Highly Diastereoselective and Enantioselective Direct Organocatalytic *anti*-selective Mannich Reactions Employing *N*-tosylimines

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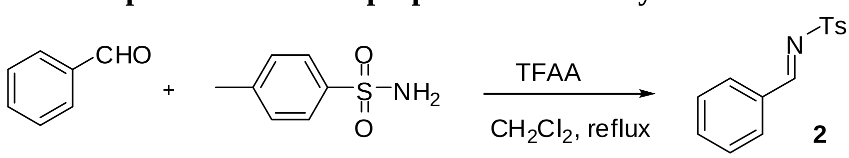
General methods

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300MHz) or AMX500 (500MHz) spectrometer. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference. Low resolution mass spectra were obtained on a VG Micromass 7035 spectrometer in EI mode, a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin-layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F_{254}) was used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with 5% ninhydrin in ethanol, ceric ammonium molybdate or $KMnO_4$ solution followed by heating on a hot plate. Flash chromatography separations were performed on Merck 60 (0.040 - 0.063 mm) mesh silica gel. All the Mannich reactions were performed in a closed system at ambient temperature. The assignments of *syn* and *anti* isomers and the diastereomeric ratios of the Mannich products were determined by ^{1}H NMR analysis of the crude products. The enantiomeric excesses were determined by chiral-phase HPLC analysis.

All the *N*-tosylimine substrates were prepared using literature procedure,[1] and organocatalysts **1a-c** were prepared according to our previously published procedure.[2]

The representative procedure for the preparation of *N*-tosylimines



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To a stirred mixture of benzaldehyde (318 mg, 3 mmol) and *p*-toluenesulfonamide (513 mg, 3 mmol) in dry CH_2Cl_2 (15 ml) was added trifluoroacetic anhydride (0.46 ml, 3.3 mmol), and the resulting mixture was heated to reflux for 12 hours. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude product, which was then subjected to recrystallization (hexane/CH_2Cl_2) to afford the desired product as of a white silky crystal (520 mg, 67%).

4-Nitrophenyl-*N*-tosylmethanimine[3]**:**
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.37-7.39 (d, *J* = 8.2 Hz, 2H), 7.90-7.92 (d, *J* = 8.2 Hz, 2H), 8.09-8.11 (d, *J* = 8.9 Hz, 2H), 8.32-8.34 (d, *J* = 8.9 Hz, 2H), 9.10 (s, 1H).

4-Tosyliminomethyl benzonitrile[4]**:**
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.36-7.38 (d, *J* = 8.2 Hz, 2H), 7.77-7.79 (d, *J* = 8.2 Hz, 2H), 7.88-7.90 (d, *J* = 8.2 Hz, 2H), 8.02-8.04 (d, *J* = 8.9 Hz, 2H), 9.05 (s, 1H).

4-Bromophenyl-*N*-tosylmethanimine[5]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.35-7.38 (d, *J* = 8.0 Hz, 2H), 7.74-7.76 (d, *J* = 8.2 Hz, 2H), 7.88-7.91 (d, *J* = 8.4 Hz, 2H), 8.03-8.06 (d, *J* = 8.2 Hz, 2H), 9.07 (s, 1H).

4-Chlorophenyl-*N*-tosylmethanimine[6, 7]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.34-7.37 (d, *J* = 8.2 Hz, 2H), 7.45-7.48 (d, *J* = 8.6 Hz, 2H), 7.84-7.89 (m, 4H), 8.98 (s, 1H).

4-Fluorophenyl-*N*-tosylmethanimine[7]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.15-7.20 (t, 2H), 7.33-7.36 (d, *J* = 8.4 Hz, 2H), 7.86-7.89 (d, *J* = 8.3 Hz, 2H), 7.93-7.98 (t, 2H), 8.99 (s, 1H).

Phenyl-*N*-tosylmethanimine[4, 6, 7]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.33-7.36 (d, *J* = 8.6 Hz, 2H), 7.46-7.51 (t, 2H), 7.59-7.64 (t, 1H), 7.88-7.94 (m, 4H), 9.03 (s, 1H).

Naphthalen-1-yl-*N*-tosylmethanimine[6]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.34-7.37 (d, *J* = 8.0 Hz, 2H), 7.56-7.71 (m, 3H), 7.92-7.96 (m, 3H), 8.09-8.18 (m, 2H), 8.98-9.01 (d, *J* = 8.7 Hz, 1H), 9.62 (s, 1H).

Naphthalen-2-yl-*N*-tosylmethanimine[4, 7]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.34-7.37 (d, *J* = 8.3 Hz, 2H), 7.58-7.65 (m, 2H), 7.87-7.97 (m, 5H), 8.02-8.05 (m, 1H), 8.34 (s, 1H), 9.18 (s, 1H).

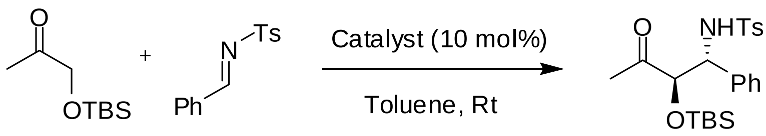
***p*-Tolyl-*N*-tosylmethanimine**[7]**:**
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 2.44 (s, 3H), 7.28-7.29 (d, *J* = 7.6 Hz, 2H), 7.33-7.35 (d, *J* = 8.2 Hz, 2H), 7.81-7.82 (d, *J* = 8.2 Hz, 2H), 7.87-7.89 (d, *J* = 8.2 Hz, 2H), 8.99 (s, 1H).

***o*-Tolyl-*N*-tosylmethanimine**[7]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.61 (s, 3H), 7.25-7.36 (m, 4H), 7.45-7.47 (m, 1H), 7.88-7.90 (d, *J* = 8.2 Hz, 2H), 7.99-8.02 (d, *J* = 7.9 Hz, 1H), 9.34 (s, 1H).

4-Methoxyphenyl-*N*-tosylmethanimine[6]**:**
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.88 (s, 3H), 6.95-6.98 (d, *J* = 8.7 Hz, 2H), 7.30-7.34 (m, 2H), 7.85-7.89 (m, 4H), 8.94 (s, 1H).

2-(Trifluoromethyl)phenyl-*N*-tosylmethanimine[8]**:**
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.36-7.38 (d, *J* = 8.2 Hz, 2H), 7.65-7.70 (m, 2H), 7.77-7.79 (d, *J* = 7.6 Hz, 1H), 7.88-7.90 (d, *J* = 8.2 Hz, 2H), 8.33-8.35 (d, *J* = 7.6 Hz, 1H), 9.35 (s, 1H).

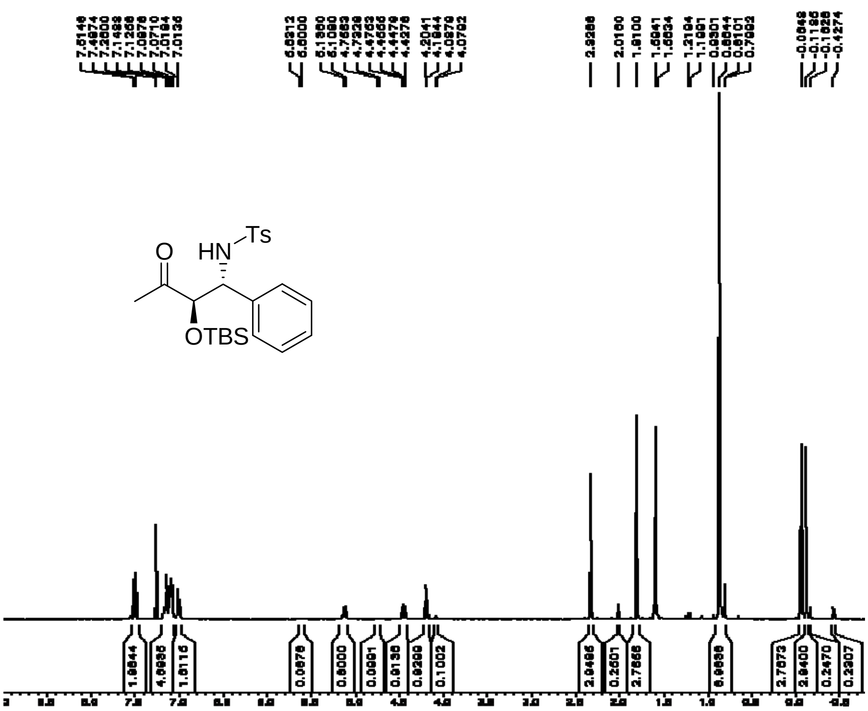
Representative procedure for the direct Mannich reaction with preformed *N*-tosylarylimine:

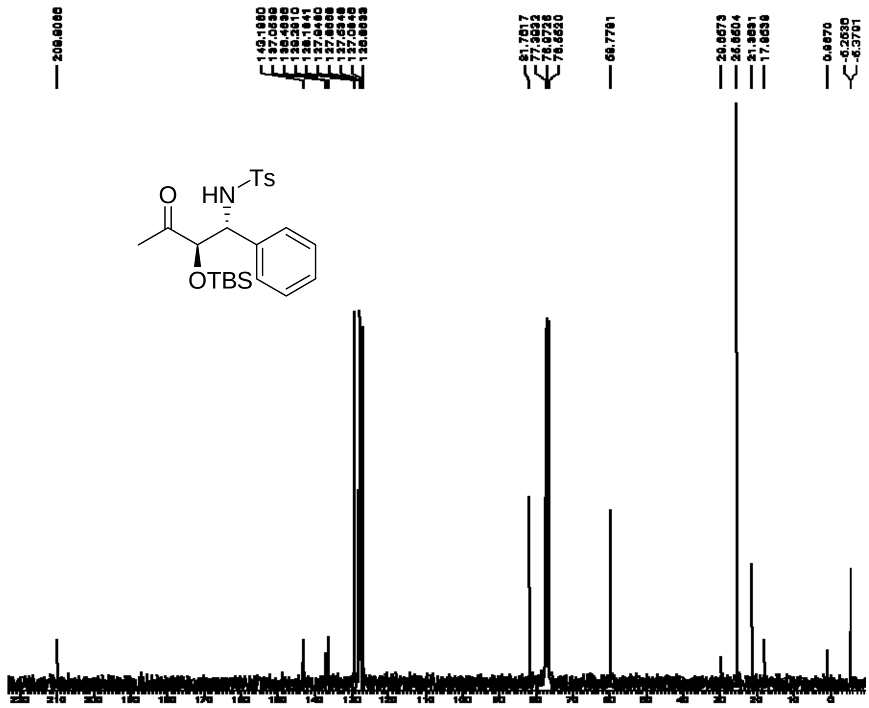


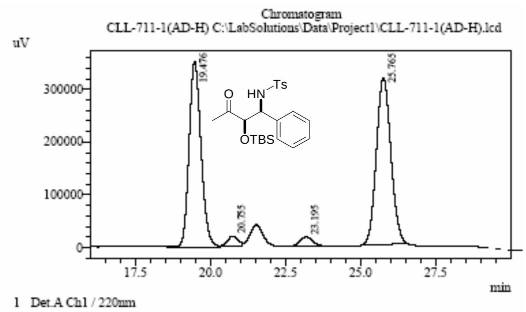
A mixture of phenyl-*N*-tosylmethanimine (25.9 mg, 0.1 mmol), *O*-TBS hydroxyacetone (21 mg, 0.11 mmol) and catalyst **1a** (2.33 mg, 0.01 mmol) in toluene (0.2 mL) was stirred at room temperature for 40 hours. The reaction mixture was filtered through a small pad of silica gel to remove the catalyst, and washed with ethyl acetate (30 mL). The filtrate was concentrated *in vacuo*, and the crude product was purified by column chromatography using mixtures of hexane/ethyl acetate as eluants (12/1 to 7/1) to afford the Mannich product **3** as a white solid (34 mg, 76% yield).

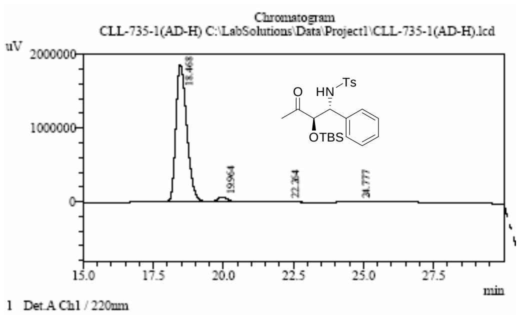
The characterizations of Mannich products

Compound **3**: a white solid; t_r (major) = 18.5 min, t_r (minor) = 24.8 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.12 (s, 3H), -0.06 (s, 3H), 0.86 (s, 9H), 1.81 (s, 3H), 2.33 (s, 3H), 4.18-4.20 (d, *J* = 5.9 Hz, 1H), 4.43-4.48 (m, 1H), 5.60-5.63 (d, *J* = 9.4 Hz, 1H), 7.01-7.02 (d, *J* = 1.5 Hz, 2H), 7.07-7.15 (m, 5H), 7.49-7.51 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.4, -5.3, 17.9, 21.3, 25.7, 59.7, 81.8, 116.8, 126.8, 127.5, 127.9, 128.2, 129.3, 136.5, 137.1, 143.2, 209.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{33}NO_4SSi$ $[M+Na]^+$ 470.1792, found 470.1800; $[\alpha]_D^{20}$ = +11.9 (c = 1.2, $CHCl_3$).









PeakTable

Detector A Ch1 220nm

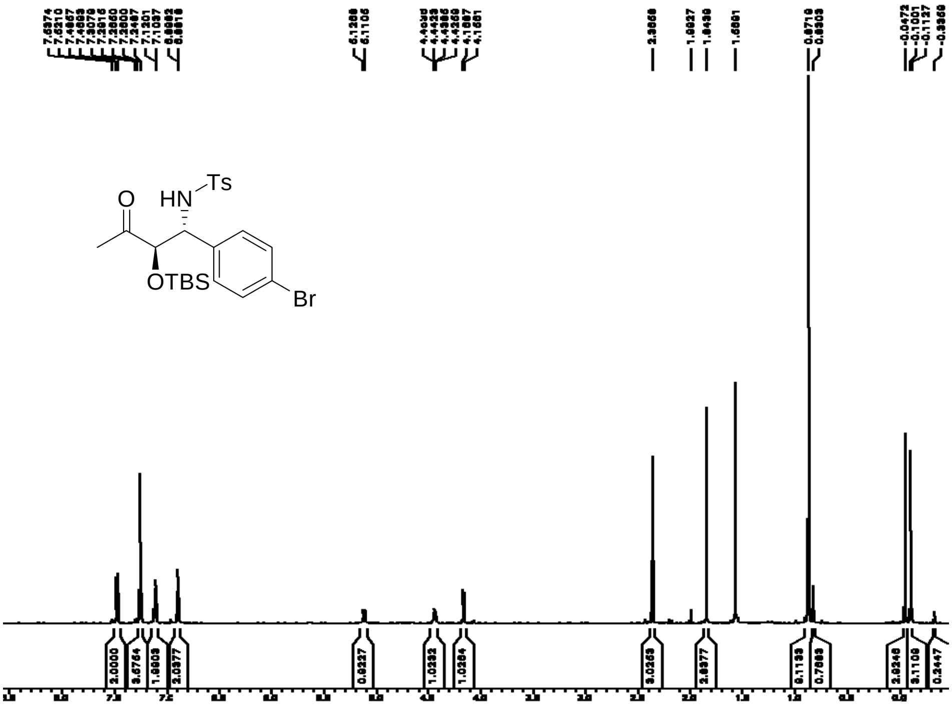
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.476	9728266	352134	45.792	50.050
2	20.755	456243	19042	2.148	2.707
3	23.195	466338	16332	2.195	2.321
4	25.765	10593820	316054	49.866	44.922
Total		21244667	703561	100.000	100.000

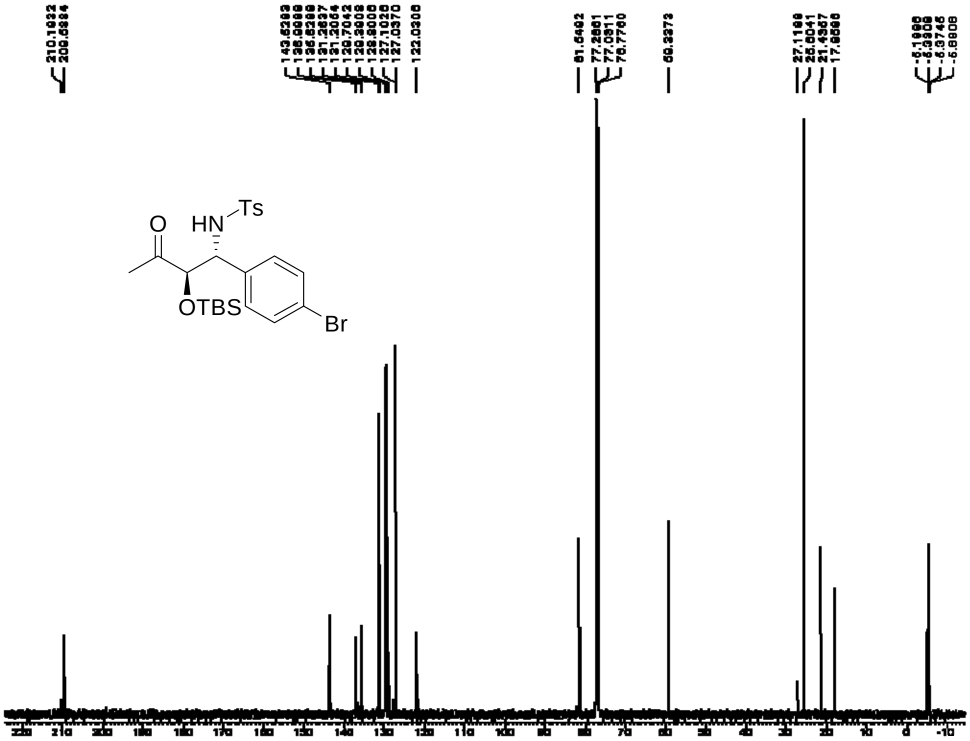
PeakTable

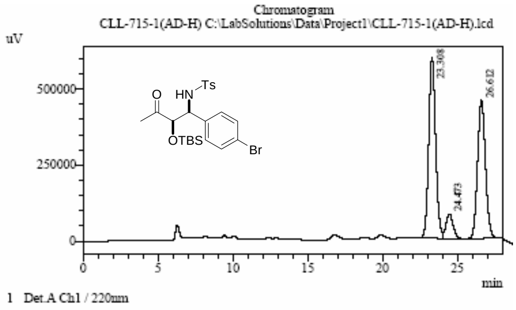
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.468	50948289	1872405	95.640	95.524
2	19.964	1723355	66806	3.235	3.408
3	22.264	346137	12550	0.650	0.640
4	24.777	252998	8388	0.475	0.428
Total		53270780	1960149	100.000	100.000

Compound **4**: a white solid; t_r (major) = 27.4 min, t_r (minor) = 31.6 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.10 (s, 3H), -0.05 (s, 3H), 0.87 (s, 9H), 1.84 (s, 3H), 2.37 (s, 3H), 4.15-4.16 (d, J = 6.3 Hz, 1H), 4.42-4.45 (m, 1H), 5.62-5.64 (d, J = 8.8 Hz, 1H), 6.88-6.89 (d, J = 8.2 Hz, 2H), 7.10-7.12 (d, J = 8.2 Hz, 2H), 7.24-7.26 (d, J = 8.2 Hz, 2H), 7.47-7.48 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.7, -5.2, 17.9, 21.4, 25.6, 27.1, 59.3, 81.5, 122.0, 127.1, 129.3, 129.7, 131.2, 135.6, 137.0, 143.5, 209.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{32}BrNO_4SSi$ $[M+Na]^+$ 548.0897, found 548.0907. $[\alpha]_D^{20}$ = -44.7 (c = 1.03, $CHCl_3$).



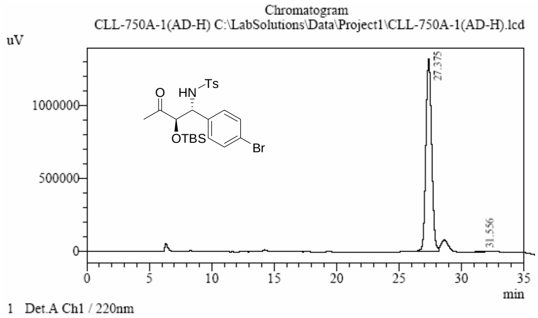




PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.308	19142299	596320	49.717	52.735
2	24.473	2713936	80883	7.049	7.153
3	26.612	16646116	453579	43.234	40.112
Total		38502350	1130782	100.000	100.000

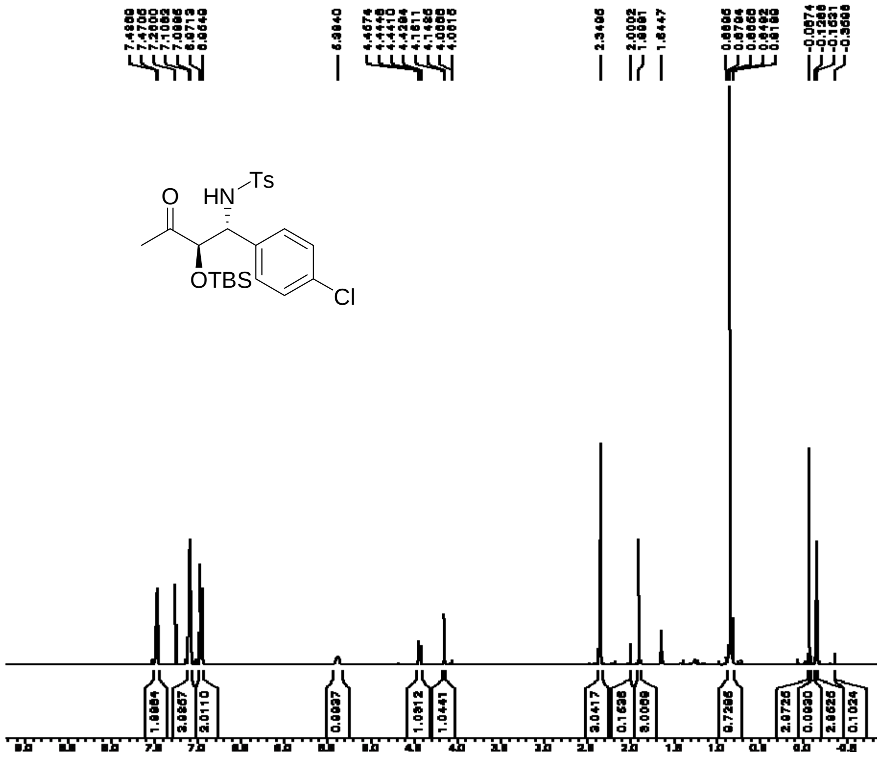


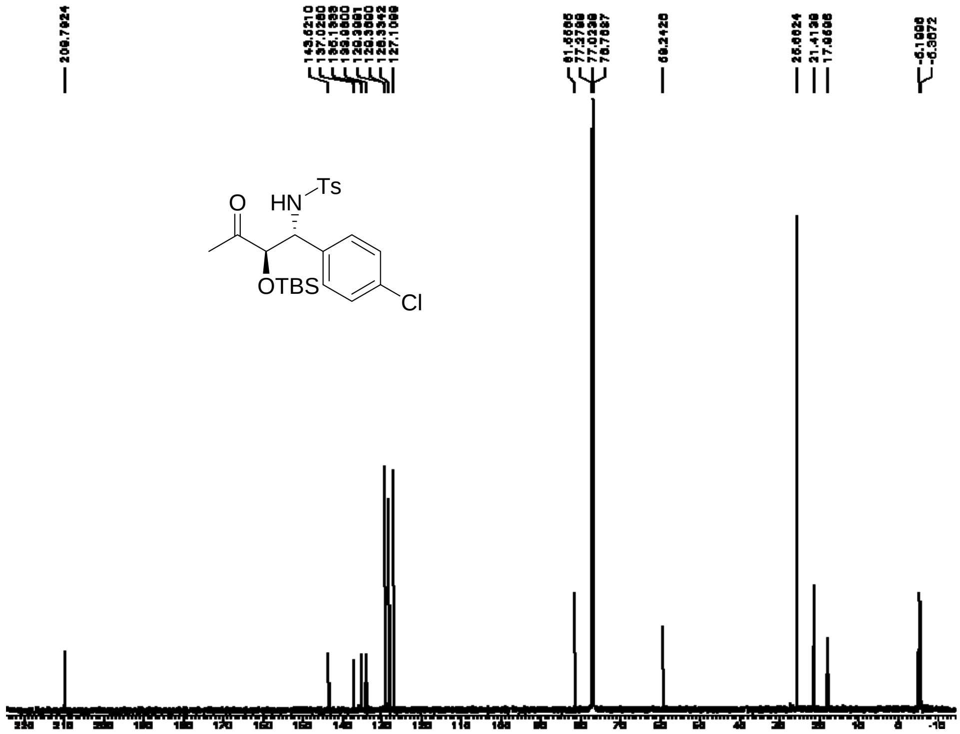
PeakTable

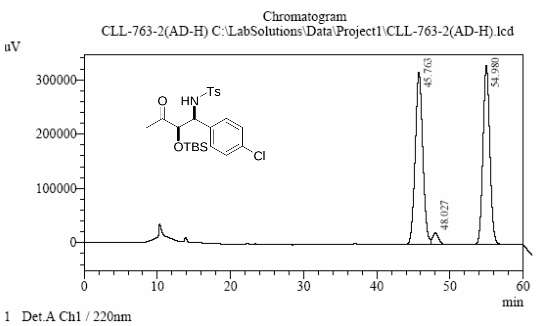
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.375	42561496	1317742	99.362	99.514
2	31.556	273373	6438	0.638	0.486
Total		42834869	1324180	100.000	100.000

Compound **5**: a white solid; t_r (major) = 45.8 min, t_r (minor) = 55.2 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.3 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.15 (s, 3H), -0.07 (s, 3H), 0.85 (s, 9H), 1.89 (s, 3H), 2.35 (s, 3H), 4.15-4.16 (d, *J* = 6.3 Hz, 1H), 4.43-4.46 (m, 1H), 5.38 (br s, 1H), 6.95-6.97 (d, *J* = 8.2 Hz, 2H), 7.08-7.10 (d, *J* = 8.9 Hz, 4H), 7.47-7.49 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, -5.2, 17.9, 21.4, 25.6, 25.7, 59.2, 81.6, 127.1, 128.3, 128.4, 129.4, 133.9, 135.1, 137.0, 143.5, 209.8; HRMS (ESI) *m/z* calcd for $C_{23}H_{32}ClNO_4SSi$ $[M+Na]^+$ 504.1402, found 504.1408. $[\alpha]_D^{20}$ = -32.9 (c = 2.23, $CHCl_3$).



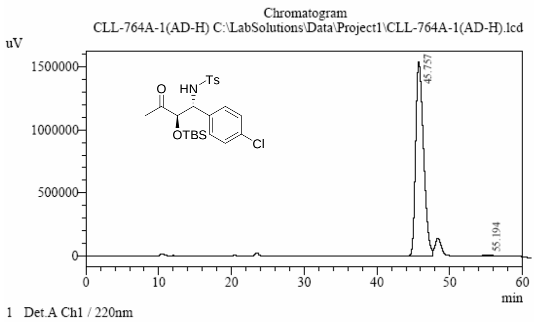




PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	45.763	22888415	317653	50.101	47.511
2	48.027	1252529	21119	2.742	3.159
3	54.980	21543488	329819	47.157	49.330
Total		45684432	668592	100.000	100.000

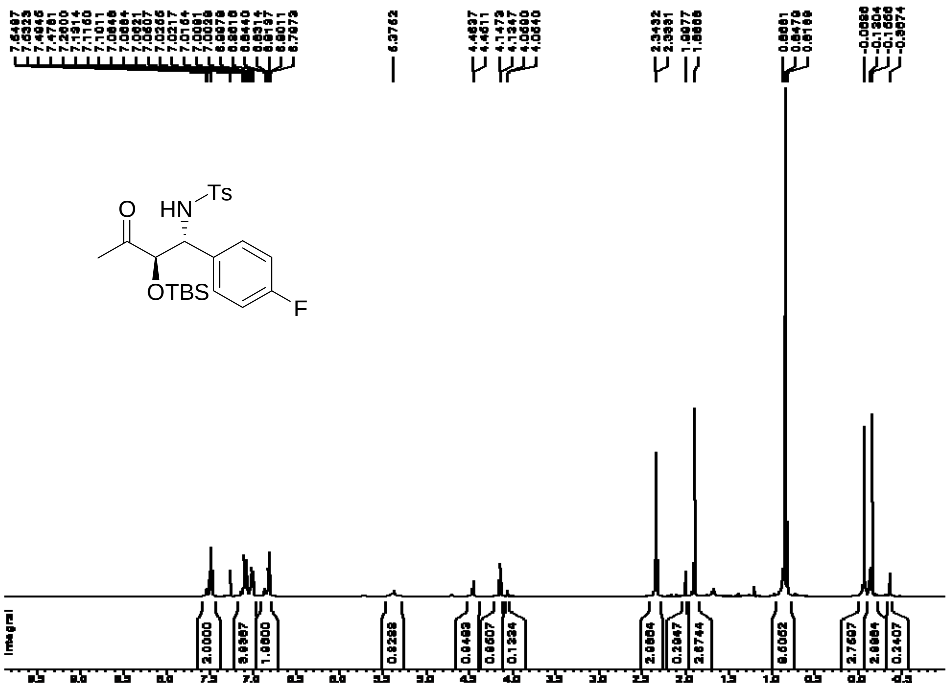


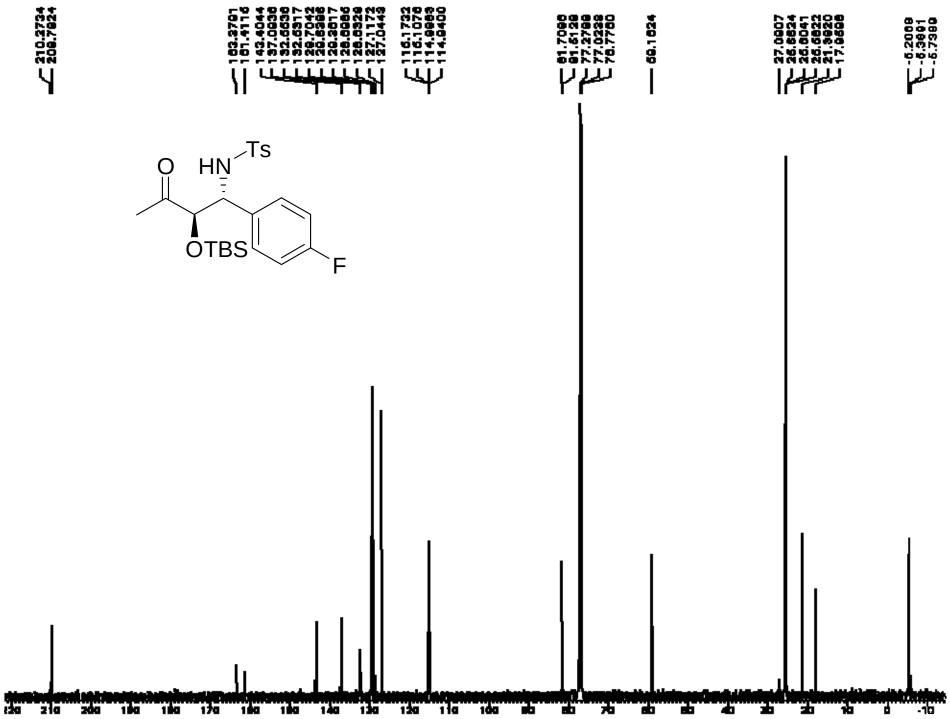
PeakTable

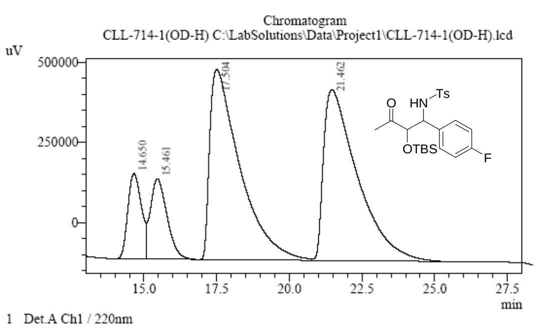
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	45.757	116779888	1539440	99.556	99.471
2	55.194	520813	8192	0.444	0.529
Total		117300700	1547632	100.000	100.000

Compound **6**: a white solid; t_r (minor) = 19.2 min, t_r (major) = 23.9 min (Chiralcel OD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.17 (s, 3H), -0.08 (s, 3H), 0.84 (s, 9H), 1.90 (s, 3H), 2.33 (s, 3H), 4.13-4.14 (d, *J* = 6.3 Hz, 1H), 4.44-4.47 (m, 1H), 5.45-5.47 (d, *J* = 7.6 Hz, 1H), 6.79-6.83 (m, 2H), 6.99-7.08 (m, 2H), 7.08-7.09 (d, *J* = 8.2 Hz, 2H), 7.47-7.49 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, -5.2, 17.9, 21.4, 25.5, 25.6, 59.2, 81.7, 114.9, 127.1, 128.6, 129.6, 132.6, 137.1, 143.4, 161.4, 209.8; HRMS (ESI) *m/z* calcd for $C_{23}H_{32}FNO_4SSi$ $[M+Na]^+$ 488.1698, found 488.1708. $[\alpha]_D^{20}$ = -13.8 (c = 1.94, $CHCl_3$).



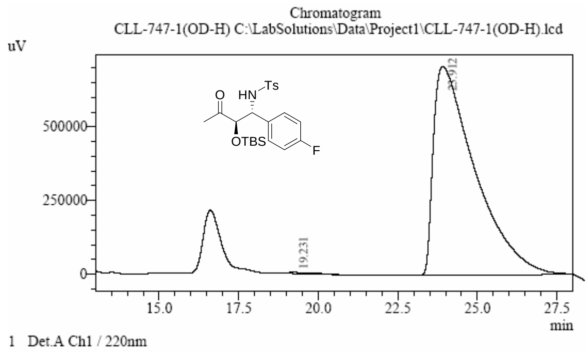




PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.650	8644301	266136	8.233	16.180
2	15.461	10024829	250817	9.548	15.249
3	17.504	42958100	594363	40.914	36.135
4	21.462	43368282	533535	41.305	32.437
Total		104995512	1644851	100.000	100.000

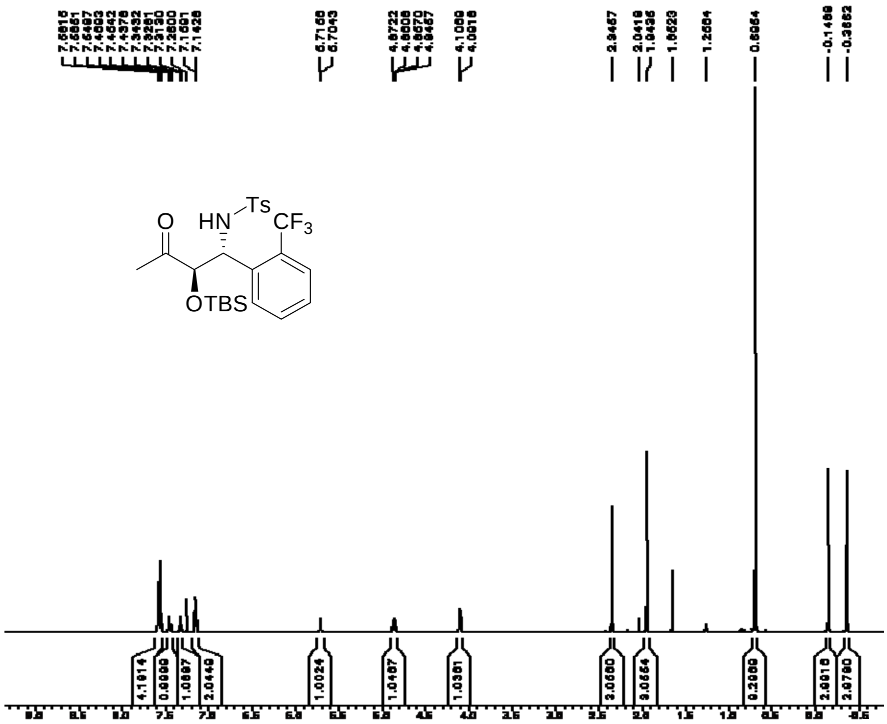


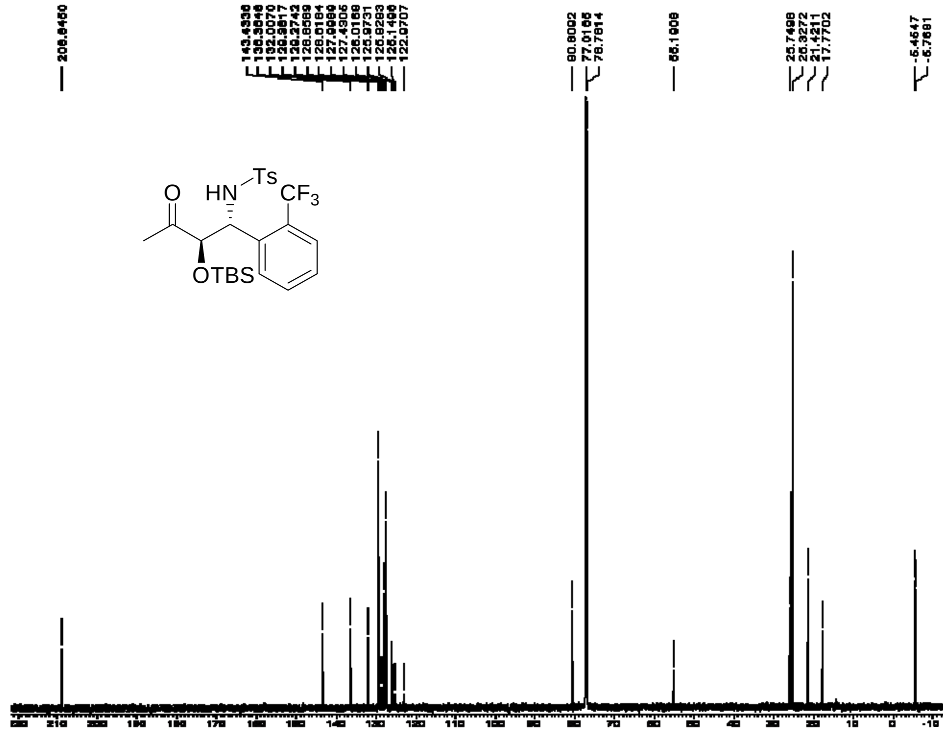
PeakTable

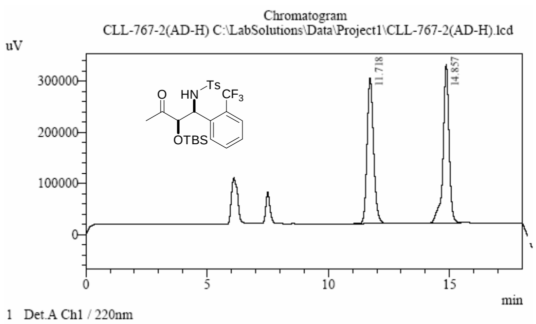
Detector A Ch1 220nm

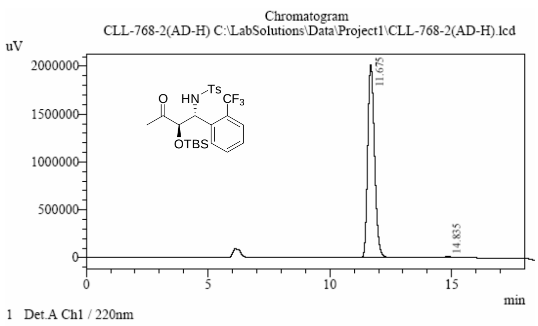
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.231	362457	3966	0.557	0.557
2	23.912	64664961	708037	99.443	99.443
Total		65027418	712003	100.000	100.000

Compound **7**: a white solid; t_r (major) = 11.7 min, t_r (minor) = 14.8 min (Chiralcel AD-H, λ = 220 nm, 10% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.37 (s, 3H), -0.15 (s, 3H), 0.69 (s, 9H), 1.94 (s, 3H), 2.35 (s, 3H), 4.09-4.11 (d, J = 7.6 Hz, 1H), 4.85-4.87 (t, 1H), 5.70-5.72 (d, J = 5.7 Hz, 1H), 7.14-7.16 (d, J = 8.2 Hz, 2H), 7.31-7.34 (t, 1H), 7.44-7.47 (t, 1H), 7.55-7.58 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.8, -5.5, 17.8, 21.4, 25.3, 25.7, 55.2, 80.6, 122.9, 125.9, 126.0, 127.4, 127.9, 128.6, 128.9, 129.4, 132.0, 136.4, 143.4, 208.8; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}F_3NO_4SSi$ $[M+Na]^+$ 538.1666, found 538.1664. $[\alpha]_D^{20}$ = -49.4 (c = 2.7, $CHCl_3$).









PeakTable

Detector A Ch1 220nm

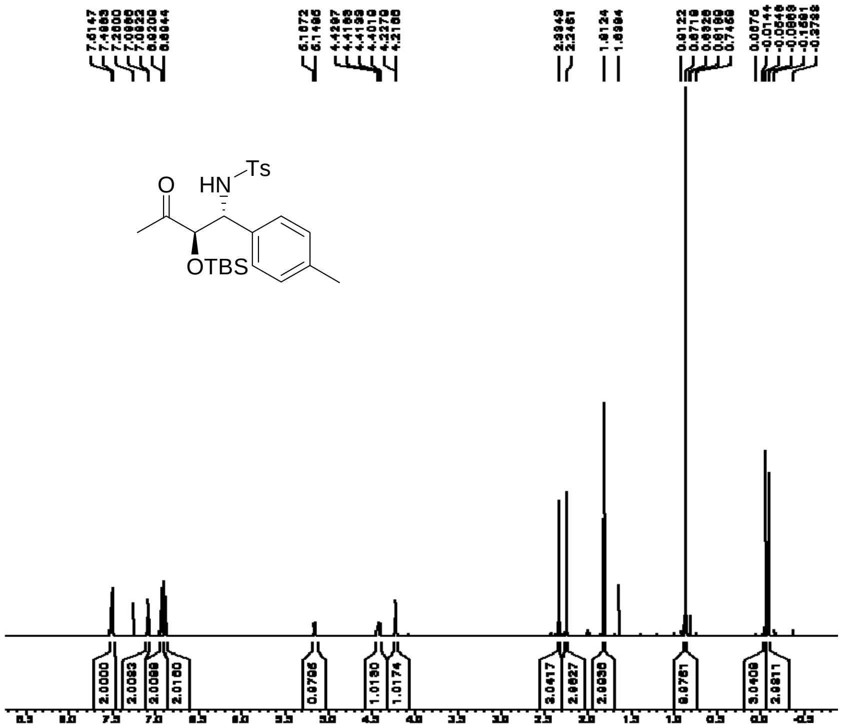
Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.718	5321491	284662	49.929	47.840
2	14.857	5336528	310363	50.071	52.160
Total		10658019	595025	100.000	100.000

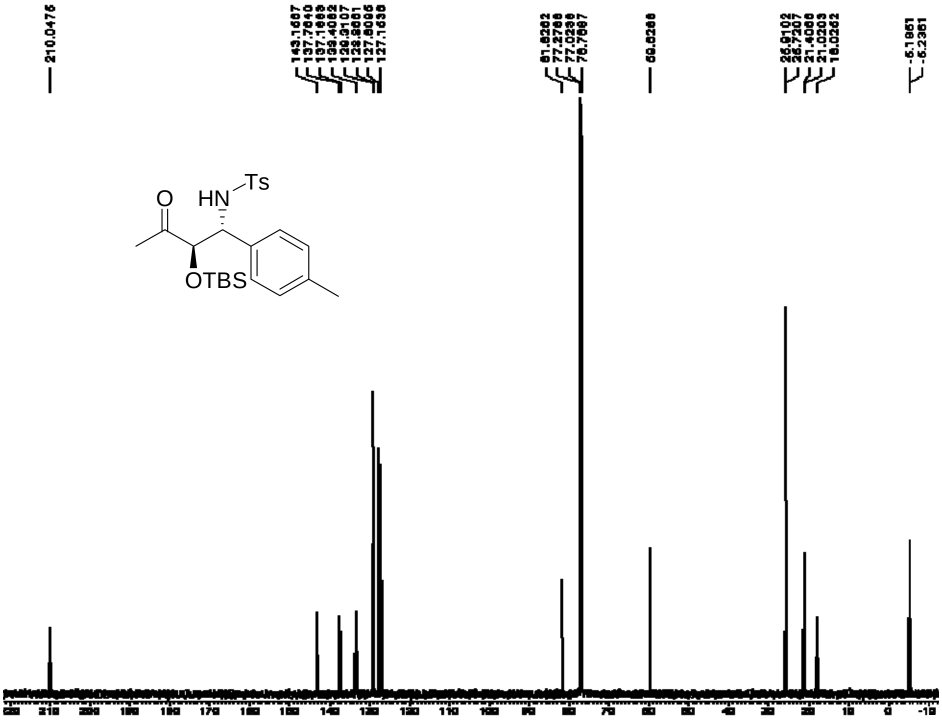
PeakTable

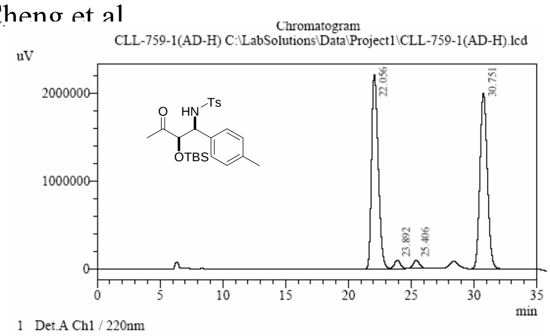
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.675	39698002	2016949	99.331	99.237
2	14.835	267452	15510	0.669	0.763
Total		39965453	2032460	100.000	100.000

Compound **8**: a white solid; t_r (major) = 22.2 min, t_r (minor) = 30.9 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.09 (s, 3H), -0.01 (s, 3H), 0.87 (s, 9H), 1.81 (s, 3H), 2.25 (s, 3H), 2.33 (s, 3H), 4.21-4.23 (d, *J* = 5.7 Hz, 1H), 4.40-4.43 (t, 1H), 5.15-5.17 (d, *J* = 8.9 Hz, 1H), 6.89-6.92 (m, 4H), 7.08-7.09 (d, *J* = 8.2 Hz, 2H), 7.49-7.51 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.24, -5.19, 18.0, 21.0, 21.4, 25.7, 25.9, 59.6, 81.8, 127.2, 127.8, 128.9, 129.3, 133.4, 137.2, 137.8, 143.2, 210.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{35}NO_4SSi$ $[M+Na]^+$ 484.1948, found 484.1944. $[\alpha]_D^{20}$ = -33.3 (c = 1.9, $CHCl_3$).


O
HN
Ts
OTBS

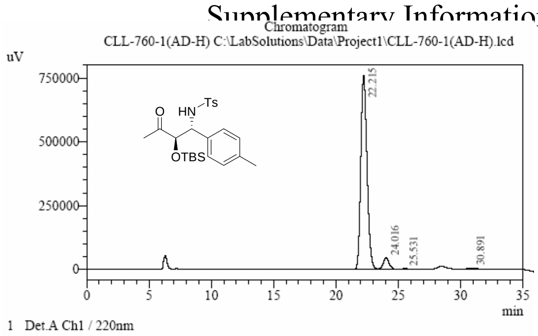

O
HN
Ts
OTBS



PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.056	81301841	2205141	47.816	50.164
2	23.892	3207488	98258	1.886	2.235
3	25.406	3253196	94960	1.913	2.160
4	30.751	82268997	1997503	48.385	45.441
Total		170031523	4395862	100.000	100.000

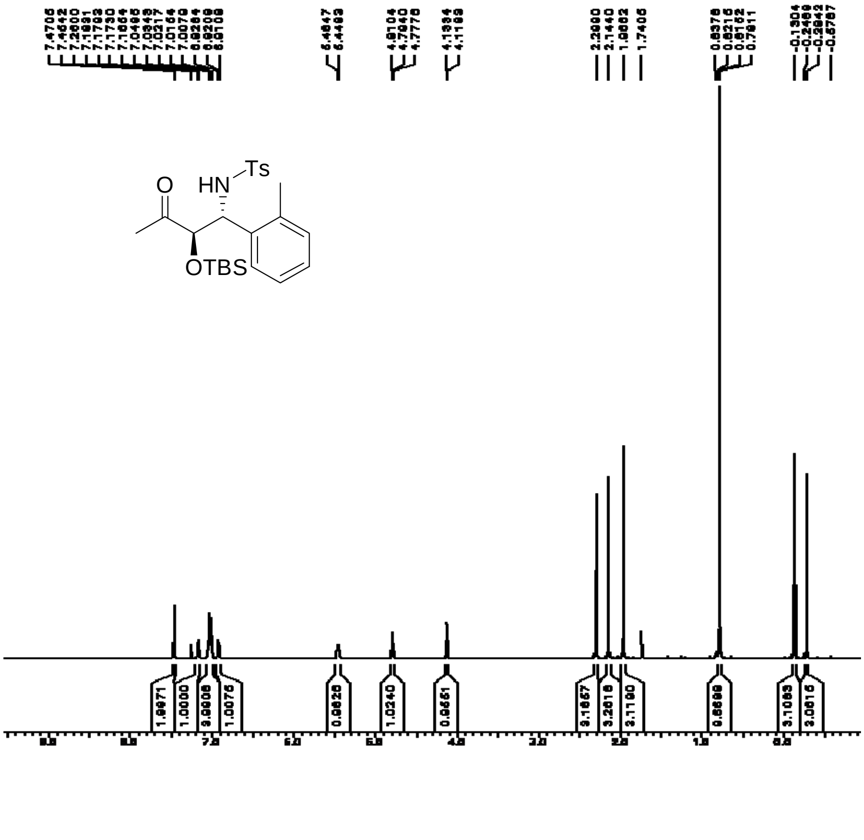


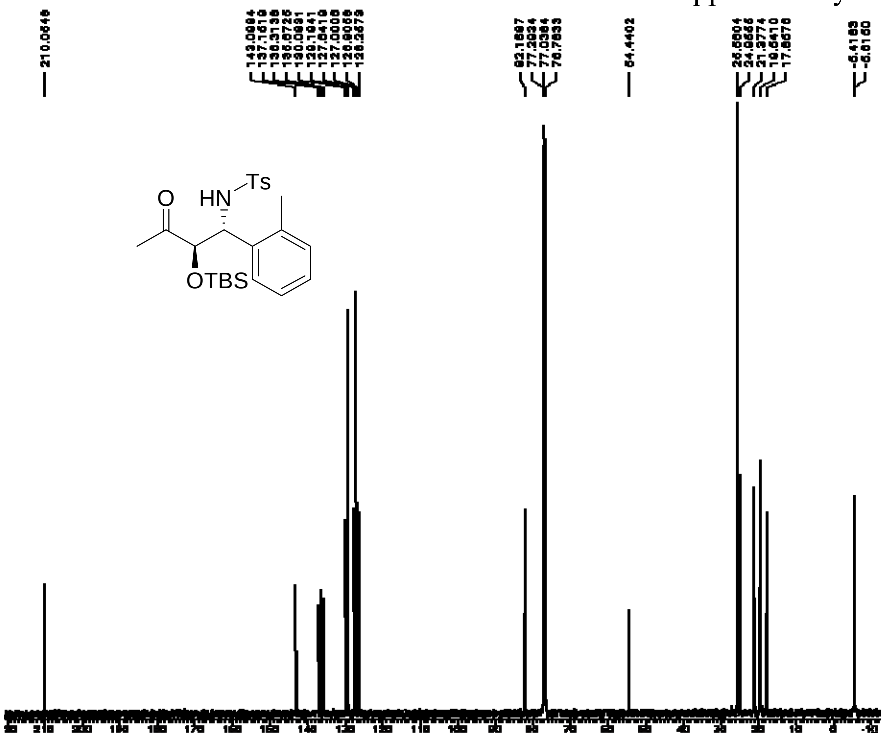
PeakTable

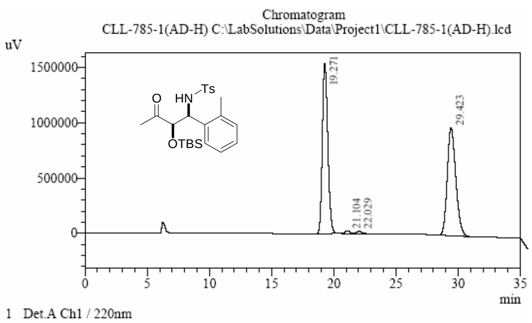
Detector A Ch1 220nm

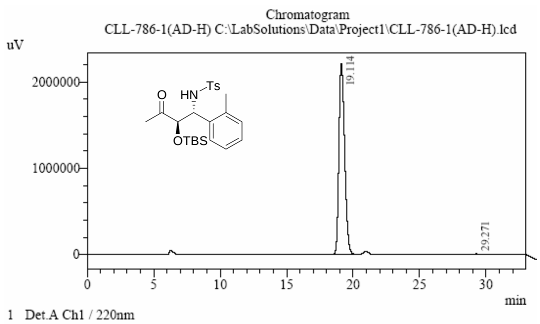
Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.215	26446715	759545	93.721	93.606
2	24.016	1475688	44468	5.229	5.480
3	25.531	93289	2776	0.331	0.342
4	30.891	202841	4641	0.719	0.572
Total		28218534	811431	100.000	100.000

Compound **9**: a white solid; t_r (major) = 19.1 min, t_r (minor) = 29.3 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.28 (s, 3H), -0.13 (s, 3H), 0.78 (s, 9H), 1.96 (s, 3H), 2.14 (s, 3H), 2.30 (s, 3H), 4.12-4.13 (d, *J* = 7.6 Hz, 1H), 4.78-4.81 (t, 1H), 5.45-5.46 (d, *J* = 8.2 Hz, 1H), 6.91-6.93 (m, 1H), 7.01-7.05 (m, 4H), 7.17-7.18 (m, 1H), 7.45-7.47 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.6, -5.4, 17.9, 19.5, 21.4, 24.9, 25.6, 54.4, 82.2, 126.3, 126.9, 127.0, 127.6, 129.2, 130.1, 135.7, 1363, 137.2, 143.1, 210.1; HRMS (ESI) *m/z* calcd for $C_{24}H_{35}NO_4SSi$ $[M+Na]^+$ 484.1948, found 484.1953. $[\alpha]_D^{20}$ = +3.6 (c = 2.8, $CHCl_3$).









PeakTable

Detector A Ch1 220nm

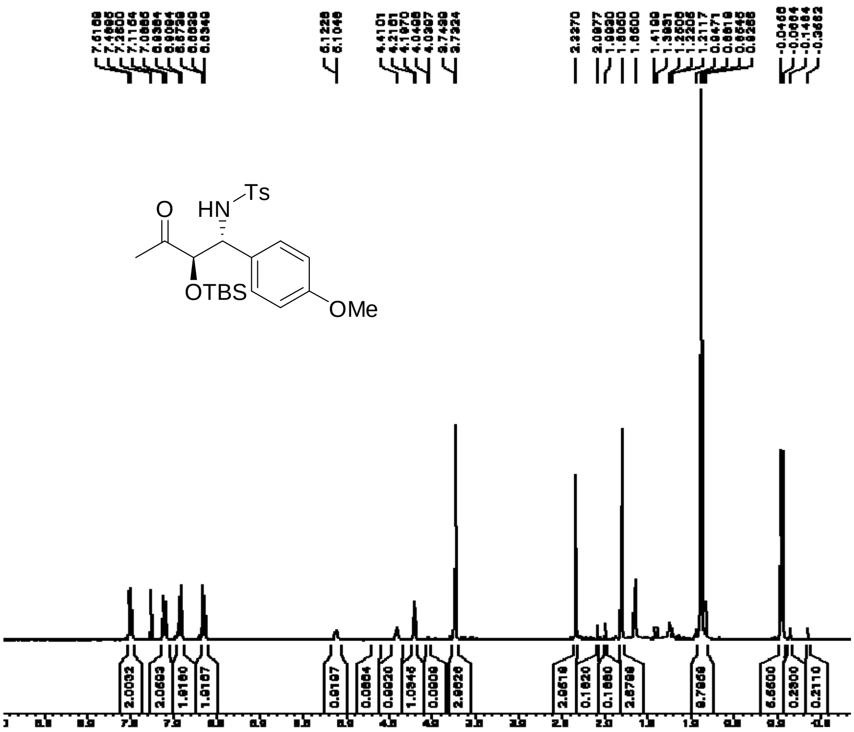
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.271	46934136	1538193	49.414	60.090
2	21.104	582594	23331	0.613	0.911
3	22.029	621517	21909	0.654	0.856
4	29.423	46842652	976394	49.318	38.143
Total		94980898	2559826	100.000	100.000

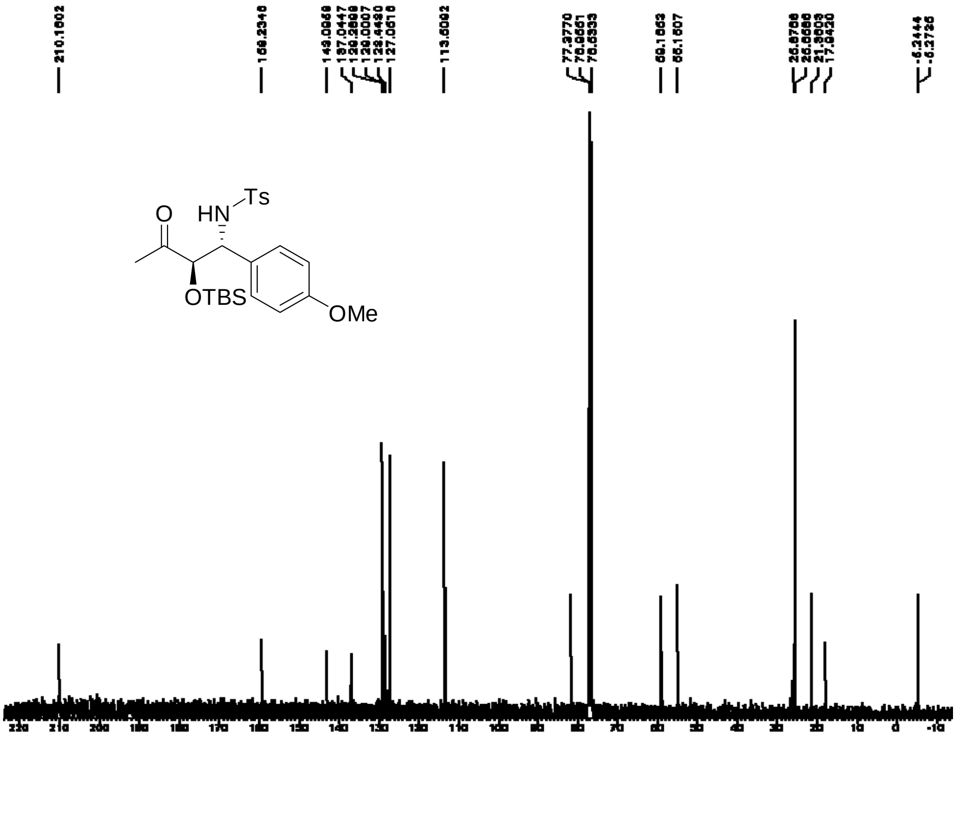
PeakTable

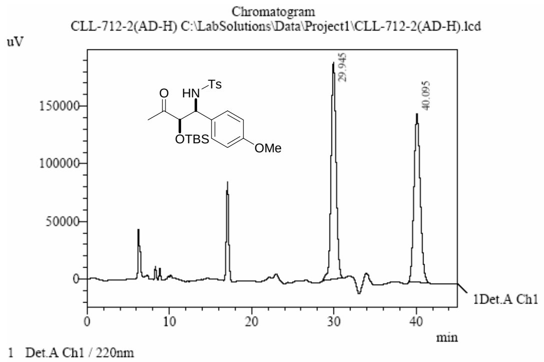
Detector A Ch1 220nm

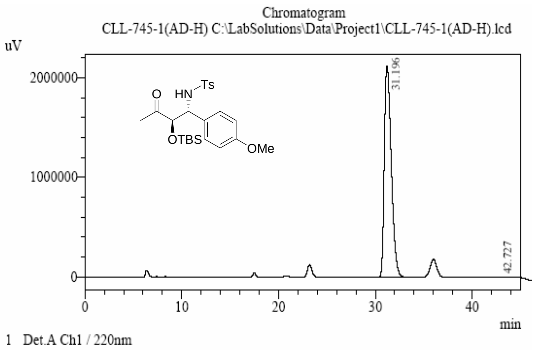
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.114	67060895	2211470	99.457	99.606
2	29.271	365916	8742	0.543	0.394
Total		67426811	2220213	100.000	100.000

Compound **10**: a white solid; t_r (major) = 31.2 min, t_r (minor) = 42.7 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.05 (s, 3H), -0.04 (s, 3H), 0.89 (s, 9H), 1.80 (s, 3H), 2.34 (s, 3H), 3.73 (s, 3H), 4.20-4.22 (d, *J* = 5.6 Hz, 1H), 4.39-4.43 (t, 1H), 5.10 (br s, 1H), 6.64-6.67 (d, *J* = 8.7 Hz, 2H), 6.91-6.94 (d, *J* = 8.7 Hz, 2H), 7.09-7.12 (d, *J* = 7.9 Hz, 2H), 7.49-7.52 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, -5.2, 17.9, 21.4, 25.7, 25.9, 55.2, 59.2, 82.1, 113.5, 127.1, 128.4, 129.0, 129.3, 137.0, 143.1, 159.2, 210.2; HRMS (ESI) *m/z* calcd for $C_{24}H_{35}NO_5SSi$ $[M+Na]^+$ 500.1897, found 500.1896; $[\alpha]_D^{20}$ = -42.6 (c = 1.03, $CHCl_3$).









PeakTable

Detector A Ch1 220nm

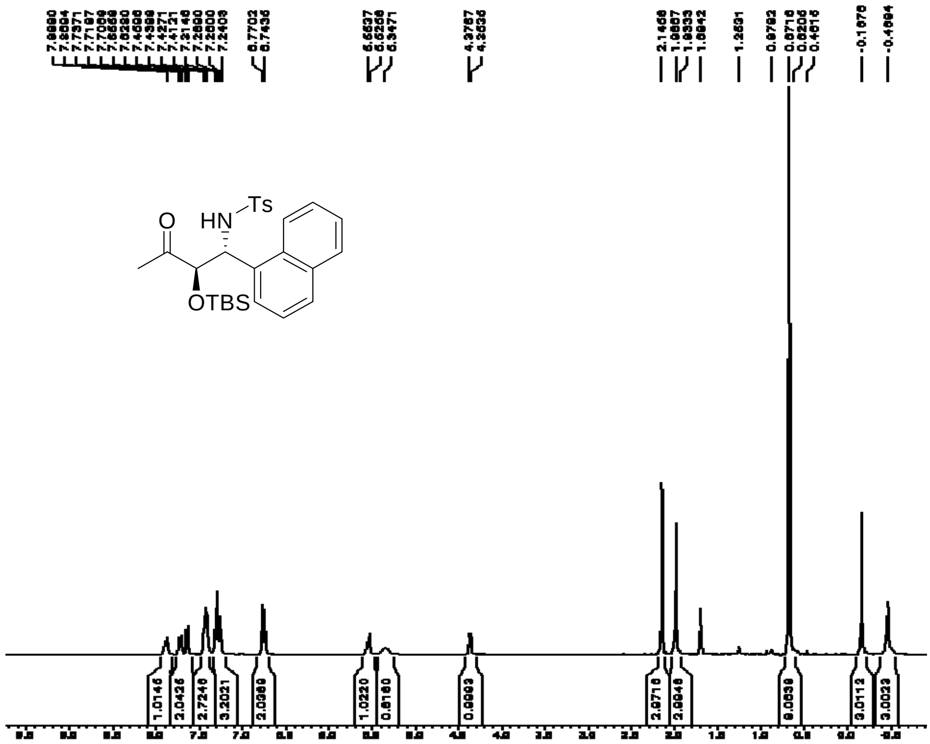
Peak#	Ret. Time	Area	Height	Area %	Height %
1	29.945	7891628	188094	50.374	56.225
2	40.095	7774418	146446	49.626	43.775
Total		15666047	334540	100.000	100.000

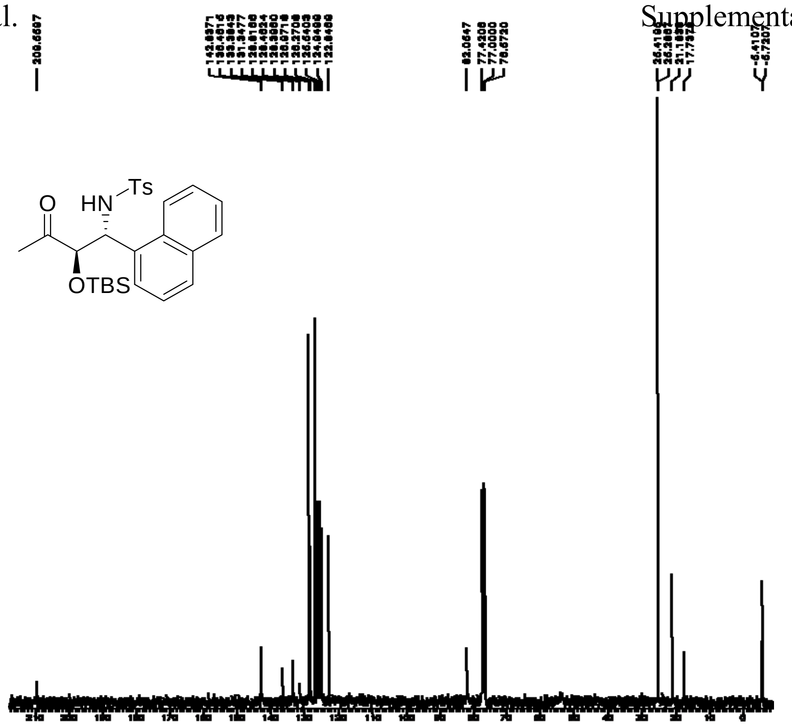
PeakTable

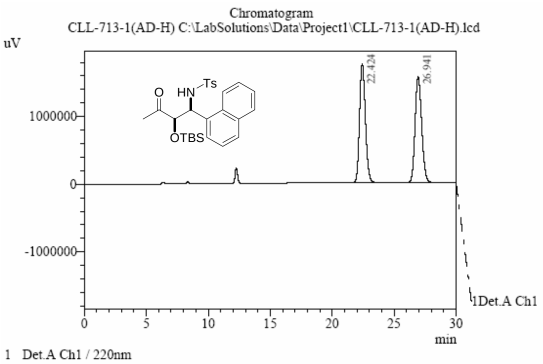
Detector A Ch1 220nm

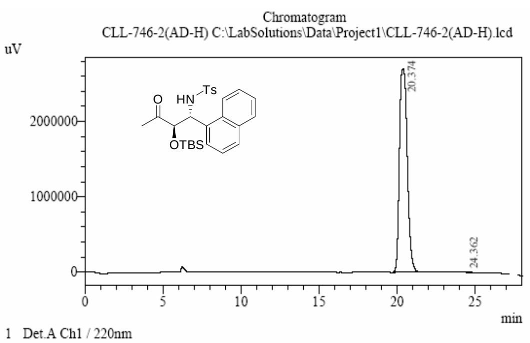
Peak#	Ret. Time	Area	Height	Area %	Height %
1	31.196	106566146	2120768	99.741	99.734
2	42.727	276442	5646	0.259	0.266
Total		106842587	2126415	100.000	100.000

Compound **11**: a white solid; t_r (major) = 20.4 min, t_r (minor) = 24.4 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.47 (s, 3H), -0.17 (s, 3H), 0.67 (s, 9H), 1.98 (s, 3H), 2.14 (s, 3H), 4.35 - 4.37 (d, *J* = 6.9 Hz, 1H), 5.35 (br s, 1H), 5.53-5.55 (d, *J* = 8.4 Hz, 1H), 6.74-6.77 (d, *J* = 8.0 Hz, 2H), 7.24-7.31 (m, 3H), 7.41-7.45 (m, 3H), 7.62-7.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ-5.73, -5.42, 17.7, 21.2, 25.3, 25.4, 82.0, 116.8, 122.8, 124.9, 125.5, 126.3, 126.9, 128.4, 128.8, 131.3, 133.1, 133.4, 136.5, 142.8, 209.6; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}NO_4SSi$ $[M+Na]^+$ 520.1948, found 520.1955; $[\alpha]_D^{20}$ = +73.9 (c = 2.13, $CHCl_3$).









PeakTable

Detector A Ch1 220nm

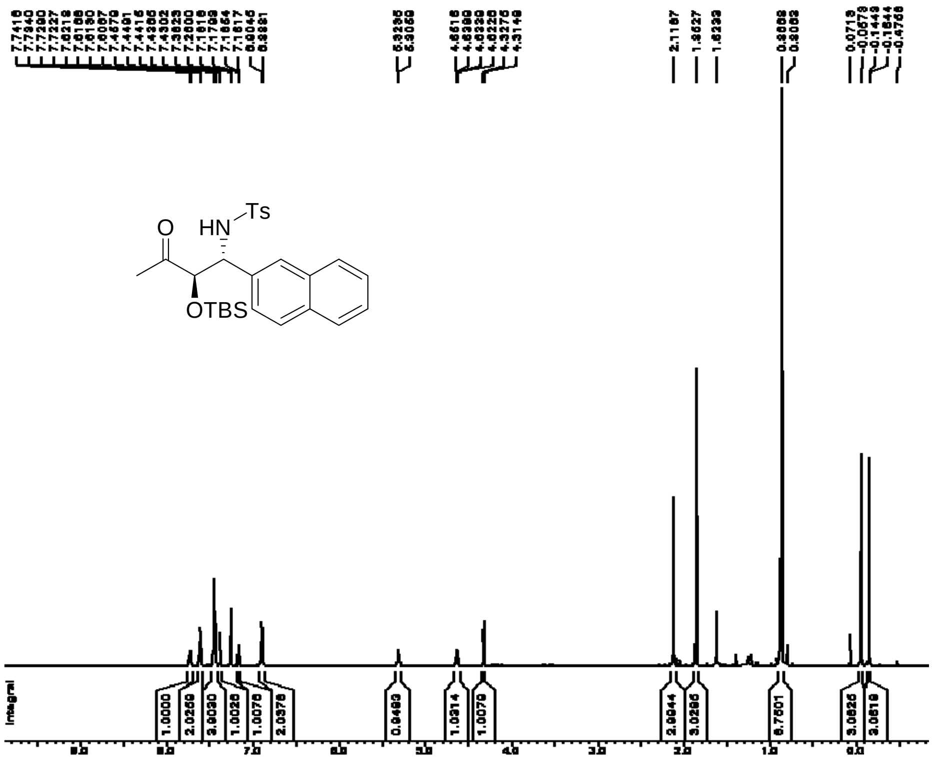
Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.424	57534491	1755251	49.553	52.879
2	26.941	58572926	1564118	50.447	47.121
Total		116107417	3319369	100.000	100.000

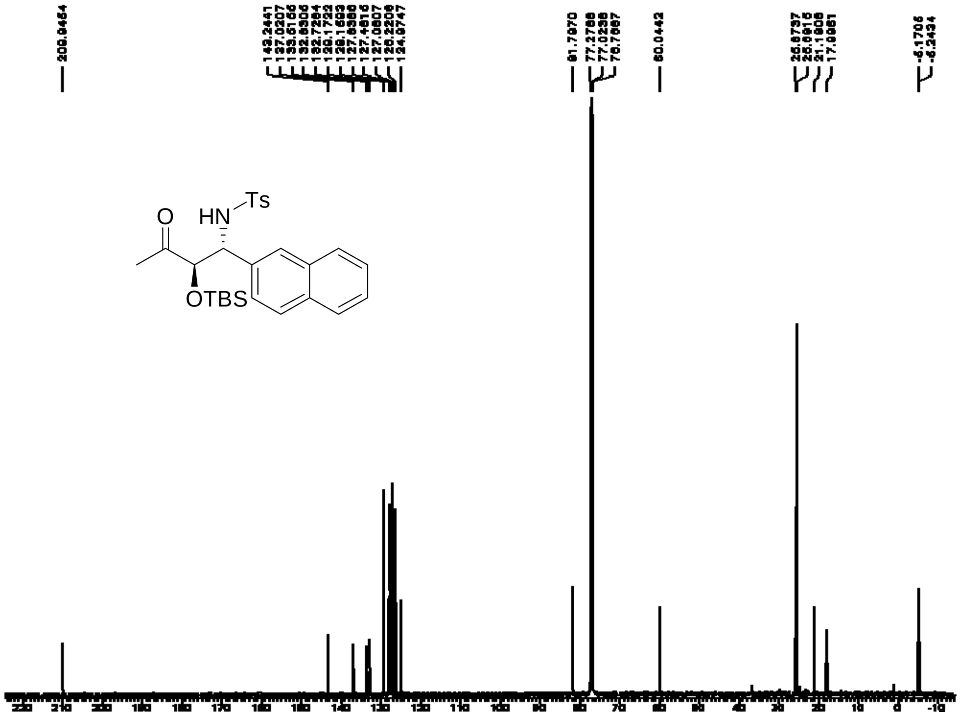
PeakTable

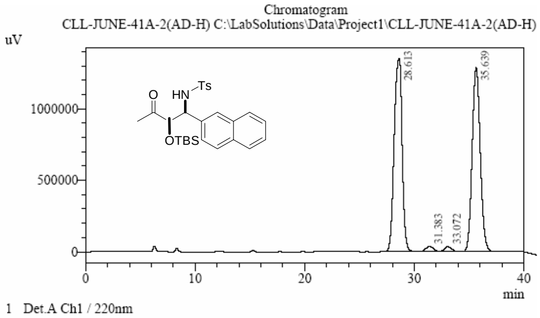
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.374	94494181	2702922	99.604	99.528
2	24.362	375783	12813	0.396	0.472
Total		94869964	2715735	100.000	100.000

Compound **12**: a white solid; t_r (major) = 28.3 min, t_r (minor) = 35.7 min (Chiralcel AD-H, λ = 220 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.14 (s, 3H), -0.06 (s, 3H), 0.87 (s, 9H), 1.85 (s, 3H), 2.12 (s, 3H), 4.31-4.33 (d, *J* = 6.3 Hz, 1H), 4.63-4.65 (t, 1H), 5.31-5.32 (d, *J* = 8.8 Hz, 1H), 6.89-6.90 (d, *J* = 8.2 Hz, 2H), 7.16-7.18 (m, 1H), 7.38 (s, 1H), 7.43-7.46 (m, 4H), 7.61-7.62 (m, 2H), 7.72-7.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.24, -5.17, 17.9, 21.2, 25.7, 25.9, 60.0, 81.8, 124.9, 126.2, 127.1, 127.5, 127.8, 128.2, 129.2, 132.7, 132.8, 133.5, 137.0, 143.2, 209.9; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}NO_4SSi$ $[M+Na]^+$ 520.1948, found 520.1948. $[\alpha]_D^{20}$ = -25.3 (c = 1.3, $CHCl_3$).



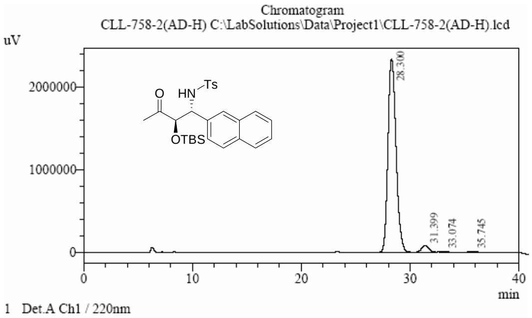




PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.613	67818886	1349112	49.606	49.948
2	31.383	1569770	34834	1.148	1.290
3	33.072	1473465	32660	1.078	1.209
4	35.639	65852788	1284418	48.168	47.553
Total		136714910	2701023	100.000	100.000

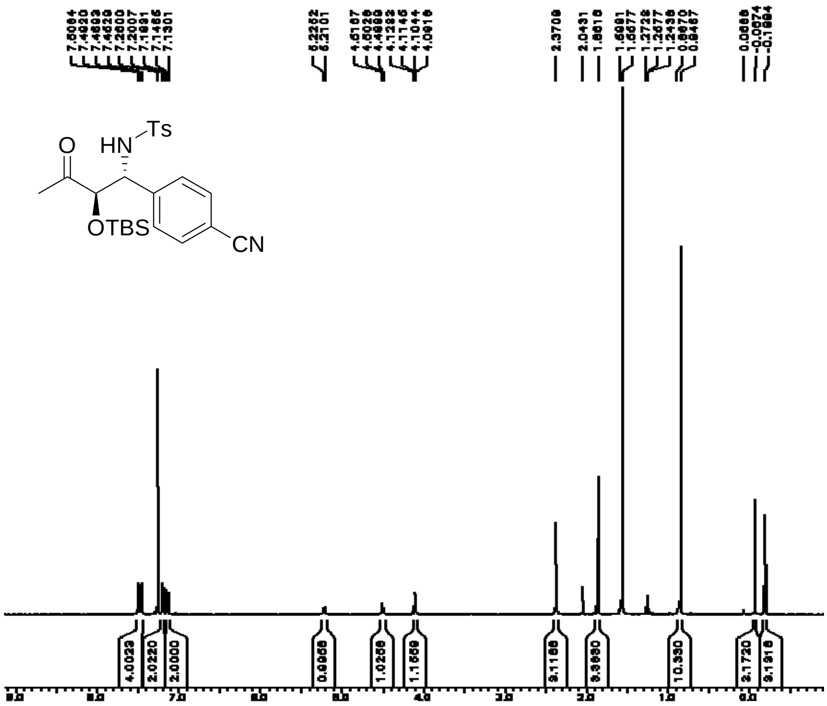


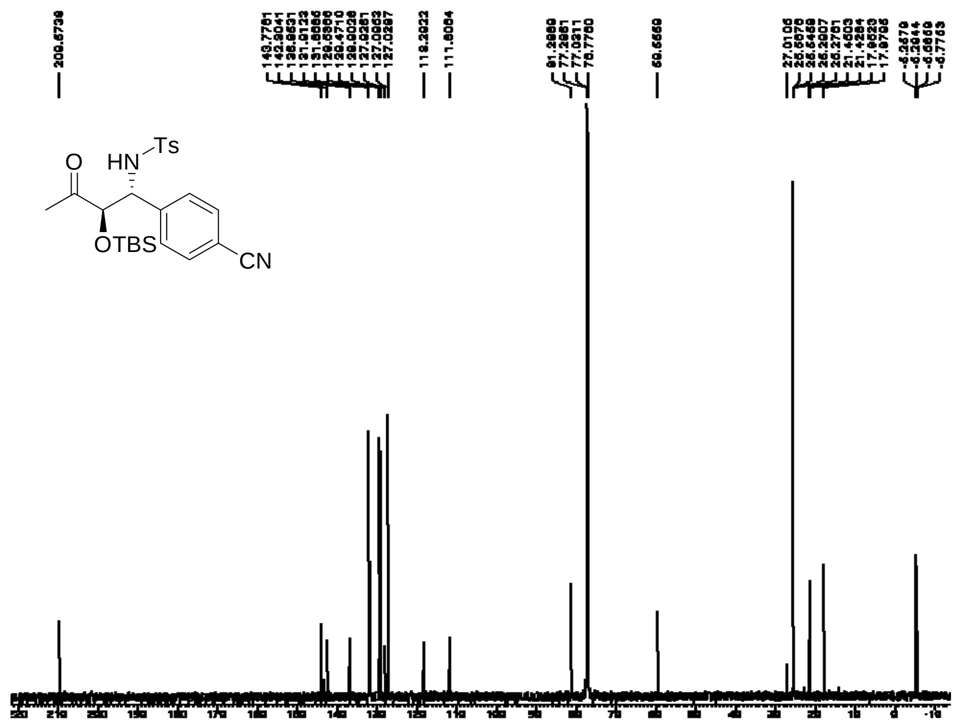
PeakTable

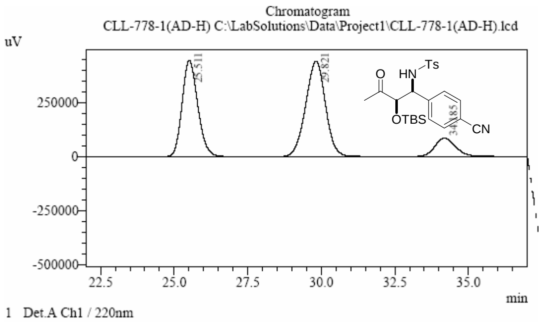
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.300	120819090	2336391	96.344	95.806
2	31.399	3630426	78464	2.895	3.217
3	33.074	444380	11540	0.354	0.473
4	35.745	510207	12277	0.407	0.503
Total		125404103	2438673	100.000	100.000

Compound **13**: a white solid; t_r (major) = 26.0 min, t_r (minor) = 30.5 min (Chiralcel AD-H, λ = 220 nm, 10% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.19 (s, 3H), -0.07 (s, 3H), 0.85 (s, 9H), 1.86 (s, 3H), 2.37 (s, 3H), 4.09-4.10 (d, *J* = 6.3 Hz, 1H), 4.48-4.52 (t, 1H), 5.21-5.22 (d, *J* = 7.6 Hz, 1H), 7.13-7.14 (d, *J* = 8.2 Hz, 2H), 7.18-7.20 (d, *J* = 8.8 Hz, 2H), 7.45-7.47 (d, *J* = 8.2 Hz, 2H), 7.49-7.51 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.8, -5.3, 17.9, 21.4, 25.3, 25.5, 59.6, 81.3, 111.8, 118.3, 127.1, 127.9, 128.9, 131.9, 136.8, 143.8, 209.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_2O_4SSi$ $[M+Na]^+$ 495.1744, found 495.1744. $[\alpha]_D^{20}$ = -35.4 (c = 1.81, $CHCl_3$).



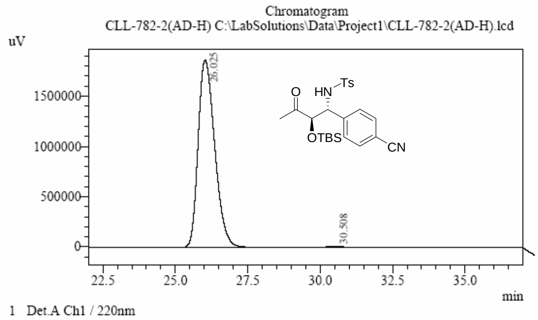




PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.511	16500983	445119	40.025	45.919
2	29.821	20620639	440538	50.017	45.446
3	34.185	4105415	83706	9.958	8.635
Total		41227036	969364	100.000	100.000

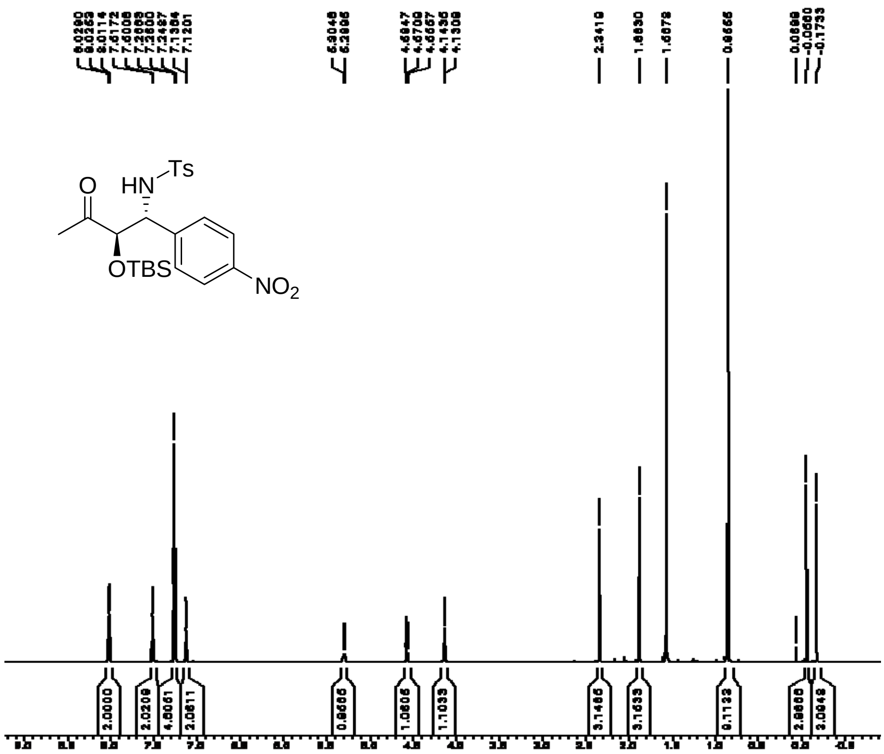


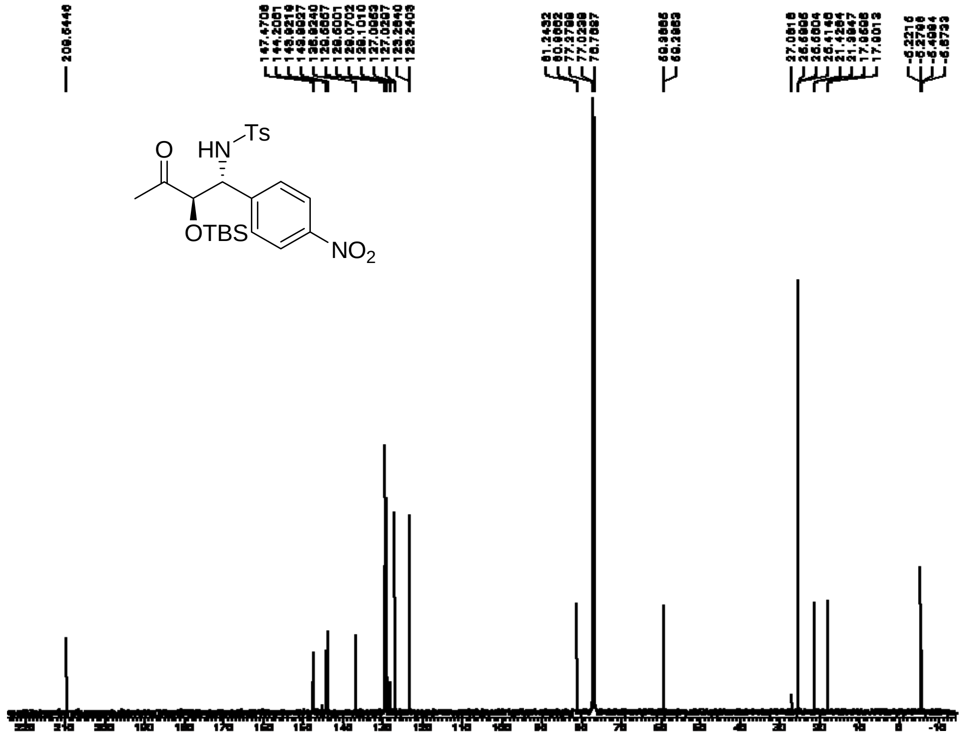
PeakTable

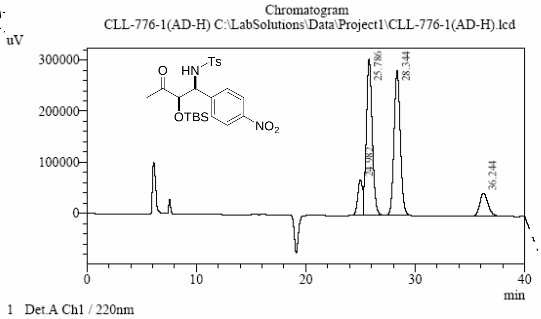
Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.025	74744307	1868765	99.296	99.328
2	30.508	529612	12650	0.704	0.672
Total		75273919	1881415	100.000	100.000

Compound **14**: a white solid; t_r (major) = 25.5 min, t_r (minor) = 28.1 min (Chiralcel AD-H, λ = 220 nm, 10% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.17 (s, 3H), -0.06 (s, 3H), 0.86 (s, 9H), 1.88 (s, 3H), 2.34 (s, 3H), 4.13-4.14 (d, J = 6.3 Hz, 1H), 4.55-4.58 (t, 1H), 5.28-5.30 (d, J = 7.6 Hz, 1H), 7.12-7.13 (d, J = 8.2 Hz, 2H), 7.24-7.26 (d, J = 8.8 Hz, 2H), 7.50-7.51 (d, J = 8.2 Hz, 2H), 8.01-8.03 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.7, -5.3, 17.9, 21.4, 25.4, 25.5, 59.3, 81.2, 123.2, 127.1, 129.0, 129.5, 136.8, 143.8, 144.2, 147.5, 209.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{32}N_2O_6SSi$ $[M+Na]^+$ 515.1643, found 515.1660. $[\alpha]_D^{20}$ = -34.5 (c = 2.82, $CHCl_3$).



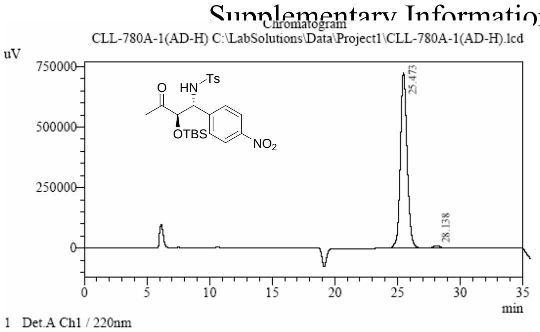




PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.982	2065353	69028	7.618	9.856
2	25.786	11540271	305198	42.568	43.579
3	28.344	11253350	282127	41.510	40.285
4	36.244	2251118	43975	8.304	6.279
Total		27110092	700328	100.000	100.000

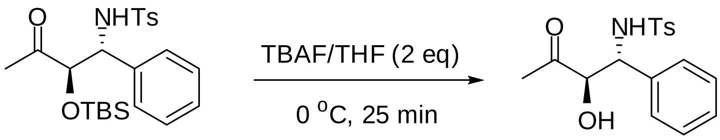


PeakTable

Detector A Ch1 220nm

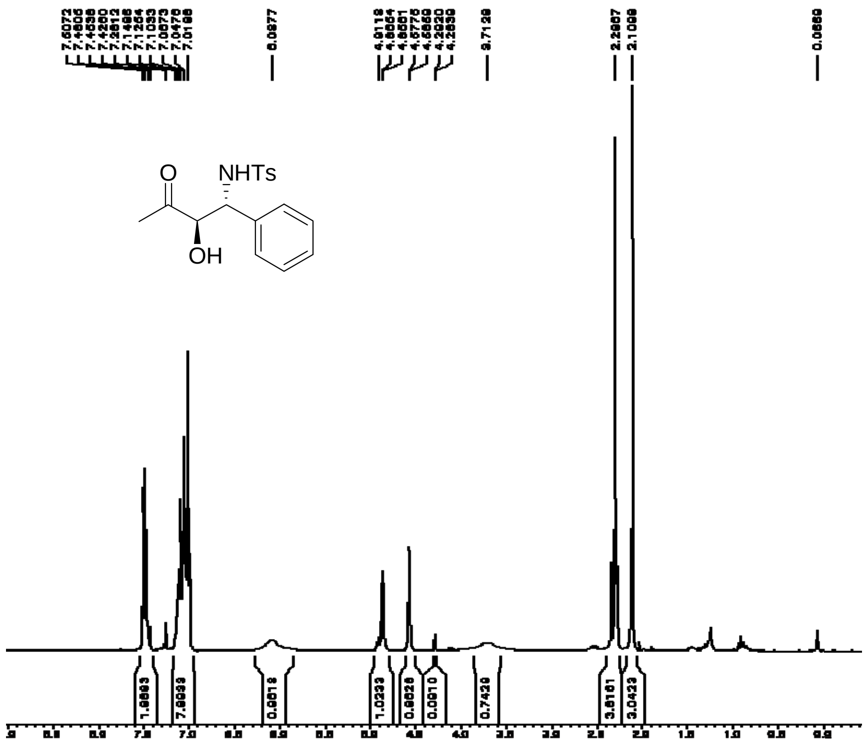
Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.473	27409820	726013	98.446	98.592
2	28.138	432670	10370	1.554	1.408
Total		27842490	736383	100.000	100.000

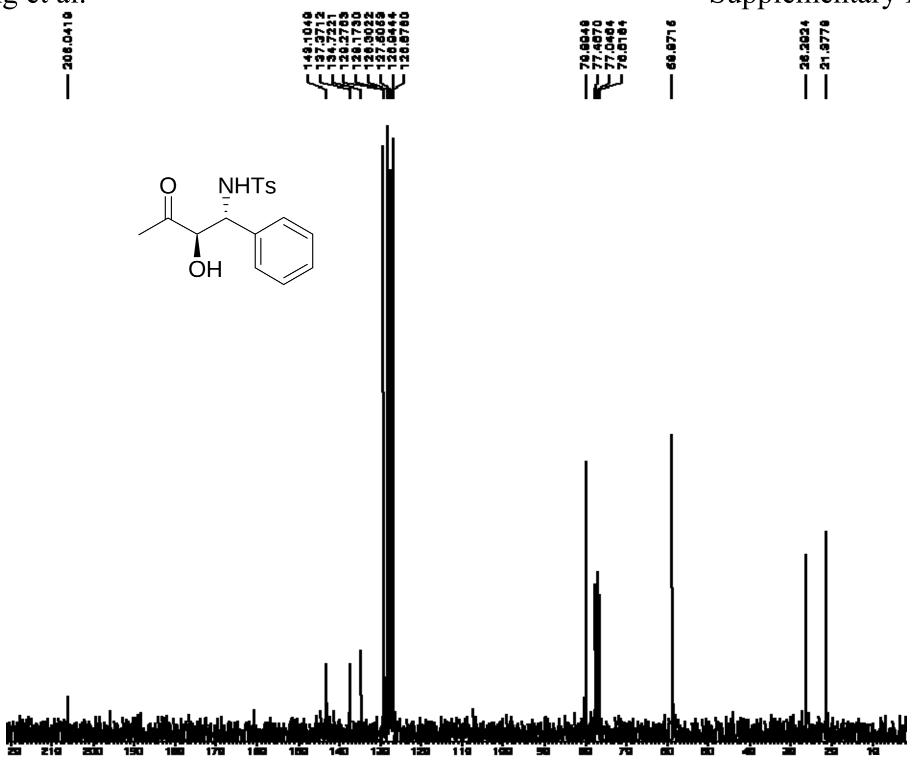
Representative procedure for the desilylation of Mannich product

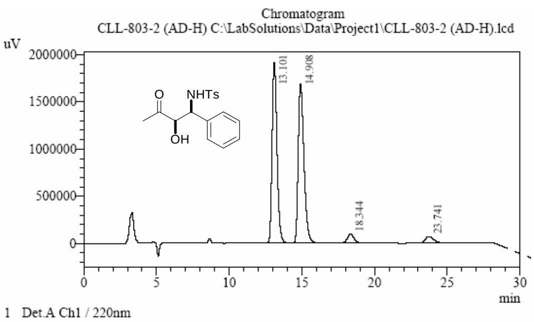


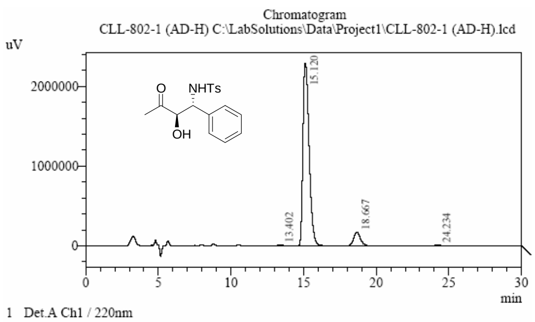
3 (>99% ee) >99% ee

A solution of TBAF (1 M in THF, 0.8 mL) was injected into compound **3** (181 mg, 0.4 mmol) in a round bottom flask at 0 °C. The mixture was vigorously stirred at 0 °C till the TLC showed the disappearance of compound **3**. The reaction mixture was directly subjected to column chromatographic purification using mixtures of hexane/ethyl acetate as eluants (2/1 to 7/5) to afford the desired product as a white solid (109 mg, 81% yield).









PeakTable

Detector A Ch1 220nm

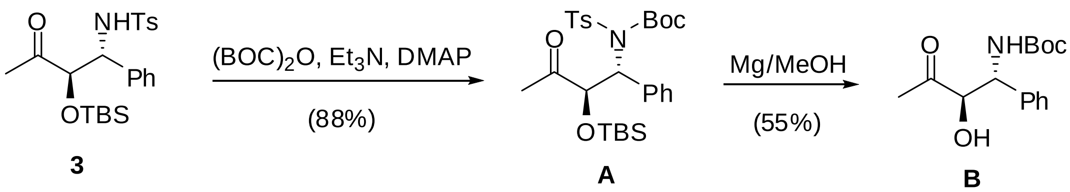
Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.101	44825915	1911220	46.512	50.948
2	14.908	45838816	1677406	47.563	44.715
3	18.344	2888949	93844	2.998	2.502
4	23.741	2821551	68822	2.928	1.835
Total		96375232	3751292	100.000	100.000

PeakTable

Detector A Ch1 220nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.402	226550	9515	0.308	0.385
2	15.120	67747993	2287390	92.043	92.462
3	18.667	5344227	169618	7.261	6.856
4	24.234	286034	7353	0.389	0.297
Total		73604805	2473877	100.000	100.000

Representative procedure for the cleavage of Tosyl protective group

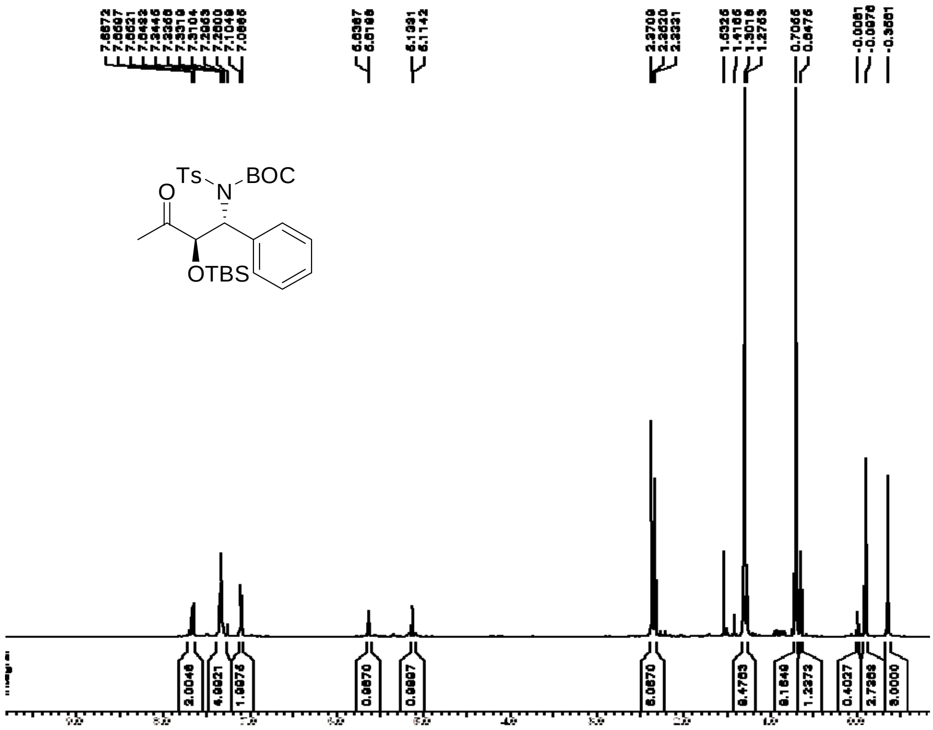


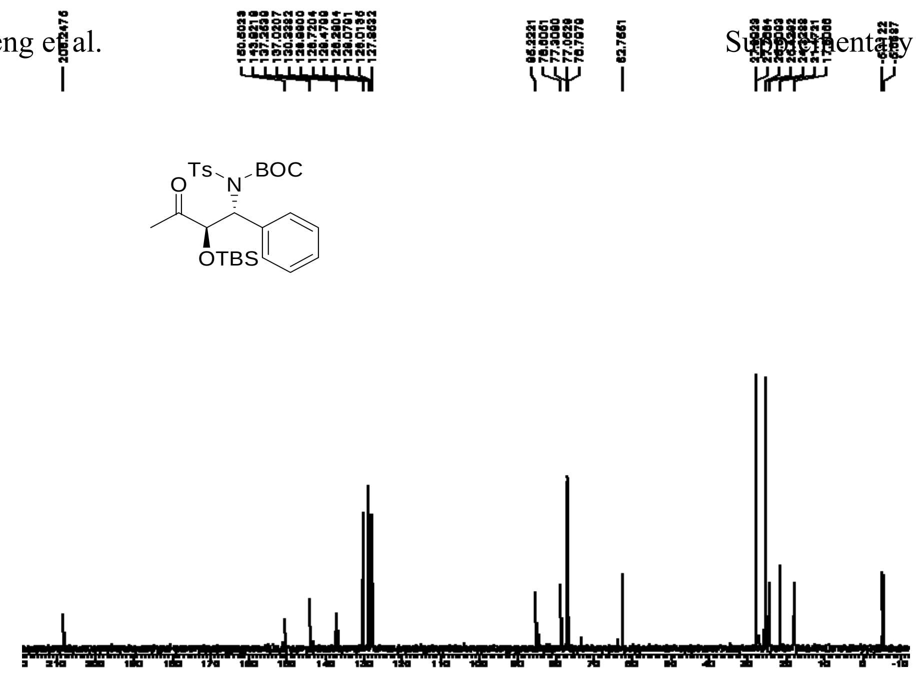
The Mannich product **3** (136 mg, 0.3 mmol) was placed in a 25 ml round bottom flask which was evacuated and filled with N_2. Anhydrous CH_2Cl_2 (5 mL) was added, followed by the addition of triethylamine (0.1 mL, 0.75 mmol), $(BOC)_2O$ (206 μl, 0.9 mmol) and

DMAP (7.5 mg, 0.06 mmol) at 0 ^{o}C. After stirring at 0 ^{o}C for 3 hours, the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried, filtered, and concentrated, purification by column chromatography (hexane/ethyl acetate = 10:1) furnished **A** as a colorless oil (144 mg, 88%).

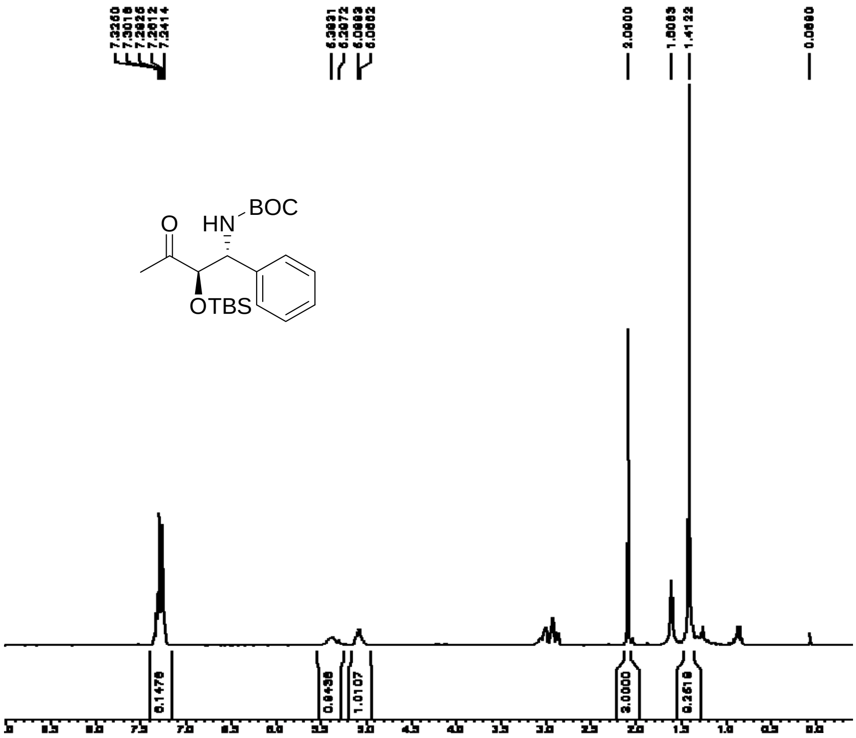
Compound **A** (54mg, 0.1 mmol) was transferred to an oven-dried schlenk flask equipped with a magnetic stirring bar. The schlenk flask was evacuated and filled with N_2, dry MeOH (3 mL) and Magnesium powder (24 mg, 1 mmol) were then added. The reaction mixture was sonicated for 45 minutes and then poured into a solution of 1M HCl (5 mL) and extracted with diethyl ether (2 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine, respectively. After filtration and concentration of the crude *in vacuo*, purification by column chromatography (hexane/ethyl acetate = 8/1 to 3/1) afforded the desired product **B** as a white solid (15.5 mg, 55%)

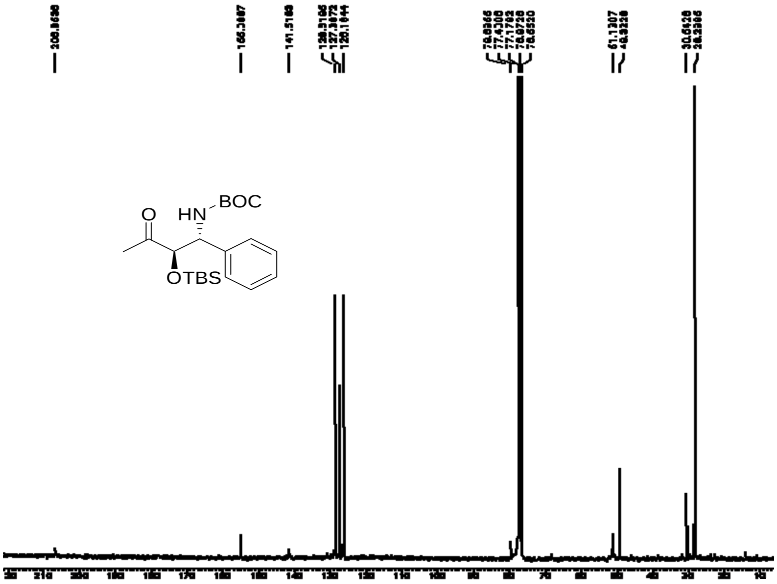
Compound **A**: ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.35 (s, 3H), -0.09 (s, 3H), 0.70 (s, 9H), 1.30 (s, 9H), 2.33 (s, 3H), 2.37 (s, 3H), 5.11-5.13 (d, *J* = 9.5 Hz, 1H), 5.61-5.63 (d, *J* = 9.5 Hz, 1H), 7.08-7.10 (d, *J* = 8.2 Hz, 2H), 7.26-7.34 (m, 5H), 7.64-7.65 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.7, -5.1, 17.8, 21.5, 24.3, 25.4, 27.7, 62.8, 78.6, 85.2, 127.8, 128.3, 128.5, 128.9, 130.3, 137.0, 137.2, 143.9, 150.5, 208.2.





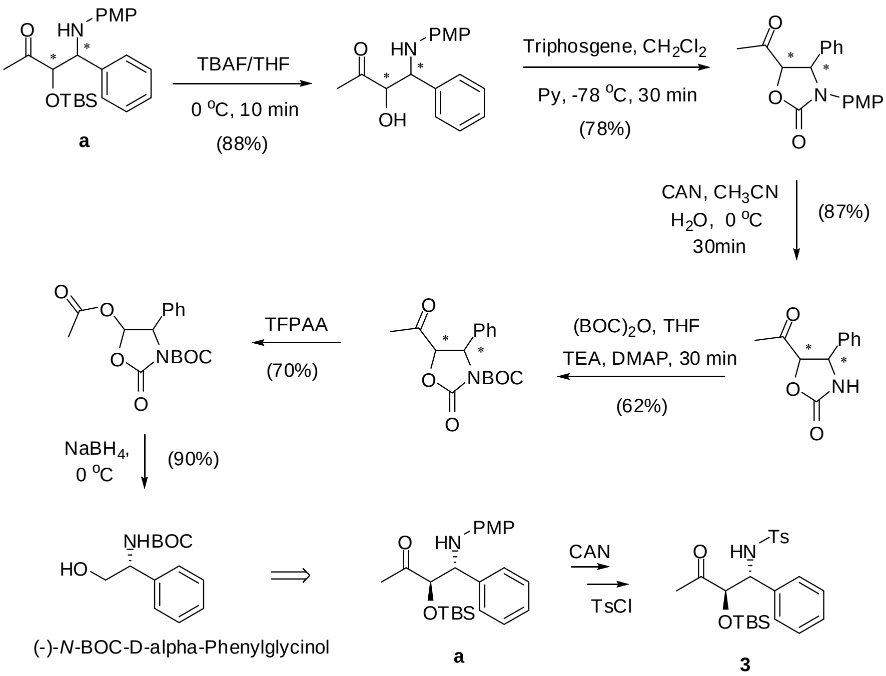
Compound **B**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.09 (s, 3H), 5.07 (br s, 1H), 5.37 (br s, 1H), 7.25-7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 30.5, 49.3, 76.9, 79.7, 126.2, 127.4, 128.6, 141.5, 155.1, 206.9.





Determination of absolute configurations of the Mannich products

The absolute configuration of the *N*-PMP Mannich product **a** was determined by using the procedure reported by List[9] through its conversion into the corresponding *N*-BOC oxazolidinone. The absolute configuration of **3** was assigned by comparison with **a**. The configurations of other Mannich products are assigned by analogy to **3**.



Transition state calculation

All calculations were calculated out using the Gaussian 03 programs. Cartesian coordinates for the HF/3-21G optimized geometry of the transition state for the major *anti*- product:

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H,-2.9230683263,0.9224427449,0.3108924045
N,-1.3765261967,0.6314289394,-1.0927327322
N,0.8407638167,0.5249888154,0.7197405069
S,-1.4949945749,-1.0448613815,-1.2204952593
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