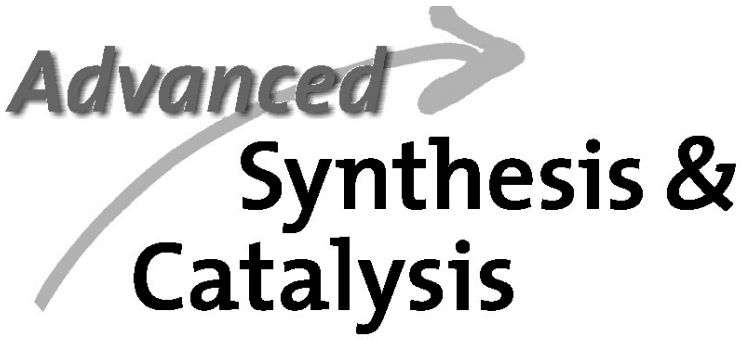


Supporting Information

Highly Enantioselective Aza-Baylis-Hillman Reactions Catalyzed by Chiral Thiourea Derivatives

Izzat T. Raheem, Eric N. Jacobsen*

Department of Chemistry and Chemical Biology

Harvard University, 12 Oxford Street, Cambridge, MA 02138 USA

Fax: (+1)-617-496-1880, e-mail: jacobsen@chemistry.harvard.edu

Supporting Information

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

Materials. Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Mercury-400 (400 MHz) or Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual NMR solvent peak ($CHCl_3$: δ 7.26, $(CD_3)_2SO$: δ 2.49). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0, $(CD_3)_2SO$: δ 39.5). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration.

The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility using a Micromass Platform II single quadrupole instrument.

Chiral HPLC analysis was performed on a Hewlett-Packard 1050 instrument.

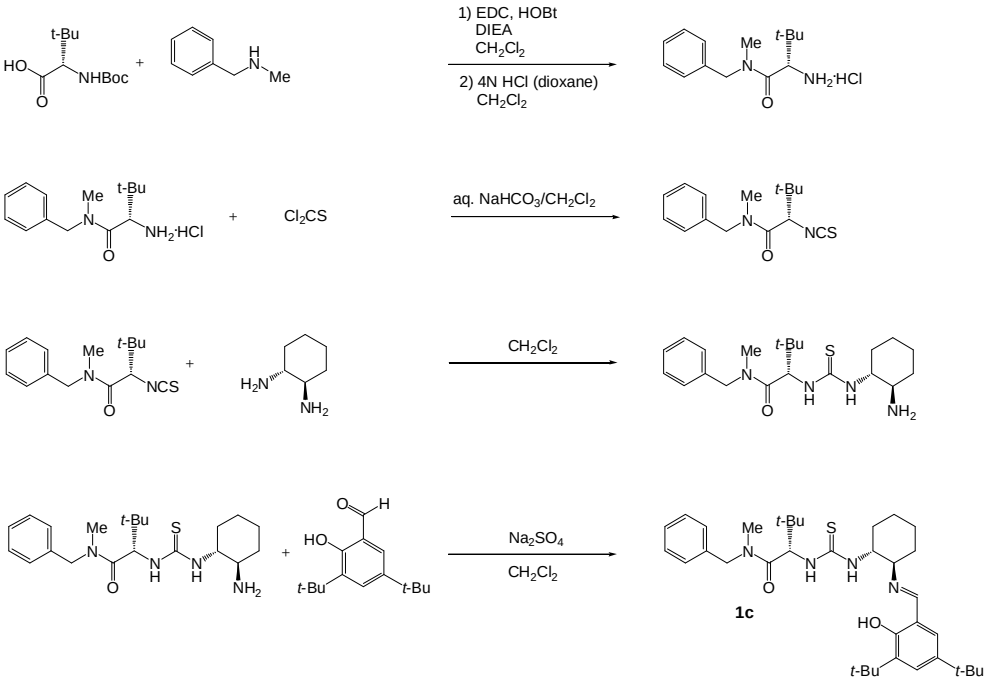
Achiral gas chromatography (GC) analyses were performed on Hewlett-Packard 5890 Series II instruments equipped with FID detectors, a Hewlett-Packard 7673 Automatic Liquid Sampler and an HP-5 capillary column (30 m x 0.32 mm i.d. x 0.25 m film) using hydrogen as a carrier gas.

Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak).

Abbreviations used: EtOAc – ethyl acetate, THF – tetrahydrofuran, EtOH – ethanol, MeOH – methanol, Et_2O – diethyl ether, IPA – isopropyl alcohol, TEA – triethylamine, MS – molecular seives, LAH – lithium aluminum hydride, DBU - 1,8-Diazabicyclo-[5.4.0]undec-7-ene, DABCO - 1,4-Diazabicyclo[2.2.2]octane, EDC - 1-(3-(dimethyl-amino)propyl)-3-ethyl-carbodiimide hydrochloride, HOBt - 1-Hydroxybenzotriazole, Boc – *t*-butyl carbamate, Moc – methyl carbamate, DMSO – dimethyl sulfoxide, Ts – *p*-toluene sulfonyl, Ns (nosyl) – *p*-nitrobenzene sulfonyl, TLC – thin layer chromatography, dr – diastereomeric ratio, ee – enantiomeric excess.

Representative Experimental Procedures:

Thiourea catalyst (1c).



A. **L-*tert*-leucine *N',N'*-benzylmethylamide hydrochloride**. An oven-dried, 250 mL round-bottomed flask is charged with a stir bar, EDC (3.64 g, 19.02 mmol), and HOBt (2.57 g, 19.02 mmol). Freshly distilled CH_2Cl_2 (100 mL) is added, and the solution stirred for two minutes. Next, diisopropylethylamine (4.52 mL, 25.94 mmol) then *N*-benzylmethylamine (2.45 mL, 19.02 mmol), are added *via* syringe in one portion, at room temperature. Boc-L-*tert*-Leucine (4.00 g, 17.29 mmol) is added in one portion, the flask is sealed with a rubber septum, and the reaction is stirred vigorously under N_2 for 16 h at room temperature. The reaction is diluted with Et_2O (200 mL), and washed

with 0.5N HCl (2x 200 mL). The acidic aqueous layer is extracted with 100 mL Et_2O, and the combined organics are washed with saturated aqueous $NaHCO_3$ (1x 150 mL) and brine (1x 150 mL). The organics are dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude Boc-amino amide as a white to light yellow oily semi-solid, which is sufficiently pure to use in the subsequent step.

In a 250 mL round-bottomed flask, the crude product is dissolved in anhydrous CH_2Cl_2 (45 mL) at room temperature. With vigorous stirring, 4N HCl in 1,4-dioxane (43.25 mL) is added over 5 minutes via syringe, and the reaction stirred for 1.5 h. The reaction is concentrated *in vacuo*, and subjected to high vacuum (=1 Torr) for 1 h to afford the crude salt as a white to light yellow semi-crystalline solid which is sufficiently pure to use in the subsequent step.

B. ***N,N*-benzylmethyl-(*2S*)-isothiocyanato-3,3-dimethylbutyramide**. In a 1 L round-bottomed flask equipped with a stir bar, the crude product from the previous step is dissolved in anhydrous CH_2Cl_2 (180 mL), and cooled to 0 ^oC with an external ice/brine bath. Saturated aqueous $NaHCO_3$ (180 mL) is added, and the biphasic mixture stirred vigorously (~500 rpm) for 10 minutes. The stirring is stopped, and thiophosgene (1.33 mL, 17.46 mmol) is added via syringe *to the organic layer*. Immediately, vigorous stirring is restored, the reaction is removed from the ice bath, and allowed to stir for 30 min at room temperature. The layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2x 100 mL). The combined organics are dried over Na_2SO_4, filtered, concentrated *in vacuo*, and subjected to high vacuum (=1 Torr) for 10 min, to afford the crude isothiocyanate as a light orange oil. The isothiocyanate is sufficiently pure to use in the next step.

C. ***N*-[(*1R,2R*)-2-amino-1-cyclohexylaminothiocarbonyl]-*L*-*tert*-leucine *N',N'*-benzylmethyl-amide**. In a flame-dried 250 mL round-bottomed flask, (*R,R*)-1,2-cyclohexanediamine (2.47 g, 21.61 mmol) is dissolved in anhydrous CH_2Cl_2 (75 mL). The crude isothiocyanate from the previous step, dissolved in anhydrous CH_2Cl_2 (5 mL), is added dropwise *via* syringe over 5 minutes. An additional 3x 2.5 mL portions of CH_2Cl_2 are used to effect quantitative transfer. The reaction is stirred at room temperature for 3 h, and then concentrated directly to a yellow to light orange, semi-crystalline solid. The solid is purified by flash chromatography to yield the pure thiourea as a semi-crystalline solid (5.00 g, 84% from Boc-L-*tert*-Leucine). FTIR (thin film) cm^{-1}: 2932 (m), 2858 (w), 1624 (s), 1537 (s); ^1H NMR (500 MHz, $CDCl_3$, 20 °C; compound exists as a ~5.5:1 mixture of rotamers: the major rotamer is denoted by *) δ 7.42-7.20 (10H, m, Ar**H**, Ar**H***), 5.75 (1H, d, *J* = 9.0 Hz, C**H**(*t*Bu)), 5.50 (1H, d, *J* = 7.5 Hz, C**H**(*t*Bu)*), 5.05 (1H, d, *J* = 15.5 Hz, PhC$\mathbf{H}_2$), 4.98 (1H, d, *J* = 14.5 Hz, PhC$\mathbf{H}_2$*), 4.64 (1H, d, *J* = 15.5 Hz, PhC$\mathbf{H}_2$), 4.28 (1H, d, *J* = 14.5 Hz, PhC$\mathbf{H}_2$*), 3.22 (3H, s, NC$\mathbf{H}_3$*), 2.87 (3H, s, NC$\mathbf{H}_3$), 2.57 (2H, m, C**H**(NH_2), C**H**(NH_2)*), 2.38 (4H, s, N$\mathbf{H}_2$, N$\mathbf{H}_2$*), 2.05 (2H, d, *J* = 12.0 Hz, C**H**N, C**H**N* thiourea), 1.88 (2H, d, *J* = 10.0 Hz, C$\mathbf{H}_2$($CHNH_2$), C$\mathbf{H}_2$($CHNH_2$)*), 1.71 (6H, m, C$\mathbf{H}_2$($CHNH_2$), C$\mathbf{H}_2$($CHNH_2$)*, C$\mathbf{H}_2$(CHN), C$\mathbf{H}_2$(CHN)*), 1.33-1.19 (8H, m, C$\mathbf{H}_2$, C$\mathbf{H}_2$* cycl) 1.09 (9H, s, C(C$\mathbf{H}_3$)$_3$)*, 1.07 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C; compound exists as a mixture of rotamers) δ 182.9, 171.6, 171.4, 137.5, 137.1, 128.9, 128.4, 128.2, 128.1, 127.9, 127.7, 127.5, 127.1, 125.3, 59.4, 58.7, 54.2, 53.2, 50.2, 36.1, 35.8, 35.5, 34.3, 33.0, 31.4, 26.6, 26.5, 24.4, 24.3; LRMS (ApCI): 391.1 (100%) $[M+H]^+$.

D. ***N*-[(*1R,2R*)-2-(2-hydroxy-3,5-di-*tert*-butylbenzylidine)amino-1-cyclohexyl-amino-thiocarbon-yl]-*L*-*tert*-leucine *N',N'*-benzylmethylamide** (**1c**). To a flame-dried, 50 mL round-bottomed flask equipped with a stir bar is added the free amine thiourea from the previous step (1.00 g, 2.56 mmol), 3,5-di-*tert*-butylsalicylaldehyde (588 mg, 2.51 mmol), and Na_2SO_4 (2.30 g), and the flask is sealed with a rubber septum. Next, the flask is evacuated, anhydrous CH_2Cl_2 (15 mL) is added in one portion *via* syringe with vigorous stirring, and the flask is re-filled with N_2. The solution turns bright yellow, and the reaction is stirred under N_2 for 1.5 h at room temperature. The entire reaction mixture is concentrated under reduced pressure, and the yellow residue is re-dissolved in anhydrous hexanes (45 mL). The mixture is filtered through an oven-dried sintered glass funnel into a flame-dried, pre-tared, 250-mL round-bottomed flask. The flask and filter pad are washed with additional anhydrous hexanes (3x 25 mL), and the filtrate is concentrated *in vacuo* and subjected to high vacuum (= 1 Torr) for 2 h to afford the pure catalyst as a yellow solid (1.51 g, >99%, 84% from Boc-L-*tert*-Leucine). The catalyst requires no additional purification. FTIR (thin film) cm^{-1}: 2957 (s), 2864 (w), 1630 (s), 1534 (s); ^{1}H NMR (600 MHz, $CDCl_3$, 20 °C; compound exists as a ~4:1 mixture of rotamers: the major rotamer is denoted by *) δ 13.25 (2H, s, ArO**H**, ArO**H***), 8.35 (1H, s, C**H**=N*), 8.33 (1H, s, C**H**=N), 7.35-7.18 (10H, m, Ar**H**, Ar**H***), 7.06 (1H, d, *J* = 2.2 Hz, Ar**H***), 7.05 (1H, d, *J* = 2.6 Hz, Ar**H**), 6.41 (2H, br, N**H**, N**H***), 6.08 (2H, br, N**H**, N**H***), 5.70 (1H, br, C**H**(*t*Bu)), 5.58 (1H, d, *J* = 9.2 Hz, C**H**(*t*Bu)*), 4.91 (1H, d, *J* = 15.4 Hz, PhC**H**$_2$), 4.86 (1H, d, *J* = 14.6 Hz, PhC**H**$_2$*), 4.46 (1H, d, *J* = 15.4 Hz, PhC**H**$_2$), 4.18 (1H, d, *J* = 14.3 Hz, PhC**H**$_2$*), 3.78 (2H, br, C**H**N, C**H**N*), 3.09 (3H, s, C**H**3*), 2.78 (3H, s, C**H**3), 2.14 (2H, m, C**H**N, C**H**N*), 1.9-1.58 (8H, m, C**H**$_2$, C**H**$_2$* cycl), 1.50-1.27 (8H, m, C**H**$_2$, C**H**$_2$* cycl), 1.39 (9H, s, C(C**H**$_3$)$_3$*), 1.38 (9H, s, C(C**H**$_3$)$_3$) 1.26 (9H, s, C(C**H**$_3$)$_3$*), 1.25 (9H, s, C(C**H**$_3$)$_3$), 0.89 (9H, s, C(C**H**$_3$)$_3$*), 0.85 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, DMSO-*d*$_6$, 20 °C; compound exists as a mixture of rotamers) δ 182.5, 171.4, 166.1, 157.5, 139.4, 137.4, 135.5, 128.3. 127.5, 127.0, 126.3, 126.1, 117.7, 69.6, 58.3, 56.3, 52.9, 50.0, 36.1, 35.7, 34.5, 33.8, 33.1, 31.3, 29.3, 26.5, 26.4, 23.5, 23.3; LRMS (ApCI): 607.2 (100%) $[M+H]^+$.

General procedure for the preparation of nitro-benzenesulfonyl imines:

A flame-dried 50 mL round-bottom flask was charged with activated 4Å MS (800 mg), amberlyst 15 (25 mg), *p*-nitrobenzenesulfonamide (1.01g, 5.00 mmol), and a stirbar. Freshly distilled toluene (20 mL) was added *via* syringe at room temperature, followed by aldehyde (5.50 mmol). A Dean-Stark trap equipped with reflux condenser was attached, all joints sealed with teflon tape, and the reaction heated to a vigorous reflux for 20 h. The reaction was allowed to cool to room temperature, and was then filtered through a pad of Celite. The pad was washed with 350 mL toluene, and the filtrate concentrated in vacuo to a solid. The solids were washed with 3 x 100 mL hexanes, and the solid collected on a scintered glass funnel. This material was sufficiently pure to use in the subsequent step, but could be further recrystallized in high yield from EtOAc/hexanes.

N-Benzylidene-4-nitro-benzenesulfonamide (6a). The product was isolated as a light tan powder (85%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1606 (s), 1569 (s), 1528 (s), 1450 (w), 1350 (m), 1333 (w), 1310 (m), 1224 (w), 1161 (s), 1088 (m), 856 (m), 796 (s), 739 (m); ^1H NMR (500 MHz, $CDCl_3$) d 9.13 (s, 1H), 8.39 (d, *J*=8.8 Hz, 2H), 8.21 (d, *J*=8.8 Hz, 2H), 7.96 (d, *J*=7.2 Hz, 2H), 7.67 (t, *J*=7.5 Hz, 1H), 7.53 (t, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 172.62, 150.84, 144.43, 136.06, 131.96, 129.97, 129.62, 129.41, 124.59; LRMS (ApCI): 291.0 (5%) $[M+H]^+$, 261.0 (100%) $[M\text{-}NO^+]^+$.

N-(3-Methyl-benzylidene)-4-nitro-benzenesulfonamide (6b). The product was isolated as an off-white powder (81%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1600 (s), 1575 (s), 1529 (s), 1477 (w), 1347 (m), 1336 (m), 1311 (m), 1301 (m), 1257 (w), 1157 (s), 1087 (m), 1010 (w), 745 (m), 682 (w); ^1H NMR (400 MHz, $CDCl_3$) d 9.09 (s, 1H), 8.38 (d, *J*=8.8 Hz, 2H), 8.21 (d, *J*=8.4 Hz, 2H), 7.78 (s, 1H), 7.73 (d, *J*=7.3 Hz, 1H), 7.48 (d, *J*=7.3 Hz, 1H), 7.41 (t, *J*=7.3 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 172.86, 150.79, 144.49, 139.65, 137.01, 132.14, 131.96, 129.70, 129.58, 129.49, 124.59, 21.40; LRMS (ApCI): 305.0 (2%) $[M+H]^+$, 275.0 (100%) $[M\text{-}NO^+]^+$.

N-(3-Methoxy-benzylidene)-4-nitro-benzenesulfonamide (6c). The product was isolated as an off-white powder (79%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1600 (m), 1573 (s), 1531 (s), 1463 (w), 1349 (m), 1334 (m), 1311 (m), 1270 (m), 1161 (s), 1088 (m), 1038 (m), 856 (w), 811 (m), 762 (m), 682 (w), 645 (m); ^1H NMR (400 MHz, $CDCl_3$) d 9.08 (s, 1H), 8.37 (d, *J*=8.8 Hz, 2H), 8.20 (d, *J*=8.8 Hz, 2H), 7.35-7.55 (m, 3H), 7.19 (d, *J*=8.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 172.66, 160.38, 150.83, 144.33, 133.41, 130.58, 129.62, 126.06, 124.61, 123.25, 113.84, 55.81; LRMS (ApCI): 321.0 (2%) $[M+H]^+$, 291.0 (100%) $[M\text{-}NO^+]^+$.

N-(4-Chloro-benzylidene)-4-nitro-benzenesulfonamide (6d). The product was isolated as a white powder (87%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1602 (m), 1590 (s), 1561 (m), 1529 (s), 1401 (w), 1349 (m), 1333 (m), 1307 (m), 1159 (s), 1085 (s), 823 (w), 795 (s), 740 (s), 690 (m), 615 (m), 558 (m); ^1H NMR (400 MHz, $CDCl_3$) d 9.09 (s, 1H), 8.39 (d, *J*=8.8 Hz, 2H), 8.20 (d, *J*=8.8 Hz, 2H), 7.89 (d, *J*=8.4 Hz, 2H), 7.50 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.12, 150.90, 144.16, 142.72, 132.98, 130.57, 130.11, 129.65, 124.64; LRMS (ApCI): 325.1 (1%) $[M+H]^+$, 295.0 (100%) $[M\text{-}NO^+]^+$.

N-(3-Chloro-benzylidene)-4-nitro-benzenesulfonamide (6e). The product was isolated as a white powder (82%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1608 (s), 1563 (s), 1531 (s), 1351 (s), 1335 (m), 1312 (m), 1217 (w), 1162 (s), 1088 (m), 800 (m), 743 (m), 640 (m); ^1H NMR (500 MHz, $CDCl_3$) d 9.08 (s, 1H), 8.39 (d, *J*=9.3 Hz, 2H), 8.21 (d, *J*=8.8 Hz, 2H), 7.95 (s, 1H), 7.81 (d, *J*=7.8 Hz, 1H), 7.62 (d, *J*=9.3 Hz, 1H), 7.46 (t, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.12, 150.97, 143.98, 135.93, 135.76, 133.77, 130.88, 130.78, 130.45, 129.73, 124.67; LRMS (ApCI): 325.1 (2%) $[M+H]^+$, 295.0 (100%) $[M\text{-}NO^+]^+$.

N-(3-Bromo-benzylidene)-4-nitro-benzenesulfonamide (6f). The product was isolated as a white powder (85%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1606 (m), 1558 (m), 1530 (s), 1349 (s), 1335 (m), 1311 (m), 1161 (s), 1089 (m), 855 (w), 804 (m), 741 (m), 679 (w),

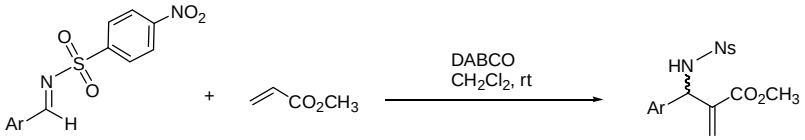
641 (w); ^{1}H NMR (400 MHz, $CDCl_3$) d 9.07 (s, 1H), 8.40 (d, *J*=8.8 Hz, 2H), 8.21 (d, *J*=8.4 Hz, 2H), 8.11 (s, 1H), 7.85 (d, *J*=7.7 Hz, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 7.42 (apparent t, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.00, 150.97, 143.95, 138.67, 133.95, 133.76, 131.08, 130.88, 129.74, 124.67, 123.79; LRMS (ApCI): 370.8 (3%) $[M+H]^+$, 338.8 (100%) $[M\text{-}NO^+]^+$.

N-Naphthalen-1-ylmethylene-4-nitro-benzenesulfonamide (6g). The product was isolated as an off-white powder (72%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1599 (m), 1585 (s), 1575 (m), 1528 (s), 1348 (m), 1333 (m), 1309 (m), 1161 (s), 1087 (m), 1013 (w), 826 (m), 763 (m), 613 (w); ^{1}H NMR (400 MHz, $CDCl_3$) d 9.27 (s, 1H), 8.36-8.46 (m, 3H), 8.24 (d, *J*=8.8 Hz, 2H), 8.02 (d, *J*=8.4 Hz, 1H), 7.97 (d, *J*=8.1 Hz, 1H), 7.91 (d, *J*=8.4 Hz, 1H), 7.89 (d, *J*=8.1 Hz, 1H), 7.69 (apparent t, *J*=7.5 Hz, 1H), 7.61 (apparent t, *J*=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 172.50, 150.82, 144.54, 137.49, 137.12, 132.82, 130.29, 129.94, 129.87, 129.72, 129.60, 128.40, 127.77, 124.61, 124.12; LRMS (ApCI): 340.9 (100%) $[M+H]^+$, 311.0 (87%) $[M\text{-}NO^+]^+$, 295.0 (25%) $[M\text{-}NO_2]^+$.

4-Nitro-N-thiophen-2-ylmethylene-benzenesulfonamide (6h). The product was isolated as a light tan powder (68%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1602 (m), 1563 (m), 1531 (s), 1341 (s), 1332 (m), 1160 (s), 1091 (m), 804 (m), 740 (m); ^{1}H NMR (500 MHz, $CDCl_3$) d 9.19 (s, 1H), 8.38 (d, *J*=8.8 Hz, 2H), 8.19 (d, *J*=9.3 Hz, 2H), 7.80-7.90 (m, 2H), 7.52 (t, *J*= 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.62, 150.77, 144.21, 137.72, 128.49, 128.33, 127.22, 126.12, 126.01; LRMS (ApCI): 296.3 (3%) $[M+H]^+$, 266.3 (100%) $[M\text{-}NO^+]^+$.

N-Furan-3-ylmethylene-4-nitro-benzenesulfonamide (6i). The product was isolated as a brown powder (48%, ~90% pure). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1605 (m), 1566 (m), 1536 (s), 1349 (s), 1332 (m), 1161 (s), 1087 (m), 804 (m), 742 (m), 679 (w); ^{1}H NMR (500 MHz, $CDCl_3$) d 9.08 (s, 1H), 8.38 (d, *J*=8.8 Hz, 2H), 8.17 (m, 3H), 7.54 (s, 1H), 6.84 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.14, 153.43, 150.98, 146.09, 144.46, 129.53, 124.58, 123.47, 108.13; LRMS (ApCI): 281.3 (3%) $[M+H]^+$, 251.3 (100%) $[M\text{-}NO^+]^+$.

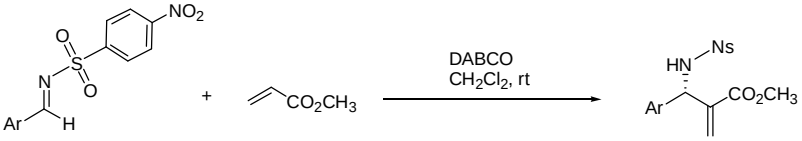
General procedure for the preparation of racemic aza-Baylis-Hillman adducts:



A flame dried 10 mL round-bottom flask was charged with N-Benzylidene-4-nitro-benzenesulfonamide (600 mg, 2.07 mmol) and DABCO (232 mg, 2.07 mmol). The flask was evacuated and purged with N_2. CH_2Cl_2 (5 mL) and methyl acrylate (745 μL, 8.27 mmol) were added via syringe at room temperature, and the reaction stirred for 24 hours. The reaction was then quenched with 625 μL 4 N HCl in dioxane. The reaction was diluted with 30 mL CH_2Cl_2, and washed 2 x 30 mL H_2O and 1 x 30 mL brine. The crude adduct was purified by flash chromatography (100% CH_2Cl_2) to afford the pure racemic aza-Baylis-Hillman adduct as a white solid (641 mg, 82.2%). This material was

determined to be racemic (ChiralPak AS, 1.0 mL/min, 254 nm, 40% IPA/hexanes, t_r(ent 1) = 11.760 min, t_r(ent 2) = 17.481 min). FTIR (CH_2Cl_2 thin film, cm^{-1}): 3293 (br), 3108 (w), 3068 (w), 1720 (s), 1632 (w), 1607 (w), 1531 (s), 1440 (m), 1350 (s), 1312 (m), 1166 (s), 1091 (m), 1062 (m), 855 (m), 738 (s); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.22 (d, *J*=8.8 Hz, 2H), 7.92 (d, *J*=8.8, 3 Hz, 2H), 7.14-7.27 (m, 5H), 6.23 (s, 1H), 6.15 (d, *J*=9.3 Hz, 1H), 5.82 (s, 1H), 5.40 (d, *J*=9.3 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.96, 150.08, 146.74, 138.49, 138.01, 128.94, 128.50, 128.41, 128.32, 126.64, 124.30, 59.86, 52.50; LRMS (ApCI): 377.0 (2%) $[M+H]^+$, 347.0 (30%) $[M\text{-}NO^+]^+$, 330.0 (32%) $[M\text{-}NO_2]^+$, 175.0 (100%) [M-sulfonamide]$^+$.

General procedure for the preparation of enantioenriched aza-Baylis-Hillman adducts:



An oven-dried 0.5-dram vial was charged with N-Benzylidene-4-nitro-benzenesulfonamide (29 mg, 0.100 mmol), catalyst (6 mg, 0.010 mmol), DABCO (11.2 mg, 0.100 mmol), and activated 3Å MS (40 mg). The vial was evacuated and purged with N_2. Pre-cooled, freshly distilled, anhydrous xylenes (700 μL) and methyl acrylate (75 μL, 0.800 mmol) were added via syringe at 4 ^{o}C, and the reaction stirred for specified period of time. The reaction was diluted with anhydrous MeOH (150 μL) then *immediately* quenched with 60 μL 4 N HCl in dioxane. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct.

2-[(4-Nitro-benzenesulfonylamino)-(*S*)-phenyl-methyl]-acrylic acid methyl ester (7a). The reaction was run for 36h. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct as a white solid (49%). This material was determined to be 95% ee (ChiralPak AS, 1.0 mL/min, 280 nm, 40% IPA/hexanes, t_r(major) = 11.566 min, t_r(minor) = 17.618 min). $[\alpha]^{23}_D$ = +27.7^o (c=2 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3293 (br), 3108 (w), 3068 (w), 1720 (s), 1632 (w), 1607 (w), 1531 (s), 1440 (m), 1350 (s), 1312 (m), 1166 (s), 1091 (m), 1062 (m), 855 (m), 738 (s); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.22 (d, *J*=8.8 Hz, 2H), 7.92 (d, *J*=8.8, 3 Hz, 2H), 7.14-7.27 (m, 5H), 6.23 (s, 1H), 6.15 (d, *J*=9.3 Hz, 1H), 5.82 (s, 1H), 5.40 (d, *J*=9.3 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.96, 150.08, 146.74, 138.49, 138.01, 128.94, 128.50, 128.41, 128.32, 126.64, 124.30, 59.86, 52.50; LRMS (ApCI): 377.0 (2%) $[M+H]^+$, 347.0 (30%) $[M\text{-}NO^+]^+$, 330.0 (32%) $[M\text{-}NO_2]^+$, 175.0 (100%) [M-sulfonamide]$^+$.

2-[(4-Nitro-benzenesulfonylamino)-(*S*)-*m*-tolyl-methyl]-acrylic acid methyl ester (7b). The reaction was run for 24h. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct as a white solid (40%). This material was determined to be 93% ee (ChiralPak AS, 1.0 mL/min, 280 nm, 40% IPA/hexanes, t_r(major) = 10.938 min, t_r(minor) = 16.007 min). $[\alpha]^{23}_D$ = +49.6^o (c=0.50 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3295 (m), 1720 (s), 1632 (w), 1608 (m), 1531 (s),

1440 (m), 1349 (s), 1312 (w), 1166 (s), 1093 (w), 1065 (w), 855 (w), 738 (m); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.24 (d, *J*=8.8 Hz, 2H), 7.92 (d, *J*=8.8 Hz, 2H), 7.04 (t, *J*=7.5 Hz, 1H), 6.95 (d, *J*=7.3 Hz, 1H), 6.84-6.87 (m, 2H), 6.16 (s, 1H), 5.97 (d, *J*=8.8 Hz, 1H), 5.75 (s, 1H), 5.28 (d, *J*=9.3 Hz, 1H), 3.58 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.81, 150.16, 146.11, 138.21, 138.01, 137.17, 129.47, 128.81, 128.44, 128.27, 127.93, 126.31, 124.11, 59.21, 52.31, 21.33; LRMS (ApCI): 391.0 (5%) $[M+H]^+$, 361.0 (50%) $[M-NO^+]^+$, 189.0 (100%), [M-sulfonamide]$^+$.

2-[(*S*)-(3-Methoxy-phenyl)-(4-nitro-benzenesulfonylamino)-methyl]-acrylic acid methyl ester (7c). The reaction was run for 24h. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct as an off-white solid (42%). This material was determined to be 96% ee (ChiralPak AS, 1.0 mL/min, 280 nm, 40% IPA/hexanes, t_r(major) = 14.252 min, t_r(minor) = 23.276 min). $[\alpha]^{26}_{D}$ = +47.1^o (c=2 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3289 (s), 3106 (w), 2955 (m), 2927 (m), 1720 (s), 1606 (m), 1531 (s), 1439 (m), 1350 (s), 1313 (m), 1268 (m), 1166 (s), 1092 (w), 1062 (w), 855 (w), 737 (m); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.24 (d, *J*=8.8 Hz, 2H), 7.93 (d, *J*=8.8 Hz, 2H), 7.12 (t, *J*=8.0 Hz, 1H), 6.71-6.79 (m, 2H), 6.65 (s, 1H), 6.25 (s, 1H), 6.06 (d, *J*=9.3 Hz, 1H), 5.82 (s, 1H), 5.35 (d, *J*=9.3 Hz, 1H), 3.69 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.96, 159.96, 150.05, 146.69, 139.57, 138.46, 130.02, 128.58, 128.40, 124.27, 118.92, 113.14, 112.92, 59.62, 55.40, 52.50; LRMS (ApCI): 405.9 (2%) $[M+H]^+$, 359.9 (20%) $[M-NO_2]^+$, 205.1 (100%), [M-sulfonamide]$^+$.

2-[(*S*)-(4-Chloro-phenyl)-(4-nitro-benzenesulfonylamino)-methyl]-acrylic acid methyl ester (7d). The reaction was run for 24h. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct as a white solid (36%). This material was determined to be 87% ee (ChiralPak AS, 1.0 mL/min, 270 nm, 40% IPA/hexanes, t_r(major) = 11.457 min, t_r(minor) = 17.787 min). $[\alpha]^{23}_{D}$ = +27.0^o (c=0.35 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3280 (m), 2955 (s), 2930 (s), 2859 (m), 2251 (w), 1722 (s), 1676 (s), 1633 (s), 1504 (m), 1472 (s), 1354 (m), 1252 (s), 1184 (m), 1098 (s), 982 (w), 837 (s), 777 (m), 710 (m); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.27 (d, *J*=8.8 Hz, 2H), 7.96 (d, *J*=9.3 Hz, 2H), 7.24 (d, *J*=8.6 Hz), 7.10 (d, *J*=8.6 Hz), 6.23 (s, 1H), 6.06 (d, *J*=9.3 Hz, 1H), 5.81 (s, 1H), 5.48 (d, *J*=9.3 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.88, 150.41, 146.65, 137.41, 137.21, 130.94, 128.66, 128.31, 128.01, 127.24, 124.62, 59.65, 52.51; LRMS (ApCI): 410.9 (32%) $[M+H]^+$, 381.0 (83%) $[M-NO^+]^+$, 364.0 (67%) $[M-NO_2]^+$, 209.0 (100%), [M-sulfonamide]$^+$.

2-[(*S*)-(3-Chloro-phenyl)-(4-nitro-benzenesulfonylamino)-methyl]-acrylic acid methyl ester (7e). The reaction was run for 16h. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct as a white solid (33%). This material was determined to be 94% ee (ChiralPak AS, 1.0 mL/min, 220 nm, 40% IPA/hexanes, t_r(major) = 11.018 min, t_r(minor) = 17.408 min). $[\alpha]^{23}_{D}$ = +39.5^o (c=0.35 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3282 (m), 1715 (s), 1531 (s), 1439 (m), 1350 (s), 1312 (m), 1197 (w), 1166 (s), 1093 (w), 1065 (w), 855 (w), 738 (m); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.26 (d, *J*=9.3 Hz, 2H), 7.93 (d, *J*=8.8 Hz, 2H), 7.05-7.14 (m, 2H), 7.17-7.21 (m, 2H), 6.25 (s, 1H), 6.17 (d, *J*=9.3 Hz, 1H), 5.82 (s, 1H), 5.36 (d, *J*=9.8 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.78, 150.20, 146.60, 140.05, 137.84, 134.92, 130.23, 129.07, 128.52, 126.83, 124.80, 124.67, 124.38, 59.54, 52.65; LRMS

(ApCI): 410.9 (32%) $[M+H]^+$, 381.0 (83%) $[M-NO^+]^+$, 364.0 (67%) $[M-NO_2]^+$, 209.0 (100%), [M-sulfonamide]$^+$.

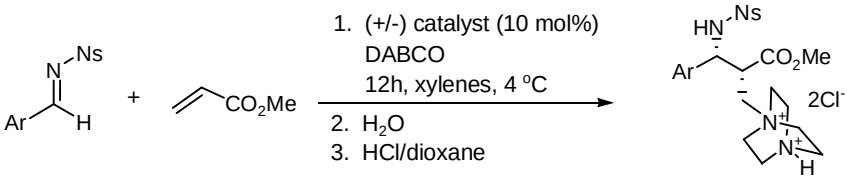
2-[(*S*)-(3-Bromo-phenyl)-(4-nitro-benzenesulfonylamino)-methyl]-acrylic acid methyl ester (7f). The reaction was run for 16h. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct as an off-white solid (39%). This material was determined to be 92% ee (ChiralPak AS, 1.0 mL/min, 280 nm, 40% IPA/hexanes, t_r(major) = 11.594 min, t_r(minor) = 20.227 min). $[\alpha]^{23}_D$ = +40.8^o (c=0.75 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3294 (m), 1719 (s), 1631 (w), 1531 (s), 1440 (m), 1350 (s), 1313 (w), 1166 (s), 1092 (w), 1066 (w), 855 (w), 738 (m); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.26 (d, *J*=9.0 Hz, 2H), 7.92 (d, *J*=8.5 Hz, 2H), 7.35 (m, 1H), 7.22 (s, 1H), 7.11-7.13 (m, 2H), 6.26 (s, 1H), 6.08 (d, *J*=9.0 Hz, 1H), 5.83 (s, 1H), 5.35 (d, *J*=9.5 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.74, 150.19, 146.52, 140.29, 137.90, 131.39, 130.49, 129.74, 129.06, 128.55, 125.38, 124.44, 123.01, 59.27, 52.70; LRMS (ApCI): 454.7, 456.7 (10%, 12%) $[M+H]^+$, 424.8, 426.8 (45%, 52%) $[M-NO^+]^+$, 407.9, 409.8 (49%, 56%) $[M-NO_2]^+$, 252.9, 254.9 (96%, 100%) [M-sulfonamide]$^+$.

2-[(*S*)-Naphthalen-1-yl-(4-nitro-benzenesulfonylamino)-methyl]-acrylic acid methyl ester (7g). The reaction was run for 24h. The crude adduct was purified by flash chromatography to afford the aza-Baylis-Hillman adduct as an off-white solid (27%). This material was determined to be 91% ee (ChiralPak AS, 1.0 mL/min, 280 nm, 40% IPA/hexanes, t_r(major) = 12.531 min, t_r(minor) = 29.498 min). $[\alpha]^{23}_D$ = +24.1^o (c=0.50 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3291 (br), 1720 (s), 607 (w), 1530 (s), 1441 (m), 1352 (s), 1310 (m), 1165 (s), 1090 (m), 1057 (m), 736 (s), 609 (w); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.07 (d, *J*=8.8 Hz, 2H), 7.90 (m, 1H), 7.80 (m, 3H), 7.72 (m, 1H), 7.46 (m, 2H), 7.29 (m, 2H), 6.37 (s, 1H), 6.30 (d, *J*=8.0 Hz, 1H), 5.84 (s, 1H), 5.66 (d, *J*=8.5 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.66, 151.47 142.94, 140.74, 136.82, 134.61, 131.41, 128.55, 128.49, 128.04, 126.26, 126.17, 125.73, 125.14, 124.88, 123.50, 123.01, 53.26, 51.38; LRMS (ApCI): 427.1 (2%) $[M+H]^+$, 397.1 (51%) $[M-NO^+]^+$, 381.1 (40%) $[M-NO_2]^+$, 225.0 (44%) [M-sulfonamide]$^+$.

2-[(4-Nitro-benzenesulfonylamino)-(*S*)-thiophen-2-yl-methyl]-acrylic acid methyl ester (7h). The reaction was run for 36h. The crude adduct was purified by flash chromatography to afford the pure aza-Baylis-Hillman adduct as a white solid (30%). This material was determined to be 99% ee (ChiralPak AS, 1.0 mL/min, 280 nm, 10% EtOH/hexanes, t_r(major) = 28.247 min, t_r(minor) = 36.662 min). $[\alpha]^{23}_D$ = +26.0^o (c=0.8 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3295 (br), 3108 (w), 2956 (w), 2920 (w), 1714 (s), 1632 (m), 1531 (s), 1440 (m), 1350 (s), 1313 (m), 1167 (s), 1092 (w), 1064 (w), 855 (m), 738 (s); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.27 (d, *J*=8.5 Hz, 2H), 7.97 (d, *J*=9 Hz, 2H), 7.16 (d, *J*=5.0 Hz, 1H), 6.84 (t, *J*=3.5 Hz, 1H), 6.76 (d, *J*=3.5 Hz, 1H), 6.27 (d, *J*=10.0 Hz, 1H), 6.25 (s, 1H), 5.87 (s, 1H), 5.57 (d, *J*=9.5 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.88, 150.65, 146.66, 142.31, 137.99, 128.68, 128.62, 127.36, 126.14, 125.65, 124.36, 56.63, 52.64; LRMS (ApCI): 381.1 (4%) $[M+H]^+$, 353.0 (10%) $[M-NO^+]^+$, 335.9 (5%) $[M-NO_2]^+$, 181.0 (100%), [M-sulfonamide]$^+$.

2-[(*S*)-Furan-3-yl-(4-nitro-benzenesulfonylamino)-methyl]-acrylic acid methyl ester (7i). The reaction was run for 36h. The crude adduct was purified by flash chromatography afford the pure aza-Baylis-Hillman adduct as an off-white solid (25%). This material was determined to be 98% ee (ChiralPak AS, 1.0 mL/min, 280 nm, 40% IPA/hexanes, t_r(major) = 14.313 min, t_r(minor) = 20.353 min). $[\alpha]^{23}_D$ = +27.3^o (c=0.5 EtOH); FTIR (CH_2Cl_2 thin film, cm^{-1}): 3292 (m), 2956 (m), 2930 (w), 1718 (s), 1631 (w), 1607 (w), 1531 (s), 1439 (m), 1350 (s), 1312 (m), 1165 (s), 1092 (m), 1062 (m), 855 (w), 738 (m), 610 (w); ^{1}H NMR (500 MHz, $CDCl_3$) d 8.29 (d, *J*=8.8 Hz, 2H), 7.97 (d, *J*=8.8 Hz, 2H), 7.28 (m, 1H), 7.19 (s, 1H), 6.15 (m, 2H), 6.06 (d, *J*=9.8 Hz, 1H), 5.78 (s, 1H), 5.29 (d, *J*=9.8 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.96, 150.17, 146.84, 143.99, 140.00, 137.86, 128.61, 128.21, 124.50, 124.35, 109.21, 53.44, 52.55; LRMS (ApCI): 367.1 (2%) $[M+H]^+$, 337.1 (32%) $[M\text{-}NO^+]^+$, 320.0 (32%) $[M\text{-}NO_2]^+$, 165.1 (80%), [M-sulfonamide]$^+$.

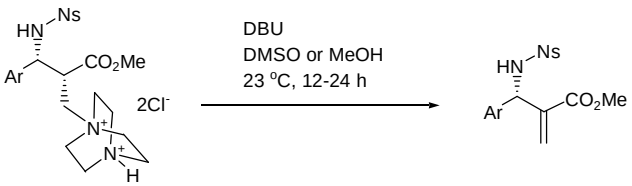
Isolation of aza-Baylis-Hillman intermediate as the dihydrochloride salt (10a):



5

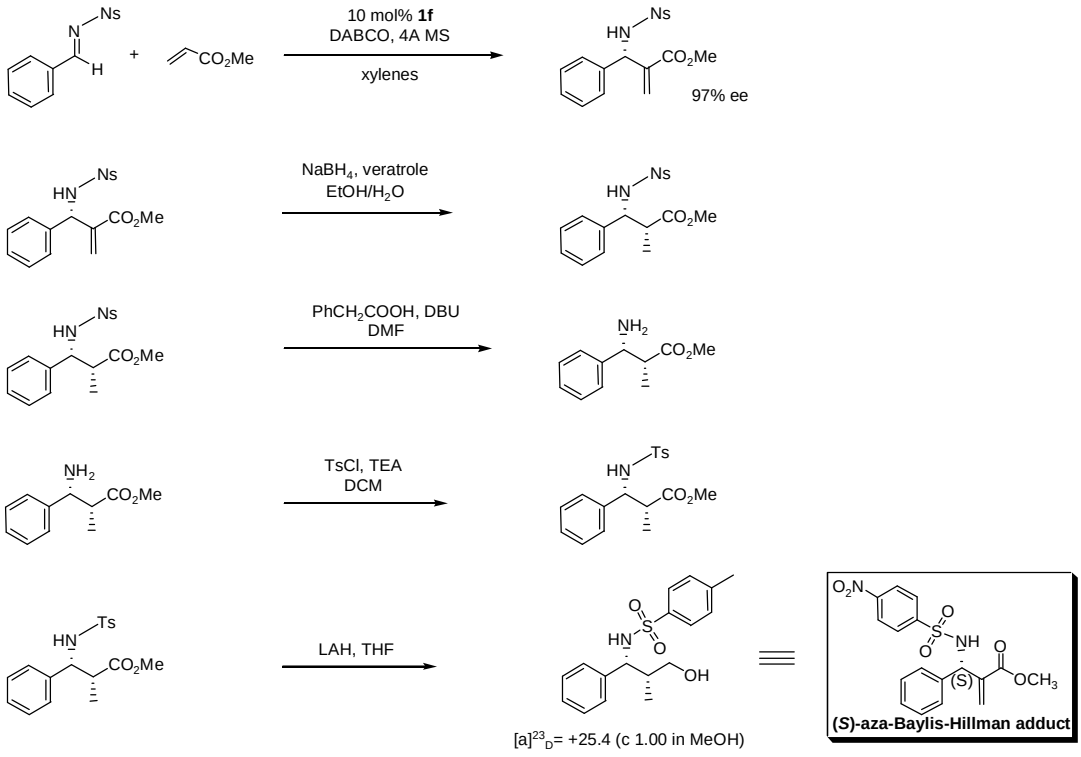
A flame dried 10 mL round-bottom flask was charged with a stir bar, imine (**6a**) (75 mg, 0.259 mmol), thiourea catalyst (**1c**, 15.6 mg, 0.026 mmol), and DABCO (29 mg, 0.259 mmol). The flask was cooled to 4 ^{o}C, and charged with pre-cooled, freshly distilled xylenes (1.75 mL) and methyl acrylate (187 μL, 2.07 mmol). The reaction was allowed to stir for 12 h at 4 ^{o}C, over which time a bright yellow precipitate formed. Distilled H_2O (1.75 mL) was added, and the biphasic mixture was stirred vigorously for an additional 3-6 hours at 4 ^{o}C. HCl (200 μL, 4 N in dioxane) was added. An additional 5 mL H_2O was added, and the reaction was stirred vigorously for 5 mins. The layers were allowed to separate, and the organic layer removed. The aqueous layer was washed 3x 20 mL CH_2Cl_2 and the combined organic layers were back-extracted with 3x 5 mL H_2O and the combined *aqueous* layers were concentrated directly *in vacuo* at 60 ^{o}C. The resulting clear oil was further pumped on high vacuum for 24 h to removed residual H_2O, affording the dihydrochloride salt of the aza-Baylis-Hillman intermediate (**10a**) as a glassy solid (61.2 mg, 42%). FTIR (CH_2Cl_2 thin film, cm^{-1}): 1734 (s), 1630 (w), 1530 (s), 1459 (w), 1438 (w), 1351 (s), 1313 (w), 1166 (s), 1089 (w), 853 (w), 739 (m); ^{1}H NMR (500 MHz, d_6-DMSO, 10-16 : 1 mixture of diastereomers, with signal corresponding to major indicated) d 9.72 (d, *J*=10.3 Hz 1H), 8.07 (d, *J*=8.3 Hz, 2H), 7.79 (d, *J*=8.3 Hz, 2H), 7.18 (d, *J*= 4.9 Hz, 2H), 6.95-7.10 (m, 3H), 4.93 (dd, *J*=10.5, 6.0 Hz, 1H), 4.16 (d, *J*=13.2 Hz, 1H), 3.72-3.91 (m, 7H), 3.70 (s, 3H), 3.42-3.63 (m, 6H), 2.90 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) d 170.97, 149.69, 146.80, 136.04, 128.93, 128.80, 128.62, 127.95, 124.56, 61.69, 59.24, 53.62, 51.10, 46.24, 43.45; LRMS (ESI): 489.2 (100%) $[M\text{-}2HCl]^+$.

Base-mediated elimination of 10:



A flame-dried 5 mL round-bottom flask was charged with dihydrochloride salt (**10a** from above, 150 mg, 0.267 mmol) and dissolved in anhydrous DMSO (2 mL) or MeOH (2 mL) at room temperature. Freshly distilled DBU (84 μL, 0.560 mmol) was added *via* syringe, and the reaction stirred for 16 h. The reaction was then diluted with 5 mL CH_2Cl_2, 1 N HCl (5 mL) was added with vigorous stirring, the layers were allowed to separate, and the organic layer removed. The aqueous layer was extracted with 3x 10 mL CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude aza-Baylis-Hillman adduct (7**a**), which matched the ^1H NMR and ^{13}C NMR spectra as previously reported (*vide supra*). As discussed, ee's of this product were substantially eroded (ranging between 12-67% ee based on reaction time, reaction temperature, and choice of base).

Determination of absolute configuration (not discussed in Communication):



$[a]^{23}_D$= +25.4 (c 1.00 in MeOH)

2-Methyl-3-(4-nitro-benzenesulfonylamino)-3-phenyl-propionic acid methyl ester. A flame-dried 10mL round-bottom flask was charged with a stir bar, aza-Baylis-Hillman adduct **7a** (131 mg, 0.350 mmol), and sodium borohydride (133 mg, 3.50 mmol). Anhydrous absolute ethanol (16 mL) was added followed by veratrole (134 uL, 1.05 mmol). The reaction was allowed to stir at ambient temperature for 16 h. The solvent was removed under reduced pressure, and the residual yellow oil partitioned between water (25 mL) and CH_2Cl_2 (25 mL). The organic layer was extracted, and the aqueous layer extracted an additional 2x with 25 mL CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography (100% CH_2Cl_2) to

afford the desired product (109 mg, 81%), from which a total of 66 mg was the diastereomerically pure *cis*-product.

3-Amino-2-methyl-3-phenyl-propionic acid methyl ester. A flame-dried 5mL round-bottom flask was charged with the pure cis propionic acid methyl ester (66 mg, 0.175 mmol) and anhydrous DMF (1 mL). Mercapto acetic acid (24.2 uL, 0.348 mmol) was added via syringe, followed by DBU (267 uL, 1.75 mmol). The reaction was stirred under N_2 for 24 h. The reaction was diluter with EtOAc (20 mL) and washed 3x 25 mL $NaHCO_3$. The combined aqueous extracts were washed with 2x 15mL EtOAc, and the organic extracts dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude product (38 mg crude). The crude product was sufficiently pure by ^{1}HNMR to be carried on to the next step without further purification.

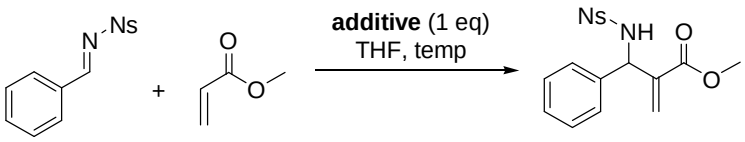
2-Methyl-3-phenyl-3-(toluene-4-sulfonylamino)-propionic acid methyl ester. A flame-dried 5 mL round-bottom flask was charged with the crude cis deprotected propionic acid methyl ester (38 mg) and anhydrous CH_2Cl_2 (0.5 mL). Freshly distilled triethylamine (31 uL, 0.215 mmol) was added via syringe in one portion under N_2, followed by addition of *p*-toluensulfonyl chloride (41 mg, 0.215 mmol) in one portion as a solid. The mixture was stirred at room temperature of 6h, at which point TLC analysis showed complete consumption of starting material. The reaction was diluted with 10mL CH_2Cl_2, and washed 2x $NaHCO_3$ (sat'd), and 1x with H_2O. The crude product was purified by flash chromatography (5:1 to 2:1 hexanes/EtOAc) to afford the desired tosylated product (28 mg, 46% over 2 steps). All spectral data matched literature values.[16]

N-(3-Hydroxy-2-methyl-1-phenyl-propyl)-4-methyl-benzenesulfonamide. LAH (8.1mg, 0.231 mmol) was suspended in anhydrous THF (0.5 mL) at 0 ^oC. A solution of pure tosylated propionic acid methyl ester dissolved in anhydrous THF (0.25 mL) was added dropwise to the LAH suspension under N_2. The reaction was slowly warmed to room temperature, and allowed to stir for 2.5h. The reaction was quenched with 3 drops of H_2O, diluted with 10 mL CH_2Cl_2, and filtered through a short pad of Celite. The Celite pad was washed exhaustively with excess CH_2Cl_2 and MeOH, and the collected solvent removed *in vacuo*. The crude product was purified by preparative thin layer chromatography (1:1 hexanes/EtOAc) to afford the desired product (23.7 mg, 91%). All spectral data matched literature values,[17] confirming the absolute configuration of the adducts to be (*S*). $[\alpha]^{26}_D = +25.4^o$ (c=1 MeOH) (lit: $[\alpha]^{26}_D = +26.1^o$ (c=1 MeOH)).[18]

[16] T. Muraoka, S. Kamiya, I. Matsuda, K. Itoh, *Chem. Commun.* **2002**, *12*, 1284 - 1285.
[17] K. Burgess, M.J. Ohlmeyer, *J. Org. Chem.* **1991**, *56*, 1027-1036.
[18] F.A. Davis, G.V. Reddy, C.-H. Liang, *Tetrahedron Lett.* **1997**, *38*, 5139-5142.

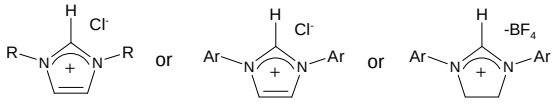
Screen of Nucleophilic Additives:

Initial screen for reactivity:



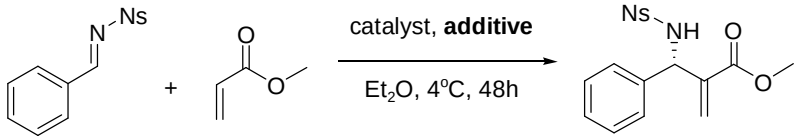
additive	conversion	comments
PPh_3	**12%**	**3d at RT**
PPh_2Me	**85%**	**24h at 4°C**
PMe_3		decomposition
$O=PPh_3$	NR	
DABCO	**65%**	**24h at 4°C**
quinuclidine	**60%**	**24h at 4°C**
3-HQD	**40%**	**3d at 4°C**
3-NH_2-quinuclidine	**20%**	**3d at 4°C**
quinine	<2%	3d at RT
quinidine	<2%	3d at RT
DBU	25% 70%	24h at 4°C 48h at RT (much decomp)
DMAP	NR	
pyridine	NR	
N,N'-dimethyl piperazine	<2%	
vaious NHCs		messy, complete decomp.

N-heterocyclic carbenes screened (reaction tested with both direct free carbene addition, as well as in situ generated carbene):



R= *t*Bu, Ar= Mes, 2,4-diisopropylphenyl

Nucleophilic additive screen for enantioselectivity and reactivity:



additive	equivalents	ee
Ph_2PMe	0.2	60%
Ph_2PMe	0.5	52%
Ph_2PMe	1	40%
DABCO	0.1	ND
DABCO	**0.2**	**76.2%**
DABCO	**0.5**	**86.8%**
DABCO	**1**	**93%** (92.6%, 93.5%)
DABCO	4	NR
Quinuclidine	1	95.2%
3-HQD	1	61%
DBU	1	NR
Quinine	1	NR

Synthetic transformations:

2-[(4-Nitro-benzenesulfonylamino)-phenyl-methyl]-acrylic acid (8a). A 5 mL round-bottom flask was charged with a stirbar, **7a** (30 mg, 0.08 mmol) and 20% aqueous HCl (600 μL). The flask was equipped with a reflux condenser, and the reaction brought to reflux for 2 h. The reaction was cooled to room temperature, and then extracted with 3x 10 mL EtOAc. The combined organics were dried over Na_2SO_4, and then concentrated *in vacuo*. The resulting crude product was purified by flash chromatography to afford the desired nosyl amino acid as an off-white solid (27.5 mg, 92%). ^{1}H NMR (500 MHz, CD_3OD) d 8.24 (d, *J*=8.8 Hz, 2H), 7.93 (d, *J*=8.8 Hz, 2H), 7.05-7.25 (m, 5H), 6.26 (s, 1H), 5.78 (s, 1H), 5.48 (s, 1H).

2-{[Benzyl-(4-nitro-benzenesulfonyl)-amino]-phenyl-methyl}-acrylic acid methyl ester (8b). A flame dried 10 mL round-bottom flask was charged with **7a** (25 mg, 0.067 mmol), a stirbar, and anhydrous DMF (500 μL). Cs_2CO_3 (33.2 mg, 0.102 mmol) was added in one portion, followed by addition of 4-bromobenzyl bromide (16.6 mg, 0.067

mmol). The resulting mixture was stirred at room temperature for 16 h, and then diluted with 1:1 Et_2O/EtOAc (20 mL). The organics were washed with 3x 25 mL brine, dried over Na_2SO_4, filtered, and dried *in vacuo*. Purification by flash chromatography (1:5 EtOAc/hexanes) afforded the pure product as a white solid (29.7 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) d 8.17 (d, *J*=8.8 Hz, 2H), 7.68 (d, *J*=8.8 Hz, 2H), 7.15-7.25 (m, 5H), 7.03 (d, *J*=7.3 Hz, 2H), 6.81 (d, *J*=8.3 Hz, 2H) 6.43 (s, 1H), 6.18 (s, 1H), 5.70 (s, 1H), 4.50 (m, 2H), 3.59 (s, 3H).

2-Methyl-3-(4-nitro-benzenesulfonylamino)-3-phenyl-propionic acid methyl ester (8c). A flame-dried 5 mL round-bottom flask was charged with **7a** (30 mg, 0.08 mmol) and a stirbar. In a glovebox was added the Pfaltz catalyst (CAS#: 583844-38-6, 3.46 mg, 2 μmol, 2.5 mol%). The flask was evacuated, filled with CH_2Cl_2, and then back-filled five times with H_2. The reaction was stirred under an H_2 atmosphere (balloon) for 12 h. The crude reaction mixture was filtered through a short pad of silica, eluting with EtOAc, and concentrated *in vacuo* to afford the desired product in >95% purity (29 mg, 97%). The product was formed in an 8.5:1 mixture of diastereomers, with chemical shifts for the major diastereomer reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.04 (d, *J*=8.8 Hz, 2H), 7.70 (d, *J*=8.8 Hz, 2H), 6.90-7.15 (m, 5H), 6.19 (d, *J*=8.8 Hz, 1H), 4.64 (dd, J=9.3, 6.4 Hz, 1H), 3.55 (s, 3H), 2.97(dq, *J*=6.9, 6.9, 1H), 1.15 (d, *J*=7.3 Hz, 3H).

2-Hydroxy-2-hydroxymethyl-3-(4-nitro-benzenesulfonylamino)-3-phenyl-propionic acid methyl ester (8d). A flame-dried 5 mL round-bottom flask was charged with a stirbar, NMO (7 mg, 0.059 mmol), H_2O (0.20 mL) and acetone (0.10 mL). The flask was cooled to 0 ^{o}C, and OsO_4 (2.5% by wt in *t*-BuOH, 30 μL, 2.7 μmol, 5 mol%) was added *via* syringe. Next, **7a** (20 mg, 0.053 mmol) was added as a solution in acetone (0.10 mL). The reaction was warmed to room temperature, and stirred for 16 h. Na_2SO_3 (25 mg) was added, the reaction stirred for an additional 1 h, and then diluted with CH_2Cl_2 (10 mL). The organics were washed with 1x 10 mL H_2O, and 1x 10 mL brine. The combined aqueous washes were then further extracted with 1x 10 mL EtOAc, and the combined organics dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% MeOH in CH_2Cl_2) afforded the pure diol (14.2 mg, 66%) as a 4:1 mixture of diastereomers. The chemical shifts for the major diastereomer are reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.95 (d, *J*=8.8 Hz, 2H), 7.62 (d, *J*=8.8 Hz, 2H), 6.90-7.15 (m, 5H), 6.19 (d, *J*=9.8 Hz, 1H), 4.82 (d, J=9.3 Hz, 1H), 3.96 (s, 3H), 3.70 (d, *J*=11.2 Hz, 1H), 3.18 (d, *J*= 11.7 Hz, 3H).

2-[(4-Nitro-benzenesulfonylamino)-(3-vinyl-phenyl)-methyl]-acrylic acid methyl ester (8e). A flame-dried 0.5-dram round-bottom flask was charged with $Pd(OAc)_2$ (< 1 mg, 3.2 μmol, 5 mol%) and S-Phos (3 mg, 7 μmol). Anhydrous DMF (100 μL) was added, and the mixture stirred at room temperature for 30 min, until the reaction was homogenous. A flame-dried 5 mL round-bottom flask was charged with **7f** (25 mg, 0.055 mmol), vinyl tributyltin (23.3 μL, 0.08 mmol), and anhydrous DMF (0.25 mL). The flask was purged, and back-filled with N_2 twice. To this stirring mixture was added the catalyst/ligand solution from above via syringe. A condenser was attached, and the reaction heated to 90 ^{o}C for 24 h. The reaction was then cooled to room temperature, and diluted with 10 mL Et_2O/EtOAc (1:1), the organics were washed with 1x 10 mL H_2O and

1x 10 mL brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (1:4 EtOAc/hexanes) to afford the desired product (13.2 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) d 8.21 (d, *J*=8.8 Hz, 2H), 7.90 (d, *J*=8.8 Hz, 2H), 7.05-7.25 (m, 4H), 6.55 (m, 1H), 6.25 (s, 1H), 6.08 (d, *J*=9.2 Hz, 1H), 5.84 (s, 1H), 5.62 (d, *J*=17.6 Hz, 1H), 5.15-5.45 (m, 2H), 3.65 (s, 3H).

5-[(4-Nitro-benzenesulfonylamino)-methyl]-3-phenyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (8f). A flame-dried 5 mL round-bottom flask was charged with chlorobenzaldoxime[19] (10.5 mg, 0.067 mmol) and anhydrous CH_2Cl_2 (0.5 mL) and cooled to –78 ^{o}C *via* a dry ice/acetone bath. Et_3N (10 μL, 0.067 mmol) was added *via* syringe, and the reaction stirred for 10 mins at this temperature. Next, **7a** (30 mg, 0.08 mmol) dissolved in CH_2Cl_2 (150 μL) was added dropwise *via* syringe, and the reaction was warmed slowly to –30 ^{o}C for 1 h, and then further warmed to 4 ^{o}C, and stirred for 12 h. The reaction was further allowed to warm to room temperature, and poured onto saturated aqueous NH_4Cl (15 mL), and extracted with 3x CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by preparative thin layer chromatography (3% MeOH in CH_2Cl_2) to afford the desired product as an off-white solid (28.5 mg, 86%). The product was obtained as a 1.7:1 mixture of diastereomers, with chemical shifts for the major diastereomer reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.97 (d, *J*=8.8 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 7.20-7.40 (m, 5H), 6.95-7.15 (m, 5H), 6.37 (d, *J*=10.3 Hz, 1H), 5.01 (d, J=10.3 Hz, 1H), 3.79 (s, 3H), 3.55 (m, 2H).

2-[(4-Nitro-benzenesulfonylamino)-phenyl-methyl]-oxirane-2-carboxylic acid methyl ester (8g). A flame-dried 5 mL round-bottom flask was charged with **7a** (25 mg, 0.067 mmol) and anhydrous THF (0.4 mL) at room temperature. Benzyltrimethylammonium hydroxide (Triton B, 42 mg, 0.10 mmol) was added, followed by dropwise addition of *t*-BuOOH (23 mL, 0.133 mmol). The reaction was allowed to stir at room temperature for 16 h. The reaction was then diluted with CH_2Cl_2, and the organic layer washed with 2x 10 mL saturated aqueous $NaHCO_3$ and 1x 10 mL H_2O. The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by preparative thin layer chromatography (1:1 EtOAc/hexanes) to afford the desired product as a white solid. The product was obtained as an 8:1 mixture of diastereomers, with the chemical shifts for the major diastereomer reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.12 (d, *J*=8.8 Hz, 2H), 7.81 (d, *J*=8.8 Hz, 2H), 7.05-7.23 (m, 5H), 6.13 (d, *J*=9.8 Hz, 1H), 4.86 (d, *J*=9.8 Hz, 1H), 3.71 (s, 3H), 3.06 (d, *J*=5.9 Hz, 1H), 2.77 (d, *J*=5.4 Hz, 1H).

4-Methyl-4-nitro-2-[(4-nitro-benzenesulfonylamino)-phenyl-methyl]-pentanoic acid methyl ester (8h). A flame-dried 5 mL round-bottom flask was charged with 2-nitropropane (9 μL, 0.096 mmol) and anhydrous THF (0.1 mL). At room temperature, DBU (24.2 μL, 0.176 mmol) was added, and the reaction stirred for 5 mins. Finally, **7a** (30 mg, 0.08 mmol) dissolved in THF (100 mL) was added dropwise *via* syringe, and the reaction stirred at room temperature for 4 h. The reaction was then poured onto a 1:1:1 mixture of brine, H_2O, and 1 N HCl, extracted with 3x 10 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer

[19] S. Kanemasa, S. Kobayashi, *J. Chem. Soc. Jpn.* **1993**, *66*, 2685-2693.

chromatography (1:2 EtOAc/hexanes) afforded the pure product as a white solid (19 mg, 51%). The primary byproduct was elimination of sulfonamide. The product was formed as a 1:1 mixture of diastereomers, with the chemical shifts of both diastereomers reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.06 (d, *J*=8.8 Hz, 2H), 8.01 (d, *J*=8.8 Hz, 2H), 7.73 (d, *J*=8.8 Hz, 2H), 7.68 (d, *J*=8.8 Hz, 2H), 6.85-7.12 (m, 10 H), 6.32 (d, *J*=10.0 Hz, 1H), 5.82 (d, *J*= 9.0 Hz, 1H), 4.66 (dd, *J*=9.5, 6.0 Hz, 1H), 4.48 (dd, *J*=9.5, 9.5 Hz, 1H), 3.51 (s, 3H), 3.30 (s, 3H), 2.75 (m, 1H), 2.60-2.73 (m, 2H), 2.54 (m, 1H), 2.43 (m, 1H), 2.24 (m, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H).

2,4-Bis-methoxycarbonyl-5-(4-nitro-benzenesulfonylamino)-5-phenyl-pentanoic acid methyl ester (8i). A flame-dried 5 mL round-bottom flask was charged with pentane-2,4-dione (10 μL, 0.096 mmol) in anhydrous THF (100 μL). At room temperature, DBU (24.2 μL, 0.176 mmol) was added, and the reaction stirred for five minutes. Finally, **7a** (30 mg, 0.08 mmol) dissolved in THF (100 mL) was added dropwise *via* syringe, and the reaction stirred at room temperature for 6 h. The reaction was then poured onto a 1:1:1 mixture of brine, H_2O, and 1 N HCl, extracted with 3x 10 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (3% MeOH in CH_2Cl_2) afforded the pure product as an off-white solid (27.5 mg, 72%). The product was formed as a 5:1 mixture of diastereomers, with the chemical shifts of the major diastereomer reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.03 (d, *J*=8.8 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 6.85-7.15 (m, 5H), 6.21 (d, *J*=9.3 Hz, 1H), 4.62 (dd, *J*=8.8, 8.8 Hz, 1H), 3.69 (dd, *J*=10.3, 3.9 Hz, 1H), 3.42 (s, 3H), 2.70 (ddd, *J*=10.5, 9.0, 3.0, 1H), 2.46 (ddd, *J*=14.0, 10.5, 3.5 Hz, 1H), 2.21 (s, 3H), 2.15 (s, 3H), 2.05 (m, 1H).

4-Acetyl-2-[(4-nitro-benzenesulfonylamino)-phenyl-methyl]-5-oxo-hexanoic acid methyl ester (8j). A flame-dried 5 mL round-bottom flask was charged with dimethyl malonate (11 μL, 0.096 mmol) in anhydrous THF (100 μL). At room temperature, DBU (24.2 μL, 0.176 mmol) was added, and the reaction stirred for 5 minutes. Next, **7a** (30 mg, 0.08 mmol) dissolved in THF (100 mL) was added dropwise *via* syringe, and the reaction stirred at room temperature for 3 h. The reaction was then poured onto a 1:1:1 mixture of brine, H_2O, and 1 N HCl, extracted with 3x 10 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (1:2 EtOAc/hexanes) afforded the pure product as an off-white solid (38.5 mg, 95%). The product was formed as a 5:1 mixture of diastereomers, with the chemical shifts of the major diastereomer reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.04 (d, *J*=8.8 Hz, 2H), 7.70 (d, *J*=8.8 Hz, 2H), 6.90-7.15 (m, 5H), 6.27 (d, *J*=8.5 Hz, 1H), 4.65 (dd, *J*=8.0, 8.0 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.44 (s, 3H), 3.40-3.48 (m, 1H), 2.86 (m, 1H), 2.35 (m, 1H), 2.17 (m, 1H).

3-Cyano-2-[(4-nitro-benzenesulfonylamino)-phenyl-methyl]-propionic acid methyl ester (8k). A flame-dried 5 mL round-bottom flask was charged with **7a** (30 mg, 0.08 mmol) and dissolved in absolute EtOH (0.25 mL). KCN dissolved in H_2O (100 μL) was added *via* syringe and the reaction stirred at room temperature for 24 h. The reaction was then diluted with CH_2Cl_2 (20 mL), and poured onto saturated aqueous $NaHCO_3$. The layers were separated, the aqueous layer extracted with 3x 15 mL CH_2Cl_2, and the

combined organics dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (1:1 EtOAc/hexanes) afforded the pure product as an off-white solid (27.6 mg, 86%). The product was formed as a 1.8:1 mixture of diastereomers, with the chemical shifts of the major diastereomer reported. ^{1}H NMR (500 MHz, $CDCl_3$) d 8.05 (d, *J*=8.8 Hz, 2H), 7.74 (d, *J*=8.8 Hz, 2H), 7.85-6.92 (m, 5H), 6.44 (d, *J*=9.8 Hz, 1H), 4.76 (m, 1H), 3.59 (s, 3H), 3.24 (m, 1H), 2.60-2.80 (m, 2H).

Representative Data for GC Kinetics:

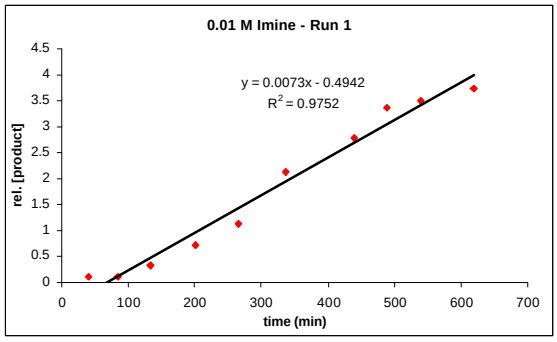
General procedure for all GC kinetics experiments:

An oven-dried 0.5-dram vial was charged with an oven-dried stirbar, DABCO, biphenyl (internal standard), and imine. $CHCl_3$ (1 mL) was added, and the reaction was stirred until homogenous (usually < 1 min). A t=0 time point was taken by removing 25 μL of the reaction mixture, diluting it to 100 μL, and directly subjecting it to GC analysis. The reaction was initiated by addition of freshly distilled methyl acrylate *via* syringe, and subsequent GC monitoring was carried out under identical sampling methods. Conversion is reported in terms of relative product appearance as determined by GC.

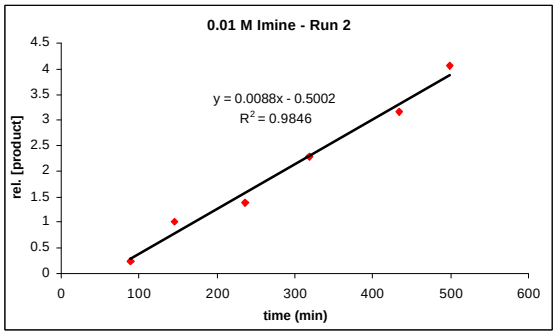
Determination of order in Imine.

[Imine] = 0.010 M
Average relative rate = 0.0081

Run 1

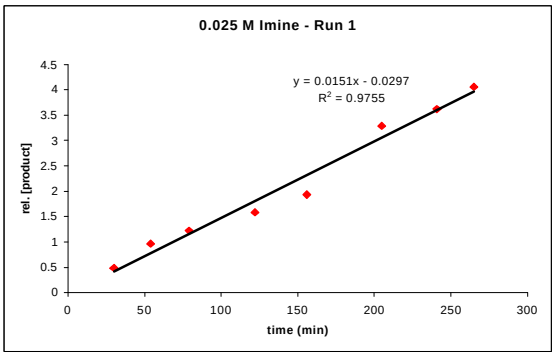


Run 2

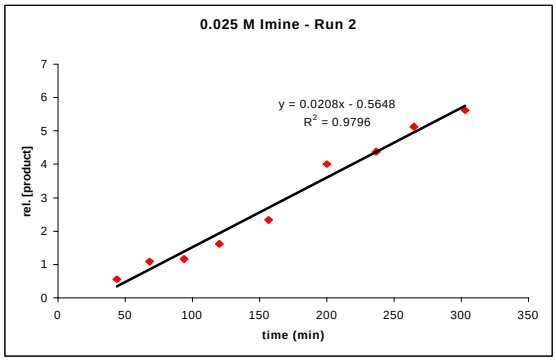


[Imine] = 0.025 M
Average relative rate = 0.0186

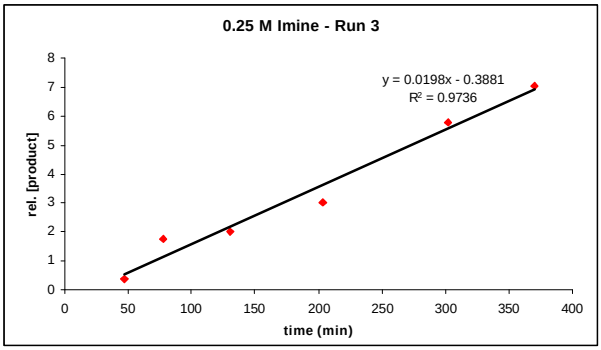
Run 1



Run 2

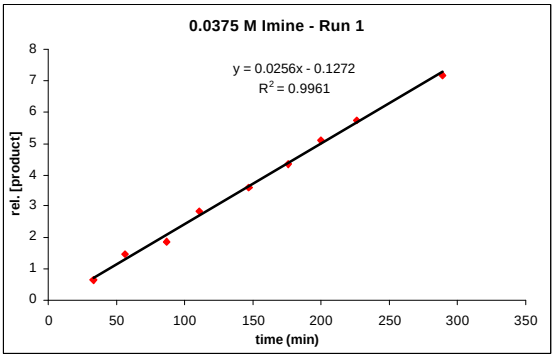


Run 3

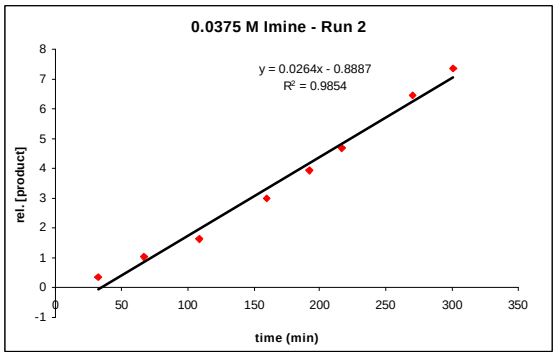


[Imine] = 0.0375 M
Average relative rate = 0.0260

Run 1

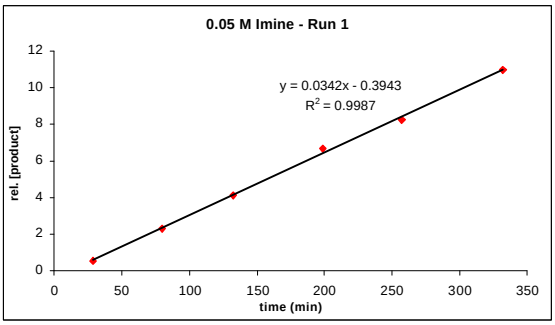


Run 2

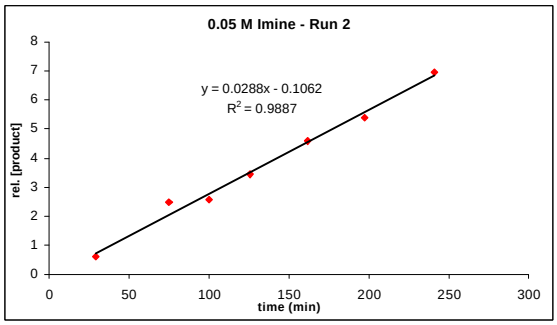


[Imine] = 0.05 M
Average relative rate = 0.0320

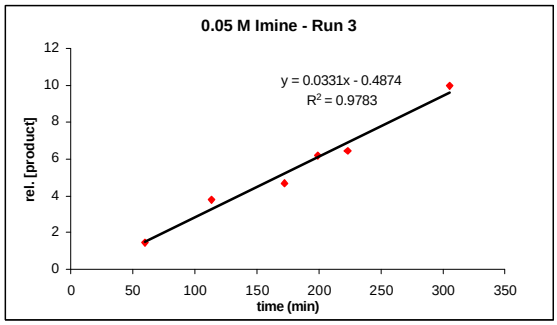
Run 1



Run 2

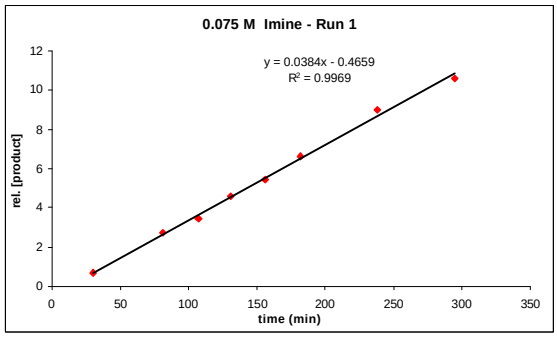


Run 3

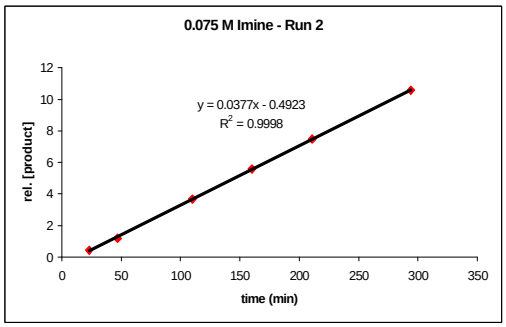


[Imine] = 0.075 M
Average relative rate = 0.0385

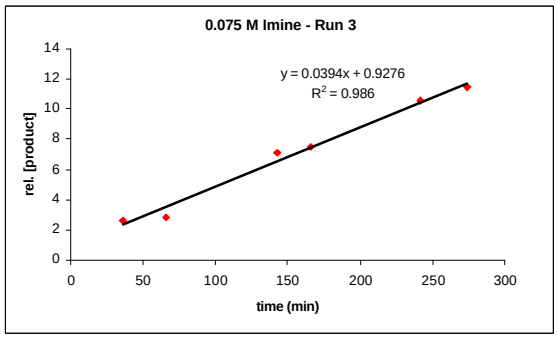
Run 1



Run 2

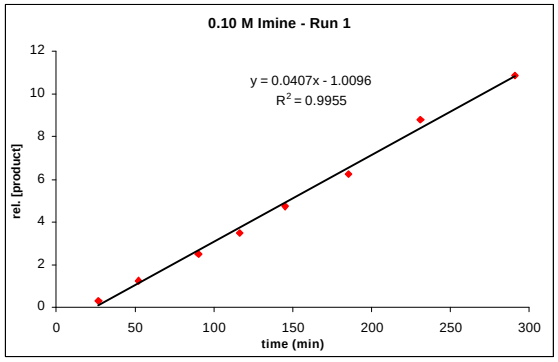


Run 3

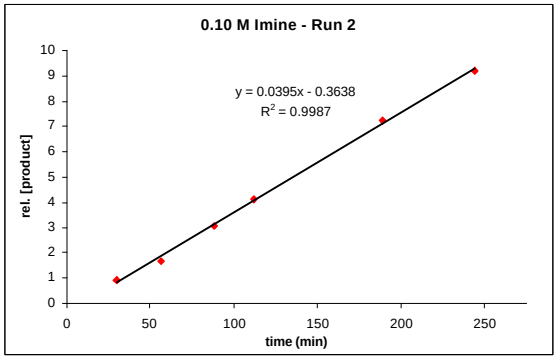


[Imine] = 0.10 M
Average relative rate = 0.0406

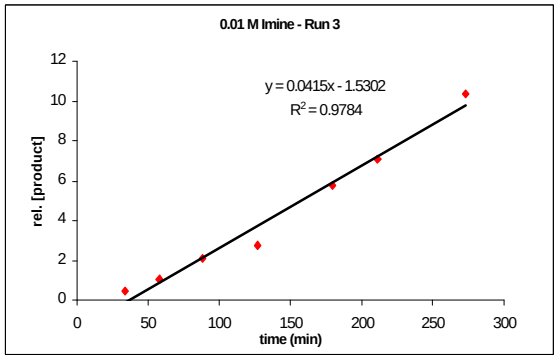
Run 1



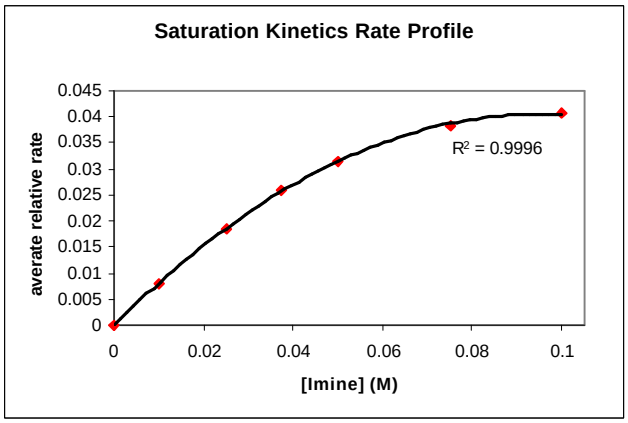
Run 2



Run 3



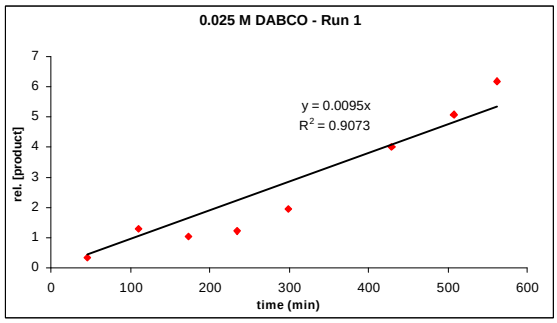
Imine Rate Profile: Saturation Kinetics



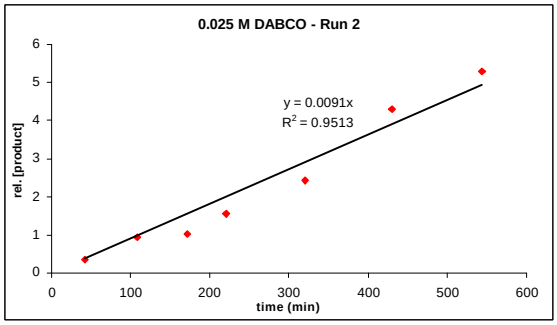
Determination of order in DABCO.

[DABCO] = 0.025 M
Average relative rate = 0.0093

Run 1

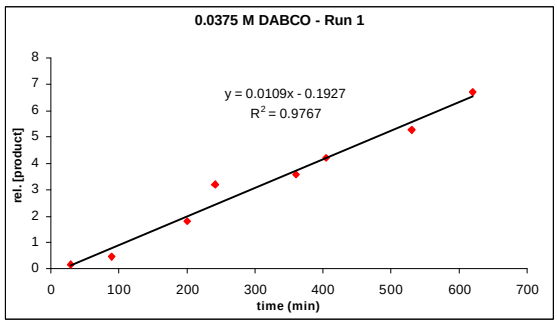


Run 2

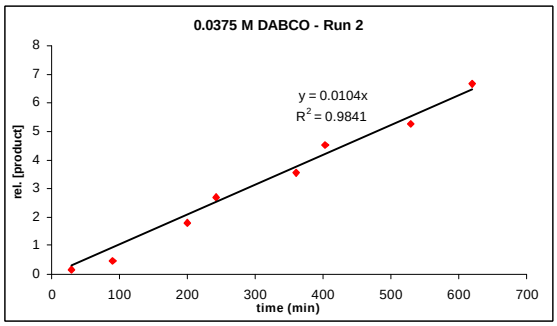


[DABCO] = 0.0375 M
Average relative rate = 0.0107

Run 1

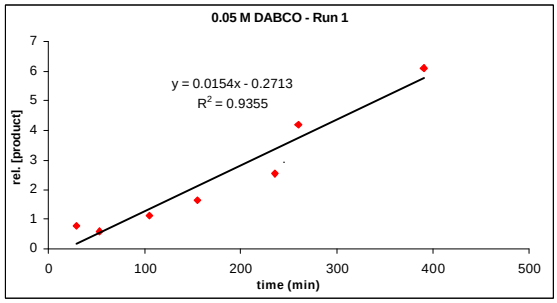


Run 2

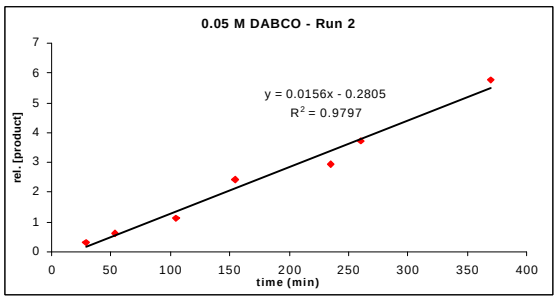


[DABCO] = 0.050 M
Average relative rate = 0.0155

Run 1

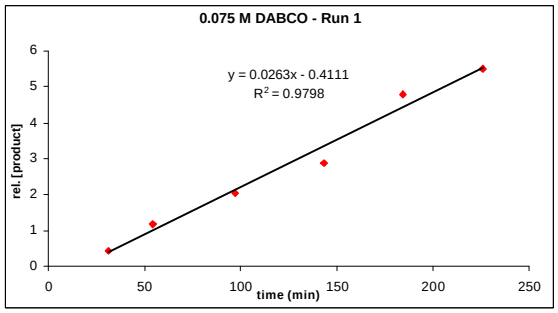


Run 2

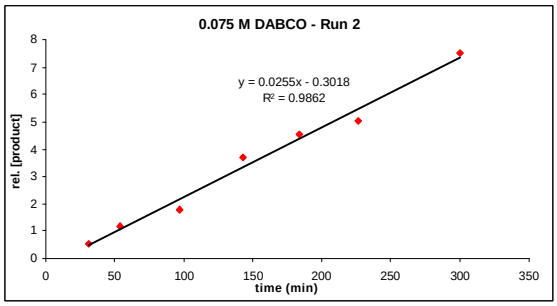


[DABCO] = 0.075 M
Average relative rate = 0.0259

Run 1

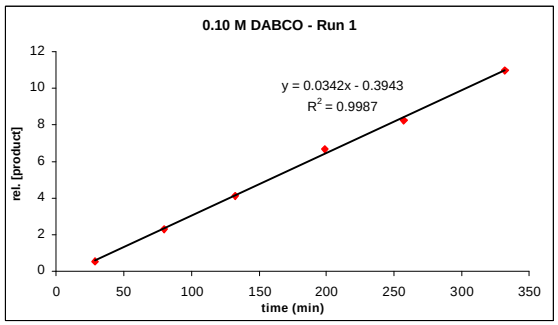


Run 2

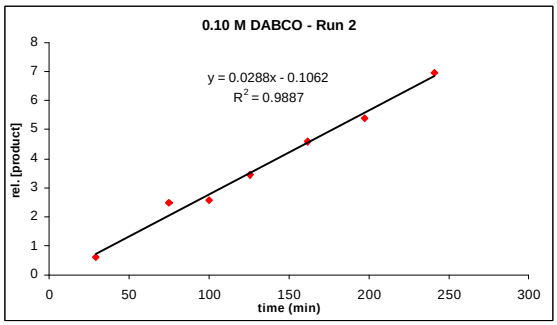


[DABCO] = 0.10 M
Average relative rate = 0.0315

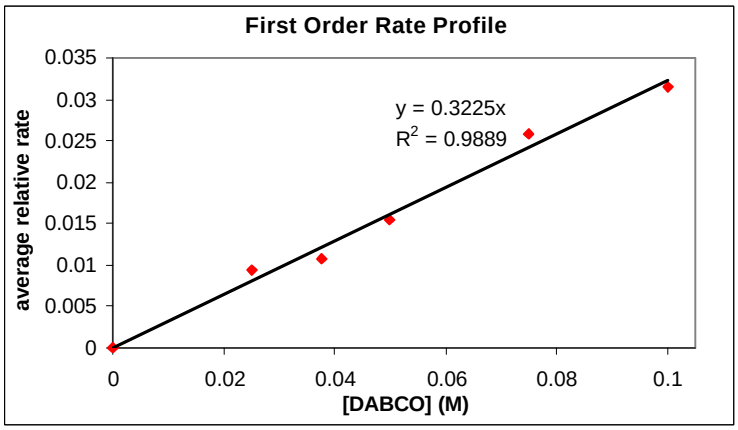
Run 1



Run 2



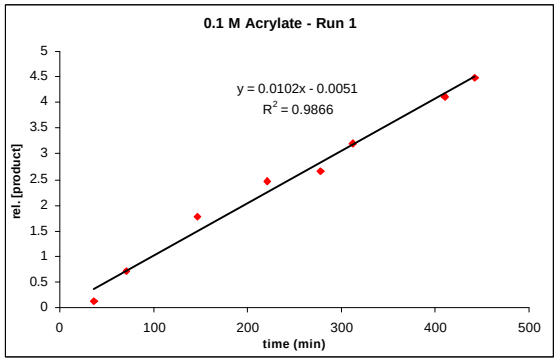
DABCO Rate Profile: First Order



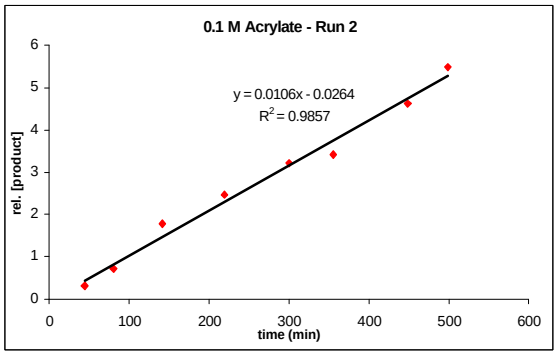
Determination of order in Acrylate.

[Acrylate] = 0.10 M
Average relative rate = 0.0104

Run 1

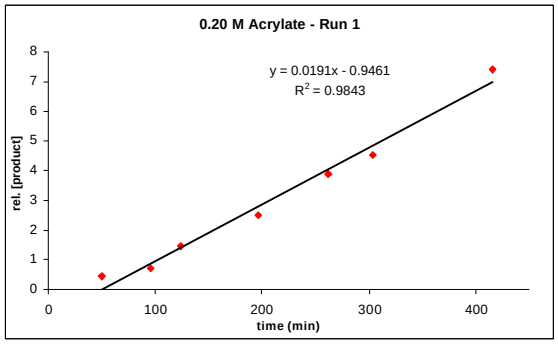


Run 2

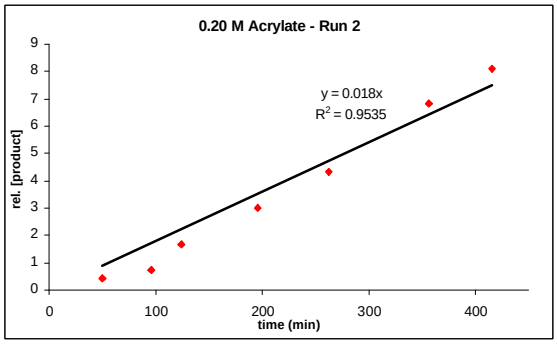


[Acrylate] = 0.20 M
Average relative rate = 0.0186

Run 1

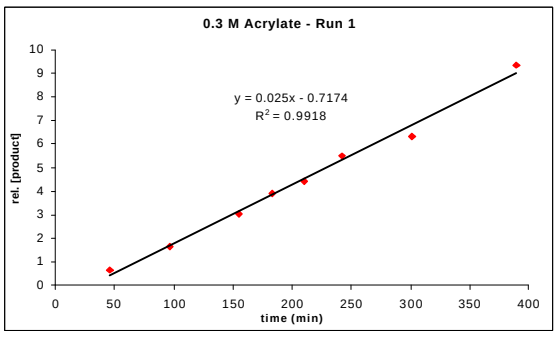


Run 2

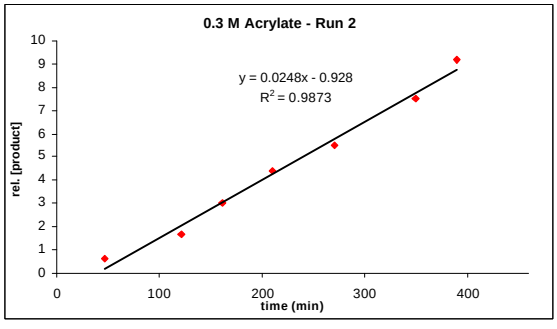


[Acrylate] = 0.30 M
Average relative rate = 0.0249

Run 1

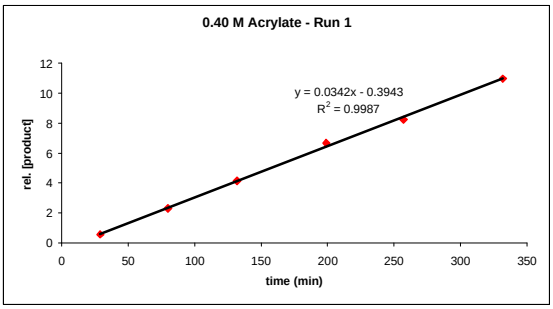


Run 2

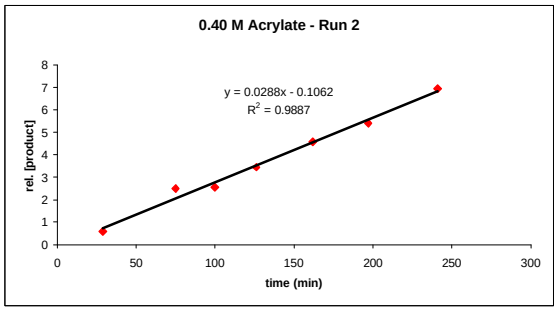


[Acrylate] = 0.40 M
Average relative rate = 0.0315

Run 1

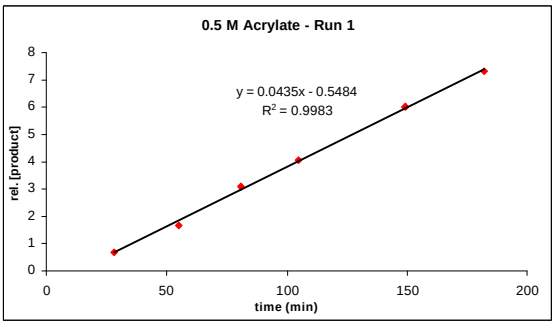


Run 2

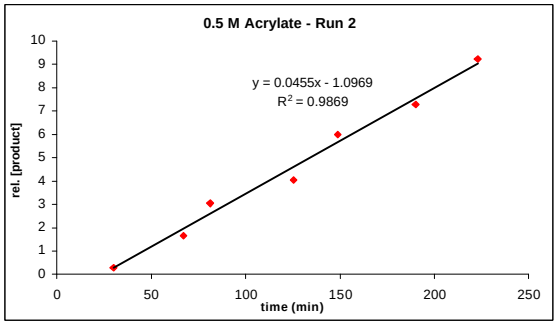


[Acrylate] = 0.50 M
Average relative rate = 0.0445

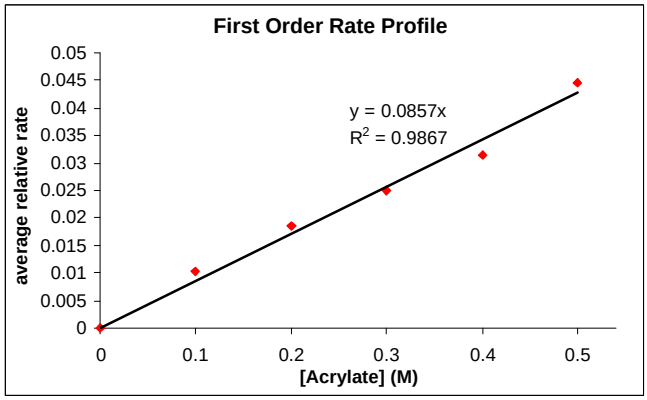
Run 1



Run 2



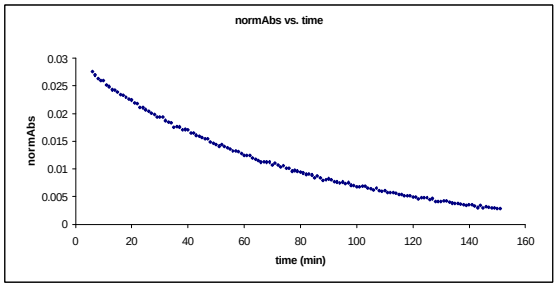
Acrylate Rate Profile: First Order



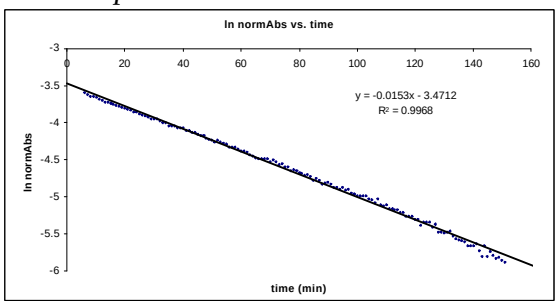
ReactIR Kinetics data:

Standard Order Plots:

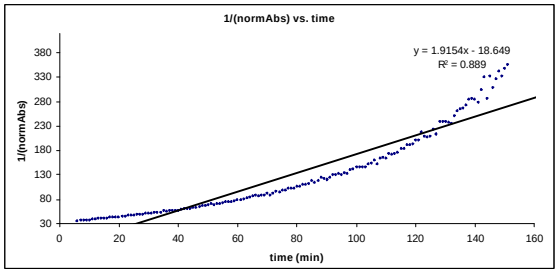
0th order plot



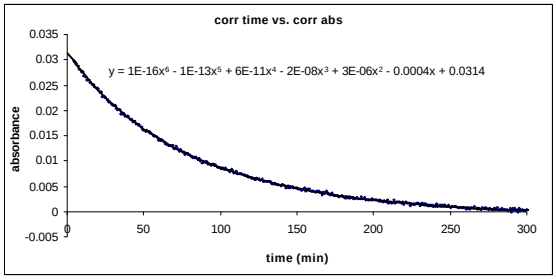
1st order plot



2nd order plot

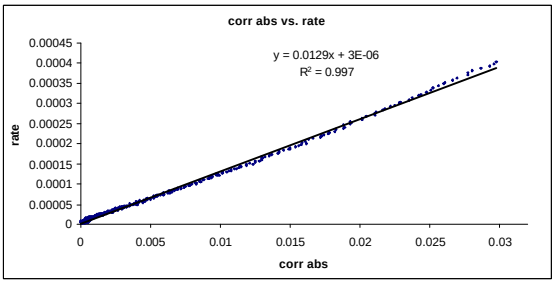


Modeled Rate Plots:

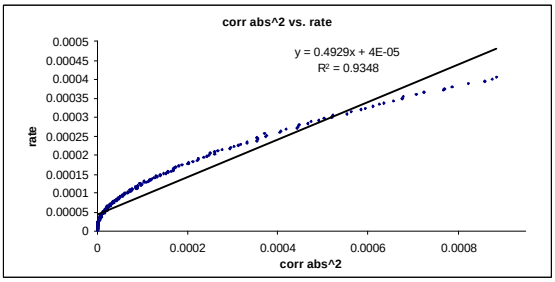


poynomial coefficients:	1.16983E-16
	-1.30985E-13
	6.28658E-11
	-1.7495E-08
	3.26827E-06
	-0.000430389
	0.031445952
6th order polynomial: y = 1E-16x6 - 1E-13x5 + 6E-11x4 - 2E-08x3 + 3E-06x2 - 0.0004x + 0.0314	

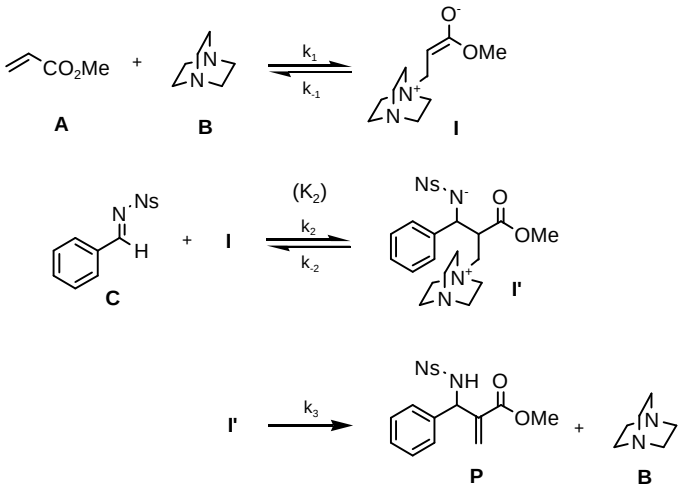
rate = k[I'']



rate = k[I'']^2



Derivation of rate law:



Rate Law 1: assuming no retro reaction (no contribution from k_{-2})

rate = d**P**/dt = k_3[**I'**]

$$K_2 = \frac{[\mathbf{I'}]}{[\mathbf{I}][\mathbf{C}]}$$ (equilibrium approximation)

d[**I**]/dt = 0 (steady-state approximation)

$0 = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{C}]$

$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}] + k_2[\mathbf{I}][\mathbf{C}]$

$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_{-1} + k_2[\mathbf{C}]}$$

$$K_2 = \frac{[\mathbf{I'}]}{\left(\frac{k_1[\mathbf{A}][\mathbf{B}][\mathbf{C}]}{k_{-1} + k_2[\mathbf{C}]}\right)} \Longrightarrow [\mathbf{I'}] = K_2\left(\frac{k_1[\mathbf{A}][\mathbf{B}][\mathbf{C}]}{k_{-1} + k_2[\mathbf{C}]}\right)$$

$$\Longrightarrow \text{rate} = \frac{k_3K_2k_1[\mathbf{A}][\mathbf{B}][\mathbf{C}]}{k_{-1} + k_2[\mathbf{C}]}$$

Rate Law 2: assuming there is a retro reaction

rate = d**P**/dt = k_3[**I'**]

$$K_2 = \frac{[\mathbf{I'}]}{[\mathbf{I}][\mathbf{C}]}$$ (equilibrium approximation)

d[**I**]/dt = 0 (steady-state approximation)

$$0 = k_1[\mathbf{A}][\mathbf{B}] + k_{-2}[\mathbf{I'}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{C}]$$
$$0 = k_1[\mathbf{A}][\mathbf{B}] + k_{-2}K_2[\mathbf{I}][\mathbf{C}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{C}]$$
$$0 = k_1[\mathbf{A}][\mathbf{B}] - [\mathbf{I}]\,(-k_{-2}K_2[\mathbf{C}] + k_{-1} + k_2[\mathbf{C}])$$
$$[\mathbf{I}]\,(-k_{-2}K_2[\mathbf{C}] + k_{-1} + k_2[\mathbf{C}]) = k_1[\mathbf{A}][\mathbf{B}]$$
$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_{-1} + (k_2 - k_{-2}K_2)[\mathbf{C}]}$$

$$K_2 = \frac{[\mathbf{I'}]}{\left(\frac{k_1[\mathbf{A}][\mathbf{B}][\mathbf{C}]}{k_{-1} + (k_2 - k_{-2}K_2)[\mathbf{C}]} \right)} \Longrightarrow [\mathbf{I'}] = K_2 \left(\frac{k_1[\mathbf{A}][\mathbf{B}][\mathbf{C}]}{k_{-1} + (k_2 - k_{-2}K_2)[\mathbf{C}]} \right)$$

$$\Longrightarrow \text{rate} = \frac{k_3K_2k_1[\mathbf{A}][\mathbf{B}][\mathbf{C}]}{k_{-1} + (k_2 - k_{-2}K_2)[\mathbf{C}]}$$

Both derivations give a rate law in the form:

$$\text{rate} = \frac{a[\mathbf{A}][\mathbf{B}][\mathbf{C}]}{1 + b[\mathbf{C}]}$$

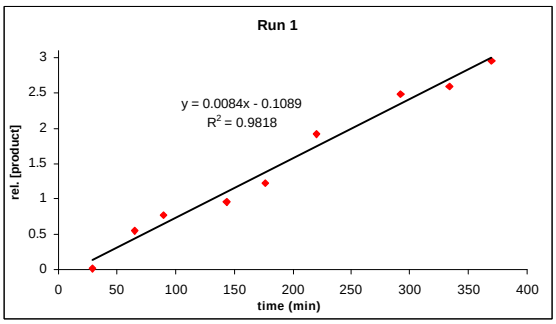
(implies saturation kinetics in imine)

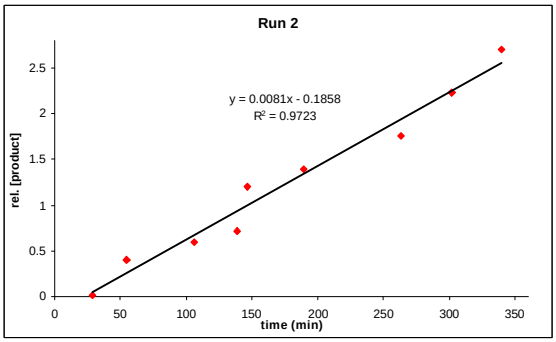
KIE experiments:

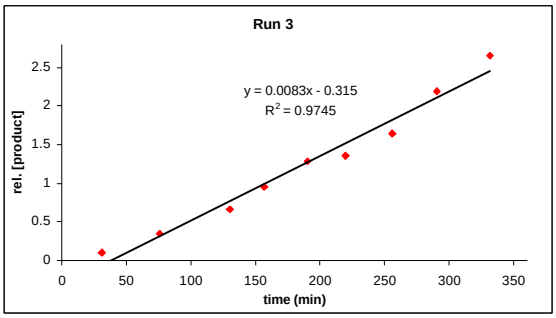
Preparation of a**-deuterio-methyl acrylate.** This material was prepared in an analogous manner to that described by McQuade *et. al.*[13a] but an increase in the deuterium incorporation could be realized by a double cycling of the reaction.

a**-deuterio-methyl acrylate.** A flame-dried 250 mL round-bottom flask was charged with a stirbar and DABCO (31.1 g, 277.6 mmol). CH_3OD (45 mL) was added, followed by addition of freshly distilled methyl acrylate (25 mL, 277.6 mmol) *via* syringe. The reaction was stirred vigorously for 48 hours, and then diluted with *o*-dichlorobenzene (120 mL). The combined organics were washed with 4x 200 mL H_2O and 1x 200 mL brine, and the rigorously dried over Na_2SO_4 and $MgSO_4$. The product was purified by fractional distillation to afford α-deuterio-methyl acrylate (79% d-incorporation, 20-35% yield). This material was then re-subjected to the above reaction conditions. A flame-dried 100 mL round-bottom flask was charged with a stirbar and DABCO (9.96 g, 88.8 mmol). CH_3OD (20 mL) was added, followed by addition of α-deuterio-methyl acrylate (8 mL, 88.8 mmol) *via* syringe. The reaction was stirred vigorously for 48 hours, and then diluted with *o*-dichlorobenzene (50 mL). The combined organics were washed with 4x 100 mL H_2O and 1x 100 mL brine, and the rigorously dried over Na_2SO_4 and $MgSO_4$. The product was purified by fractional distillation to afford α-deuterio-methyl acrylate (94% d-incorporation, 20-35% yield). ^{1}H-NMR (300 MHz, CDCl3): d 6.40 (m, 1H), 6.12 (m, 0.06 H), 5.83 (m, 1H), 3.75 (s, 3H). This material could be stored at 0 ^oC without a noticeable loss in d-incorporation, and was used in all KIE experiments.

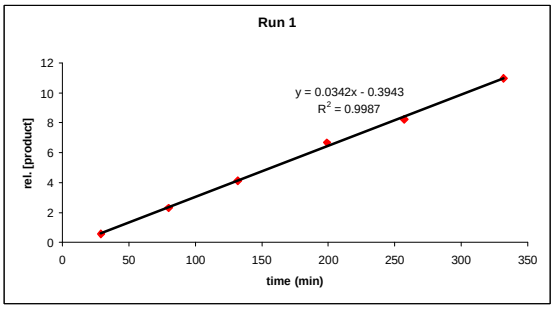
D : Average rate = 0.0083

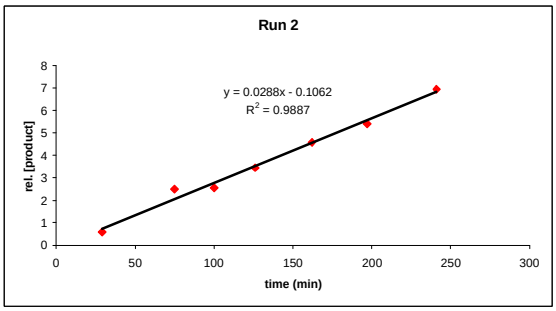






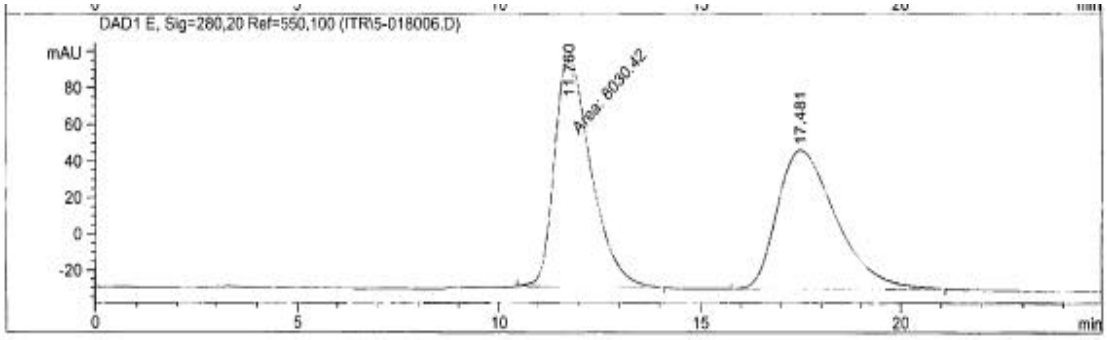
H : Average rate = 0.0315





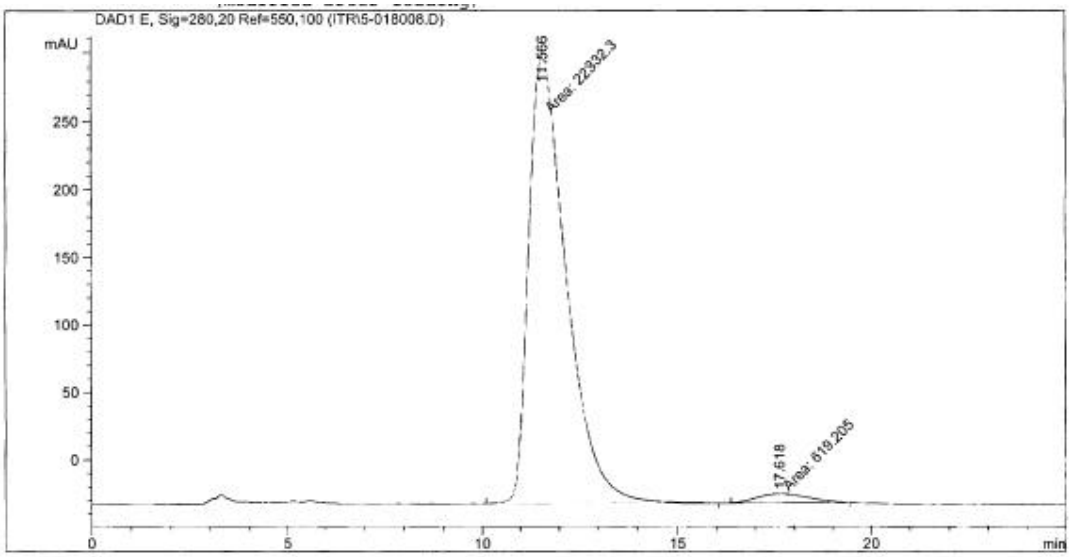
[13a] K.E. Price, S.J. Broadwater, H.M. Jung, D.T. McQuade, Org. Lett. 2005, 7, 147-150.

3a - racemate



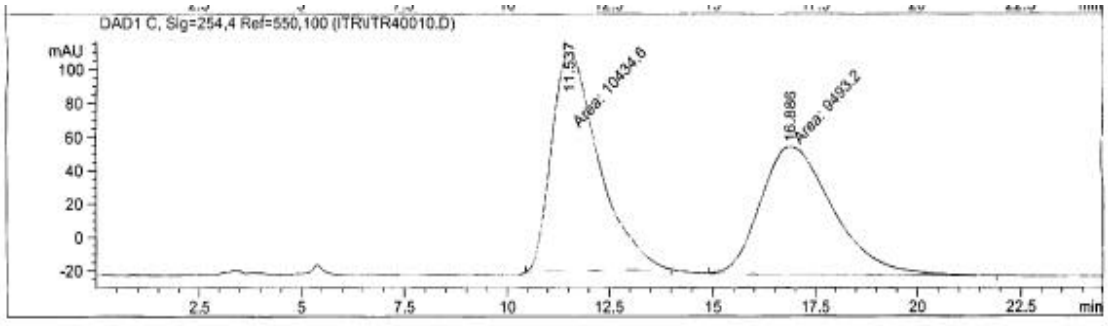
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.760	MM	1.0534	8030.41650	127.05696	50.7869
2	17.481	BV	1.3632	7781.56396	76.35723	49.2131
Totals :				1.58120e4	203.41419	

3**a** - 95% ee




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 E, Sig=280,20 Ref=550,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.566 MM    1.1323 2.23323e4   328.70859  97.3021
   2  17.618 MM    1.5303  619.20538    6.74371   2.6979

Totals :                  2.29515e4   335.45230
```

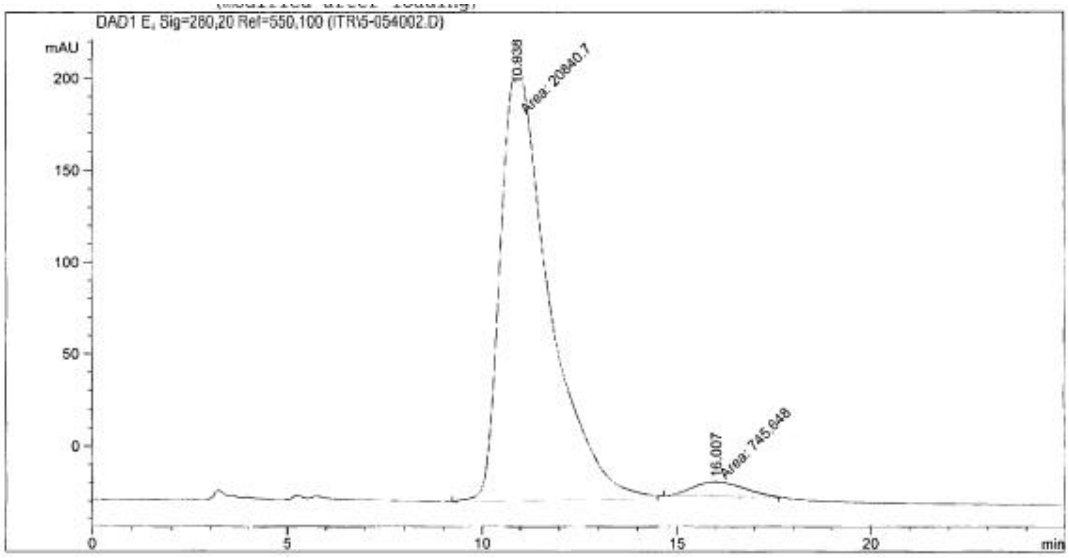
3b – racemate



Signal 2: DAD1 C, Sig=254,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.537	MM	1.3349	1.04346e4	130.27666	52.3621
2	16.886	MM	2.0703	9493.19824	76.42282	47.6379
Totals :				1.99278e4	206.69948	

3b – 93% ee



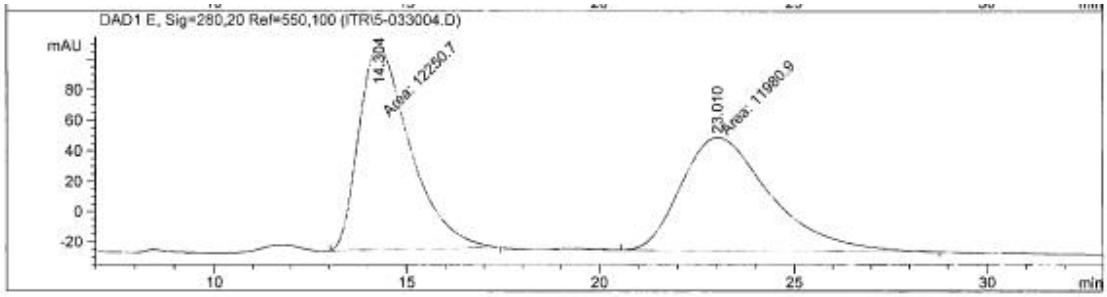
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 E, Sig=280,20 Ref=550,100

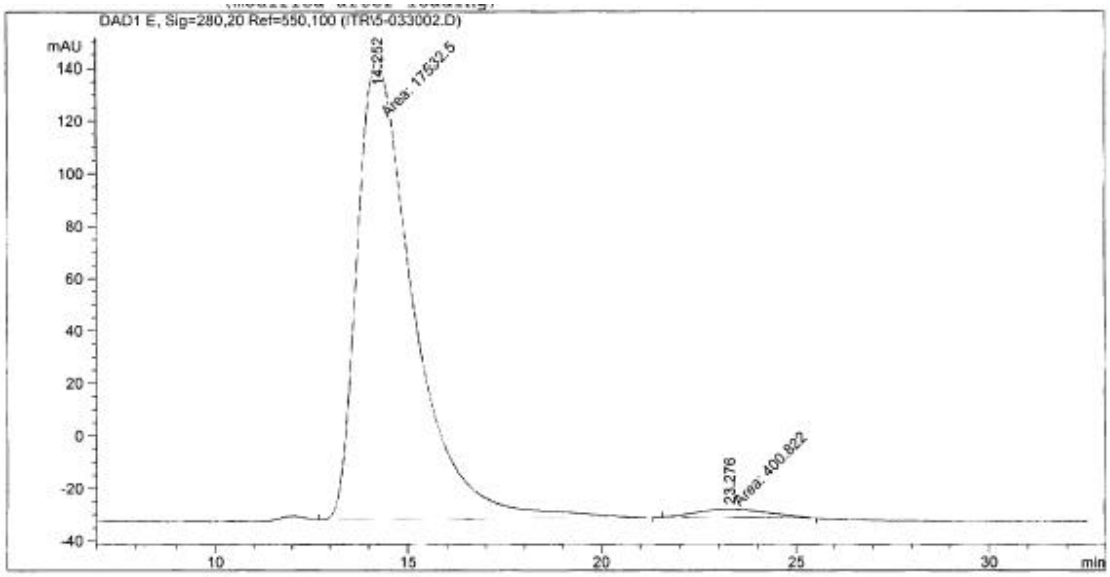
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.938	MM	1.4507	2.08407e4	239.43286	96.5457
2	16.007	MM	1.5266	745.64832	8.14074	3.4543
Totals :				2.15864e4	247.57360	

3c – racemate



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.304	MM	1.5322	1.22507e4	133.25697	50.5567
2	23.010	MM	2.6806	1.19809e4	74.49181	49.4433
Totals :				2.42315e4	207.74879	

3c – 96% ee



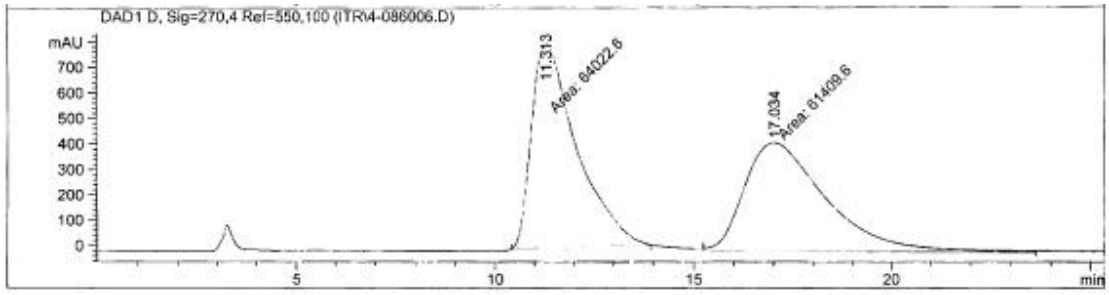
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 E, Sig=280,20 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.252	MM	1.6734	1.75325e4	174.62372	97.7649
2	23.276	MM	2.0342	400.82190	3.28405	2.2351
Totals :				1.79333e4	177.90777	

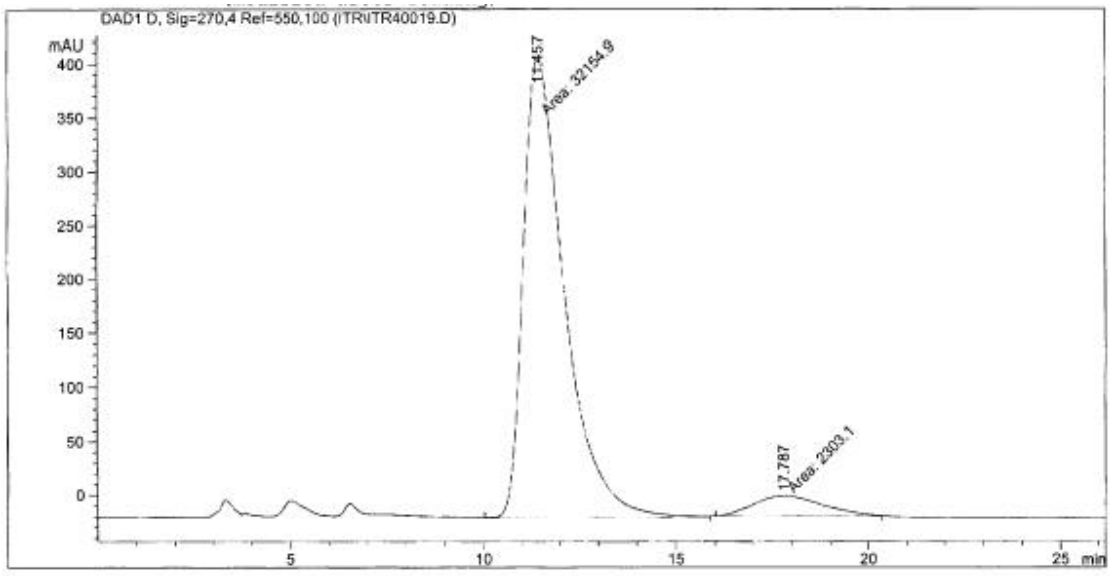
3d – racemate



Signal 2: DAD1 D, Sig=270,4 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.313	MM	1.3347	6.40226e4	799.45789	51.0416
2	17.034	MM	2.3959	6.14096e4	427.17865	48.9584
Totals :				1.25432e5	1226.63654	

3d – 87% ee



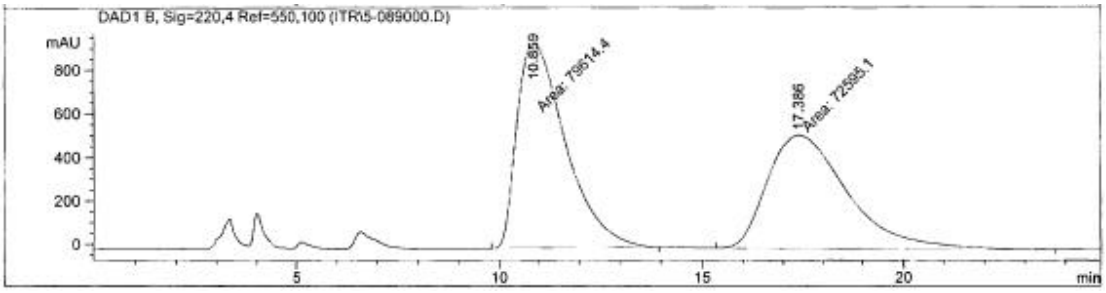
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)

Signal 1: DAD1 D, Sig=270,4 Ref=550,100

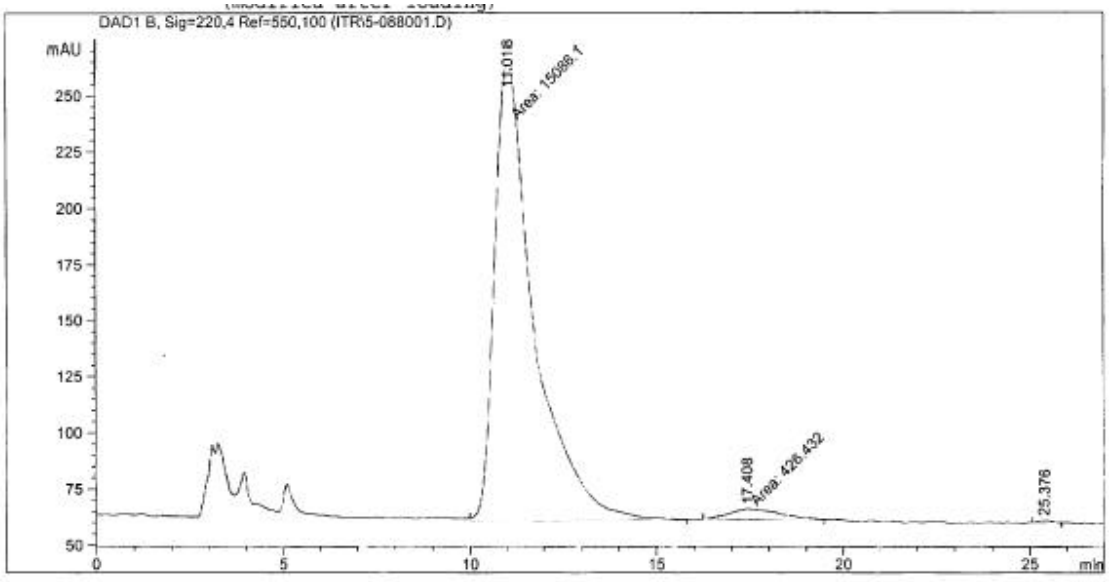
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.457	MM	1.2604	3.21549e4	425.20624	93.3162
2	17.787	MM	2.0711	2303.10278	18.53348	6.6838
Totals :				3.44580e4	443.73972	

3e – racemate



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.859	MM	1.4107	7.96144e4	940.63281	52.3058
2	17.386	MM	2.3175	7.25951e4	522.07269	47.6942
Totals :				1.52209e5	1462.70551	

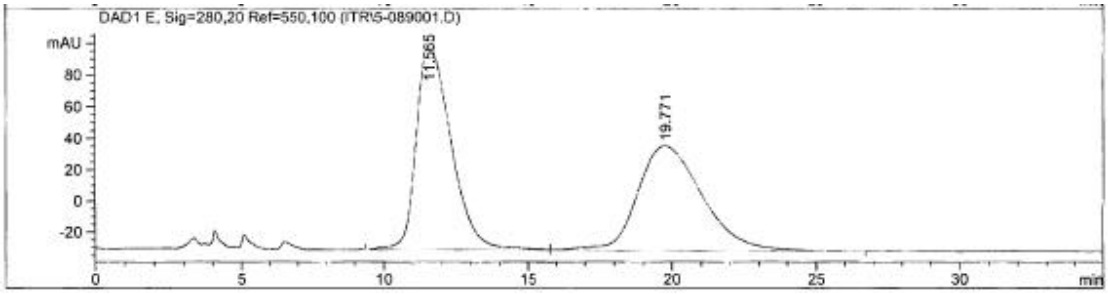
3e – 94% ee




```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 B, Sig=220,4 Ref=550,100
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.018	MM	1.2381	1.50861e4	203.08276	97.1144
2	17.408	MM	1.5623	426.43204	4.54928	2.7451
3	25.376	VV	0.3047	21.82516	9.81826e-1	0.1405
Totals :				1.55343e4	208.61387	

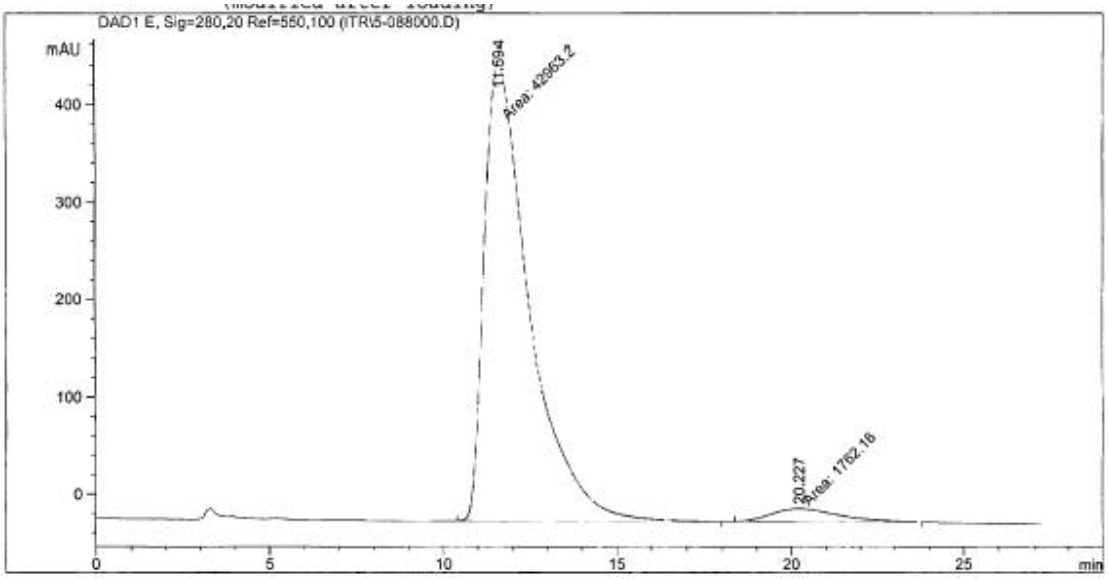
3f – racemate



Signal 2: DAD1 E, Sig=280,20 Ref=550,100

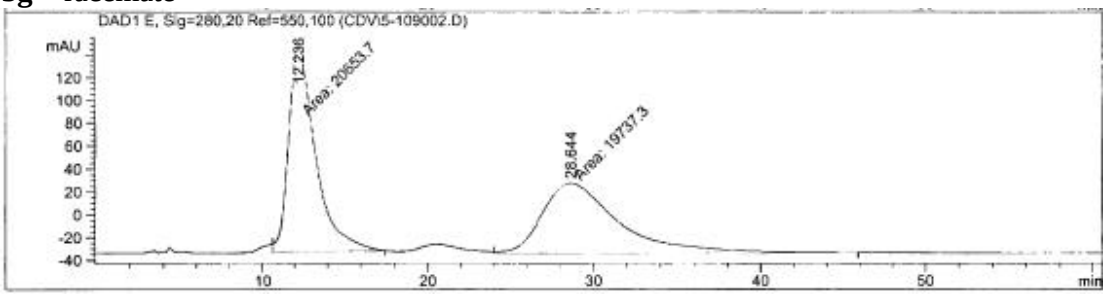
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.565	BV	1.1857	1.09957e4	130.85185	51.6300
2	19.771	VB	1.8734	1.03014e4	67.01318	48.3700
Totals :				2.12971e4	197.86503	

3f – 92% ee




```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 E, Sig=280,20 Ref=550,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.594 MM    1.5265 4.29632e4   469.07443  96.0601
   2  20.227 MM    2.2087 1762.15698   13.29734   3.9399

Totals :                  4.47254e4   482.37177
```

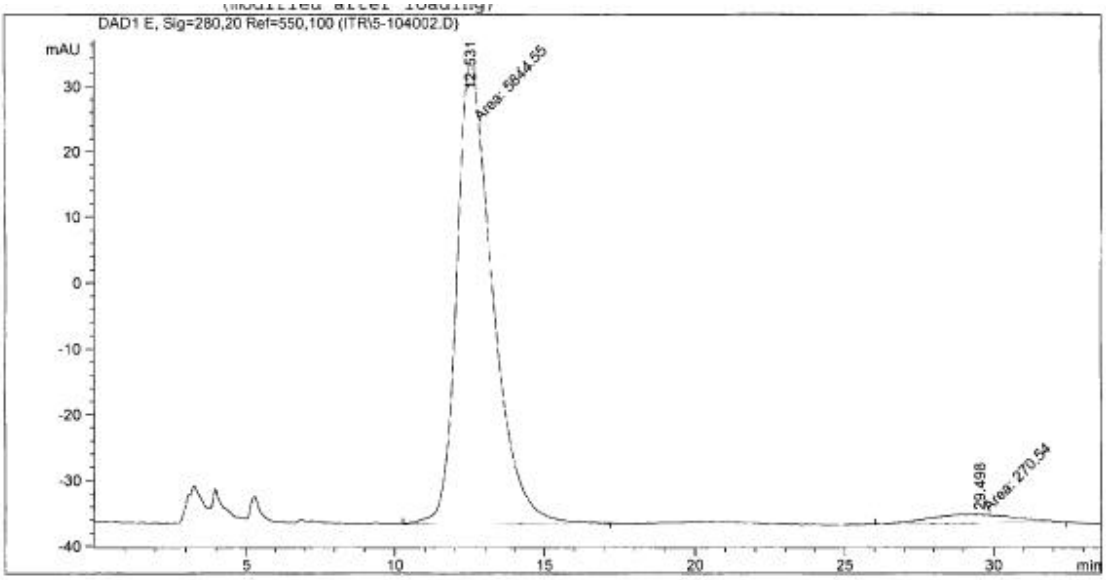
3g – racemate



Signal 2: DAD1 E, Sig=280,20 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.236	FM	1.9191	2.06537e4	179.36861	51.1345
2	28.644	MM	5.3161	1.97373e4	61.87867	48.8655
Totals :				4.03910e4	241.24728	

3g – 91% ee



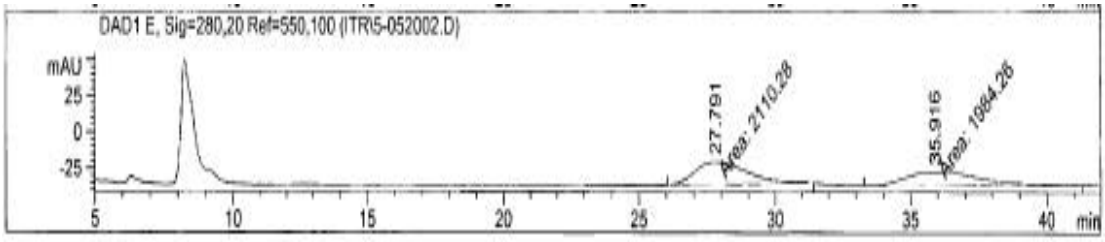
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: DAD1 E, Sig=280,20 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.531	MM	1.3946	5844.54883	69.84622	95.5759
2	29.498	MM	3.2800	270.53976	1.37468	4.4241
Totals :				6115.08859	71.22090	

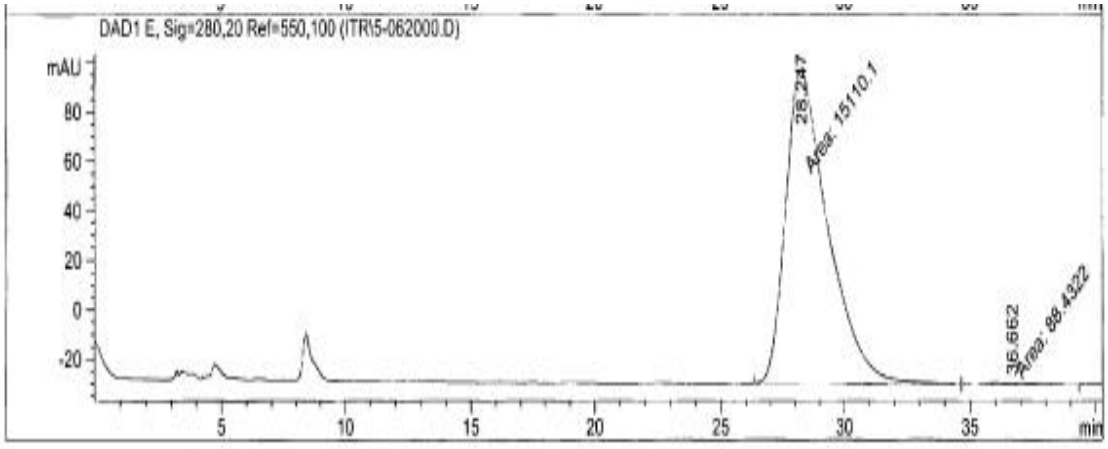
3h – racemate



Signal 4: DAD1 E, Sig=280,20 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.791	MM	2.2371	2110.28223	15.72216	51.5389
2	35.916	MM	3.3391	1984.25977	9.90420	48.4611
Totals :				4094.54199	25.62636	

3i– 99% ee

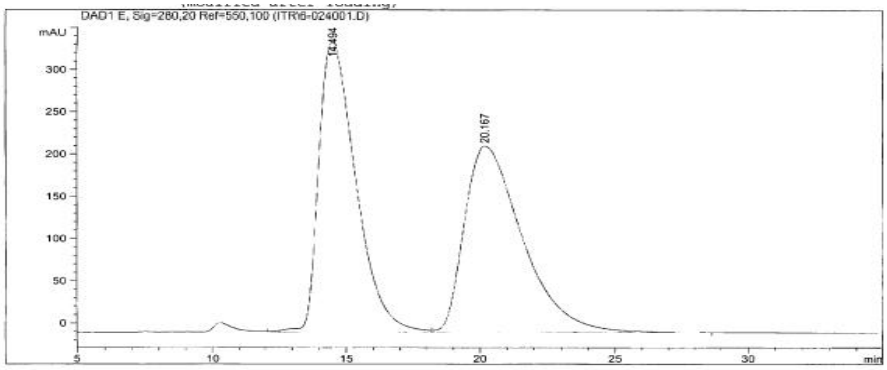


Signal 2: DAD1 E, Sig=280,20 Ref=550,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.247	MM	1.9800	1.51101e4	127.18702	99.4182
2	36.662	MM	2.0704	88.43224	7.11881e-1	0.5818

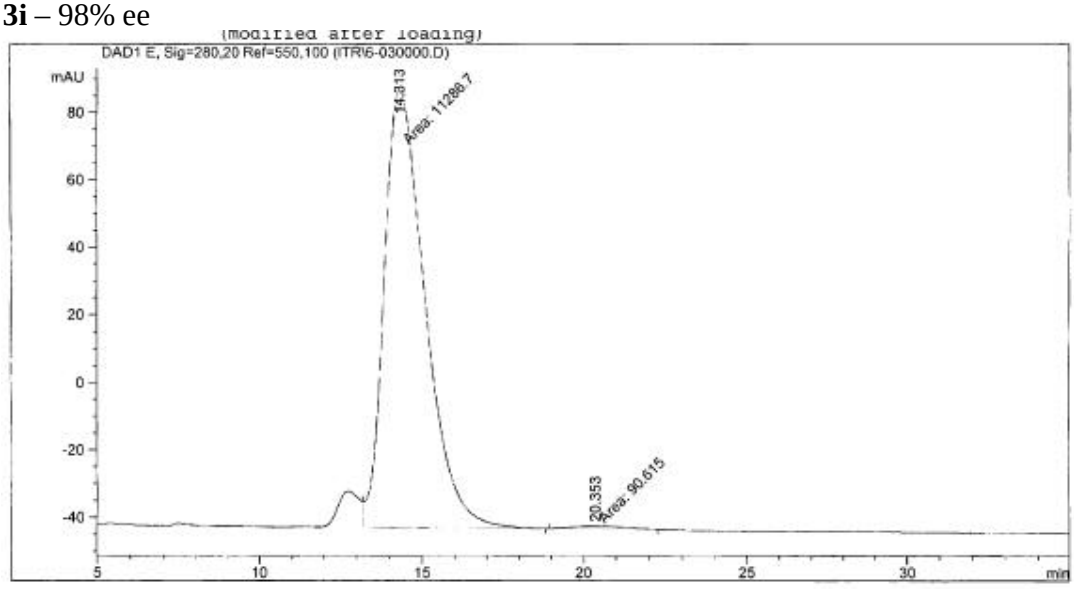
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
Totals :				1.51985e4	127.89890	

3i – racemate



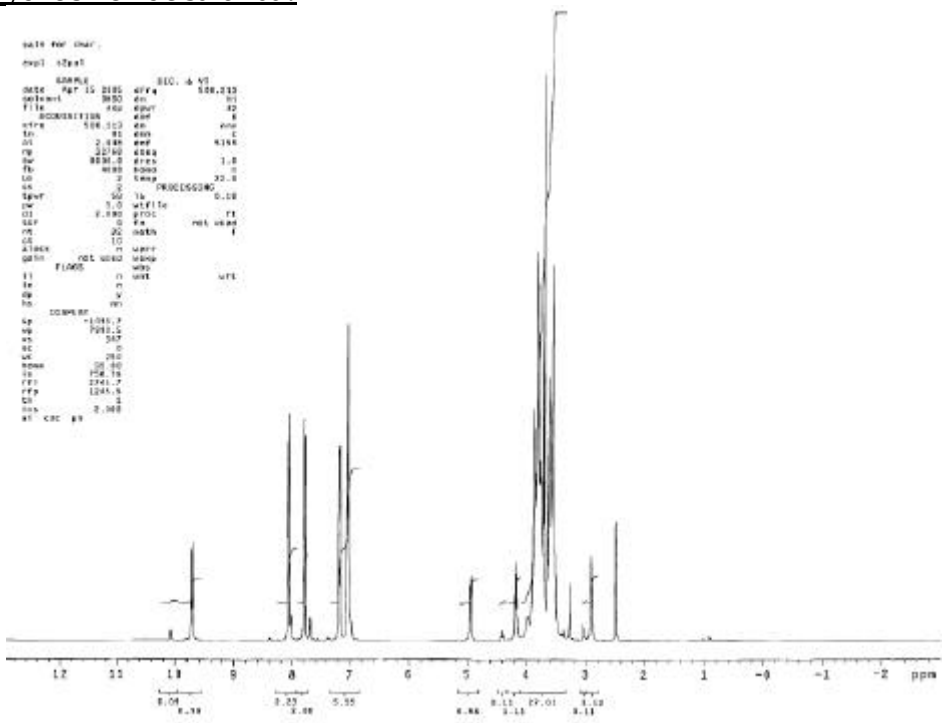

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 E, Sig=280,20 Ref=550,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.494 VV    1.3901 3.28911e4   343.88736  50.0534
   2  20.167 VB    1.9599 3.28209e4   220.66702  49.9466
```

3i – 98% ee

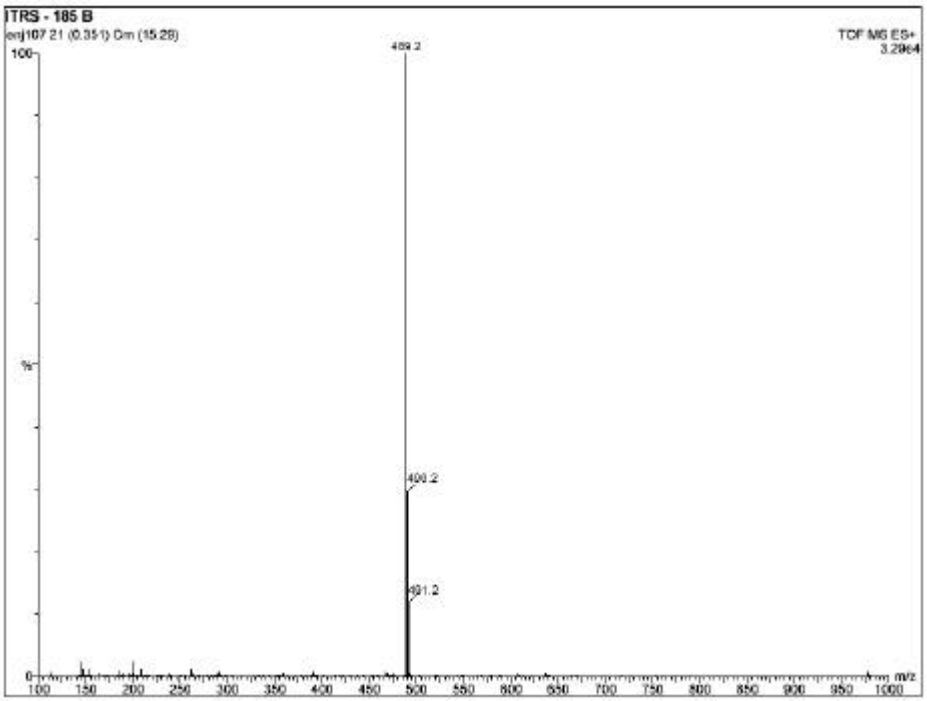



```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 E, Sig=280,20 Ref=550,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.313 FM    1.4529 1.12867e4   129.47752  99.2035
   2  20.353 MM    1.7279   90.61502 8.74062e-1   0.7965

Totals :                  1.13773e4   130.35159
```

dihydrochloride salt 10a:



ESI-MS of dihydrochloride salt 10a:



<u>dihydrochloride salt 10a + 2 equiv. DBU at t=4 min:</u>

(note: immediate appearance of methyl acrylate, loss of N-H proton, and change in splitting pattern of a**-C-H proton)**