Copper-Catalysed Enantioselective Michael Addition of Malonic Esters to β-Trifluoromethyl-α,β-Unsaturated Imines

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General Experimental Methods

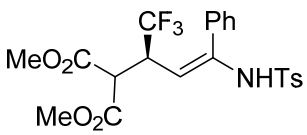
Reactions were carried out under nitrogen in round bottom flasks oven-dried overnight at 120 ºC. Commercial reagents were used as purchased. Dichloromethane was distilled from CaH_2. 4 Å molecular sieves (8-12 mesh, beads Aldrich 208604) were dried at the flame under vacuum (oil pump) and stored in a closed flask and used before a week. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^1H and at 75 MHz for ^{13}C NMR using residual nondeuterated solvent ($CHCl_3$) as internal standard (δ 7.26 and 77.0 ppm, respectively), and at 282 MHz for ^{19}F NMR using $CFCl_3$ as internal standard. Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV (ESI). Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or from Phenomenex. *N*-Tosyl unsaturated imines **2** were prepared according to the procedure described by A. D. Smith.[1]

General procedure for the enantioselective conjugate addition of methyl malonate to β-trifluoromethyl α,β-usaturated *N*-sulfonylimines 2

$Cu(OTf)_2$ (4.5 mg, 0.0125 mmol) was dried in a Schlenk tube under vacuum. **BOX7** (4.4 mg, 0.0125 mmol) was added and the tube was filled with nitrogen. CH_2Cl_2 (0.55 mL) was added via syringe and the mixture was stirred for 30 min. A solution of imine **2** (0.125 mmol) dissolved in dry CH_2Cl_2 (0.5 mL), was added via syringe, followed by 4 Å MS (110 mg) and dimethyl malonate (34 μL, 0.3 mmol). The mixture was stirred at room temperature for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **3**.

Racemic compounds for comparative purpose were prepared by following the same procedure, using $La(OTf)_3$-pyBOX (rac) at 40 °C.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-phenylbut-3-en-2-yl)malonate (3a)



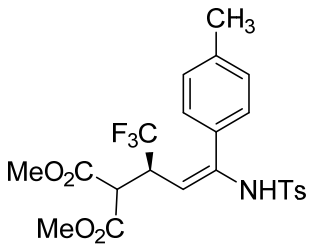
Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 8.4 min, *minor enantiomer (R)* tr = 14.0 min; *Z*-diastereomer: *major enantiomer* tr = 12.4 min, *minor enantiomer* tr = 9.4 min.

Major *E*-diastereomer: White solid, m.p. 159-161 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -54.0 (*c* 1.0, $CHCl_3$) for the mixture of diastereomers; white solid, M.p. 153.4-160.2 °C (hexane-

EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.4 Hz, Ar), 7.40-7.27 (5H, m, Ar), 7.10 (2H, m, Ar), 6.21 (1H, s, NH), 5.57 (1H, d, *J* = 10.8 Hz, =CH), 3.73 (3H, s, MeO), 3.68 (1H, d, *J* = 8.4 Hz, $CHCO_2Me$), 3.64 (1H, m, $CHCF_3$), 3.63 (3H, s, MeO), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 166.4 (C), 144.2 (C), 141.3 (C), 135.9 (C), 134.0 (C), 129.6 (CH), 129.5 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 264.8 Hz), 102.9 (CH, q, $J_{C\text{-}F}$ = 2.4 Hz), 52.93 (CH_3), 52.90 (CH_3), 51.0 (CH), 42.7 (CH, q, $J_{C\text{-}F}$ = 27.9 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.1 (s, CF_3) ppm; HRMS (ESI) *m/z* 486.1197, $C_{22}H_{23}F_3NO_6S$ requires 486.1193.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.59 (2H, d, *J* = 8.4 Hz, Ar), 7.41 (2H, dd, *J* = 8.1, 1.5 Hz, Ar), 7.36-7.26 (3H, m, Ar), 7.22 (2H, d, *J* = 8.4 Hz, Ar), 5.22 (1H, d, *J* =11.1 Hz, =CH), 3.81 (3H, s, MeO), 3.76-3.48 (2H, m, CH-CF_3, $CHCO_2Me$), 3.68 (3H, s, MeO), 2.39 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(*p*-tolyl)but-3-en-2-yl)malonate (3b)

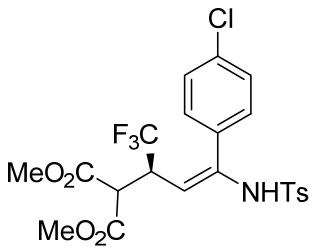


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 85:15, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 13.4 min, *minor enantiomer (R)* tr = 16.1 min; *Z*-diastereomer: *major enantiomer* tr = 14.5 min, *minor enantiomer* tr = 11.9 min.

Major *E*-diastereomer: White solid, m.p. 138-146 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -38.6 (*c* 0.95, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.4 Hz, Ar), 7.32 (2H, d, *J* = 8.4 Hz, Ar), 7.13 (2H, d, *J* = 8.1 Hz, Ar), 6.97 (2H, d, *J* = 8.1 Hz, Ar), 6.18 (1H, s, NH), 5.52 (1H, d, *J* = 10.8 Hz, =CH), 3.72 (3H, s, MeO), 3.67 (1H, d, *J* = 8.1 Hz, $CHCO_2Me$), 3.64 (1H, m, $CHCF_3$), 3.63 (3H, s, MeO), 2.45 (3H, s, Me-Ar), 2.33 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.5 (C), 144.2 (C), 141.3 (C), 139.5 (C), 135.9 (C), 131.2 (C), 129.6 (CH), 129.5 (CH), 128.4 (CH), 127.7 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 249.7 Hz), 102.6 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 52.94 (CH_3), 52.91 (CH_3), 51.0 (CH), 42.7 (CH, q, $J_{C\text{-}F}$ = 27.9 Hz), 21.5 (CH_3), 21.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3) ppm; HRMS (ESI) *m/z* 500.1356 $(M+H)^+$ $C_{23}H_{25}F_3NO_6S$ requires 500.1349.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1}H NMR of the diastereomer mixtures, δ 7.91 (1H, s, NH), 7.86 (2H, d, *J* = 8.1 Hz, Ar), 7.60 (2H, d, *J* = 8.1 Hz, Ar), 7.25 (2H, d, *J* = 8.1 Hz, Ar), 7.22 (2H, d, *J* = 8.1 Hz, Ar), 5.16 (1H, d, *J* = 10.8 Hz, =CH), 3.82-3.60 (2H, m, CH-CF_3, $CHCO_2Me$), 3.76 (3H, s, MeO), 3.67 (3H, s, MeO), 2.43 (3H, s, Me-Ar), 2.39 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(4-(4-chlorophenyl)-1,1,1-trifluoro-4-((4-methylphenyl)-sulfonamido)-but-3-en-2-yl)malonate (3c)

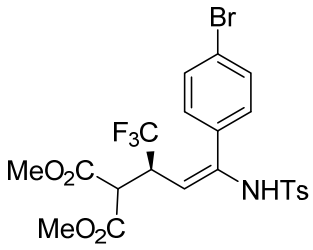


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 95:05, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 38.4 min, *minor enantiomer (R)* tr = 47.9 min; *Z*-diastereomer: *major enantiomer* tr = 48.4 min, *minor enantiomer* tr = 33.9 min.

Major *E*-diastereomer: White solid, m.p. 142-150 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -21.3 (*c* 0.95, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 8.4 Hz, Ar), 7.34-7.24 (4H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.42 (1H, s, NH), 5.52 (1H, d, *J* = 10.8 Hz, =CH), 3.72 (3H, s, MeO), 3.67 (1H, d, *J* = 8.4 Hz, $CHCO_2Me$), 3.64 (3H, s, MeO), 3.55 (1H, m, $CHCF_3$), 2.44 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 144.3 (C), 140.4 (C), 135.9 (C), 135.6 (C), 132.3 (C), 130.2 (CH), 129.7 (CH), 129.0 (CH), 127.6 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 278 Hz), 104.23 (CH, q, $J_{C\text{-}F}$ = 2.5 Hz), 53.04 (CH_3), 52.99 (CH_3), 50.9 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 28.0 Hz), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.1 (s, CF_3) ppm; HRMS (ESI) *m/z* 520.0795 $(M+H)^+$, $C_{22}H_{22}ClF_3NO_6S$ requires 520.0803.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1}H NMR of the diastereomer mixtures, δ 8.01 (1H, s, NH), 7.57 (2H, d, J = 8.4 Hz, Ar), 7.40-7.19 (6H, m, Ar), 5.19 (1H, d, *J* = 11.4 Hz, =CH), 3.80 (3H, s, MeO), 3.76 (1H, d, J = 7.2 Hz, $CHCO_2Me$), 3.68 (3H, s, MeO), 3.51 (1H, m, $CHCF_3$), 2.39 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(4-(4-bromophenyl)-1,1,1-trifluoro-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (3d)



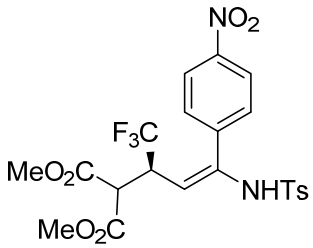
Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 95:05, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 47.9 min, *minor enantiomer (R)* tr = 57.1 min; *Z*-diastereomer: *major enantiomer* tr = 31.9 min, *minor enantiomer* tr = 40.2 min.

Major *E*-diastereomer: Yellow solid, m.p. 130-133 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -12.8 (*c* 1.02 , $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (2H, d, *J* = 8.4 Hz, Ar), 7.45 (2H, d, *J* = 8.4 Hz, Ar), 7.31 (2H, d, *J* = 8.4 Hz, Ar), 7.04 (2H, d, *J* = 8.4 Hz, Ar), 6.29 (1H, s, NH), 5.53 (1H, d, *J* = 10.8 Hz, =CH), 3.73 (3H, s, MeO), 3.68 (1H, d, *J* = 8.4 Hz, $CHCO_2Me$), 3.65 (3H, s, MeO), 3.55 (1H, m, $CHCF_3$), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 144.4 (C), 140.4 (C), 135.9 (C), 132.8 (C), 132.0 (CH), 130.4 (CH), 129.7 (CH), 127.6 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 278 Hz), 124.0 (C), 104.3 (CH, q, $J_{C\text{-}F}$ = 2.3 Hz), 53.07 (CH_3), 53.01

(CH_3), 50.9 (CH), 42.6 (CH, q, J_{C-F} = 28.0 Hz), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.0 (s, CF_3) ppm; HRMS (ESI) *m/z* 564.0295 $(M+H)^+$, $C_{22}H_{22}BrF_3NO_6S$ requires 564.0298.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^1H NMR of the diastereomer mixtures, δ 8.01 (1H, s, NH), 7.58 (2H, d, *J* = 8.4 Hz, Ar), 7.41 (2H, d, *J* = 8.4 Hz, Ar), 7.31 (2H, d, *J* = 8.4 Hz, Ar), 7.25 (2H, d, *J* = 8.4 Hz, Ar), 5.21 (1H, d, *J* = 11.4 Hz, =CH), 3.80 (3H, s, MeO), 3.77 (1H, d, J = 7.2 Hz, $CHCO_2Me$), 3.68 (3H, s, MeO), 3.52 (1H, m, $CHCF_3$), 2.40 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.8 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(4-nitrophenyl)but-3-en-2-yl)malonate (3e)

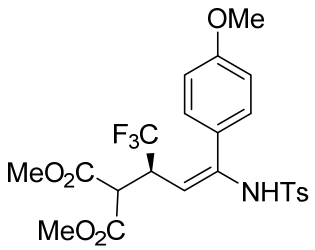


Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 60.4 min, *minor enantiomer (R)* tr = 69.2 min; *Z*-diastereomer: *major enantiomer* tr = 50.2 min, *minor enantiomer* tr = 94.8 min.

Major *E*-diastereomer: Orange oil; $[\alpha]_D^{20}$ 1.1 (*c* 1.0, $CHCl_3$) for the mixture of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* = 9.0 Hz, Ar), 7.68 (2H, d, *J* = 8.1 Hz, Ar), 7.37.34-7,28 (4H, m, Ar), 6.80 (1H, s, NH), 5.58 (1H, d, *J* = 11.1 Hz, =CH), 3.73 (3H, s, MeO), 3.68 (1H, d, *J* = 8.4 Hz, $CHCO_2Me$), 3.65 (3H, s, MeO), 3.49 (1H, m, $CHCF_3$), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 166.4 (C), 148.2 (C), 144.6 (C), 140.1 (C), 139.6 (C), 135.7 (C), 130.2 (CH), 129.7 (CH), 127.6 (CH), 125.2 (C, q, J_{C-F} = 279 Hz), 123.8 (C), 106.5 (CH, q, J_{C-F} = 2.1 Hz), 53.2 (CH_3), 53.1 (CH_3), 50.7 (CH), 42.6 (CH, q, J_{C-F} = 28.2 Hz), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3) ppm; HRMS (ESI) *m/z* 531.1034 $(M+H)^+$, $C_{22}H_{22}ClF_3N_2O_8S$ requires 531.1043.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^1H NMR of the diastereomer mixture, δ 8.19 (1H, s, NH), 8.14 (2H, d, *J* = 9.0 Hz, Ar), 7.60 (4H, m, Ar), 7.25 (2H, d, *J* = 8.0 Hz, Ar), 5.40 (1H, d, *J* = 10.8 Hz, =CH), 3.83 (3H, s, MeO), 3.80 (1H, d, *J* = 5.7 Hz, $CHCO_2Me$), 3.69 (3H, s, MeO), 3.49 (1H, m, $CHCF_3$), 2.40 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 166.9 (C), 148.2 (C), 144.4 (C), 143.2 (C), 140.0 (C), 136.5 (C), 129.7 (CH), 128.7 (CH), 126.9 (CH), 125.2 (C, q, J_{C-F} = 279 Hz), 123.3 (C), 114.8 (CH, q, J_{C-F} = 2.1 Hz), 54.0 (CH_3), 53.4 (CH_3), 50.7 (CH), 41.8 (CH, q, J_{C-F} = 29.0 Hz), 21.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.6 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-(4-methoxyphenyl)-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (3f)

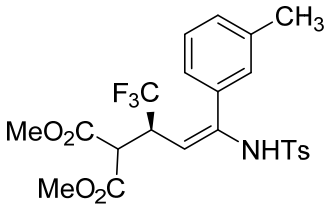


Chiral HPLC analysis: Chiralpak IC, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 44.2 min, *minor enantiomer (R)* tr = 63.8 min; *Z*-diastereomer: *major enantiomer* tr = 38.0 min, *minor enantiomer* tr = 50.9 min.

Major *E*-diastereomer: Yellow oil; $[\alpha]_D^{20}$ -16.3 (*c* 1.0, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.1 Hz, Ar), 7.32 (2H, d, *J* = 8.1 Hz, Ar), 7.03 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.16 (1H, s, NH), 5.48 (1H, d, *J* = 10.8 Hz, =CH), 3.79-3.66 (2H, m, CH-CF_3, $CHCO_2Me$), 3.80 (3H, s, MeO), 3.73 (3H, s, MeO), 3.64 (3H, s, MeO), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.5 (C), 160.3 (C), 144.1 (C), 141.2 (C), 136.0 (C), 130.0 (CH), 129.6 (CH), 127.7 (CH), 125.6 (C, q, $J_{C\text{-}F}$ = 279 Hz, CF_3), 114.1 (CH), 102.7 (C, q, $J_{C\text{-}F}$ = 2.0 Hz, CF_3), 55.2 (CH_3), 52.96 (CH_3), 52.91 (CH_3), 51.1 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 27.8 Hz, CF_3), 21.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3) ppm; HRMS (ESI) *m/z* 516.1294 $(M+H)^+$, $C_{23}H_{25}F_3NO_7S$ requires 516.1298.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1}H NMR of the diastereomer mixture, δ 7.60 (2H, d, *J* = 8.1 Hz, Ar), 7.23 (2H, d, *J* = 8.1 Hz, Ar), 6.93 (2H, d, *J* = 9.0 Hz, Ar), 6.79 (2H, d, *J* = 9.0 Hz, Ar), 5.09 (1H, d, *J* = 11.4 Hz, =CH), 2.43 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(*m*-tolyl)but-3-en-2-yl)malonate (3g)

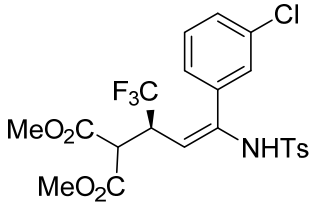


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 7.0 min, *minor enantiomer (R)* tr = 10.7 min; *Z*-diastereomer: *major enantiomer* tr = 9.5 min, *minor enantiomer* tr = 7.8 min.

Major *E*-diastereomer: White solid, m.p. 117-120 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -40.7 (*c* 1.0, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.1 Hz, Ar), 7.32 (2H, d, *J* = 8.1 Hz, Ar), 7.21-7.13 (2H, m, Ar), 6.89 (1H, d, *J* = 7,5 Hz, Ar), 6.81 (1H, s, Ar), 6.18 (1H, s, NH), 5.55 (1H, d, *J* = 10.8 Hz, =CH), 3.76-3.67 (2H, m, CH-CF_3, $CHCO_2Me$), 3.73 (3H, s, MeO), 3.63 (3H, s, MeO), 2.45 (3H, s, Me-Ar), 2.28 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.5 (C), 144.2 (C), 141.4 (C), 138.5 (C), 136.0 (C), 134.0 (C), 130.2 (CH), 129.6 (CH), 129.1 (CH), 128.7 (CH), 127.7 (CH), 125.6 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 255 Hz), 102.9 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 52.93 (CH_3), 52.91 (CH_3), 51.1 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 27.9 Hz), 21.5 (CH_3), 21.3 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3) ppm; HRMS (ESI) *m/z* 500.1354 $(M+H)^+$, $C_{23}H_{25}F_3NO_6S$ requires 500.1349.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1}H NMR of the diastereomer mixture, δ 7.90 (1H, s, NH), 7.58 (2H, d, *J* = 8.4 Hz, Ar), 7.35-6.75 (6H, m, Ar), 5.22 (1H, d, *J* = 11.4 Hz, =CH), 3.82-3.60 (2H, m, CH-CF_3, $CHCO_2Me$), 3.80 (3H, s, MeO), 3.68 (3H, s, MeO), 2.43 (3H, s, Me-Ar), 2.26 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = - 69.8 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(4-(3-chlorophenyl)-1,1,1-trifluoro-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (3h)

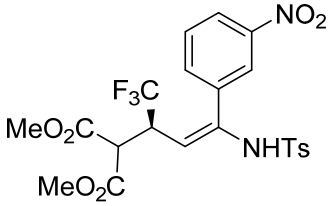


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 7.2 min, *minor enantiomer (R)* tr = 11.1 min; *Z*-diastereomer: *major enantiomer* tr = 9.5 min, *minor enantiomer* tr = 8.2 min.

Major *E*-diastereomer: yellow solid, m.p. 100-107 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -20.8 (*c* 0.96, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (2H, d, *J* = 8.4 Hz, Ar), 7.32 (2H, d, *J* = 8.4 Hz, Ar), 7.31-7.17 (2H, m, Ar), 7.05 (1H, dt, *J* = 7.2, 1.5 Hz, Ar), 6.93 (1H, t, *J* = 1.5 Hz, Ar), 6.34 (1H, s, NH), 5.58 (1H, d, *J* = 10.8 Hz, =CH), 3.74 (3H, s, MeO), 3.68 (1H, d, J = 8.1 Hz, $CHCO_2Me$), 3.64 (3H, s, MeO), 3.56 (1H, m, $CHCF_3$), 2.45 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 166.4 (C), 144.4 (C), 140.1 (C), 135.8 (C), 135.5 (C), 134.5 (C), 130.0 (CH), 129.7 (CH), 129.6 (CH), 128.8 (CH), 127.6 (CH), 127.0 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 280 Hz), 104.9 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 53.03 (CH_3), 52.98 (CH_3), 50.9 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 28.0 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.0 (s, CF_3) ppm; HRMS (ESI) *m/z* 520.0801 $(M+H)^+$, $C_{22}H_{22}ClF_3NO_6S$ requires 520.0803.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1}H NMR of the diastereomer mixture, δ 8.00 (1H, s, NH), 7.57 (2H, d, *J* = 8.4 Hz, Ar), 7.33-7.20 (6H, m, Ar), 5.26 (1H, dd, *J* = 10.8, 0.6 Hz, =CH), 3.81 (3H, s, MeO), 3.78 (1H, d, *J* = 6.3 Hz, $CHCO_2Me$), 3.69 (3H, s, MeO), 3.56 (1H, m, CH-CF_3), 2.39 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.7 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(3-nitrophenyl)but-3-en-2-yl)malonate (3i)



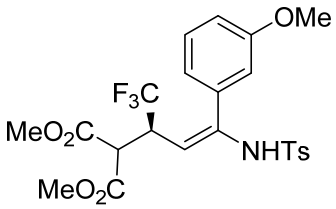
Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 95:05, 2 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 42.9 min, *minor enantiomer (R)* tr = 78.2 min; *Z*-diastereomer: *major enantiomer* tr = 50.6 min, *minor enantiomer* tr = 30.9 min.

Major *E*-diastereomer: Yellow oil; $[\alpha]_D^{20}$ -9.5 (*c* 0.97, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (1H, m, Ar), 7.82 (1H, ddd, *J* = 7.8, 1.8, 1.2 Hz, Ar), 7.76 (1H, t, *J* = 1.8 Hz, Ar), 7.65 (2H, d, *J* = 8.0 Hz, Ar), 7.54 (1H, t, *J* = 8.0 Hz, Ar), 7.30 (2H, d, *J* = 8.0 Hz, Ar), 6.62 (1H, s, NH), 5.63 (1H, d, *J* = 11.1 Hz, =CH), 3.76 (3H, s, MeO), 3.67 (1H, d, *J* = 7.4 Hz, $CHCO_2Me$), 3.65 (3H, s, MeO), 3.48 (1H, m, $CHCF_3$), 2.44 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 166.4

(C), 148.1 (C), 144.7 (C), 139.5 (C), 135.7 (C), 135.2 (CH), 135.1 (C), 129.8 (CH, overlaped signals), 127.5 (CH), 125.3 (C, q, $J_{C\text{-}F}$ = 279 Hz), 124.2 (CH), 124.1 (CH), 106.9 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 53.17 (CH_3), 53.12 (CH_3), 50.7 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 28.2 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.9 (s, CF_3) ppm; HRMS (ESI) *m/z* 531.1036 $(M+H)^+$, $C_{22}H_{22}ClF_3N_2O_8S$ requires 531.1043.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^1H NMR of the diastereomer mixture, δ 8.19 (1H, s, NH), 8.16 (1H, m, Ar), 8.11 (1H, t, *J* = 1.9 Hz, Ar), 7.63-7.53 (3H, m, Ar), 7.50 (1H, t, *J* = 8.1 Hz, Ar), 7.23 (2H, d, *J* = 8.0 Hz, Ar), 5.38 (1H, dd, *J* = 10.8, 0.6 Hz, =CH), 3.83 (3H, s, MeO), 3.81 (1H, d, *J* = 6.3 Hz, $CHCO_2Me$), 3.71 (3H, s, MeO), 3.58 (1H, m, $CH\text{-}CF_3$), 2.39 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 167.0 (C), 148.0 (C), 144.4 (C), 139.8 (C), 138.5 (C), 136.6 (C), 134.1 (CH), 129.7 CH), 129.2 (CH), 126.9 (CH), 125.3 (C, q, $J_{C\text{-}F}$ = 279 Hz), 123.9 (CH), 122.7 (CH), 113.8 (CH, q, $J_{C\text{-}F}$ = 2.4 Hz), 54.0 (CH_3), 53.4 (CH_3), 50.7 (CH), 41.9 (CH, q, $J_{C\text{-}F}$ = 28.29 Hz), 21.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.6 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-(3-methoxyphenyl)-4-((4-methylphenyl) sulfonamido)but-3-en-2-yl)malonate (3j)

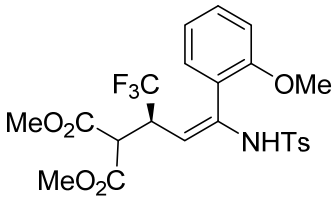


Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 19.4 min, *minor enantiomer (R)* tr = 30.7 min; *Z*-diastereomer: *major enantiomer* tr = 26.5 min, *minor enantiomer* tr = 21.8 min.

Major *E*-diastereomer: Yellow solid, m.p. 102-105 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -40.3 (*c* 0.95, $CHCl_3$) for the mixture of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.4 Hz, Ar), 7.38 (2H, d, *J* = 8.4 Hz, Ar), 7.28-7.25 (1H, m, Ar), 6.93 (1H, ddd, *J* = 8.4, 2.4, 1.2 Hz, Ar), 6.71-6.69 (2H, m, Ar), 6.31 (1H, s, NH), 5.65 (1H, d, *J* = 10.8 Hz, =CH), 3.88 (1H, d, *J* = 8.7 Hz, $CHCO_2Me$), 3.80 (3H, s, MeO), 3.79 (3H, s, MeO), 3.76-3.75 (1H, m, $CH\text{-}CF_3$), 3.70 (3H, s, MeO), 2.50 (3H, s, Me-Ar); ^{13}C NMR(75 MHz, $CDCl_3$) δ 166.8 (C), 166.6 (C), 159.6 (C), 144.2 (C), 141.1 (C), 135.9 (C), 135.3 (C), 129.9 (CH), 129.6 (CH), 127.7 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 257.3 Hz), 120.6 (CH), 115.7 (CH), 113.6 (CH), 102.9 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 55.2 (CH_3), 52.95 (CH_3), 52.94 (CH_3), 51.0 (CH), 42.6 (CH, q, $J_{C\text{-}F}$ = 27.9 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3) ppm; HRMS (ESI) *m/z* 516.1294 $(M+H)^+$, $C_{23}H_{25}F_3NO_7S$ requires 516.1298.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1H} NMR of the diastereomer mixture, δ 7.99 (1H, s, NH), 7.65 (2H, d, *J* = 8.4 Hz, Ar), 7.37-7.32 (1H, m, Ar), 7.06 (dt, *J* = 7,8, 1,2 Hz, Ar), 6.75-6.65 (2H, m, Ar), 5.31 (1H, d, *J* = 11.4 Hz, =CH), 3.89-3.67 (2H, m, $CH\text{-}CF_3$, $CHCO_2Me$), 3.86 (3H, s, MeO), 3.80 (3H, s, MeO), 3.75 (3H, s, MeO), 2.45 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = - 69.8 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-(2-methoxyphenyl)-4-((4-methylphenyl)-sulfonamido)but-3-en-2-yl)malonate (3k)

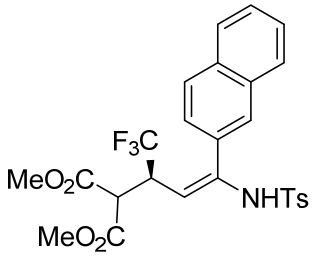


Chiral HPLC analysis: Chiralpak AD-H, hexane-*i*PrOH 90:10, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 21.6 min, *minor enantiomer (R)* tr = 47.2 min; *Z*-diastereomer: *major enantiomer* tr = 38.3 min, *minor enantiomer* tr = 32.7 min.

Major *E*-diastereomer: Yellow solid, m.p. 129-133 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -32.2 (*c* 0.92, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.4 Hz, Ar), 7.28-7.25 (2H, m, Ar), 7.03-7.00 (2H, m, Ar), 6.89 (1H, dt, *J* = 7.5, 1.2 Hz, Ar), 6.82 (1H, dd, *J* = 8.4, 1.2 Hz, Ar), 6.18 (1H, s, NH), 5.69 (1H, d, *J* = 10.8 Hz, =CH), 3.75 (3H, s, MeO), 3.69-3.55 (2H, m, CH-CF_3, $CHCO_2Me$), 3.65 (3H, s, MeO), 3.60 (3H, s, MeO), 2.42 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.6 (C), 156.7 (C), 143.8 (C), 138.8 (C), 136.1 (C), 131.2 (C), 131.0 (C), 129.3 (CH), 128.9 (CH), 127.9 (CH), 127.1 (CH), 125.0 (C, q, $J_{C\text{-}F}$ = 258.8 Hz), 120.6 (CH), 111.0 (CH), 113.6 (CH), 105.6 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 55.1 (CH_3), 52.9 (CH_3), 51.1 (CH), 42.8 (CH, q, $J_{C\text{-}F}$ = 27.8 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.2 (s, CF_3) ppm; HRMS (ESI) *m/z* 516.1302 $(M+H)^+$, $C_{23}H_{25}F_3NO_7S$ requires 516.1298.

Minor *Z*-diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^{1}H NMR of the diastereomer mixture, δ 7.81 (2H, d, *J* = 8.1 Hz, Ar), 7.38-6.49 (7H, m, Ar, NH), 5.44 (1H, d, *J* = 10.8 Hz, =CH), 3.82-3.60 (2H, m, CH-CF_3, $CHCO_2Me$), 3.83 (3H, s, MeO), 3.73 (3H, s, MeO), 3.55 (3H, s, MeO), 2.31 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.5 (s, CF_3) ppm.

Dimethyl (*S*,*E*)-2-(1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-(naphthalen-2-yl)but-3-en-2-yl)malonate (3l)



Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 80:20, 1 mL/min, *E*-diastereomer: *major enantiomer (S)* tr = 11.3 min, *minor enantiomer (R)* tr = 13.8 min; *Z*-diastereomer: *major enantiomer* tr = 12.3 min, *minor enantiomer* tr = 9.4 min

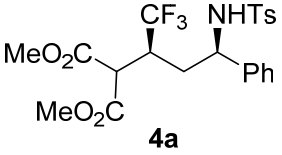
Major *E*-diastereomer: Yellow solid, m.p. 98-103 °C (hexane-EtOAc); $[\alpha]_D^{20}$ 1.0 (*c* 0.96, $CHCl_3$) for the mixture of diastereomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.74 (5H, m, Ar), 7.59-7.58 (1H, m, Ar), 7.53-7.49 (2H, m, Ar), 7.30 (2H, d, *J* = 8.1 Hz Ar), 7.14 (1H, dd, *J* = 8.1, 1.8 Hz, Ar), 6.38 (1H, s, NH), 5.65 (1H, d, *J* = 10.8 Hz, =CH), 3.82-3.69 (2H, m, CH-CF_3, $CHCO_2Me$), 3.76 (3H, s, MeO), 3.60 (3H, s, MeO), 2.44 (3H, s, Me-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 166.5 (C), 144.2 (C), 141.4 (C), 136.0 (C), 133.3 (C), 132.8 (C), 131.2 (C), 129.6 (CH), 128.64 (CH), 128.57 (CH), 128.3 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 125.5 (CH), 125.4 (C, q, $J_{C\text{-}F}$ = 264.8 Hz), 123.7 (CH), 104.0 (CH, q, $J_{C\text{-}F}$ = 2.0 Hz), 53.0 (CH_3), 52.9 (CH_3), 51.1 (CH), 42.7

(CH, q, $J_{C\text{-}F}$ = 28.5 Hz), 21.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.0 (s, CF_3) ppm; HRMS (ESI) *m/z* 536.1346 $(M+H)^+$, $C_{26}H_{25}F_3NO_6S$ requires 536.1349.

Minor *Z*-diastereomer: ^1H NMR (300 MHz, $CDCl_3$), representative signals taken from the ^1H NMR of the diastereomer mixture, δ 8.05 (1H, s, NH), 7.87-6.94 (11H, m, Ar), 5.37 (1H, d, *J* = 11,1 Hz, =CH), 3.82 (3H, s, MeO), 3.80-3.60 (2H, m, CH-CF_3, $CHCO_2Me$), 3.68 (3H, s, MeO), 2.34 (3H, s, Me-Ar); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -69.6 (s, CF_3) ppm.

Synthetic transformations of compound 3a

Dimethyl 2-((2*S*,4*R*)-1,1,1-trifluoro-4-((4-methylphenyl)sulfonamido)-4-phenyl-butan-2-yl)malonate (4a)



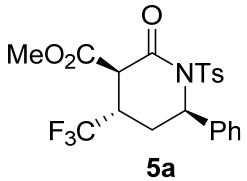
4a

To a sample of compound (*S,E*)-**3a** (52.0 mg, 0.11 mmol, *E/Z* 96:4, ee = 89%/69%), dissolved in dry CH_2Cl_2 (3.3 mL) under nitrogen atmosphere was added triethylsilane (50 μL, 0.428 mmol) followed by $BF_3{\cdot}Et_2O$ (67 μL, 0.471 mmol). Afer stirring for 48 h h at room temperature, the mixture was chromatographed on silica gel eluting with hexane:EtOAc (80:20) to give 48.1 mg (92%) of compound **4a**, as a c.a. 88:12 of two diastereomers. Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min, **(2*S*,4*R*) major diastereomer** (ee = 87%), *major enantiomer* tr = 16.4 min, *minor enantiomer* tr = 15.0 min; **(2*S*,4*S*) minor diastereomer** unresolved tr = 8.3 min. Chiralpak IC, hexane-*i*PrOH 95:05, 2 mL/min, **(2*S*,4*R*) major diastereomer**, tr > 120 min; **(2*S*,4*S*) minor diastereomer** (ee = 89%) *major enantiomer* tr = 37.6 min, *minor enantiomer* tr = 35.8 min;

(2*S*,4*R*)-4a (major): colorless oil; $[\alpha]_D^{20}$ 7.8 (*c* 0.97, $CHCl_3$) for the diastereomer mixture; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.1 Hz, Ar), 7.20-7.13 (3H, m, Ar), 7.10 (2H, d, *J* = 8.1 Hz, Ar), 7.02-7.6.90 (2H, m, Ar), 5.13 (1H, d, *J* = 8.1 Hz, NH), 4.47 (1H, q, *J* = 7.8 Hz, CHPh), 3.73 (3H, s, MeO), 3.69 (1H, d, *J* = 5.4 Hz, $CHCO_2Me$), 2.83 (1H, m, $CHCF_3$), 2.34 (3H, s, Me-Ar), 2.32-2.10 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 167.0 (C), 143.1 (C), 138.8 (C), 137.2 (C), 129.3 (CH), 128.6 (CH), 128.5 (C), 127.9 (CH), 127.0 (CH), 126.8 (CH), 126.6 (C, q, $J_{C\text{-}F}$ = 278 Hz), 56.4 (CH), 53.1 (CH_3), 52.8 (CH_3), 49.9 (CH), 40.0 (CH, q, $J_{C\text{-}F}$ = 26.8 Hz), 33.4 (CH_2), 21.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -68.5 (s, CF_3) ppm; HRMS (ESI) *m/z* 488.1357 $(M+H)^+$, $C_{22}H_{25}F_3NO_6S$ requires 488.1349.

(2*S*,4*S*)-4a (minor): ^{1}H NMR (300 MHz, $CDCl_3$), representative signals taken from the diastereomer mixture δ 7.58 (2H, d, *J* = 8.4 Hz, Ar), 7.40-6.90 (7H, m, Ar), 5.95 (1H, d, *J* = 6.9 Hz, NH), 4.45 (1H, m, CHPh), 3.81 (3H, s, MeO), 3.72 (3H, s, MeO), 2.83 (1H, m, $CHCF_3$), 2.34 (3H, s, Me-Ar), 2.32-2.10 (2H, m, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -70.1 (s, CF_3) ppm.

Methyl (3*R*,4*S*,6*R*)-2-oxo-6-phenyl-1-tosyl-4-(trifluoromethyl)piperidine-3-carboxylate.



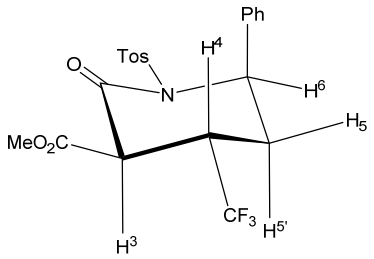
5a

A 25% solution of tetraethylammonium hydroxyde in MeOH (24 μL, 0.14 mmol) was added to a solution of compound **4a** (28.0 mg, 0.037 mmol, ee = 87%) in dimethylsulfoxide (1.6 mL) under nitrogen, and the reaction flask was introduced in a bath at 80 °C. After 14 h, the reaction mixture was diluted with EtOAc (75 mL), washed with water (5 × 5 mL), brine (5 mL), and dried over $MgSO_4$. Purification by column chromatography eluting with hexane:EtOAc (80:20) gave 13.2 mg (78%) of compound **5a**. Chiral HPLC analysis: Lux Amylose-1, hexane-*i*PrOH 90:10, 1 mL/min,

major enantiomer tr = 24.0 min, *minor enantiomer* tr = 22.1 min. White solid, m.p. 177-179 °C (hexane-EtOAc); $[\alpha]_D^{20}$ -4.5 (*c* 1.0, $CHCl_3$, ee = 87%); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.5 Hz, Ar), 7.40-7.32 (3H, m, Ar), 7.20-7.14 (4H, m, Ar), 5.93 (1H, t, J = 3.8 Hz, CH-Ph), 3.78 (3H, s, OMe), 3.65 (1H, d, *J* = 11.4 Hz, $CHCO_2Me$), 3.11 (1H, m, $CHCF_3$), 2.40 (3H, s, Me-Ar), 2.35-2.28 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C), 164.3 (C), 145.4 (C), 138.1 (C), 134.5 (C), 129.7 (CH), 129.0 (CH), 128.5 (C), 126.5 (CH), 125.6 (C, q, J_{C-F} = 278 Hz), 58.3 (CH), 53.4 (CH_3), 52.8 (CH_3), 50.2 (CH), 37.1 (CH, q, J_{C-F} = 28.5 Hz), 29.9 (CH_2), 21.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ = -73.1 (s, CF_3) ppm; HRMS (ESI) *m/z* 456.1087 $(M+H)^+$, $C_{21}H_{21}F_3NO_5S$ requires 456.1077.

Determination of the relative stereochemistry of compounds 4a and 5a

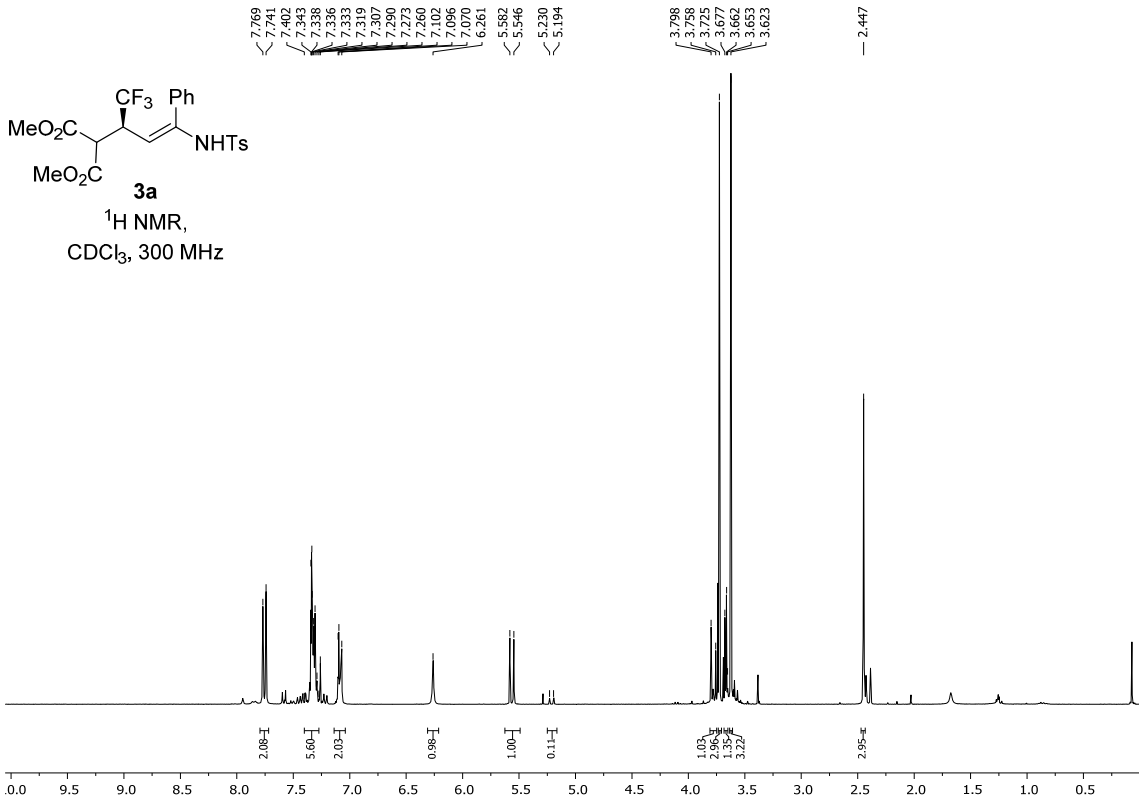
The relative stereochemistry of compound **5a**, and hence, of its precursor, the major diastereomer of compound **4a**, was established considering the coupling constants of the ring-attached protons (see figure):

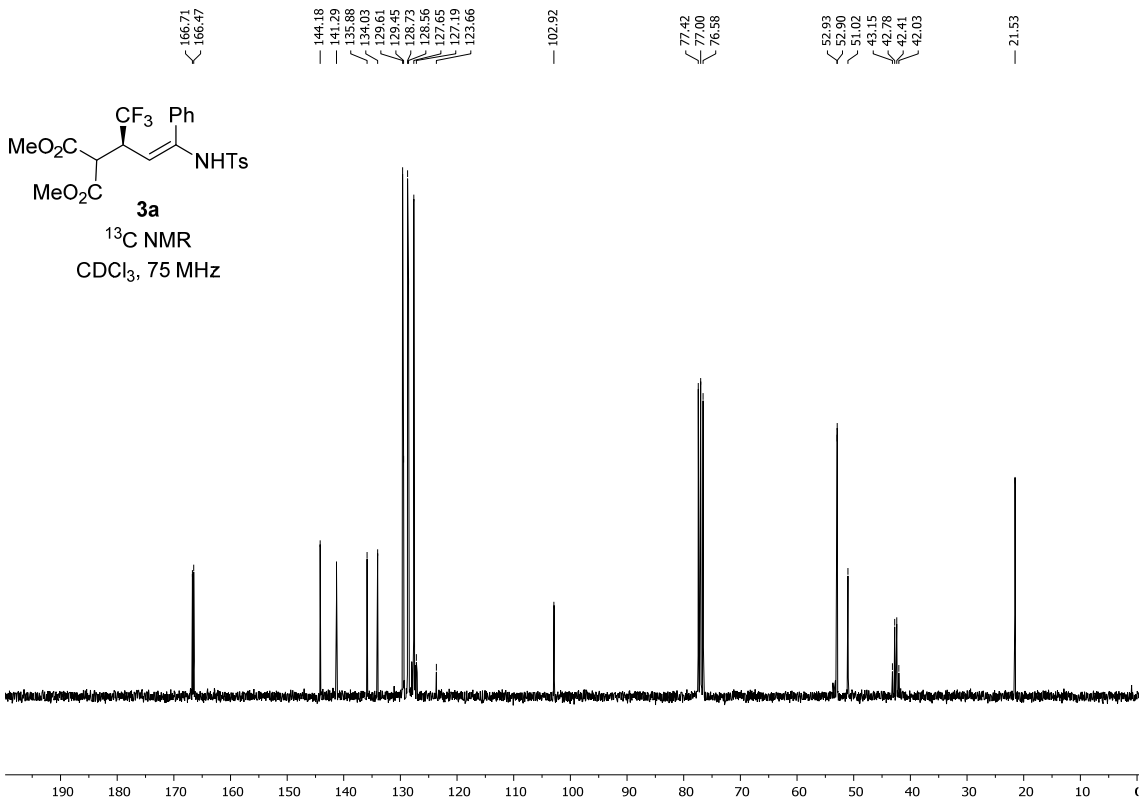


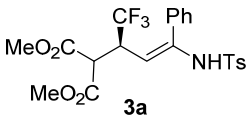
H6 5.93 ppm (t) $J_{6,5}$ = 3.8 Hz (eq-eq), $J_{6,5'}$ = 3.8 Hz (eq-ax)
H3 3.65 ppm (d) $J_{3,4}$ =11.4 Hz (ax-ax),

Figure S1. Coupling constants in compound **5a**

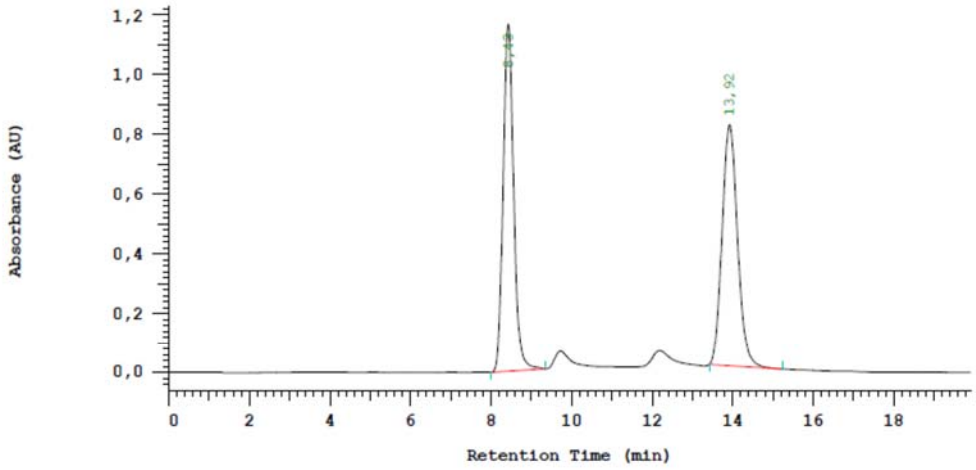
1 D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M.Z. Slawin, T. J. C. O'Riordan, A. D. Smith, *Angew. Chem.Int. Ed.* **2013**, *52*, 11642.


7.769
7.741
7.402
7.343
7.338
7.336
7.333
7.319
7.307
7.290
7.273
7.260
7.102
7.096
7.070
6.261
5.582
5.546
5.230
5.194
3.798
3.758
3.725
3.677
3.662
3.653
3.623
2.447
CF3 Ph
MeO2C
NHTs
MeO2C
3a
1H NMR,
CDCl3, 300 MHz
2.08
5.60
2.03
0.98
1.00
0.11
1.03
2.96
1.35
3.22
2.95
0.0 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

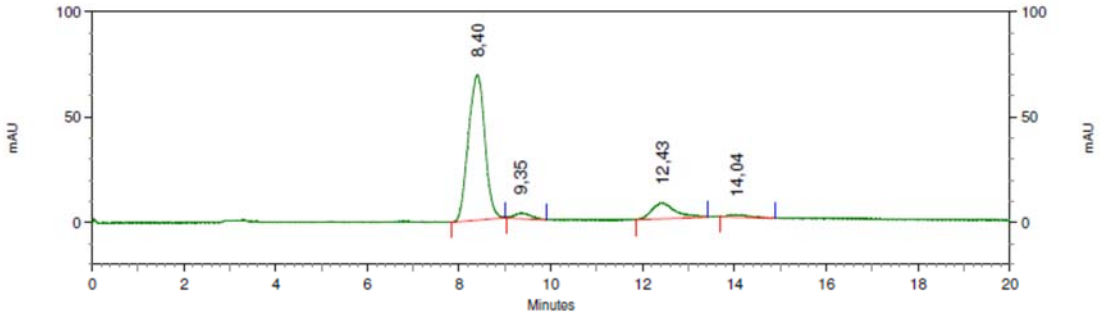

166.71
166.47
144.18
141.29
135.88
134.03
129.61
129.45
128.73
128.56
127.65
127.19
123.66
102.92
77.42
77.00
76.58
52.93
52.90
51.02
43.15
42.78
42.41
42.03
21.53
CF3 Ph
MeO2C
NHTs
MeO2C
3a
13C NMR
CDCl3, 75 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10



3a

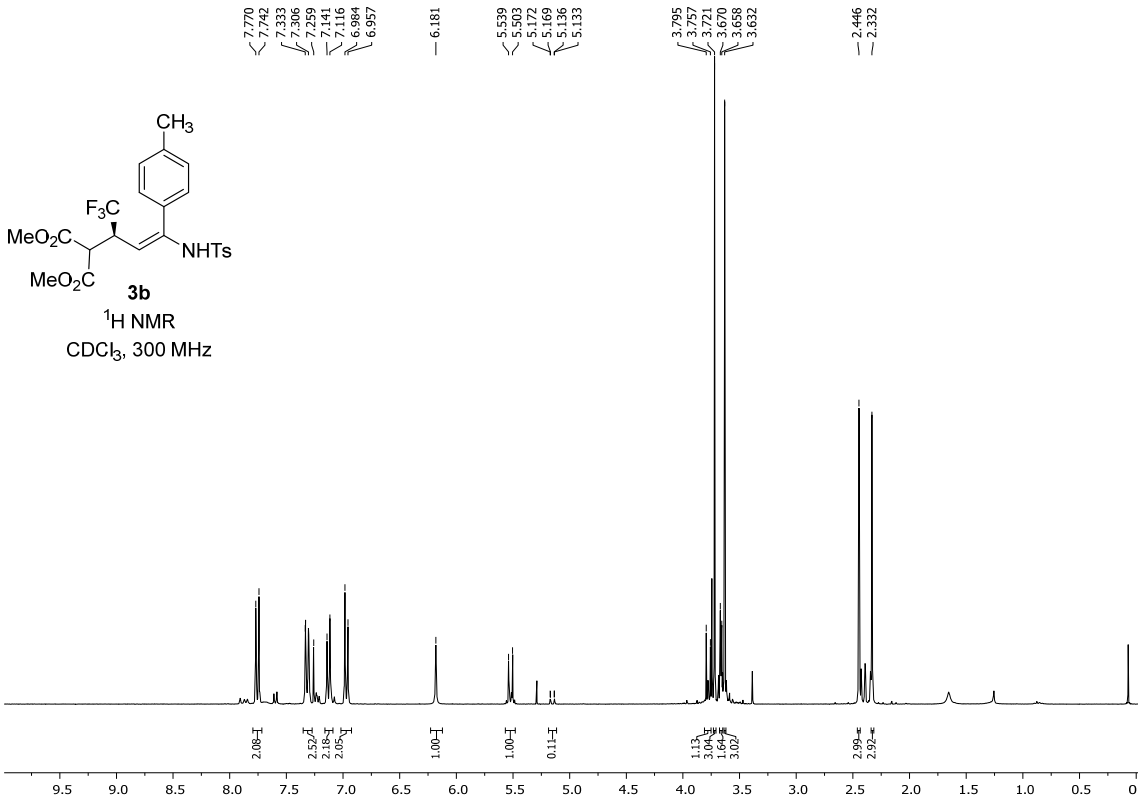


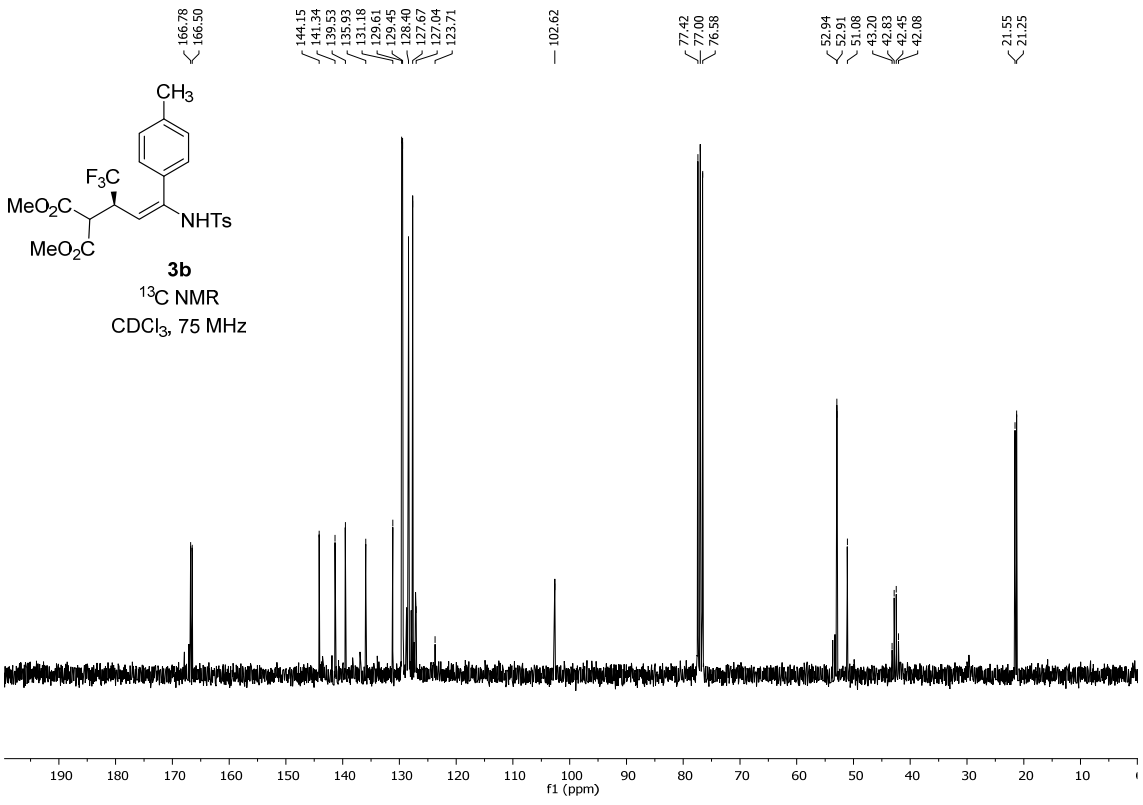
No.	RT	Area	Area %	Name
1	8,43	10584244	49,555	
2	13,92	10774280	50,445	
		21358524	100,000	

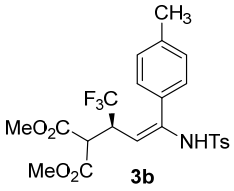


6: 280 nm, 4 nm Results

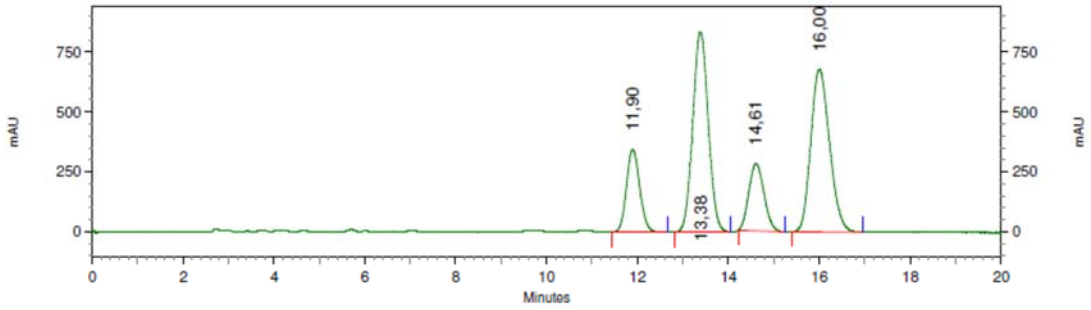
Retention Time	Area	Area Percent
8,40	6869947	81,639
9,35	281947	3,351
12,43	1096977	13,036
14,04	166126	1,974


7.770
7.742
7.333
7.306
7.259
7.141
7.116
6.984
6.957
6.181
5.539
5.503
5.172
5.169
5.136
5.133
3.795
3.757
3.721
3.670
3.658
3.632
2.446
2.332
CH3
F3C
MeO2C
NHTs
MeO2C
3b
1H NMR
CDCl3, 300 MHz
2.08
2.52
2.18
2.05
1.00
1.00
0.11
1.13
3.04
1.64
3.02
2.99
2.92
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


166.78
166.50
144.15
141.34
139.53
135.93
131.18
129.61
129.45
128.40
127.67
127.04
123.71
102.62
77.42
77.00
76.58
52.94
52.91
51.08
43.20
42.83
42.45
42.08
21.55
21.25
CH3
F3C
MeO2C
NHTs
MeO2C
3b
13C NMR
CDCl3, 75 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

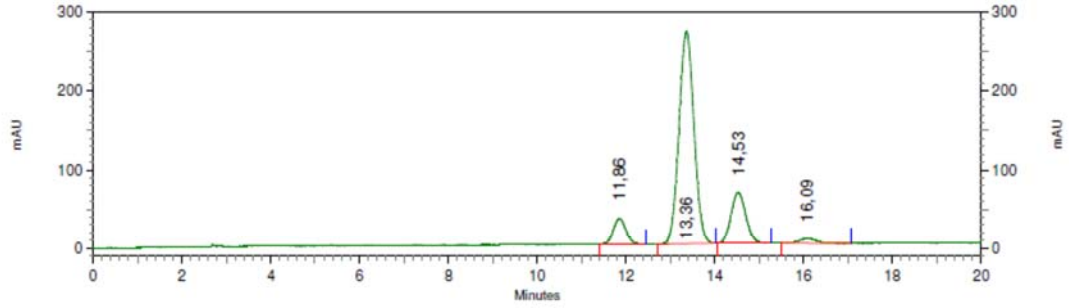


3b



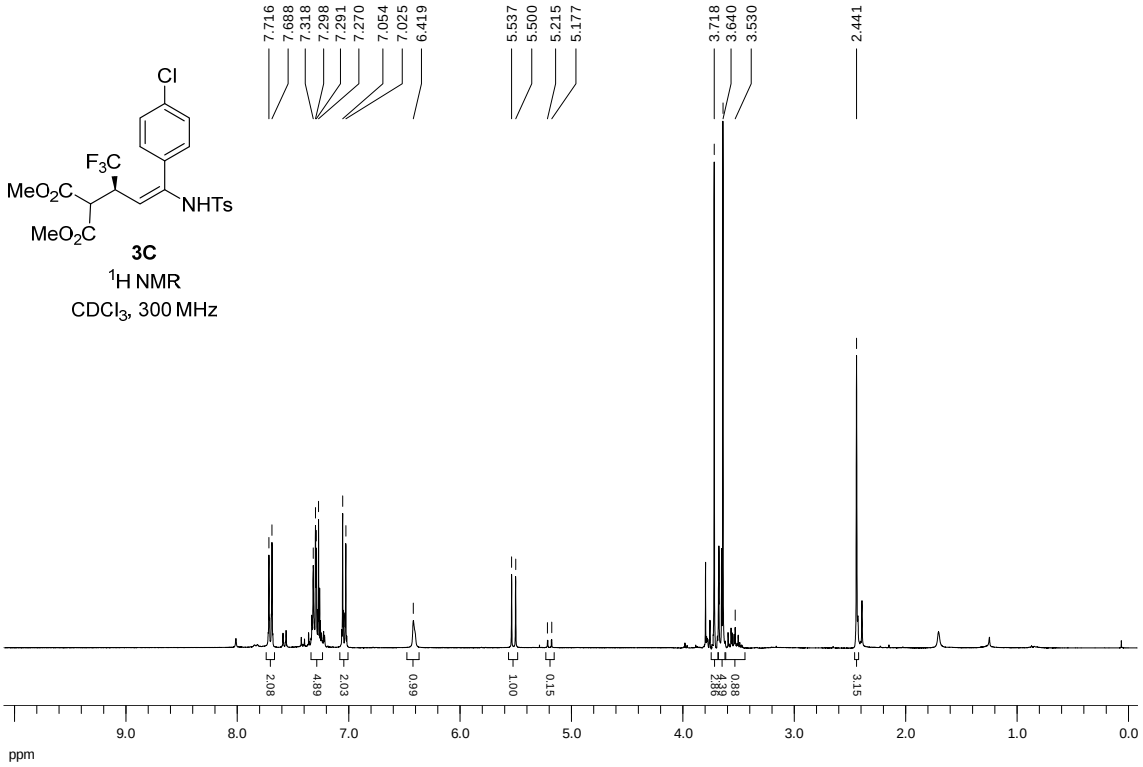
3: 240 nm, 4 nm Results

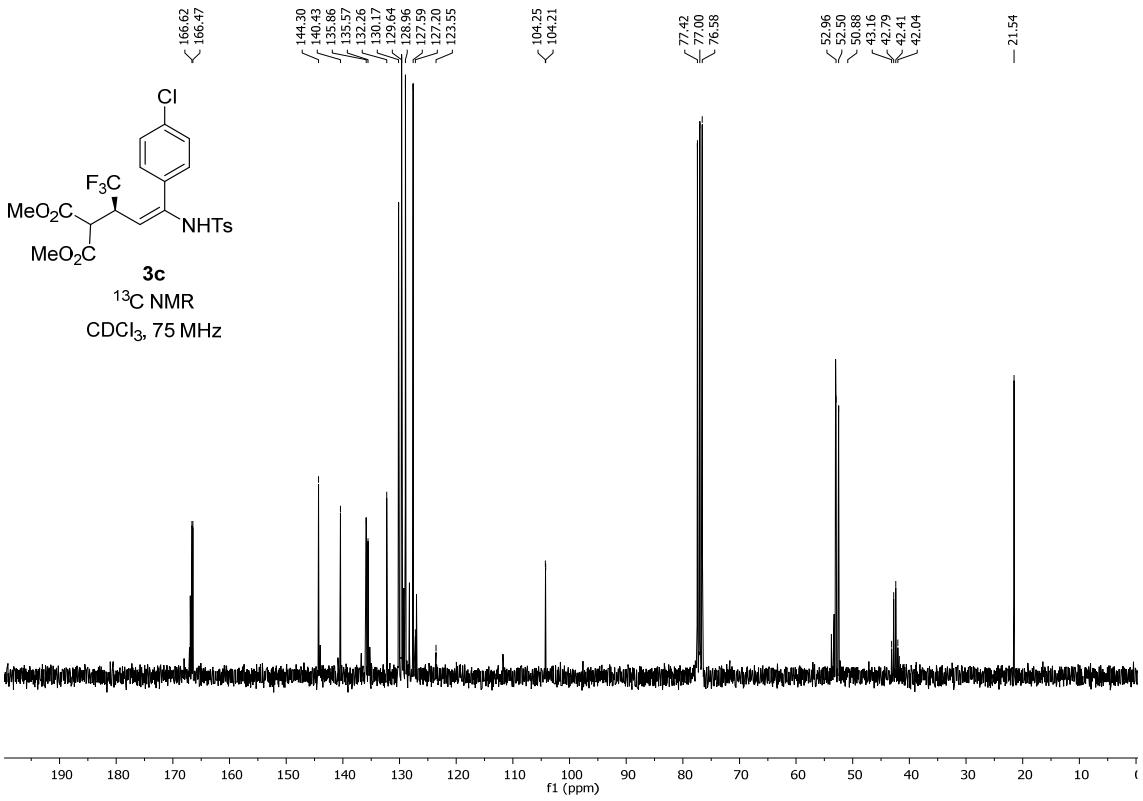
Retention Time	Area	Area Percent
11,90	28064804	13,267
13,38	79174978	37,428
14,61	26352385	12,458
16,00	77944696	36,847

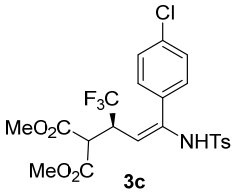


7: 270 nm, 4 nm Results

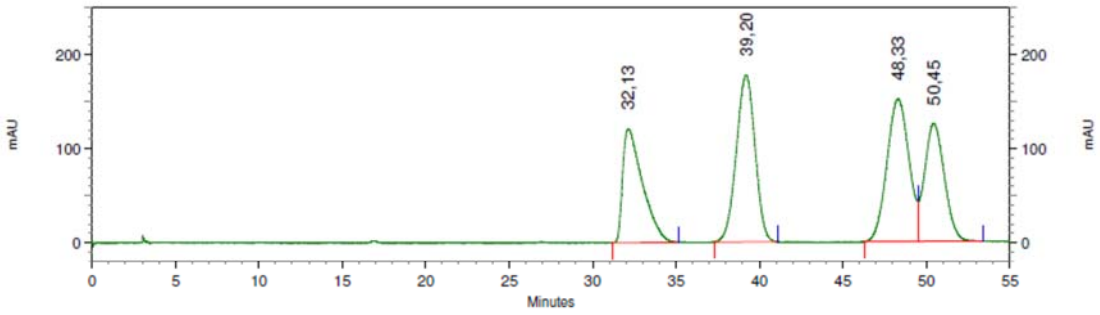
Retention Time	Area	Area Percent
11,86	2621585	7,556
13,36	25321055	72,982
14,53	6091668	17,558
16,09	660655	1,904


7.716
7.688
7.318
7.298
7.291
7.270
7.054
7.025
6.419
5.537
5.500
5.215
5.177
3.718
3.640
3.530
2.441
Cl
F3C
MeO2C
NHTs
MeO2C
3C
1H NMR
CDCl3, 300 MHz
2.08
4.89
2.03
0.99
1.00
0.15
4.89
4.86
0.88
3.15
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm


166.62
166.47
144.30
140.43
135.86
135.57
132.26
130.17
129.64
128.96
127.59
127.20
123.55
104.25
104.21
77.42
77.00
76.58
52.96
52.50
50.88
43.16
42.79
42.41
42.04
21.54
Cl
F3C
MeO2C
NHTs
MeO2C
3c
13C NMR
CDCl3, 75 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

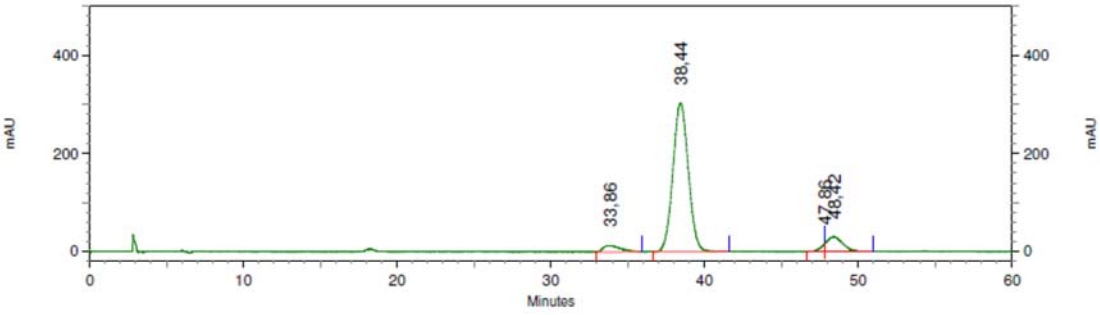


3c



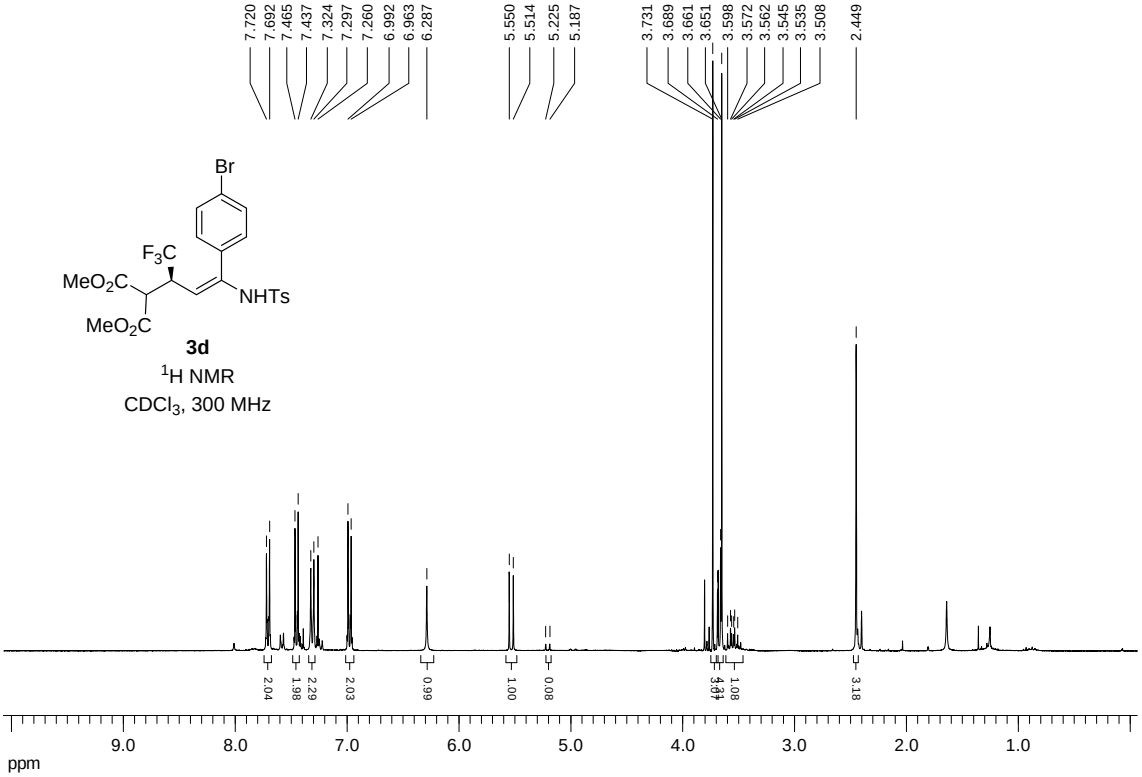
13: 250 nm, 4 nm
Results

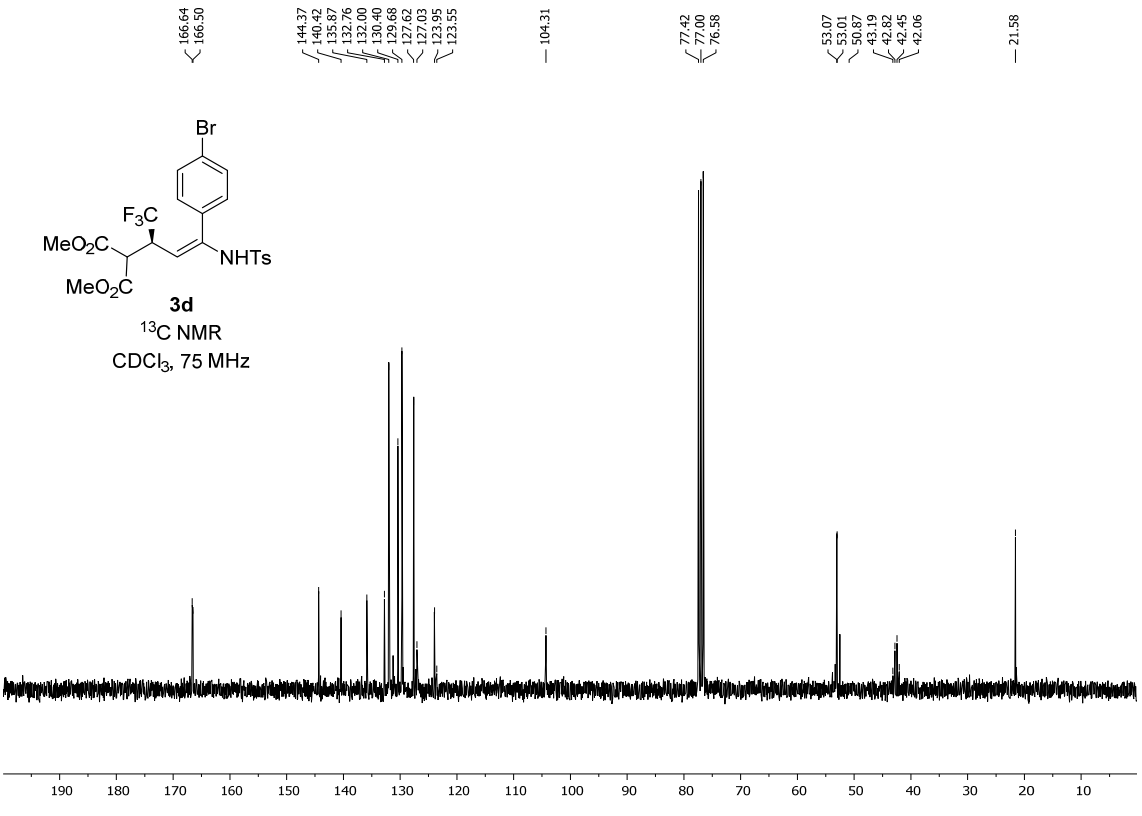
Retention Time	Area	Area Percent
32,13	40066660	20,800
39,20	55590059	28,859
48,33	55632362	28,881
50,45	41336988	21,460

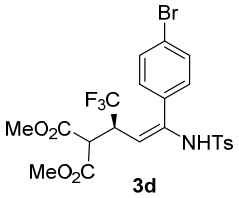


12: 220 nm, 4 nm
Results

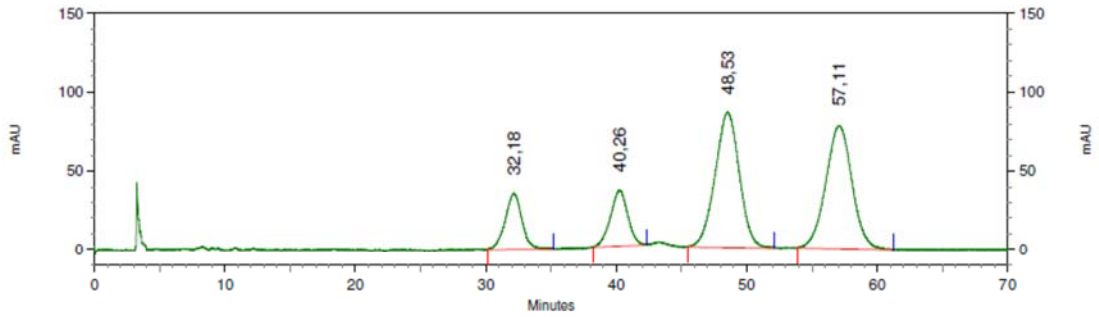
Retention Time	Area	Area Percent
33,86	4277468	4,322
38,44	84913788	85,800
47,86	1448248	1,463
48,42	8327505	8,414


7.720
7.692
7.465
7.437
7.324
7.297
7.260
6.992
6.963
6.287
5.550
5.514
5.225
5.187
3.731
3.689
3.661
3.651
3.598
3.572
3.562
3.545
3.535
3.508
2.449
Br
F3C
MeO2C
NHTs
MeO2C
3d
1H NMR
CDCl3, 300 MHz
2.04
1.88
2.22
2.03
0.96
1.00
0.80
3.07
1.08
3.18
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm


166.64
166.50
144.37
140.42
135.87
132.76
132.00
130.40
129.68
127.62
127.03
123.95
123.55
104.31
77.42
77.00
76.58
53.07
53.01
50.87
43.19
42.82
42.45
42.06
21.58
Br
F3C
MeO2C
NHTs
MeO2C
3d
13C NMR
CDCl3, 75 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

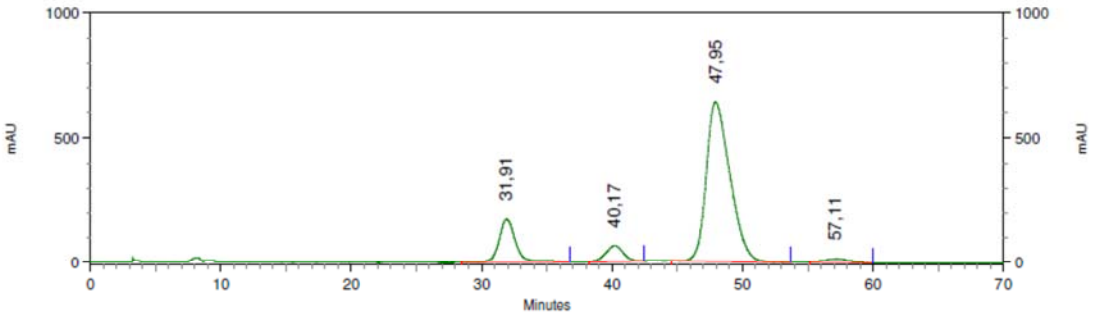


3d



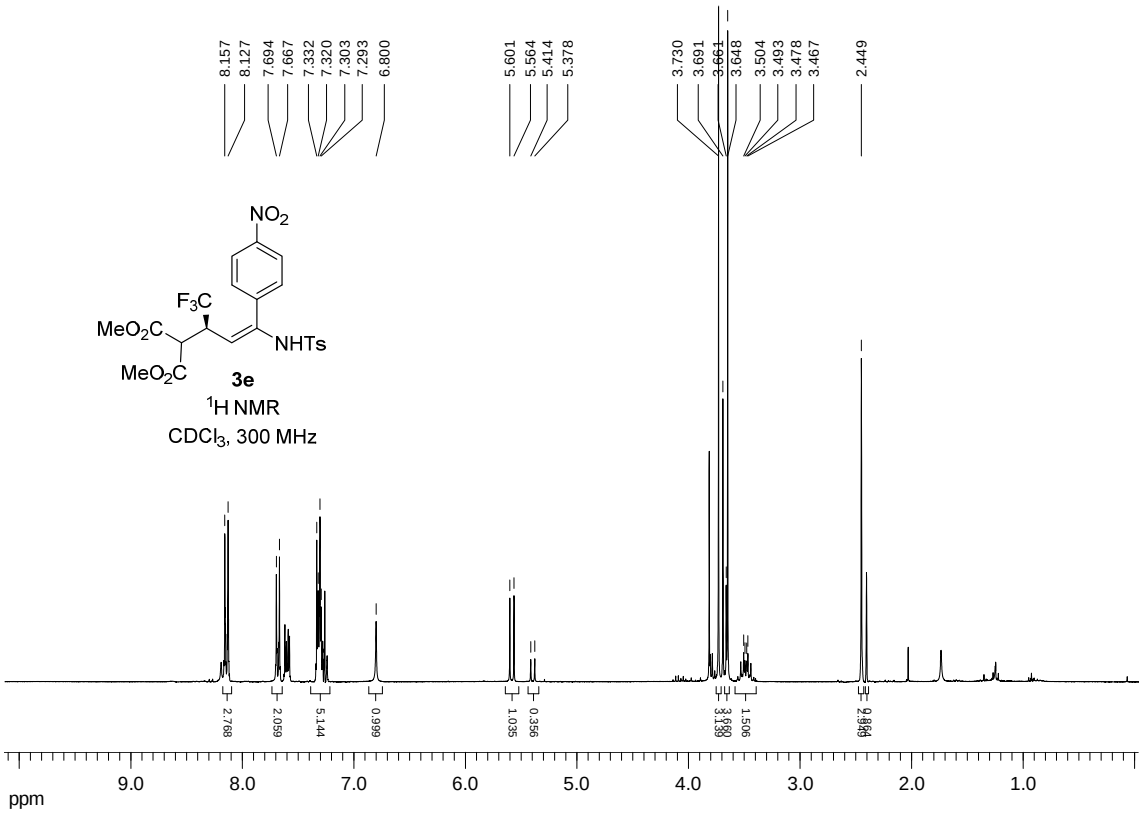
3: 220 nm, 4 nm Results

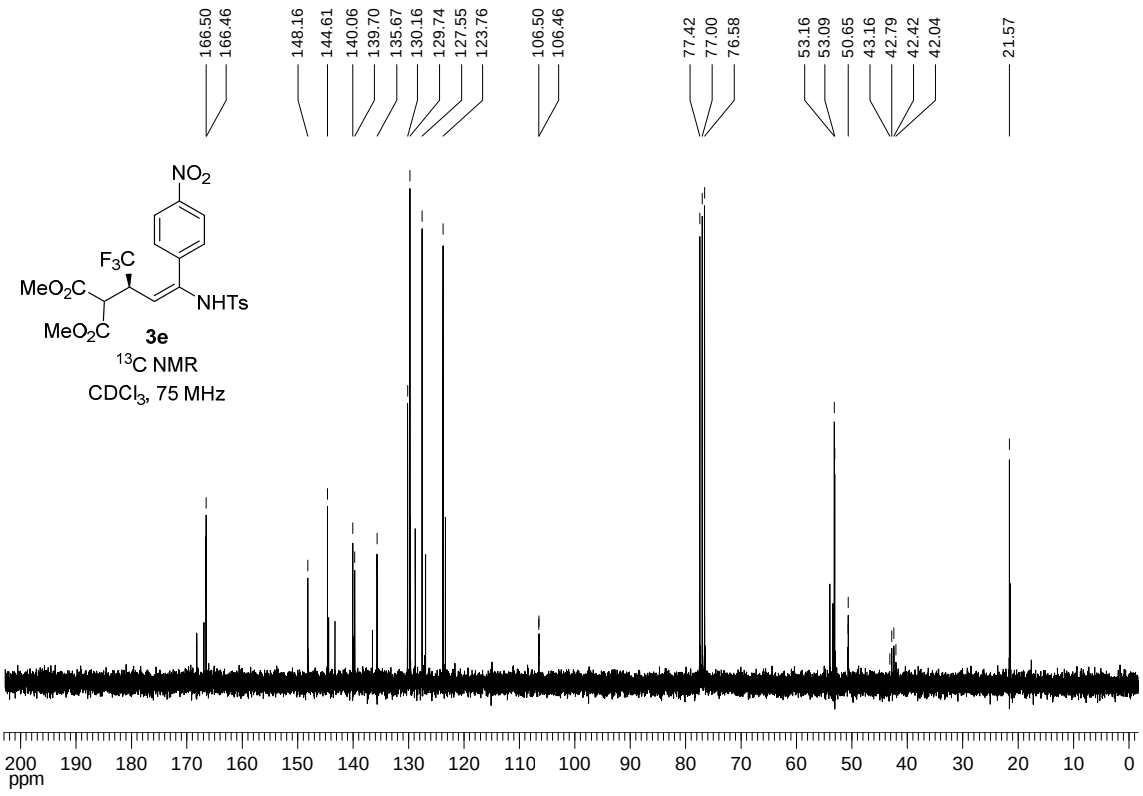
Retention Time	Area	Area Percent
32,18	12831961	11,192
40,26	13210649	11,523
48,53	44536148	38,845
57,11	44070703	38,440

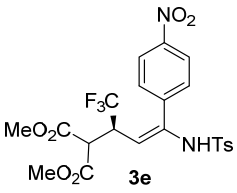


2: 240 nm, 4 nm Results

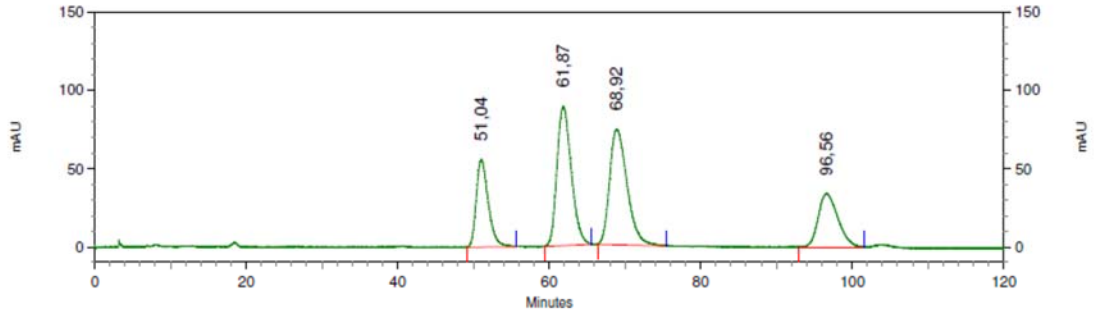
Retention Time	Area	Area Percent
31,91	61799367	14,738
40,17	24333799	5,803
47,95	325343204	77,586
57,11	7855823	1,873


8.157
8.127
7.694
7.667
7.332
7.320
7.303
7.293
6.800
5.601
5.564
5.414
5.378
3.730
3.691
3.661
3.648
3.504
3.493
3.478
3.467
2.449
NO2
F3C
MeO2C
NHTs
MeO2C
3e
1H NMR
CDCl3, 300 MHz
2.78
2.09
5.14
0.99
1.04
0.36
3.17
1.51
9.00
ppm
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


166.50
166.46
148.16
144.61
140.06
139.70
135.67
130.16
129.74
127.55
123.76
106.50
106.46
77.42
77.00
76.58
53.16
53.09
50.65
43.16
42.79
42.42
42.04
21.57
NO2
F3C
MeO2C
NHTs
MeO2C
3e
13C NMR
CDCl3, 75 MHz
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

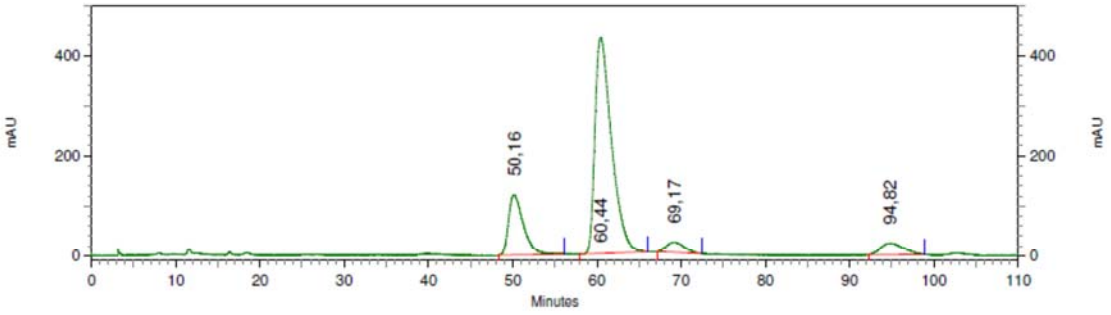


3e



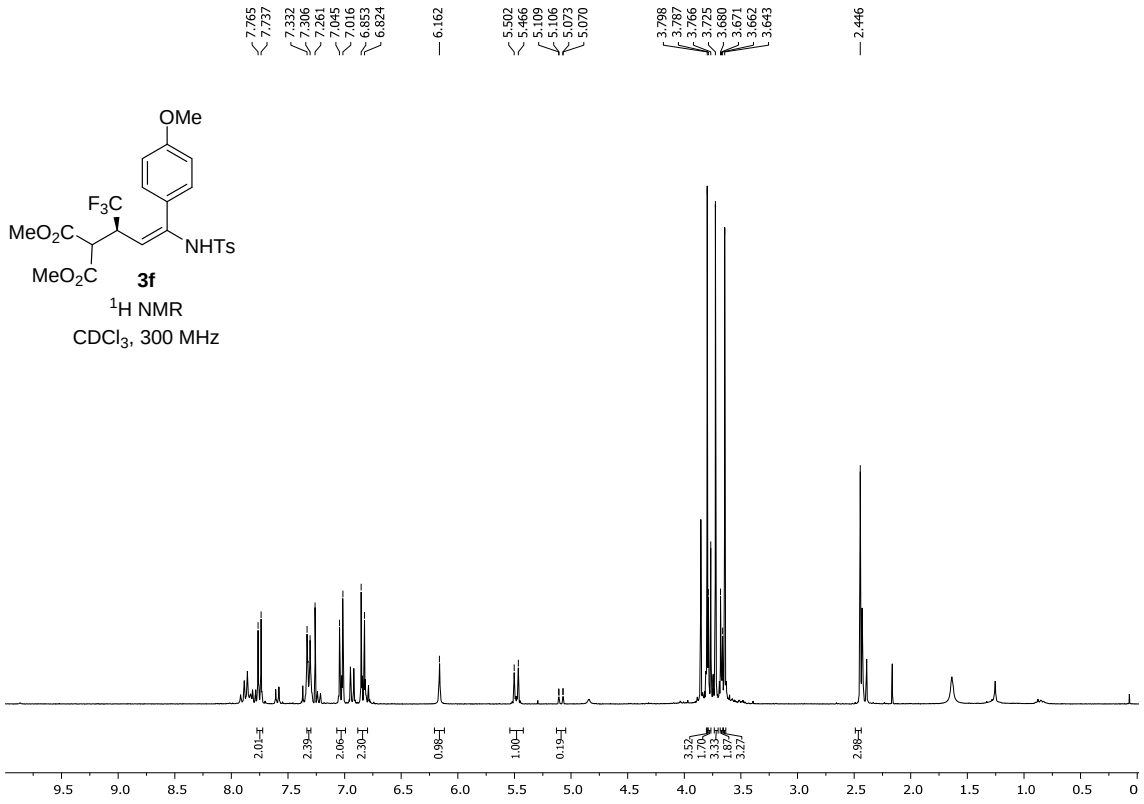
2: 250 nm, 4 nm Results

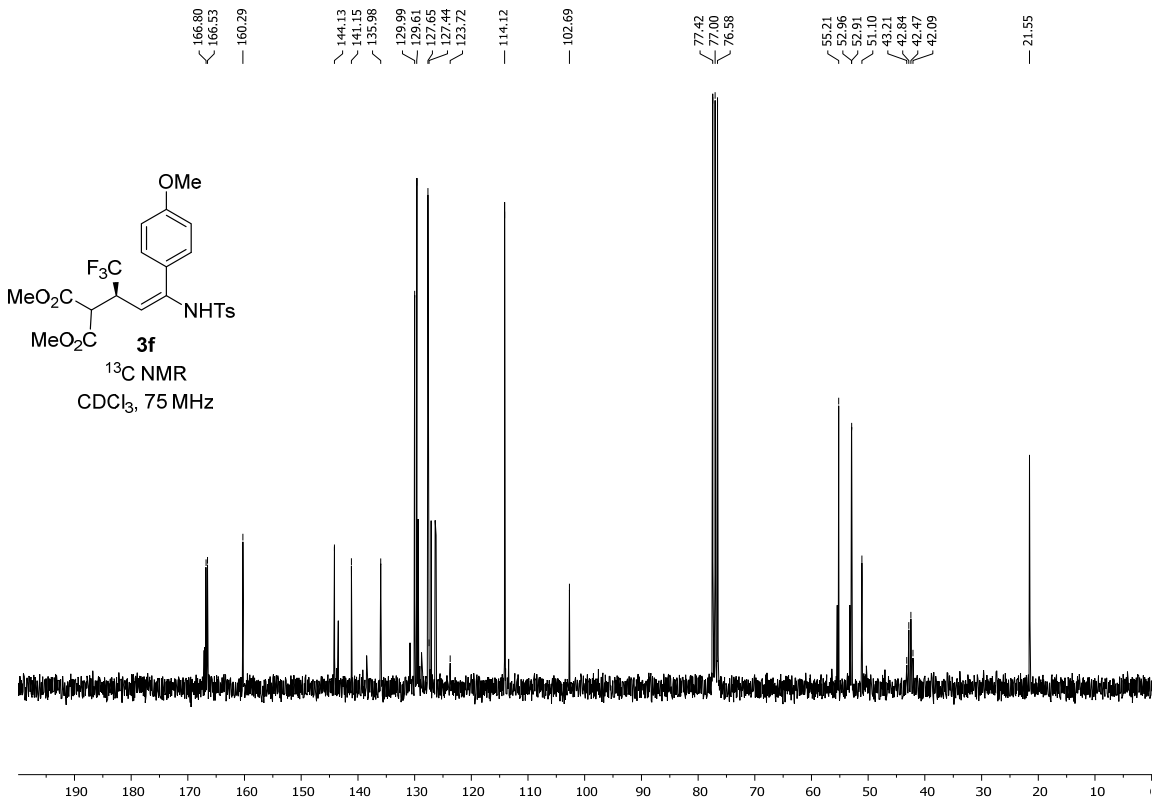
Retention Time	Area	Area Percent
51,04	24653841	17,171
61,87	46674020	32,507
68,92	47423624	33,029
96,56	24830845	17,294

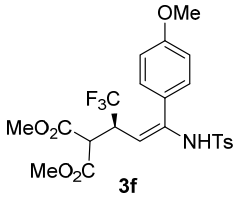


2: 250 nm, 4 nm Results

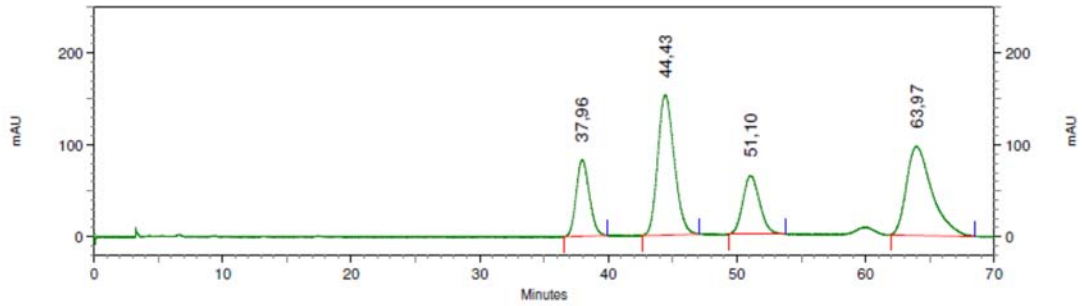
Retention Time	Area	Area Percent
50,16	60239223	18,377
60,44	237092235	72,329
69,17	12432840	3,793
94,82	18034406	5,502


OMe
F3C
MeO2C
NHTs
MeO2C
3f
1H NMR
CDCl3, 300 MHz


OMe
F3C
MeO2C
NHTs
MeO2C
3f
13C NMR
CDCl3, 75 MHz

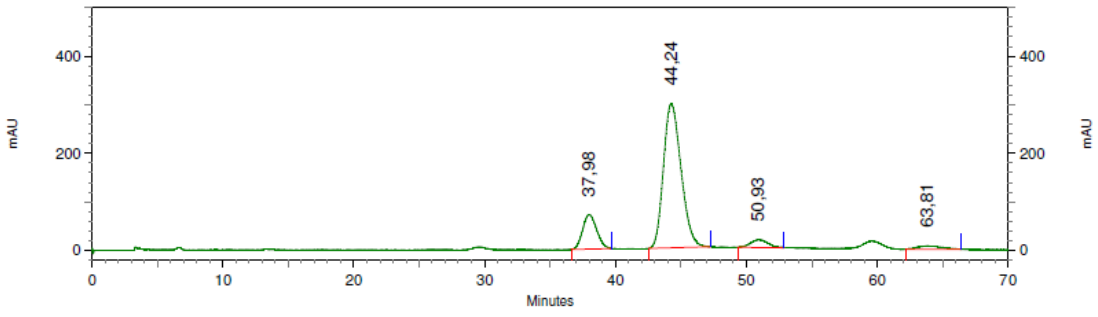


3f



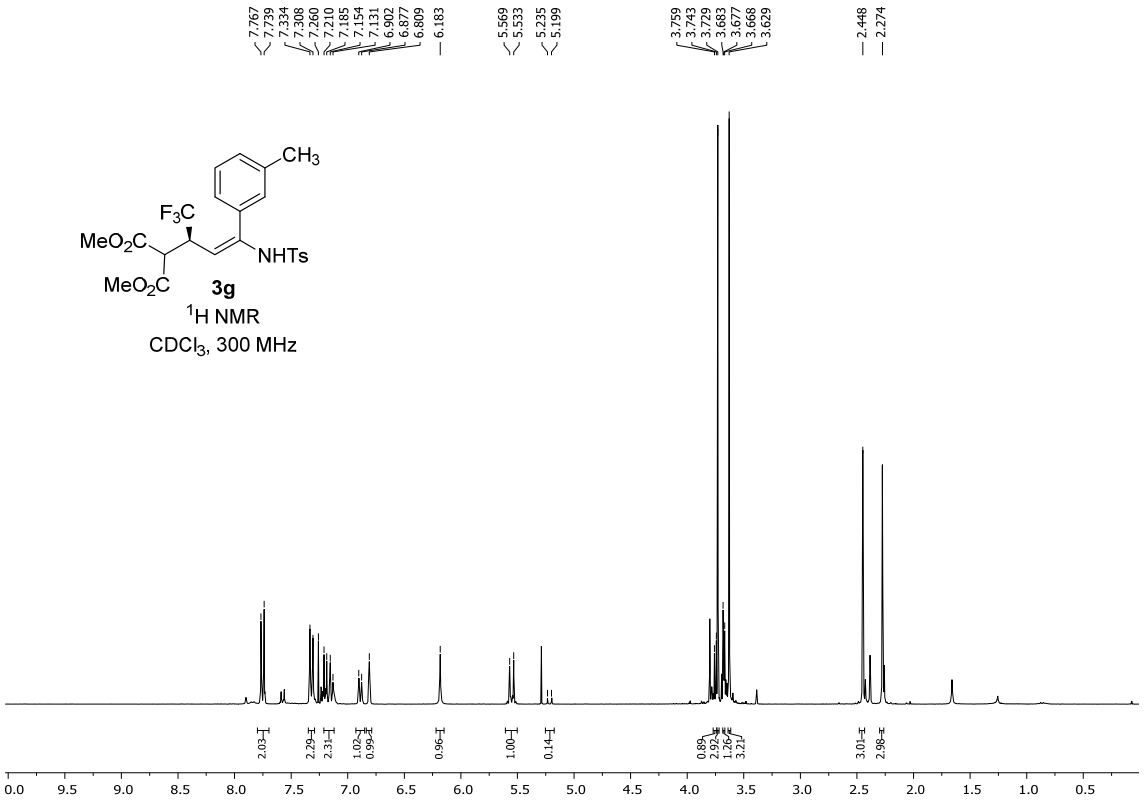
13: 250 nm, 4 nm
Results

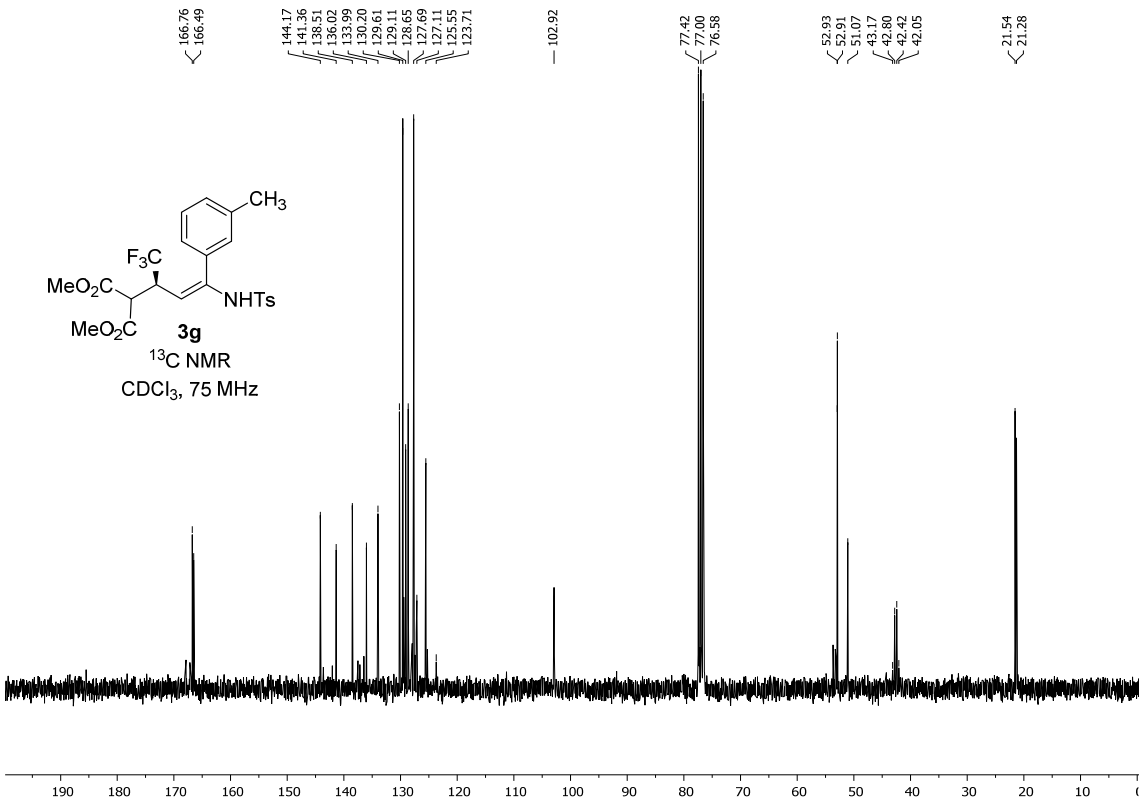
Retention Time	Area	Area Percent
37,96	23906621	15,390
44,43	54493135	35,081
51,10	23247941	14,966
63,97	53687149	34,562

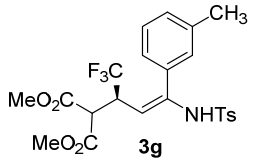


13: 250 nm, 4 nm
Results

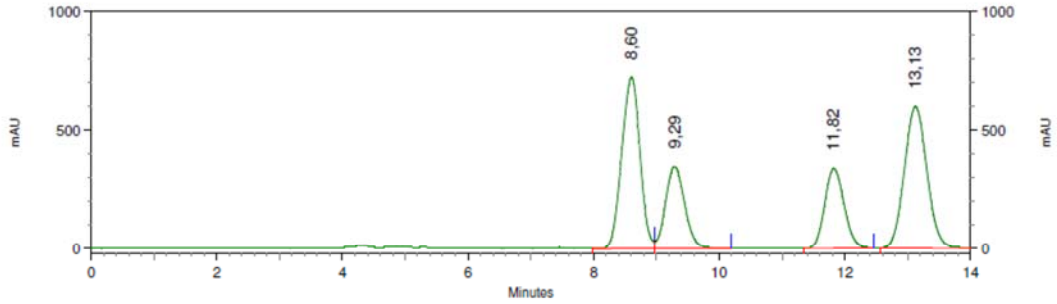
Retention Time	Area	Area Percent
37,98	21218148	14,931
44,24	111411062	78,400
50,93	5991092	4,216
63,81	3486368	2,453


7.767
7.739
7.334
7.308
7.260
7.210
7.185
7.154
7.131
6.902
6.877
6.809
6.183
5.569
5.533
5.235
5.199
3.759
3.743
3.729
3.683
3.677
3.668
3.629
2.448
2.274
CH3
F3C
MeO2C
NHTs
MeO2C
3g
1H NMR
CDCl3, 300 MHz
2.03
2.29
2.31
1.02
0.99
0.96
1.00
0.14
0.88
2.92
1.26
3.21
3.01
2.98
0.0 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


166.76
166.49
144.17
141.36
138.51
136.02
133.99
130.20
129.61
129.11
128.65
127.69
127.11
125.55
123.71
102.92
77.42
77.00
76.58
52.93
52.91
51.07
43.17
42.80
42.42
42.05
21.54
21.28
CH3
F3C
MeO2C
NHTs
MeO2C
3g
13C NMR
CDCl3, 75 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

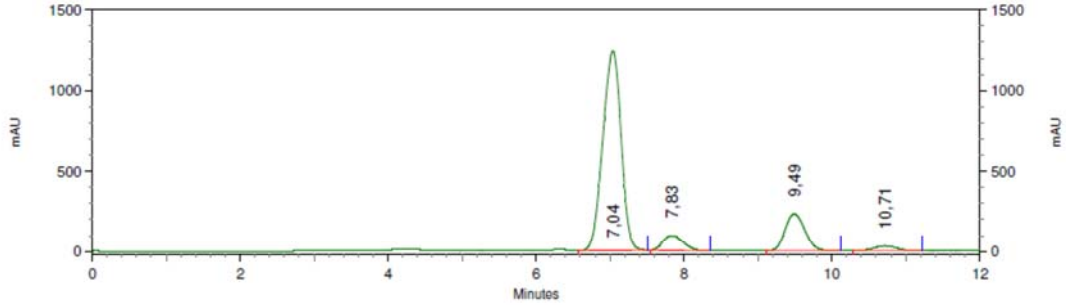


3g



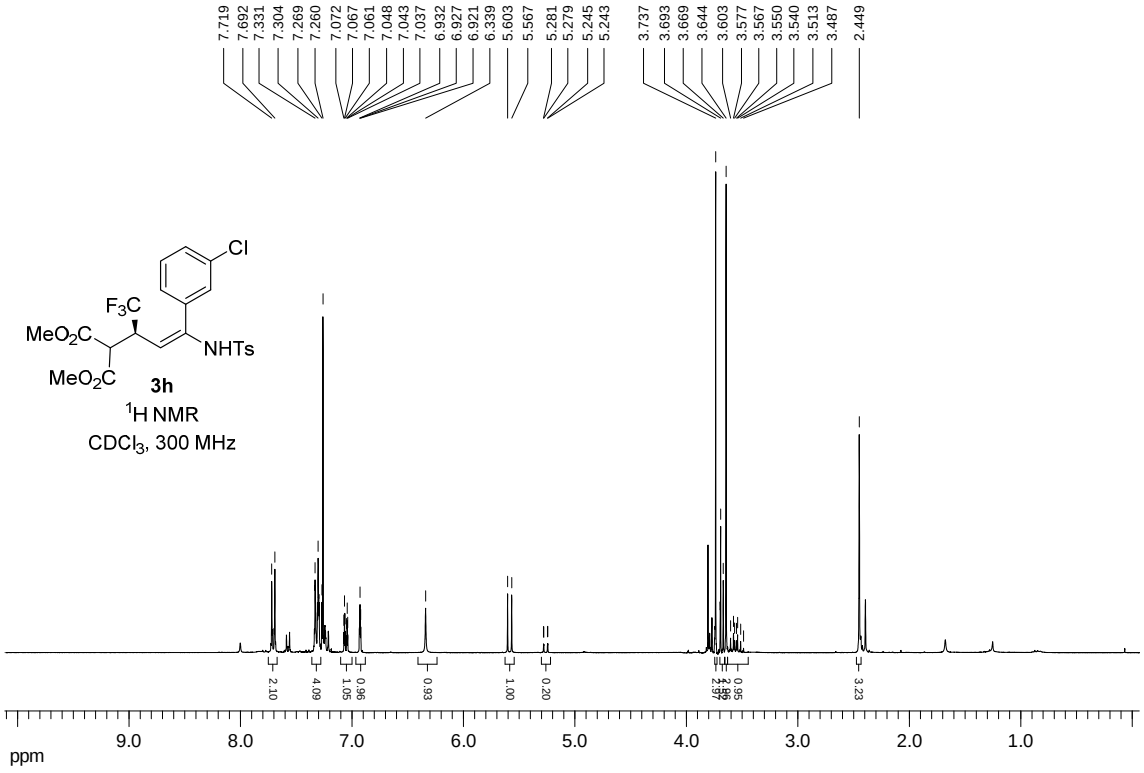
5: 250 nm, 4 nm Results

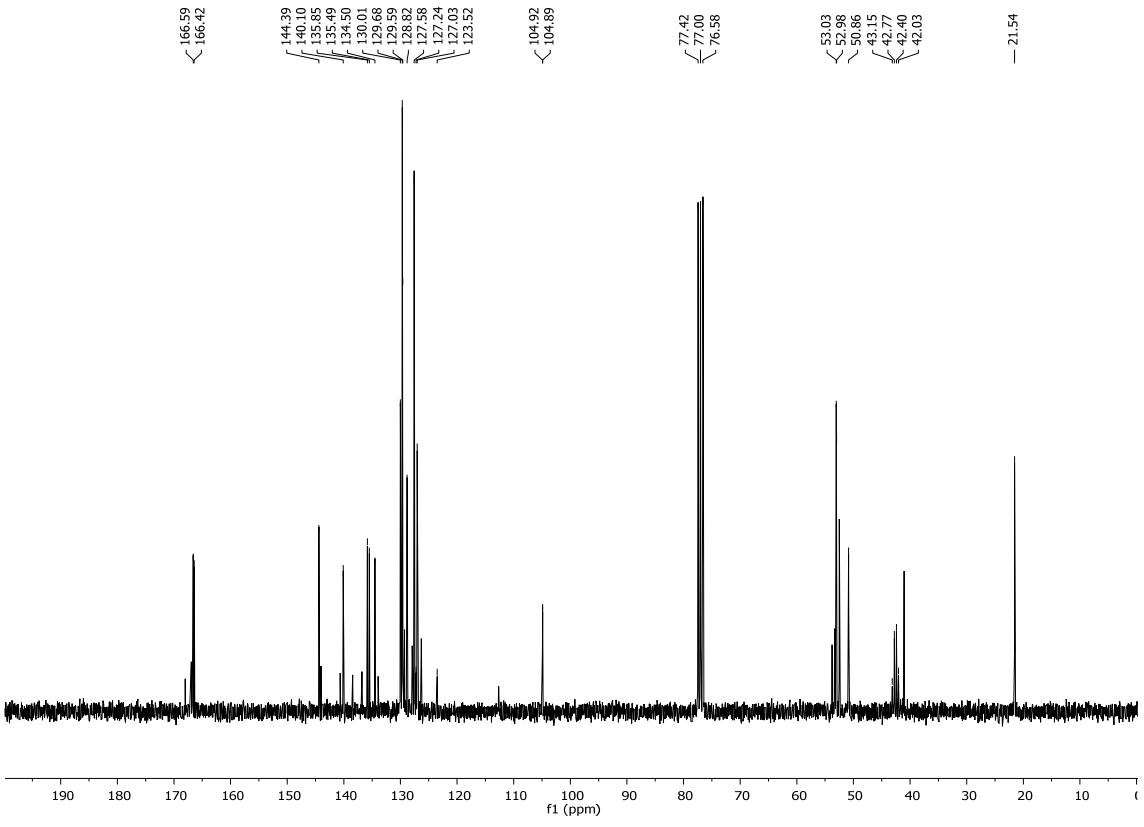
Retention Time	Area	Area Percent
8,60	58401268	32,954
9,29	29577670	16,690
11,82	29173969	16,462
13,13	60066740	33,894

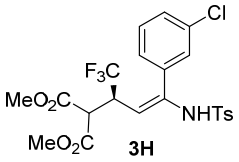


7: 260 nm, 4 nm Results

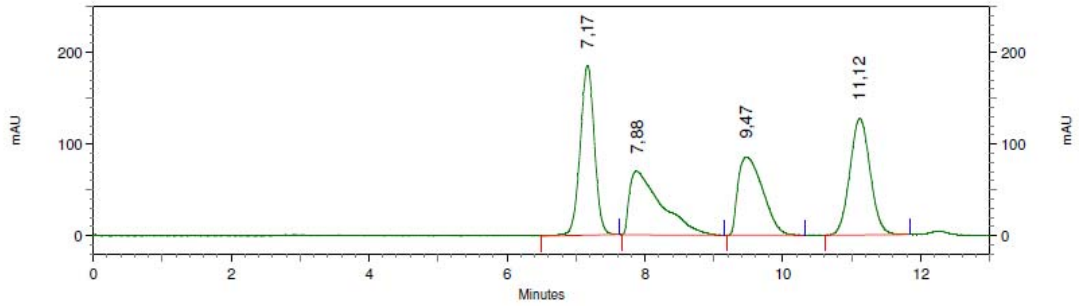
Retention Time	Area	Area Percent
7,04	85744726	75,785
7,83	7274374	6,429
9,49	17477257	15,447
10,71	2646307	2,339


7.719
7.692
7.331
7.304
7.269
7.260
7.072
7.067
7.061
7.048
7.043
7.037
6.932
6.927
6.921
6.339
5.603
5.567
5.281
5.279
5.245
5.243
3.737
3.693
3.669
3.644
3.603
3.577
3.567
3.550
3.540
3.513
3.487
2.449
Cl
F3C
MeO2C
NHTs
MeO2C
3h
1H NMR
CDCl3, 300 MHz
2.10
4.09
1.05
0.96
0.93
1.00
0.20
0.95
3.32
ppm
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


166.59
166.42
144.39
140.10
135.85
135.49
134.50
130.01
129.68
129.59
128.82
127.58
127.24
127.03
123.52
104.92
104.89
77.42
77.00
76.58
53.03
52.98
50.86
43.15
42.77
42.40
42.03
21.54
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

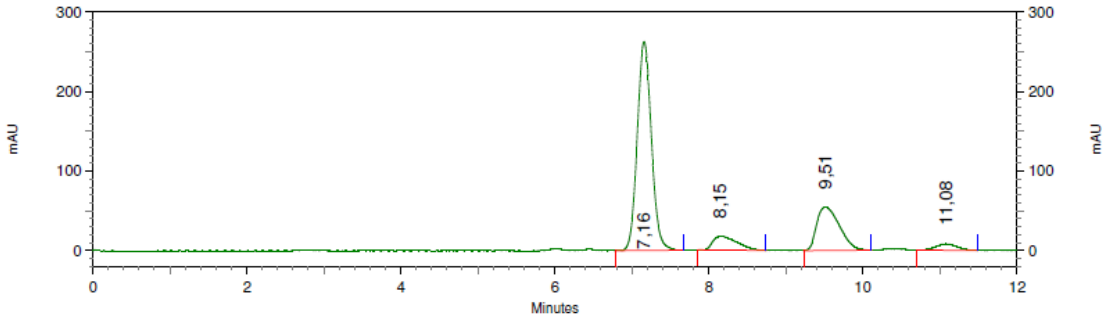


3H



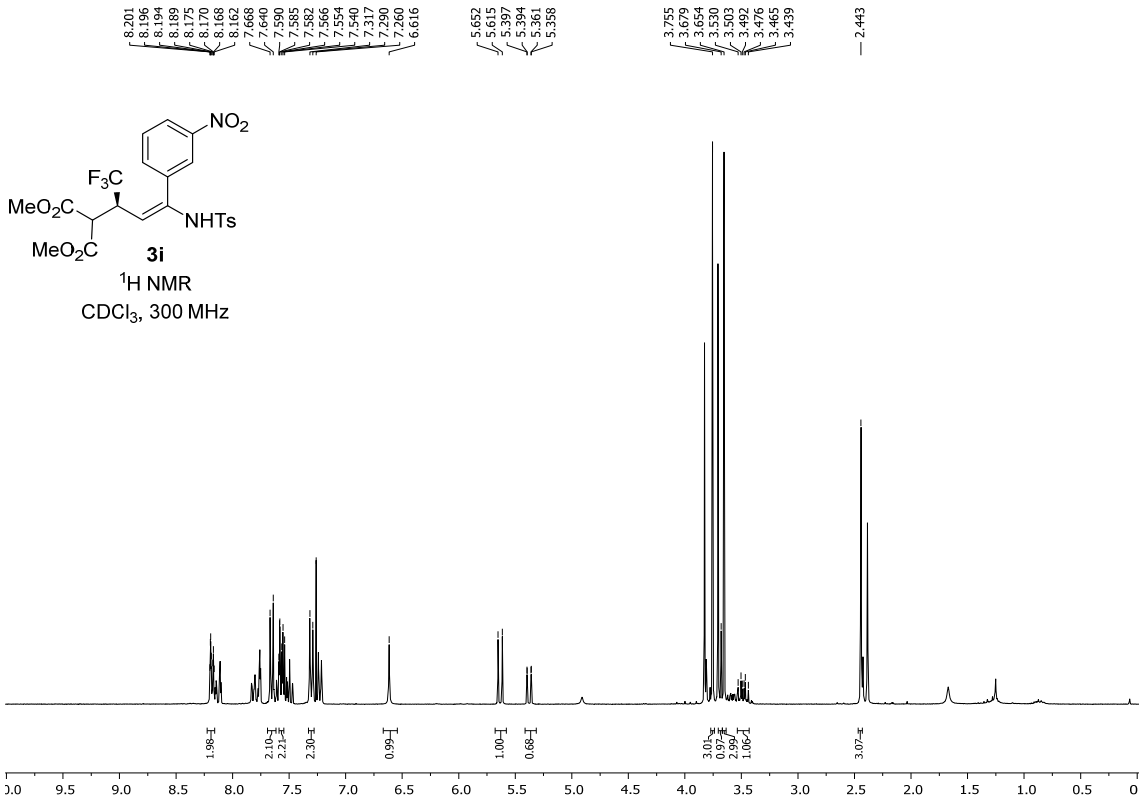
8: 270 nm, 4 nm Results

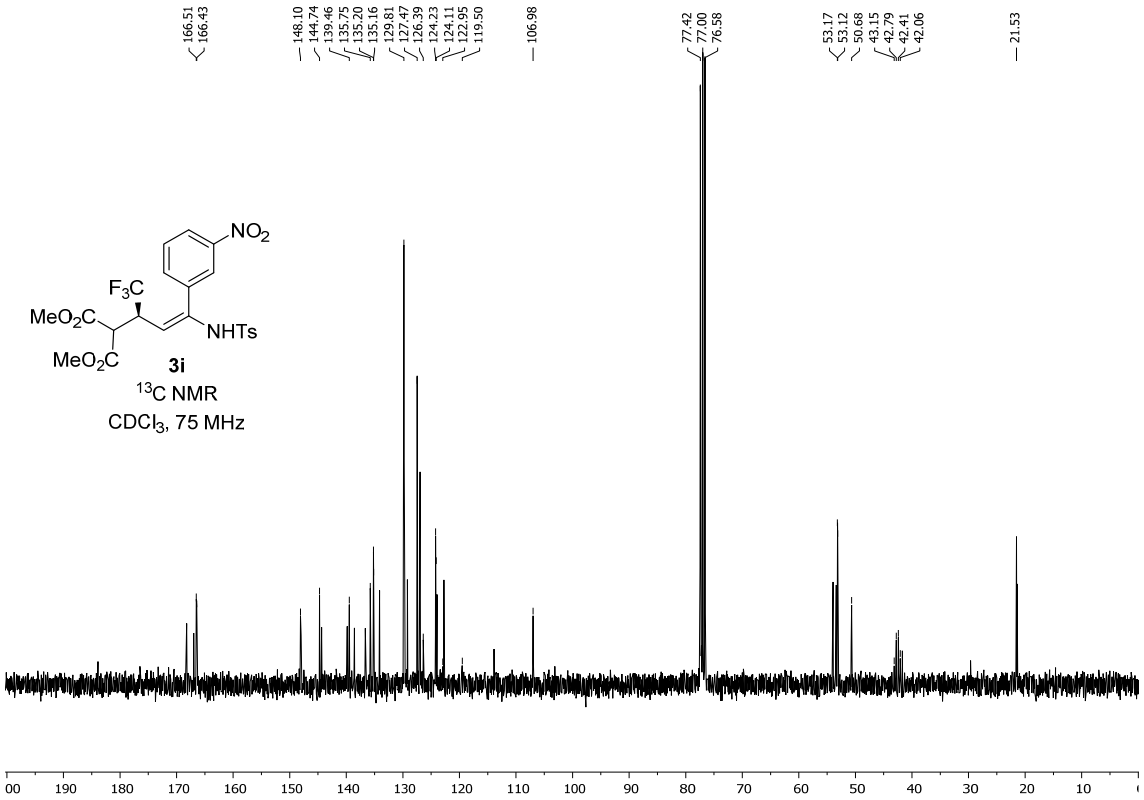
Retention Time	Area	Area Percent
7,17	10579681	27,533
7,88	8899930	23,162
9,47	8513973	22,157
11,12	10431744	27,148

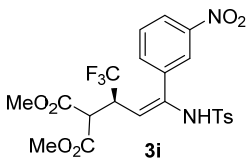


8: 270 nm, 4 nm Results

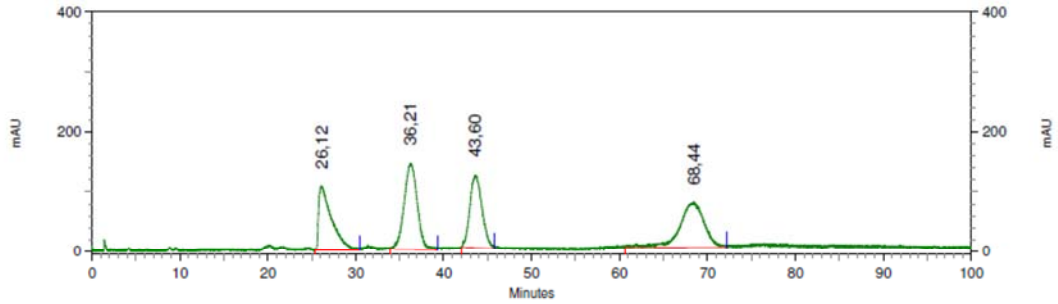
Retention Time	Area	Area Percent
7,16	13408638	66,894
8,15	1539248	7,679
9,51	4467929	22,290
11,08	628647	3,136


8.201
8.196
8.194
8.189
8.175
8.170
8.168
8.162
7.668
7.640
7.590
7.585
7.582
7.566
7.554
7.540
7.317
7.290
7.260
6.616
5.652
5.615
5.397
5.394
5.361
5.358
3.755
3.679
3.654
3.530
3.503
3.492
3.476
3.465
3.439
2.443
NO2
F3C
MeO2C
NHTs
MeO2C
3i
1H NMR
CDCl3, 300 MHz
1.98
2.10
2.24
2.30
0.99
1.00
0.68
3.01
0.97
2.99
1.06
3.07


166.51
166.43
148.10
144.74
139.46
135.75
135.20
135.16
129.81
127.47
126.39
124.23
124.11
122.95
119.50
106.98
77.42
77.00
76.58
53.17
53.12
50.68
43.15
42.79
42.41
42.06
21.53
NO2
F3C
MeO2C
NHTs
MeO2C
3i
13C NMR
CDCl3, 75 MHz

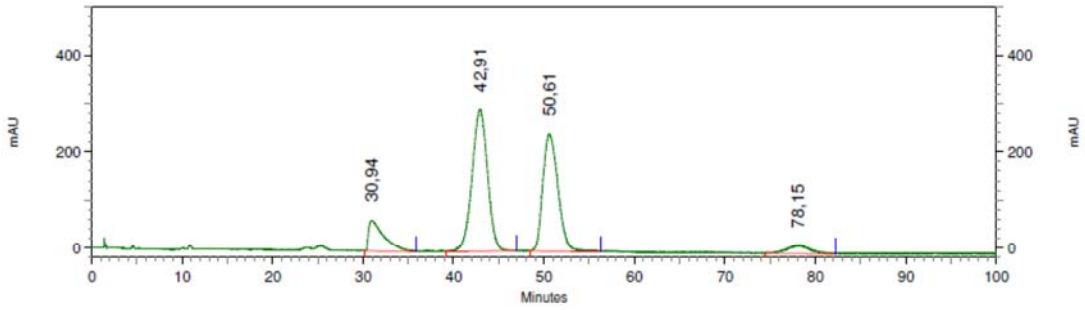


3i



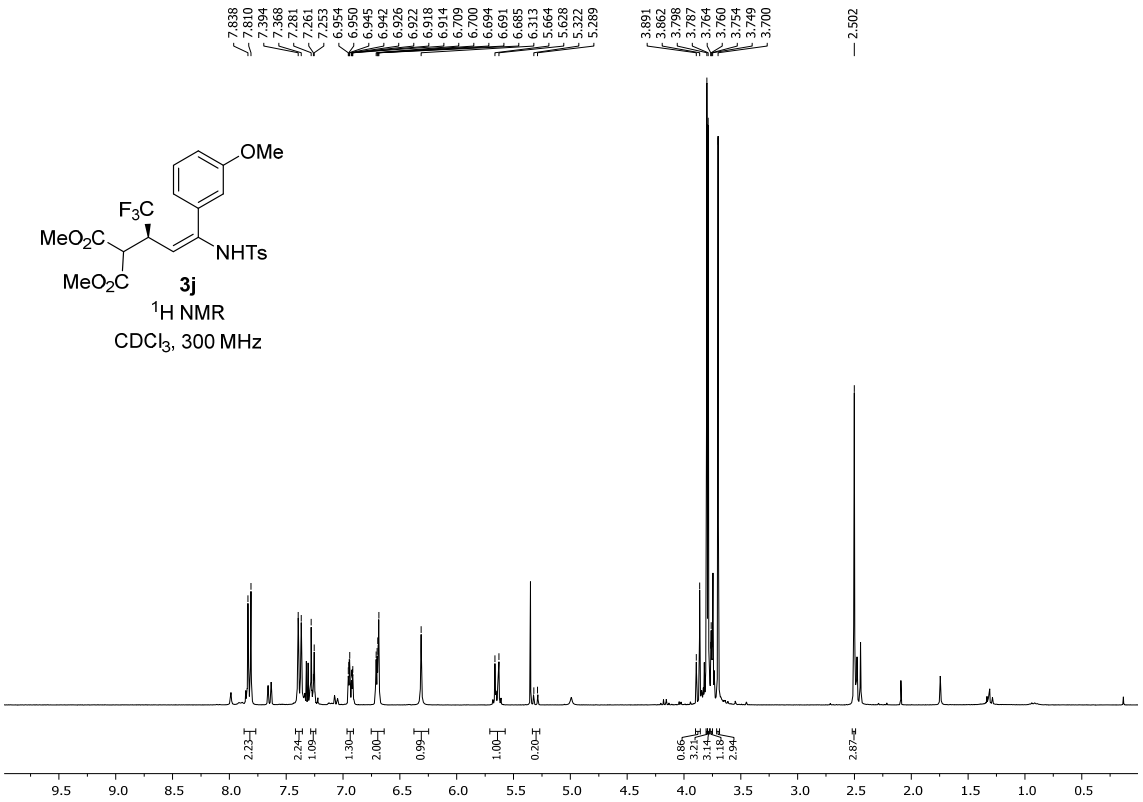
2: 240 nm, 4 nm Results

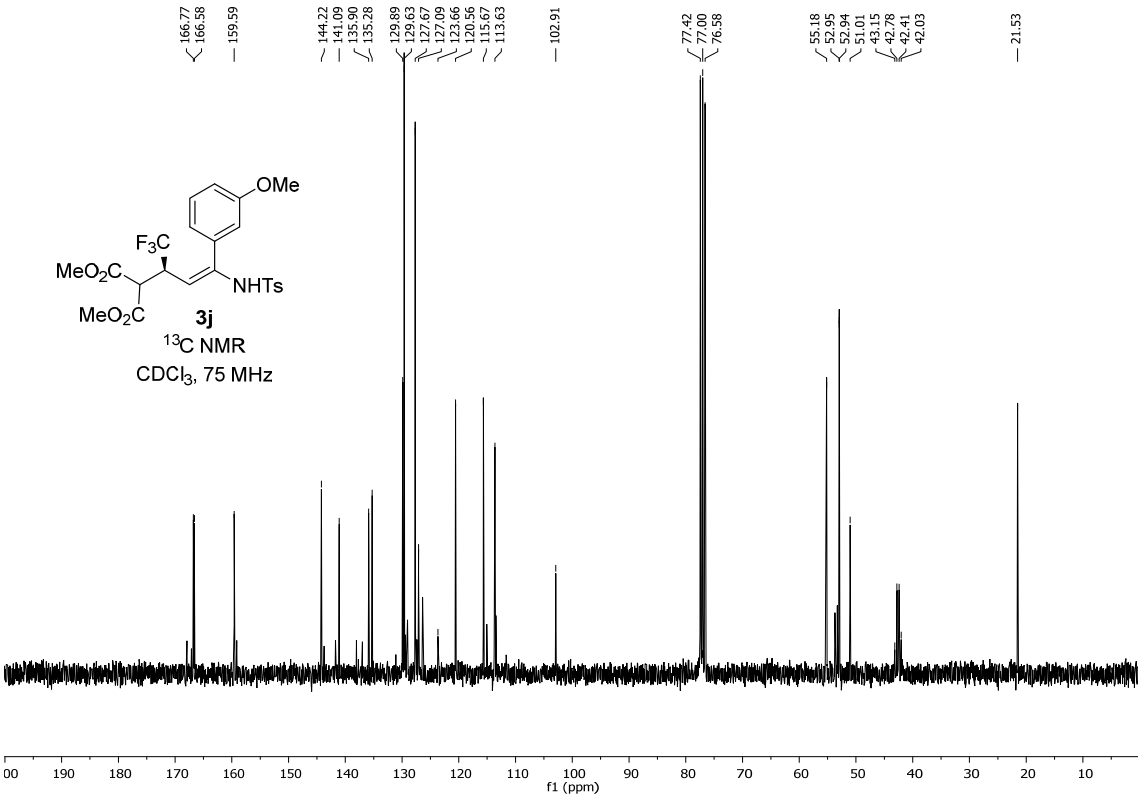
Retention Time	Area	Area Percent
26,12	44278354	20,864
36,21	60686427	28,596
43,60	47134471	22,210
68,44	60124210	28,331

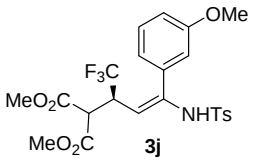


2: 240 nm, 4 nm Results

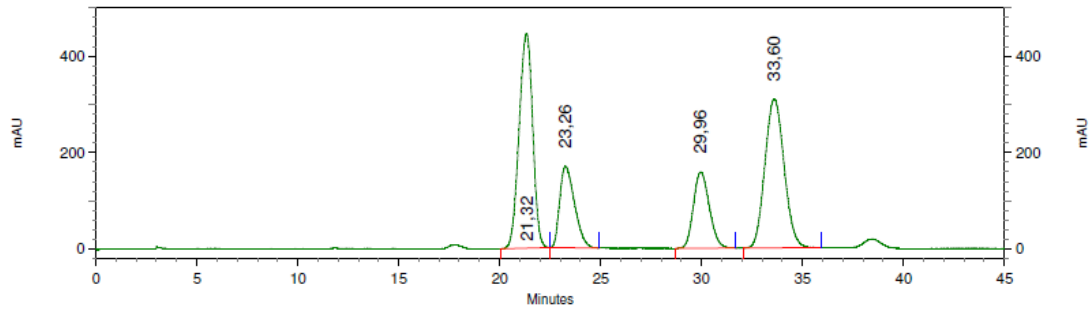
Retention Time	Area	Area Percent
30,94	30715284	10,243
42,91	141508952	47,190
50,61	114674553	38,242
78,15	12969103	4,325


7.838
7.810
7.394
7.368
7.281
7.261
7.253
6.954
6.950
6.945
6.942
6.926
6.922
6.918
6.914
6.709
6.700
6.694
6.691
6.685
6.313
5.664
5.628
5.322
5.289
3.891
3.862
3.798
3.787
3.764
3.760
3.754
3.749
3.700
2.502
OMe
F3C
MeO2C
NHTs
MeO2C
3j
1H NMR
CDCl3, 300 MHz
2.23
2.24
1.09
1.30
2.00
0.99
1.00
0.20
0.86
3.21
3.14
1.18
2.94
2.87
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


166.77
166.58
159.59
144.22
141.09
135.90
135.28
129.89
129.63
127.67
127.09
123.66
120.56
115.67
113.63
102.91
77.42
77.00
76.58
55.18
52.95
52.94
51.01
43.15
42.78
42.41
42.03
21.53
OMe
F3C
MeO2C
NHTs
MeO2C
3j
13C NMR
CDCl3, 75 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

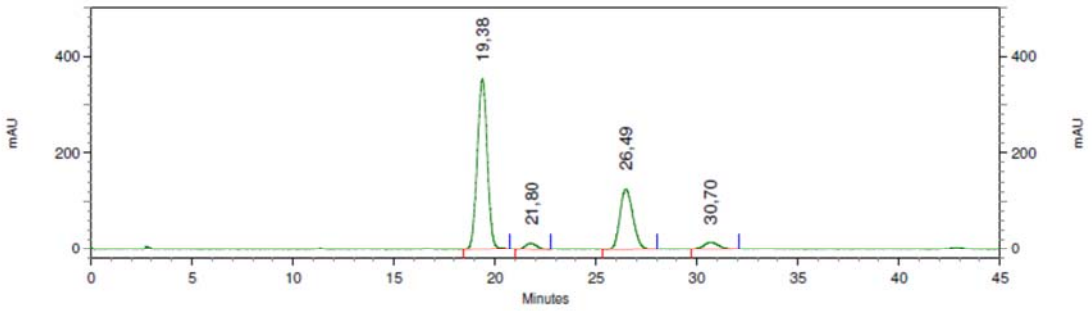


3j



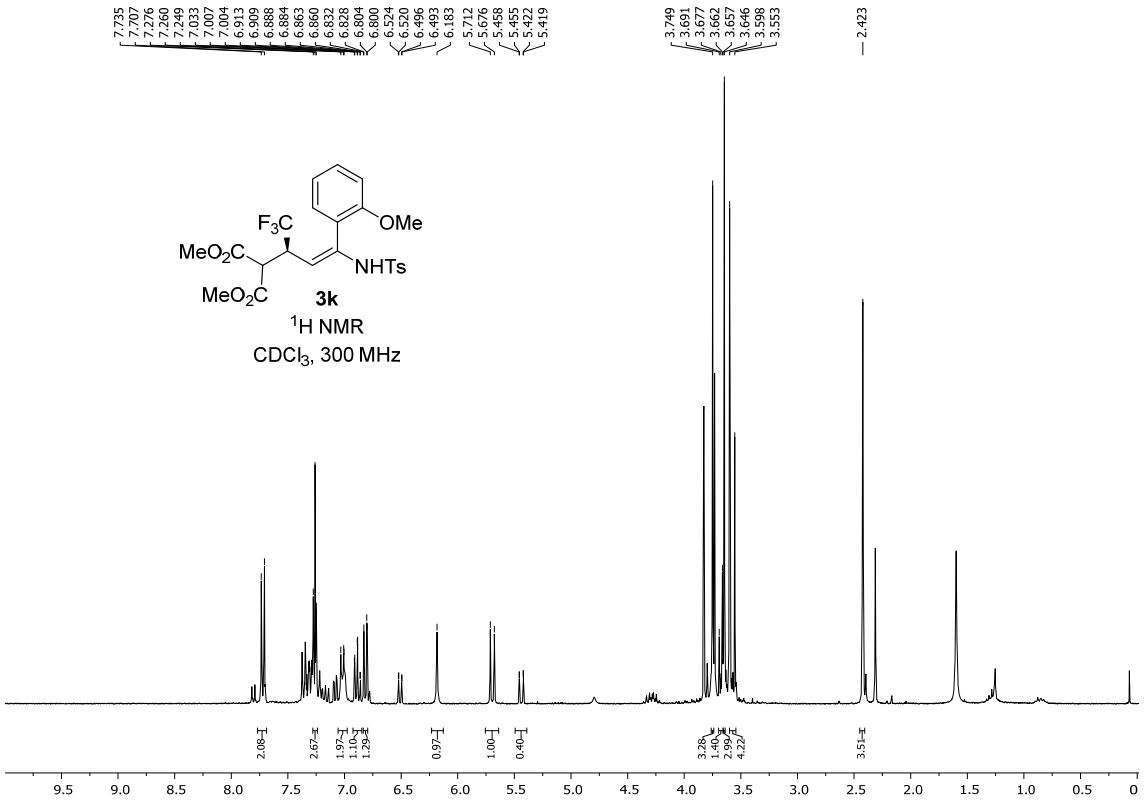
5: 250 nm, 4 nm Results

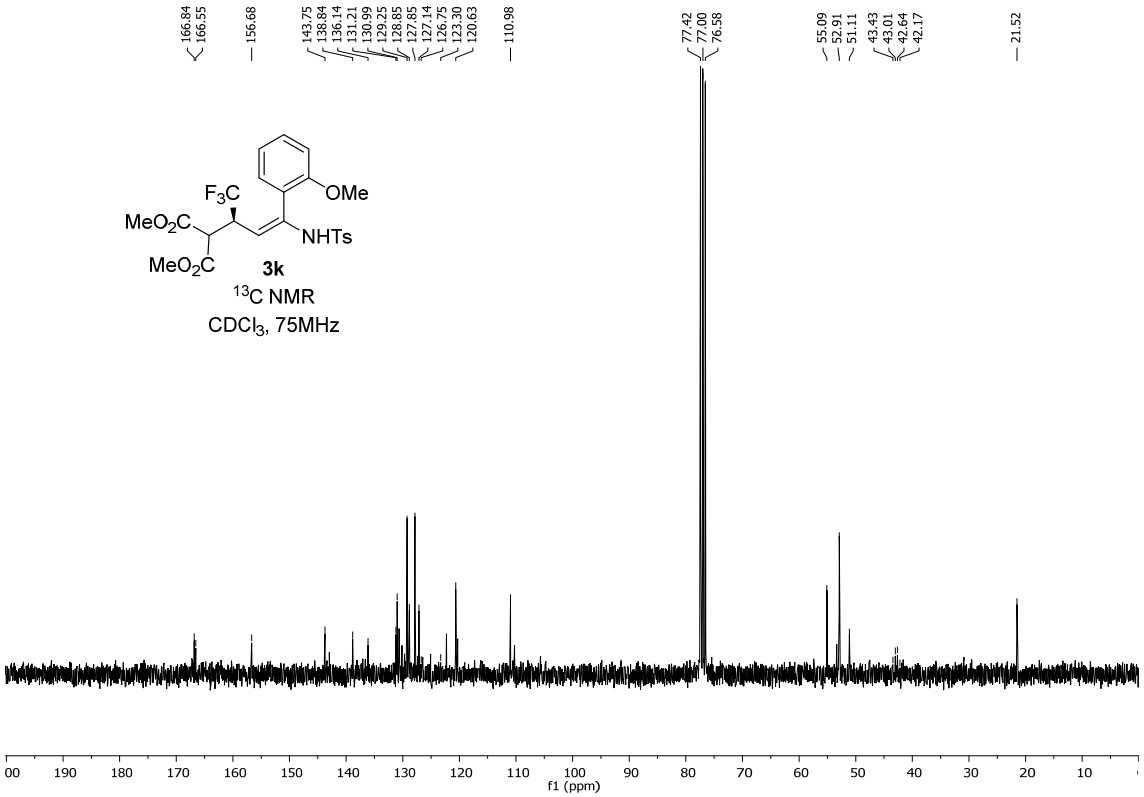
Retention Time	Area	Area Percent
21,32	83433064	35,597
23,26	34464298	14,704
29,96	34604433	14,764
33,60	81878917	34,934

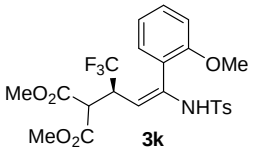


5: 250 nm, 4 nm Results

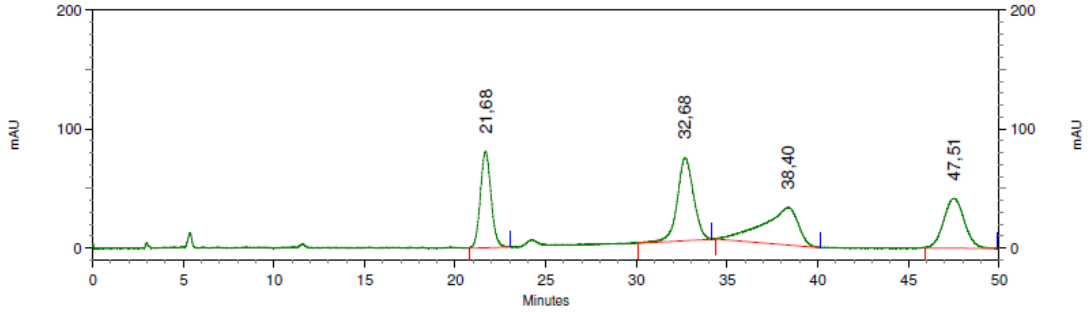
Retention Time	Area	Area Percent
19,38	49004176	63,381
21,80	2251250	2,912
26,49	22751614	29,426
30,70	3310239	4,281


7.735
7.707
7.276
7.260
7.249
7.033
7.007
7.004
6.913
6.909
6.888
6.884
6.863
6.860
6.832
6.828
6.804
6.800
6.524
6.520
6.496
6.493
6.183
5.712
5.676
5.458
5.455
5.422
5.419
3.749
3.691
3.677
3.662
3.657
3.646
3.598
3.553
2.423
F3C
OMe
MeO2C
NHTs
MeO2C
3k
1H NMR
CDCl3, 300 MHz
2.08
2.67
1.97
1.10
1.29
0.97
1.00
0.40
3.28
1.40
2.99
4.22
3.51


166.84
166.55
156.68
143.75
138.84
136.14
131.21
130.99
129.25
128.85
127.85
127.14
126.75
123.30
120.63
110.98
77.42
77.00
76.58
55.09
52.91
51.11
43.43
43.01
42.64
42.17
21.52
F3C
OMe
MeO2C
NHTs
MeO2C
3k
13C NMR
CDCl3, 75MHz
f1 (ppm)

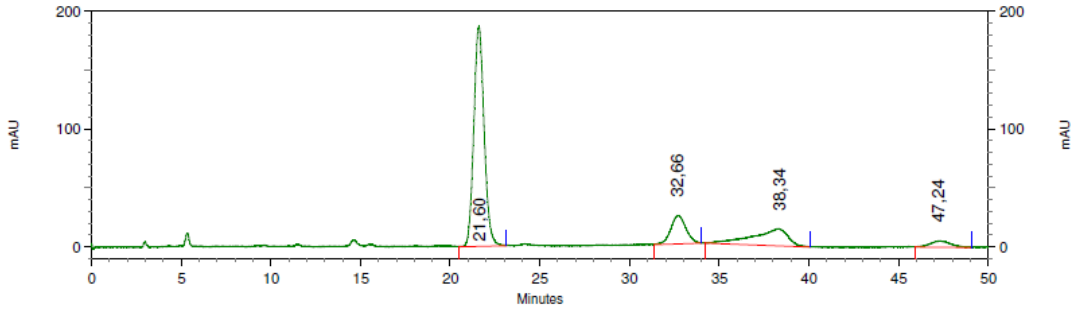


3k



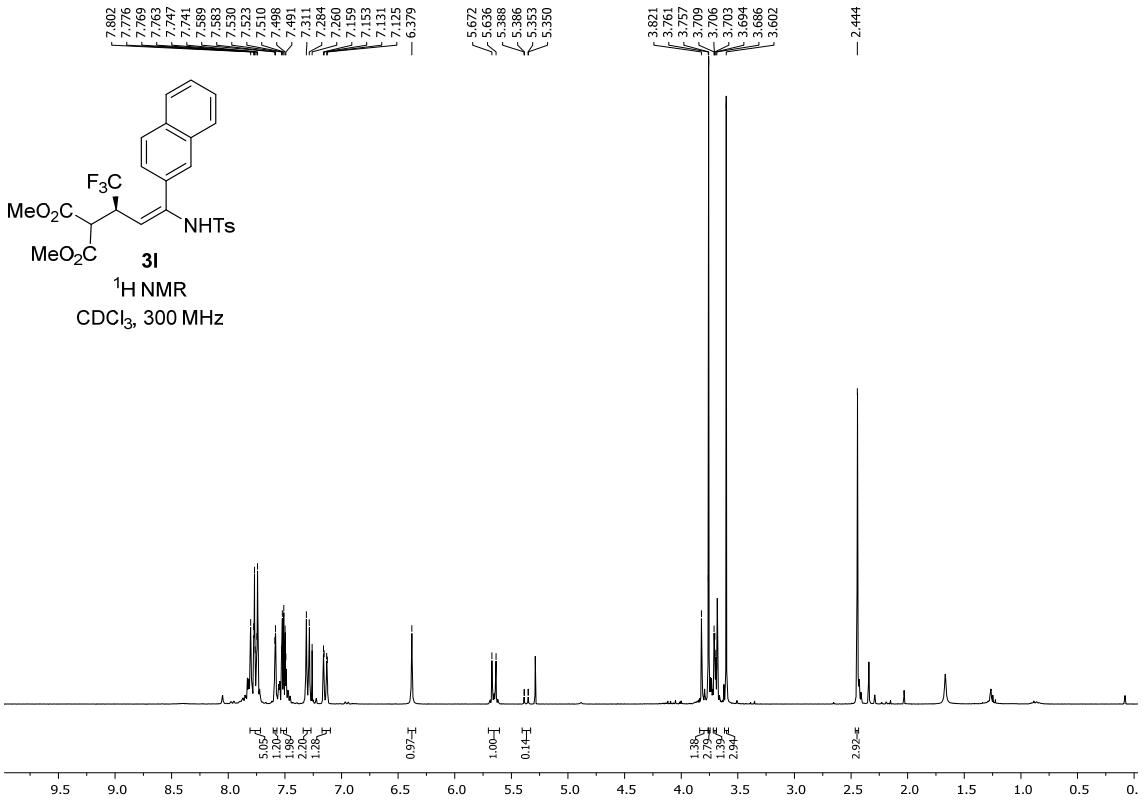
5: 250 nm, 4 nm Results

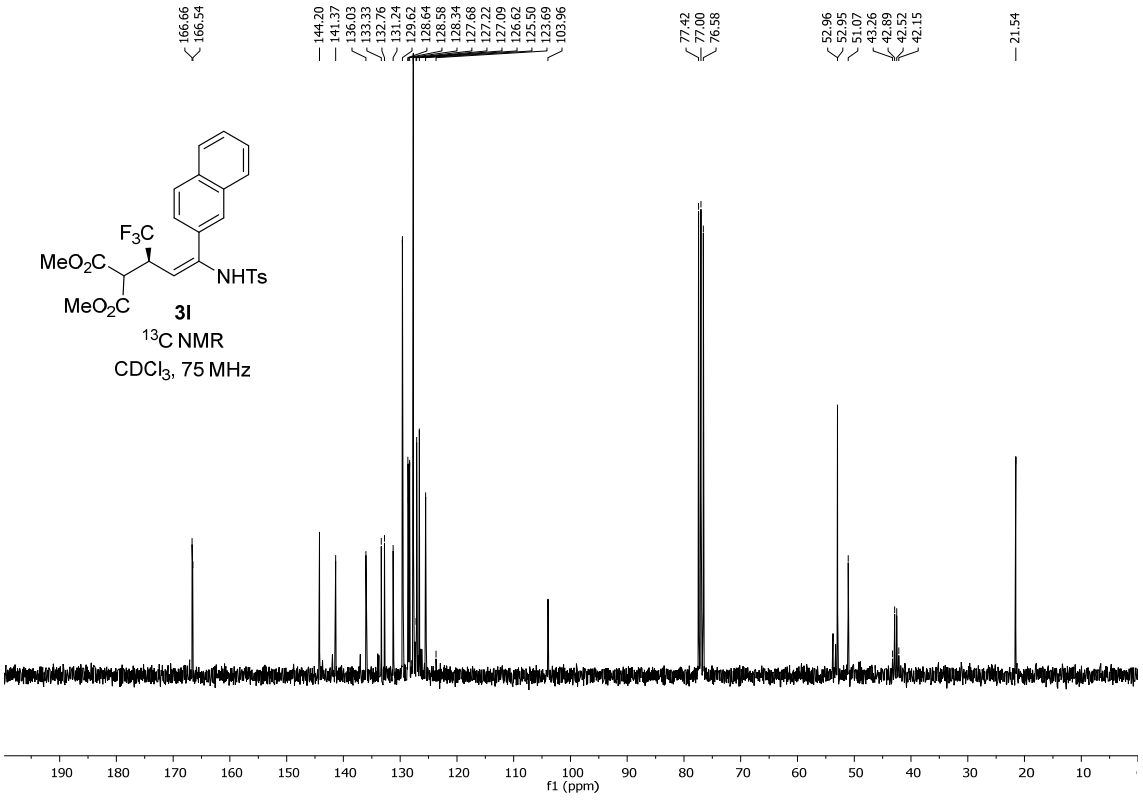
Retention Time	Area	Area Percent
21,68	13274995	21,691
32,68	17429237	28,479
38,40	17140324	28,007
47,51	13356633	21,824

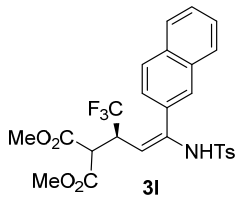


5: 250 nm, 4 nm Results

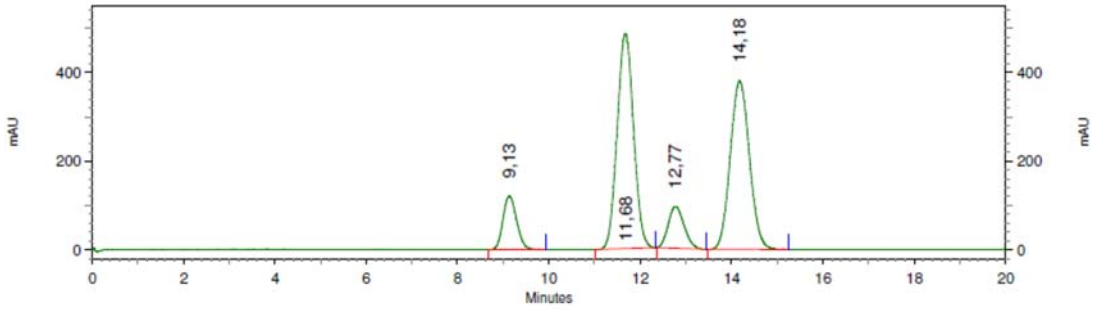
Retention Time	Area	Area Percent
21,60	29945092	65,926
32,66	5642658	12,423
38,34	8015853	17,647
47,24	1818970	4,005


7.802
7.776
7.769
7.763
7.747
7.741
7.589
7.583
7.530
7.523
7.510
7.498
7.491
7.311
7.284
7.260
7.159
7.153
7.131
7.125
6.379
5.672
5.636
5.388
5.386
5.353
5.350
3.821
3.761
3.757
3.709
3.706
3.703
3.694
3.686
3.602
2.444
F3C
MeO2C
MeO2C
NHTs
3l
1H NMR
CDCl3, 300 MHz
5.05
1.20
1.98
2.20
1.28
0.97
1.00
0.14
1.38
2.79
1.39
2.94
2.92
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.


166.66
166.54
144.20
141.37
136.03
133.33
132.76
131.24
129.62
128.64
128.58
128.34
127.68
127.22
127.09
126.62
125.50
123.69
103.96
77.42
77.00
76.58
52.96
52.95
51.07
43.26
42.89
42.52
42.15
21.54
F3C
MeO2C
MeO2C
NHTs
3l
13C NMR
CDCl3, 75 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

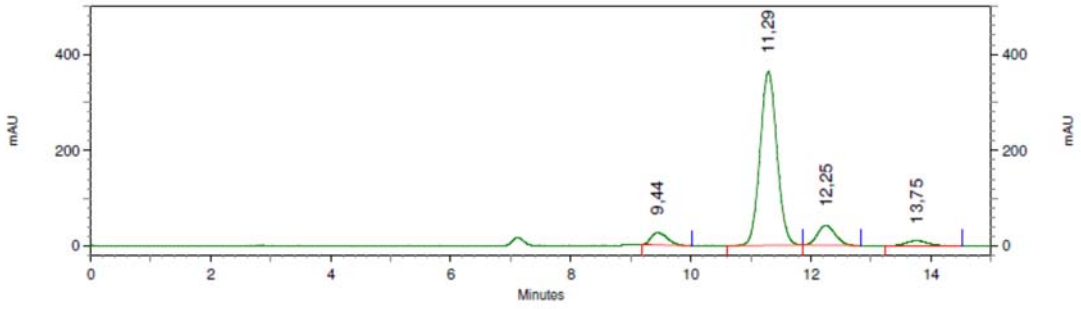


3l



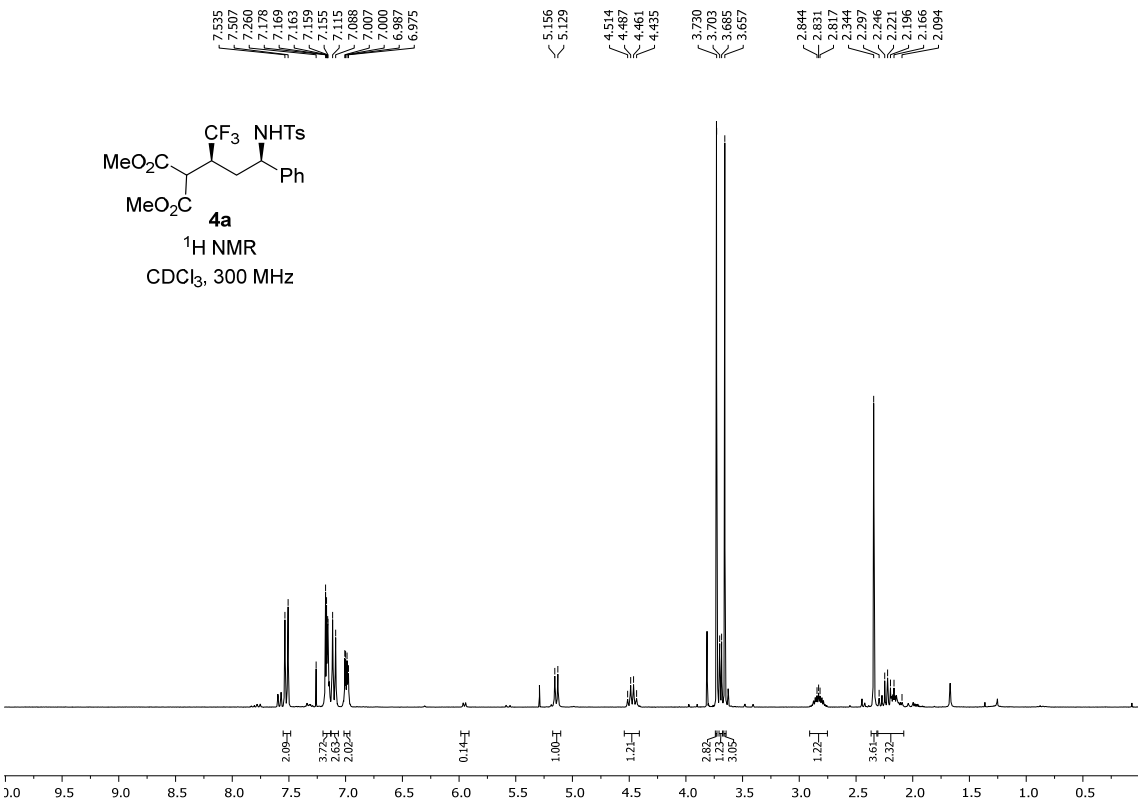
1: 280 nm, 4 nm Results

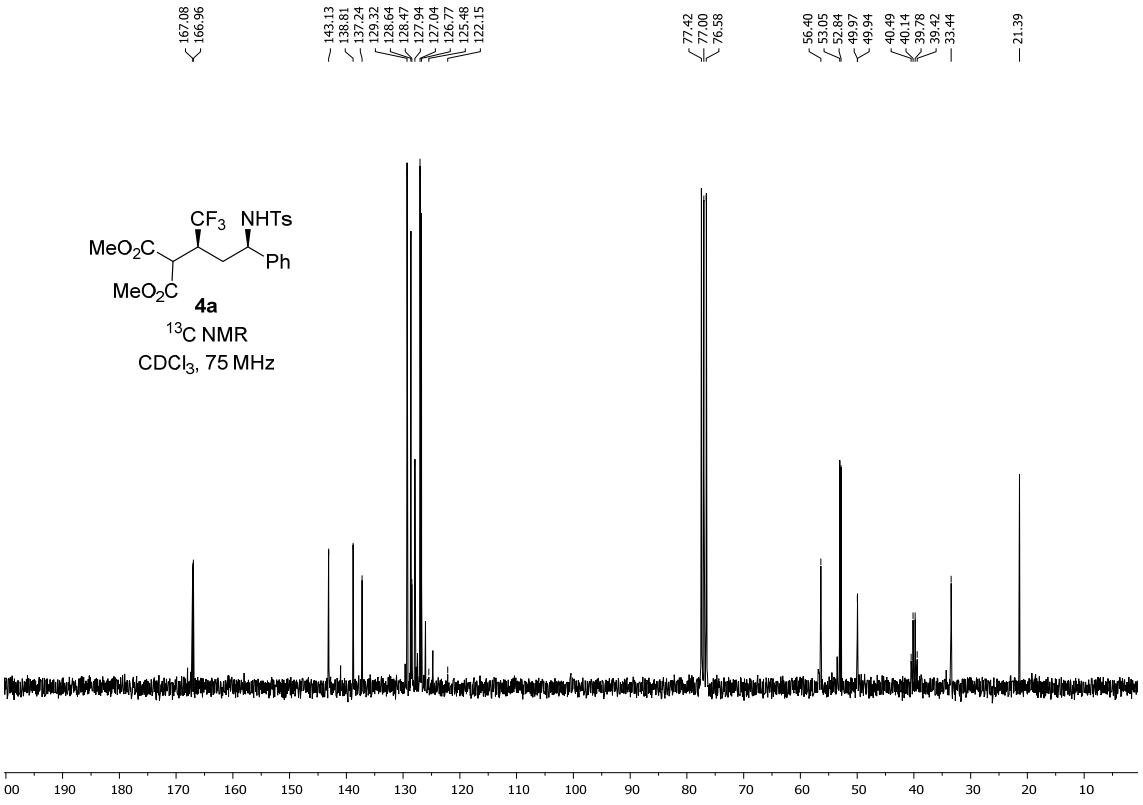
Retention Time	Area	Area Percent
9,13	10055071	8,990
11,68	48362788	43,240
12,77	9063996	8,104
14,18	44365277	39,666

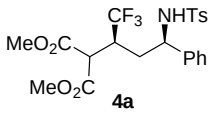


6: 280 nm, 4 nm Results

Retention Time	Area	Area Percent
9,44	1956733	5,608
11,29	28423861	81,464
12,25	3431501	9,835
13,75	1079387	3,094


7.535
7.507
7.260
7.178
7.169
7.163
7.159
7.155
7.115
7.088
7.007
7.000
6.987
6.975
5.156
5.129
4.514
4.487
4.461
4.435
3.730
3.703
3.685
3.657
2.844
2.831
2.817
2.344
2.297
2.246
2.221
2.196
2.166
2.094
CF3 NHTs
MeO2C
Ph
MeO2C
4a
1H NMR
CDCl3, 300 MHz
2.09
3.73
2.63
2.02
0.14
1.00
1.21
2.82
1.23
3.05
1.22
3.61
2.32

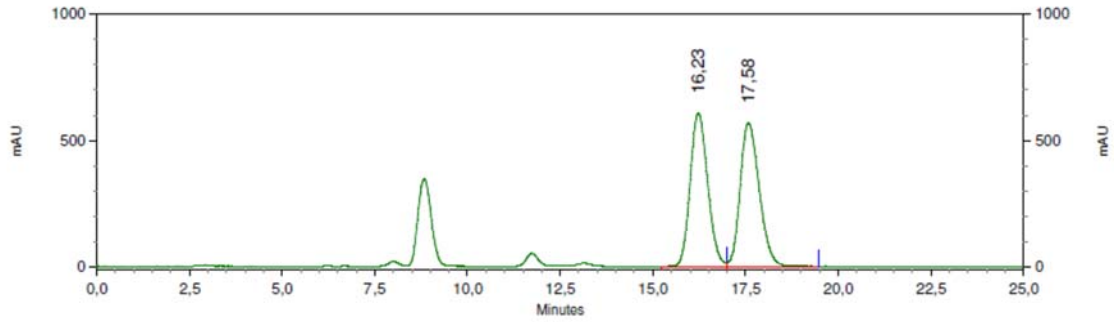

167.08
166.96
143.13
138.81
137.24
129.32
128.64
128.47
127.94
127.04
126.77
125.48
122.15
77.42
77.00
76.58
56.40
53.05
52.84
49.97
49.94
40.49
40.14
39.78
39.42
33.44
21.39
CF3 NHTs
MeO2C
Ph
MeO2C
4a
13C NMR
CDCl3, 75 MHz



4a

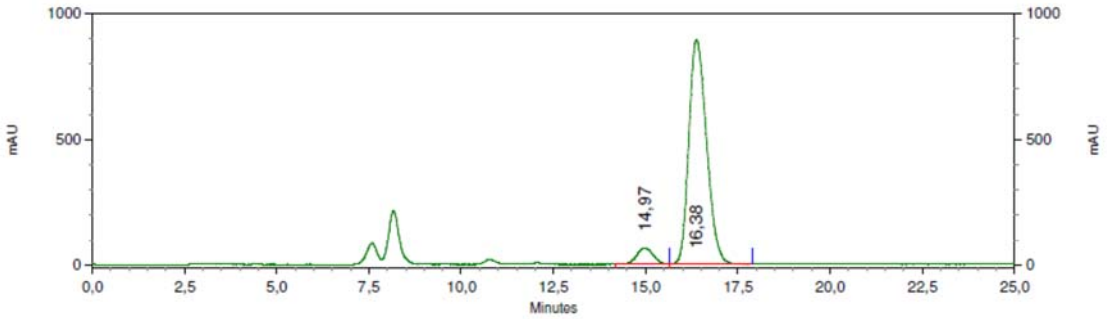
major diastereomer

Lux-Amylose 1



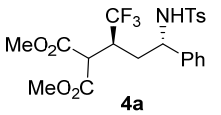
3: 240 nm, 4 nm Results

Retention Time	Area	Area Percent
16,23	80079138	49,517
17,58	81640326	50,483



3: 240 nm, 4 nm Results

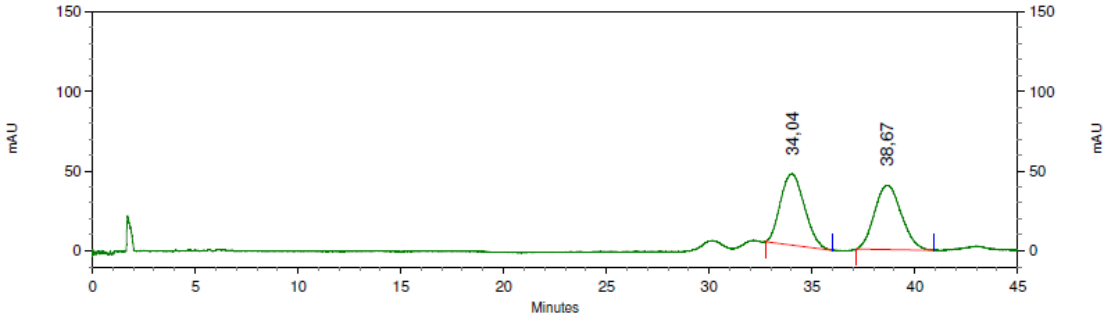
Retention Time	Area	Area Percent
14,97	8051805	6,292
16,38	119921166	93,708



4a

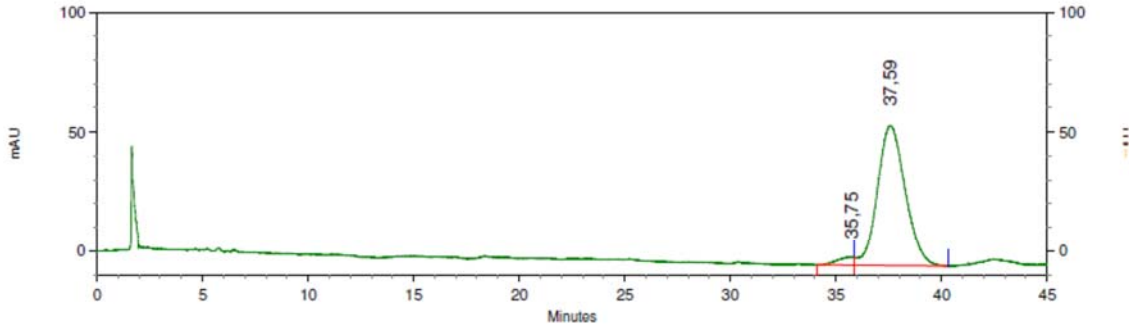
Minor diastereomer

Chiralpak IC



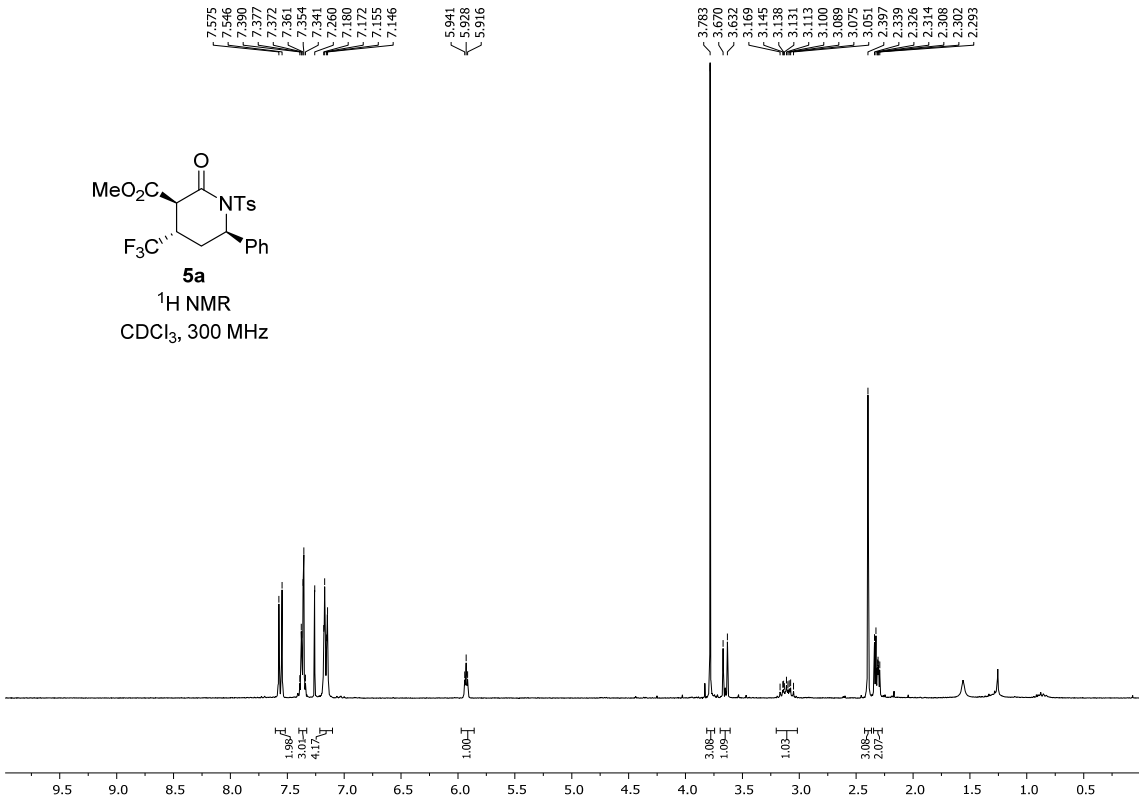
6: 220 nm, 4 nm Results

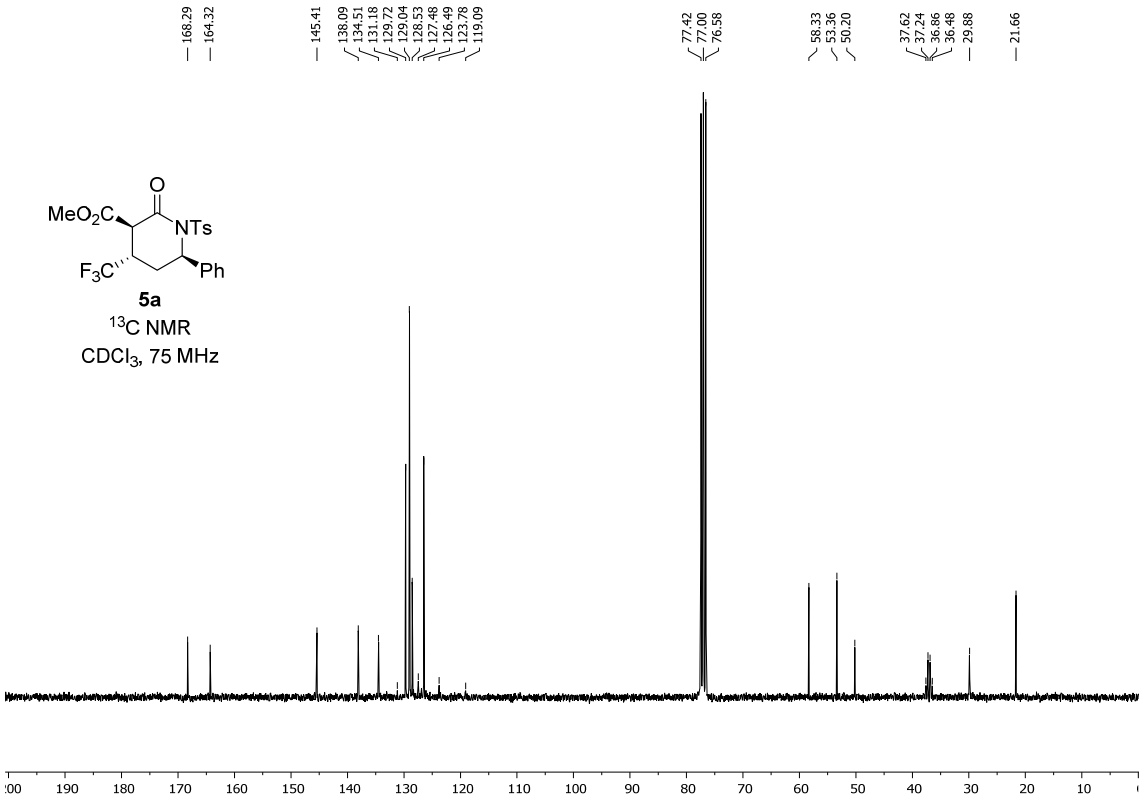
Retention Time	Area	Area Percent
34,04	14547165	49,809
38,67	14658732	50,191

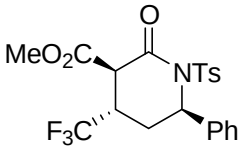


6: 220 nm, 4 nm Results

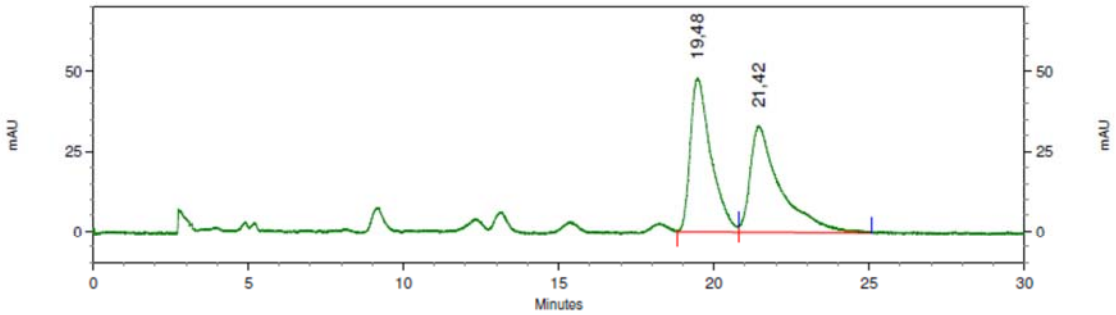
Retention Time	Area	Area Percent
35,75	696319	3,104
37,59	21738335	96,896


7.575
7.546
7.390
7.377
7.372
7.361
7.354
7.341
7.260
7.180
7.172
7.155
7.146
5.941
5.928
5.916
3.783
3.670
3.632
3.169
3.145
3.138
3.131
3.113
3.100
3.089
3.075
3.051
2.397
2.339
2.326
2.314
2.308
2.302
2.293
O
MeO2C
NTs
F3C
Ph
5a
1H NMR
CDCl3, 300 MHz
1.98
3.01
4.17
1.00
3.08
1.09
1.03
3.08
2.07
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


168.29
164.32
145.41
138.09
134.51
131.18
129.72
129.04
128.53
127.48
126.49
123.78
119.09
77.42
77.00
76.58
58.33
53.36
50.20
37.62
37.24
36.86
36.48
29.88
21.66
O
MeO2C
NTs
F3C
Ph
5a
13C NMR
CDCl3, 75 MHz
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

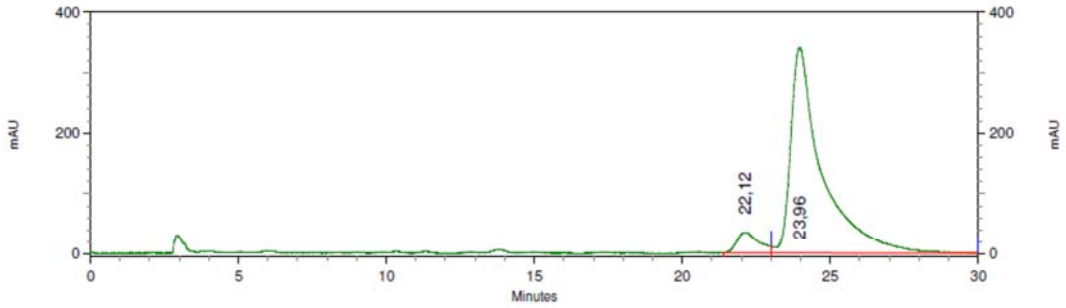


5a



13: 250 nm, 4 nm
Results

Retention Time	Area	Area Percent
19,48	8876376	49,765
21,42	8960049	50,235



12: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
22,12	7086461	6,584
23,96	100551429	93,416

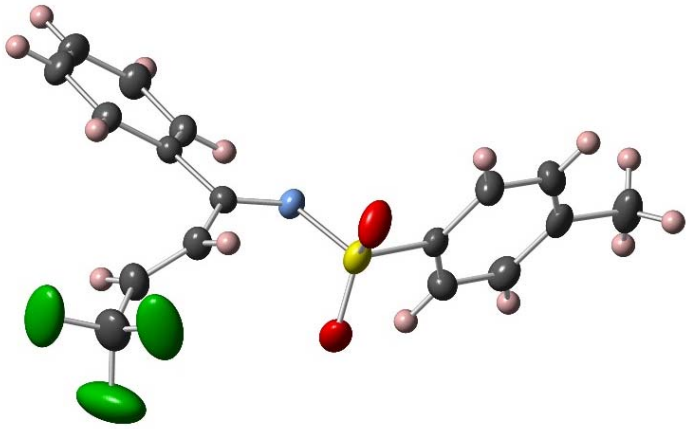


Figure 2S. Ortep plot for the X-ray structure of compound **2a**. The thermal ellipsoids are drawn at the 50% probability level.

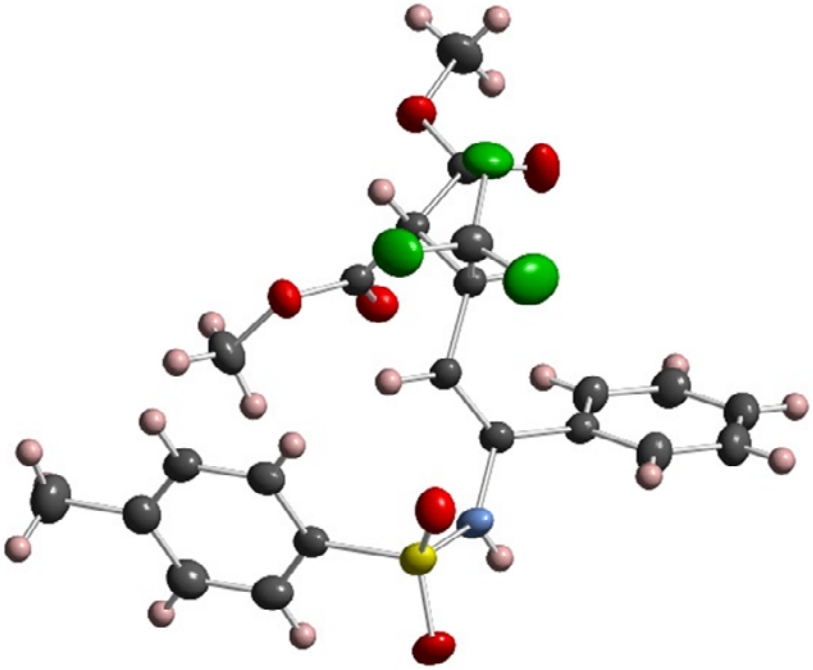
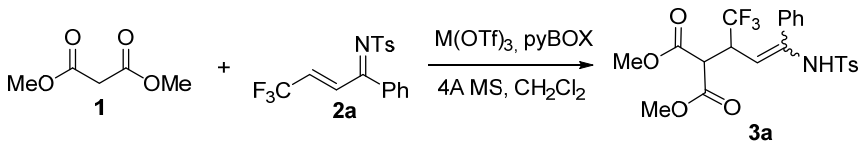
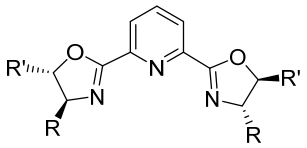


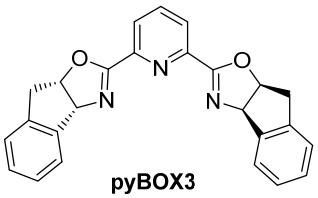
Figure 3S. Ortep plot for the X-ray structure of compound **3a**. The thermal ellipsoids are drawn at the 50% probability level.

Table S-1. Enantioselective conjugate addition of dimethyl malonate **2** to imine **2a** catalyzed by trivalent metal complexes.[a]

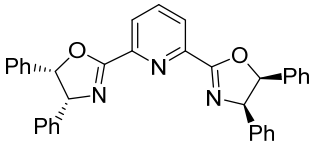




pyBOX1: R = Ph, R'= H
pyBOX2: R = *i*-Pr, R'= H
pyBOX4: R = $PhCH_2CH_2$, R'= H
pyBOX5: R = 1-NaphthylCH_2, R'= H
pyBOX6: R = Me, R'= Ph



pyBOX3



pyBOX7

Entry	$La(OTf)_3$	**pyBOX**	t (h)	Yield (%)[b]	dr (*E:Z*)	ee (%) (*E/Z*)[c]
1	$La(OTf)_3$	**pyBOX1**	16h	>99	72:28	75/34
2	$La(OTf)_3$	**pyBOX2**	43h	>99	78:23	-15/-2
3	$La(OTf)_3$	**pyBOX3**	48	>99	77:23	45/-3
4	$La(OTf)_3$	**pyBOX4**	40h	>99	82;18	-18/-9
5	$La(OTf)_3$	**pyBOX5**	40h	>99	82:18	-28/-11
6	$La(OTf)_3$	**pyBOX6**	37h	79	89:11	-16/5
7	$La(OTf)_3$	**pyBOX7**	44h	86	73:27	-76/-39
8	$Sc(OTf)_3$	**pyBOX1**	96	--[d]	--	--
9	$Yb(OTf)_3$	**pyBOX1**	96	19	43:57	69/42
10	$In(OTf)_3$	**pyBOX1**	96	--[d]	--	--

[a] Reaction conditions: **2** (0.3 mmol), **11** (0.12 mmol), ligand (0.012 mmol, $M(OTf)_3$ (0.012 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases. [d] Little advance of the reaction was observed after the indicated time.