  | 1.444000  | 5.175677  | 1.223933  |
| C  | -1.085391  | 7.344083  | 0.543012  |
| C  | -2.757930  | 6.925892  | -0.750458 |
| H  | 0.689053  | 7.465377  | 1.764580  |
| H  | -1.408874  | 8.356306  | 0.771078  |
| C  | 2.168432  | -2.080864 | 2.061160  |
| C  | 0.976411  | -2.772436 | 2.306831  |
| C  | 2.964862  | -1.709150 | 3.156549  |
| C  | 0.600285  | -3.099816 | 3.613504  |
| H  | 0.324336  | -3.050994 | 1.484223  |
| C  | 2.587133  | -2.030549 | 4.458935  |
| H  | 3.892658  | -1.168881 | 2.985381  |
| C  | 1.402197  | -2.733278 | 4.692930  |
| C  | -0.326642  | -3.642538 | 3.778456  |
| H  | 3.220198  | -1.734171 | 5.291535  |
| H  | 1.108845  | -2.989968 | 5.707415  |
| C  | 4.043394  | -1.964858 | 0.287526  |
| C  | 4.698118  | -1.129338 | -0.629252 |
| C  | 4.735983  | -3.069674 | 0.798345  |
| C  | 6.006699  | -1.394776 | -1.031990 |
| H  | 4.177662  | -0.260334 | -1.024508 |
| C  | 6.046685  | -3.337088 | 0.397523  |
| H  | 4.254747  | -3.718475 | 1.524209  |
| C  | 6.685700  | -2.502391 | -0.519810 |
| H  | 6.497448  | -0.734090 | -1.741984 |
| H  | 6.567600  | -4.199502 | 0.805072  |
