Asymmetric Synthesis of γ-Branched Amines \textit{via} Rhodium-Catalyzed Reductive Amination

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Supplementary methods

General Experimental Information: All reactions were carried out in flame-dried (or oven-dried at 140 °C for at least 2 h) glassware under an atmosphere of nitrogen unless otherwise indicated. Nitrogen was dried using a drying tube equipped with Drierite™ unless otherwise noted. Air- and moisture-sensitive reagents were handled in a nitrogen-filled glovebox (working oxygen level ~ 0.1 ppm). Column chromatography was performed with 1) basic aluminium oxide from ACROS Organics (50-200 μm, 60 A), Brockmann I grade, activated upon addition of certain amount of water according to the substrates, dry loading of activated aluminium oxide was applied followed by flush with eluent to get rid of air bubbles; 2) silica gel from Grace Davison Discovery Sciences (35-75 μm) with a column mixed as a slurry with the eluent and was packed, rinsed, and run under air pressure. Analytical thin-layer chromatography (TLC) was performed on precoated glass silica gel plates (by EMD Chemicals Inc.) with F254 indicator. Visualization was either by short wave (254 nm) ultraviolet light, or by staining with potassium permanganate followed by brief heating on a hot plate or by a heat gun. Distillations were performed using a 3 cm short-path column under reduced pressure or by using a Hickman still at ambient pressure.

Instrumentation: 1H NMR and 13C NMR were recorded on a Varian Unity 400/500 MHz (100/125 MHz respectively for 13C) or a VXR-500 MHz spectrometer. Spectra were referenced using either CDCl3 or C6D6 as solvents (unless otherwise noted) with the residual solvent peak as the internal standard (1H NMR: δ 7.26 ppm, 13C NMR: δ 77.00 ppm for CDCl3 and 1H NMR: δ 7.15 ppm, 13C NMR: δ 128.60 ppm for C6D6). Chemical shifts were reported in parts per million and multiplicities are as indicated: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). Coupling constants, J, are reported in Hertz and integration is provided, along with assignments, as indicated. Analysis by Gas Chromatography-Mass Spectrometry (GC-MS) was performed using a Shimadzu GC-2010 Plus Gas chromatograph fitted with a Shimadzu GCMS-QP2010 SE mass spectrometer using electron impact (EI) ionization after analytes traveled through a SHRXI–5MS- 30m x 0.25 mm x 0.25 μm column using a helium carrier gas. Data are reported in the form of m/z (intensity relative to base peak = 100). Gas Chromatography (GC) was performed on a Shimadzu GC-2010 Plus gas chromatograph with SHRXI–MS- 15m x 0.25 mm x 0.25 μm column with nitrogen carrier gas and a flame ionization detector (FID). Enantiomeric ratios were measured on Shimadzu Prominence HPLC system with SPD-M20A UV/VIS Photodiode array detector using Chiralpak IA-3, IB-3, IC-3, ID-3 or Chiralcel OJ-H columns. Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at University of Illinois at Urbana-Champaign. The glove box, MBraun LABmaster sp, was maintained under nitrogen atmosphere. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Materials: Solvents used for extraction and column chromatography were reagent grade and used as received. Reaction solvents tetrahydrofuran (Fisher, unstabilized HPLC ACS grade), diethyl ether (Fisher, BHT stabilized ACS grade), methylene chloride (Fisher, unstabilized HPLC grade), dimethoxyethane (Fisher, certified ACS), toluene (Fisher, optima ACS grade), 1,4-dioxane (Fisher, certified ACS), acetonitrile (Fisher, HPLC grade), and hexanes (Fisher, ACS HPLC grade) were dried on a Pure Process Technology Glass Contour Solvent Purification System using activated Stainless Steel columns while following manufacture’s recommendations for solvent preparation and dispensation unless otherwise noted. All amines were distilled and degassed by the freeze-pump-thaw method, and were stored under an atmosphere of nitrogen in glove box before use. All starting allylic diethylamine materials were distilled before use (often gave better reactivity after distillation).
General procedure for trisubstituted allylic amine synthesis

Allylic diethylamine substrates 1a-1e, 4a, 4b, 4d, 4f, 4i, 4k were synthesized according to our previous report. The \(^1\)H and \(^{13}\)C NMRs are marched with literature.\(^1\)

Allylic diethylamine substrates 4c and 4e were synthesized by following method, modified from our previous report.\(^1\)

**Procedure**: To a dry 100 mL schlenk flask was charged with a stir bar and 0.292 g \(\text{Cp}_2\text{ZrCl}_2\) (1 mmol, 20 mol %), purged with nitrogen followed by the addition of 25 mL DCM. Cooled to -10 °C, 7.5 mL 2 M \(\text{AlMe}_3/\text{hexanes}\) solution (15 mmol, 3.0 equiv) was added slowly. The reaction was allowed to stir at -10 °C for 15 min followed by the slow addition of 168 \(\mu\)L \(\text{H}_2\text{O}\) (8.2 mmol, 1.65 equiv). The resulting mixture was stirred vigorously at -10 °C for 20 min then added the alkyne (5 mmol, 1.0 equiv). The reaction flask was then warmed up to rt and stir overnight. A solution of the iminium chloride salt (10 mmol, 2 equiv) in 5 mL dry DCM was added slowly to the flask at 0 °C, then reaction was warmed up to rt and stir for another 3 hrs. The reaction is quenched by careful addition of 2 M \(\text{NaOH}\) solution at 0 °C, then filtered through celite and washed with warm DCM. The resulting mixture was then extract by DCM three time and combined organic layers were dried by \(\text{Na}_2\text{SO}_4\), concentrated \(\text{in vacuo}\), and distilled under vacuum to afford desired allylic diethylamines.

\((\text{E})-3\)-(5-bromo-2-fluorophenyl)-\(\text{N,N}\)-diethylbut-2-en-1-amine (4c), prepared according to previously described procedure in 60% yield.

\(^1\)H NMR (500 MHz, \(\text{CDCl}_3\)) \(\delta\): 7.36 (dd, \(J = 6.8, 2.6\) Hz, 1H), 7.30 (ddd, \(J = 8.7, 4.3, 2.6\) Hz, 1H), 6.90 (dd, \(J = 10.2, 8.7\) Hz, 1H), 5.73 (t, \(J = 6.6\) Hz, 1H), 3.25 (d, \(J = 6.6\) Hz, 2H), 2.58 (q, \(J = 7.2\) Hz, 4H), 2.01 (s, 3H), 1.07 (t, \(J = 7.1\) Hz, 6H).

\(^{13}\)C NMR (125 MHz, \(\text{CDCl}_3\)) \(\delta\): 159.06 (d, \(J = 247.5\) Hz), 134.53 (d, \(J = 15.7\) Hz), 132.48 (d, \(J = 4.6\) Hz), 132.32, 131.08 (d, \(J = 8.4\) Hz), 130.28, 117.57 (d, \(J = 24.6\) Hz), 116.46 (d, \(J = 3.4\) Hz), 50.92, 47.20, 17.20 (d, \(J = 3.8\) Hz), 12.09.

\((\text{E})-3\)-cyclopropyl-\(\text{N,N}\)-diethylbut-2-en-1-amine (4e), prepared according to previously described procedure in 78% yield.

\(^1\)H NMR (500 MHz, \(\text{CDCl}_3\)) \(\delta\): 5.29 (t, \(J = 6.8\) Hz, 3H), 3.05 (d, \(J = 6.8\) Hz, 2H), 2.49 (q, \(J = 7.2\) Hz, 4H), 1.54 (s, 3H), 1.42 – 1.33 (m, 1H), 1.02 (t, \(J = 7.2\) Hz, 6H), 0.57 – 0.51 (m, 2H), 0.46 – 0.42 (m, 2H).

\(^{13}\)C NMR (125 MHz, \(\text{CDCl}_3\)) \(\delta\): 138.44, 120.19, 50.66, 46.81, 19.01, 14.54, 11.91, 4.61.
Allylic diethylamine substrate 4g was synthesized by following method\textsuperscript{2} and the starting vinyl bromide was synthesized according to our previous report\textsuperscript{1} and literature\textsuperscript{2}.

**Procedure:** To a 50 ml round bottom flask was charged with a stir bar and 11 mg Pd(OAc)\textsubscript{2} (0.050 mmol, 1.0 mol %), 26 mg PPh\textsubscript{3} (0.10 mmol, 2.0 mol %), 0.560 g KOH (10 mmol, 2.0 equiv), starting material vinyl bromide (1.34g, 5 mmol, 1.0 equiv), 0.880 g 4-methyl boronic acid (6.5 mmol, 1.3 equiv) and 5 mL THF and 5 mL MeOH. The reaction was stirred at rt overnight followed by dilution with EtOAc, and washed by 1 N NaOH solution and brine. The organic layer was then dried over MgSO\textsubscript{4}, concentrated in vacuo, purified by Al\textsubscript{2}O\textsubscript{3} column chromatography: 200 g Al\textsubscript{2}O\textsubscript{3} + 12 g H\textsubscript{2}O, 30 : 1 hexanes/EtOAc with 0.5% MeOH as eluent.

\( \text{(E)-N,N-diethyl-3-phenyl-3-(p-tolyl)prop-2-en-1-amine (4g), prepared according to previously described procedure in 70\% yield.} \)

\( ^1\text{H NMR (500 MHz, CDCl}_3 \)\( \delta: 7.40 - 7.34 \) (m, 2H), 7.33 - 7.28 (m, 1H), 7.20 - 7.12 (m, 4H), 7.11 - 7.05 (m, 2H), 6.19 (t, J = 6.7 Hz, 1H), 3.15 (d, J = 6.7 Hz, 2H), 2.52 (q, J = 7.1 Hz, 4H), 2.32 (s, 3H), 0.96 (t, J = 7.1 Hz, 6H).

\( ^{13}\text{C NMR (125 MHz, CDCl}_3 \)\( \delta: 143.23, 140.11, 139.65, 137.01, 129.97, 128.96, 128.21, 127.27, 127.15, 126.55, 51.86, 47.13, 21.20, 11.96. \)

The cyclic allylic diethylamine substrates 4j and 4l were synthesized by following method\textsuperscript{3} and the starting diethyl (2-(diethylamino)-2-oxoethyl) phosphonate was synthesized according to our previous report\textsuperscript{1} and literature.\textsuperscript{3}

\( \text{Olefination: A dry 100mL round-bottom flask was charged with a stir bar and 0.48g NaH (60 wt \%, 12 mmol, 1.2 equiv), purged with nitrogen followed by the addition of 15 mL toluene. Cooled to 0 \textdegree C, diethyl (2-(diethylamino)-2-oxoethyl)phosphonate was added dropwise (2.8 mL, 12 mmol, 1.2 equiv). The reaction was allowed to stir at 0 \textdegree C for 30 min until the solution become clear. Ketone was added dropwise (10 mmol, 1.0 equiv) to the reaction over 5 min, then warmed up to 80 \textdegree C, stirring overnight. The reaction was quenched with sat. NH\textsubscript{4}Cl solution, and the aqueous layer was extracted with DCM three times. The combined organic layers were dried over MgSO\textsubscript{4}, and purified by silica column chromatography.} \)
**Reduction:** To a dry 20 mL round-bottom flask was charged with a stir bar, purged with N\textsubscript{2} three times, followed by the addition of unsaturated amide (4.0 mmol), dry THF (3 mL) and dry toluene (6 mL, V(tol)/V(THF)=2). The flask was then cooled in ice bath, and added RedAl solution (2.0 equiv, 3.5 M) dropwise. The reaction was allowed to stir at 0 °C for 2 hours then warmed up to rt for another 4 hours. The reaction crude was cooled in ice bath and quenched by the addition of 10 mL 5 M NaOH solution and 20 mL toluene. After stirring for 30 minutes, the crude was transferred to a separatory funnel. Organic layer was separated, washed by 5 M NaOH solution twice, dried over MgSO\textsubscript{4}, concentrated *in vacuo* and further purified by Al\textsubscript{2}O\textsubscript{3} column chromatography.

\[(E)-2-(2,3-dihydro-1H-inden-1-ylidene)-N,N-diethyl-1-amine (4j),\] prepared according to previously described procedure at 25% overall yield.

\[^{1}H\text{ NMR} (500\text{ MHz}, \text{CDCl}_3) \delta: 7.51 - 7.44 (m, 1H), 7.25 - 7.23 (m, 1H), 7.21 - 7.14 (m, 2H), 6.05 (ddd, J = 7.0, 4.3, 2.6 Hz, 1H), 3.25 (d, J = 6.8 Hz, 2H), 3.06 - 2.90 (m, 2H), 2.80 - 2.71 (m, 2H), 2.58 (q, J = 7.2 Hz, 4H), 1.07 (t, J = 7.2 Hz, 6H).

\[^{13}C\text{ NMR} (125\text{ MHz}, \text{CDCl}_3) \delta: 146.06, 144.18, 141.52, 127.87, 126.57, 125.38, 120.33, 116.74, 52.33, 47.08, 30.28, 28.12, 12.04.\]

\[(Z)-N,N-diethyl-2-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ylidene)ethan-1-amine (4l),\] prepared according to previously described procedure at 46% overall yield.

\[^{1}H\text{ NMR} (500\text{ MHz}, \text{CDCl}_3) \delta: 7.17 - 7.09 (m, 3H), 7.02 - 6.97 (m, 1H), 5.64 (t, J = 6.8 Hz, 1H), 3.00 (d, J = 6.8 Hz, 2H), 2.77 - 2.67 (m, 2H), 2.47 (q, J = 7.1 Hz, 2H), 2.33 - 2.24 (m, 2H), 1.85 (p, J = 5.9 Hz, 2H), 1.72 - 1.61 (m, 2H), 0.92 (t, J = 7.1 Hz, 6H).

\[^{13}C\text{ NMR} (125\text{ MHz}, \text{CDCl}_3) \delta: 145.62, 141.73, 141.18, 129.12, 128.98, 126.92, 125.59, 124.99, 51.08, 46.81, 38.10, 36.63, 33.30, 27.87, 11.76.\]

The \(E\)-selective \(\beta\)-CF\textsubscript{3} or CF\textsubscript{2}H substituted allylic diethylamine substrates \(4m, 4o, \text{ and } 4p\) were synthesized by following method.\(^4\)

\[\text{Olefination: A dry 100mL round-bottom flask was charged with a stir bar and 0.60 g NaH (60 wt %, 15 mmol, 1.5 equiv), purged with nitrogen followed by the addition of 30 mL THF. Cooled to 0 °C, ethyl 2-(diethoxyphosphoryl)acetate was added dropwise (3.0 mL, 15 mmol, 1.5 equiv). The reaction was allowed to stir at 0 °C for 30 min until the solution become clear. Fluoroalkyl ketone was added dropwise (10 mmol, 1.0 equiv) to the reaction over 5 min, then warmed up to 50 °C, stirring overnight. The reaction was quenched with sat. NH\textsubscript{4}Cl solution, and the aqueous layer was extracted with DCM}\]
three times. The combined organic layers were dried over MgSO₄, concentrated in vacuo and purified by silica column chromatography to afford (E)-R₃-substituted allylic ester. (Yields: 60% to 80% for desired isomer)

**Reduction:** To a dry 250 mL round-bottom flask was charged with a stir bar, purged with N₂ three times, followed by the addition of unsaturated ester (4.8 mmol), dry THF (24 mL). The flask was then cooled in ice bath, then added DIBAL-H solution (2.5 equiv, 1 M in hexanes) dropwise. The reaction was allowed to stir at 0 °C for 2 hours then quenched by the addition of 10 mL sat. Rochelle salt solution. After stirring at rt overnight, the crude was extracted with Et₂O three times, combined organic layer dried over MgSO₄, concentrated in vacuo and purified by silica column chromatography to afford (E)-R₃-substituted allylic ester. (Yields: 60% to 80% for desired isomer)

**Chlorination:** To a dry 50 mL round-bottom flask was charged with a stir bar, purged with N₂ three times, followed by the addition of allylic alcohol (4.6 mmol), dry DCM (20 mL), and 1.9 mL Et₃N (13.8 mmol, 3.0 equiv). The flask was then cooled in ice bath, then added MeSO₂Cl (13.8 mmol, 3.0 equiv) dropwise. The reaction was allowed to stir at 0 °C for 5 hours followed by the addition of another 2.0 equiv of MeSO₂Cl. The resulting mixture was then warmed up to rt, and stirred overnight. The reaction crude was diluted in DCM, washed sequentially with 1 N HCl solution, sat. NaHCO₃ solution and brine. The organic layer was then dried over MgSO₄, concentrated in vacuo and purified by silica column chromatography to afford the corresponding allylic chloride. (Yield: 85% to 95%, two steps)

**SN₂:** To a dry 50 mL round-bottom flask was charged with a stir bar, allylic chloride (4.0 mmol), HNEt₂ (6.0 mmol, 1.5 equiv), K₂CO₃ (10 mmol, 2.5 equiv), and 22 mL acetone. The reaction mixture was then refluxed under N₂ at 70 °C overnight. The reaction crude was then filtered through celite, concentrated in vacuo to remove solvent, re-diluted in Et₂O, extracted with 1 N HCl three time. The aqueous layer was then basified by the addition of 3 N NaOH solution, (pH>11) and extracted with DCM three times. The combined DCM layers were MgSO₄, concentrated in vacuo and distilled under vacuum to afford the desired allylic amines (Yields: 82% to 88%)

(E)-**N,N-diethyl-4,4,4-trifluoro-3-phenylbut-2-en-1-amine (4m)**, prepared according to previously described procedure.

**1H NMR** (500 MHz, CDCl₃) δ: 7.44 – 7.36 (m, 3H), 7.25 – 7.21 (m, 2H), 6.55 (ddt, J = 6.6, 5.0, 1.6 Hz, 1H), 3.13 – 2.94 (m, 2H), 2.46 (q, J = 7.1 Hz, 4H), 0.95 (t, J = 7.1 Hz, 6H).

**13C NMR** (125 MHz, CDCl₃) δ: 134.83 (q, J = 5.3 Hz), 132.38 (q, J = 29.7 Hz), 132.04, 129.52, 128.57, 128.40, 123.22 (q, J = 273.2 Hz), 50.39, 47.12, 11.81.

**19F NMR** (471 MHz, CDCl₃) δ -65.91 (d, J = 1.9 Hz).

(E)-**3-benzyl-N,N-diethyl-4,4,4-trifluorobut-2-en-1-amine (4o)**, prepared according to previously described procedure.

**1H NMR** (500 MHz, CDCl₃) δ: 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 1H), 7.19 – 7.16 (m, 2H), 6.45 (t, J = 6.2 Hz, 1H), 3.60 (s, 2H), 3.18 (dq, J = 5.1, 2.4 Hz, 2H), 2.49 (q, J = 7.1 Hz, 4H), 1.00 (t, J = 7.1 Hz, 6H).

**13C NMR** (125 MHz, CDCl₃) δ: 137.92, 135.13 (q, J = 5.8 Hz), 129.40 (q, J = 28.6 Hz), 128.77, 128.33, 126.71, 124.30 (q, J = 273.4 Hz), 50.52, 47.45, 31.89, 12.11.
\[ ^{19} \text{F NMR} (471 \text{ MHz, CDCl}_3) \delta: -67.01 (d, J = 2.2 \text{ Hz}). \]

\[ (E)-3\text{-benzyl-N,N-diethyl-4,4-difluorobut-2-en-1-amine (4p), prepared according to previously described procedure.} \]

\[ ^{1} \text{H NMR} (500 \text{ MHz, CDCl}_3) \delta: 7.31 - 7.26 (m, 2H), 7.22 - 7.17 (m, 3H), 6.10 - 6.05 (m, 1H), 5.99 (t, J = 56.1 \text{ Hz, 1H}), 3.57 (s, 2H), 3.17 (dt, J = 6.8, 3.7 \text{ Hz, 2H}), 2.49 (q, J = 7.1 \text{ Hz, 3H}), 1.00 (t, J = 7.2 \text{ Hz, 6H}). \]

\[ ^{13} \text{C NMR} (125 \text{ MHz, CDCl}_3) \delta: 138.58, 134.22 (t, J = 9.9 \text{ Hz}), 133.73 (t, J = 20.5 \text{ Hz}), 128.63, 128.51, 126.41, 117.00 (t, J = 237.6 \text{ Hz}), 50.37, 47.25, 31.10 (t, J = 1.8 \text{ Hz}), 11.96. \]

\[ ^{19} \text{F NMR} (471 \text{ MHz, CDCl}_3) \delta: -114.38 (d, J = 55.8 \text{ Hz}). \]

The \((Z)\)-selective \(\beta\)-\(\text{CF}_3\) substituted allylic diethylamine substrates \(4n\) was synthesized by following method.\(^5\)

\[
\begin{align*}
\text{Ph} & \text{CF}_3 + (\text{CF}_3\text{CH}_2\text{O})_2\text{P(\text{CF}_3\text{CH}_2\text{O})}_2\text{OEt} & \xrightleftharpoons[1.1\text{eq KHMDS}]{18\text{-crown-6 \text{THF, -78} \text{ °C}}} \text{Ph} & \text{CF}_3\text{O} \quad (Z)
\end{align*}
\]

**Olefination:** A dry 50 mL round-bottom flask was charged with a stir bar and 1.76 g KHMDS (8.8 mmol, 1.1 equiv) and 2.56 g 18-crown-6 (9.6 mmol, 1.2 equiv) purged with nitrogen followed by the addition of 15 mL THF. Cooled to -78 °C, ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)acetate was added dropwise (8.8 mmol, 1.1 equiv). The reaction was allowed to stir at -78 °C for 45 min followed by the addition of trifluoroacetophenone (8.0 mmol, 1.0 equiv) to the reaction, stirred at -78 °C for another 3 h then warmed up to rt, quenched with sat. \(\text{NH}_4\text{Cl}\) solution, and the aqueous layer was extracted with DCM three times. The combined organic layers were dried over \(\text{MgSO}_4\), concentrated \textit{in vacuo} and purified by silica column chromatography to afford \((Z)\)-R\(_1\)-substituted allylic ester at 58% yield.

**Reduction, Chlorination, and \(\text{SN}_2\)** were carried out under same conditions as described above.

\[ \text{(Z)-N,N-diethyl-4,4-trifluoro-3-phenylbut-2-en-1-amine (4n), prepared according to previously described procedure. Purity: Z/E=22:1.} \]

\[ ^{1} \text{H NMR} (500 \text{ MHz, CDCl}_3) \delta: 7.42 - 7.30 (m, 5H), 6.19 (td, J = 6.2, 0.9 \text{ Hz, 1H}), 3.49 (dq, J = 5.8, 2.8 \text{ Hz, 2H}), 2.58 (q, J = 7.1 \text{ Hz, 4H}), 1.07 (t, J = 7.1 \text{ Hz, 6H}). \]

\[ ^{13} \text{C NMR} (125 \text{ MHz, CDCl}_3) \delta: 140.93 (q, J = 2.8 \text{ Hz}), 136.28 (q, J = 1.8 \text{ Hz}), 132.15 (q, J = 30.5 \text{ Hz}), 128.41, 128.29, 128.15, 124.03 (q, J = 275.7 \text{ Hz}), 51.29 (q, J = 2.4 \text{ Hz}), 47.49, 12.09. \]

\[ ^{19} \text{F NMR} (471 \text{ MHz, CDCl}_3) \delta: -57.30 (d, J = 3.1 \text{ Hz}). \]
β-Silyl substituted allylic diethylamine substrate 4q was synthesized by following method, modified from literature. To a dry 100 mL schlenk flask was charged with a stir bar, purged with N₂ three times, followed by the addition of dry THF (30 mL) and 2.8 mL RedAl solution (8.5 mmol, 1.7 equiv). The flask was then cooled in ice bath, then added 5 mL THF solution of 3-phenyl-2-propyn-1-ol (5.0 mmol, 1.0 equiv) dropwise. The reaction was allowed to warm up to rt and stir for 4 hours. Then, the reaction flask was then cooled to -10 °C followed by the slow addition of 2.0 mL EtOAc to quench excess Red-Al then stirred at -10 °C for another 15 min. The resulting mixture was then cooled to -78 °C, followed by the addition of I₂ (10 mmol, 2.0 equiv) in one portion under nitrogen flow. The reaction crude was then allowed to stir at -78 °C for another hour before being quenched by 15 mL sat. Rochelle salt solution and 25 mL sat. Na₂S₂O₃ solution at 0 °C. The biphasic mixture was then stirred vigorously at rt overnight, and extracted by Et₂O three times. The combined organic layer was then dried over MgSO₄, concentrated in vacuo and used for next step without further purification.

Chlorination and SN₂ were carried out under same conditions as described above.

Vinyl silane synthesis: To a dry 200 mL schlenk flask was charged with a stir bar, purged with N₂ three times, followed by the addition of dry THF (25 mL) and starting vinyl iodine (5.0 mmol, 1.0 equiv). The flask was then cooled to -78 °C, followed by the slow addition of nBuLi (12 mmol, 2.4 equiv) over 10 min. The resulting crude was allowed to stir at -78 °C for another 30 min, before the addition of chloro(dimethyl)phenylsilane (15 mmol, 3.0 equiv). The resulting mixture was then cooled to -78 °C for another 2 hours followed by being quenched with sat. NaHCO₃ solution, extracted by Et₂O three times. The combined organic layer was then dried over MgSO₄, concentrated in vacuo and further purified by Al₂O₃ column chromatography.

(Z)-3-(dimethyl(phenyl)silyl)-N,N-diethyl-3-phenylprop-2-en-1-amine (4q), prepared according to previously described procedure.

¹H NMR (500 MHz, CDCl₃) δ: 8.762 – 7.55 (m, 2H), 7.35 (dd, J = 4.8, 1.9 Hz, 3H), 7.29 – 7.23 (m, 2H), 7.21 – 7.14 (m, 1H), 7.12 – 7.05 (m, 2H), 6.33 (t, J = 6.3 Hz, 1H), 3.10 (d, J = 6.3 Hz, 2H), 2.40 (q, J = 7.1 Hz, 4H), 0.91 (t, J = 7.1 Hz, 6H), 0.34 (s, 6H).

¹³C NMR (125 MHz, CDCl₃) δ: 146.66, 146.50, 142.37, 139.34, 133.99, 129.11, 128.02, 127.97, 127.72, 125.73, 54.79, 46.89, 12.04, -0.34.
General procedure for Rh-catalyzed reductive amination of allylic diethylamine with secondary amine nucleophiles (General procedure A)

General procedure A: [Rh(COD)Cl]2 (2.0 mg, 0.0036 mmol, 1.5 mol %), (R)-BINAP (4.5 mg, 0.0072 mmol, 3.0 mol %), NaBArF4 (6.4 mg, 0.0072 mmol, 3.0 mol %), and THF (0.2 mL) were added to a 4 mL vial equipped with a stir bar in the glove box under nitrogen atmosphere. To the vial was added sequentially allylic diethylamine (1, 0.24 mmol, 1.0 equiv), and secondary amine (2, 0.29 mmol, 1.2 equiv). The resulting solution was allowed to stir for 22 h at 40 °C (unless otherwise noted). After 22 h, formic acid (0.36 mmol, 3.0 equiv) was added into reaction vial via syringe and the reaction was allowed to stir for another 2 h at 60 °C (unless otherwise noted). The reaction crude was quenched by the addition of DCM, concentrated in vacuo and then purified by basic alumina chromatography to afford the desired product 3.

General procedure for Rh-catalyzed reductive amination of allylic diethylamine with aryl amine nucleophiles (General procedure B)

General procedure B: [Rh(COD)Cl]2 (2.0 mg, 0.0036 mmol, 1.5 mol %), (R)-BINAP (4.5 mg, 0.0072 mmol, 3.0 mol %), NaBArF4 (6.4 mg, 0.0072 mmol, 3.0 mol %), and THF (0.2 mL) were added to a 4 mL vial equipped with a stir bar in the glove box under nitrogen atmosphere. To the vial was added sequentially allylic diethylamine (1, 0.24 mmol, 1.0 equiv), and aryl amine (2, 0.29 mmol, 1.2 equiv). The resulting solution was allowed to stir for 22 h at 40 °C (unless otherwise noted). After 22 h, the reaction vial was cooled to 0 °C followed by the addition of NaBH4 (0.18 mmol, 1.5 equiv) and 1.0 ml MeOH. The resulting mixture was allowed to stir at 0 °C for 1 h then warmed up to rt for another 1 h. The crude reaction was quenched by the addition of DCM, concentrated in vacuo and then re-dissolved in DCM, washed with sat. NaHCO3 solution. The organic layer was dried over MgSO4, concentrated in vacuo, and purified by silica gel chromatography to afford the desired product 3.

General procedure for Rh-catalyzed reductive amination of allylic diethylamine with primary alkyl amine nucleophiles (General procedure C)
**General procedure C**: [Rh(COD)Cl]$_2$ (2.0 mg, 0.0036 mmol, 1.5 mol %), (R)-BINAP (4.5 mg, 0.0072 mmol, 3.0 mol %), NaBArF$_4$ (6.4 mg, 0.0072 mmol, 3.0 mol %), THF (0.2 mL), and allylic diethylamine (1, 0.24 mmol, 1.0 equiv) were added to a 4 mL vial equipped with a stir bar in the glove box under nitrogen atmosphere. The resulting solution was allowed to stir for 6 h at 40 °C (unless otherwise noted), followed by the addition of primary alkyl amine (2, 0.29 mmol, 1.2 equiv) then continued stirring at 60 °C for another 12 h. After 12 h, the reaction vial was cooled to 0 °C followed by the addition of NaBH$_4$ (0.18 mmol, 1.5 equiv) and 1.0 ml MeOH. The resulting mixture was allowed to stir at 0 °C for 1 h then warmed up to rt for another 1 h. The reaction crude was then quenched by the addition of DCM, concentrated *in vacuo* and then re-dissolved in DCM, washed with sat. NaHCO$_3$ solution. The organic layer was dried over MgSO$_4$, concentrated *in vacuo*, and purified by basic alumina chromatography to afford the desired product 3.

**Column Chromatography Condition**: 100 g Al$_2$O$_3$ + 9 g H$_2$O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH to 15 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

**HRMS (ESI-TOF) m/z**: [M+H$^+$] calculated for C$_{14}$H$_{28}$NO, 226.2171; found, 226.2175.

**Column Chromatography Condition**: 100 g Al$_2$O$_3$ + 9 g H$_2$O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH as eluent.

**HRMS (ESI-TOF) m/z**: [M+H$^+$] calculated for C$_{15}$H$_{37}$N$_2$O$_2$, 325.2855; found, 325.2850.
Nucleophiles 2c and 2d were observed to slow down the isomerization of allylic amine 1a, therefore the addition of 2c or 2d together with formic acid led to increased conversion of 1a.

(S)-2-(3,7-dimethyloct-6-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (3c, Figure 3):
Prepared according to modified General procedure A from geranyl diethyl amine (1a) with 1,2,3,4-tetrahydroisoquinoline (2c) in 66% isolated yield.

Column Chromatography Condition: 100 g Al2O3 + 6 g H2O, 50 : 1 hexanes/ EtOAc with 0.5% MeOH to 30 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

1H NMR (500 MHz, CDCl3) δ: 7.16 - 7.07 (m, 3H), 7.05 - 6.97 (m, 1H), 5.11 (t, J = 6.9 Hz, 1H), 3.63 (s, 2H), 2.91 (t, J = 6.0 Hz, 2H), 2.73 (td, J = 7.1, 3.4 Hz, 2H), 2.52 (dt, J = 9.5, 5.5 Hz, 2H), 2.10 - 1.88 (m, 2H), 1.69 (s, 3H), 1.67 - 1.63 (m, 1H), 1.16 (s, 3H), 1.55 - 1.48 (m, 1H), 1.46 - 1.32 (m, 2H), 1.24 - 1.15 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H).

13C NMR (125 MHz, CDCl3) δ: 135.09, 134.53, 131.30, 128.76, 126.73, 126.17, 125.66, 125.00, 56.73, 56.49, 51.25, 37.44, 34.39, 31.27, 29.30, 25.88, 25.66, 19.91, 17.82.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C19H30N, 272.2378; found, 272.2377.

(S)-2-(4-(3,7-dimethyloct-6-en-1-yl)piperazin-1-yl)pyrimidine (3d, Figure 3):
Prepared according to modified General procedure A from geranyl diethyl amine (1a) with 2-(piperazin-1-yl)pyrimidine (2d) in 83% isolated yield.

Column Chromatography Condition: 100 g Al2O3 + 9 g H2O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH to 15 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

1H NMR (500 MHz, CDCl3) δ: 8.30 (d, J = 4.7 Hz, 2H), 6.47 (t, J = 4.7 Hz, 1H), 5.09 (t, J = 7.0 Hz, 1H), 3.92 - 3.76 (br, 4H), 2.54 - 2.45 (br, 4H), 2.44 - 2.30 (m, 2H), 2.09 - 1.87 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 - 1.53 (m, 1H), 1.51 - 1.43 (m, 1H), 1.39 - 1.29 (m, 2H), 1.22 - 1.13 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H).

13C NMR (125 MHz, CDCl3) δ: 161.83, 157.83, 131.34, 124.93, 190.91 57.10, 53.41, 43.84, 37.37, 34.01, 31.27, 25.87, 25.63, 19.87, 17.81.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C19H31N4, 303.2549; found, 303.2549.
(S)-N,N-diethyl-3,7-dimethyloct-6-en-1-amine (3e, Figure 3): Prepared according to General procedure A from geranyl diethyl amine (1a) without any nucleophilic amine added in 83% isolated yield.

**Column Chromatography Condition:** 100 g Al₂O₃ + 9 g H₂O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH as eluent.

**¹H NMR** (500 MHz, CDCl₃) δ: 5.09 (t, J = 7.1 Hz, 1H), 2.51 (q, J = 7.1, 4H), 2.46 – 2.36 (m, 2H), 1.97 (qq, J = 14.5, 7.1 Hz, 2H), 1.67 (d, J = 1.6 Hz, 3H), 1.59 (s, 3H), 1.53 – 1.38 (m, 2H), 1.36 – 1.21 (m, 2H), 1.16 (m, 1H), 1.01 (t, J = 7.1 Hz, 6H), 0.88 (d, J = 6.5 Hz, 3H).

**¹³C NMR** (125 MHz, CDCl₃) δ: 131.21, 125.05, 50.97, 47.05, 37.44, 34.01, 31.31, 25.87, 25.66, 19.90, 17.77, 11.84.

**HRMS (ESI-TOF) m/z:** [M+H⁺] calculated for C₁₉H₃₀N, 212.2378; found, 212.2385.

(S)-N,N-dibenzyl-3,7-dimethyloct-6-en-1-amine (3f, Figure 3): Prepared according to General procedure A from geranyl diethyl amine (1a) with dibenzylamine (2f) in 70% isolated yield.

**Column Chromatography Condition:** silica gel, 20 : 1 hexanes/ EtOAc as eluent.

**¹H NMR** (500 MHz, CDCl₃) δ: 8.7.39 – 7.34 (m, 4H), 7.33 – 7.28 (m, 4H), 7.24 – 7.18 (m, 2H), 5.06 (tq, J = 7.1, 1.4 Hz, 1H), 3.58 (d, J = 13.7 Hz, 2H), 3.50 (d, J = 13.7 Hz, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.04 – 1.83 (m, 2H), 1.67 (brs, 3H), 1.57 (brs, 4H, overlap), 1.52 – 1.42 (m, 1H), 1.37 – 1.27 (m, 1H), 1.27 – 1.17 (m, 1H), 1.13 – 1.00 (m, 1H), 0.76 (d, J = 6.5 Hz, 3H).

**¹³C NMR** (125 MHz, CDCl₃) δ: 140.17, 131.13, 128.93, 128.24, 126.83, 125.05, 58.42, 51.44, 37.26, 34.15, 33.02, 25.87, 25.61, 19.75, 17.79.

**HRMS (ESI-TOF) m/z:** [M+H⁺] calculated for C₂₄H₃₄N, 336.2691; found, 336.2695.

(R)-N-methyl-3-phenyl-N-((S)-1-phenylethyl)butan-1-amine (3g, Figure 3): Prepared according to General procedure A from (E)-N,N-diethyl-3-phenylbut-2-en-1-amine (1b) with (S)-N-methyl-1-phenylethanol-1-amine (2g) and (R)-BNIAP as ligand in 64% isolated yield.

**Column Chromatography Condition:** 100 g Al₂O₃ + 3 g H₂O, 50 : 1 hexanes/ EtOAc with 0.5% MeOH to 30 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

**¹H NMR** (500 MHz, CDCl₃) δδ 7.31 – 7.23 (m, 5H), 7.23 – 7.19 (m, 2H), 7.19 – 7.12 (m, 3H), 3.52 (q, J = 6.8 Hz, 1H), 2.70 (h, J = 7.1 Hz, 1H), 2.38 (dd, J = 12.6, 9.4, 6.0 Hz, 1H), 2.18 (dd, J = 12.5, 9.3, 5.3 Hz, 1H), 2.13 (s, 3H), 1.79 (dd, J = 13.3, 9.4, 8.0, 5.3 Hz, 1H), 1.71 (dtt, J = 13.4, 9.3, 6.2 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H).

**¹³C NMR** (125 MHz, CDCl₃) δ: 147.74, 144.08, 128.42, 128.16, 127.82, 127.08, 126.77, 125.94, 63.22, 52.72, 38.47, 37.96, 35.76, 22.66, 18.24.

**HRMS (ESI-TOF) m/z:** [M+H⁺] calculated for C₁₉H₂₇N, 268.2065; found, 268.2073.
(S)-N-methyl-3-phenyl-N-((S)-1-phenylethyl)butan-1-amine (3g’, Figure 3): Prepared according to General procedure A from (E)-N,N-diethyl-3-phenylbut-2-en-1-amine (1b) with (S)-N-methyl-1-phenylethan-1-amine (2g) and (S)-BNIAP as ligand in 60% isolated yield.

**Column Chromatography Condition:** 100 g Al$_2$O$_3$ + 3 g H$_2$O, 50 : 1 hexanes/ EtOAc with 0.5% MeOH to 30 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

$^1$H NMR (500 MHz, CDCl$_3$) δ: 7.30 – 7.26 (m, 3H), 7.25 – 7.18 (m, 4H), 7.17 – 7.11 (m, 3H), 3.49 (q, J = 6.7 Hz, 1H), 2.70 (t, J = 7.0 Hz, 1H), 2.36 – 2.20 (m, 2H), 2.12 (s, 3H), 1.81 – 1.67 (m, 2H), 1.26 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 147.77, 144.23, 128.41, 128.19, 127.80, 127.07, 126.79, 125.93, 63.34, 52.58, 38.60, 37.79, 35.65, 22.48, 18.55.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for C$_{15}$H$_{26}$N, 268.2065; found, 268.2066.

(3)-N-(3,7-dimethyloct-6-en-1-yl)aniline (3h, Figure 3): Prepared according to General procedure B from geranyl diethyl amine (1a) with aniline (2h) in 81% isolated yield.

**Column Chromatography Condition:** silica gel, 50 : 1 hexanes/ EtOAc as eluent.

$^1$H NMR (500 MHz, CDCl$_3$) δ: 7.22 – 7.14 (m, 2H), 6.75 – 6.66 (m, 1H), 6.64 – 6.58 (m, 2H), 5.11 (t, J = 7.0 Hz, 1H), 3.60 (b, 1H), 3.26 – 3.00 (m, 2H), 2.12 – 1.91 (m, 2H), 1.70 (s, 3H), 1.68 – 1.63 (m, 1H), 1.61 (s, 3H), 1.59 – 1.54 (m, 1H), 1.49 – 1.34 (m, 2H), 1.28 – 1.17 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 148.64, 131.49, 129.36, 124.79, 117.27, 112.87, 42.12, 37.24, 36.84, 30.58, 25.88, 25.62, 19.75, 17.83.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for C$_{16}$H$_{26}$N, 232.2065; found, 232.2064.

(3)-N-(3,7-dimethyloct-6-en-1-yl)benzo[d][1,3]dioxol-5-amine (3i, Figure 3): Prepared according to General procedure B from geranyl diethyl amine (1a) with benzo[d][1,3]dioxol-5-amine aniline (2i) in 74% isolated yield.

**Column Chromatography Condition:** silica gel, 30 : 1 hexanes/ EtOAc as eluent.

$^1$H NMR (500 MHz, CDCl$_3$) δ: 6.65 (d, J = 8.2 Hz, 1H), 6.24 (d, J = 2.3 Hz, 1H), 6.04 (dd, J = 8.3, 2.3 Hz, 1H), 5.85 (s, 2H), 5.12 (t, J = 7.0 Hz, 1H), 3.35 (b, 1H), 3.15 – 2.91 (m, 2H), 2.13 – 1.88 (m, 2H), 1.69 (s, 3H), 1.66 – 1.62 (m, 1H), 1.61 (s, 3H), 1.57 – 1.50 (m, 1H), 1.46 – 1.31 (m, 2H), 1.28 – 1.14 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ: 148.46, 144.52, 139.55, 131.49, 124.78, 108.75, 104.44, 100.65, 96.00, 43.15, 37.24, 36.85, 30.58, 25.88, 25.61, 19.75, 17.83.

HRMS (ESI-TOF) m/z: [M+H$^+$] calculated for C$_{17}$H$_{26}$NO$_2$, 276.1964; found, 276.1961.
(S)-N-(3,7-dimethyloct-6-en-1-yl)-4-( trifluoromethyl)aniline (3j, Figure 3): Prepared according to General procedure B from geranyl diethyl amine (1a) with 4-trifluoromethyl aniline (2j) in 61% isolated yield (as a mixture of 12:1 desired product and hydrogenated product).

**Column Chromatography Condition:** silica gel, 99 : 1 hexanes/ EtOAc as eluent.

**1H NMR** (500 MHz, CDCl₃) δ: 8 7.32 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.05 – 4.99 (m, 1H), 3.87 (brs, 1H), 3.21 – 2.84 (m, 2H), 2.06 – 1.80 (m, 2H), 1.62 (d, J = 1.3 Hz, 3H), 1.60 – 1.55 (m, 1H), 1.53 (d, J = 1.4 Hz, 3H), 1.51 – 1.45 (m, 1H), 1.44 – 1.35 (m, 1H), 1.34 – 1.25 (m, 1H), 1.17 – 1.10 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H).

**13C NMR** (125 MHz, CDCl₃) δ: 151.04, 131.72, 128.62, 127.87, 126.82 (q, J = 3.8 Hz), 147.49, 128.49, 127.07, 126.06, 57.93, 46.03, 43.12, 39.00, 38.35, 30.77, 28.09, 26.92, 24.66, 26.66, 22.74, 16.87.

HRMS (ESI-TOF) m/z: [M+H⁺] calculated for C₁₃H₂₅N₃F₃, 300.1939; found, 300.1947.

(S)-N-benzyl-3,7-dimethyloct-6-en-1-amine (3k, Figure 3): Prepared according to General procedure C from geranyl diethyl amine (1a) with benzylamine (2k) in 70% isolated yield.

**Column Chromatography Condition:** 100 g Al₂O₃ + 9 g H₂O, 20 : 1 hexanes/ EtOAc with 0.5% MeOH to 10 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

**1H NMR** (500 MHz, CDCl₃) δ: 7.34 – 7.30 (m, 4H), 7.26 – 7.21 (m, 1H), 5.09 (dddd, J = 7.1, 5.7, 2.9, 1.4 Hz, 1H), 3.79 (s, 2H), 2.72 – 2.58 (m, 2H), 2.06 – 1.88 (m, 2H), 1.68 (d, J = 1.3 Hz, 3H), 1.59 (s, 3H), 1.56 – 1.44 (m, 2H), 1.39 – 1.28 (m, 2H), 1.21 – 1.10 (m, 1H), 0.88 (d, J = 6.5 Hz, 3H).

**13C NMR** (125 MHz, CDCl₃) δ: 140.70, 131.31, 128.51, 128.25, 127.00, 124.97, 54.35, 47.60, 37.43, 37.38, 30.77, 25.87, 25.64, 19.78, 17.80.

HRMS (ESI-TOF) m/z: [M+H⁺] calculated for C₁₄H₂₆N, 246.2222; found, 246.2228.

(R)-N-(1-cyclohexylethyl)-3-phenylbutan-1-amine (3l, Figure 3): Prepared according to General procedure C from (E)-N,N-diethyl-3-phenylbut-2-en-1-amine (1b) with (R)-1-cyclohexylethyl-1-amine (2l) in 61% isolated yield.

**Column Chromatography Condition:** 100 g Al₂O₃ + 9 g H₂O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH to 15 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

**1H NMR** (500 MHz, CDCl₃) δ: 8 7.32 – 7.27 (m, 2H), 7.22 – 7.15 (m, 3H), 2.77 (h, J = 7.1 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.42 – 2.29 (m, 2H), 1.80 – 1.68 (m, 4H), 1.67 – 1.57 (m, 3H), 1.25 (d, J = 6.9 Hz, 4H, overlap), 1.20 – 1.04 (m, 4H), 0.99 – 0.92 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H).

**13C NMR** (125 MHz, CDCl₃) δ: 147.49, 128.49, 127.07, 126.06, 57.93, 46.03, 43.12, 39.00, 38.35, 30.07, 28.09, 26.92, 26.80, 26.66, 22.74, 16.87.
HRMS (ESI-TOF) m/z: [M+H+] calculated for C_{18}H_{30}N, 260.2378; found, 260.2381.

(R)-N-(tert-butyl)-3-phenylbutan-1-amine (3m, Figure 3): Prepared according to General procedure B from (E)-N,N-diethyl-3-phenylbut-2-en-1-amine (1b) with t-butylamine (2m) in 58% isolated yield.

Column Chromatography Condition: silica gel, 30 : 1 hexanes/ EtOAc to 10 : 1 hexanes/EtOAc as gradient eluent.

^1H NMR (500 MHz, CDCl₃) δ: 7.39 – 7.30 (m, 3H), 7.26 – 7.19 (m, 2H), 2.84 (h, J = 7.0 Hz, 1H), 2.62 – 2.43 (m, 2H), 1.87 – 1.75 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H), 1.08 (s, 9H).

^13C NMR (125 MHz, CDCl₃) δ: 147.38, 128.47, 127.07, 126.06, 50.34, 40.91, 39.60, 38.34, 29.16, 22.80.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C_{14}H_{24}N, 206.1909; found, 206.1913.

(S)-3,7-dimethyl-N-(2-morphinoethyl)oct-6-en-1-amine (3n, Figure 3): Prepared according to General procedure C from geranyl diethyl amine (1a) with 2-morphinoethan-1-amine (2n) in 66% isolated yield.

Purification: No column chromatography needed. Reaction crude was concentrated to remove solvent then re-dissolve in Et₂O followed by an acid/base extraction to afford the desired product 3n.

^1H NMR (500 MHz, CDCl₃) δ: 5.09 (ddt, J = 8.9, 7.2, 1.6 Hz, 1H), 3.93 (h, J = 6.2 Hz, 2H), 2.62 (dddd, J = 20.9, 11.4, 10.4, 5.7 Hz, 2H), 2.49 (t, J = 6.1 Hz, 2H), 2.45 – 2.40 (m, 4H), 1.96 (m, 2H), 1.81 (brs, 1H), 1.67 (d, J = 1.6 Hz, 3H), 1.59 (s, 3H), 1.57 – 1.44 (m, 2H), 1.40 – 1.28 (m, 2H), 1.18 – 1.11 (m, 1H), 0.88 (d, J = 6.4 Hz, 3H).

^13C NMR (125 MHz, CDCl₃) δ: 131.32, 124.92, 67.18, 58.42, 53.91, 48.14, 46.35, 37.36, 37.32, 30.80, 25.86, 25.64, 19.74, 17.79.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C_{16}H_{33}N₂O, 269.2593; found, 269.2593.

(R)-4-(3-phenylbutyl)morpholine (5a, Figure 4): Prepared according to General procedure A from (E)-N,N-diethyl-3-phenylbut-2-en-1-amine (4a) with morpholine (2a) in 77% isolated yield.

Column Chromatography Condition: 100 g Al₂O₃ + 9 g H₂O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH to 15 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

^1H NMR (500 MHz, CDCl₃) δ: 7.35 – 7.27 (m, 2H), 7.22 – 7.15 (m, 3H), 3.69 (t, J = 4.7 Hz, 4H), 2.75 (h, J = 7.1 Hz, 1H), 2.47 – 2.33 (m, 4H), 2.27 (ddd, J = 12.1, 8.5, 6.5 Hz, 1H), 2.19 (dd, J = 12.1, 8.6, 6.6 Hz, 1H), 1.83 – 1.73 (m, 2H), 1.26 (d, J = 6.9 Hz, 3H).

^13C NMR (125 MHz, CDCl₃) δ: 147.30, 128.51, 127.08, 126.13, 67.18, 57.45, 53.94, 38.24, 35.18, 22.64.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C_{14}H_{22}NO, 220.1701; found, 220.1706.
\textbf{(R)-4-(3-phenylheptyl)morpholine (5b, Figure 4):} Prepared according to General procedure A from (E)-N,N-diethyl-3-phenylhept-2-en-1-amine (4b) with morpholine (2a) in 86\% isolated yield.

\textbf{Column Chromatography Condition:} 100 g Al₂O₃ + 9 g H₂O, 30 : 1 hexanes/ EtOAc with 0.5\% MeOH to 15 : 1 hexanes/ EtOAc with 1.0\% MeOH as gradient eluent.

\textbf{1H NMR (500 MHz, CDCl₃) δ: }7.31 – 7.25 (m, 2H), 7.21 – 7.16 (m, 1H), 7.15 – 7.10 (m, 2H), 3.68 (t, J = 4.7 Hz, 4H), 2.53 (tt, J = 9.7, 5.4 Hz, 1H), 2.43 – 2.29 (m, 4H), 2.21 (dd, J = 12.1, 10.2, 5.8 Hz, 1H), 2.10 (ddd, J = 12.1, 10.2, 4.9 Hz, 1H), 1.85 (ddt, J = 13.1, 10.5, 5.4 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.67 – 1.50 (m, 2H), 1.38 – 1.00 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H).

\textbf{13C NMR (125 MHz, CDCl₃) δ: }145.76, 128.41, 127.73, 126.08, 67.17, 57.46, 53.94, 44.27, 36.96, 33.75, 29.89, 22.88, 14.15.

\textbf{HRMS (ESI-TOF) m/z: }[M+H⁺] calculated for C₁₄H₂₉NNO, 262.2171; found, 262.2177.

\textbf{(R)-4-(3-(5-bromo-2-fluorophenyl)butyl)morpholine (5c, Figure 4):} Prepared according to General procedure A from (E)-3-(5-bromo-2-fluorophenyl)-N,N-diethylbut-2-en-1-amine (4c) with morpholine (2a) in 74\% isolated yield.

\textbf{Column Chromatography Condition:} 100 g Al₂O₃ + 9 g H₂O, 50 : 1 hexanes/ EtOAc with 0.5\% MeOH to 15 : 1 hexanes/ EtOAc with 1.0\% MeOH as gradient eluent.

\textbf{1H NMR (500 MHz, CDCl₃) δ: }7.32 (dd, J = 6.5, 2.5 Hz, 1H), 7.29 – 7.22 (m, 1H), 6.88 (dd, J = 9.9, 8.6 Hz, 1H), 3.68 (t, J = 4.7 Hz, 4H), 3.08 (h, J = 7.0 Hz, 1H), 2.44 – 2.34 (m, 4H), 2.29 (ddd, J = 12.3, 9.2, 6.0 Hz, 1H), 2.22 (ddd, J = 12.2, 9.3, 5.9 Hz, 1H), 1.86 – 1.68 (m, 2H), 1.25 (d, J = 6.9 Hz, 3H).

\textbf{13C NMR (125 MHz, CDCl₃) δ: }159.90 (d, J = 245.2 Hz), 136.23 (d, J = 16.3 Hz), 131.19 (d, J = 5.4 Hz), 130.34 (d, J = 8.4 Hz), 117.31 (d, J = 24.8 Hz), 116.79 (d, J = 3.2 Hz), 67.11, 57.06, 53.87, 33.80, 31.15, 31.14, 20.93.

\textbf{HRMS (ESI-TOF) m/z: }[M+H⁺] calculated for C₁₄H₂₀NBrF, 316.0712; found, 316.0716.

\textbf{(S)-3-butyl-N-methyl-N-((S)-1-phenylethyl)octan-1-amine (5d, Figure 4):} Prepared according to General procedure A from (E)-3-butyl-N,N-diethyloct-2-en-1-amine (4d) with (S)-N-methyl-1-phenylethan-1-amine (2g) in 61\% isolated yield. [α]D⁰₂³ = -21.09 (c = 1.05)

\textbf{Column Chromatography Condition:} 100 g Al₂O₃ + 3 g H₂O, 50 : 1 hexanes/ EtOAc with 0.5\% MeOH as eluent.

\textbf{1H NMR (500 MHz, CDCl₃) δ: }7.32 – 7.29 (m, 4H), 7.24 – 7.20 (m, 1H), 3.55 (q, J = 6.7 Hz, 1H), 2.40 (ddd, J = 12.5, 9.8, 6.0 Hz, 1H), 2.29 – 2.20 (m, 1H), 2.18 (s, 3H), 1.45 – 1.38 (m, 2H), 1.36 (d, J = 6.8 Hz, 3H), 1.32 – 1.22 (m, 6H), 1.22 – 1.10 (m, 9H), 0.87 (t, J = 7.1 Hz, 6H).

\textbf{13C NMR (125 MHz, CDCl₃) δ: }144.35, 128.19, 127.82, 126.81, 63.55, 52.39, 38.79, 35.89, 33.82, 33.60, 32.47, 31.03, 28.96, 26.41, 23.25, 22.85, 18.91, 14.29, 14.28.
HRMS (ESI-TOF) m/z: [M+H+] calculated for C_{21}H_{30}N, 304.3004; found, 304.3006.

(R)-N,N-dibenzyl-3-cyclopropylbutan-1-amine (5e, Figure 4): Prepared according to General procedure A from (E)-3-cyclopropyl-N,N-diethylbut-2-en-1-amine (4e) with dibenzylamine (2f) in 69% isolated yield.

**Column Chromatography Condition:** silica gel, 30 : 1 hexanes/ EtOAc as eluent.

**1H NMR (500 MHz, CDCl₃)** δ: 7.37 (d, J = 7.1 Hz, 4H), 7.31 (dd, J = 8.4, 6.7 Hz, 4H), 7.25 – 7.19 (m, 2H), 3.62 (d, J = 13.6 Hz, 2H), 3.51 (d, J = 13.6 Hz, 2H), 2.54 (dd, J = 12.8, 9.0, 6.4 Hz, 1H), 2.46 (ddd, J = 12.7, 9.1, 5.1 Hz, 1H), 1.74 (ddt, J = 12.7, 9.2, 6.0 Hz, 1H), 1.54 – 1.39 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H), 0.79 – 0.64 (m, 1H), 0.50 – 0.38 (m, 1H), 0.36 – 0.28 (m, 2H), 0.02 – 0.05 (m, 2H).

**13C NMR (125 MHz, CDCl₃)** δ: 140.14, 128.98, 128.23, 126.83, 58.36, 51.49, 36.71, 34.59, 19.89, 18.35, 4.49, 3.23.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C_{21}H_{30}N, 294.2222; found, 294.2220.

(R)-4-(3-(2-(benzyloxy)ethyl)heptyl)morpholine (5f, Figure 4): Prepared according to General procedure A from (E)-3-(2-(benzyloxy)ethyl)-N,N-diethylhept-2-en-1-amine (4f) with morpholine (2a) in 66% isolated yield.

**Column Chromatography Condition:** 100 g Al₂O₃ + 6 g H₂O, 15 : 1 hexanes/ EtOAc with 0.5% MeOH as eluent.

**1H NMR (500 MHz, CDCl₃)** δ: 7.35 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.49 (s, 2H), 3.70 (t, J = 4.7 Hz, 4H), 3.49 (t, J = 6.9 Hz, 2H), 2.47 – 2.38 (m, 4H), 2.35 – 2.28 (m, 2H), 1.60 (qd, J = 6.8, 1.4 Hz, 2H), 1.53 – 1.49 (m, 1H), 1.48 – 1.42 (m, 2H), 1.29 – 1.23 (m, 8H), 0.88 (dt, J = 6.8 Hz, 3H).

**13C NMR (125 MHz, CDCl₃)** δ: 138.75, 128.48, 127.76, 127.64, 73.07, 68.70, 67.15, 57.00, 54.06, 33.93, 33.66, 33.34, 30.59, 28.84, 23.17, 14.25.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C_{20}H_{31}NO₂, 320.2590; found, 320.2598.

(S)-4-(3-phenyl-3-(p-tolyl)propyl)morpholine (5g, Figure 4): Prepared according to General procedure A from (E)-N,N-diethyl-3-phenyl-3-(p-tolyl)prop-2-en-1-amine (4g) with morpholine (2a) in 66% isolated yield.

**Column Chromatography Condition:** 100 g Al₂O₃ + 9 g H₂O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH to 15 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

**1H NMR (500 MHz, CDCl₃)** δ: 7.31 – 7.26 (m, 3H), 7.25 – 7.24 (m, 1H), 7.21 – 7.14 (m, 3H), 7.12 – 7.08 (m, 2H), 3.98 (t, J = 7.4 Hz, 1H), 3.77 – 3.68 (m, 4H), 2.46 – 2.37 (m, 4H), 2.32 (s, 3H), 2.30 – 2.27 (m, 2H), 2.27 – 2.20 (m, 2H).
\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \&: 145.19, 141.90, 135.81, 129.29, 128.57, 127.90, 127.81, 126.23, 67.19, 57.46, 53.94, 48.74, 32.61, 21.12.

**HRMS (ESI-TOF) m/z**: [M+H\textsuperscript{+}] calculated for C\textsubscript{26}H\textsubscript{26}NO, 296.2014; found, 296.2006.

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{image1.png}
\caption{(S)-4-(3-(4-methoxyphenyl)-3-phenylpropyl)morpholine (5h, Figure 4): Prepared according to General procedure A from (E)-N,N-diethyl-3-(4-methoxyphenyl)-3-phenylprop-2-en-1-amine (4h) with morpholine (2a) in 81\% isolated yield.}
\end{figure}

**Column Chromatography Condition**: 100 g Al\textsubscript{2}O\textsubscript{3} + 8 g H\textsubscript{2}O, 10 : 1 hexanes/ EtOAc with 1.0\% MeOH as eluent.

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{image2.png}
\caption{(S)-4-(3-phenyl-3-(4-(trifluoromethyl)phenyl)propyl)morpholine (5i, Figure 4): Prepared according to General procedure A from (E)-N,N-diethyl-3-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine (4i) with morpholine (2a) in 78\% isolated yield.}
\end{figure}

**Column Chromatography Condition**: 100 g Al\textsubscript{2}O\textsubscript{3} + 9 g H\textsubscript{2}O, 30 : 1 hexanes/ EtOAc with 0.5\% MeOH to 15 : 1 hexanes/ EtOAc with 1.0\% MeOH as gradient eluent.

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{image3.png}
\caption{(R)-N,N-dibenzyl-2-(2,3-dihydro-1H-inden-1-yl)ethan-1-amine (5j, Figure 4): Prepared according to General procedure A from (E)-2-(2,3-dihydro-1H-inden-1-ylidene)-N,N-diethylethan-1-amine (4j) with dibenzylamine (2f) in 69\% isolated yield.}
\end{figure}

**Column Chromatography Condition**: silica gel, 99 : 1 hexanes/ EtOAc as eluent.

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{image4.png}
\caption{(R)-N,N-dibenzyl-2-(2,3-dihydro-1H-inden-1-yl)ethan-1-amine (5j, Figure 4): Prepared according to General procedure A from (E)-2-(2,3-dihydro-1H-inden-1-ylidene)-N,N-diethylethan-1-amine (4j) with dibenzylamine (2f) in 69\% isolated yield.}
\end{figure}
Hz, 1H), 2.84 (ddd, J = 15.8, 8.6, 4.5 Hz, 1H), 2.75 (dt, J = 15.9, 8.1 Hz, 1H), 2.61 (dd, J = 12.9, 7.6 Hz, 1H), 2.55 (ddt, J = 13.0, 8.4, 4.4 Hz, 1H), 2.16 – 2.07 (m, 1H), 2.03 (dtt, J = 12.4, 7.9, 4.1 Hz, 1H), 1.61 – 1.55 (m, 1H), 1.47 (dq, J = 12.4, 8.0 Hz, 1H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 147.77, 144.07, 140.03, 129.06, 128.33, 126.97, 126.32, 126.14, 124.50, 123.59, 58.58, 51.70, 42.74, 32.64, 32.22, 31.52.

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{25}\)H\(_{28}\)N, 342.2222; found, 342.2221.

\((S)-N,N\text{-dibenzyl-2-}(\text{chroman-4-yl})\text{ethan-1-amine (5k, Figure 4):}\) Prepared according to General procedure A from \((E)-2-(\text{chroman-4-ylidene})N,N\text{-diethylethan-1-amine (4k} with dibenzylamine (2f) in 77\% isolated yield.

\textbf{Column Chromatography Condition:} silica gel, 30 : 1 hexanes/ EtOAc as eluent.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.39 (d, J = 7.1 Hz, 4H), 7.33 (dd, J = 8.4, 6.7 Hz, 4H), 7.28 – 7.23 (m, 2H), 7.11 – 7.03 (m, 1H), 7.02 – 6.94 (m, 1H), 6.83 – 6.74 (m, 2H), 4.05 (dd, J = 6.5, 4.3 Hz, 2H), 3.74 (d, J = 13.5 Hz, 2H), 3.48 (d, J = 13.5 Hz, 2H), 2.94 (dq, J = 9.9, 5.0 Hz, 1H), 2.61 (dt, J = 12.9, 7.6 Hz, 1H), 2.51 (dd, J = 12.7, 7.3, 4.7 Hz, 1H), 2.06 (ddt, J = 14.0, 7.7, 4.1 Hz, 1H), 1.84 – 1.70 (m, 1H), 1.62 (ddd, J = 14.2, 10.0, 7.0, 4.6 Hz, 1H), 1.51 – 1.40 (m, 1H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 154.64, 139.89, 129.12, 128.38, 127.24, 127.07, 126.96, 120.24, 116.83, 63.54, 58.75, 50.54, 34.08, 31.06, 26.58.

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{25}\)H\(_{28}\)N, 358.2171; found, 358.2171.

\((S)-4-(2-(6,7,8,9\text{-tetrahydro-5H-benzo[7]}\text{annulen-5-yl})\text{ethyl})\text{morpholine (5l, Figure 3):}\) Prepared according to General procedure A from \((Z)-N,N\text{-diethyl-2-(6,7,8,9-tetrahydro-5H-benzo[7]}\text{annulen-5-ylidene})\text{ethan-1-amine (4l} with morpholine (2a) in 75\% isolated yield.

\textbf{Column Chromatography Condition:} 100 g Al\(_2\)O\(_3\) + 6 g H\(_2\)O, 30 : 1 hexanes/ EtOAc with 0.5\% MeOH to 15 : 1 hexanes/ EtOAc with 1.0\% MeOH as gradient eluent.

\(^1\)H NMR (500 MHz, Benzene-d\(_6\)) \(\delta\): 7.13 (dd, J = 7.5, 1.8 Hz, 1H), 7.10 (td, J = 7.2, 1.8 Hz, 1H), 7.06 (td, J = 7.1, 1.8 Hz, 1H), 7.03 (dd, J = 7.4, 1.8 Hz, 1H), 3.61 (t, J = 4.8 Hz, 4H), 2.90 (qd, J = 7.1, 2.3 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.71 – 2.64 (m, 1H), 2.19 – 2.11 (m, 6H), 1.91 (dq, J = 13.8, 7.4 Hz, 1H), 1.79 – 1.44 (m, 7H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 145.14, 142.59, 130.03, 128.03, 126.06, 126.04, 67.15, 57.99, 54.02, 43.20, 36.26, 33.40, 29.85, 29.72, 28.22.

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{17}\)H\(_{26}\)NO, 260.2014; found, 260.2017.
\((S)\)-\(N,N\)-dibenzyl-4,4,4-trifluoro-3-phenylbutan-1-amine (5m, Figure 4): Prepared according to General procedure A from \((E)\)-\(N,N\)-diethyl-4,4,4-trifluoro-3-phenylbut-2-en-1-amine (4m) with dibenzylamine (2f) in 63% isolated yield.

**Column Chromatography Condition:** silica gel, 50 : 1 hexanes/ EtOAc as eluent.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.34 – 7.27 (m, 9H), 7.25 – 7.18 (m, 4H), 7.01 (dd, \(J = 7.5, 1.8\) Hz, 2H), 3.67 (d, \(J = 13.5\) Hz, 2H), 3.43 – 3.34 (m, 1H), 3.32 (d, \(J = 13.5\) Hz, 2H), 2.37 (ddd, \(J = 12.1, 8.6, 6.1\) Hz, 1H), 2.33 – 2.27 (m, 1H), 2.27 – 2.19 (m, 1H), 2.02 – 1.88 (m, 1H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 139.41, 134.82 (q, \(J = 1.9\) Hz), 129.15, 129.13, 128.60, 128.39, 127.97, 127.31 (q, \(J = 279.5\) Hz), 127.09, 58.46, 50.19, 47.49 (q, \(J = 26.6\) Hz), 26.95 (q, \(J = 1.7\) Hz).

\(^19\)F NMR (471 MHz, CDCl\(_3\)) \(\delta\): -69.58 (d, \(J = 9.8\) Hz).

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{23}\)H\(_{25}\)NF\(_3\), 384.1939; found, 384.1927.

\((R)\)-\(N,N\)-dibenzyl-4,4,4-trifluoro-3-phenylbutan-1-amine (5n, Figure 3): Prepared according to General procedure A from \((Z)\)-\(N,N\)-diethyl-4,4,4-trifluoro-3-phenylbut-2-en-1-amine (4n) with dibenzylamine (2f) in 71% isolated yield.

**Column Chromatography Condition:** silica gel, 50 : 1 hexanes/ EtOAc as eluent.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 8.735 – 7.26 (m, 9H), 7.24 – 7.17 (m, 4H), 7.08 – 6.95 (m, 2H), 3.67 (d, \(J = 13.4\) Hz, 2H), 3.43 – 3.34 (m, 1H), 3.32 (d, \(J = 13.5\) Hz, 2H), 2.43 – 2.33 (m, 1H), 2.32 – 2.20 (m, 2H), 1.94 (dt, \(J = 15.2, 6.8, 3.3\) Hz, 1H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 139.41, 134.82 (q, \(J = 1.8\) Hz), 129.15, 129.13, 128.60, 128.39, 127.97, 127.31 (q, \(J = 279.0\) Hz), 127.09, 58.47, 50.19, 47.49 (q, \(J = 26.6\) Hz), 26.96 (q, \(J = 1.8\) Hz).

\(^19\)F NMR (471 MHz, CDCl\(_3\)) \(\delta\): -69.58 (d, \(J = 9.8\) Hz).

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{23}\)H\(_{25}\)NF\(_3\), 384.1939; found, 384.1952.

\((R)\)-\(N,N,3\)-tribenzyl-4,4,4-trifluorobutan-1-amine (5o, Figure 4): Prepared according to General procedure A from \((E)\)-3-benzyl\(N,N\)-diethyl-4,4,4-trifluorobut-2-en-1-amine (4o) with dibenzylamine (2f) in 59% isolated yield.

**Column Chromatography Condition:** silica gel, 50 : 1 hexanes/ EtOAc as eluent.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.30 (dd, \(J = 8.1, 6.8\) Hz, 4H), 7.26 – 7.15 (m, 9H), 7.04 – 6.99 (m, 2H), 3.54 – 3.46 (m, 2H), 3.38 (d, \(J = 13.6\) Hz, 2H), 2.94 – 2.81 (m, 1H), 2.54 – 2.45 (m, 2H), 2.45 – 2.34 (m, 2H), 1.82 (ddt, \(J = 14.5, 7.3, 4.9\) Hz, 1H), 1.60 (dd, \(J = 13.6, 7.7, 5.6\) Hz, 1H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 139.40, 138.26, 129.28, 129.02, 128.58, 128.44 (q, \(J = 280.4\) Hz), 128.33, 127.05, 126.61, 58.14, 50.53, 42.39 (q, \(J = 24.8\) Hz), 34.40 (q, \(J = 2.9\) Hz), 24.96 (q, \(J = 1.8\) Hz).
\[^{19}\text{F NMR}\] (471 MHz, CDCl\(_3\)) \(\delta\): -70.26 (d, \(J = 8.3\) Hz).

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{25}\)H\(_{27}\)NF\(_3\)= 398.2096; found, 398.2090.

(R)-\(N,N,3\)-tribenzyl-4,4-difluorobutan-1-amine (5p, Figure 4): Prepared according to General procedure A from (E)-3-benzyl-N\(_2\),N-diethyl-4,4-difluorobut-2-en-1-amine (4p) with dibenzylamine (2f) in 70% isolated yield.

**Column Chromatography Condition:** silica gel, 30 : 1 hexanes/ EtOAc as eluent.

\[^{1}\text{H NMR}\] (500 MHz, CDCl\(_3\)) \(\delta\): 7.34 - 7.28 (m, 7H), 7.26 - 7.22 (m, 4H), 7.21 - 7.16 (m, 1H), 7.08 - 7.02 (m, 2H), 5.54 (td, \(J = 56.7, 2.9\) Hz, 1H), 3.57 - 3.48 (m, 2H), 3.44 (d, \(J = 13.4\) Hz, 2H), 2.67 (dd, \(J = 13.9, 6.9\) Hz, 1H), 2.49 - 2.47 (m, 1H), 2.45 (t, \(J = 6.8\) Hz, 2H), 2.33 - 2.11 (m, 1H), 1.83 - 1.67 (m, 1H), 1.53 - 1.46 (m, 1H).

\[^{13}\text{C NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\): 139.60, 139.00, 129.28, 129.11, 128.60, 128.37, 127.09, 126.42, 117.96 (t, \(J = 241.7\) Hz), 58.37, 50.35, 41.73 (t, \(J = 19.1\) Hz), 33.89 (dd, \(J = 6.2, 3.6\) Hz), 24.20 (t, \(J = 3.9\) Hz).

\[^{19}\text{F NMR}\] (471 MHz, CDCl\(_3\)) \(\delta\): -124.91 (ddd, \(J = 277.8, 56.7, 17.6\) Hz), -126.24 (ddd, \(J = 277.8, 56.7, 17.6\) Hz).

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{25}\)H\(_{28}\)NF\(_3\)= 380.2190; found, 380.2182.

(R)-4-(3-(dimethyl(phenyl)silyl)-3-phenylpropyl)morpholine (5q, Figure 4): Prepared according to General procedure A from (Z)-3-(dimethyl(phenyl)silyl)-N\(_2\),N-diethyl-3-phenylprop-2-en-1-amine (4q) with morpholine (2a) in 75% isolated yield.

**Column Chromatography Condition:** 100 g Al\(_2\)O\(_3\) + 9 g H\(_2\)O, 30 : 1 hexanes/ EtOAc with 0.5% MeOH to 15 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

\[^{1}\text{H NMR}\] (500 MHz, CDCl\(_3\)) \(\delta\): 7.42 - 7.36 (m, 2H), 7.39 - 7.28 (m, 3H), 7.23 - 7.15 (m, 2H), 7.12 - 7.05 (m, 1H), 6.98 - 6.91 (m, 2H), 3.65 (t, \(J = 4.7\) Hz, 4H), 2.32 - 2.23 (m, 5H), 2.20 (dd, \(J = 12.1, 7.9, 6.0\) Hz, 1H), 2.11 (dt, \(J = 12.1, 7.7\) Hz, 1H), 1.90 (dt, \(J = 8.1, 7.0\) Hz, 2H), 0.25 (s, 3H), 0.16 (s, 3H).

\[^{13}\text{C NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\): 142.71, 137.57, 134.24, 129.19, 128.20, 128.00, 127.75, 124.75, 67.11, 58.83, 53.86, 34.51, 26.45, -3.73, -5.29.

HRMS (ESI-TOF) \(m/z\): [M+H\(^+\)] calculated for C\(_{21}\)H\(_{30}\)NOBSi, 340.2097; found, 340.2091.

(S)-1-(2-(chroman-4-yl)ethyl)-4-(3,4-dimethoxyphenyl)piperidine

(Terikanlant, Scheme 2): Prepared according to General procedure A from (E)-2-(chroman-4-ylidene)-N\(_2\),N-diethylethen-1-amine (4k) with 4-(3,4-dimethoxyphenyl)piperidine\(^7\) in 75% isolated yield.

**Column Chromatography Condition:** 100 g Al\(_2\)O\(_3\) + 6 g H\(_2\)O, 12 : 1 hexanes/ EtOAc with 0.5% MeOH to 6 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.
1H NMR (500 MHz, CDCl3) δ: 7.20 (d, J = 7.6 Hz, 1H), 7.13 (ddd, J = 8.7, 7.4, 1.7 Hz, 1H), 6.90 (td, J = 7.4, 1.3 Hz, 1H), 6.87 – 6.80 (m, 4H), 4.31 – 4.19 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.23 – 3.06 (m, 2H), 2.94 (dq, J = 10.2, 5.3 Hz, 1H), 2.55 (t, J = 7.7 Hz, 2H), 2.49 (dt, J = 11.7, 4.2 Hz, 1H), 2.21 – 2.03 (m, 4H), 1.95 – 1.75 (m, 6H).

13C NMR (125 MHz, CDCl3) δ: 154.61, 148.92, 147.42, 139.23, 129.22, 127.47, 126.34, 120.27, 118.66, 116.95, 111.25, 110.24, 63.62, 56.71, 56.03, 55.91, 54.85, 54.43, 42.50, 33.91, 33.89, 33.85, 32.19, 27.24.

HRMS (ESI-TOF) m/z: [M+H+] calculated for C24H32NO3, 382.2382; found, 382.2375.

Enantioselective Synthesis of (R)-Tolterodine

Vinyl bromide 6 was prepared from trans-cinnamyl chloride according to literature.2

Suzuki coupling: To an oven-dried 100 ml round bottom flask was charged with a stir bar, purged with N2 three times then added 11 mg Pd(OAc)2 (0.050 mmol, 1.0 mol %), 26 mg PPh3 (0.10 mmol, 2.0 mol %), 0.560 g KOH (10 mmol, 2.0 equiv), starting material vinyl bromide (1.48g, 5 mmol, 1.0 equiv) ,0.996 g (2-methoxy-5-methylphenyl)boronic acid 7 (6.5 mmol, 1.3 equiv) and 20 mL THF and 20 mL MeOH. The reaction was stirred at rt overnight followed by dilution with EtOAc, and washed by 1 N NaOH solution and brine. Acid-base extraction: the organic layer was concentrated in vacuo, re-dissolved in Et2O, and extracted with 3 N HCl solution three times. The resulting acidic aqueous layer was then basified by the addition of 5N NaOH solution until the pH > 11, followed by the extraction with DCM. The combined organic layers was then dried over MgSO4, concentrated in vacuo, purified by Al2O3 column chromatography: 200 g Al2O3 + 8 g H2O, 50 : 1 hexanes/ EtOAc with 0.5% MeOH as eluent to afford allylic amine 8 in 91% isolated yield. For 1n: 1H NMR (500 MHz, CDCl3) δ: 7.30 – 7.26 (m, 2H), 7.24 – 7.19 (m, 1H), 7.18 – 7.14 (m, 2H), 7.06 – 7.00 (m, 2H), 6.72 (d, J = 8.0 Hz, 1H), 5.89 (t, J = 6.4 Hz, 1H), 3.51 (s, 3H), 3.28 (d, J = 6.4 Hz, 2H), 3.06 (p, J = 6.5 Hz, 2H), 2.29 (p, J = 0.8 Hz, 3H), 0.96 (d, J = 6.6 Hz, 12H). 13C NMR (125 MHz, CDCl3) δ: 155.24, 141.08, 138.59, 134.18, 133.49, 131.64, 129.79, 129.20, 128.69, 127.55, 126.42, 111.95, 55.99, 48.96, 43.99, 20.96, 20.62. The geometry of double bond was confirmed by NOE experiment (See Supplementary Figure 64 for details).
Tolterodine synthesis: [Rh(COD)Cl]_2 (4.0 mg, 0.75 mol %), (S)-BINAP (9.6 mg, 1.5 mol %), NaBArF (12.8 mg, 1.5 mol %), and 1,4-dioxane (0.8 mL) were added to a 20 mL vial equipped with a stir bar in the glove box under nitrogen atmosphere. To the vial was added allylic diisopropyl amine (8, 1.0 mmol, 1.0 equiv). The resulting solution was allowed to stir for 10 h at 100 °C. After 10 h, formic acid (3.0 mmol, 3.0 equiv) was added into reaction vial via syringe and the reaction was allowed to stir for another 5 h at 100 °C. The reaction crude was then diluted in DCM, filtered through basic alumina, and concentrated in vacuo (to get rid of 1,4-dioxane solvent). The residue was then transferred into another 20 mL vial, followed by the addition of HBr solution (2.2 mL, 13.2 equiv) and HOAc (2.0 mL), and allowed to stir at 115 °C for 4 h. After 4 h, the reaction crude was then diluted in water, extracted with EtOAc three times. Combined organic layers were washed with 1 N NaOH solution three times. The pH of last basic wash was verified to be >10. The organic layer was washed with brine, dried over MgSO_4, concentrated in vacuo and then purified by basic alumina chromatography to afford the desired product (R)-Tolterodine in 88% isolated yield.

Column Chromatography Condition: 100 g Al_2O_3 + 5 g H_2O, 15 : 1 hexanes/ EtOAc with 0.5% MeOH to 8 : 1 hexanes/ EtOAc with 1.0% MeOH as gradient eluent.

^1H NMR (500 MHz, CDCl_3) δ: 10.33 (brs, 1H), 7.33 (d, J = 4.3 Hz, 4H), 7.23 (d, J = 4.3 Hz, 1H), 6.85 (dd, J = 8.2, 2.1 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 4.49 (dd, J = 11.3, 4.0 Hz, 1H), 3.23 (p, J = 6.7 Hz, 2H), 2.73 (dt, J = 12.7, 3.6 Hz, 1H), 2.50 – 2.25 (m, 2H), 2.12 (s, 3H), 2.10 – 2.03 (m, 1H), 1.13 (d, J = 6.7 Hz, 6H), 1.08 (d, J = 6.6 Hz, 6H).

^13C NMR (125 MHz, CDCl_3) δ: 153.34, 144.88, 132.55, 129.53, 128.78, 128.66, 128.42, 127.88, 126.28, 118.32, 48.03, 42.21, 39.46, 33.37, 20.91, 20.10, 19.69.

HRMS (ESI-TOF) m/z: [M+H]^+ calculated for C_{22}H_{32}NO, 326.2484; found, 326.2489.
Determination of enantiomeric ratio of product 3m.

Procedure: Product 3bm was prepared according to the General Procedure B, followed by the amidation with [(R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride to afford the desired amide product 3m-amide. The corresponding rac-3m-amide was prepared using same method but with (±)-BINAP as ligand.

Supplementary Figure 1. Crude $^1$H NMR of rac-3m-amide and 3m-amide
Determination of enantiomeric ratio of product 3n.

3n-amide and rac-3n-amide were prepared as described above.

Supplementary Figure 2. Zoom-in of Supplementary Figure 1

for 3m-amide dr=27.11:1, therefore, the er of 3bm = 96.5 : 3.5. \([\alpha]_D^{23} = -16.29 (c = 0.81)\).

Supplementary Figure 3. Crude \(^1\)H NMR of rac-3n-amide and 3n-amide
Supplementary Figure 4. Zoom-in of Supplementary Figure 3

for 3n-amide dr=25.0:1, therefore, the er of 3bm = 96.2 : 3.8. $[\alpha]_D^{23} = +2.39 \ (c = 1.98)$

Control Experiment of Enamine Reduction

![Control Experiment Diagram]

Supplementary Figure 5. Control experiments

Procedure: A pre-made geranyl diethyl enamine was subjected to reduction conditions with and without the rhodium catalyst as shown above. After 2 hours, the reaction crude was concentrated under vacuum, and analyzed using NMR spectroscopy in CDCl₃.
25% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 75% hexanes, 1.0 mL/min, CHIRALPAK® IA3

$\text{er} = 96.2:3.8$

$\left[\alpha\right]_{D}^{23} = +5.26 \ (c = 1.03)$

Supplementary Figure 6. HPLC spectra for racemic and chiral 3a
10% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 90% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 95.5:4.5 \]

\[ [\alpha]_D^{23} = +0.96 \ (c = 1.06) \]

**Supplementary Figure 7.** HPLC spectra for racemic and chiral 3b
15% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 85% hexanes, 0.5 mL/min, CHIRALPAK® IA3

$$\text{er} = 97.9:2.1$$

$$[\alpha]_{D}^{23} = +4.99 \ (c = 1.22)$$

**Supplementary Figure 7.** HPLC spectra for racemic and chiral 3c
35% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 65% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

er = 97.1:2.9

[α]D$^21$ = +6.54 (c = 1.24)

Supplementary Figure 8. HPLC spectra for racemic and chiral 3d
25% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 75% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H 

$er = 95.8:4.2$

$[\alpha]_{D}^{23} = +5.90 \ (c = 1.5.0)$

**Supplementary Figure 9.** HPLC spectra for racemic and chiral 3e
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

$$\text{er} = 95.8 : 4.2$$

$$[\alpha]_{D}^{23} = -0.90 \ (c = 1.27)$$

Supplementary Figure 10. HPLC spectra for racemic and chiral 3f
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

$\text{er} = 99.8:0.2$

$[\alpha]_D^{23} = -53.81 \ (c = 1.41)$

**Supplementary Figure 11.** HPLC spectra for racemic and chiral 3g
50% (95% hexanes, 5% EtOH, 0.3% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALPAK® IB3

\[ \text{er} = 97.9:2.1 \]

\[ [\alpha]_D^{23} = +5.06 \ (c = 1.82) \]

**Supplementary Figure 12.** HPLC spectra for racemic and chiral 3g'
10% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 90% hexanes, 0.5 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 96.6:3.4 \]

\[ [\alpha]_{b}^{23} = +0.94 \ (c = 1.57) \]

**Supplementary Figure 13.** HPLC spectra for racemic and chiral 3h
15% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 85% hexanes, 0.5 mL/min, CHIRALCEL® OJ-H

$er = 96.9:3.1$

$[\alpha]_{D}^{23} = +2.92 \ (c = 1.37)$

Supplementary Figure 14. HPLC spectra for racemic and chiral 3i
3j was hydrogenated to \( \text{H}_2\cdot3j \) for the determination of er.

8% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 92% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 96.1 : 3.9, [\alpha]_D^{23} = +3.89 \ (c = 1.39) \]

Supplementary Figure 15. HPLC spectra for racemic and chiral \( \text{H}_2\cdot3j \)
15% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 85% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 97.1 : 2.9 \]

\[ [\alpha]_D^{23} = +2.30 \ (c = 1.22) \]

Supplementary Figure 16. HPLC spectra for racemic and chiral 3k
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALPAK® ID3

er = 98.7:1.3

\[ [\alpha]_D^{23} = -29.98 \ (c = 1.04) \]

**Supplementary Figure 17.** HPLC spectra for racemic and chiral 3l
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALCEL® OJ-H

$\text{er} = 98.7:1.3$

$[\alpha]_D^{23} = -22.61 \ (c = 1.15)$

**Supplementary Figure 18.** HPLC spectra for racemic and chiral 5a
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALPAK® IA3

er = 99.1:0.9

\([\alpha]_D^{23} = -10.85 \ (c = 2.12)\)

Supplementary Figure 19. HPLC spectra for racemic and chiral 5b
30% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 70% hexanes, 0.8 mL/min, CHIRALPAK® IA3

\[ \text{er} = 97.8:2.2 \]

\[ [\alpha]_D^{23} = -33.09 \ (c = 1.06) \]

**Supplementary Figure 20.** HPLC spectra for racemic and chiral 5c
10% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 90% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

$er = 98.9 : 1.1$

$[\alpha]_D^{23} = 8.84 \ (c = 1.74)$

Supplementary Figure 21. HPLC spectra for racemic and chiral 5e
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 98.1 : 1.9 \]

\[ [\alpha]_D^{23} = 0.72 \quad (c = 1.77) \]

**Supplementary Figure 22.** HPLC spectra for racemic and chiral 5f
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

$er = 96.5 : 3.5$

$[\alpha]_D^{23} = 2.63 (c = 2.28)$

**Supplementary Figure 23.** HPLC spectra for racemic and chiral 5g
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALCEL® OJ-H

$$\text{er} = 97.6 : 2.4$$

$$[\alpha]_D^{23} = 1.49 \ (c = 1.05)$$

**Supplementary Figure 24.** HPLC spectra for racemic and chiral 5h
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALPAK® IA3 

$er = 98.6 : 1.4$

$[\alpha]_D^{23} = -1.38 \ (c = 1.97)$

Supplementary Figure 25. HPLC spectra for racemic and chiral 5i
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALPAK® IB3

er = 92.5 : 7.5

\[ \alpha_d^{23} = 1.70 \text{ (c = 1.80)} \]

**Supplementary Figure 26.** HPLC spectra for racemic and chiral 5j
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALPAK® IB3

\[ \text{er} = 97.2 : 2.8 \]

\[ [\alpha]_D^{23} = -13.51 \ (c = 2.32) \]

**Supplementary Figure 27.** HPLC spectra for racemic and chiral 5k
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALPAK® IB3

\[ \text{er} = 96.0 : 4.0 \]

\[ [\alpha]_{D}^{23} = 16.81 \] \( (c = 1.16) \)

**Supplementary Figure 28.** HPLC spectra for racemic and chiral 5l
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 98.6 : 1.4 \]

\[ [\alpha]_D^{23} = 85.78 \ (c = 2.12) \]

**Supplementary Figure 29.** HPLC spectra for racemic and chiral 5m
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALCEL® OJ-H

er = 98.2 : 1.8

$[\alpha]_D^{23} = -79.65 \ (c = 1.94)$

Supplementary Figure 30. HPLC spectra for racemic and chiral 5n
25% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 75% hexanes, 0.8 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 97.1 : 2.9 \]

\[ [\alpha]_{D}^{23} = -2.22 \ (c = 1.71) \]

Supplementary Figure 31. HPLC spectra for racemic and chiral 5o
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALPAK® IB3

\[ \text{er} = 97.2 : 2.8 \]

\[ [\alpha]_{D}^{23} = 0.96 \ (c = 1.68) \]

Supplementary Figure 32. HPLC spectra for racemic and chiral 5p
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 0.8 mL/min, CHIRALPAK® IA3
er = 98.8 : 1.2

$[\alpha]_D^{23} = 8.10 \ (c = 1.98)$

**Supplementary Figure 33.** HPLC spectra for racemic and chiral 5q
100% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 0.8 mL/min, CHIRALPAK® IB3

$$\text{er} = 96.7 : 3.3$$

$$[\alpha]_D^{23} = -8.85 \ (c = 2.68)$$

Supplementary Figure 34. HPLC spectra for racemic and chiral Terikalant
50% (95% hexanes, 5% EtOH, 0.2% TFA, 0.1% DEA), 50% hexanes, 1.0 mL/min, CHIRALCEL® OJ-H

\[ \text{er} = 96.0:4.0 \]

\[ [\alpha]_{D}^{23} = 114.94 \ (c = 2.99) \]

**Supplementary Figure 35.** HPLC spectra for racemic and chiral Tolterodine
**Supplementary Figure 36.** $^1$H NMR spectra of compound 4c

**Supplementary Figure 37.** $^{13}$C NMR spectra of compound 4c
Supplementary Figure 38. $^1$H NMR spectra of compound 4e

Supplementary Figure 39. $^{13}$C NMR spectra of compound 4e
Supplementary Figure 40. $^1$H NMR spectra of compound 4g

Supplementary Figure 41. $^{13}$C NMR spectra of compound 4g
**Supplementary Figure 42.** $^1$H NMR spectra of compound 4j

**Supplementary Figure 43.** $^{13}$C NMR spectra of compound 4j
Supplementary Figure 44. $^1$H NMR spectra of compound 4l

Supplementary Figure 45. $^{13}$C NMR spectra of compound 4l
Supplementary Figure 46. NOE spectra of compound 4l

Supplementary Figure 47. 1H NMR spectra of compound 4m
Supplementary Figure 48. $^{13}$C NMR spectra of compound 4m

Supplementary Figure 49. $^{19}$F NMR spectra of compound 4m
**Supplementary Figure 50.** $^1$H NMR spectra of compound 4n

**Supplementary Figure 51.** $^{13}$C NMR spectra of compound 4n
**Supplementary Figure 52.** $^{19}$F NMR spectra of compound 4n

**Supplementary Figure 53.** $^1$H NMR spectra of compound 4o
Supplementary Figure 54. $^{13}$C NMR spectra of compound 4o

Supplementary Figure 55. $^{19}$F NMR spectra of compound 4o
**Supplementary Figure 56.** $^1$H NMR spectra of compound 4p

**Supplementary Figure 57.** $^{13}$C NMR spectra of compound 4p
Supplementary Figure 58. $^{19}$F NMR spectra of compound 4p

Supplementary Figure 59. NOE spectra of compound 4p
**Supplementary Figure 60.** $^1$H NMR spectra of compound 4q

**Supplementary Figure 61.** $^{13}$C NMR spectra of compound 4q
Supplementary Figure 62. $^1$H NMR spectra of compound 8

Supplementary Figure 63. $^{13}$C NMR spectra of compound 8
**Supplementary Figure 64.** NOE spectra of compound 8
**Supplementary Figure 65.** $^1$H NMR spectra of compound 3a

**Supplementary Figure 66.** $^{13}$C NMR spectra of compound 3a
Supplementary Figure 67. $^1$H NMR spectra of compound 3b

$^1$H NMR, 500 MHz, CDCl$_3$

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Supplementary Figure 68. $^{13}$C NMR spectra of compound 3b

$^{13}$C NMR, 125 MHz, CDCl$_3$
**Supplementary Figure 69.** $^1$H NMR spectra of compound 3c

**Supplementary Figure 70.** $^{13}$C NMR spectra of compound 3c
Supplementary Figure 71. $^1$H NMR spectra of compound 3d

Supplementary Figure 72. $^{13}$C NMR spectra of compound 3d
**Supplementary Figure 73.** $^1$H NMR spectra of compound 3e

**Supplementary Figure 74.** $^{13}$C NMR spectra of compound 3e
Supplementary Figure 75. ¹H NMR spectra of compound 3f

Supplementary Figure 76. ¹³C NMR spectra of compound 3f
Supplementary Figure 77. $^1$H NMR spectra of compound 3g

Supplementary Figure 78. $^{13}$C NMR spectra of compound 3g
**Supplementary Figure 79.** $^1$H NMR spectra of compound 3g'.

**Supplementary Figure 80.** $^{13}$C NMR spectra of compound 3g'.
Supplementary Figure 81. $^1$H NMR spectra of compound 3h

Supplementary Figure 82. $^{13}$C NMR spectra of compound 3h
Supplementary Figure 83. $^1$H NMR spectra of compound 3i

Supplementary Figure 84. $^{13}$C NMR spectra of compound 3i
Supplementary Figure 85. $^1$H NMR spectra of compound 3j

Supplementary Figure 86. $^{13}$C NMR spectra of compound 3j
Supplementary Figure 87. $^{19}$F NMR spectra of compound 3j

12 : 1 mixture of 3aj and hydrogenated 3aj

$^{19}$F NMR, 471 MHz, CDCl$_3$
Supplementary Figure 88. $^1$H NMR spectra of compound 3k

Supplementary Figure 89. $^{13}$C NMR spectra of compound 3k
Supplementary Figure 90. $^1$H NMR spectra of compound 3l

Supplementary Figure 91. $^{13}$C NMR spectra of compound 3l
Supplementary Figure 92. $^1$H NMR spectra of compound 3m

Supplementary Figure 93. $^{13}$C NMR spectra of compound 3m
Supplementary Figure 94. $^1$H NMR spectra of compound 3n

Supplementary Figure 95. $^{13}$C NMR spectra of compound 3n
**Supplementary Figure 95.** $^1$H NMR spectra of compound 5a

**Supplementary Figure 96.** $^{13}$C NMR spectra of compound 5a
Supplementary Figure 97. $^1$H NMR spectra of compound 5b

Supplementary Figure 98. $^{13}$C NMR spectra of compound 5b
Supplementary Figure 99. $^1$H NMR spectra of compound 5c

Supplementary Figure 100. $^{13}$C NMR spectra of compound 5c
Supplementary Figure 101. $^1$H NMR spectra of compound 5d

Supplementary Figure 102. $^{13}$C NMR spectra of compound 5d
**Supplementary Figure 103.** $^1$H NMR spectra of compound 5e

**Supplementary Figure 104.** $^{13}$C NMR spectra of compound 5e
Supplementary Figure 105. $^1$H NMR spectra of compound 5f

Supplementary Figure 106. $^{13}$C NMR spectra of compound 5f
Supplementary Figure 107. $^1$H NMR spectra of compound 5g

Supplementary Figure 108. $^{13}$C NMR spectra of compound 5g
Supplementary Figure 109. \(^1\)H NMR spectra of compound 5h

Supplementary Figure 110. \(^13\)C NMR spectra of compound 5h
Supplementary Figure 111. $^1$H NMR spectra of compound 5i

Supplementary Figure 112. $^{13}$C NMR spectra of compound 5i
Supplementary Figure 113. $^1$H NMR spectra of compound 5j
**Supplementary Figure 115.** $^{13}$C NMR spectra of compound 5j

**Supplementary Figure 116.** $^1$H NMR spectra of compound 5k
Supplementary Figure 117. $^{13}$C NMR spectra of compound 5k

Supplementary Figure 118. $^1$H NMR spectra of compound 5l
**Supplementary Figure 119.** $^{13}$C NMR spectra of compound 5l

**Supplementary Figure 120.** $^1$H NMR spectra of compound 5m
Supplementary Figure 121. $^{13}$C NMR spectra of compound 5m

Supplementary Figure 122. $^{19}$F NMR spectra of compound 5m
**Supplementary Figure 123.** $^1$H NMR spectra of compound \textit{5n}

**Supplementary Figure 124.** $^{13}$C NMR spectra of compound \textit{5n}
Supplementary Figure 125. $^{19}$F NMR spectra of compound 5n

Supplementary Figure 126. $^1$H NMR spectra of compound 5o
Supplementary Figure 127. $^{13}$C NMR spectra of compound 5o

Supplementary Figure 128. $^{19}$F NMR spectra of compound 5o
Supplementary Figure 129. $^1$H NMR spectra of compound 5p

Supplementary Figure 130. $^{13}$C NMR spectra of compound 5p
Supplementary Figure 131. $^{19}$F NMR spectra of compound 5p
Supplementary Figure 132. $^1$H NMR spectra of compound 5q

Supplementary Figure 133. $^{13}$C NMR spectra of compound 5q
Supplementary Figure 134. $^1$H NMR spectra of compound Terikalant

Supplementary Figure 135. $^{13}$C NMR spectra of compound Terikalant
Supplementary Figure 136. $^1$H NMR spectra of compound Tolterodine

Supplementary Figure 137. $^{13}$C NMR spectra of compound Tolterodine
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