Electronic Supplementary Material (ESI) for ChemComm.

Intramolecular Hydrogen-Bond Activation for the Addition of Nucleophilic Imines: 2-Hydroxybenzophenone as Chemical Auxiliary

Houcine Choubane,[a,b] Alberto F. Garrido-Castro,[a] Cuauhtemoc Alvarado,[a] Ana Martín-Somer,[c] Andrea Guerrero-Corella,[a] Mortada Daaou,[b] Sergio Díaz-Tendero,[c,d,e] M. Carmen Maestro,[a] Alberto Fraile,[a,e] and José Alemán*[a,e]

a Departamento de Química Orgánica (Módulo 1), Facultad de Ciencias, Universidad Autónoma de Madrid, 28049 Madrid, Spain. E-mail: jose.aleman@uam.es; webpage: www.uam.es/jose.aleman

b L.S.P.B.E, Département de Chimie Organique Industrielle, Faculté de Chimie, Université des Sciences et de la Technologie d'Oran- Mohamed Boudiaf- B.P 1505 El Mnaouer, Oran, 31000, Algérie.

c Departamento de Química (Módulo 13), Facultad de Ciencias, Universidad Autónoma de Madrid, 28049 Madrid, Spain.

d Condensed Matter Physics Center (IFIMAC), Universidad Autónoma de Madrid, 28049 Madrid, Spain.

e Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain

·E-mail: jose.aleman@uam.es; www.uam.es/jose.aleman

Electronic Supporting Information for

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1. General methods and materials

NMR spectra were acquired on a BRUKER AVANCE 300 MHz spectrometer running at 300 MHz for ^{1}H and 75 MHz for ^{13}C, and are internally referenced to residual solvent signals ($CDCl_3$ referenced at δ 7.26 ppm for ^{1}H NMR and δ 77.2 ppm for ^{13}C NMR, CD_3OD referenced at δ 3.31 ppm for ^{1}H NMR). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, bd = broad doublet, t = triplet, td = triple doublet, tt = triple triplet, p = quintuplet, m = multiplet), coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons.

High-Resolution Mass Spectra (HRMS) were obtained on an Agilent Technologies 6120 Quadrupole LC/MS coupled with an SFC Agilent Technologies 1260 Infinity Series instrument for the MS (ESI) (Electrospray Ionization). MassWorks software version 4.0.0.0 (Cerno Bioscience) was used for the formula identification. MassWorks is an MS calibration software which calibrates isotope profiles to achieve high mass accuracy and enables elemental composition determination on conventional mass spectrometers of unit mass resolution allowing highly accurate comparisons between calibrated and theoretical spectra.

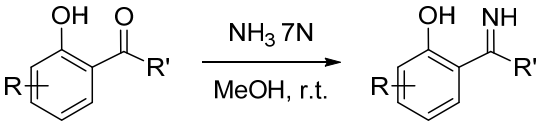
Enantiomeric purity was determined with an Agilent Technologies 1260 Infinity Supercritical Fluid Chromatography (SFC) System equipped with a UV-VIS detector, using Chiralpak IC or IG-3 chiral columns.

Optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter and are reported as follows: $[\alpha]_D^T$ (c in g/100 mL, solvent).

Commercial grade reagents and solvents were purchased from Sigma-Aldrich, Alfa Aesar, Fluorochem, TCI Chemicals and used as received without further purification unless otherwise stated. Ketimine **1a**, as well as all aldehydes (**2a-i**) are commercially available. Organocatalysts **3a-d** and **3f** were purchased from Sigma-Aldrich. Organocatalysts **3e** and **3f** were synthesized following previously described methodologies in the literature.[1]

Analytical TLC was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F_{254}) and visualized by ultraviolet irradiation. Stain solutions can be employed, using heat as developing agent. Chromatographic purification of products was accomplished by flash chromatography (FC) using silica gel (Merck Geduran® Si 60). Celite® 512 medium (Sigma-Aldrich) was used for filtration. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

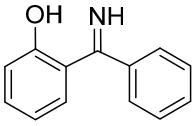
2. General procedure for the synthesis of imines 1



1

The corresponding 2-hydroxybenzophenone (1.0 equiv.) was added into an ammonia solution (7 N in MeOH, 5.0 equiv.) in a sealed tube equipped with a magnetic stir bar. The resulting mixture was stirred at room temperature to obtain a slurry (reaction was monitored by TLC). Reaction time is indicated in each case. The slurry was filtered, and the remaining solid was dried to afford imines **1**.

2-[Imino(phenyl)methyl]phenol (1b)[2]

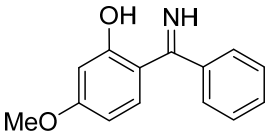


1b

The general procedure was followed with 10.0 mmol of 2-hydroxybenzophenone (2.00 g) and 50.0 mmol of the above-mentioned ammonia solution (7.1 mL). Following 15 h, ketimine **1b** was obtained as a bright yellow solid (1.90 g, 96% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.62 (bs, 1H), 9.32 (s, 1H), 7.52 – 7.44 (m, 3H), 7.40 – 7.37 (m, 2H), 7.34 – 7.31 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.75 – 6.70 (m, 1H).

2-[Imino(phenyl)methyl]-5-methoxyphenol (1c)[2]

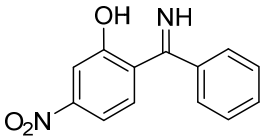


1c

The general procedure was followed with 2.0 mmol of 2-hydroxy-4-methoxybenzophenone (457 mg) and 10.0 mmol of the above-mentioned ammonia solution (1.4 mL). Following 18 h, ketimine **1c** was obtained as a bright yellow solid (436 mg, 94% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.10 (s, 1H), 8.17 (bs, 1H), 7.52 – 7.48 (m, 3H), 7.44 – 7.40 (m, 3H), 7.03 (d, *J* = 9.1 Hz, 1H), 6.42 (d, *J* = 2.5 Hz, 1H), 6.21 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.82 (s, 3H).

2-[Imino(phenyl)methyl]-5-nitrophenol (1d)

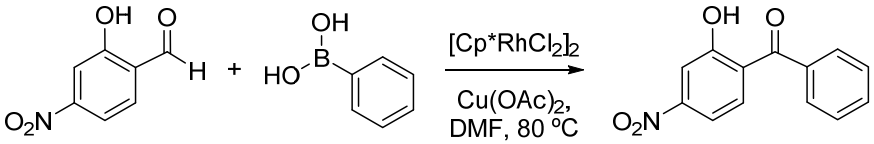


1d

The general procedure was followed with 0.3 mmol of 2-hydroxy-4-nitrobenzophenone (73.0 mg) and 1.5 mmol of the above-mentioned ammonia solution (0.2 mL). Following 15 h, ketimine **1d** was obtained as a bright orange solid (70.5 mg, 97% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.09 (bs, 1H), 9.68 (s, 1H), 7.85 (s, 1H), 7.56 – 7.51 (m, 4H), 7.44 – 7.39 (m, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 180.6, 164.7, 150.8, 138.0, 133.1, 130.9, 129.3, 127.3, 122.7, 113.9, 111.8. **HRMS calculated for $C_{13}H_9N_2O_3$ [M-H]$^-$**: 241.0608, found: 241.0586.

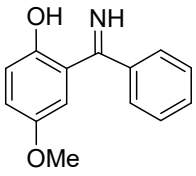
Synthesis of 2-hydroxy-4-nitrobenzophenone



According to a previously described methodology,[3] 2-hydroxy-4-nitrobenzaldehyde (125.3 mg, 0.75 mmol, 1.0 equiv.) and phenylboronic acid (182.9 mg, 1.5 mmol, 2.0 equiv.) were dissolved in 8.0 mL of anydhrous DMF, followed by addition of $[Cp^*RhCl_2]_2$ (18.5 mg, 0.03 mmol, 4 mol%) and $Cu(OAc)_2$ (272.4 mg, 1.5 mmol, 2.0 equiv.). The reaction was performed in an oven-dried sealed tube equipped with a magnetic stir bar. After being refluxed overnight, the reaction was diluted with EtOAc (20 mL) and washed with H_2O (3 x 10 mL). The organic layer was dried with Na_2SO_4 and concentrated. Column chromatography (9:1 cyclohexane:EtOAc) afforded the benzophenone as an orange solid (74.8 mg, 41% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.95 (s, 1H), 7.87 (d, *J* = 2.2 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.71 – 7.64 (m, 4H), 7.58 – 7.53 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 200.7, 163.4, 152.0, 137.0, 134.6, 133.1, 129.5, 128.8, 123.1, 113.9, 113.1. **HRMS calculated for $C_{13}H_8NO_4$ [M-H]$^-$**: 242.0448, found: 242.0465.

2-[Imino(phenyl)methyl]-4-methoxyphenol (1e)[4]

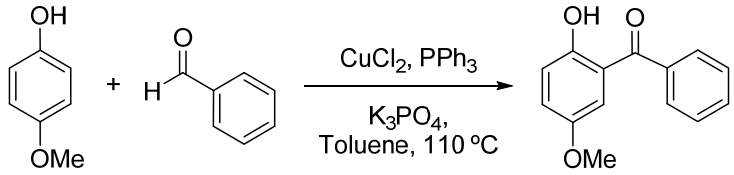


1e

The general procedure was followed with 0.25 mmol of 2-hydroxy-5-methoxybenzophenone (57.1 mg) and 1.25 mmol of the above-mentioned ammonia solution (0.2 mL). Following 17 h, ketimine **1e** was obtained as a bright yellow solid (56.7 mg, 100% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.02 (s, 1H), 9.39 (s, 1H), 7.52 – 7.37 (m, 5H), 7.00 (d, *J* = 1.8 Hz, 2H), 6.72 (t, *J* = 1.8 Hz, 1H), 3.64 (s, 3H).

Synthesis of 2-hydroxy-5-methoxybenzophenone [5]

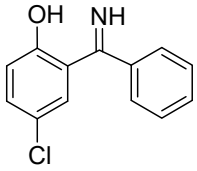


4-Methoxyphenol (161.4 mg, 1.3 mmol, 1.3 equiv.) and benzaldehyde (102 μL, 1.0 mmol, 1.0 equiv.) were dissolved in 3.0 mL of anydhrous toluene, followed by addition of $CuCl_2$ (6.7 mg, 0.05 mmol, 5 mol%), PPh_3 (19.7 mg, 0.075 mmol, 7.5 mol%), and K_3PO_4 (467.0 mg, 2.2 mmol, 2.2 equiv.). The reaction was performed in an oven-dried sealed tube equipped with a magnetic stir bar. After being refluxed overnight, the reaction was diluted with $CHCl_3$ (20 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was

dried with Na_2SO_4 and concentrated. Column chromatography (9:1 cyclohexane:EtOAc) afforded the corresponding benzophenone as a white solid (59.8 mg, 26% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 11.60 (s, 1H), 7.72 – 7.68 (m, 2H), 7.64 – 7.56 (m, 1H), 7.53 – 7.48 (m, 2H), 7.15 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.05 (d, *J* = 9.5 Hz, 1H), 7.03 (d, *J* = 15.6 Hz, 1H), 3.70 (s, 3H).

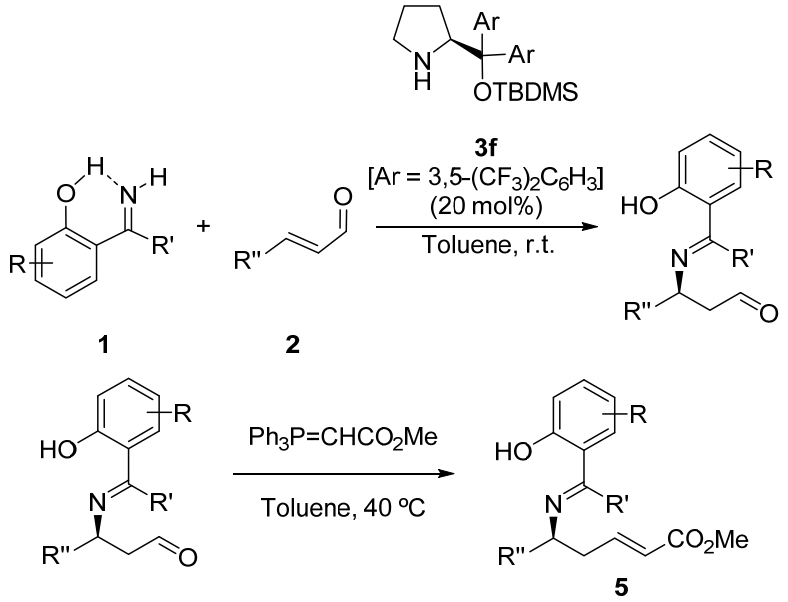
4-Chloro-2-[imino(phenyl)methyl]phenol (1f)



The general procedure was followed with 0.85 mmol of 5-chloro-2-hydroxybenzophenone (198 mg) and 4.25 mmol of the above-mentioned ammonia solution (0.6 mL). Following 4 h, ketimine **1f** was obtained as a bright yellow solid (193 mg, 98% yield).

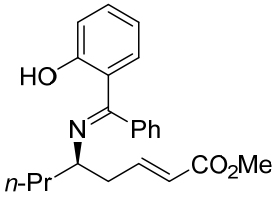
1f **^{1}H NMR (300 MHz, $CDCl_3$)**: δ 14.70 (s, 1H), 9.39 (s, 1H), 7.55 – 7.49 (m, 3H), 7.41 – 7.37 (m, 2H), 7.30 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.16 (d, *J* = 2.6 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 180.6, 162.6, 138.5, 133.6, 131.2, 130.5, 129.1, 127.3, 122.3, 120.1, 119.2. **HRMS calculated for $C_{13}H_{10}ClNONa$ $[M+Na]^+$**: 254.0343, found: 254.0360.

3. General procedure for the enantioselective aza-Michael addition



A vial equipped with a magnetic stirring bar was charged with organocatalyst **3f** (12.8 mg, 0.02 mmol, 20 mol%), the corresponding ketimine **1** (0.10 mmol, 1.0 equiv.), unsaturated aldehyde **2** (0.20 mmol, 2.0 equiv.) and 0.4 mL of toluene (0.25 M). The resulting mixture was stirred at room temperature (reaction was monitored by ^{1}H NMR). Reaction time is indicated in each case. Upon completion, methyl (triphenylphosphoranylidene)acetate (Wittig reagent) was added (80.2 mg, 0.24 mmol, 2.4 equiv.), as well as an additional 0.6 mL of toluene (0.1 M). The resulting mixture was stirred at 40 ºC. After 4 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography.

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}oct-2-enoate (5a)



5a

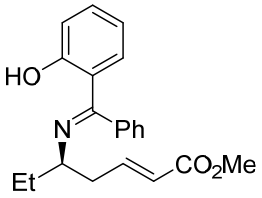
The general procedure was followed with 19.7 mg of ketimine **1b** and 23 μL of (*E*)-2-hexen-1-al **2a**. Following 4 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5a** (24.5 mg, 70% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.45 (bs, 1H), 7.48 (m, 3H), 7.30 – 7.24 (m, 2H), 7.18 – 7.12 (m, 1H), 6.97 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.78 (dt, *J* = 15.4, 7.7 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.63 (td, *J* = 7.6, 1.1 Hz, 1H), 5.81 (bd, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 3.47 – 3.38 (m, 1H), 2.46 – 2.41 (m, 2H), 1.63 – 1.52 (m, 2H), 1.37 – 1.26 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.7, 166.8, 163.3, 145.7, 134.2, 132.5, 131.9, 129.1, 127.6, 123.4, 120.0, 118.0, 117.6, 60.0, 51.6, 39.6, 38.8, 19.6, 14.2. **HRMS calculated for $C_{22}H_{26}NO_3$ $[M+H]^+$**: 352.1907; found: 352.1920. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 4.5 min, τ_{minor} = 3.7 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -8.5 (c = 0.7, $CHCl_3$).

Reaction scale-up

The general procedure was followed with 108.5 mg of ketimine **1b** (0.55 mmol), 128 μL of (*E*)-2-hexen-1-al **2a**, 70.4 mg of organocatalyst **3f** (0.11 mmol) and 2.2 mL of toluene. Following 3 h, 441.3 mg of Wittig reagent (1.32 mmol) were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5a** (131.8 mg, 68% yield).

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}hept-2-enoate (5b)

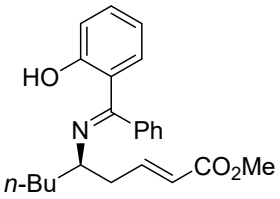


5b

The general procedure was followed with 19.7 mg of ketimine **1b** and 20 μL of (*E*)-2-pentenal **2b**. Following 3 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5b** (24.4 mg, 72% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.48 (bs, 1H), 7.53 – 7.47 (m, 3H), 7.30 – 7.24 (m, 1H), 7.17 - 7.14 (m, 2H), 7.00 - 6.96 (m, 1H), 6.83 – 6.75 (m, 1H), 6.73 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.64 (td, *J* = 7.5, 1.1 Hz, 1H), 5.81 (bd, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 3.35 (p, *J* = 6.3 Hz, 1H), 2.47 – 2.42 (m, 2H), 1.65 – 1.58 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.8, 166.8, 163.3, 145.7, 134.2, 132.5, 131.9, 129.1, 128.8, 128.7, 127.6, 123.4, 120.0, 118.0, 117.6, 61.4, 51.6, 39.2, 29.4, 10.7. **HRMS calculated for $C_{21}H_{24}NO_3$ [M+H]$^+$**: 338.1751; found: 338.1719. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 5.4 min, τ_{minor} = 4.5 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -11.3 (c = 1.0, $CHCl_3$).

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}non-2-enoate (5c)

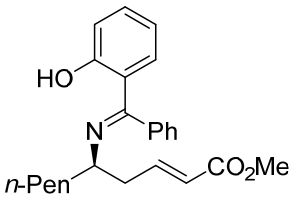


5c

The general procedure was followed with 19.7 mg of ketimine **1b** and 26 μL of (*E*)-2-heptenal **2c**. Following 4 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5c** (26.7 mg, 73% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.47 (bs, 1H), 7.49 – 7.47 (m, 3H), 7.30 – 7.24 (m, 1H), 7.16 – 7.14 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.83 – 6.75 (m, 1H), 6.73 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.64 (td, *J* = 7.5, 1.1 Hz, 1H), 5.80 (bd, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 3.40 (p, *J* = 6.1 Hz, 1H), 2.44 (t, *J* = 7.0 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.32 – 1.19 (m, 4H), 0.85 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.6, 166.8, 163.3, 145.7, 134.2, 132.5, 131.9, 129.1, 128.7, 127.6, 123.4, 120.0, 118.0, 117.5, 60.2, 51.6, 39.6, 36.31, 28.5, 22.8, 14.1. **HRMS calculated for $C_{23}H_{28}NO_3$ [M+H]$^+$**: 366.2064; found: 366.2069. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 4.7 min, τ_{minor} = 4.2 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -13.2 (c = 0.9, $CHCl_3$).

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}dec-2-enoate (5d)

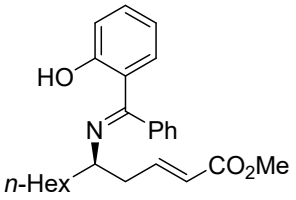


5d

The general procedure was followed with 19.7 mg of ketimine **1b** and 30 μL of (*E*)-2-octenal **2d**. Following 3 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5d** (33.4 mg, 88% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.48 (s, 1H), 7.51 – 7.47 (m, 3H), 7.30 – 7.25 (m, 1H), 7.17 – 7.14 (m, 2H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.83 – 6.75 (m, 1H), 6.73 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.63 (td, *J* = 7.4, 1.1 Hz, 1H), 5.81 (bd, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 3.45 – 3.36 (m, 1H), 2.44 (t, *J* = 7.0 Hz, 2H), 1.63 – 1.50 (m, 2H), 1.29 – 1.17 (m, 2H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.6, 166.8, 163.3, 145.7, 134.2, 132.5, 131.9, 129.1, 128.8, 127.6, 123.4, 120.0, 118.0, 117.5, 60.2, 51.6, 39.6, 36.6, 31.9, 26.0, 22.7, 14.1. **HRMS calculated for $C_{24}H_{30}NO_3$ [M+H]$^+$**: 380.2220; found: 380.2213. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 4.6 min, τ_{minor} = 4.1 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -8.4 (c = 1.0, $CHCl_3$).

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}undec-2-enoate (5e)

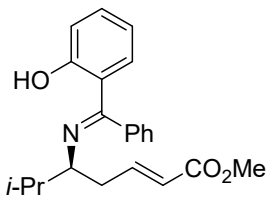


5e

The general procedure was followed with 19.7 mg of ketimine **1b** and 33 μL of (*E*)-2-nonenal **2e**. Following 4 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5e** (36.5 mg, 93% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.46 (bs, 1H), 7.48 – 7.47 (m, 3H), 7.31 – 7.22 (m, 1H), 7.17 – 7.13 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.77 (dt, *J* = 15.5, 8.0 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.63 (td, *J* = 7.5, 1.3 Hz, 1H), 5.80 (bd, *J* = 16.8 Hz, 1H), 3.71 (s, 3H), 3.40 (p, *J* = 6.5 Hz, 1H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.67 – 1.50 (m, 2H), 1.42 – 1.21 (m, 8H), 0.85 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.6, 166.8, 163.3, 145.7, 134.2, 132.5, 131.9, 129.1, 128.8, 127.6, 123.4, 120.0, 118.0, 117.5, 60.2, 51.6, 39.6, 36.6, 31.8, 29.4, 26.3, 22.8, 14.2. **HRMS calculated for $C_{25}H_{32}NO_3$ [M+H]$^+$**: 394.2377; found: 394.2417. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 4.8 min, τ_{minor} = 4.3 min, ***ee*** = 91%. $[\alpha]_D^{20}$ = +0.8 (c = 1.1, $CHCl_3$).

Methyl (*S*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}-6-methylhept-2-enoate (5f)



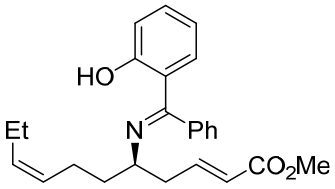
5f

The general procedure was followed with 19.7 mg of ketimine **1b** and 23 μL of 4-methyl-2-pentenal **2f**. Following 16 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5f** (29.7 mg, 85% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.65 (s, 1H), 7.48 (dd, *J* = 4.8, 1.9 Hz, 3H), 7.31 – 7.25 (m, 1H), 7.17 – 7.14 (m, 2H), 6.98 (dd, *J* = 8.2,

1.1 Hz, 1H), 6.80 – 6.74 (m, 1H), 6.72 (dd, *J* = 5.9, 1.9 Hz, 1H), 6.63 (td, *J* = 7.7, 1.0 Hz, 1H), 5.80 (dt, *J* = 15.6, 1.2 Hz, 1H), 3.72 (s, 3H), 3.30 – 3.24 (m, 1H), 2.48 – 2.43 (m, 2H), 1.90 – 1.79 (m, 1H), 0.94 (dd, *J* = 24.8, 6.8 Hz, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 174.0, 166.7, 163.59, 146.1, 134.1, 132.6, 131.9, 129.1, 128.7, 127.8, 123.3, 119.9, 118.1, 117.5, 65.2, 51.6, 36.9, 33.0, 19.7, 18.1. **HRMS calculated for $C_{22}H_{25}NO_3$ [M+H]$^+$**: 352.1907; found: 352.1931. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 5.1 min, τ_{minor} = 3.8 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -5.9 (c = 1.1, $CHCl_3$).

Methyl (*R*,2*E*,8*Z*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}undeca-2,8-dienoate (5g)

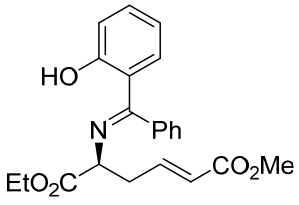


5g

The general procedure was followed with 19.7 mg of ketimine **1b** and 32 μL of 2*E*-6*Z*-nonadienal **2g**. Following 24 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5g** (37.4 mg, 96% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.34 (bs, 1H), 7.51 – 7.48 (m, 3H), 7.31 – 7.27 (m, 1H), 7.17 – 7.14 (m, 2H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.82 – 6.75 (m, 1H), 6.73 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.64 (td, *J* = 7.7, 1.0 Hz, 1H), 5.81 (bd, *J* = 15.6 Hz, 1H), 5.36 – 5.28 (m, 1H), 5.22 – 5.14 (m, 1H), 3.72 (s, 3H), 3.44 (p, *J* = 6.6 Hz, 1H), 2.45 (t, *J* = 6.9 Hz, 2H), 2.10 – 1.85 (m, 4H), 1.68 – 1.59 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.8, 166.6, 163.0, 145.4, 134.1, 132.5, 132.4, 131.8, 129.0, 128.6, 127.7, 127.5, 123.4, 119.8, 117.9, 117.5, 59.8, 51.5, 39.3, 36.5, 23.8, 20.5, 14.2. **HRMS calculated for $C_{25}H_{30}NO_3$ [M+H]$^+$**: 392.2220; found: 392.2208. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 4.7 min, τ_{minor} = 4.3 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = +5.9 (c = 0.9, $CHCl_3$).

6-Ethyl 1-methyl (*S*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}hex-2-enedioate (5h)



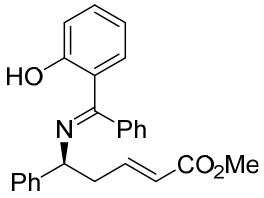
5h

The general procedure was followed with 19.7 mg of ketimine **1b** and 24 μL of ethyl (*E*)-4-oxo-2-butenoate **2h**. Following 3 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5h** (15.5 mg, 41% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.54 (bs, 1H), 7.54 – 7.49 (m, 4H), 7.33 – 7.25 (m, 2H), 7.02 – 6.99 (m, 1H), 6.82 – 6.71 (m, 2H), 6.64 (td, *J* = 7.5, 1.0 Hz, 1H), 5.86 (bd, *J* = 15.6 Hz, 1H), 4.22 – 4.12 (m, 3H), 3.72 (s, 3H), 2.83 – 2.71 (m, 2H), 1.29 – 1.24 (m, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 176.6, 170.4, 166.5, 162.6, 143.6, 133.7, 133.1, 132.3, 129.5, 129.0, 127.6, 124.4, 120.1, 118.0, 118.0, 63.2, 61.8, 51.7, 36.6, 14.3. **HRMS calculated for $C_{22}H_{24}NO_5$ [M+H]$^+$**: 382.1649; found: 382.1670. The enantiomeric excess was determined using a Chiralpak IC

column: CO_2/MeOH 95:5, flow rate 3.0 mL/min, τ_{major} = 7.4 min, τ_{minor} = 8.7 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -20.7 (c = 0.8, $CHCl_3$).

Methyl (*S*,*E*)-5-{[(*E*)-(2-hydroxyphenyl)(phenyl)methylene]amino}-5-phenylpent-2-enoate (5i)

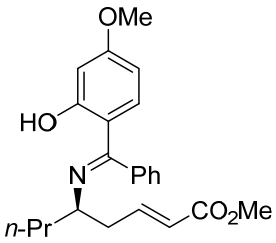


5i

The general procedure was followed with 19.7 mg of ketimine **1b** and 25 μL of (*E*)-cinnamaldehyde **2i**. Following 15 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5i** (18.1 mg, 47% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.35 (bs, 1H), 7.54 – 7.49 (m, 3H), 7.40 (t, *J* = 6.9 Hz, 1H), 7.34 – 7.19 (m, 6H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 4.7 Hz, 1H), 6.77 – 6.74 (m, 2H), 6.65 (tt, *J* = 7.5, 1.5 Hz, 1H), 5.81 (bd, *J* = 15.5 Hz, 1H), 4.47 (t, *J* = 6.5 Hz, 1H), 3.70 (s, 3H), 2.89 – 2.67 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 174.1, 166.7, 162.9, 144.9, 142.3, 134.1, 132.8, 132.1, 129.3, 129.0, 127.7, 127.5, 126.9, 123.8, 120.1, 117.9, 117.8, 64.9, 51.6, 42.1. **HRMS calculated for $C_{25}H_{24}NO_3$ $[M+H]^+$**: 386.1751; found: 386.1757. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 5.9 min, τ_{minor} = 7.5 min, ***ee*** = 41%.

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxy-4-methoxyphenyl)(phenyl)methylene]amino}oct-2-enoate (5j)

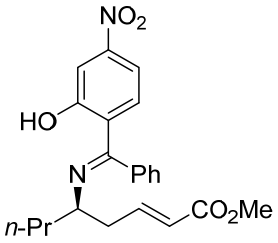


5j

The general procedure was followed with 22.7 mg of ketimine **1c** and 23 μL of (*E*)-2-hexen-1-al **2a**. Following 11 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5j** (25.8 mg, 68% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 – 7.47 (m, 3H), 7.18 – 7.15 (m, 2H), 6.77 (dt, *J* = 15.4, 7.6 Hz, 1H), 6.58 (d, *J* = 9.0 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 6.14 (dd, *J* = 8.9, 2.6 Hz, 1H), 5.80 (dt, *J* = 15.6, 1.4 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.42 – 3.34 (m, 1H), 2.43 (td, *J* = 7.0, 1.2 Hz, 2H), 1.60 – 1.31 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.0, 168.7, 166.8, 164.0, 145.5, 133.7, 133.2, 129.2, 128.8, 127.7, 123.6, 113.0, 105.8, 101.8, 58.7, 55.5, 51.6, 39.6, 38.7, 19.5, 14.2. **HRMS calculated for $C_{23}H_{28}NO_4$ $[M+H]^+$**: 382.2013; found: 382.2012. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 12.7 min, τ_{minor} = 8.5 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -17.1 (c = 0.7, $CHCl_3$).

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxy-4-nitrophenyl)(phenyl)methylene]amino}oct-2-enoate (5k)

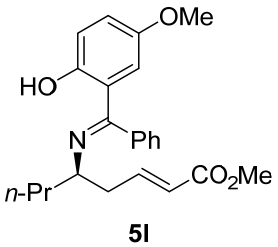


5k

The general procedure was followed with 24.2 mg of ketimine **1d** and 23 μL of (*E*)-2-hexen-1-al **2a**. Following 15 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5k** (13.5 mg, 34% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.97 (s, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.56 – 7.53 (m, 3H), 7.43 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.17 – 7.14 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.75 (dt, *J* = 15.4, 7.6 Hz, 1H), 5.82 (bd, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 3.53 – 3.45 (m, 1H), 2.47 (t, *J* = 6.5 Hz, 2H), 1.63 – 1.56 (m, 2H), 1.30 – 1.22 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.1, 166.7, 164.1, 150.0, 144.9, 133.0, 132.7, 129.8, 129.1, 127.5, 124.1, 123.9, 113.4, 111.7, 60.5, 51.7, 39.3, 38.6, 19.6, 14.1. **HRMS calculated for $C_{22}H_{25}N_2O_5$ [M+H]$^+$**: 397.1758; found: 397.1757. The enantiomeric excess was determined using a Chiralpak IC column: CO_2/MeOH gradient from 95:5 to 60:40 over 8 min, flow rate 3.0 mL/min, τ_{major} = 4.9 min, τ_{minor} = 5.1 min, ***ee*** = 74%. $[\alpha]_D^{20}$ = -24.6 (c = 0.9, $CHCl_3$).

Methyl (*R*,*E*)-5-{[(*E*)-(2-hydroxy-5-methoxyphenyl)(phenyl)methylene]amino}oct-2-enoate (5l)

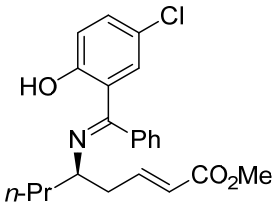


5l

The general procedure was followed with 22.7 mg of ketimine **1e** and 23 μL of (*E*)-2-hexen-1-al **2a**. Following 20 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5l** (14.3 mg, 37% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.86 (s, 1H), 7.50 – 7.46 (m, 3H), 7.16 – 7.13 (m, 2H), 6.94 – 6.88 (m, 2H), 6.77 (dt, *J* = 15.4, 7.7 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 5.80 (bd, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 3.56 (s, 3H), 3.44 – 3.36 (m, 1H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.62 – 1.52 (m, 2H), 1.25 – 1.20 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 173.2, 166.8, 157.1, 151.0, 145.8, 134.2, 129.1, 128.7, 127.5, 123.4, 119.8, 118.9, 118.3, 116.5, 60.3, 56.0, 51.7, 39.6, 38.8, 19.6, 14.21. **HRMS calculated for $C_{23}H_{27}NO_4$ [M+H]$^+$**: 382.2013; found: 382.2017. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 3.0 mL/min, τ_{major} = 12.2 min, τ_{minor} = 10.1 min, ***ee*** > 99%. $[\alpha]_D^{20}$ = -6.6 (c = 1.4, $CHCl_3$).

Methyl (*R*,*E*)-5-{[(*E*)-(5-chloro-2-hydroxyphenyl)(phenyl)methylene]amino}oct-2-enoate (5m)



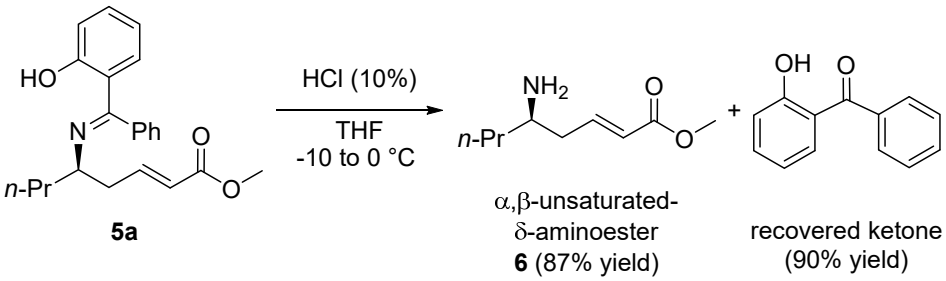
5m

The general procedure was followed with 23.2 mg of ketimine **1f** and 23 μL of (*E*)-2-hexen-1-al **2a**. Following 15 h, 80.2 mg of Wittig reagent were added. Column chromatography (19:1 cyclohexane:EtOAc) afforded **5m** (27.9 mg, 72% yield, yellow oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ 15.52 (bs, 1H), 7.55 – 7.50 (m, 3H), 7.21 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.15 – 7.12 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.75 (dt, *J* = 15.4, 7.7 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 5.81 (dd, *J* = 15.6, 1.3 Hz, 1H), 3.73 (s, 3H), 3.48 – 3.37 (m, 1H), 2.44 (t, *J* = 7.0 Hz, 2H), 1.63 – 1.52 (m, 2H), 1.39 – 1.10 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 172.9, 166.7, 162.1, 145.3, 133.3, 132.5, 130.9, 129.5, 129.0, 127.5, 123.6, 122.1, 120.6, 119.6, 60.2, 51.7, 39.5, 38.7, 19.6, 14.2. **HRMS calculated for $C_{22}H_{25}ClNO_3$ $[M+H]^+$**: 386.1517; found: 382.1492. The enantiomeric excess was determined using a Chiralpak IG-3 column: CO_2/MeOH 95:5, flow rate 2.0 mL/min, τ_{major} = 5.3 min, τ_{minor} = 4.2 min, ***ee*** = 90%. $[\alpha]_D^{20}$ = -2.5 (c = 1.1, $CHCl_3$).

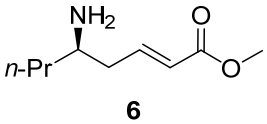
4. Preparation of δ-aminoesters

Partial hydrolysis of ketimine **5a**



Wittig product **5a** (17.6 mg, 0.05 mmol, 1.0 equiv.) was dissolved in 1 mL of THF (0.05 M) at -10 ºC under stirring during 30 min. Then, $HCl_{(aq)}$ 10% (87 μL, 0.25 mmol, 5.0 equiv.) was added at 0 ºC. After being stirred overnight at 0 ºC (reaction was monitored by TLC; ninhydrin stain solution), the crude mixture was concentrated under reduced pressure and purified through an Agilent Bond Elut SCX column using DCM as eluent to afford 2-hydroxybenzophenone (8.9 mg, 90% yield, white solid) and then NH_3 (7N) in MeOH as eluent to afford enantiopure δ-aminoester **6** (7.4 mg, 86% yield, colorless oil).

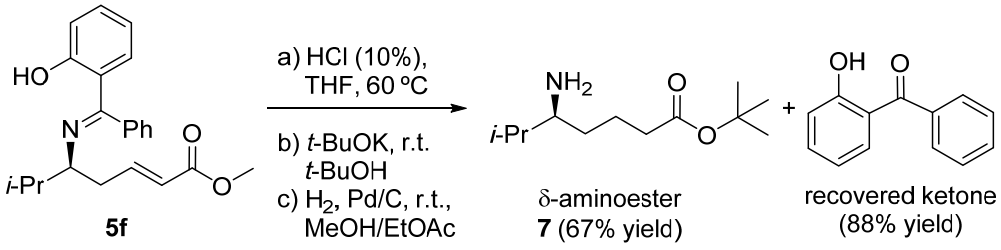
Methyl (*S*,*E*)-5-aminooct-2-enoate **6**



6

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (dt, *J* = 15.4, 7.6 Hz, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 3.73 (s, 3H), 2.92 (bs, 1H), 2.38 – 2.33 (m, 1H), 2.22 – 2.15 (m, 1H), 1.41 – 1.33 (m, 4H), 0.92 (t, *J* = 5.5 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 167.0, 146.5, 123.4, 60.0, 51.6, 31.1, 29.9, 19.4, 14.2. **HRMS calculated for $C_9H_{18}NO_2$ [M+H]$^+$**: 172.1332; found: 172.1345. $[\alpha]_D^{20}$ = -115.7 (c = 0.1, $CHCl_3$).

Configurational determination of aza-Michael and Wittig cascade products

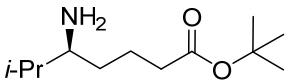


Wittig product **5f** (21.1 mg, 0.06 mmol, 1.0 equiv.) was dissolved in 0.6 mL of THF (0.1 M), followed by addition of $HCl_{(aq)}$ 10% (105 μL, 0.3 mmol, 5.0 equiv.). After being refluxed overnight in a sealed vial (reaction was monitored by TLC; ninhydrin stain solution), the crude mixture was concentrated under reduced pressure and purified through an Agilent Bond Elut SCX column using DCM as eluent to afford 2-hydroxybenzophenone (10.5 mg, 88% yield, white solid) and then NH_3 (7N) in MeOH as eluent to afford the corresponding δ-aminoacid.

The δ-aminoacid was then dissolved in 0.6 mL *t*-BuOH (0.1 M), followed by addition of *t*-BuOK (13.5 mg, 0.12 mmol, 2.0 equiv.). After being stirred overnight at room temperature in a vial (reaction was monitored by TLC; ninhydrin stain solution), the crude mixture was filtered through a plug of celite and the filter cake was washed with EtOAc (5 mL) and MeOH (5 mL). The filtrate was concentrated and used without further purification in the next step.

The filtrate was dissolved in 0.6 mL of EtOAc and 1.2 mL of MeOH (0.03 M), followed by addition of palladium on carbon, 10 wt. % loading (6.4 mg, 0.06 mmol, 1.0 equiv.). The reaction mixture was placed in a sealed vial, where it was purged by bubbling with a H_2 balloon. Finally, a new H_2 balloon was used to perform the hydrogenation reaction. After being stirred overnight at room temperature, the crude mixture was filtered through a plug of celite and the filter cake was washed with EtOAc (5 mL) and MeOH (5 mL), affording enantiopure δ-aminoester **7a** (8.6 mg, 67% yield, colorless oil).

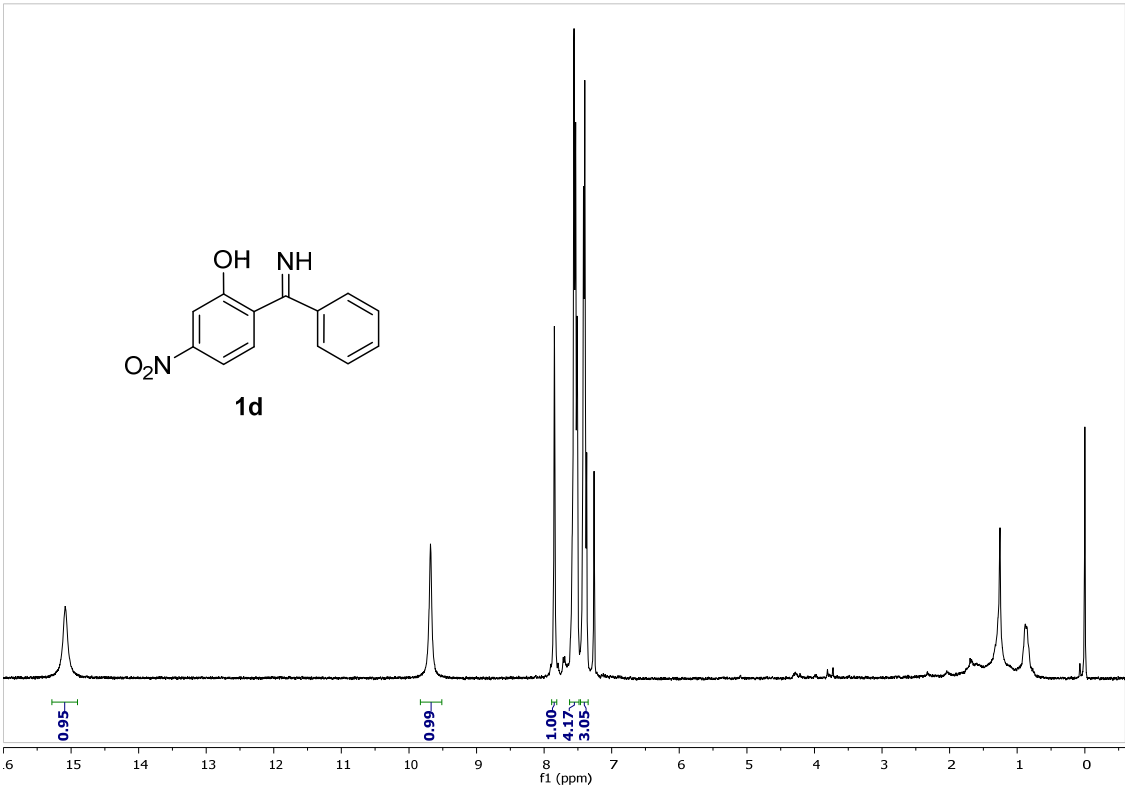
tert-Butyl (*S*)-5-amino-6-methylheptanoate **7**[6]

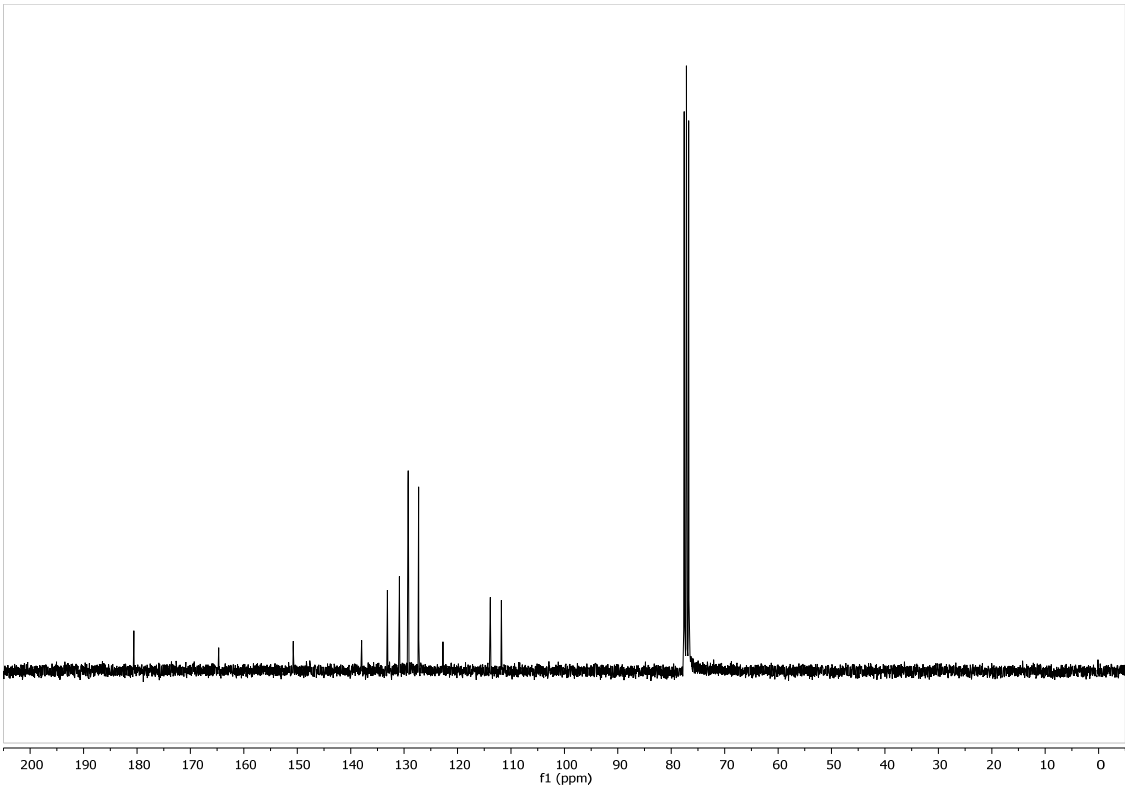


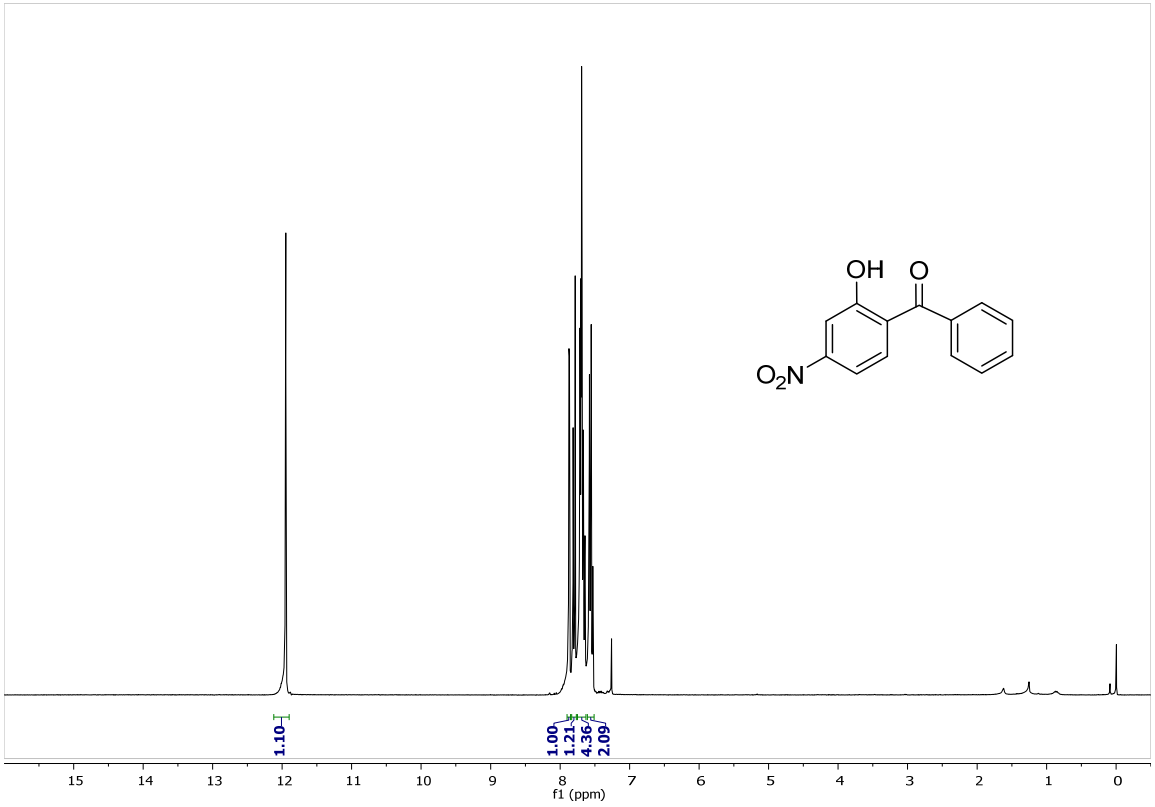
7

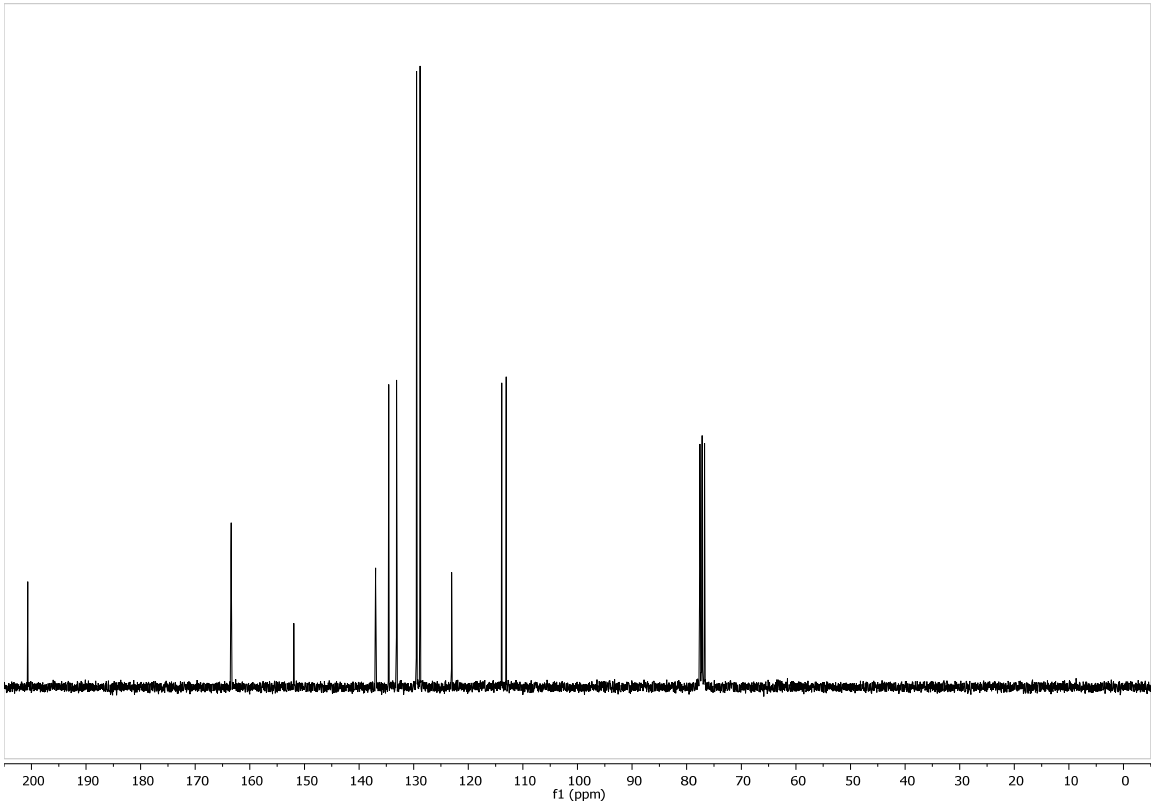
^{1}H NMR (300 MHz, CD_3OD): δ 2.93 – 2.90 (m, 1H), 2.38 – 2.32 (m, 2H), 1.97 – 1.92 (m, 1H), 1.72 – 1.55 (m, 4H), 1.40 (s, 9H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H). $[\alpha]_D^{25}$ = -3.2 (c = 0.8, $CHCl_3$); Literature,[6] (*R*)-aminoester $[\alpha]_D^{24}$ = +3.3 (c = 0.7, $CHCl_3$).

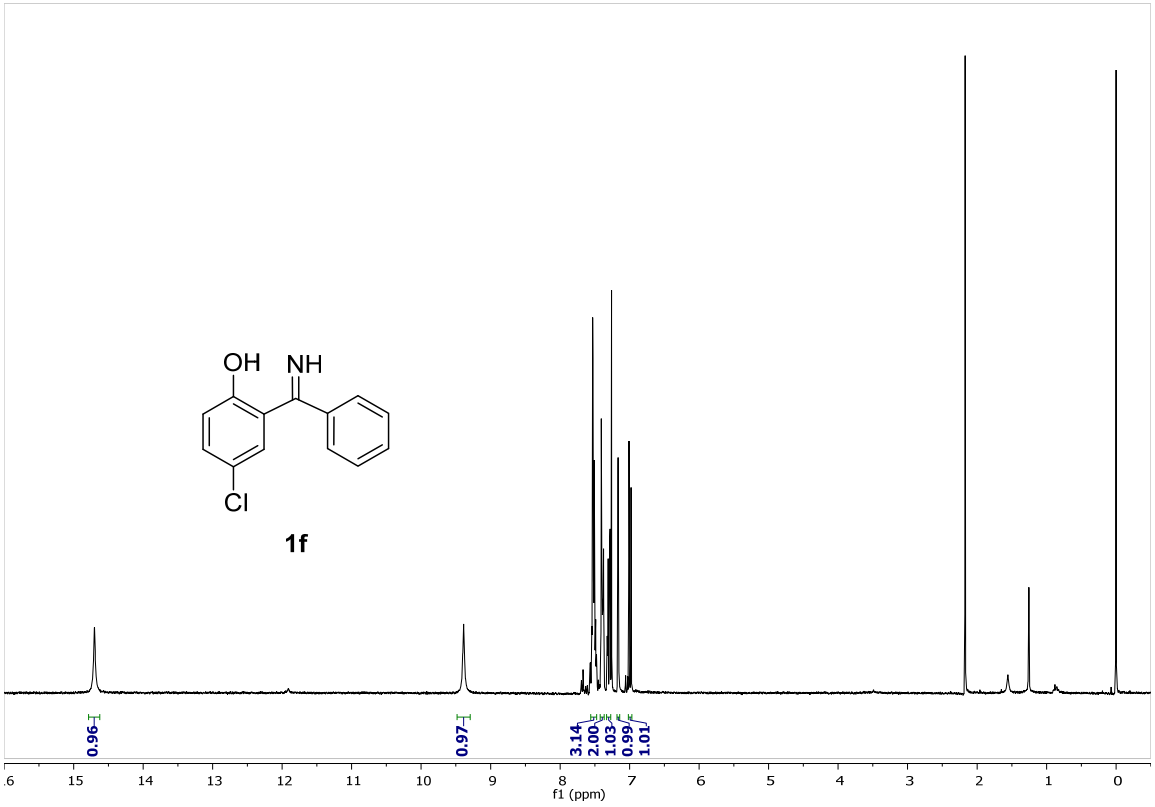
5. NMR spectra and chromatograms for chiral compounds

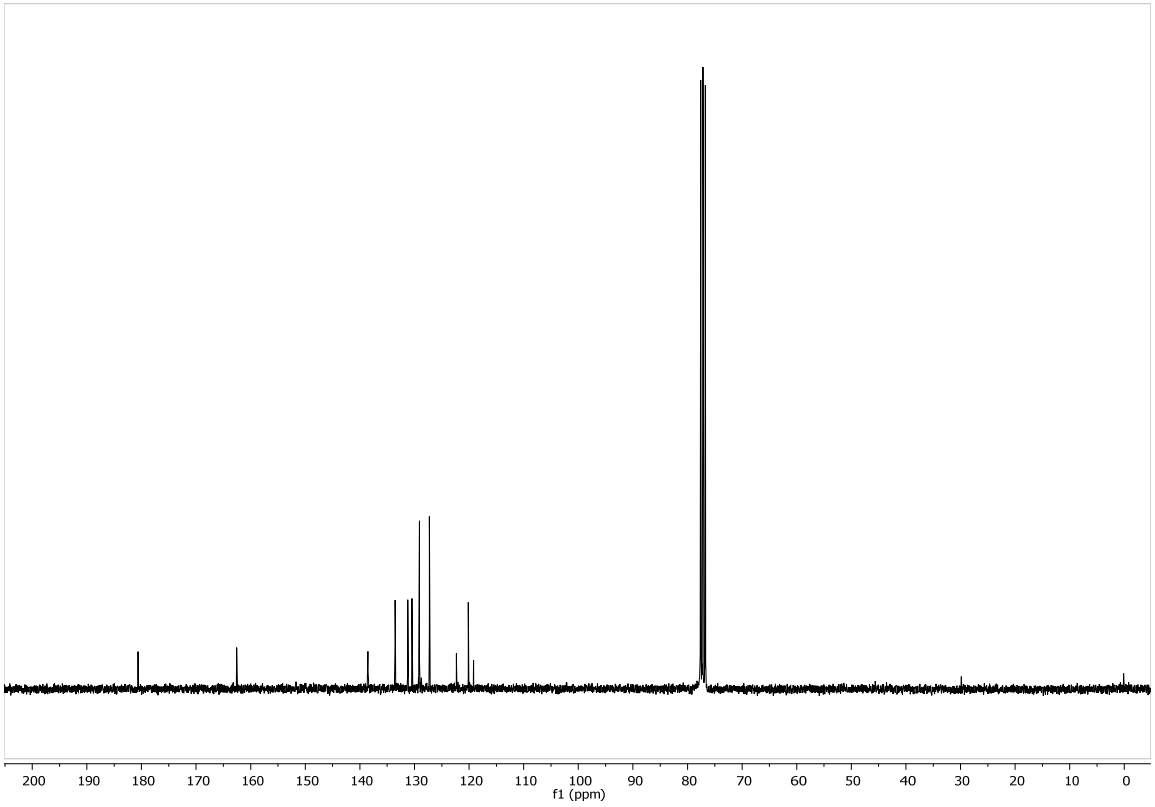


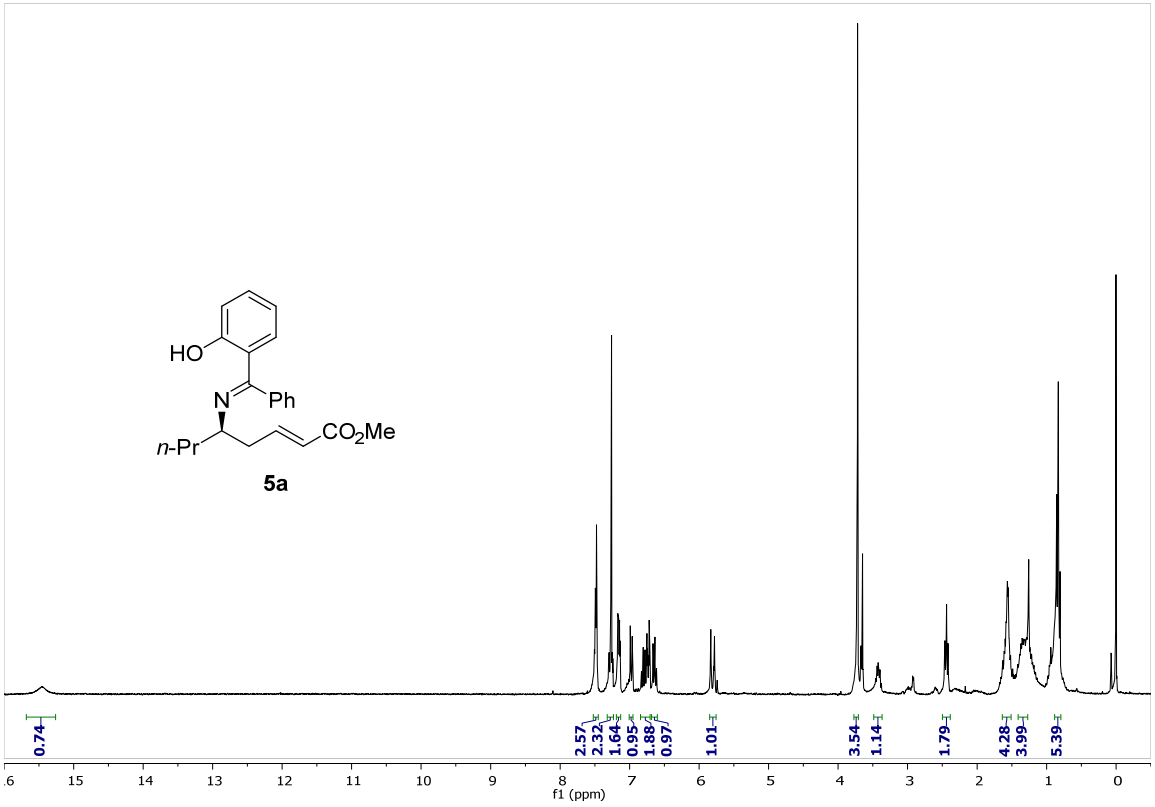



OH
O
O2N
1.10
1.00
1.21
4.36
2.09
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

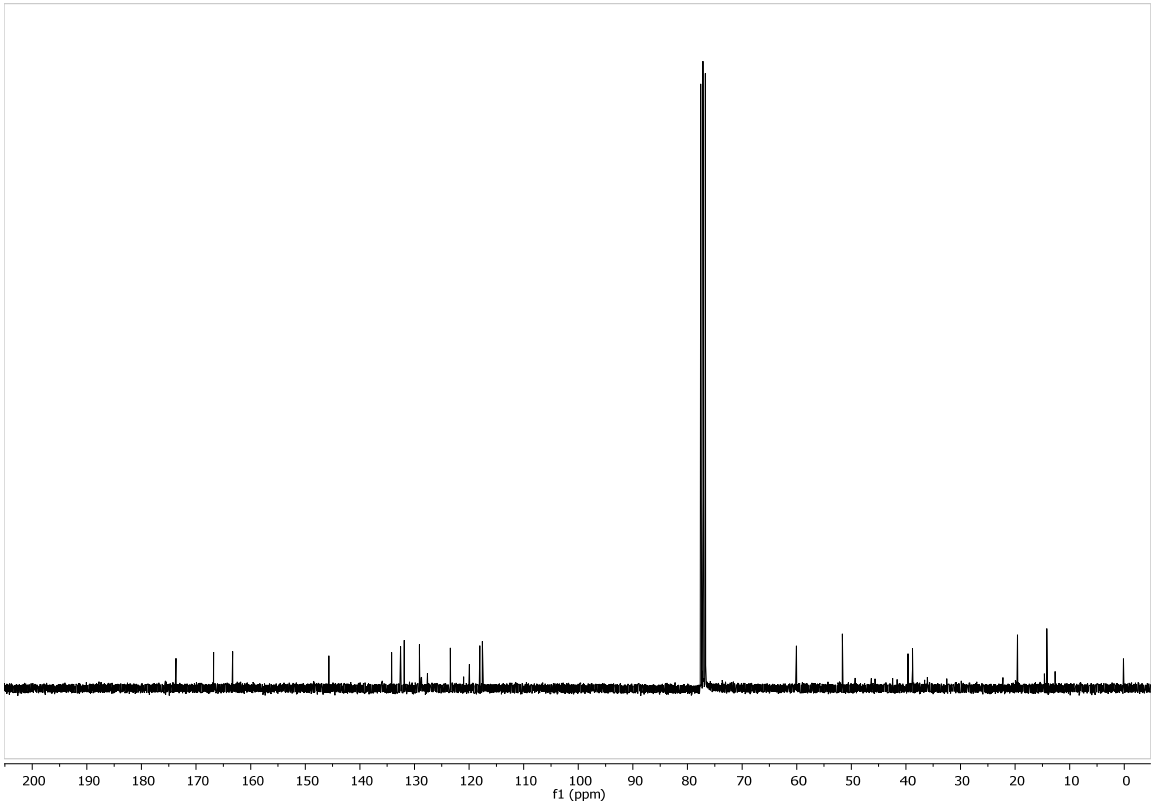

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OH
NH
Cl
1f
0.96
0.97
3.14
2.00
1.03
0.99
1.01
f1 (ppm)

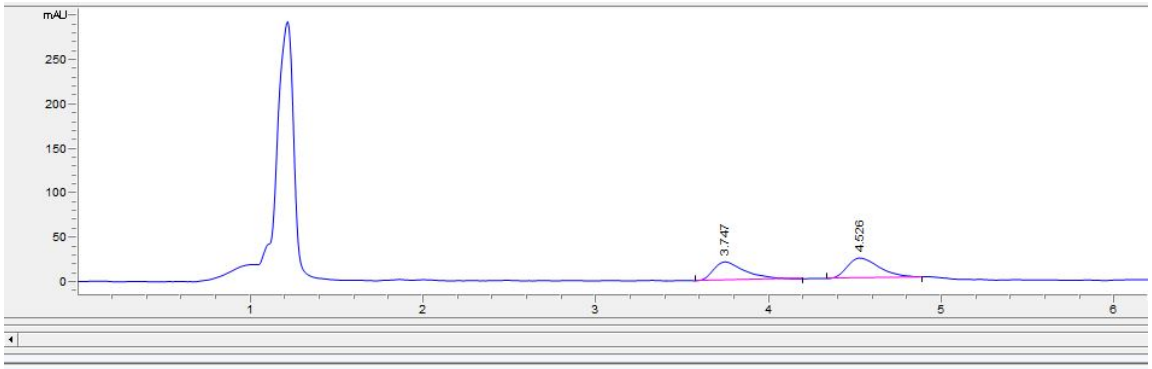

f1 (ppm)


HO
N
Ph
n-Pr
CO2Me
0.74
2.57
2.32
1.64
0.95
1.88
0.97
1.01
3.54
1.14
1.79
4.28
3.99
5.39
f1 (ppm)

5a

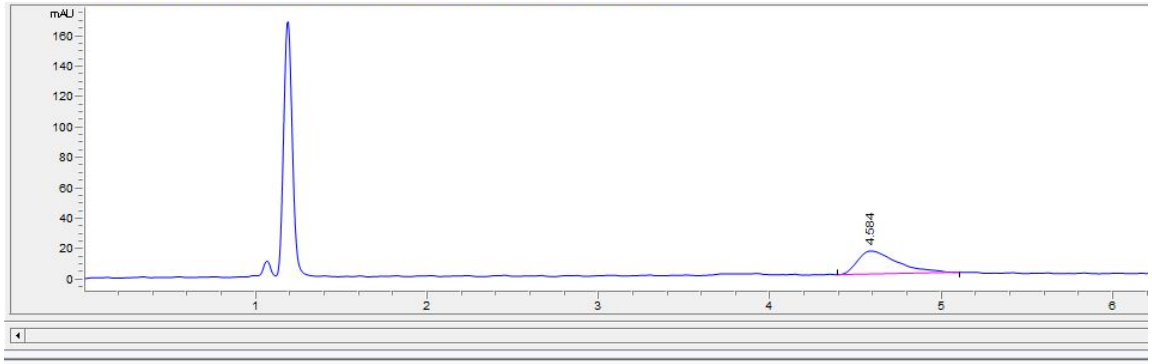

f1 (ppm)

Racemic mixture of **5a**

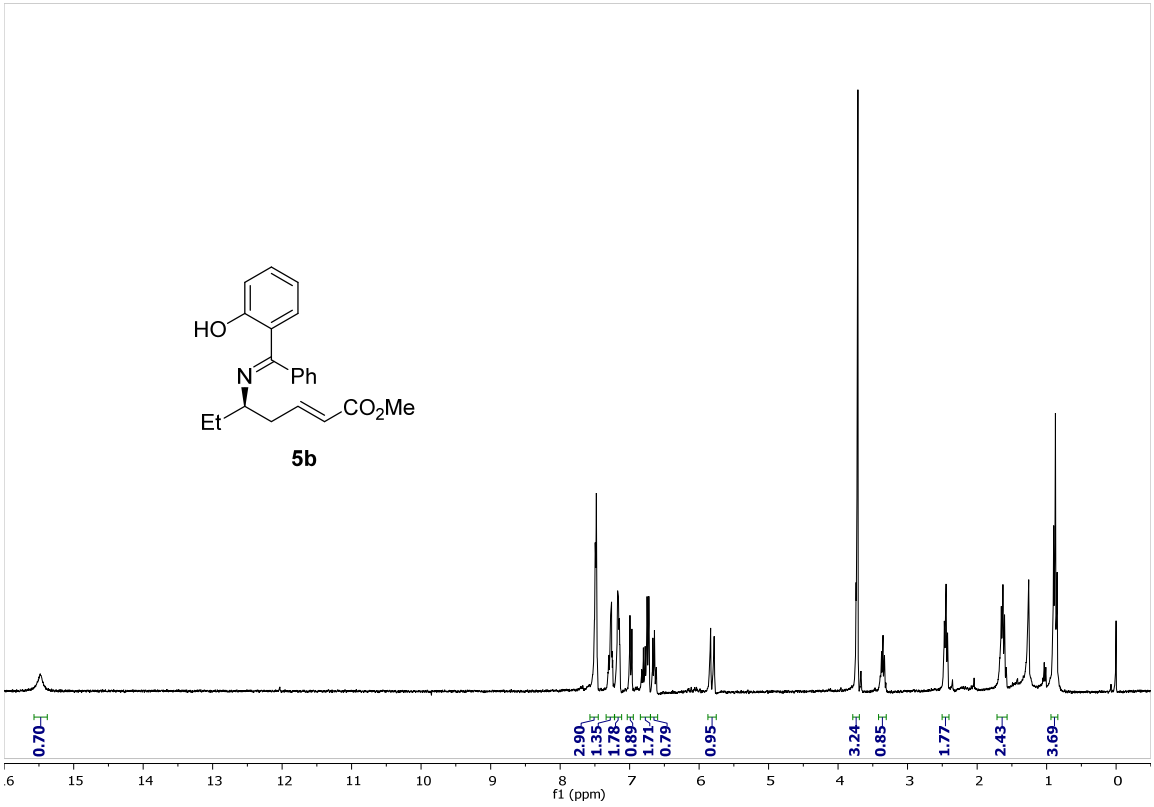


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.747	BB	264.5	20.6	0.1857	47.910	0.542
2	4.526	BB	287.6	22.4	0.2019	52.090	0.615

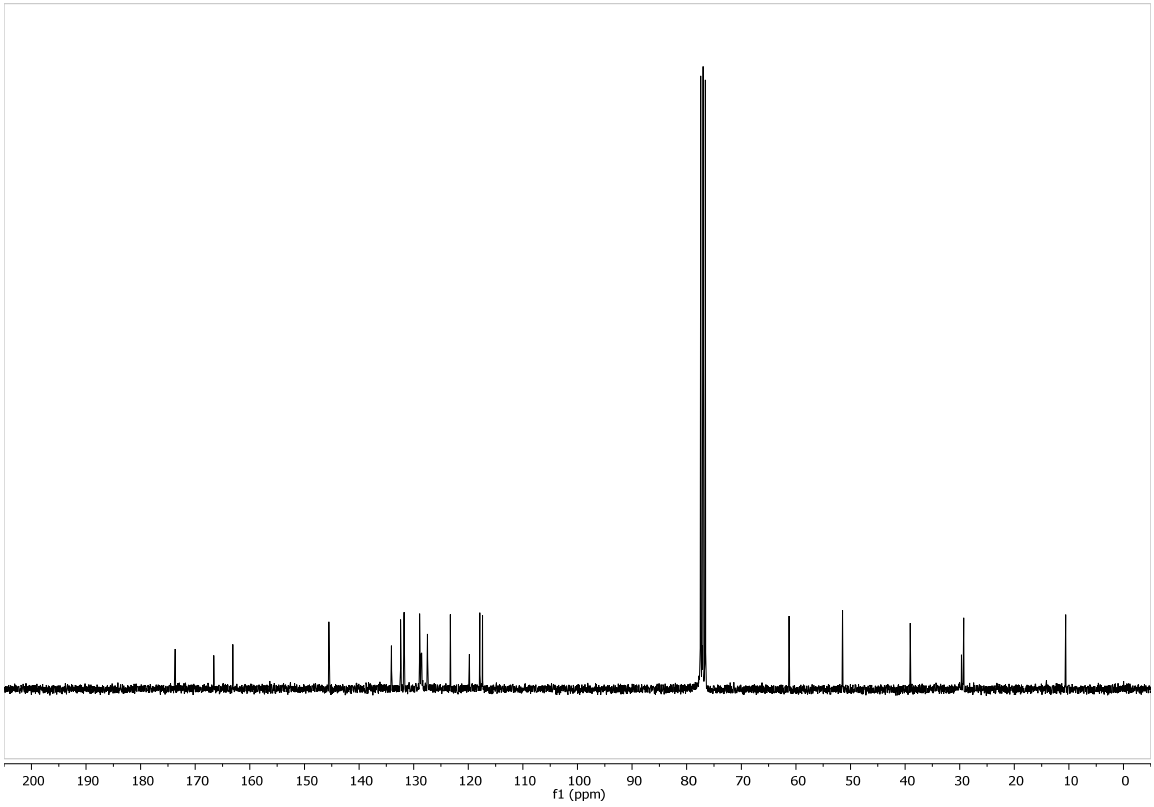
Enantiomerically enriched **5a**



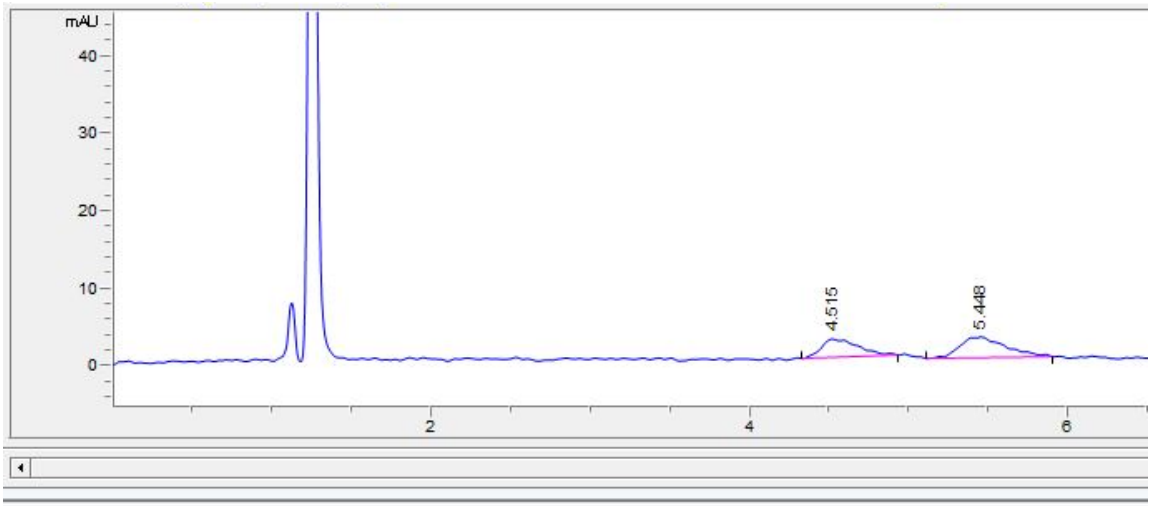
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.584	BB	251.2	15.3	0.2314	100.000	0.455


HO
N
Ph
Et
CO2Me
0.70
2.90
1.35
1.78
0.89
1.71
0.79
0.95
3.24
0.85
1.77
2.43
3.69
f1 (ppm)

5b

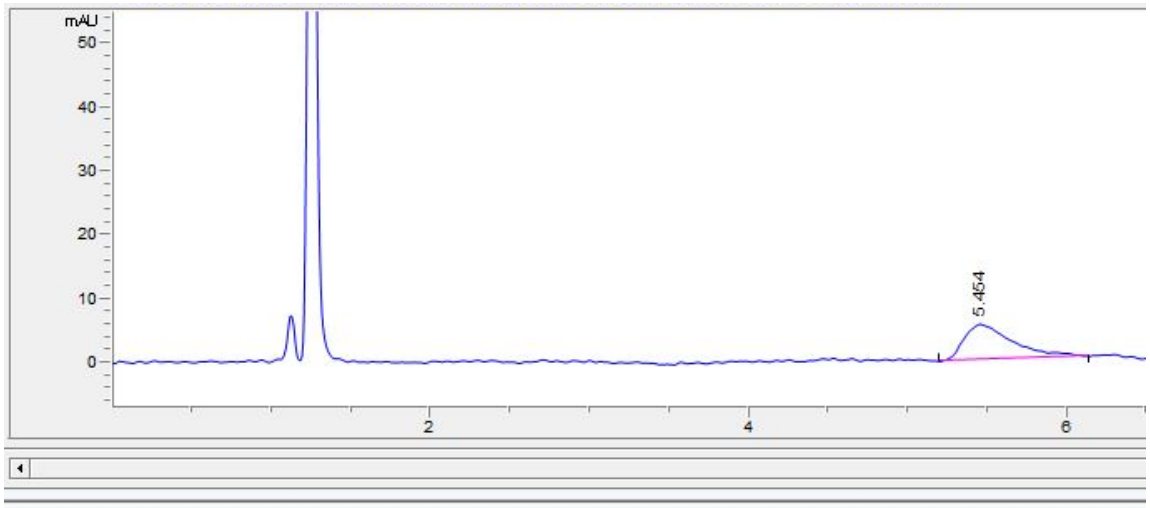

f1 (ppm)

Racemic mixture of **5b**

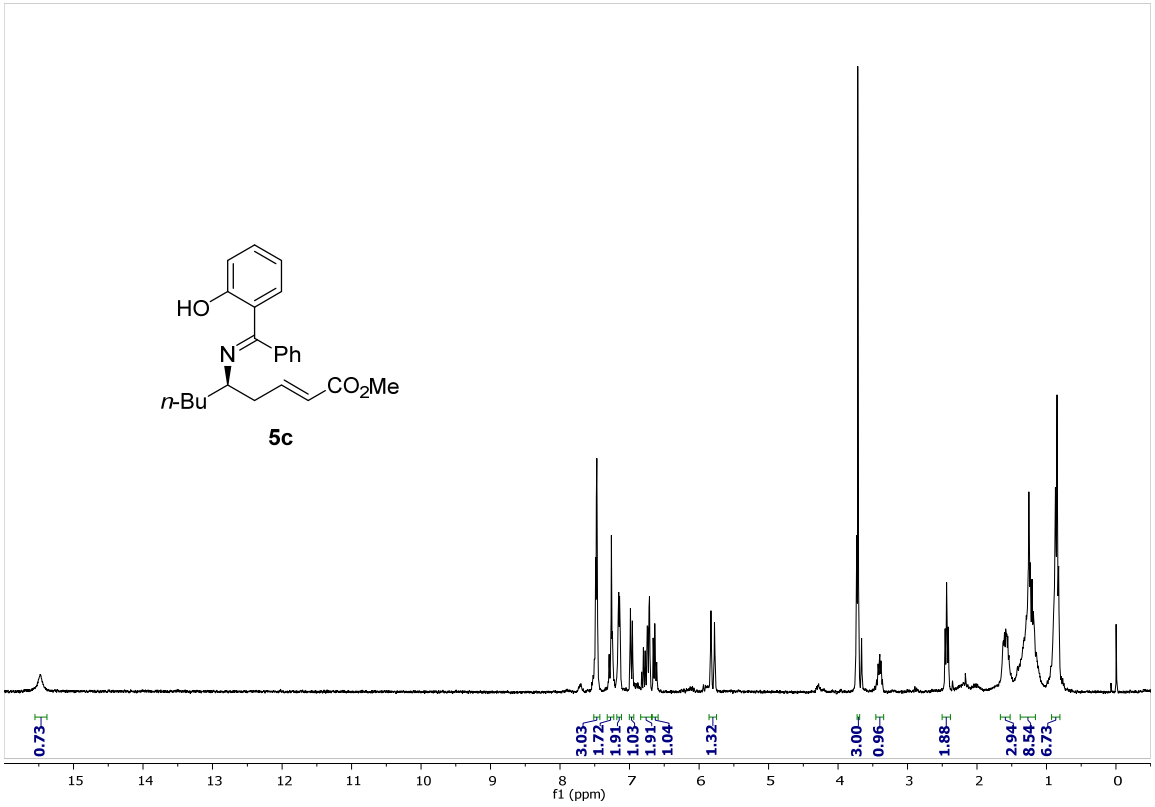


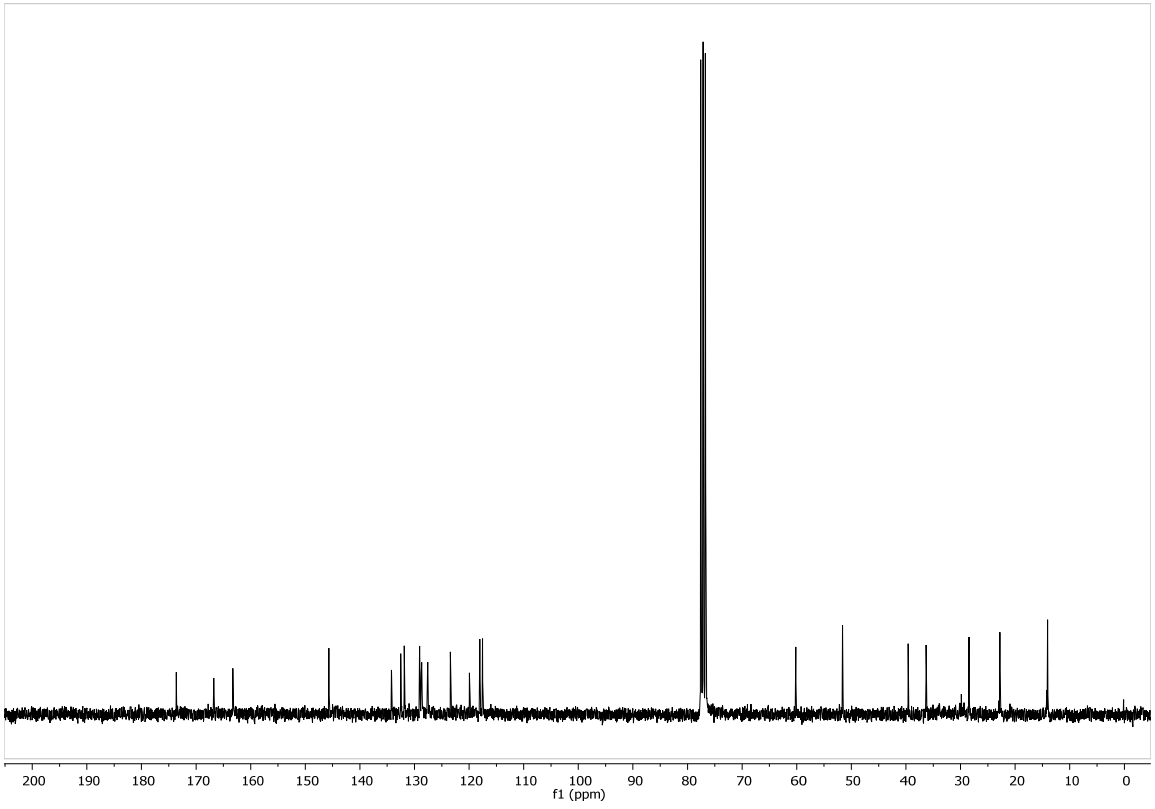
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.515	BB	38.9	2.4	0.2141	41.485	0.42
2	5.448	BB	54.9	2.7	0.2549	58.515	0.794

Enantiomerically enriched **5b**

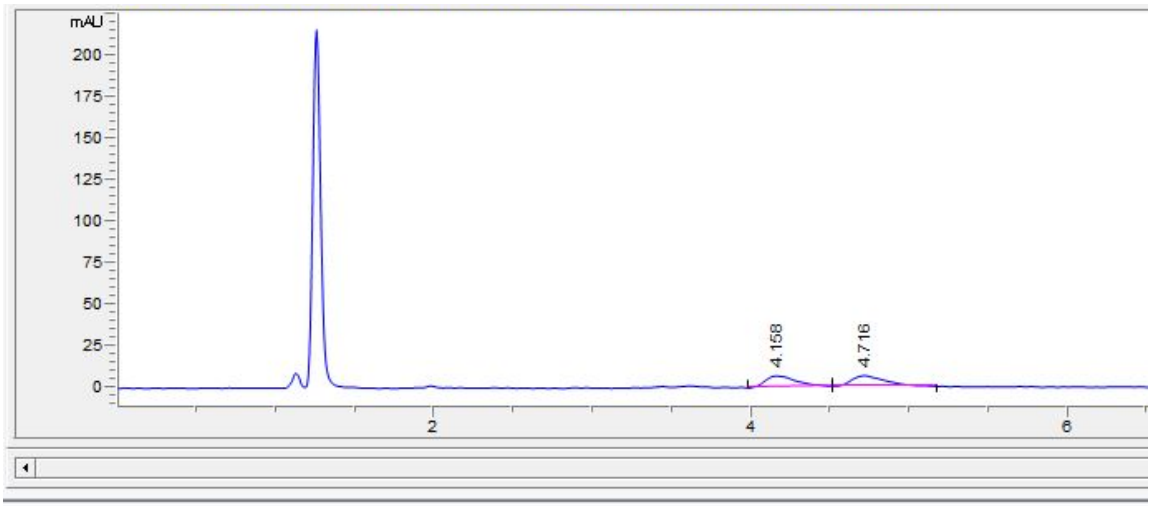


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.454	BB	120.8	5.6	0.2715	100.000	0.47


HO
N
Ph
n-Bu
CO2Me
5c
0.73
3.03
1.72
1.91
1.03
1.91
1.04
1.32
3.00
0.96
1.88
2.94
8.54
6.73
f1 (ppm)

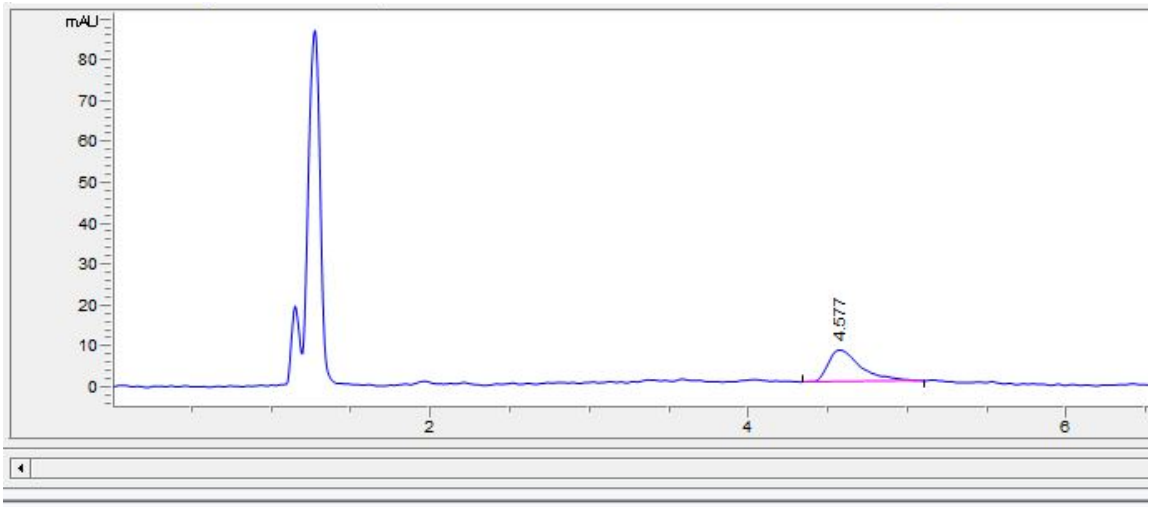

f1 (ppm)

Racemic mixture of **5c**

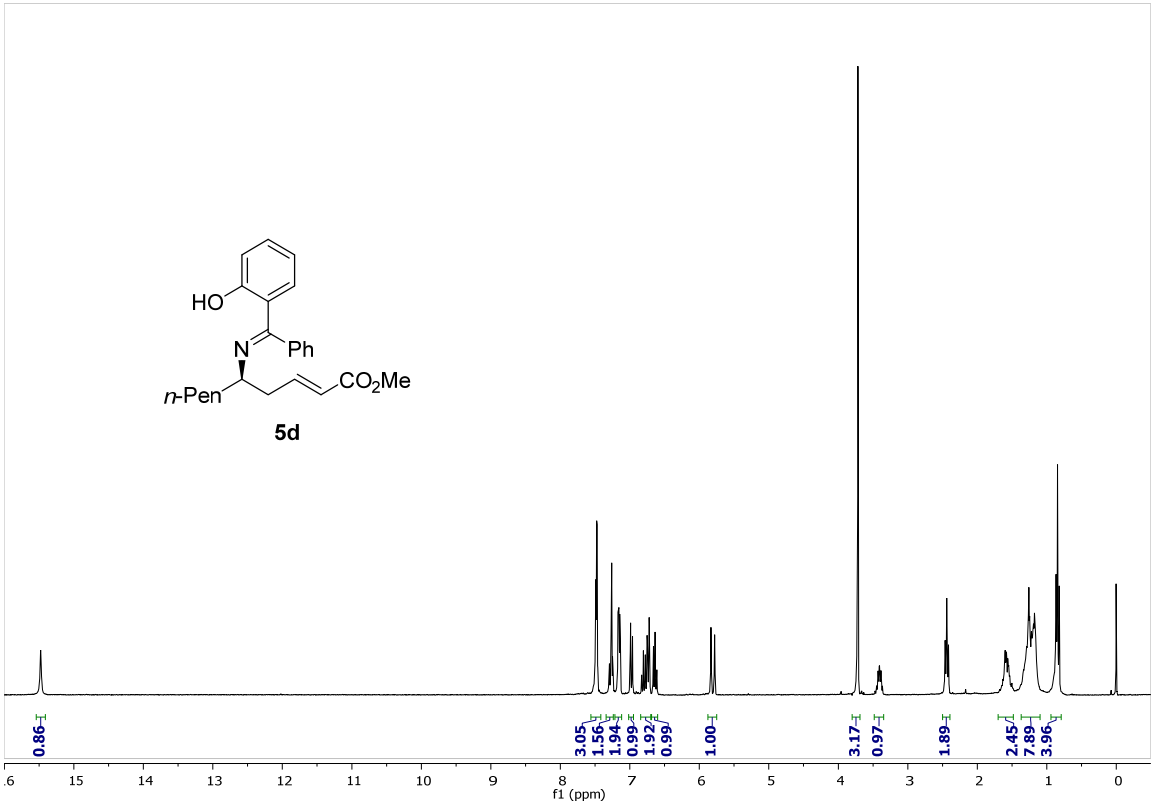


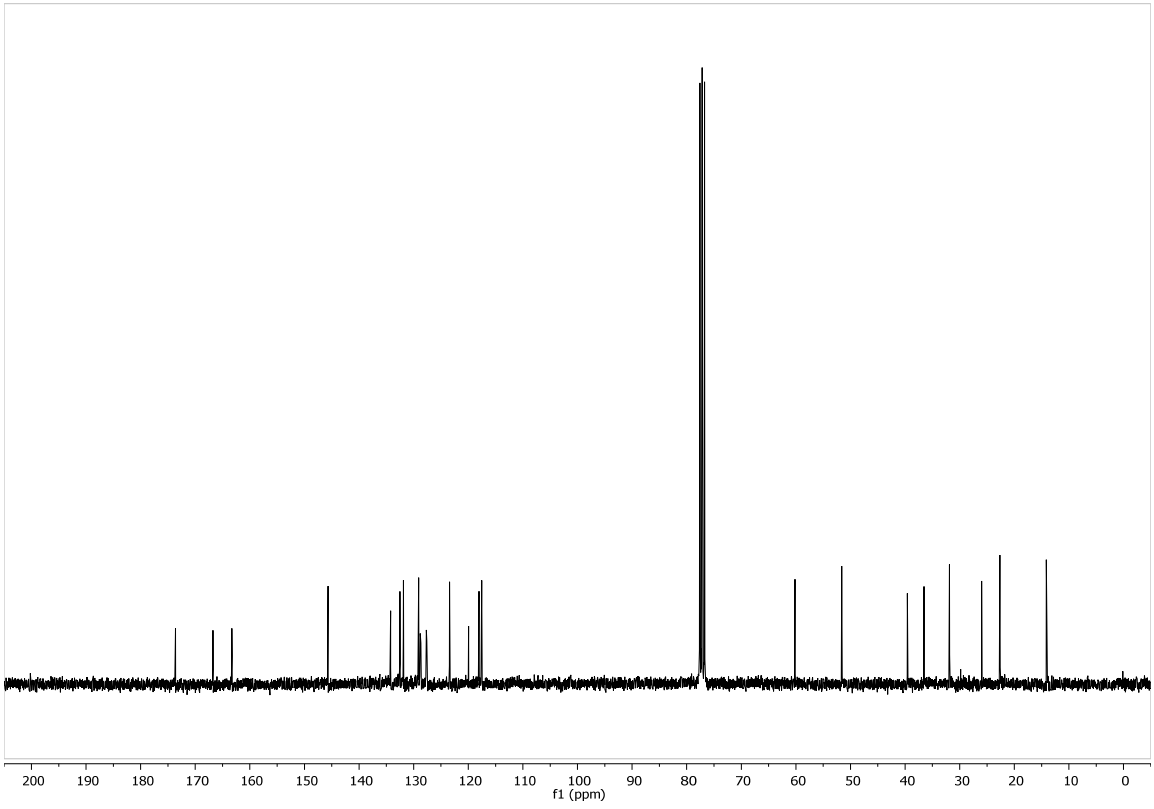
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.158	BB	96.2	6.9	0.1806	49.730	0.504
2	4.716	BB	97.2	6.4	0.2131	50.270	0.513

Enantiomerically enriched **5c**

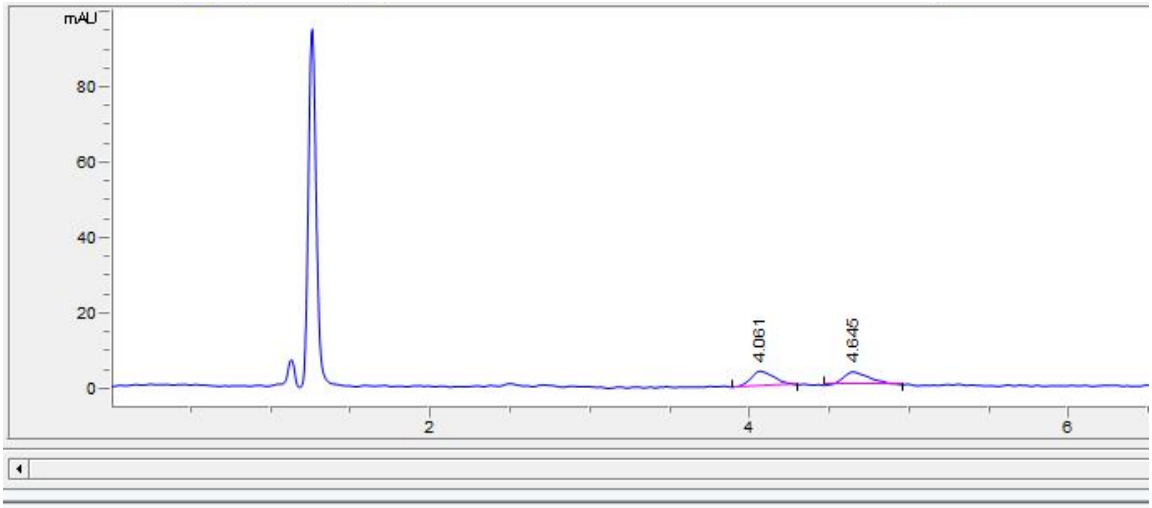


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.577	BB	111.6	7.7	0.2003	100.000	0.538


HO
N
Ph
n-Pen
CO2Me
5d
0.86
3.05
1.56
1.94
0.99
1.92
0.99
1.00
3.17
0.97
1.89
2.45
7.89
3.96
f1 (ppm)

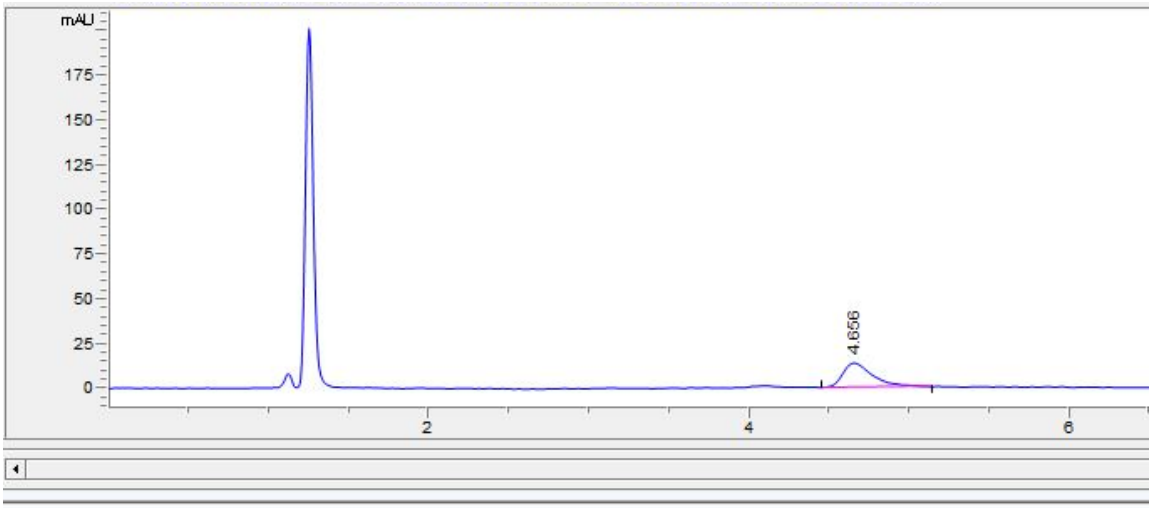

f1 (ppm)

Racemic mixture of **5d**

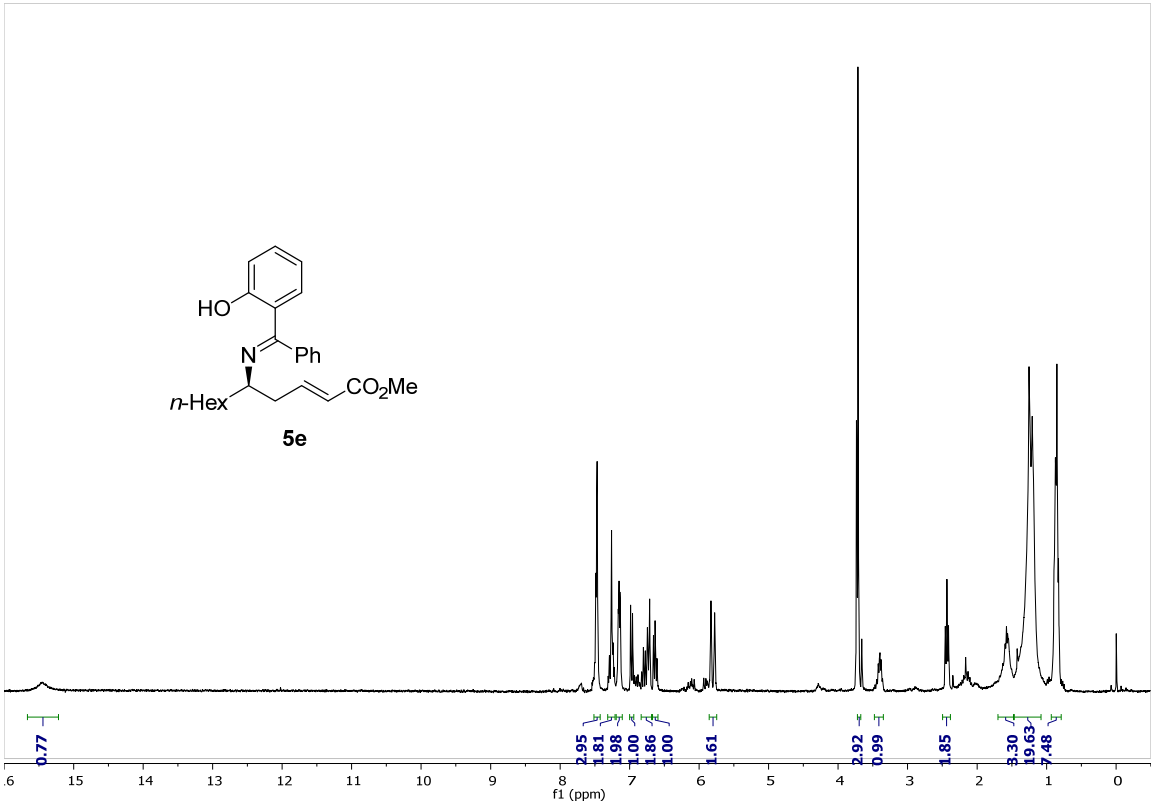


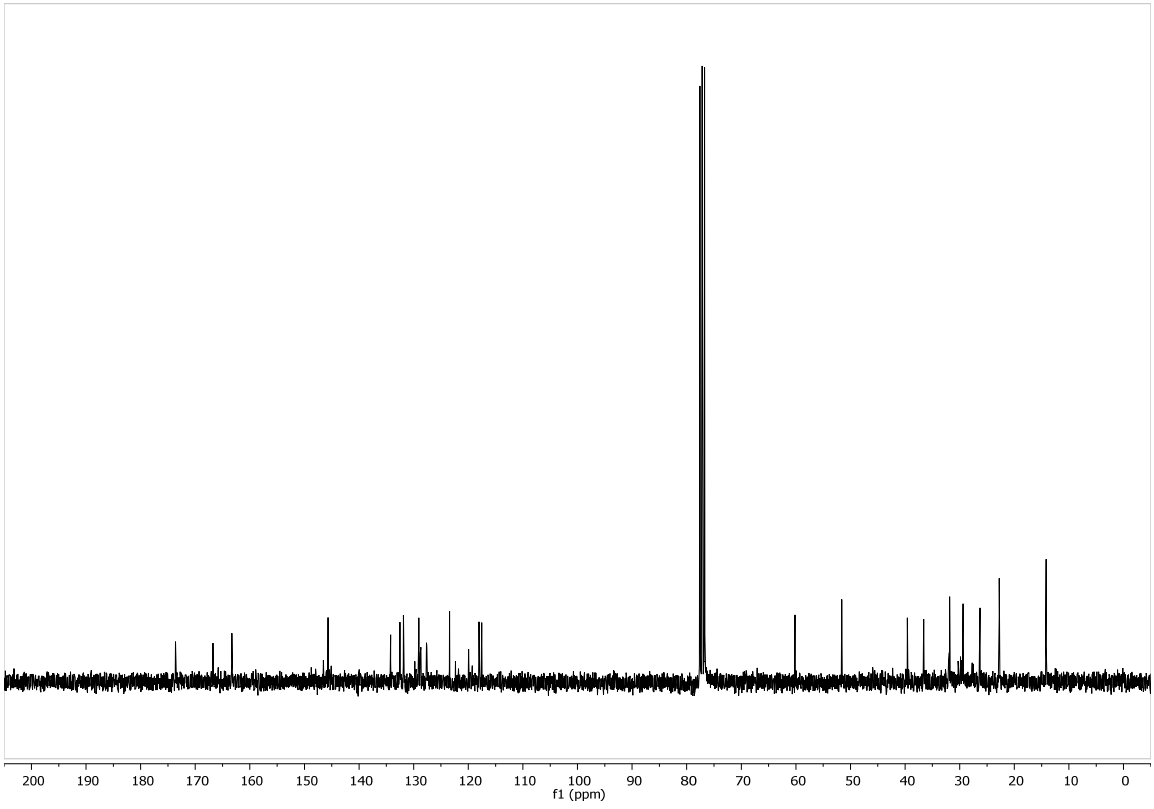
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.061	BB	41.2	4	0.145	49.426	0.628
2	4.645	BB	42.2	3.5	0.1638	50.574	0.556

Enantiomerically enriched **5d**

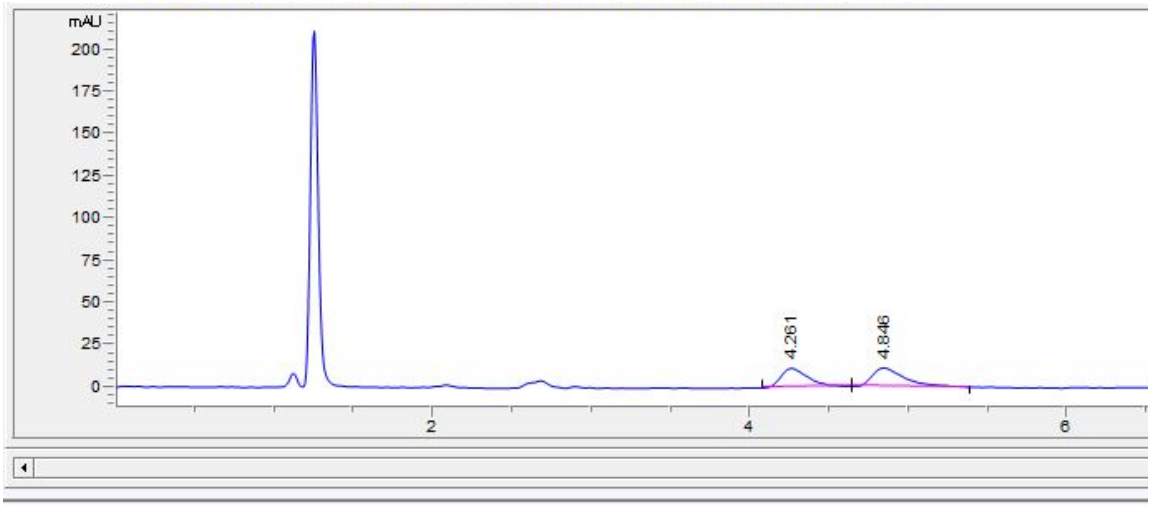


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.656	BB	179.9	13.6	0.1966	100.000	0.545


HO
N
Ph
n-Hex
CO2Me
5e
0.77
2.95
1.81
1.98
1.00
1.86
1.00
1.61
2.92
0.99
1.85
3.30
19.63
7.48
f1 (ppm)

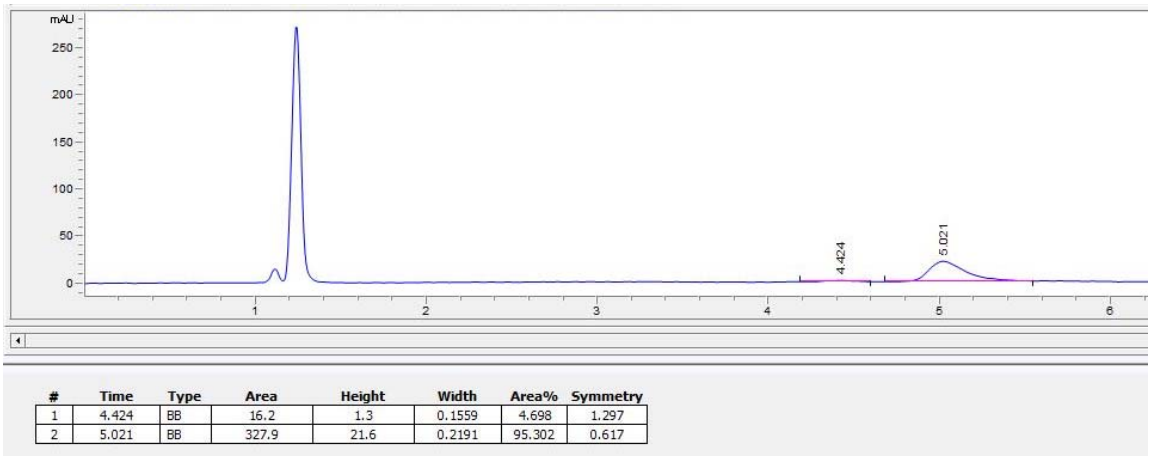

f1 (ppm)

Racemic mixture of **5e**

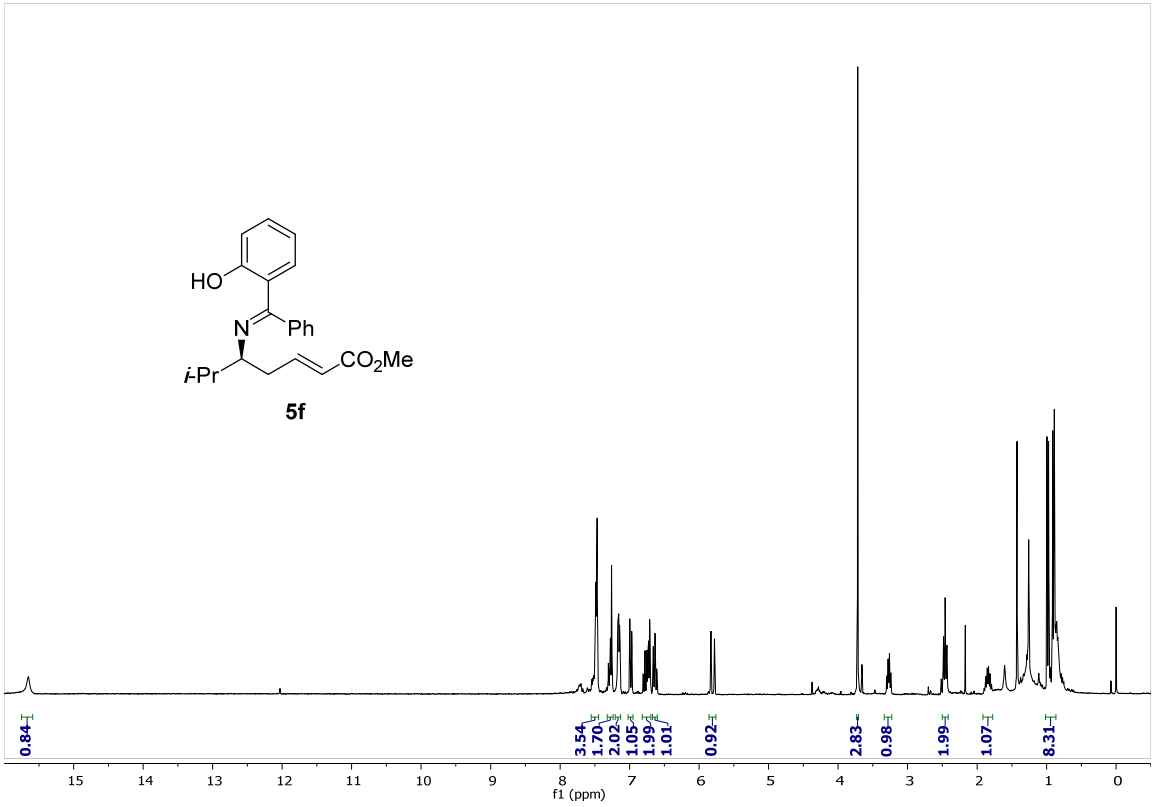


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.261	BB	137.1	11.4	0.1687	45.693	0.575
2	4.846	BB	162.9	11.2	0.2078	54.307	0.508

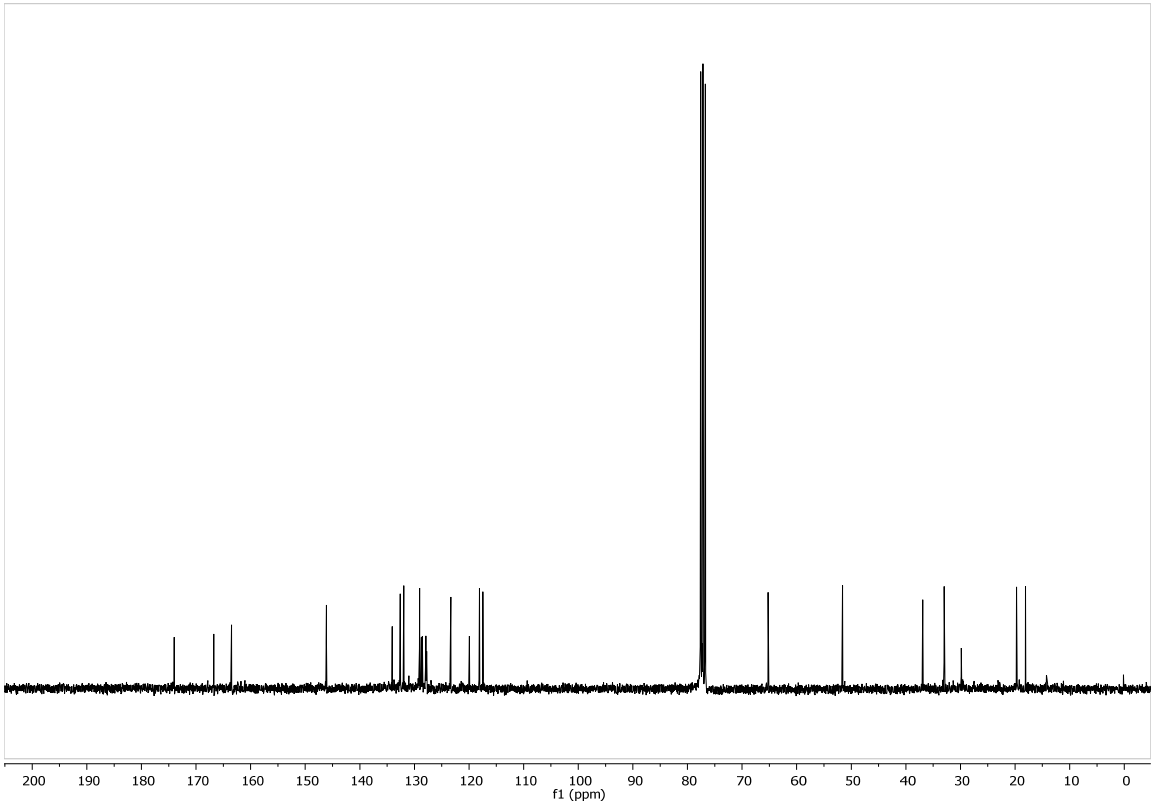
Enantiomerically enriched **5e**



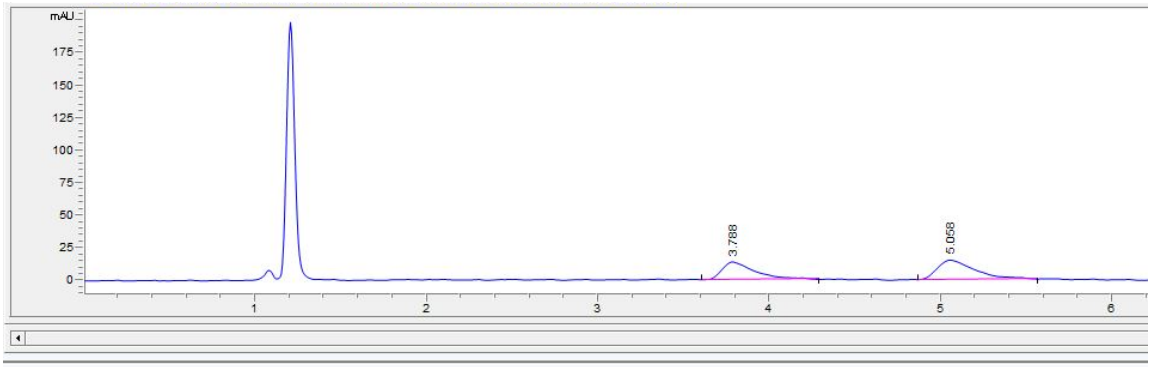
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.424	BB	16.2	1.3	0.1559	4.698	1.297
2	5.021	BB	327.9	21.6	0.2191	95.302	0.617


HO
N
Ph
i-Pr
CO2Me
0.84
3.54
1.70
2.02
1.05
1.99
1.01
0.92
2.83
0.98
1.99
1.07
8.31
f1 (ppm)

5f

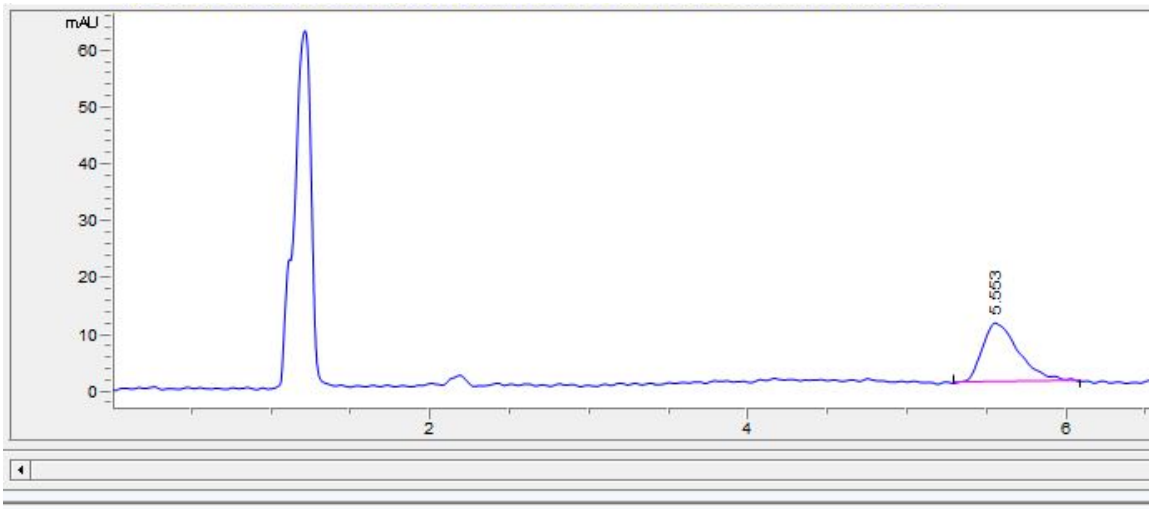

f1 (ppm)

Racemic mixture of **5f**

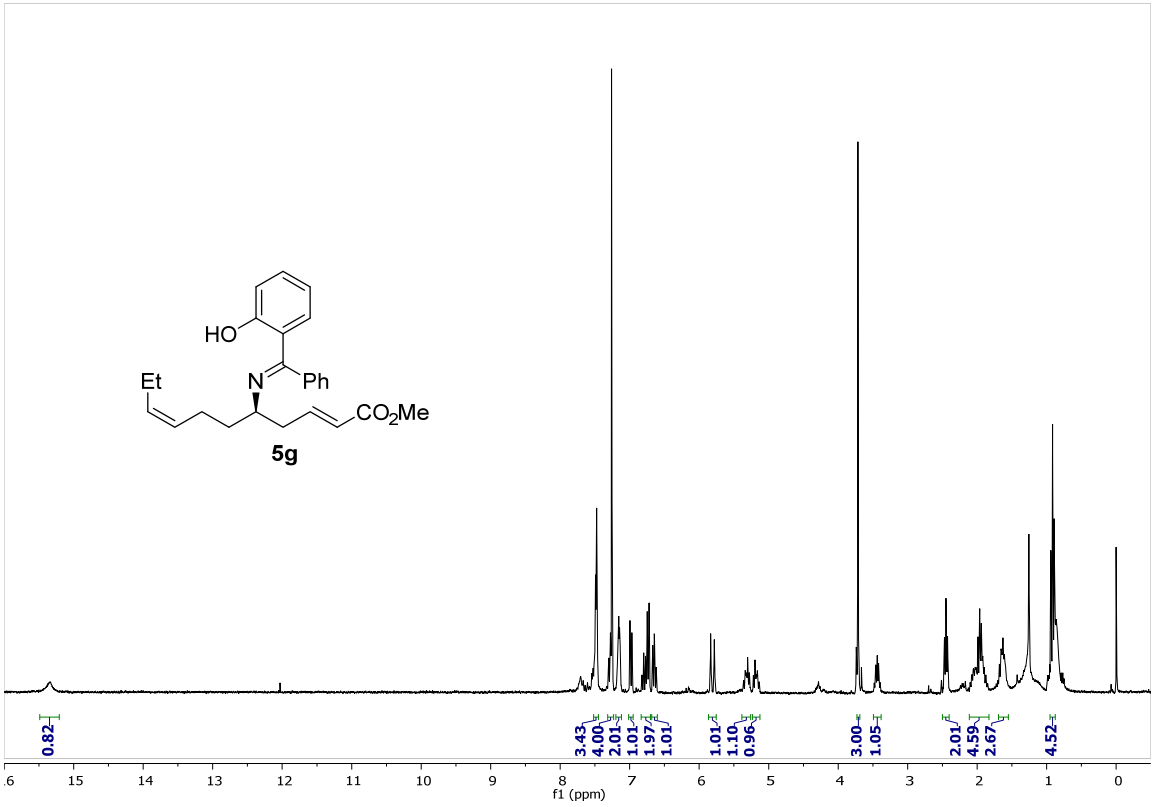


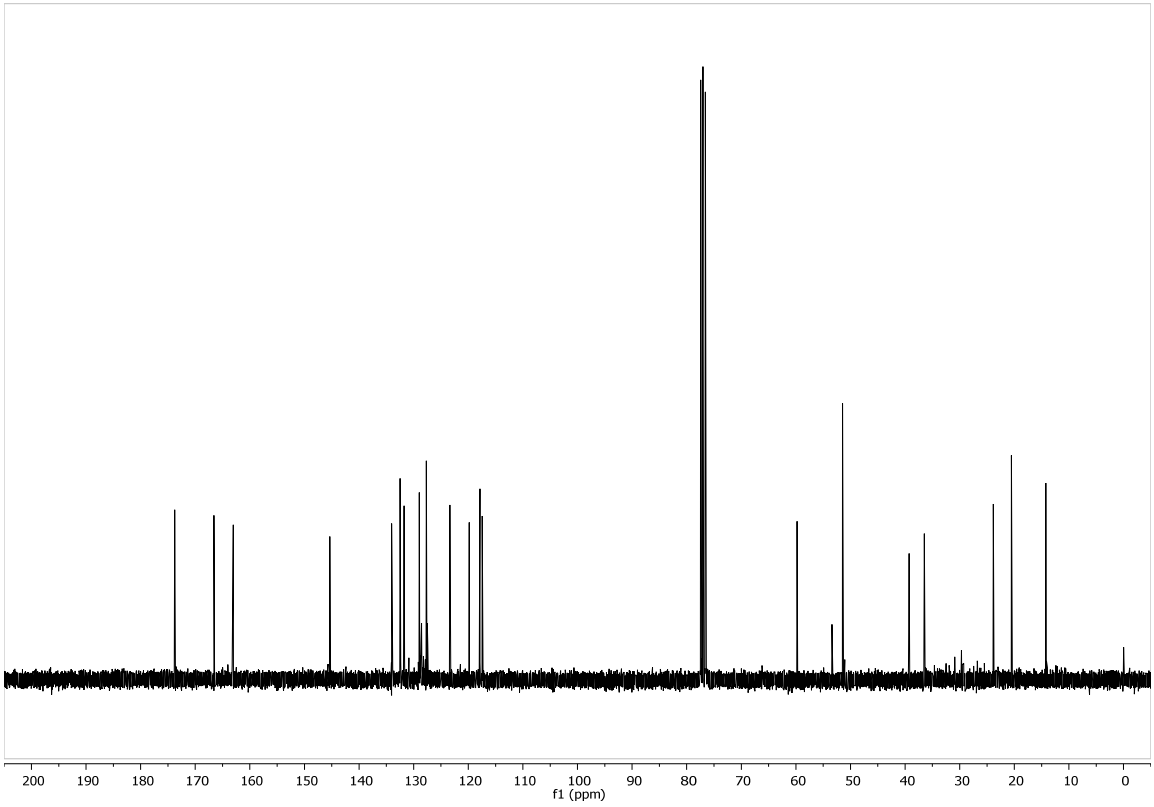
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	3.788	BB	184.6	13.6	0.1825	44.924	0.427
2	5.058	BB	226.3	14.9	0.2197	55.076	0.482

Enantiomerically enriched **5f**

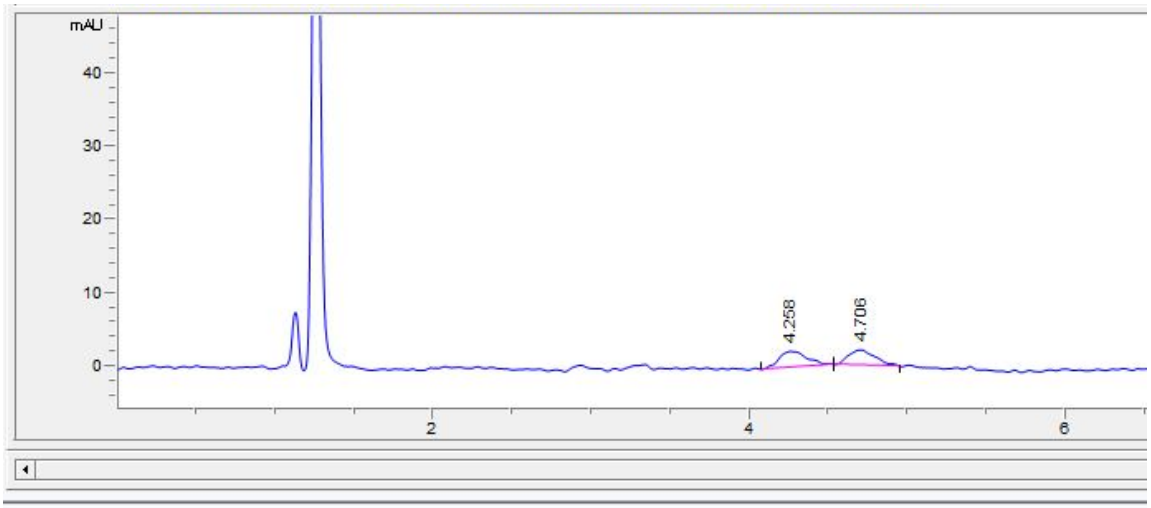


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.553	BB	172.5	10.5	0.222	100.000	0.528


HO
N
Ph
Et
CO2Me
5g
0.82
3.43
4.00
2.01
1.01
1.97
1.01
1.01
1.10
0.96
3.00
1.05
2.01
4.59
2.67
4.52
f1 (ppm)

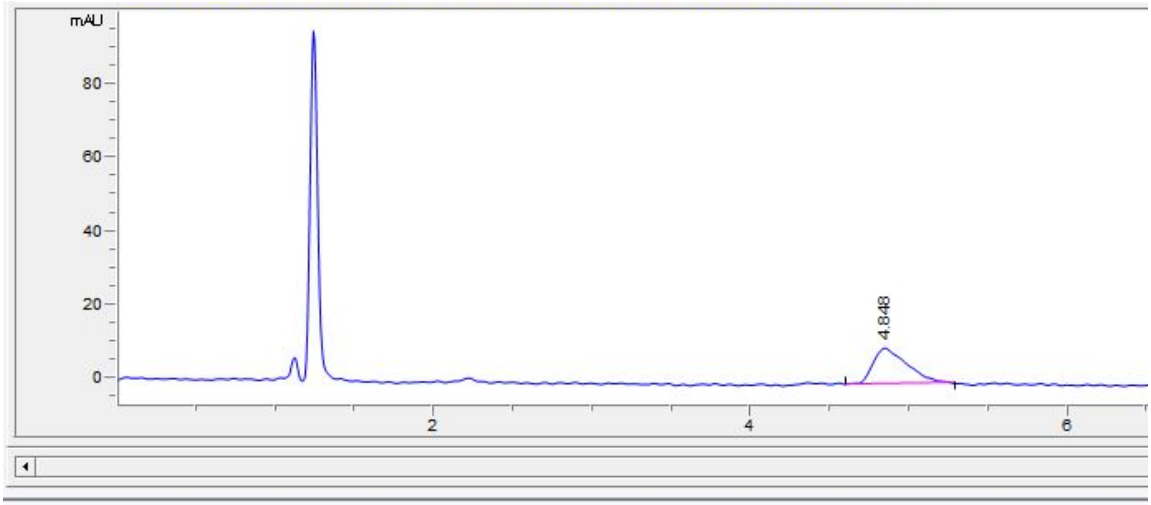

f1 (ppm)

Racemic mixture of **5g**

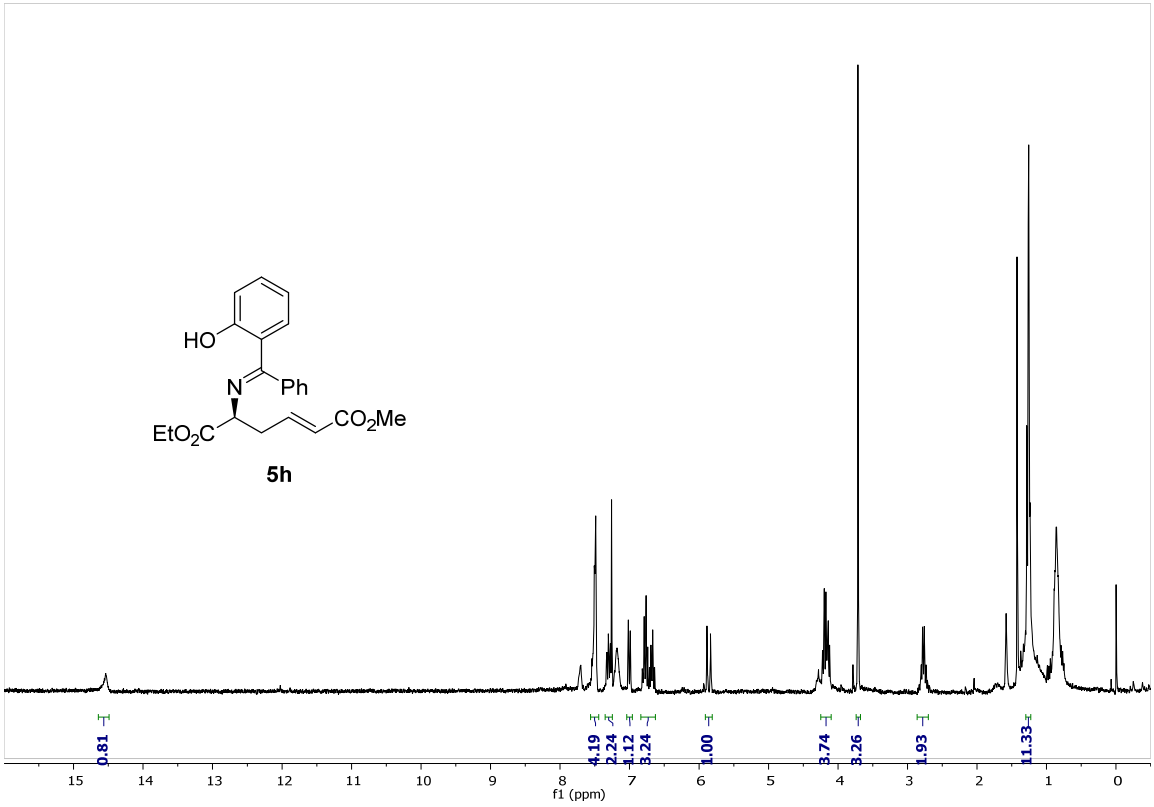


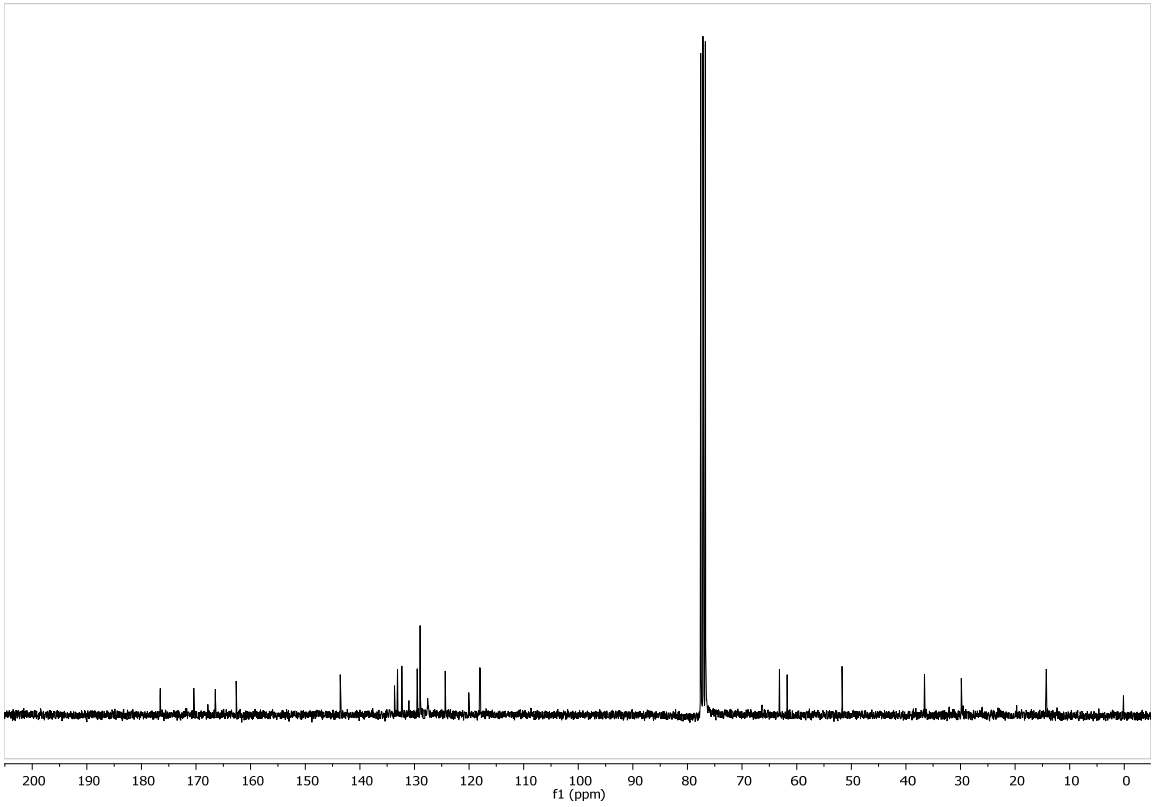
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.258	BB	27.9	2.2	0.1531	52.303	0.714
2	4.706	BB	25.4	2.1	0.1524	47.697	0.843

Enantiomerically enriched **5g**

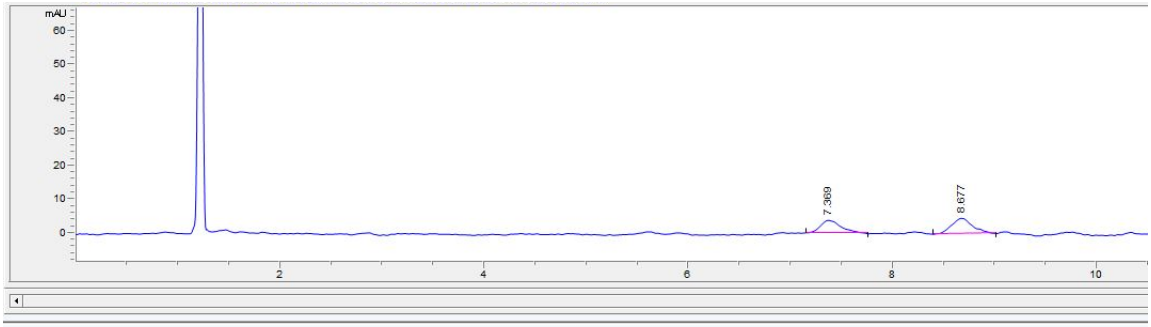


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.848	BB	151.2	9.8	0.214	100.000	0.49


HO
N
Ph
EtO2C
CO2Me
5h
0.81
4.19
2.24
1.12
3.24
1.00
3.74
3.26
1.93
11.33
f1 (ppm)

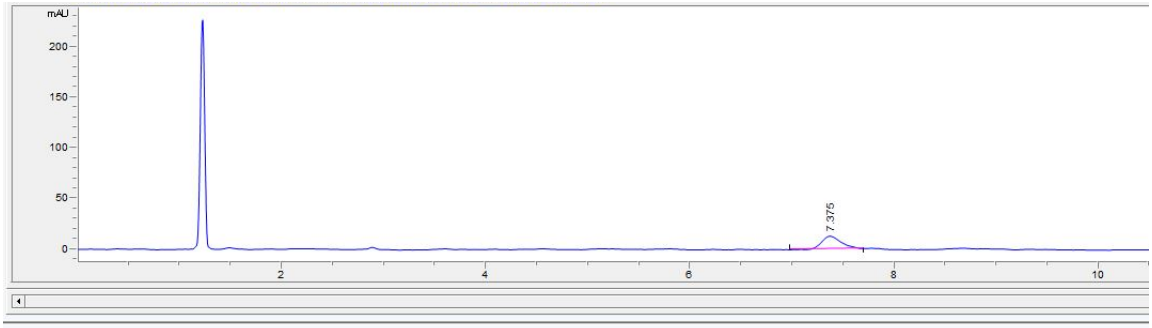

f1 (ppm)

Racemic mixture of **5h**

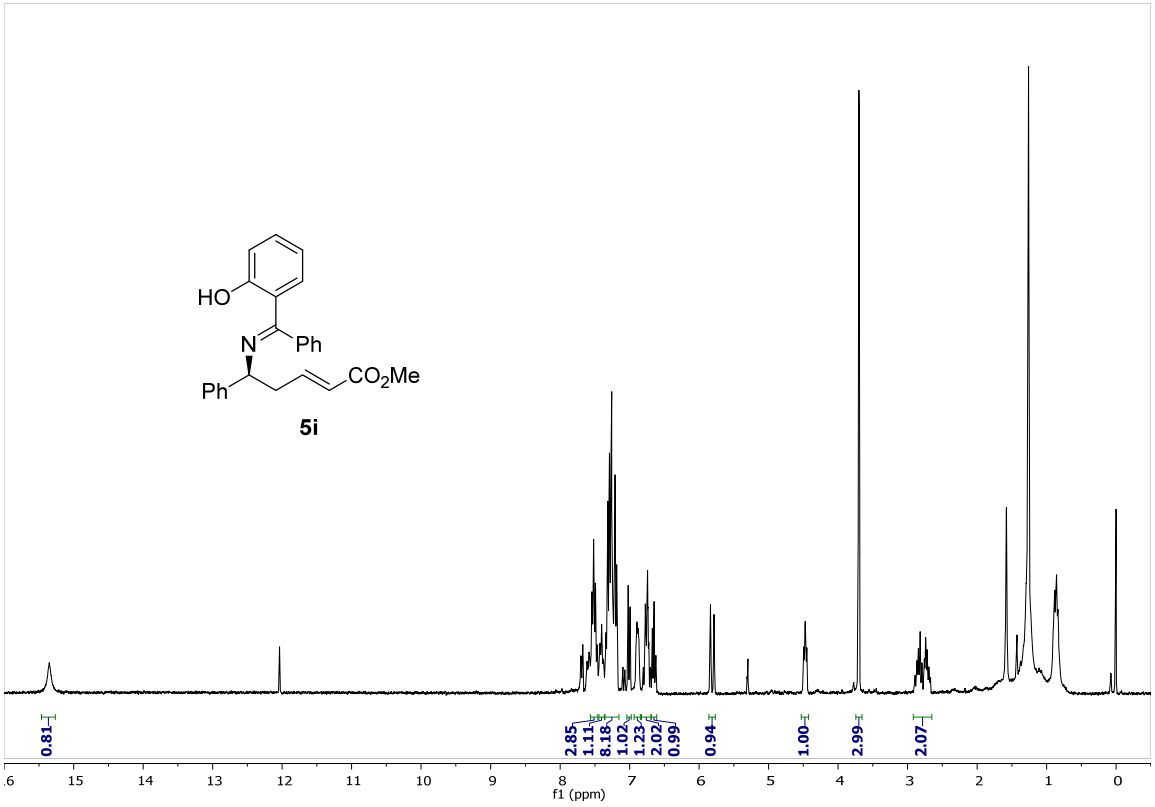


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.369	BB	55.3	3.8	0.1966	44.912	0.555
2	8.677	BB	67.9	4.6	0.203	55.088	0.867

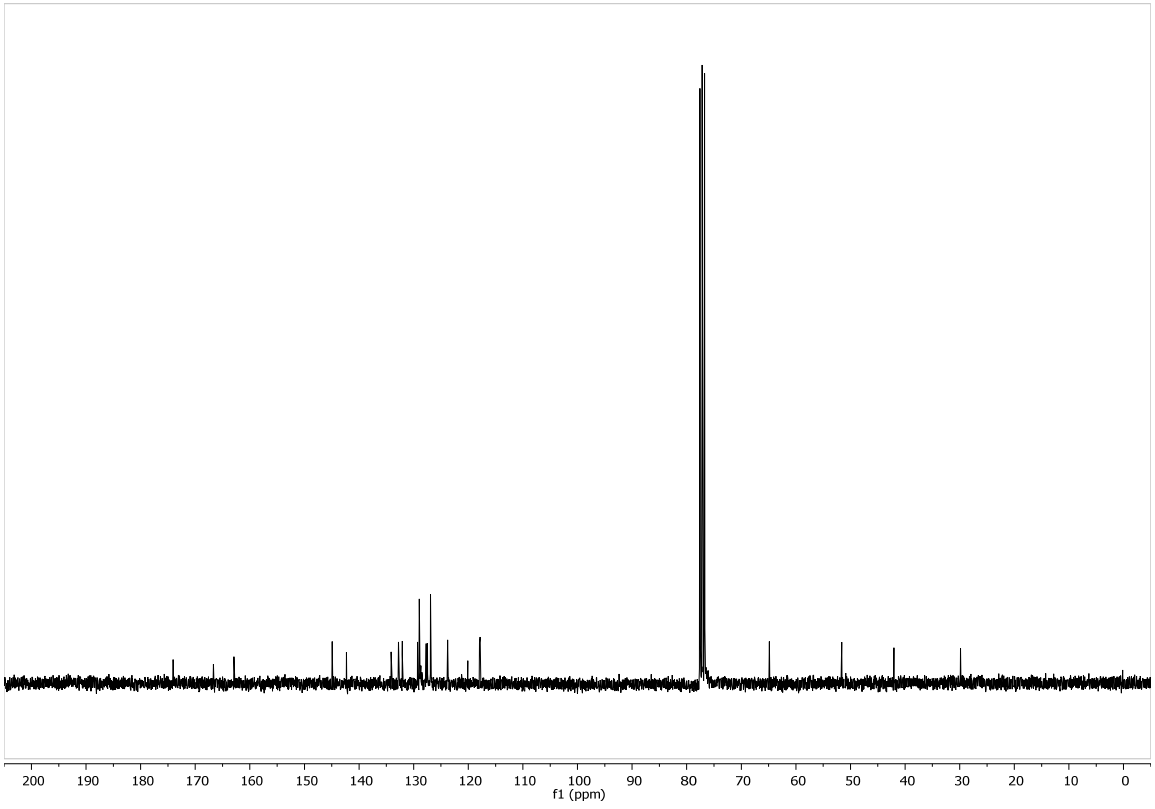
Enantiomerically enriched **5h**



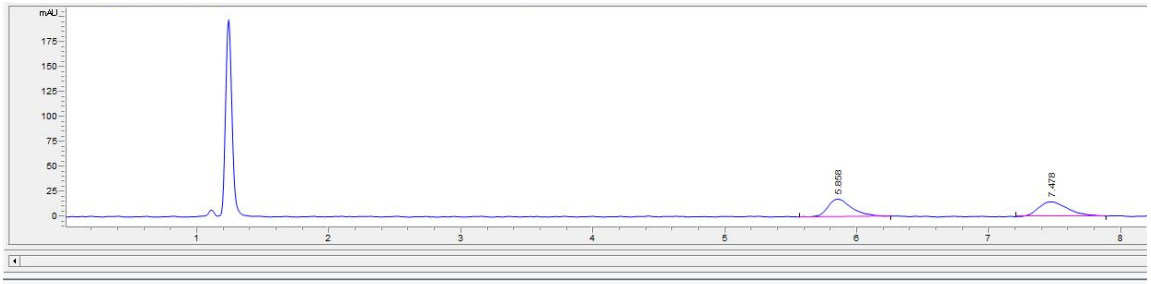
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.375	BB	171.7	12.8	0.2048	100.000	0.724


HO
N
Ph
Ph
CO2Me
0.81
2.85
1.11
8.18
1.02
1.23
2.02
0.99
0.94
1.00
2.99
2.07
f1 (ppm)

5i

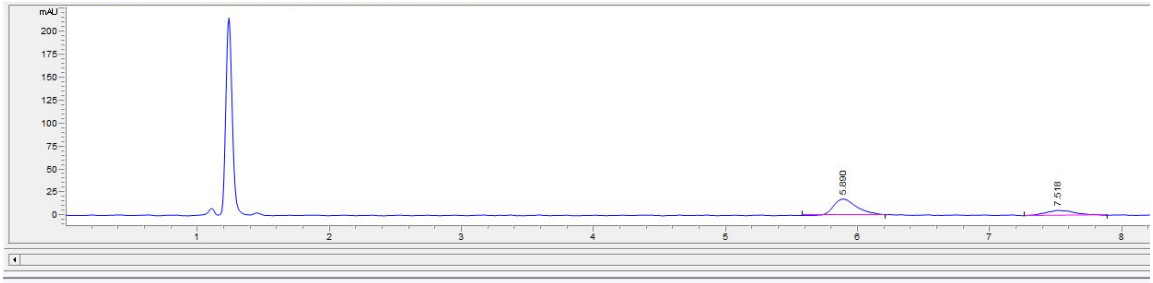

f1 (ppm)

Racemic mixture of **5i**

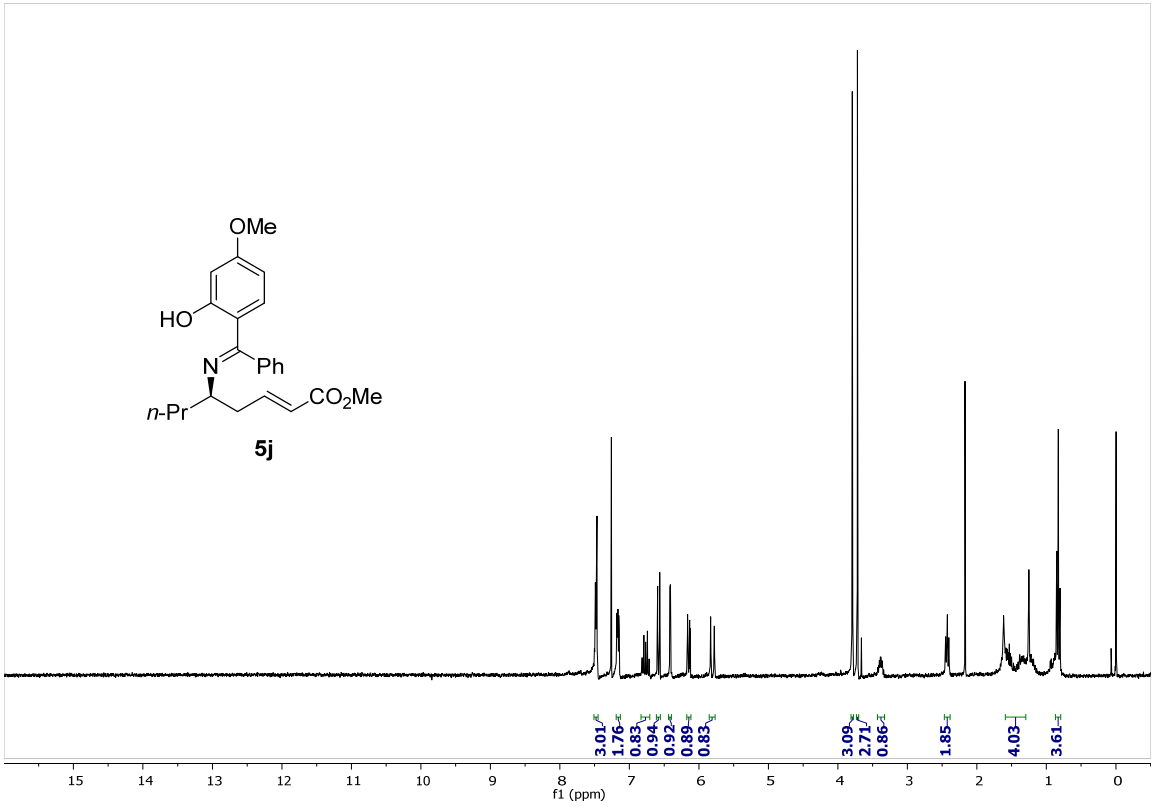


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.858	BB	223.2	17.6	0.186	49.084	0.674
2	7.478	BB	231.5	14.7	0.2254	50.916	0.72

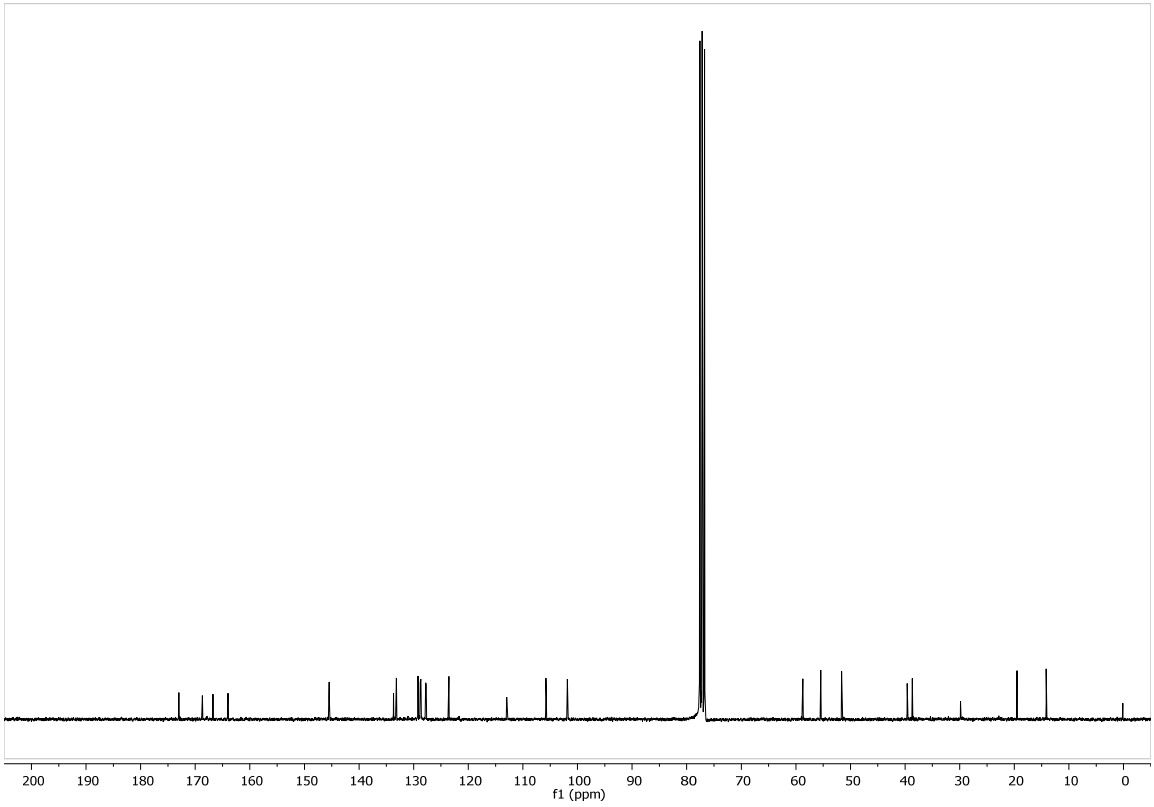
Enantiomerically enriched **5i**



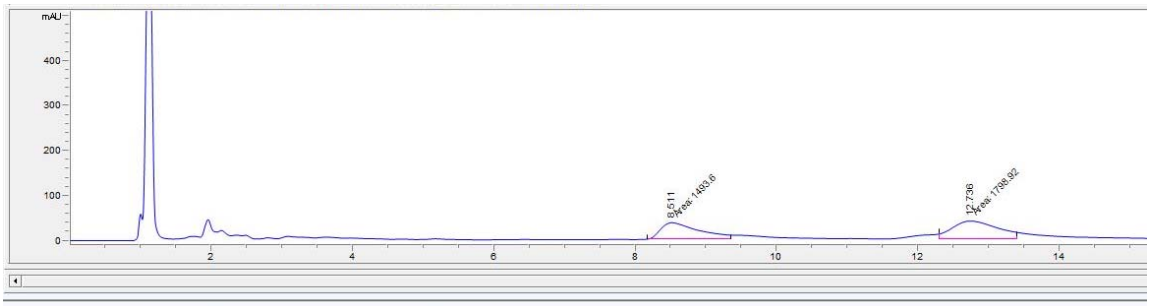
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.89	BB	216.5	17.5	0.182	70.344	0.684
2	7.518	BB	91.3	5.5	0.2082	29.656	0.707


OMe
HO
N
Ph
n-Pr
CO2Me
3.01
1.76
0.83
0.94
0.92
0.89
0.83
3.09
2.71
0.86
1.85
4.03
3.61
f1 (ppm)

5j

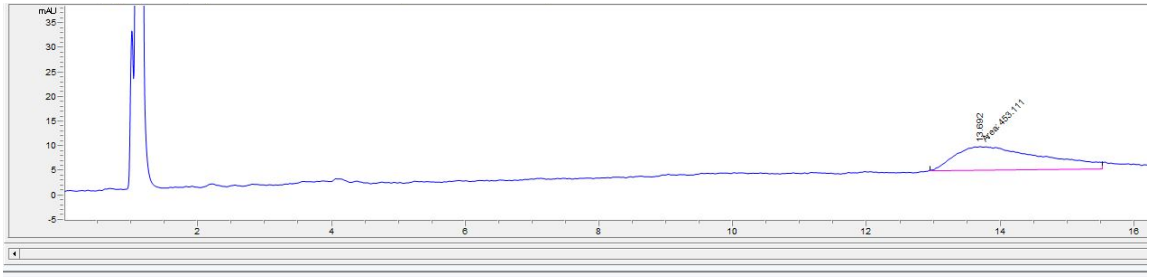

f1 (ppm)

Racemic mixture of **5j**



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.511	FM	1493.6	37.8	0.6578	45.364	0.393
2	12.736	FM	1798.9	39.8	0.7528	54.636	0.652

Enantiomerically enriched **5j**



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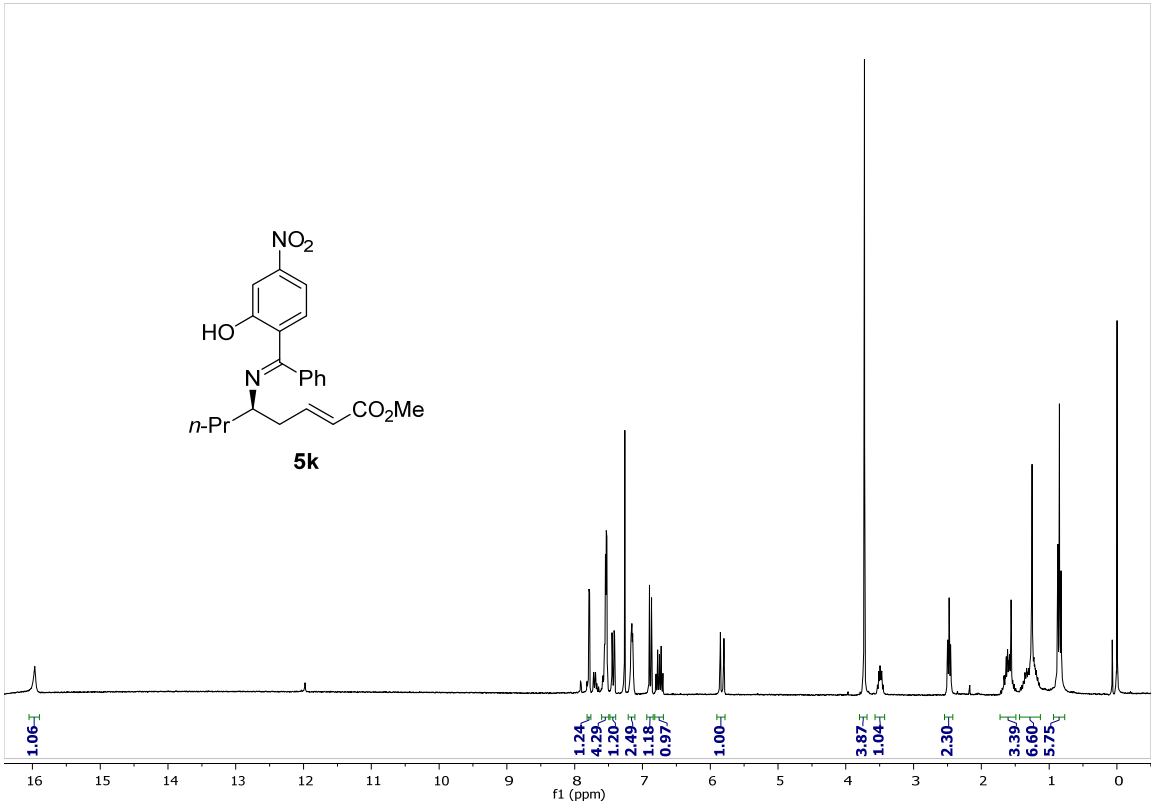
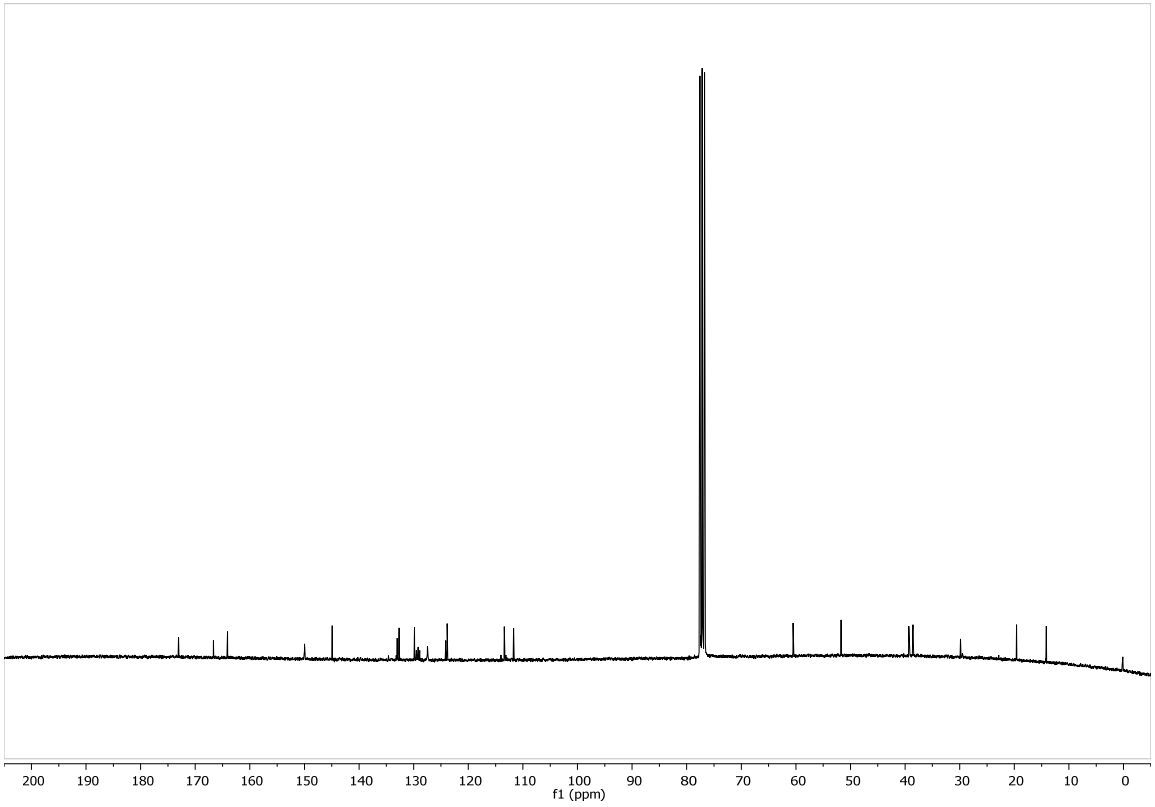
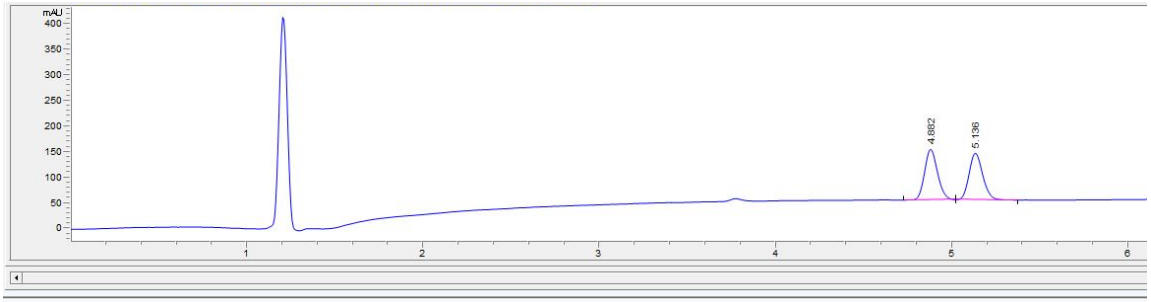

NO2
HO
N
Ph
n-Pr
CO2Me
5k
1.06
1.24
4.29
1.20
2.49
1.18
0.97
1.00
3.87
1.04
2.30
3.39
6.60
5.75
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

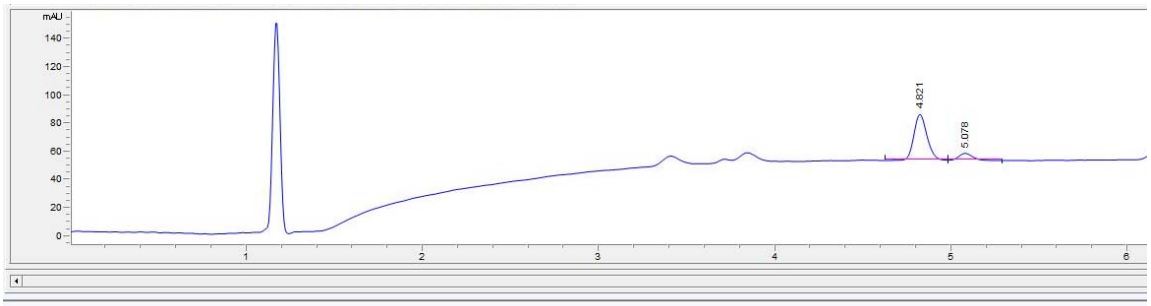

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Racemic mixture of **5k**

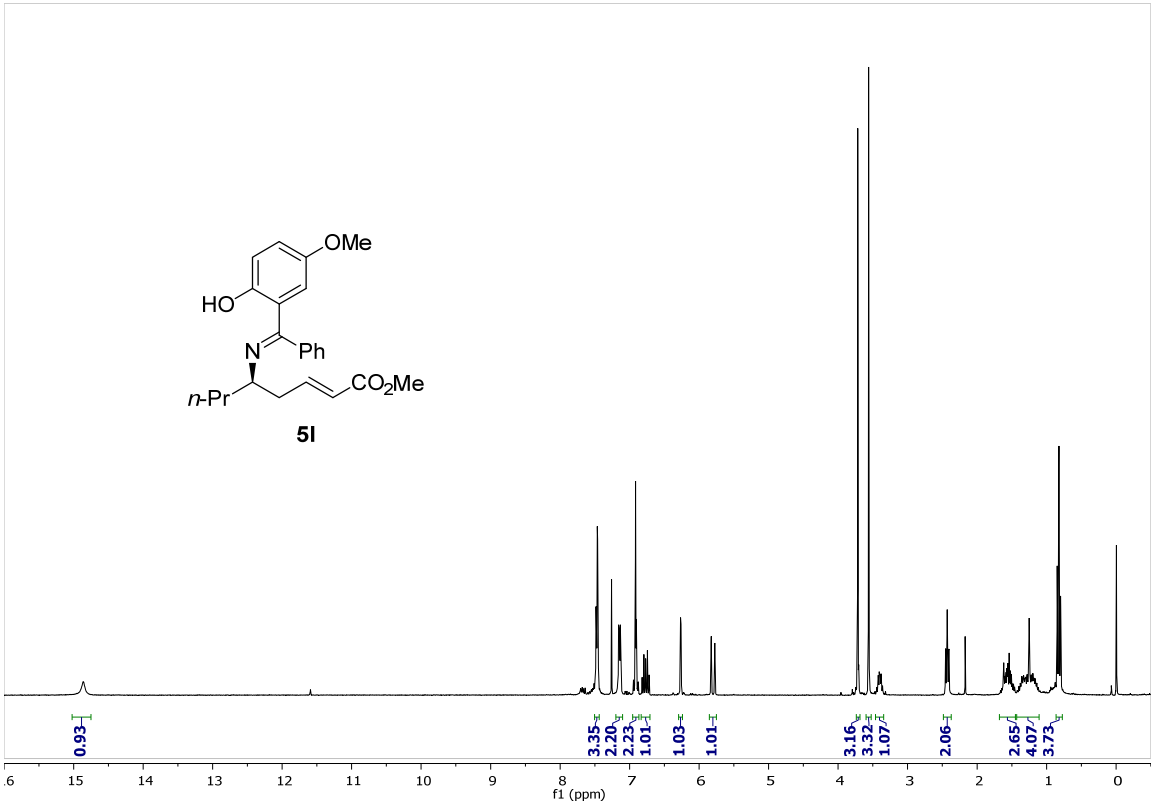


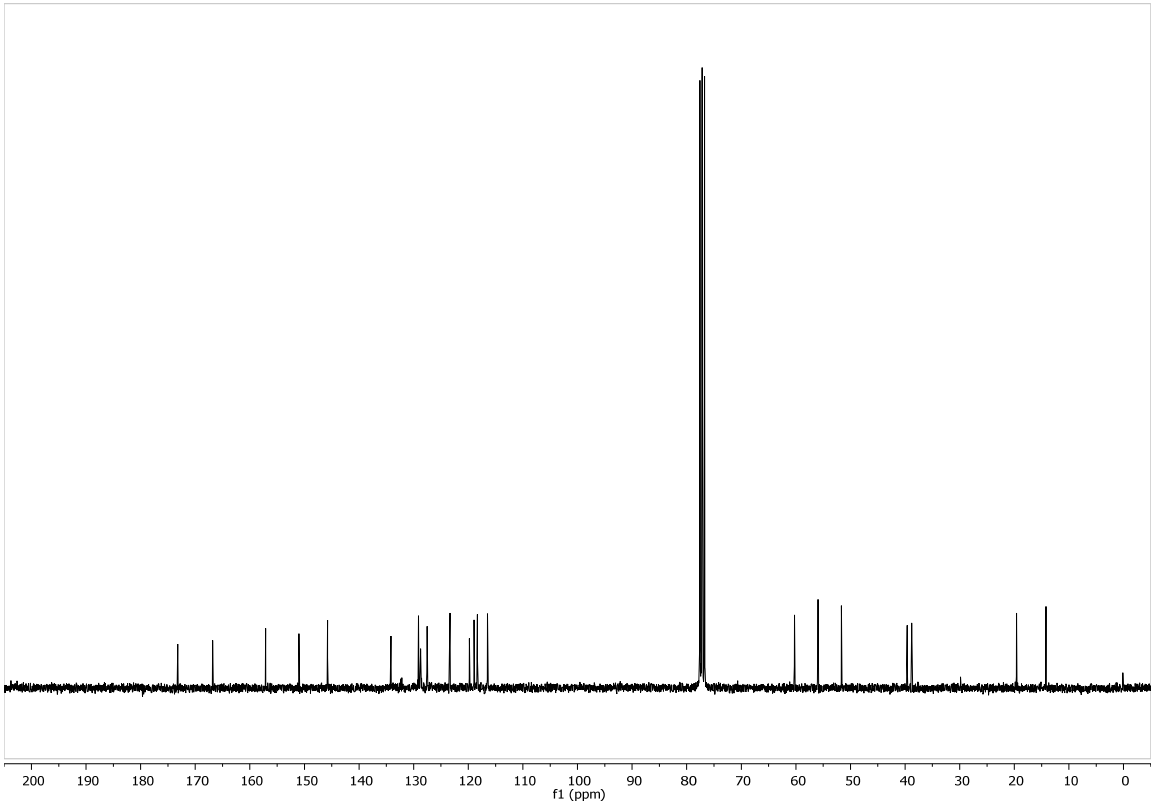
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.882	BB	502.8	98.6	0.0775	50.774	0.833
2	5.136	BB	487.5	91	0.0845	49.226	0.816

Enantiomerically enriched **5k**

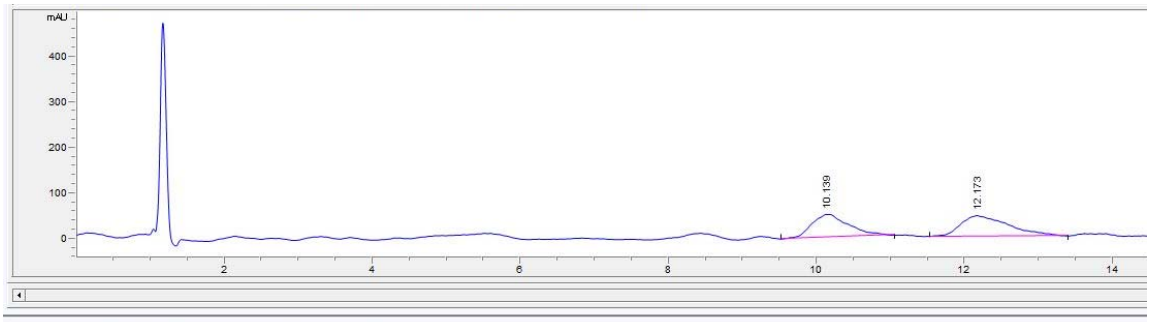


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.821	BB	169.3	32.7	0.0804	86.490	0.82
2	5.078	BB	26.4	4.9	0.0848	13.510	0.824


OMe
HO
N
Ph
n-Pr
CO2Me
5l
0.93
3.35
2.20
2.23
1.01
1.03
1.01
3.16
3.32
1.07
2.06
2.65
4.07
3.73
f1 (ppm)

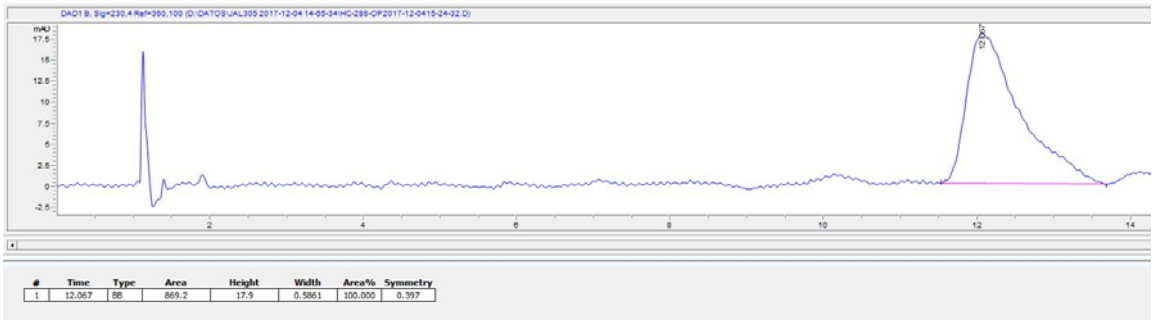

f1 (ppm)

Racemic mixture of **5l**

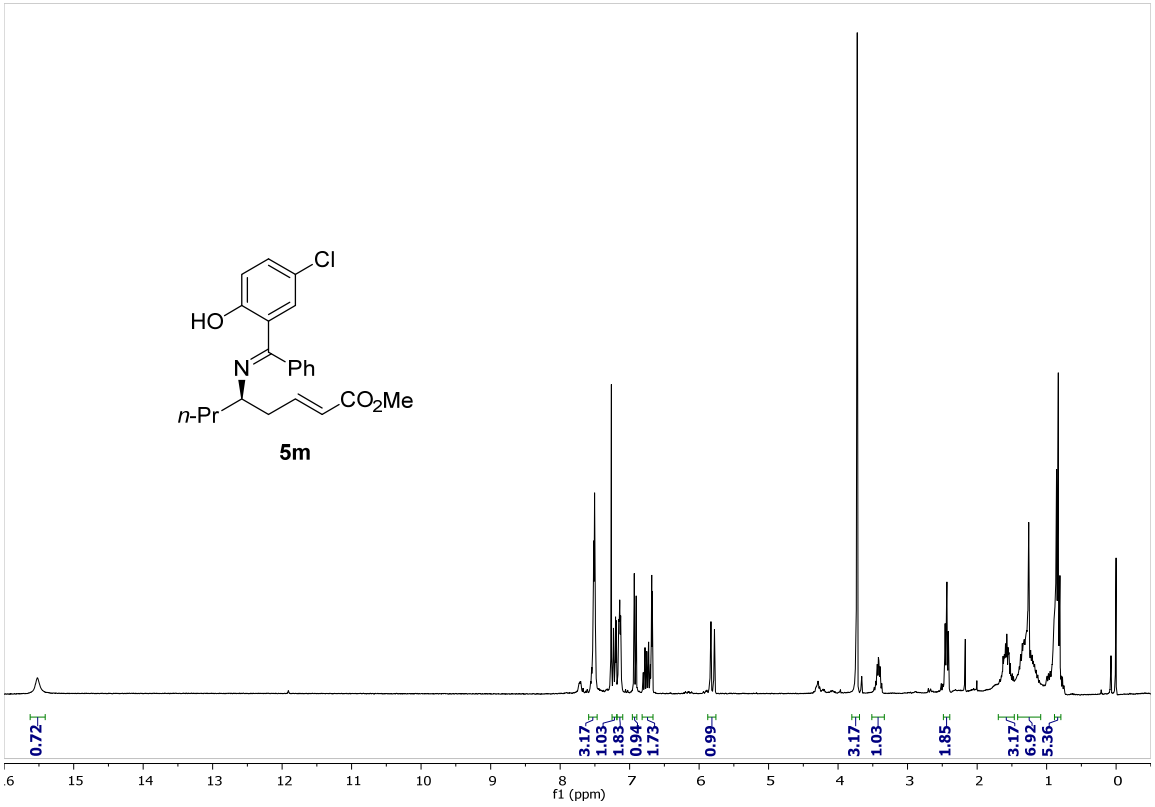


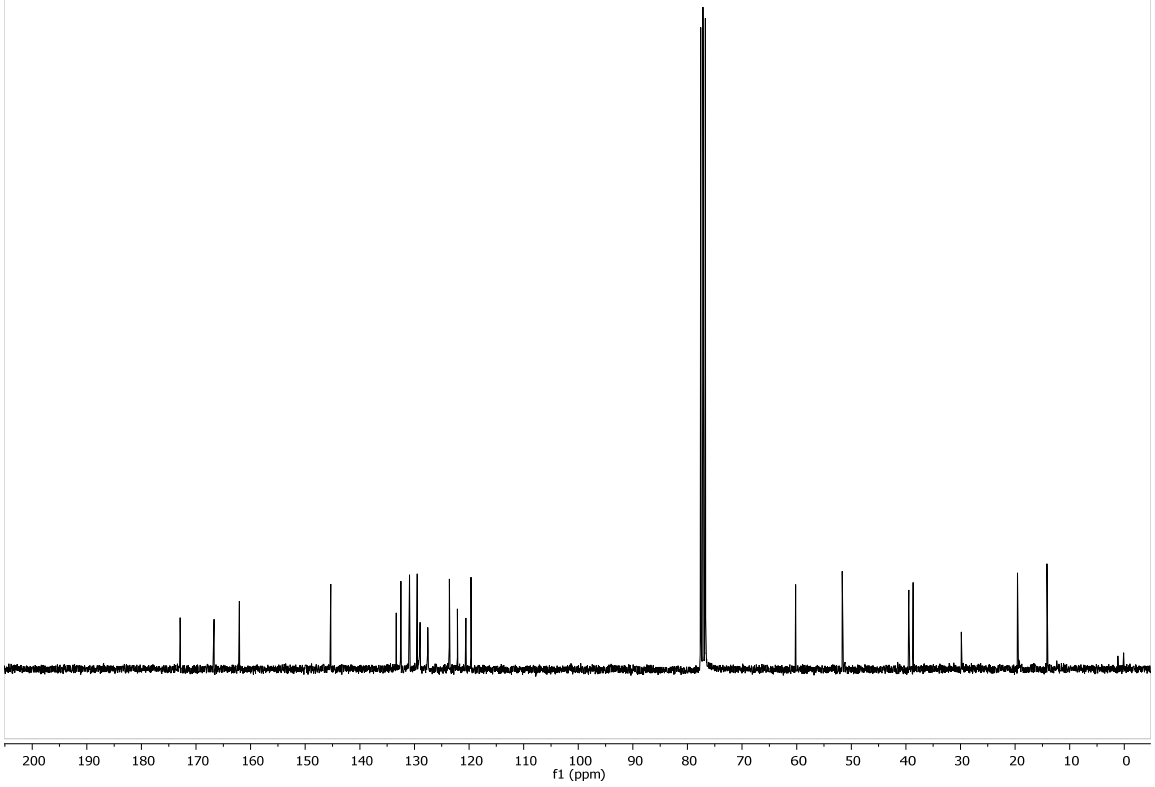
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.139	BB	1798.6	50.8	0.4312	46.347	0.66
2	12.173	BB	2082.2	45.5	0.5538	53.653	0.494

Enantiomerically enriched **5l**

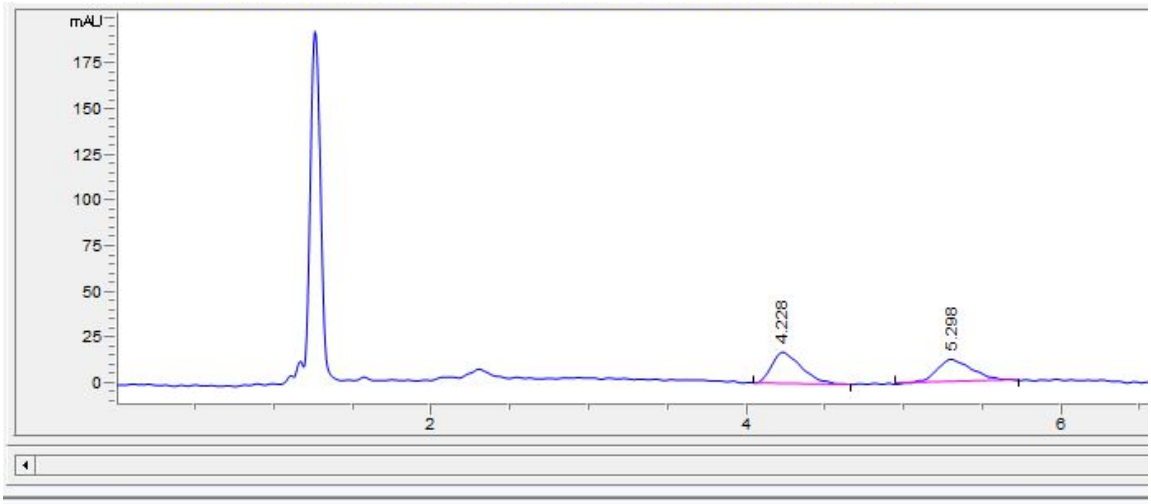


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.067	BB	869.2	17.9	0.5861	100.000	0.397


Cl
HO
N
Ph
n-Pr
CO2Me
5m
0.72
3.17
1.03
1.83
0.94
1.73
0.99
3.17
1.03
1.85
3.17
6.92
5.36
f1 (ppm)

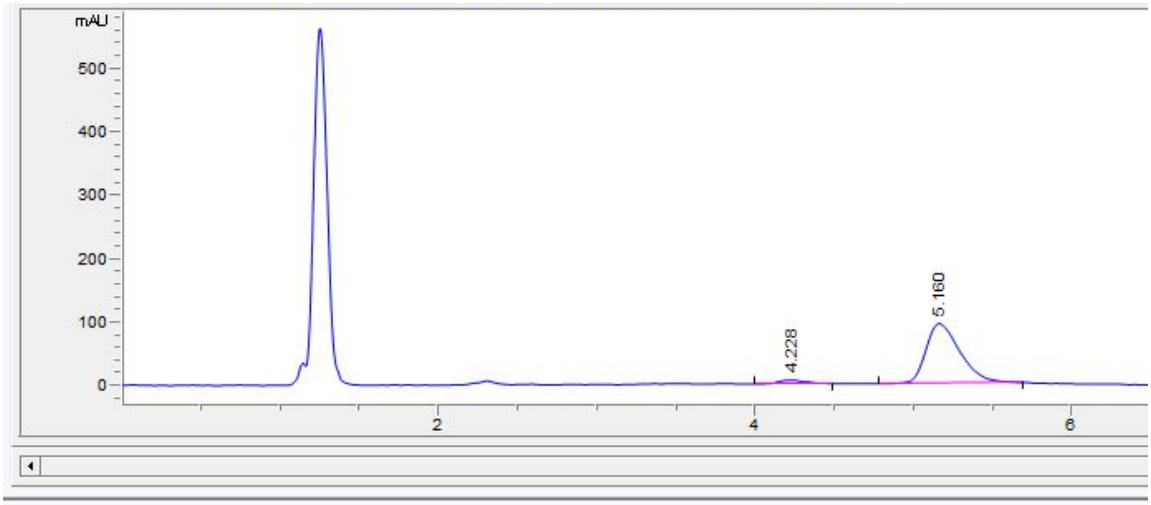

f1 (ppm)

Racemic mixture of **5m**

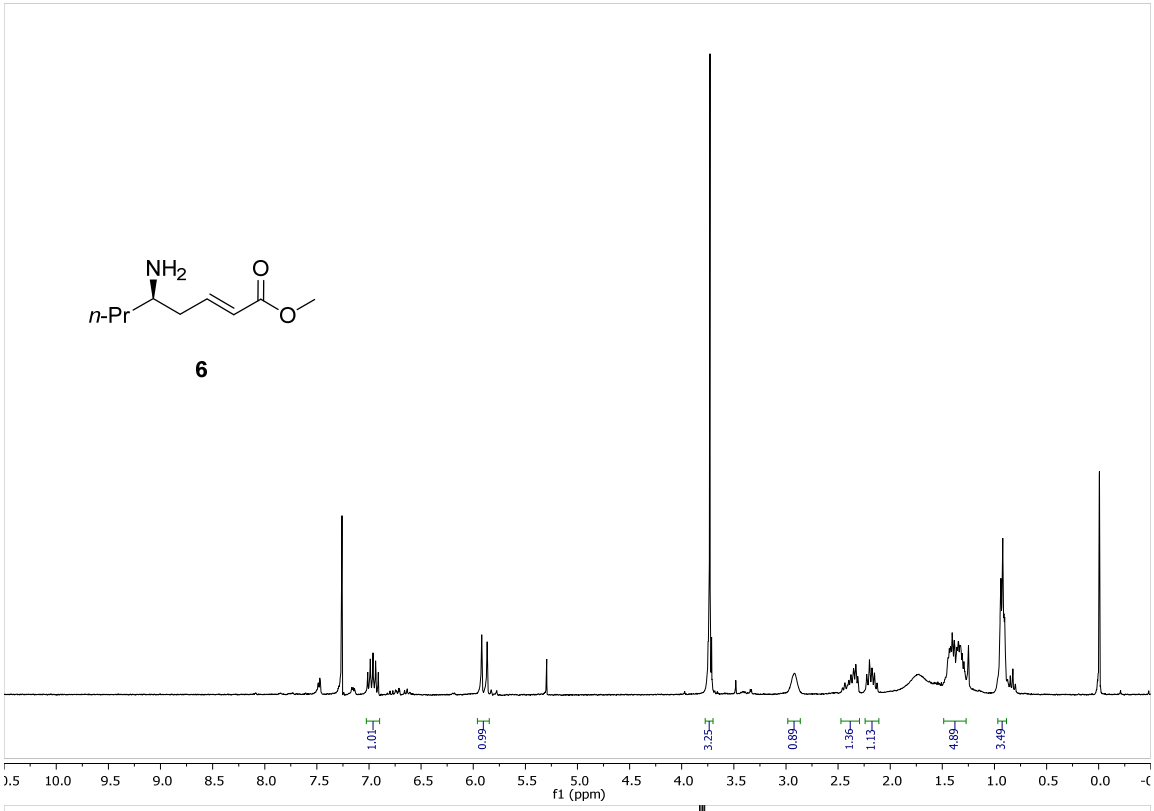


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.228	BB	225.4	17.1	0.1816	51.431	0.552
2	5.298	BB	212.9	12.8	0.2158	48.569	0.684

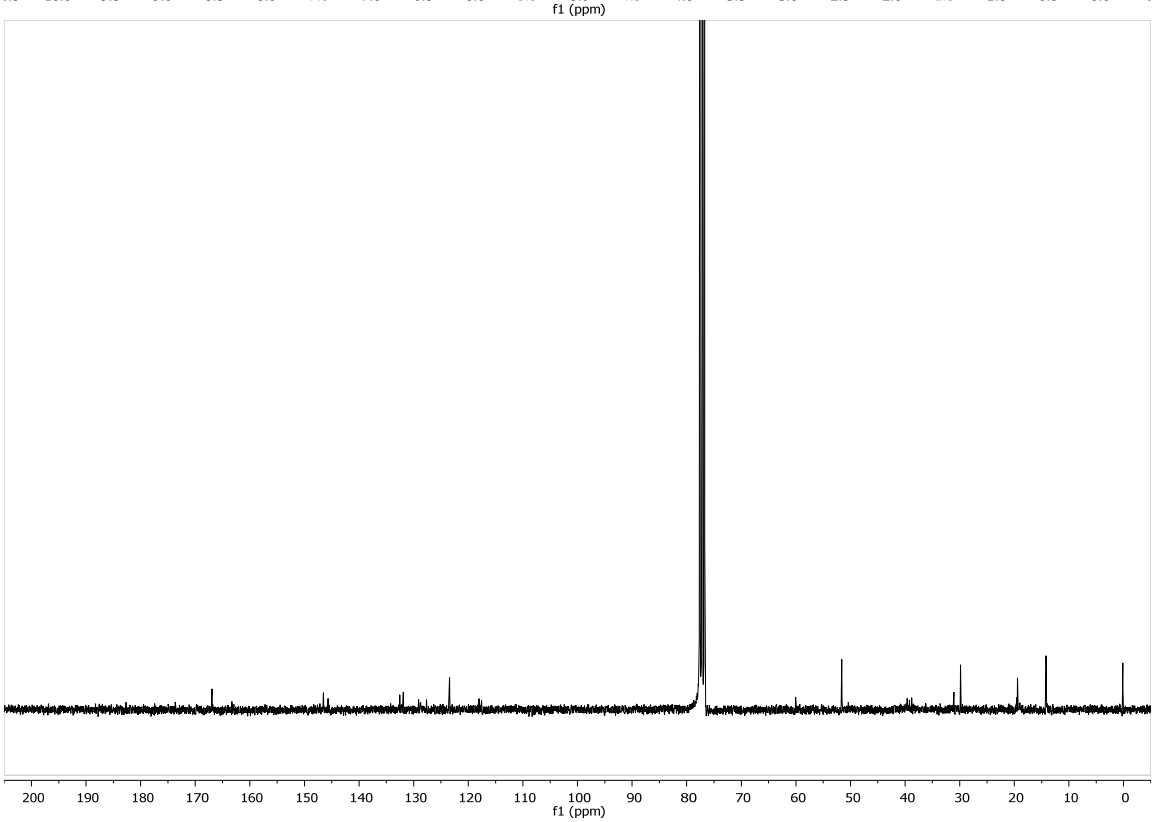
Enantiomerically enriched **5m**



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.228	BB	74.7	6	0.1882	5.035	0.842
2	5.16	BB	1409.5	93.6	0.2297	94.965	0.6


NH2
O
n-Pr
O
1.01
0.99
3.25
0.89
1.36
1.13
4.89
3.49
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

6


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

6. Computational details

Geometry optimizations were performed using Minnesota functional M06-2X, that has a broad applicability in chemistry[7,8] and is specially designed to account for dispersive interactions. Pople's double-ζ basis set with polarization and diffuse orbitals (6-31++G(d,p)) was used in this work as a compromise between accuracy and computational cost. Harmonic vibrational frequencies were evaluated at this level of theory to characterize minima and transitions states (TS) and to compute thermodynamic corrections. Connectivity between TSs and adjacent minima was verified running Intrinsic Reaction Coordinate (IRC) calculations. To further explore the potential energy surface (PES), we also ran relaxed scans calculations at the M062X/6-31G(d,p) level of theory.

To account for the effect of the reaction medium (the organic solvent toluene), the electronic energies of stationary points were further refined by means of single-point calculations over the previously optimized geometries, using a continuum solvation model: SMD.[9]

Estimation of Gibbs free energies was done by adding the thermal and entropic corrections, obtained at 298.15 K and 1 atm at the gas-phase level, to the electronic energies obtained from single-point calculations in the solvent phase (SMD=toluene).

This computational procedure has been proved to be appropriate describing these kinds of systems in previous works. All the calculations were carried out using the Gaussian09 suite of programs.[10]

An NCI analysis[11] was also carried out on key structures. This Non-Covalent Interaction approach localizes non-covalent interactions between atoms by evaluation of the behavior of the reduced density gradient, s, with respect to the electron density (ρ):

$$s = \frac{|\nabla\rho|}{c_F\rho^{4/3}}$$

The sign of the second eigenvalue (λ_2) of the electron-density Hessian matrix classifies these interactions as attractive or repulsive. A very useful tool is the visualization of the gradient isosurface in real space. For this, the product of the sign(λ_2) and the electron-density function (ρ), sign(λ_2)ρ, was used to color the different isosurfaces showed in the manuscript (Figure 1). A RGB (red-blue-green) scale is used; red isosurfaces indicate repulsive interactions, blue stands for attractive and green for very weak van der Waals-type interactions. NIC plots were computed with the NCIPLOT program[12] and visualized with Visual Molecular Dynamics (VMD) program.[13]

The natural bond orbital (NBO) analysis was also employed in order to evaluate the charge distribution on key structures. This analysis has been carried out using Gaussian NBO Version 3.1.[14]

7. Structures of ketimine derivatives

Structures for all ketimine **1** derivatives (and all the conformers for each of them) considered in this work are available online within the ioChem repository[15] (https://doi.org/10.19061/iochem-bd-8-1). Figures S1 and S2 show the schematic structures of the conformers considered for neutral and deprotonated **1b**, respectively. The equivalent structures were considered for the other derivatives (**1c**, **1d**, **1e**, and **1f**). Tables S1 and S2 list the relative energies of each conformer. In all the cases (all derivatives, neutral and deprotonated forms), the most stable is conformer a.

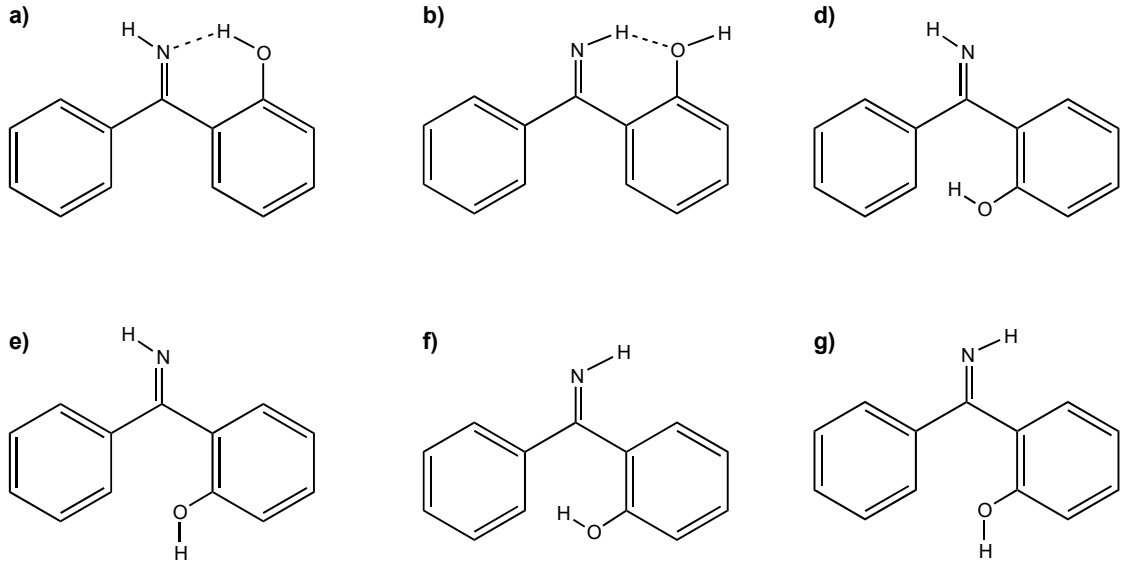


Figure S1. Scheme of the conformers considered for ketimine **1b**. The equivalent for the other derivatives were also considered. The optimized structures at the $SMD_{(toluene)}$/M06-2X/6-31++G(d,p) level of theory can be visualized at https://doi.org/10.19061/iochem-bd-8-1.

Table S1: Relative Gibbs free energies for the different conformers considered for each of the derivatives of ketimine **1**. In all the cases, the most stable is conformer a. Energies were computed at the $SMD_{(toluene)}$/M06-2X/6-31++G(d,p) level of theory. All energies are reported in kcal/mol.

Conformer	1b	1c	1d	1e	1f
a	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
b	7.89	9.26	8.22	8.20	8.89
d	7.78	8.26	7.19	7.81	8.14
e	8.60	9.97	8.42	8.59	9.52
f	6.91	7.52	6.73	6.38	7.46
g	7.93	9.05	7.79	7.29	9.02

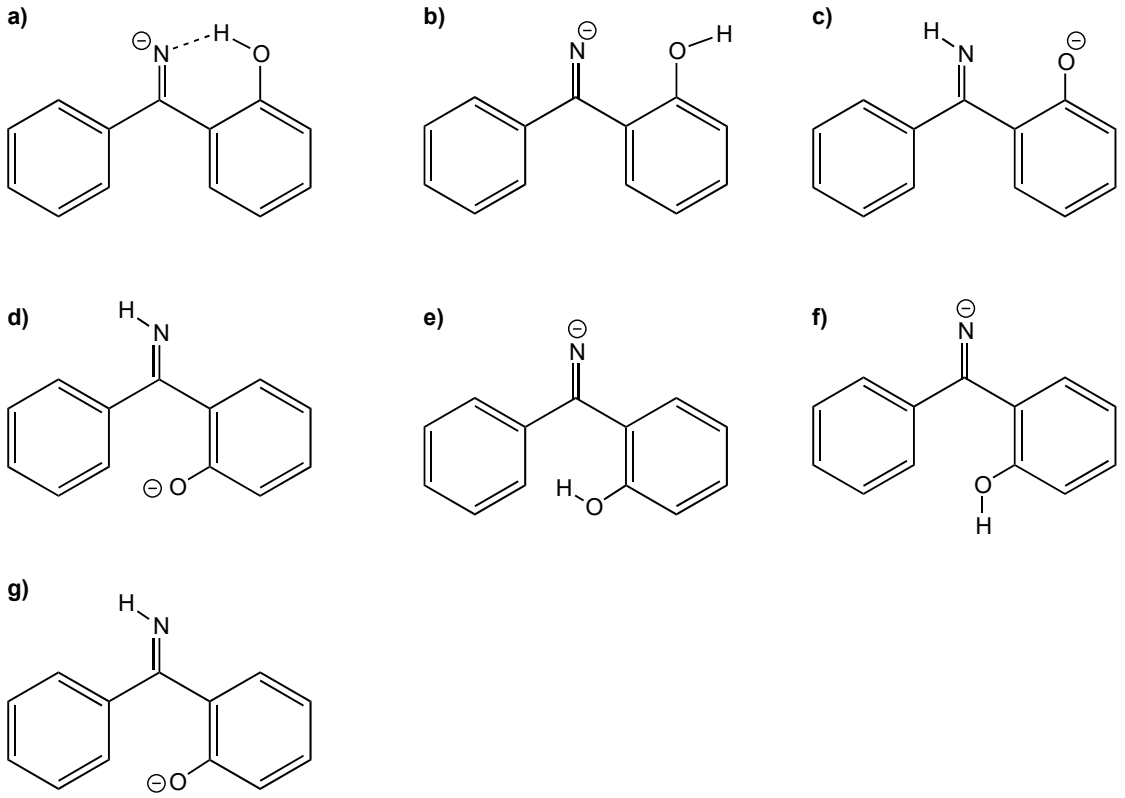


Figure S2. Scheme of the conformers considered for ketimine **1b**. The equivalent for the other derivatives were also considered. The optimized structures at the $SMD_{(toluene)}$/M06-2X/6-31++G(d,p) level of theory can be visualized at https://doi.org/10.19061/iochem-bd-8-1.

Table S2. Relative Gibbs free energies for the different conformers considered for the *deprotonated* form of each derivative of ketimines **1**. In all the cases, the most stable is conformer a. Energies were computed at the $SMD_{(toluene)}$/M06-2X/6-31++G(d,p) level of theory. All energies are reported in kcal/mol.

Conformer	1b	1c	1d	1e	1f
a	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
b	38.01	40.47	39.25	36.14	40.67
c	10.20	9.68	8.98	10.80	10.55
d	5.53	5.11	4.42	6.19	5.47
e	38.03	40.43	39.25	36.19	40.67
f	32.81	34.67	33.93	-0.03	34.86
g	3.73	3.91	3.23	4.12	3.79

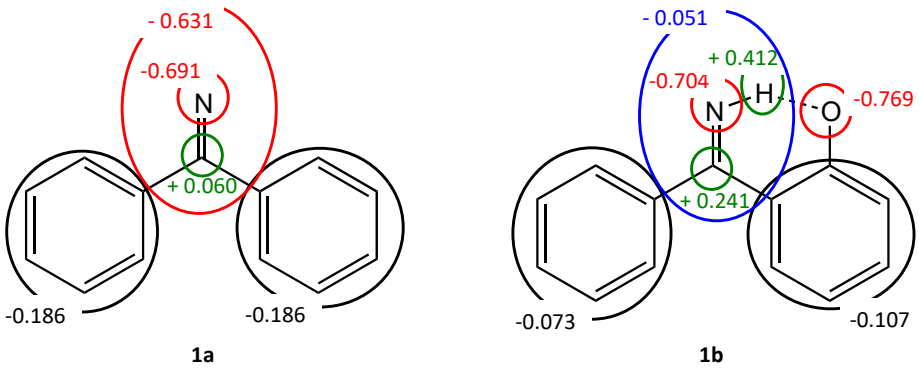
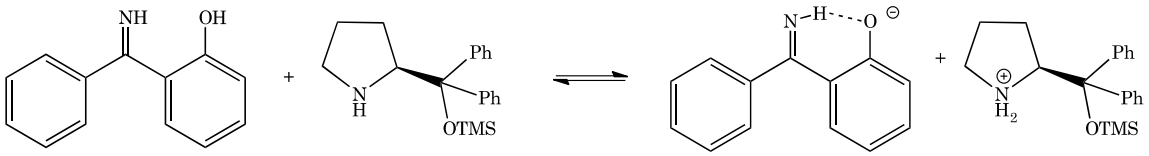


Figure S3: Charge distribution for deprotonated ketimines **1a** and **1b.**

8. Acidity of ketimine derivatives

The Gibbs deprotonation energy of the different ketimine **1** derivatives were computed as the Gibbs free energy of the reaction shown in Scheme S1. The conformer chosen for both the neutral and deprotonated forms was always conformer a, since it is the most stable for all derivatives (see previous section).



Scheme S1. Reaction for computing ketimine **1** acidity.

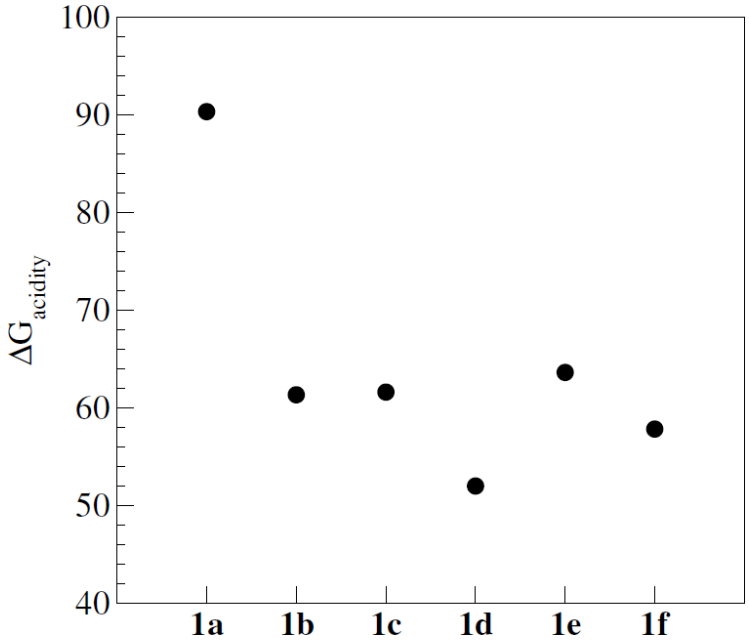


Figure S3: Gibbs free energy for deprotonation of ketimine derivatives computed at the $SMD_{(toluene)}$/M062X/6-31++G(d,p) level of theory. The acidity of the ketimine derivatives bearing an OH group is systematically 30 kcal/mol or more lower than **1a** (ketimine without OH group).

9. Mechanism

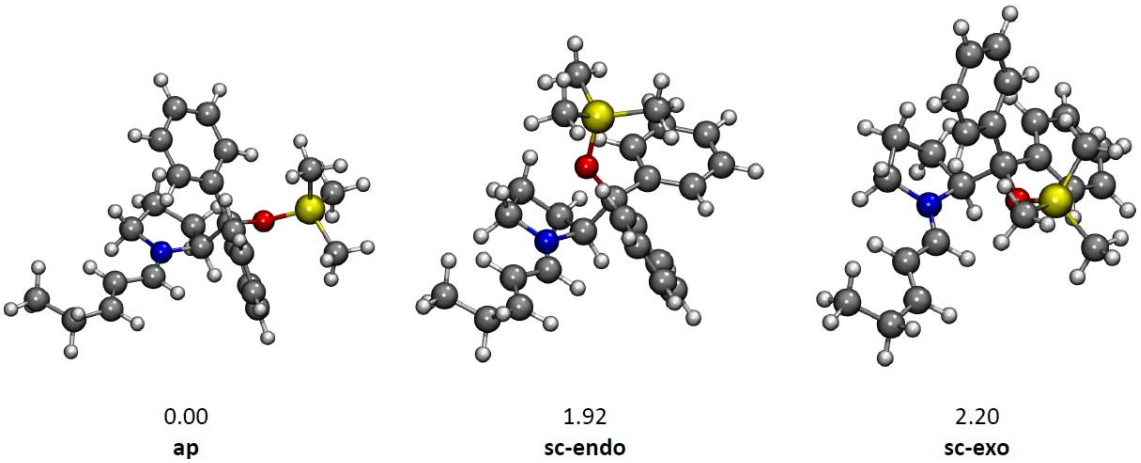


Figure S4. Structure of the three possible conformations, antiperiplanar (*ap*), synclinal-endo (*sc-endo*), and synclinal-exo (*sc-exo*), of the exocyclic C-C bond of the iminium ion. Relative Gibbs free energies (kcal/mol) computed at the M062X/6-31++G(d,p) level of theory are also shown in the figure. The 3D structures and coordinates can be visualized at http://dx.doi.org/10.19061/iochem-bd-8-1.

For the lowest energy path (path_A) we did not find a transition state for the H transfer. We performed a scan along the O-H distance to study the energy profile (Figure S4) for the H transfer from the N (intermediate) to the oxygen to form the product. The relative energy used in Figure 2 of the manuscript as TS energy corresponds to the highest energy found along the scan. From the scan, we observe that there is a negligible barrier (~ 0.02 kcal/mol) to start the elongation of the N – H distance. Therefore, the proton transfer is a practically barrierless process once the intermediate is formed.

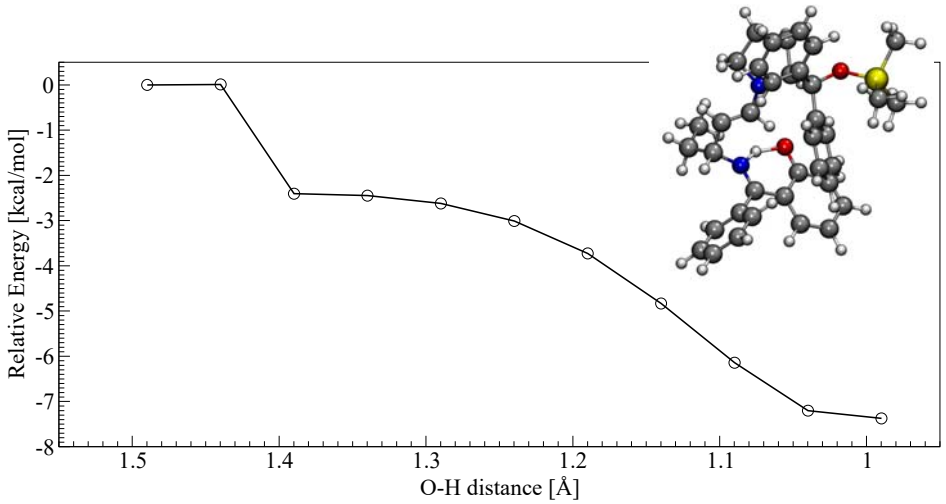


Figure S5. Potential energy scan along the O-H distance (step=0.05 Å) starting from the intermediate with the H attached to the nitrogen atom. M06-2X/6-31G(d,p) level of theory.

10. References

1. For the synthesis of organocatalyst **3e**: a) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.*, 2006, **8**, 2901-2904; for the synthesis of organocatalyst **3f**: b) Q. Lin, D. Meloni, Y. Pan, M. Xia, J. Rodgers, S. Shepard, M. Li, L. Galya, B. Metcalf, T.-Y. Yue, P. Liu, J. Zhou, *Org. Lett.*, 2009, **11**, 1999-2002.
2. Y. Bergman, P. Perlmutter, N. Thienthong, *Green. Chem.*, 2004, **6**, 539-540.
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