Electronic Supplementary Material (ESI) for Chemical Communications

Direct Asymmetric Mannich-Type Reaction of Phthalides: Facial Access to Chiral Substituted Isoquinolines and Isoquinolinones

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SUPPORTING INFORMATION

A. General Information S3

B. Preparation of Phthalide Derivatives S4

C. Representative Procedure for the Mannich Reaction S6

D. X-Ray Crystallographic Analysis of **3j** S7

E. Derivatization of Isoquinolinone and Isoquinoline from the Mannich Product S10

F. Procedure of the Gram Scale Synthesis S12

G. Analytical Data and HPLC Chromatogram of the Mannich Products S14

H. NMR Spectra of the Products S65

A. General Information

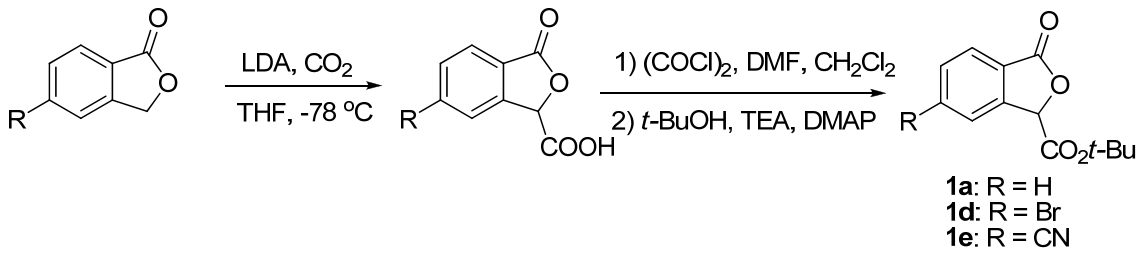
^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or DPX300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on 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. Flash chromatography separation was performed on Merck 60 (0.040 - 0.063 mm) mesh silica gel.

The enantiomeric excesses of products were determined by chiral-phase HPLC analysis, using a Daicel Chiralcel AD-H column (250 x 4.6 mm), or OD-H column (250 x 4.6 mm), or Chiralpak IA, IB, or IC column (250 x 4.6 mm).

Catalysts **Trp-1**,[1] **QD-1**,[2] **QD-2** and **Q-1**,[3] **QD-3** to **QD-5**, **C-1** and **Q-2** to **Q-6**,[4] were prepared according to procedures reported in the literature. *N*-Cbz Imine[5] and *N*-tosylimine[6,7] were prepared according to the literature procedure.

The absolute configuration of **3j** was assigned by X-ray analysis, and configurations of other Mannich products were assigned by analogy.

B. Preparation of Phthalide Derivatives



1a: R = H
1d: R = Br
1e: R = CN

tert-Butyl 3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**1a)**

To a solution of diisopropyl amine (2.6 mL, 18 mmol) in THF was added *n*-BuLi (6.9 mL, 2.5 M in hexane) at -78 ^{o}C under argon, and the resulting solution was stirred at -78 ^{o}C for 0.5 h. A solution of phthalide (2.01 g, 15 mmol) in THF (5 mL) was then introduced slowly and the resultant was further stirred at -78 ^{o}C for 50 minutes. Carbon dioxide was bubbled into the solution using a balloon for about 1.5 h at the same temperature, during which period the mixture turned to a clear red solution. Saturated aqueous NH_4Cl solution (10 mL) was added dropwise to quench the reaction, and THF was removed under reduced pressure. The residue was basified with saturated Na_2CO_3 solution till pH = 14, and the solution was washed with ethyl acetate (2×5 mL). The aqueous phase was acidified with concentrated HCl solution until pH = 1. The mixture was extracted with ethyl acetate (3×15 mL), and the combined organic extracts were dried over Na_2SO_4. Upon concentration under reduced pressure, the crude acid (2.0 g) was used directly for the subsequent reaction without further purification.

To a solution of the crude acid (2.0 g) in CH_2Cl_2 (20 mL) at 0 ^{o}C was added oxalyl chloride (1.31 mL, 15 mmol), followed by the addition of a few drops of DMF. The mixture was stirred at room temperature for 4 hrs. Then solvent was removed under

reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL), and *tert*-butanol (1.06 mL, 11 mmol), Et_3N (4.2 mL, 30 mmol) and DMAP (61 mg, 0.5 mmol) were added. The mixture was stirred at room temperature overnight. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using hexane/ethyl acetate (15:1 to 10:1) as an eluent to afford **1a** as a white solid (1.44 g, 41% yield for two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 5.76 (s, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.93, 77.79, 83.94, 122.44, 125.17. 125.96, 130.04, 134.37, 144.60, 165.49, 169.55; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}O_4$ $[M+Na]^+$= 257.0784, found = 257.0788.

tert-Butyl 6-bromo-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**1d)**

Following the same procedures described for the preparation of **1a**, phthalide **1d** was prepared in an overall yield of 37%.

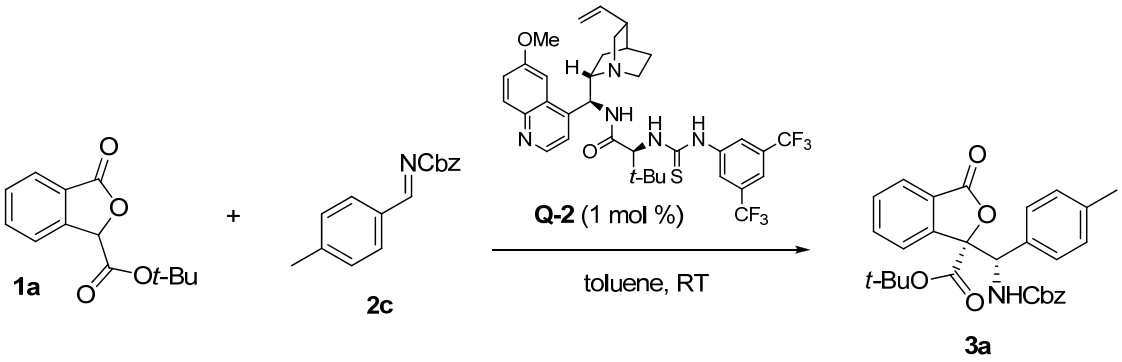
A while solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 5.73 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H),7.81 (s, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 27.96, 77.56, 84.56, 124.13, 126.01, 127.18, 129.64, 133.74, 146.23, 164.90, 168.54; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}{}^{79}BrO_4$ $[M+Na]^+$ = 334.9889, found = 334.9887; $C_{13}H_{13}{}^{81}BrO_4$ $[M+Na]^+$ = 336.9869, found = 336.9869.

tert-Butyl 6-cyano-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**1e)**

Following the same procedures described for the preparation of **1a**, phthalide **1e** was prepared in an overall yield of 23%.

A while solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 5.82 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.96 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$) δ 27.95, 77.43, 85.10, 117.19, 118.06, 126.71, 126.87, 128.87, 133.82, 144.90, 164.28, 167.42; HRMS (ESI) *m/z* calcd for $C_{14}H_{12}NO_4$ $[M-H]^-$= 258.0772, found = 258.0781.

C. Representative Procedure for the Mannich Reaction



To a solution of *tert*-butyl 3-oxo-1,3-dihydroisobenzofuran-1-carboxylate **1a** (11.7 mg, 0.05 mmol), benzyl 4-methylbenzylidenecarbamate **2c** (15.2 mg, 0.06 mmol) in toluene (0.5 mL) at room temperature was added **Q-2** (20 μL, 0.025 M solution in toluene), the catalyst solution was prepared by dissolving 17.7 mg **Q-2** in 1 mL toluene). The resulting mixture was stirred for 24 h. After concentration, the residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to afford **3a** (22.7 mg, 93% yield) as a white solid. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product, and the enantiomeric excess was measured by HPLC analysis on a chiral stationary phase.

D. X-Ray Crystallographic Analysis of 3j

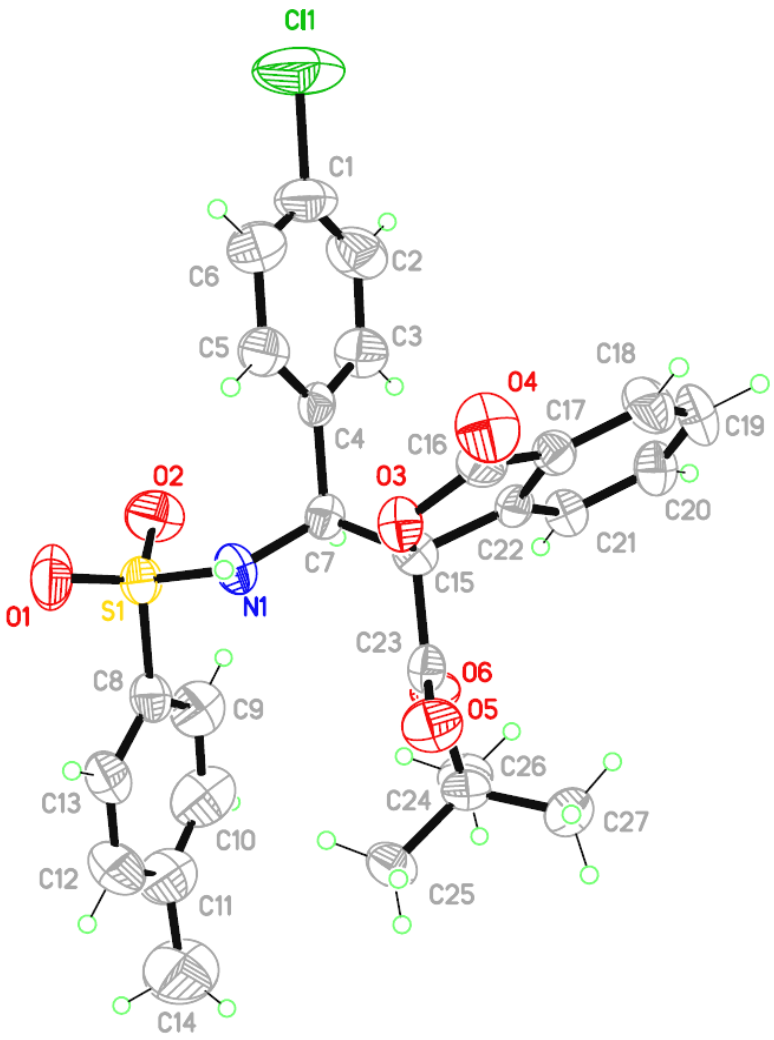


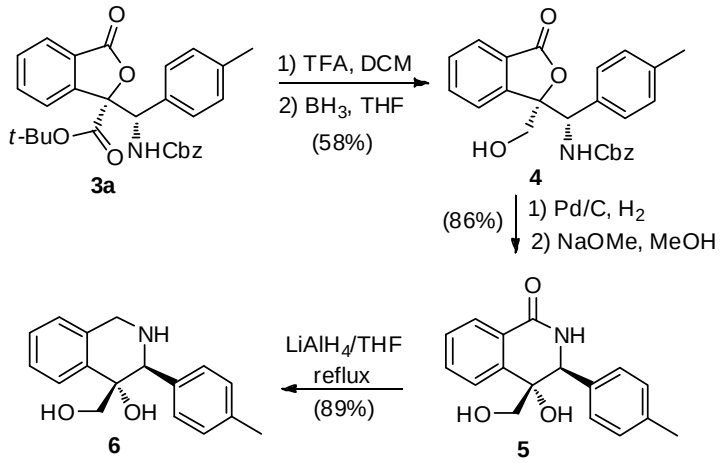
Figure 1 ORTEP Structure of Mannich Adduct **3j**

Table 1. Crystal data and structure refinement for B423.

Identification code	b423	
Empirical formula	C27 H26 Cl N O6 S	
Formula weight	528.00	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 13.4728(17) Å	α= 90°.
	b = 9.4179(12) Å	β= 90.363(3)°.
	c = 20.859(3) Å	γ = 90°.
Volume	2646.7(6) $Å^3$	
Z	4	
Density (calculated)	1.325 Mg/m^3	
Absorption coefficient	0.265 mm^{-1}	
F(000)	1104	
Crystal size	0.60 x 0.34 x 0.14 mm^3	
Theta range for data collection	1.51 to 27.50°.	
Index ranges	-17<=h<=17, -12<=k<=12, -27<=l<=20	
Reflections collected	18857	
Independent reflections	11457 [R(int) = 0.0411]	
Completeness to theta = 27.50°	99.7 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9639 and 0.8573
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11457 / 25 / 694
Goodness-of-fit on F^2	1.005
Final R indices [I>2sigma(I)]	R1 = 0.0674, wR2 = 0.1315
R indices (all data)	R1 = 0.0997, wR2 = 0.1464
Absolute structure parameter	-0.03(6)
Largest diff. peak and hole	0.295 and -0.230 e.Å^{-3}

E. Derivatization of Isoquinolinone and Isoquinoline from the Mannich Product



Benzyl (*S*)-((*R*)-1-(hydroxymethyl)-3-oxo-1,3-dihydroisobenzofuran-1-yl)(*p*-tolyl)methylcarbamate (**4**)

To a solution of **3a** (97.5 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) at 0 ^oC was added TFA (0.2 mL) dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 5 hours. The mixture was concentrated under reduced pressure, and the crude free acid **3a'**was used directly in next step without further purification.

$BH_3 \cdot Me_2S$ (0.20 mL, 2 M in THF, 0.4 mmol) was added dropwise to a solution of **3a'** in THF (1.0 mL) at 0 °C. The mixture was allowed to warm up to room temperature and stirred for another 40 h. Water was then added to the mixture, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 twice, and the combined organic extracts were washed with water and brine, respectively, and then dried over $MgSO_4$. After filtration, the solvent was removed, and the residue was purified by flash

column chromatography (hexane/EtOAc = 3/1) to afford **4** (48.4 mg, 58%) as a colorless oil.

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.48 – 7.26 (m, 6H), 6.97 – 6.82 (m, 4H), 5.69 (d, *J* = 9.1 Hz, 1H), 5.44 (d, *J* = 9.2 Hz, 1H), 5.18 (q, *J* = 12.1 Hz, 2H), 4.23 (dd, *J* = 11.8 Hz, 5.4 Hz, 1H), 4.06 (dd, *J* = 9.9 Hz, 5.4 Hz, 1H), 3.50 (t, *J* = 10.8 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.51, 157.57, 149.68, 138.01, 135.70, 133.87, 131.70, 129.28, 129.12, 128.66, 128.49, 128.20, 127.56, 125.81, 125.51, 123.25, 89.10, 67.88, 64.21, 57.07, 20.91; $[\alpha]_D^{rt}$ = -39.8 (c = 0.99, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{25}H_{23}NO_5$ $[M+Na]^+$ 440.1468, found 440.1487.

(3*S*,4*R*)-4-Hydroxy-4-(hydroxymethyl)-3-*p*-tolyl-3,4-dihydroisoquinolin-1(2*H*)-one (**5**)

To a solution of **4** (48.4 mg, 0.12 mmol) in MeOH (0.5 mL) was added Pd/C (10 mg, 10% on charcoal). The reaction mixture was allowed to stir under H_2 overnight. After filtration through celite, sodium methoxide (12.9 mg, 0.24 mmol) was added to the filtrate, and the reaction mixture was stirred at 60 °C for 20 h. The solvent was then removed and the residue was purified by flash column chromatography (hexane/EtOAc = 1/1) to afford **5** (28.3 mg, 86%) as a colorless oil.

A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.55 (s, 1H), 4.91 (s, 1H), 4.04 (br, 1H), 3.87 (dd, *J* = 11.7 Hz, 3.2 Hz, 1H), 3.52 (dd, *J* = 11.8 Hz, 7.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.07, 141.67, 138.90, 133.22, 133.07, 129.77, 128.39, 127.93, 127.26, 127.01, 125.09,

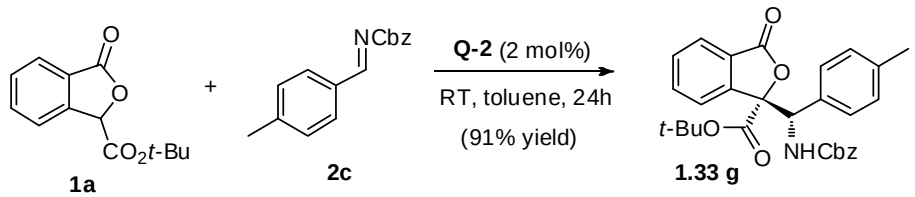
73.49, 64.75, 63.04, 21.08; $[\alpha]_D^{rt}$ = +12.7 (c = 0.86, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{17}H_{17}NO_3$ $[M+Na]^+$ 306.1101, found 306.1106.

(3*S*,4*R*)-4-(Hydroxymethyl)-3-*p*-tolyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**6**)

To a solution of **5** (28 mg, 0.1 mmol) in anhydrous THF (2 mL) at 0 °C was added slowly $LiAlH_4$ (38 mg, 1 mmol). The reaction mixture was stirred at 60 °C overnight, and then quenched carefully with the addition of 10% aq. NaOH (0.1 mL). The mixture was concentrated, and the residue was extracted with ethyl acetate several times. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography gave **6** (23.9 mg, 89%) as a light yellow oil.

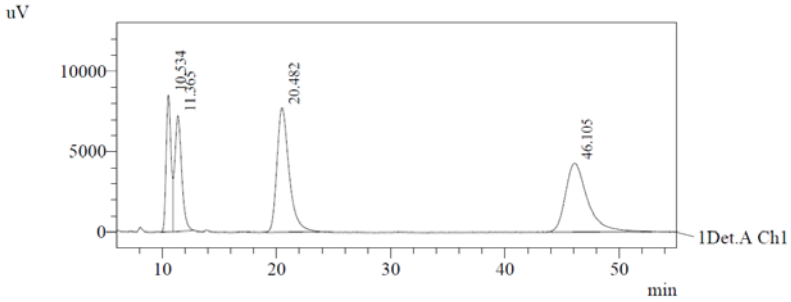
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.41 – 7.21 (m, 4H), 7.11 (d, *J* = 7.5 Hz, 1H), 4.34 (d, *J* = 15.1 Hz, 1H), 4.24 (d, *J* = 15.1 Hz, 1H), 4.09 (s, 1H), 3.73 – 3.57 (m, 3H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.37, 139.35, 138.31, 135.12, 134.98, 129.59, 127.56, 127.18, 126.16, 125.56, 71.78, 69.10, 67.75, 49.21, 21.13; $[\alpha]_D^{rt}$ = +5.2 (c = 0.78, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$ 270.1489, found 270.1497.

F. Procedure for the Gram Scale Synthesis



To a solution of *tert*-butyl 3-oxo-1,3-dihydroisobenzofuran-1-carboxylate **1a** (0.70 g, 3 mmol), benzyl 4-methylbenzylidenecarbamate **2c** (0.91 g, 3.6 mmol) in toluene

(30 mL) was added **Q-2** (42 mg, 0.06 mmol) at room temperature. The resulting mixture was stirred for 24 h, and the mixture was then concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/AcOEt = 10/1) to afford **3a** (1.33 g, 91% yield) as a white solid. The diastereomeric ratio was 87:13 and the enantiomeric excess was 93%.



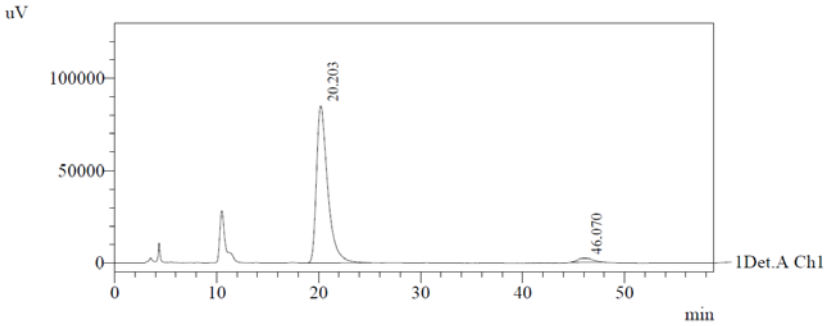
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.534	254331	8504	14.916	30.688
2	11.365	303142	7191	17.779	25.952
3	20.482	574090	7729	33.670	27.890
4	46.105	573501	4287	33.635	15.470
Total		1705065	27710	100.000	100.000

(Racemic **3a**)



1 Det.A Ch1 / 254nm

PeakTable

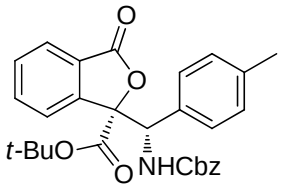
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.203	6513012	85115	96.661	97.460
2	46.070	224985	2218	3.339	2.540
Total		6737997	87333	100.000	100.000

(Enantiomerically enriched **3a**)

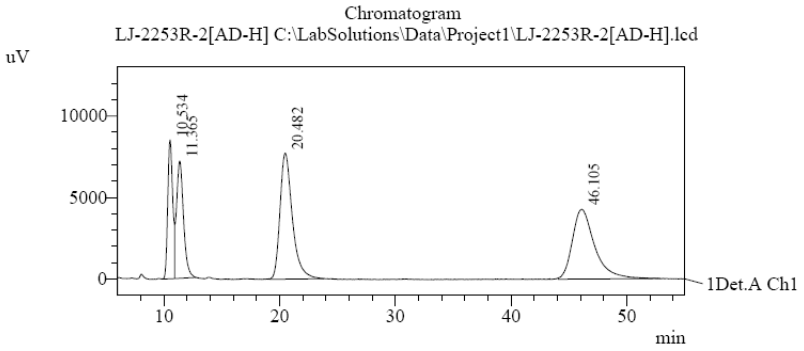
G. Analytical Data and HPLC Chromatogram of the Mannich Products

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(*p*-tolyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3a**)



3a

A white foam; diastereomeric ratio was 88:12; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.28 (m, 4H), 6.88 (dd, *J* = 23.7 Hz, 8.1 Hz, 4H), 6.08 (d, *J* = 10.1 Hz, 1H), 5.71 (d, *J* = 10.2 Hz, 1H), 5.16 (d, *J* = 12.3 Hz, 1H), 4.99 (d, *J* = 12.3 Hz, 1H), 2.15 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.30, 165.77, 155.25, 145.26, 137.93, 136.13, 134.15, 131.58, 130.17, 128.76, 128.48, 128.19, 128.17, 127.78, 125.79, 125.73, 123.00, 89.43, 84.59, 67.11, 59.91, 27.68, 20.95; HRMS (ESI) m/z calcd for $C_{29}H_{29}NO_6$ $[M+Na]^+$ 510.1887, found 510.1881; the ee value of the major isomer was 95%, t_R (major) = 20.5 min and 46.1 min, t_R (minor) = 10.5 min and 11.4 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



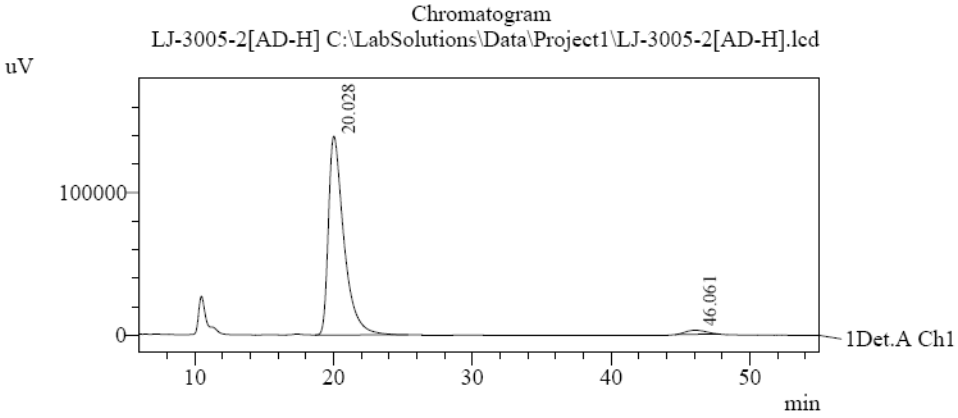
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.534	254331	8504	14.916	30.688
2	11.365	303142	7191	17.779	25.952
3	20.482	574090	7729	33.670	27.890
4	46.105	573501	4287	33.635	15.470
Total		1705065	27710	100.000	100.000

(Racemic **3a**)



1 Det.A Ch1 / 254nm

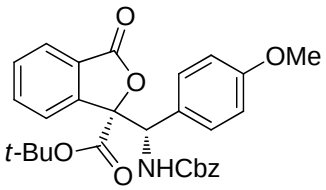
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.028	10816583	139332	97.405	97.967
2	46.061	288142	2892	2.595	2.033
Total		11104726	142223	100.000	100.000

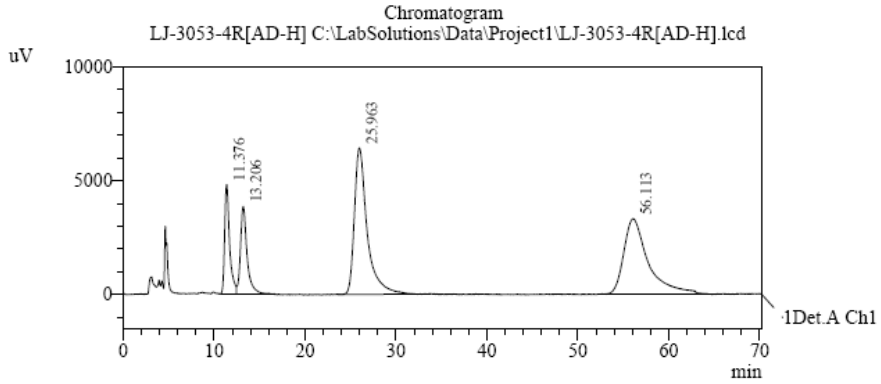
(Enantiomerically enriched **3a**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-methoxyphenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3b**)



3b

A white foam; diastereomeric ratio was 88:12; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.46 – 7.31 (m, 6H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 8.6 Hz, 2H), 6.08 (d, *J* = 10.1 Hz, 1H), 5.70 (d, *J* = 10.1 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.00 (d, *J* = 12.3 Hz, 1H), 3.65 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.28, 165.77, 159.24, 155.25, 145.27, 136.12, 134.19, 130.18, 129.06, 128.53, 128.47, 128.19, 128.11, 126.72, 125.77, 122.93, 113.46, 89.49, 84.57, 67.10, 59.64, 55.05, 27.67; HRMS (ESI) m/z calcd for $C_{29}H_{29}NO_7$ $[M+Na]^+$ 526.1836, found 526.1827; the ee value of the major isomer was 91%, t_R (major) = 25.9 min and 56.1 min, t_R (minor) = 11.4 min and 13.2 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



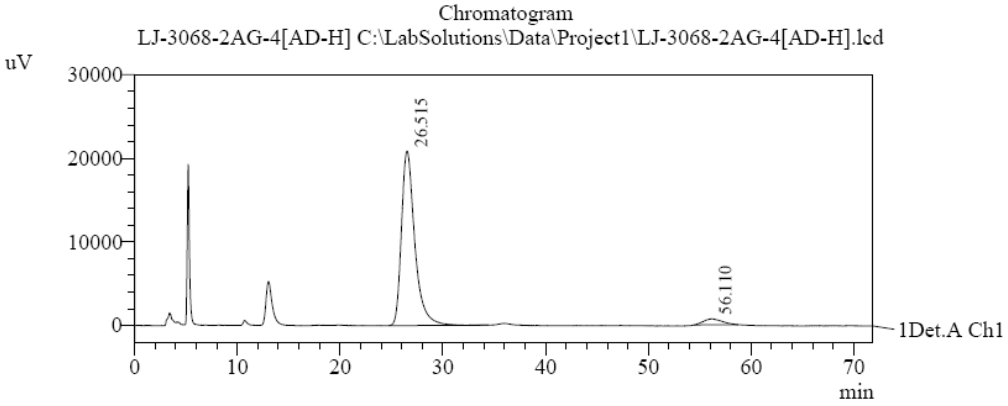
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.376	183027	4810	11.237	26.116
2	13.206	194800	3854	11.960	20.927
3	25.963	630390	6435	38.704	34.942
4	56.113	620536	3318	38.099	18.015
Total		1628753	18416	100.000	100.000

(Racemic **3b**)



1 Det.A Ch1 / 254nm

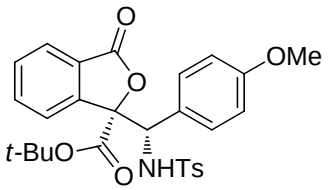
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.515	1883142	20889	95.573	96.734
2	56.110	87222	705	4.427	3.266
Total		1970364	21594	100.000	100.000

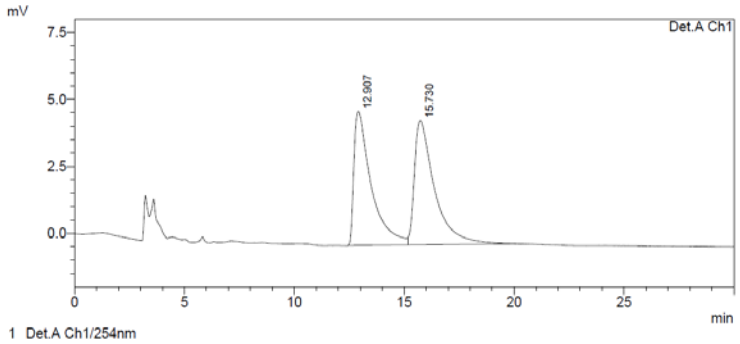
(Enantiomerically enriched **3b**)

(*R*)-*tert*-Butyl 1-((*S*)-(4-methoxyphenyl)(4-methylphenylsulfonamido)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3c**)



3c

A white solid; diastereomeric ratio was 91:9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.63 (td, *J* = 7.6 Hz, 0.9 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 2H), 6.30 (d, *J* = 8.7, 2H), 5.65 (d, *J* = 10.6 Hz, 1H), 5.39 (d, *J* = 10.6 Hz, 1H), 3.58 (s, 3H), 2.24 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.17, 165.47, 159.12, 144.89, 142.75, 137.55, 134.26, 130.24, 129.13, 128.96, 126.81, 125.76, 125.71, 124.36, 122.92, 113.19, 89.46, 85.07, 62.62, 55.02, 27.86, 21.26; $[\alpha]_D^{rt}$ = -47.0 (c = 0.97, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{28}H_{29}NO_7S$ $[M+Na]^+$ 546.1557, found 546.1562; the ee value of the major isomer was 92%, t_R (major) = 12.9 min and 15.7 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

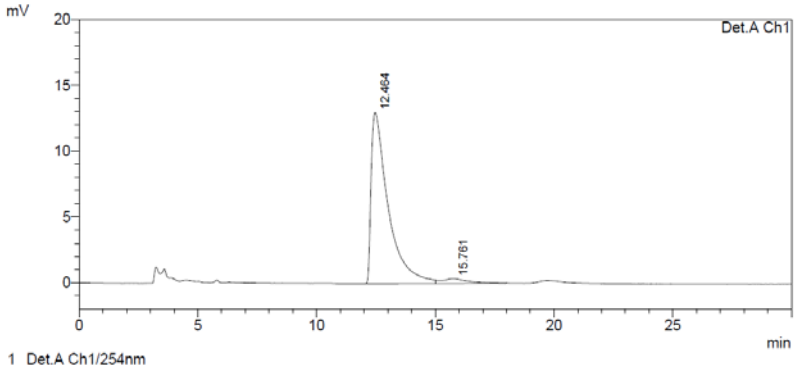


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.907	274298	4997	48.081	51.910
2	15.730	296192	4629	51.919	48.090
Total		570490	9626	100.000	100.000

(Racemic **3c**)



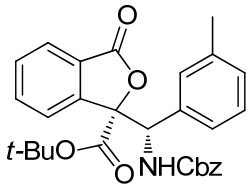
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.464	645885	12973	96.011	97.385
2	15.761	26834	348	3.989	2.615
Total		672719	13322	100.000	100.000

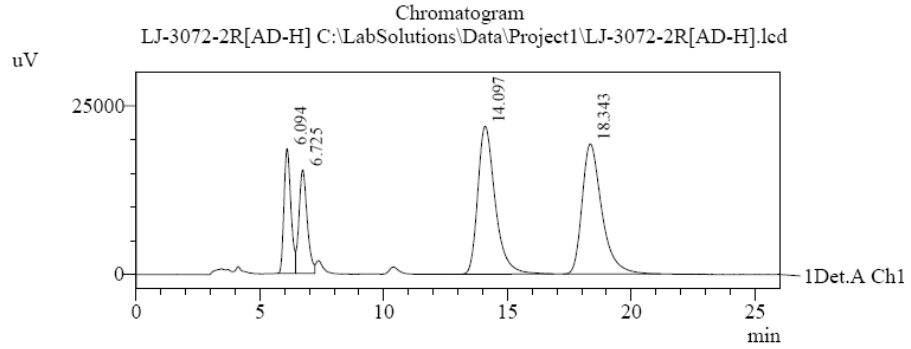
(Enantiomerically enriched **3c**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(*m*-tolyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3d**)



3d

A white foam; diastereomeric ratio was 86:14; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.30 (m, 6H), 6.97 - 6.80 (m, 4H), 6.08 (d, *J* = 10.1 Hz, 1H), 5.70 (d, *J* = 10.2 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.3 Hz, 1H), 2.14 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.23, 165.77, 155.28, 145.23, 137.66, 136.12, 134.47, 134.06, 130.15, 128.90, 128.68, 128.47, 128.19, 128.16, 127.89, 125.76, 125.67, 124.98, 123.07, 89.31, 84.59, 67.12, 60.12, 27.67, 21.12; HRMS (ESI) m/z calcd for $C_{29}H_{29}NO_6$ $[M+Na]^+$ 510.1887, found 510.1890; the ee value of the major isomer was 93%, t_R (major) = 14.1 min and 18.3 min, t_R (minor) = 6.1 min and 6.7 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



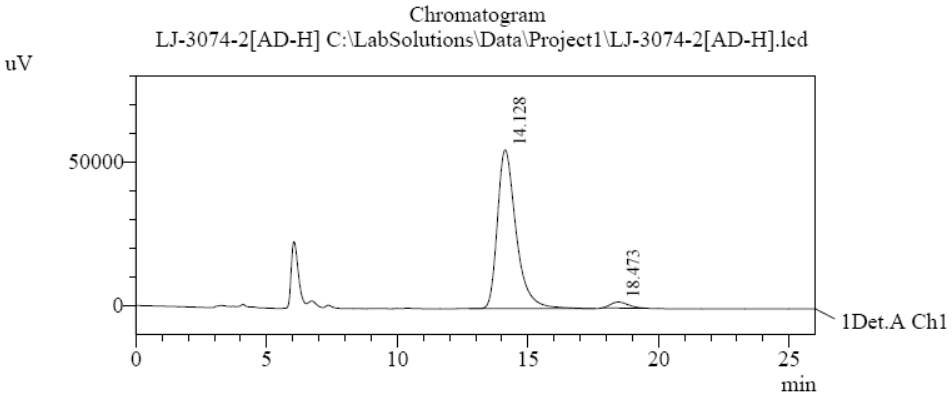
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.094	358925	18476	12.580	24.643
2	6.725	354121	15332	12.411	20.449
3	14.097	1072594	21897	37.593	29.205
4	18.343	1067565	19272	37.416	25.704
Total		2853206	74976	100.000	100.000

(Racemic **3d**)



1 Det.A Ch1 / 254nm

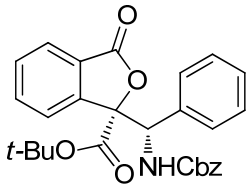
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.128	2749324	55345	96.540	96.384
2	18.473	98550	2077	3.460	3.616
Total		2847874	57422	100.000	100.000

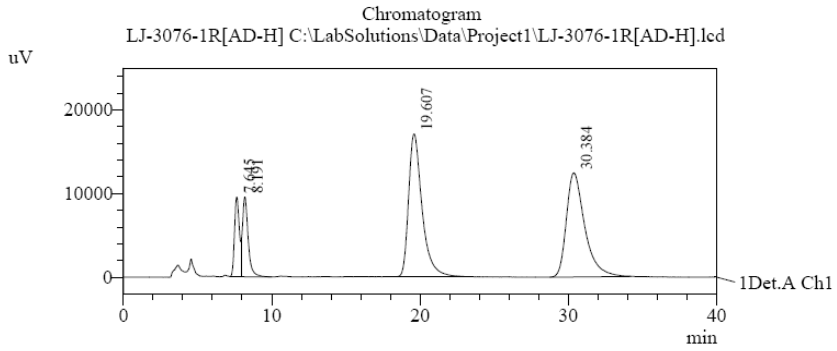
(Enantiomerically enriched **3d**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(phenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3e**)



3e

A white foam; diastereomeric ratio was 91:9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.56 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.27 (m, 6H), 7.18 – 6.98 (m, 5H), 6.12 (d, *J* = 10.1 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.00 (d, *J* = 12.3 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.19, 165.76, 155.30, 145.19, 136.12, 134.19, 130.22, 128.79, 128.67, 128.60, 128.49, 128.34, 128.20, 128.06, 127.93, 125.73, 123.04, 89.30, 84.68, 67.17, 60.16, 27.69; HRMS (ESI) m/z calcd for $C_{28}H_{27}NO_6$ $[M+Na]^+$ 496.1731, found 496.1721; the ee value of the major isomer was 95%, t_R (major) = 19.6 min and 30.4 min, t_R (minor) = 7.6 min and 8.2 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



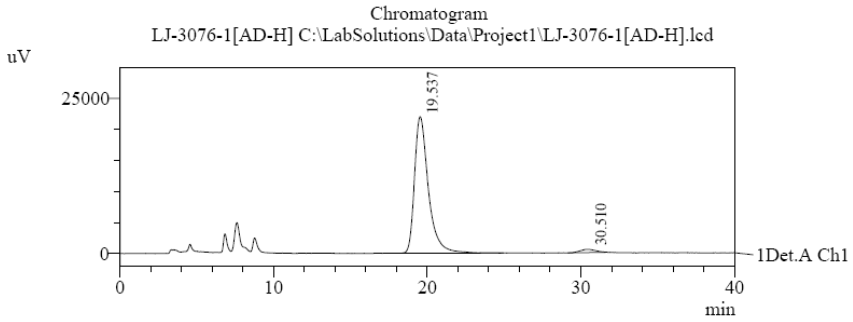
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.645	219490	9517	8.366	19.591
2	8.191	252952	9531	9.642	19.619
3	19.607	1077028	17079	41.053	35.157
4	30.384	1074064	12452	40.940	25.633
Total		2623534	48579	100.000	100.000

(Racemic **3e**)



1 Det.A Ch1 / 254nm

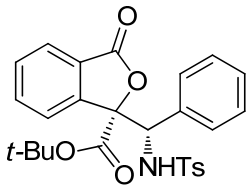
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.537	1382964	22023	97.503	97.702
2	30.510	35416	518	2.497	2.298
Total		1418379	22541	100.000	100.000

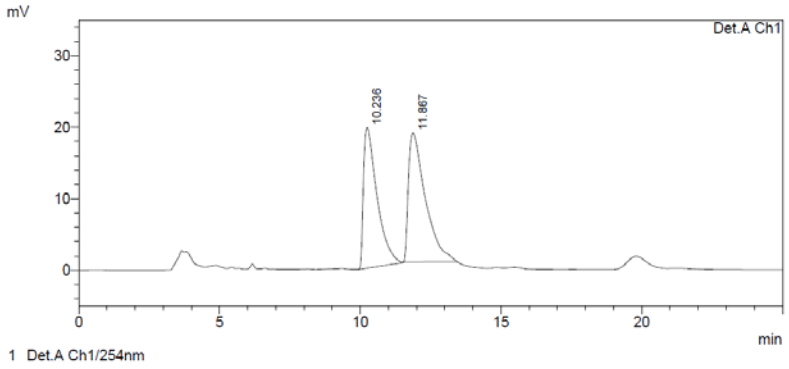
(Enantiomerically enriched **3e**)

(*R*)-*tert*-Butyl 1-((*S*)-(4-methylphenylsulfonamido)(phenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3f**)



3f

A white solid; diastereomeric ratio was 92:8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 7.8 Hz, 3H), 6.78 (t, *J* = 7.7 Hz, 2H), 6.68 (d, *J* = 7.5 Hz, 2H), 5.76 (d, *J* = 10.7 Hz, 1H), 5.44 (d, *J* = 10.7 Hz, 1H), 2.21 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.07, 165.41, 144.77, 142.88, 137.38, 134.24, 132.27, 130.26, 128.97, 127.94, 127.78, 127.76, 126.76, 125.69, 123.00, 89.29, 85.14, 63.04, 27.85, 21.25; $[\alpha]_D^{rt}$ = -79.2 (c = 0.89, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{27}H_{27}NO_6S$ $[M+Na]^+$ 516.1451, found 516.1457; the ee value of the major isomer was 91%, t_R (major) = 10.2 min and 11.9 min (Chiralcel IB, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

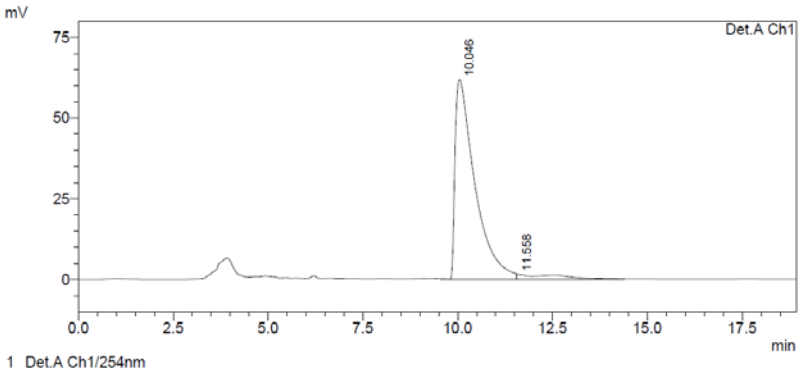


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.236	660626	19691	46.727	52.272
2	11.867	753160	17979	53.273	47.728
Total		1413787	37670	100.000	100.000

(Racemic **3f**)



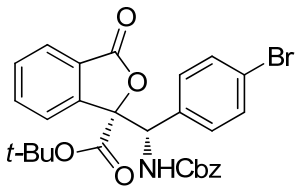
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.046	2238746	61782	95.588	97.484
2	11.558	103321	1595	4.412	2.516
Total		2342067	63376	100.000	100.000

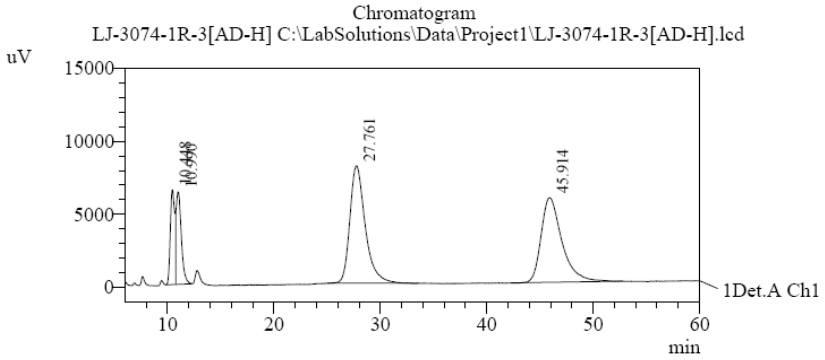
(Enantiomerically enriched **3f**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-bromophenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3g**)



3g

A light yellow foam; diastereomeric ratio was 88:12; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.72 – 7.59 (m, 2H), 7.50 – 7.44 (m, 2H), 7.39 – 7.31 (m, 4H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.10 (d, *J* = 9.9 Hz, 1H), 5.69 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.99, 165.54, 155.23, 144.88, 135.97, 134.38, 131.91, 131.28, 130.50, 130.35, 129.57, 128.51, 128.25, 126.03, 125.66, 122.88, 122.47, 88.85, 84.90, 67.29, 59.65, 27.68; HRMS (ESI) m/z calcd for $C_{28}H_{26}BrNO_6$ $[M+Na]^+$ 574.0836, found 574.0817; the ee value of the major isomer was 92%, t_R (major) = 27.8 min and 45.9 min, t_R (minor) = 10.4 min and 11.0 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



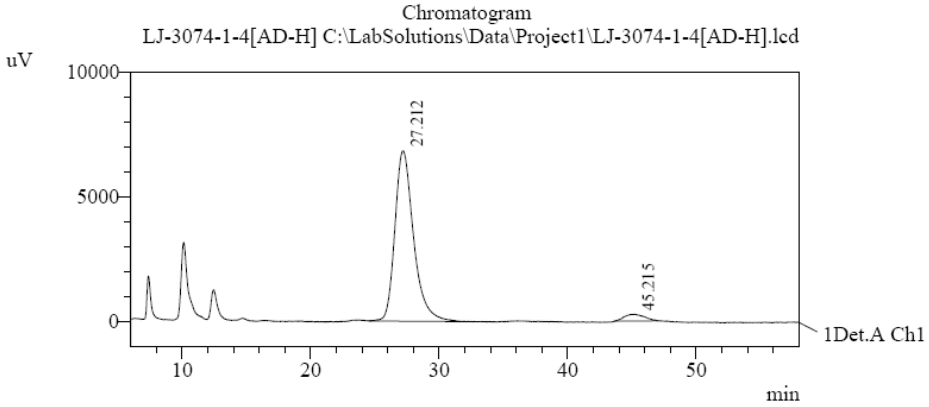
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.448	191600	6512	9.546	24.368
2	10.990	214802	6353	10.702	23.773
3	27.761	810721	8054	40.391	30.137
4	45.914	790050	5805	39.361	21.722
Total		2007173	26724	100.000	100.000

(Racemic **3g**)



1 Det.A Ch1 / 254nm

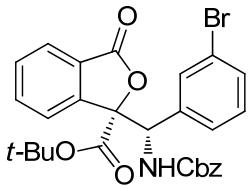
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.212	691001	6831	95.864	96.163
2	45.215	29816	273	4.136	3.837
Total		720817	7104	100.000	100.000

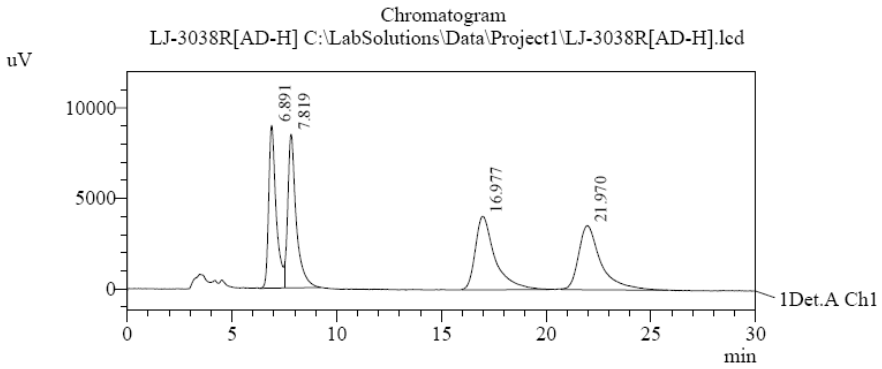
(Enantiomerically enriched **3g**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(3-bromophenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3h**)



3h

A light yellow foam; diastereomeric ratio was 83:17; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.75 – 7.58 (m, 2H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.22 (m, 6H), 7.16 (s, 1H), 7.05 – 6.96 (m, 2H), 6.13 (d, *J* = 10.0 Hz, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.02 (d, *J* = 12.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.91, 165.55, 155.25, 144.86, 134.40, 131.83, 131.36, 131.23, 130.53, 129.67, 128.62, 128.52, 128.27, 128.23, 128.20, 126.39, 125.95, 123.00, 122.06, 88.79, 84.94, 67.33, 59.69, 27.68; HRMS (ESI) m/z calcd for $C_{28}H_{26}BrNO_6$ $[M+Na]^+$ 574.0836, found 574.0825; the ee value of the major isomer was 91%, t_R (major) = 12.7 min and 16.1 min, t_R (minor) = 5.6 min and 6.1 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



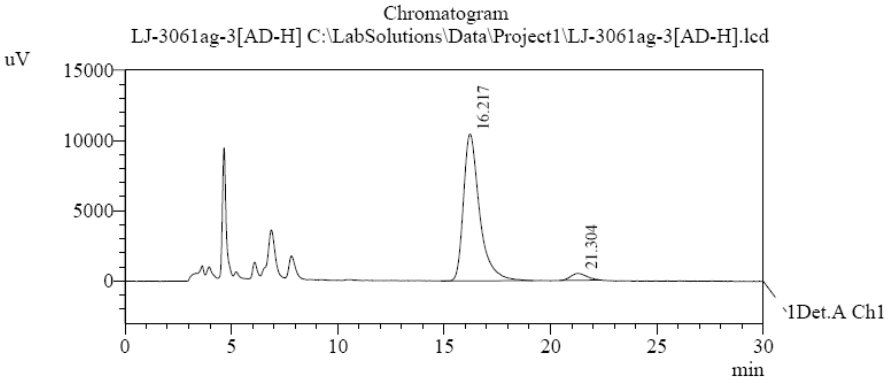
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.891	225128	9000	22.770	35.858
2	7.819	236958	8499	23.966	33.862
3	16.977	265032	4060	26.805	16.177
4	21.970	261607	3540	26.459	14.103
Total		988726	25099	100.000	100.000

(Racemic **3h**)



1 Det.A Ch1 / 254nm

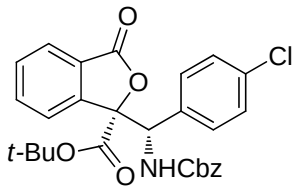
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.217	548156	10432	95.625	95.575
2	21.304	25077	483	4.375	4.425
Total		573233	10915	100.000	100.000

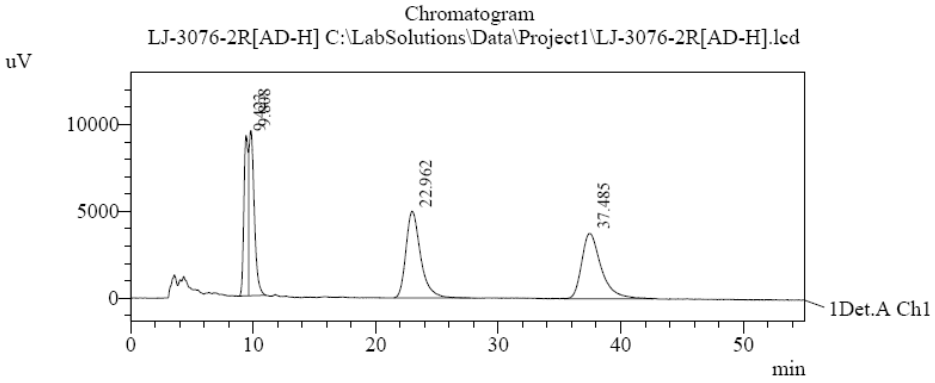
(Enantiomerically enriched **3h**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-chlorophenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3i**)



3i

A light yellow foam; diastereomeric ratio was 89:11; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.71 – 7.59 (m, 2H), 7.47 – 7.44 (m, 1H), 7.38 – 7.30 (m, 4H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.11 (d, *J* = 9.9 Hz, 1H), 5.71 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.00, 165.53, 155.24, 144.89, 135.96, 134.39, 134.23, 133.30, 130.48, 129.26, 128.94, 128.51, 128.32, 128.27, 128.23, 126.00, 122.88, 88.93, 84.88, 67.29, 59.58, 27.67; HRMS (ESI) m/z calcd for $C_{28}H_{26}ClNO_6$ $[M+Na]^+$ 530.1341, found 530.1325; the ee value of the major isomer was 97%, t_R (major) = 22.9 min and 37.5 min, t_R (minor) = 9.4 min and 9.8 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



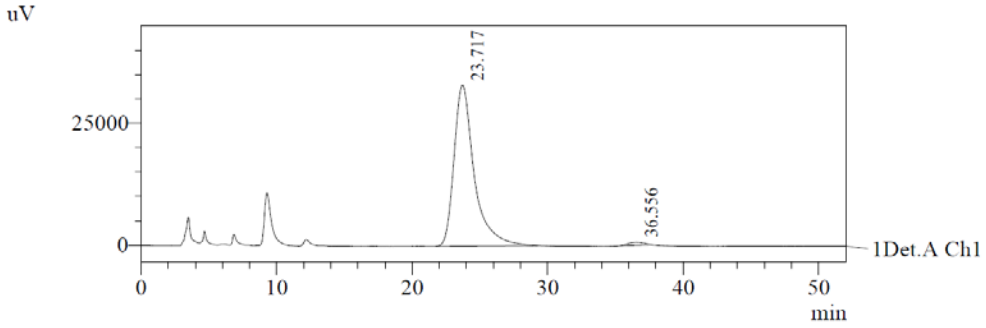
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.423	233774	9243	17.394	33.570
2	9.808	275147	9521	20.472	34.581
3	22.962	417184	5004	31.040	18.175
4	37.485	417916	3765	31.094	13.674
Total		1344021	27533	100.000	100.000

(Racemic **3i**)



1 Det.A Ch1 / 254nm

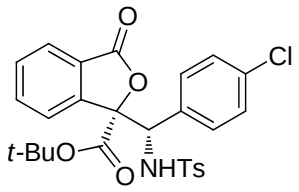
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.717	3414574	33054	98.664	98.238
2	36.556	46220	593	1.336	1.762
Total		3460794	33647	100.000	100.000

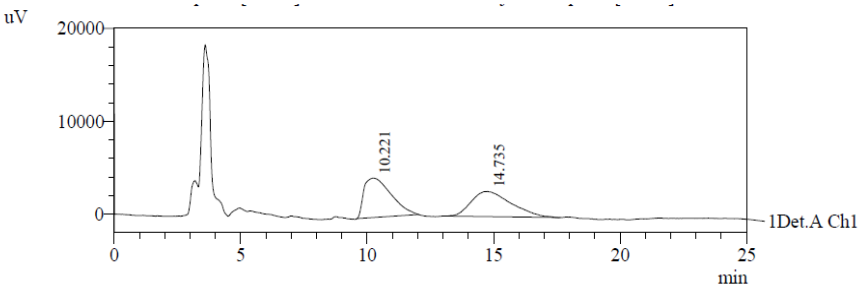
(Enantiomerically enriched **3i**)

(*R*)-*tert*-Butyl 1-((*S*)-(4-chlorophenyl)(4-methylphenylsulfonamido)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3j**)



3j

A white solid; diastereomeric ratio was 91:9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 2H), 5.83 (d, *J* = 10.6 Hz, 1H), 5.40 (d, *J* = 10.6 Hz, 1H), 2.27 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.94, 165.17, 144.47, 143.37, 137.23, 134.50, 134.01, 130.85, 130.55, 129.32, 129.09, 127.97, 126.73, 125.99, 125.54, 122.84, 88.93, 85.40, 62.42, 27.83, 21.29; $[\alpha]_D^{rt}$ = -56.1 (c = 0.87, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{27}H_{26}ClNO_6S$ $[M+Na]^+$ 550.1062, found 550.1060; the ee value of the major isomer was 92%, t_R (major) = 10.2 min and 14.7 min (Chiralcel OD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



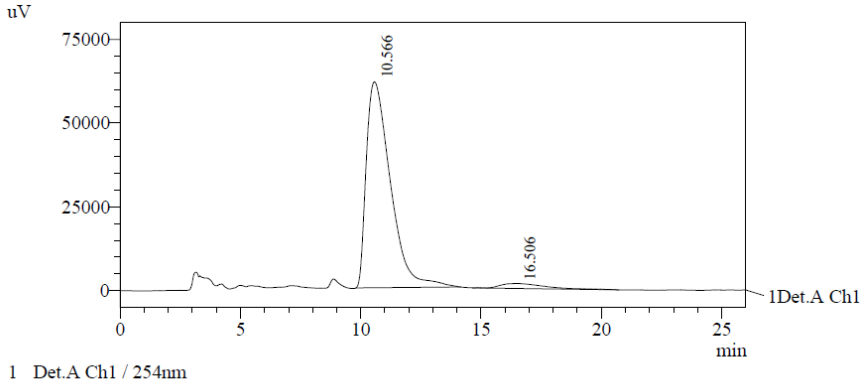
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.221	316210	4248	51.535	61.100
2	14.735	297371	2704	48.465	38.900
Total		613580	6952	100.000	100.000

(Racemic **3j**)



1 Det.A Ch1 / 254nm

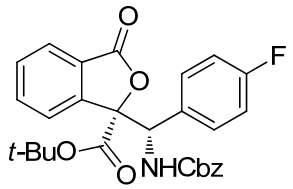
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.566	4303999	61448	95.774	97.620
2	16.506	189907	1498	4.226	2.380
Total		4493906	62946	100.000	100.000

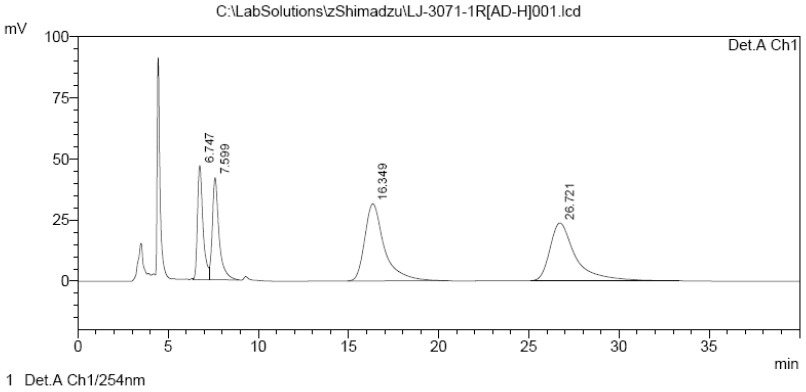
(Enantiomerically enriched **3j**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-fluorophenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3k**)



3k

A white foam; diastereomeric ratio was 85:15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.71 – 7.57 (m, 2H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.40 – 7.31 (m, 5H), 7.02 (dd, *J* = 8.4 Hz, 5.3 Hz, 2H), 6.76 (t, *J* = 8.6 Hz, 2H), 6.10 (d, *J* = 9.9 Hz, 1H), 5.72 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.05, 165.59, 162.36 (*J* = 247.5 Hz), 155.25, 145.02, 135.99, 134.34, 130.58, 130.39, 129.67, 129.60, 128.50, 128.40, 128.23, 125.89, 125.69, 122.89, 115.17, 115.00, 89.08, 84.81, 67.25, 59.53, 27.67; HRMS (ESI) m/z calcd for $C_{28}H_{26}FNO_6$ $[M+Na]^+$ 514.1636, found 514.1620; the ee value of the major isomer was 93%, t_R (major) = 16.3 min and 26.7 min, t_R (minor) = 6.7 min and 7.6 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

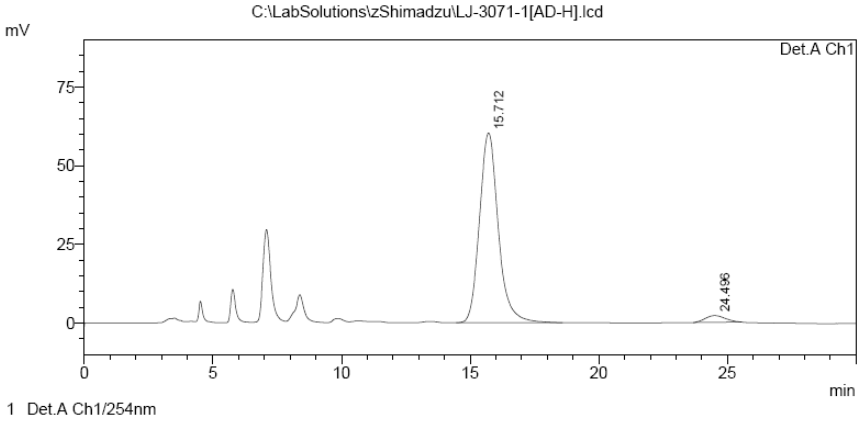


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.747	999305	46708	14.699	32.488
2	7.599	1075571	41801	15.821	29.075
3	16.349	2384489	31595	35.075	21.976
4	26.721	2338919	23667	34.405	16.462
Total		6798284	143771	100.000	100.000

(Racemic **3k**)



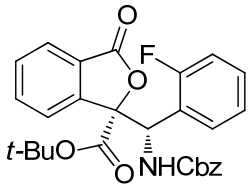
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.712	3063428	60247	96.362	96.555
2	24.496	115660	2149	3.638	3.445
Total		3179089	62396	100.000	100.000

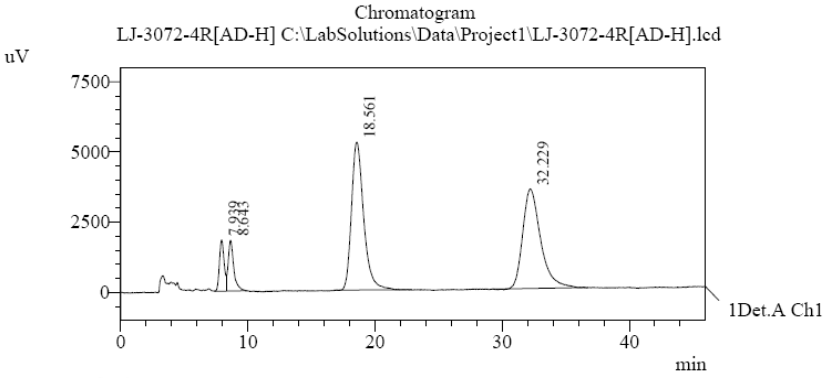
(Enantiomerically enriched **3k**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(2-fluorophenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3l**)



3l

A white foam; diastereomeric ratio was 88:12; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.6 Hz, 1H), 7.69 – 7.54 (m, 2H), 7.43 – 7.09 (m, 6H), 7.15 – 7.04 (m, 2H), 6.99 – 6.91 (m, 1H), 6.70 (t, *J* = 9.1 Hz, 1H), 6.26 (d, *J* = 10.2 Hz, 1H), 6.10 (d, *J* = 10.1 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.16, 165.43, 155.20, 144.36, 136.06, 134.10, 130.48, 130.37, 130.11, 130.04, 128.85, 128.49, 128.38, 128.21, 127.72, 125.58, 125.39, 124.19, 123.45, 115.26, 115.08, 89.28, 84.78, 67.24, 53.06, 27.68; HRMS (ESI) m/z calcd for $C_{28}H_{26}FNO_6$ $[M+Na]^+$ 514.1636, found 514.1621; the ee value of the major isomer was 91%, t_R (major) = 18.6 min and 32.2 min, t_R (minor) = 7.9 min and 8.6 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



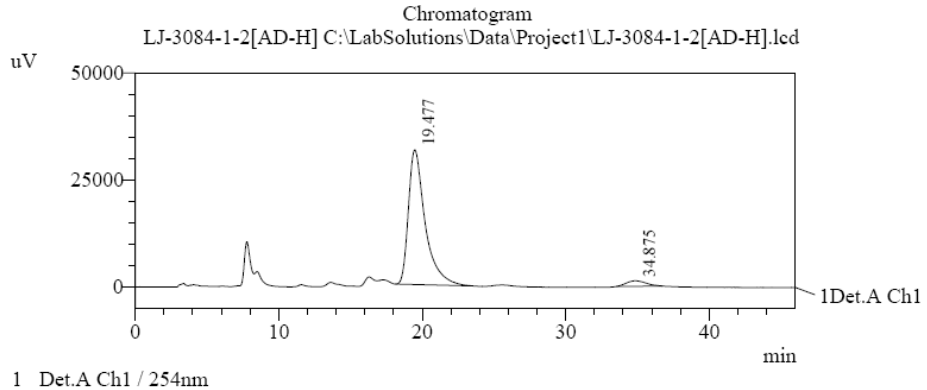
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.939	47418	1828	5.933	14.681
2	8.643	54443	1805	6.812	14.499
3	18.561	350646	5271	43.872	42.338
4	32.229	346736	3546	43.383	28.482
Total		799243	12449	100.000	100.000

(Racemic **3l**)



1 Det.A Ch1 / 254nm

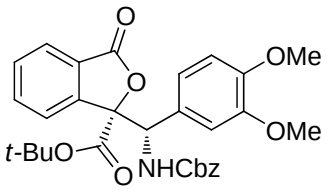
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.477	2554714	31509	95.369	96.032
2	34.875	124051	1302	4.631	3.968
Total		2678765	32811	100.000	100.000

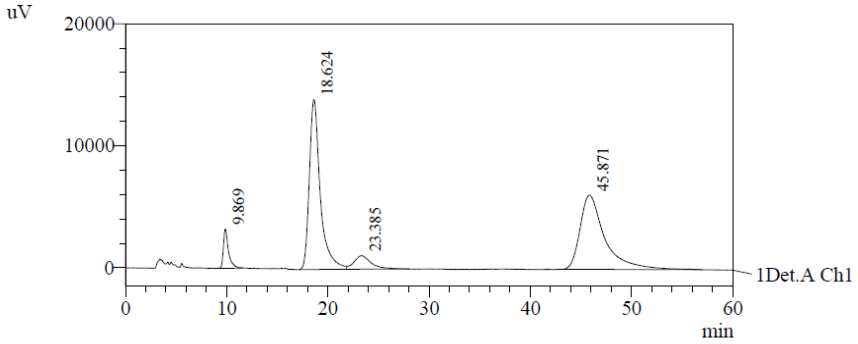
(Enantiomerically enriched **3l**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(3,4-dimethoxyphenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3m**)



3m

A white foam; diastereomeric ratio was 92:8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.54 (m, 2H), 7.43 – 7.29 (m, 5H), 6.62 – 6.55 (m, 2H), 6.49 (s, 1H), 6.04 (d, *J* = 10.0 Hz, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.27, 165.72, 155.28, 148.76, 148.38, 145.33, 136.11, 134.05, 130.35, 130.21, 128.49, 128.21, 127.64, 127.12, 125.86, 122.93, 120.59, 110.89, 110.55, 89.48, 84.63, 67.17, 59.97, 55.76, 55.66, 27.70; HRMS (ESI) m/z calcd for $C_{30}H_{31}NO_8$ $[M+Na]^+$ 556.1942, found 556.1926; the ee value of the major isomer was 85%, t_R (major) = 18.6 min and 45.9 min, t_R (minor) = 9.9 min and 23.4 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



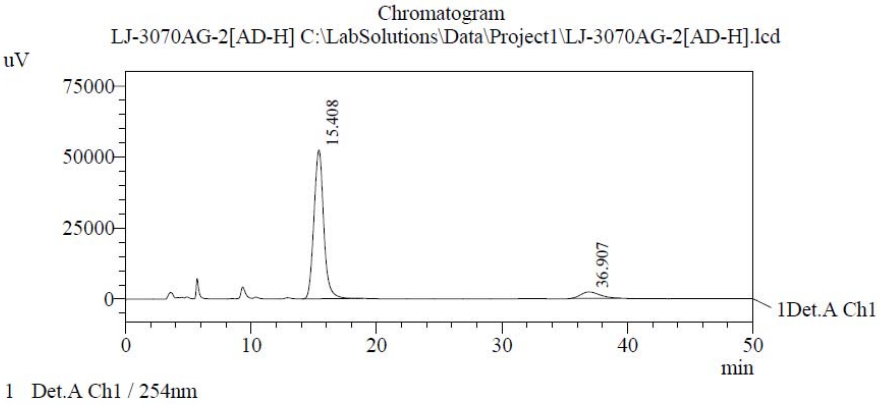
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.869	113680	3236	4.884	13.282
2	18.624	1048648	13927	45.052	57.170
3	23.385	130678	1109	5.614	4.553
4	45.871	1034627	6089	44.450	24.995
Total		2327633	24361	100.000	100.000

(Racemic **3m**)



1 Det.A Ch1 / 254nm

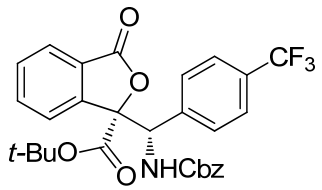
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.408	2834950	52385	92.404	95.909
2	36.907	233052	2234	7.596	4.091
Total		3068002	54619	100.000	100.000

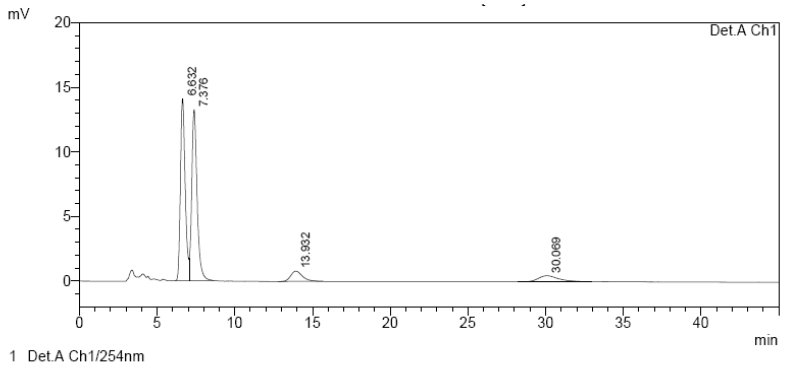
(Enantiomerically enriched **3m**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-(trifluoromethyl)phenyl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3n**)



3n

A yellow foam; diastereomeric ratio was 82:18; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.73 – 7.53 (m, 3H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.31 (m, 6H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.18 (d, *J* = 9.9 Hz, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.86, 165.49, 155.25, 144.73, 135.90, 134.47, 130.62, 129.14, 128.53, 128.40, 128.31, 128.26, 127.71, 126.05, 125.69, 125.59, 125.09, 125.04, 122.90, 88.67, 85.05, 67.38, 59.79, 27.68; HRMS (ESI) m/z calcd for $C_{29}H_{26}F_3NO_6$ $[M+Na]^+$ 564.1604, found 564.1629; the ee value of the major isomer was 85%, t_R (major) = 13.9 min and 30.1 min, t_R (minor) = 6.6 min and 7.4 min (Chiralcel IA, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

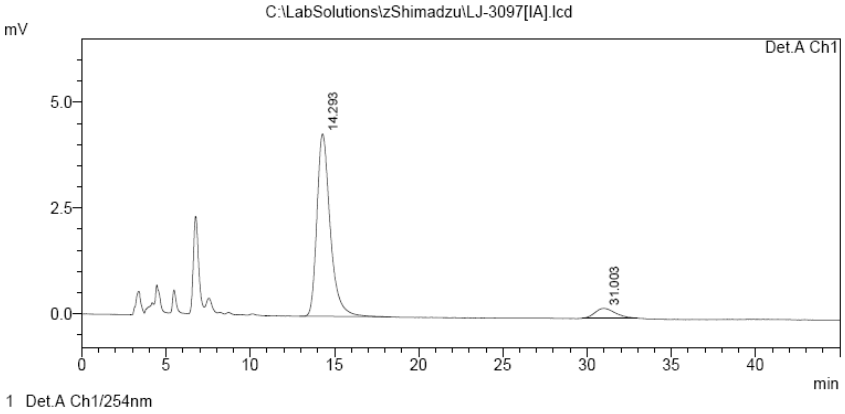


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.632	300920	14094	43.022	49.309
2	7.376	315760	13231	45.144	46.290
3	13.932	41340	796	5.910	2.786
4	30.069	41435	462	5.924	1.615
Total		699455	28583	100.000	100.000

(Racemic **3n**)



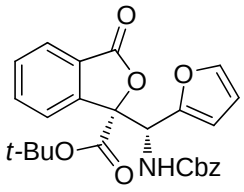
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.293	237170	4315	92.378	94.895
2	31.003	19567	232	7.622	5.105
Total		256737	4547	100.000	100.000

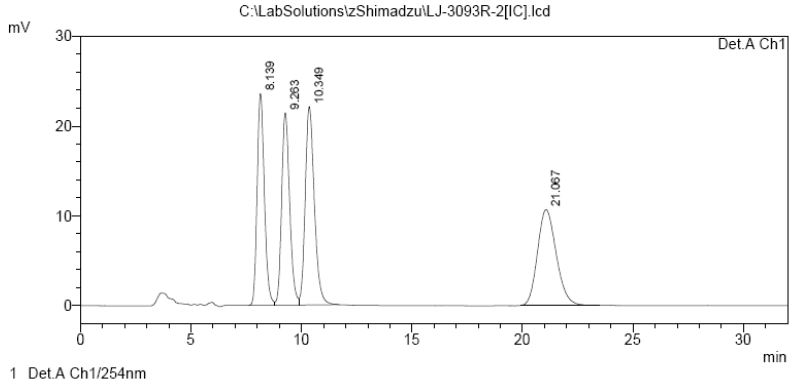
(Enantiomerically enriched **3n**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(furan-2-yl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3o**)



3o

A light brown foam; diastereomeric ratio was 67:33; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.41 – 7.27 (m, 4H), 7.10 – 7.05 (m, 1H), 6.06 (s, 1H), 5.98 (s, 1H), 5.94 (d, *J* = 10.3 Hz, 1H), 5.88 (d, *J* = 10.3 Hz, 1H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.29, 165.25, 155.30, 148.53, 144.77, 142.49, 136.04, 134.28, 130.40, 128.50, 128.20, 128.15, 125.70, 123.00, 116.51, 110.13, 108.81, 88.63, 84.73, 67.27, 54.41, 27.65; HRMS (ESI) m/z calcd for $C_{26}H_{25}NO_7$ $[M+Na]^+$ 486.1523, found 486.1533; the ee value of the major isomer was 80%, t_R (major) = 10.3 min and 21.1 min, t_R (minor) = 8.1 min and 9.3 min (Chiralcel IC, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

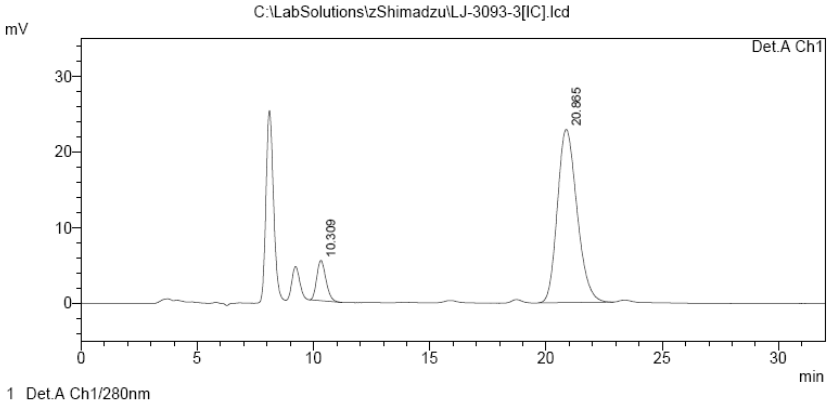


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.139	539372	23601	22.985	30.329
2	9.263	541068	21437	23.057	27.547
3	10.349	635123	22103	27.065	28.404
4	21.067	631061	10676	26.892	13.720
Total		2346624	77817	100.000	100.000

(Racemic **3o**)



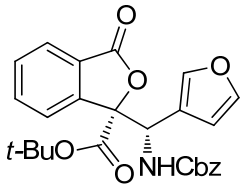
PeakTable

Detector A Ch1 280nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	10.309	146055	5313	9.800	18.840
2	20.865	1344343	22886	90.200	81.160
Total		1490399	28199	100.000	100.000

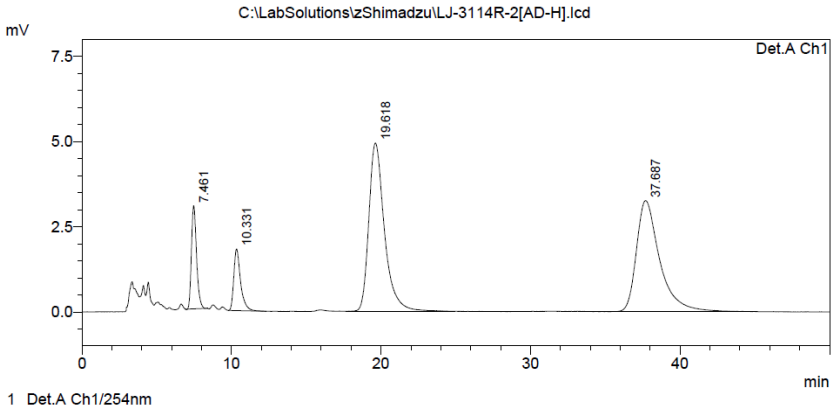
(Enantiomerically enriched **3o**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(furan-3-yl)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3p**)



3p

A light brown foam; diastereomeric ratio was 73:27; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.46 (m, 4H), 7.40 – 7.29 (m, 5H), 7.14 – 7.11 (m, 1H), 7.08 (s, 1H), 6.06 (s, 1H), 5.83 (d, *J* = 10.3 Hz, 1H), 5.72 (d, *J* = 10.3 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.03 (d, *J* = 12.2 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.41, 165.60, 155.29, 145.24, 143.24, 140.63, 134.47, 130.49, 130.41, 128.51, 128.39, 128.21, 127.57, 125.94, 122.64, 110.24, 109.01, 89.12, 84.68, 67.20, 52.99, 27.63; HRMS (ESI) m/z calcd for $C_{26}H_{25}NO_7$ $[M+Na]^+$ 486.1523, found 486.1539; the ee value of the major isomer was 83%, t_R (major) = 19.6 min and 37.7 min, t_R (minor) = 7.5 min and 10.3 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

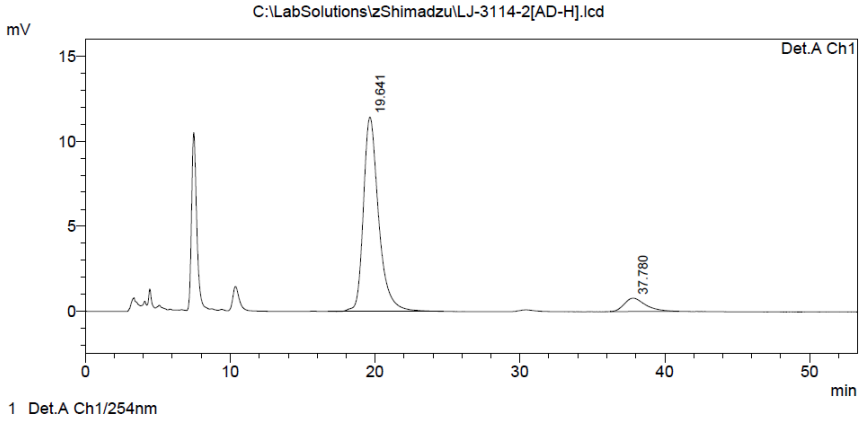


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.461	72039	3030	8.578	23.235
2	10.331	57346	1814	6.828	13.907
3	19.618	359639	4941	42.823	37.884
4	37.687	350805	3257	41.771	24.973
Total		839830	13042	100.000	100.000

(Racemic **3p**)



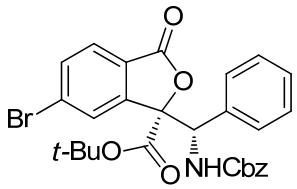
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.641	832422	11417	91.319	93.617
2	37.780	79131	778	8.681	6.383
Total		911552	12195	100.000	100.000

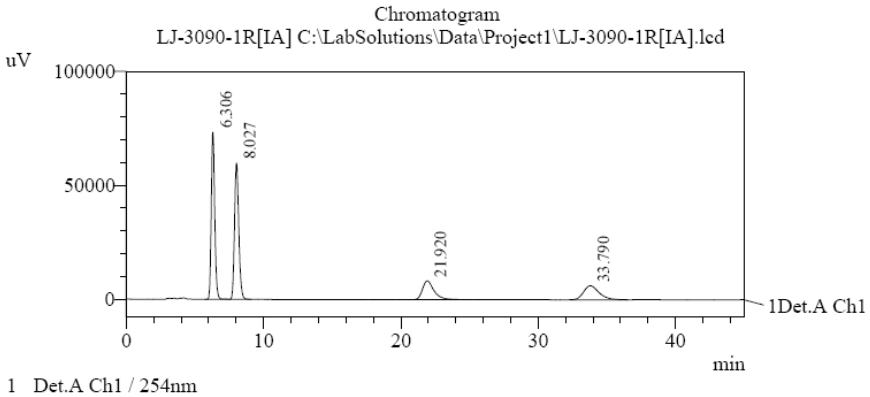
(Enantiomerically enriched **3p**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(phenyl)methyl)-6-bromo-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3q**)



3q

A yellow foam; diastereomeric ratio was 86:14; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.55 (dd, *J* = 8.1 Hz, 1.4 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.29 (m, 5H), 7.13 – 6.96 (m, 5H), 6.08 (d, *J* = 10.2 Hz, 1H), 5.69 (d, *J* = 10.2 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.17, 165.23, 155.22, 146.90, 135.98, 134.29, 133.84, 129.39, 128.84, 128.51, 128.40, 128.26, 128.22, 127.90, 126.87, 126.52, 124.67, 88.71, 85.22, 67.28, 60.23, 27.70; HRMS (ESI) m/z calcd for $C_{28}H_{26}BrNO_6$ $[M+Na]^+$ 574.0836, found 574.0831; the ee value of the major isomer was 91%, t_R (major) = 21.9 min and 33.8 min, t_R (minor) = 6.3 min and 8.0 min (Chiralcel IA, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



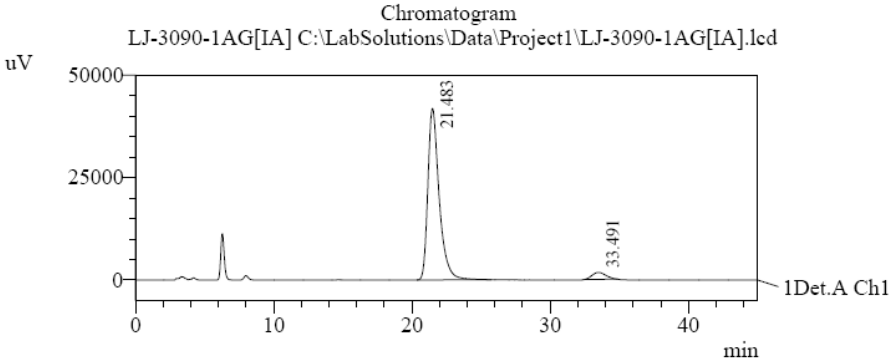
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.306	1287293	73310	36.336	49.662
2	8.027	1286389	59827	36.311	40.528
3	21.920	481879	8297	13.602	5.621
4	33.790	487148	6184	13.751	4.189
Total		3542709	147618	100.000	100.000

(Racemic **3q**)



1 Det.A Ch1 / 254nm

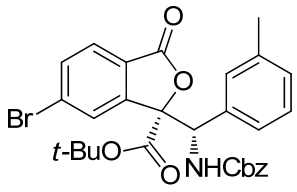
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.483	2380181	41854	95.336	96.114
2	33.491	116430	1692	4.664	3.886
Total		2496611	43546	100.000	100.000

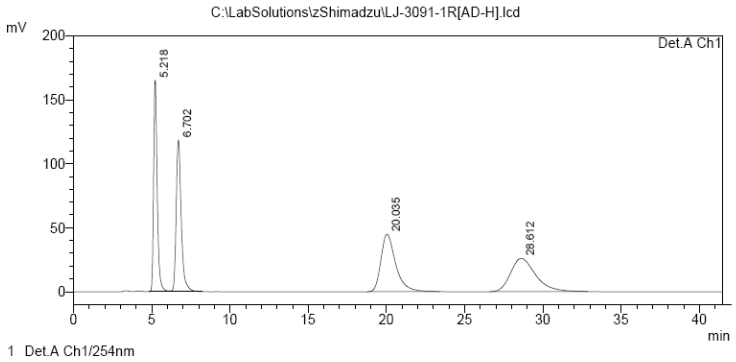
(Enantiomerically enriched **3q**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(*m*-tolyl)methyl)-6-bromo-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3r**)



3r

A yellow foam; diastereomeric ratio was 87:13; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.39 – 7.30 (m, 5H), 7.01 – 6.90 (m, 2H), 6.87 – 6.75 (m, 2H), 6.04 (d, *J* = 10.1 Hz, 1H), 5.64 (d, *J* = 10.2 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 2.17 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.23, 165.29, 155.24, 147.01, 137.94, 136.04, 134.20, 133.76, 129.26, 129.10, 128.73, 128.55, 128.51, 128.22, 128.11, 126.84, 126.63, 124.92, 124.71, 88.75, 85.16, 67.25, 60.25, 27.71, 21.16; HRMS (ESI) m/z calcd for $C_{29}H_{28}BrNO_6$ $[M+Na]^+$ 588.0992, found 588.0983; the ee value of the major isomer was 86%, t_R (major) = 20.0 min and 28.6 min, t_R (minor) = 5.2 min and 6.7 min (Chiralcel AD-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

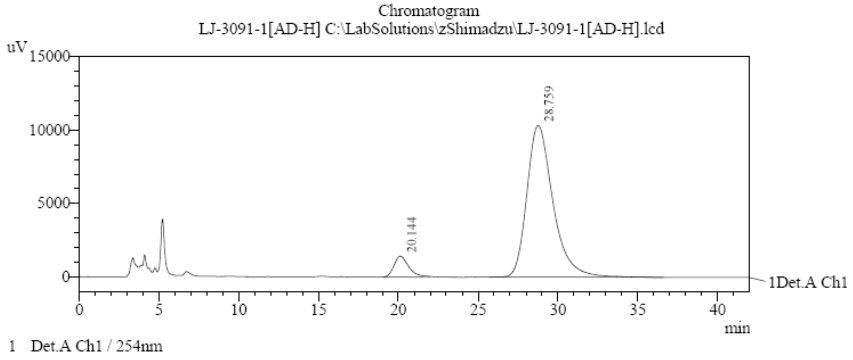


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.218	2636689	165295	23.686	46.593
2	6.702	2664190	118550	23.933	33.417
3	20.035	2940102	44958	26.412	12.672
4	28.612	2890911	25962	25.970	7.318
Total		11131892	354765	100.000	100.000

(Racemic **3r**)



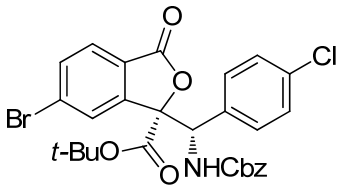
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.144	88166	1405	6.990	11.968
2	28.759	1173080	10334	93.010	88.032
Total		1261246	11739	100.000	100.000

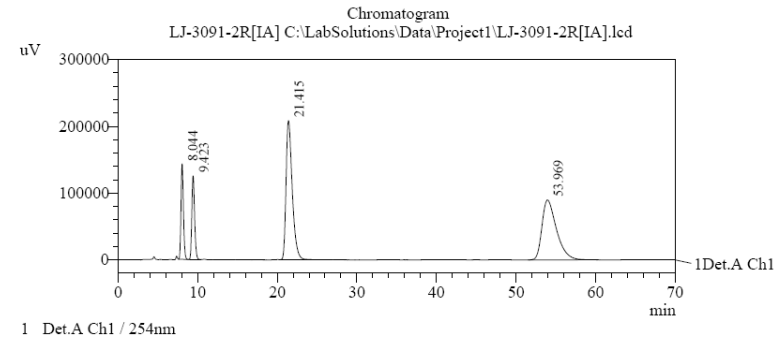
(Enantiomerically enriched **3r**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-chlorophenyl)methyl)-6-bromo-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3s**)



3s

A yellow foam; diastereomeric ratio was 84:16; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.29 (m, 5H), 7.10 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.06 (d, *J* = 10.0 Hz, 1H), 5.65 (d, *J* = 10.0 Hz, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.99, 165.06, 155.17, 146.64, 135.86, 134.49, 134.11, 133.02, 129.61, 129.25, 128.99, 128.75, 128.53, 128.25, 127.15, 126.38, 124.57, 88.35, 85.43, 67.40, 59.66, 27.69; HRMS (ESI) m/z calcd for $C_{28}H_{25}BrClNO_6$ $[M+Na]^+$ 608.0446, found 608.0476; the ee value of the major isomer was 93%, t_R (major) = 21.4 min and 53.9 min, t_R (minor) = 8.0 min and 9.4 min (Chiralcel IA, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

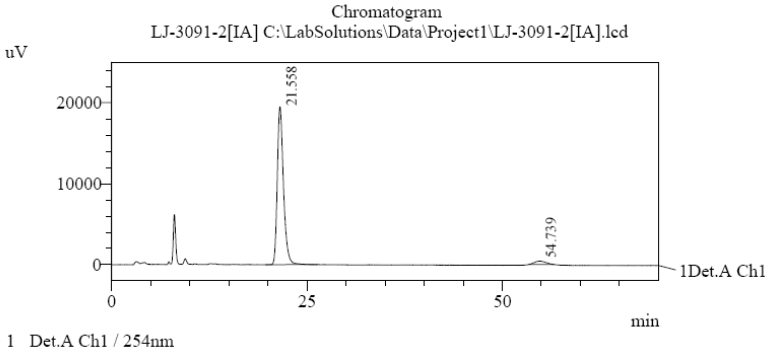


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.044	3028592	142921	10.548	25.232
2	9.423	3053270	125404	10.634	22.140
3	21.415	11278542	208383	39.281	36.790
4	53.969	11352266	89708	39.537	15.838
Total		28712670	566417	100.000	100.000

(Racemic **3s**)



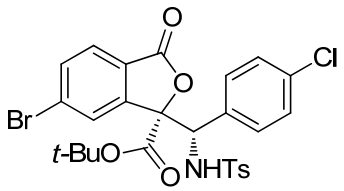
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.558	1070684	19496	96.375	97.937
2	54.739	40268	411	3.625	2.063
Total		1110953	19907	100.000	100.000

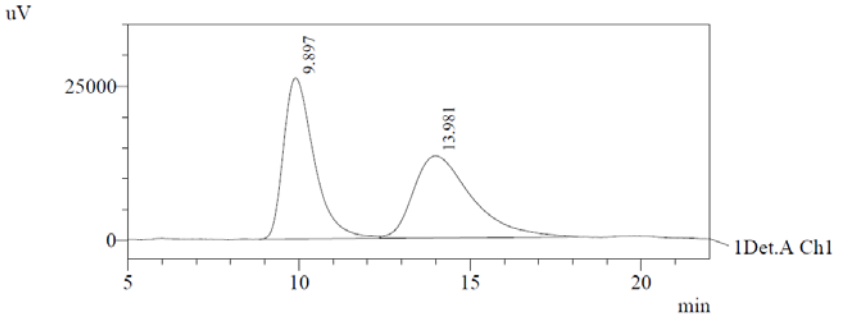
(Enantiomerically enriched **3s**)

(*R*)-*tert*-Butyl -6-bromo-1-((*S*)-(4-chlorophenyl)(4-methylphenylsulfonamido)methyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3t**)



3t

A light yellow solid; diastereomeric ratio was 88:12; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.4 Hz, 1H), 7.56 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 5.84 (d, *J* = 10.4 Hz, 1H), 5.34 (d, *J* = 10.7 Hz, 1H), 2.27 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.94, 164.66, 146.24, 143.45, 137.14, 134.26, 134.15, 130.69, 129.70, 129.33, 129.13, 128.18, 127.12, 126.79, 126.32, 124.51, 88.43, 85.93, 62.48, 27.87, 21.28; $[\alpha]_D^{rt}$ = -67.2 (c = 0.95, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{27}H_{25}BrClNO_6S$ $[M+Na]^+$ 628.0167, found 628.0195; the ee value of the major isomer was 87%, t_R (major) = 9.9 min and 14.0 min (Chiralcel OD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



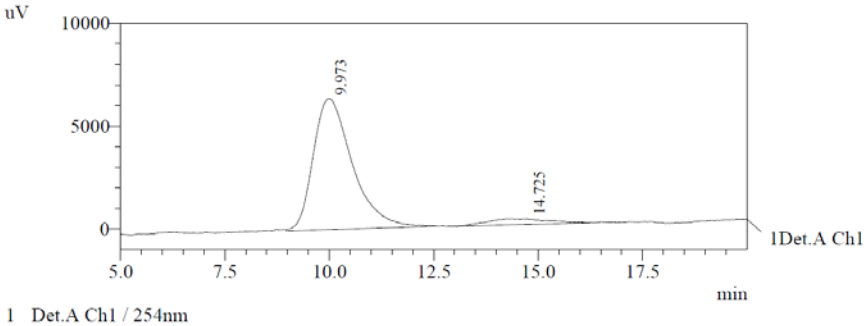
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.897	1625045	26123	50.735	66.227
2	13.981	1577983	13322	49.265	33.773
Total		3203028	39445	100.000	100.000

(Racemic **3t**)



1 Det.A Ch1 / 254nm

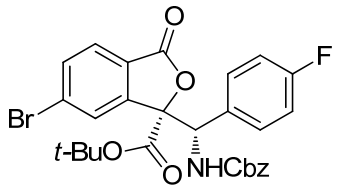
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.973	414118	6358	93.621	95.826
2	14.725	28218	277	6.379	4.174
Total		442336	6635	100.000	100.000

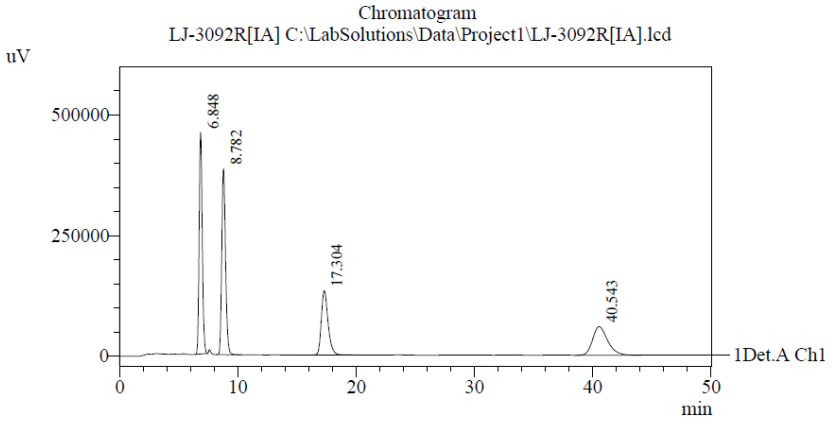
(Enantiomerically enriched **3t**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-fluorophenyl)methyl)-6-bromo-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3u**)



3u

A yellow foam; diastereomeric ratio was 85:15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.58 (dd, *J* = 8.1 Hz, 1.3 Hz, 1H), 7.47 – 7.22 (m, 6H), 7.09 – 7.01 (m, 2H), 6.82 (t, *J* = 8.6 Hz, 2H), 6.06 (d, *J* = 10.1 Hz, 1H), 5.66 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.02 (d, *J* = 12.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.03, 165.12, 162.47 (*J* = 248.4 Hz), 155.18, 146.77, 135.89, 134.02, 129.68, 129.62, 129.56, 128.59, 128.53, 128.30, 128.25, 127.92, 127.05, 126.41, 124.61, 115.41, 115.24, 88.49, 85.36, 67.37, 59.62, 27.70; HRMS (ESI) m/z calcd for $C_{28}H_{25}BrFNO_6$ $[M+Na]^+$ 592.0741, found 592.0751; the ee value of the major isomer was 91%, t_R (major) = 17.3 min and 40.5 min, t_R (minor) = 6.8 min and 8.8 min (Chiralcel IA, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



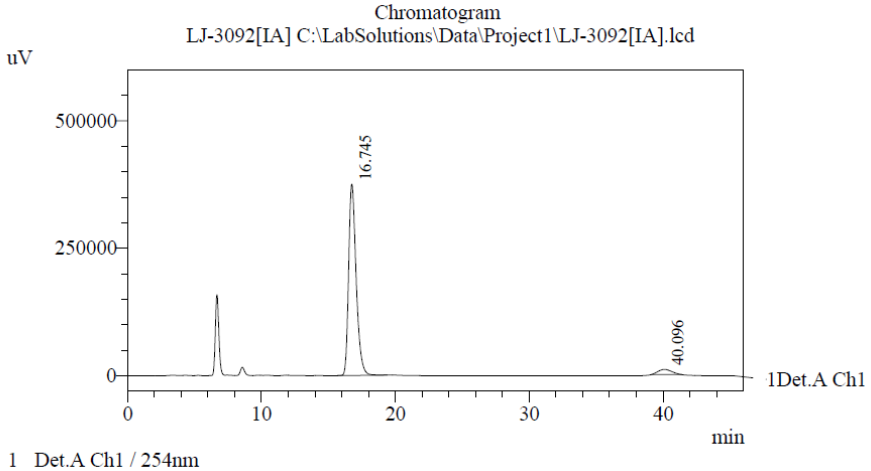
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.848	8410997	459519	30.665	44.312
2	8.782	8545134	385053	31.154	37.131
3	17.304	5279870	133264	19.250	12.851
4	40.543	5192490	59181	18.931	5.707
Total		27428491	1037016	100.000	100.000

(Racemic **3u**)



1 Det.A Ch1 / 254nm

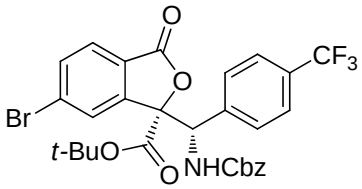
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.745	14669490	375410	95.305	97.384
2	40.096	722724	10085	4.695	2.616
Total		15392214	385495	100.000	100.000

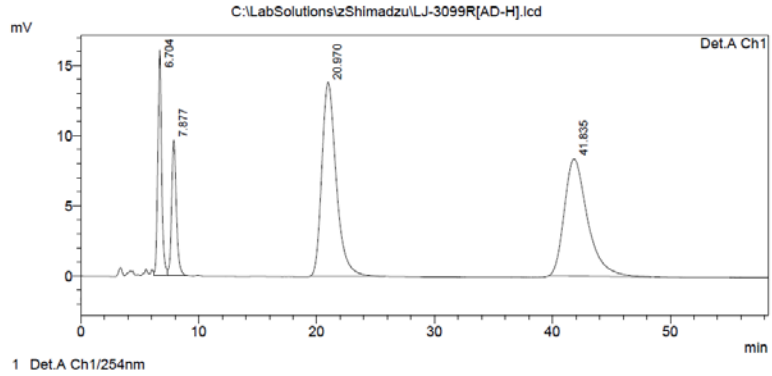
(Enantiomerically enriched **3u**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(4-(trifluoromethyl)phenyl)methyl)-6-bromo-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3v**)



3v

A yellow foam; diastereomeric ratio was 83:17; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.50 – 7.46 (m, 2H), 7.42 – 7.30 (m, 7H), 7.24 – 7.16 (m, 2H), 6.14 (d, *J* = 10.1 Hz, 1H), 5.72 (d, *J* = 9.9 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 3H), 5.02 (d, *J* = 12.1 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.85, 165.00, 155.19, 146.45, 135.77, 134.26, 129.74, 128.64, 128.57, 128.46, 128.41, 128.28, 128.17, 128.11, 127.20, 126.39, 126.10, 125.68, 125.29, 88.08, 85.61, 67.50, 59.85, 27.69; HRMS (ESI) m/z calcd for $C_{29}H_{25}BrF_3NO_6$ $[M+Na]^+$ 642.0710, found 642.0717; the ee value of the major isomer was 82%, t_R (major) = 20.9 min and 41.8 min, tR (minor) = 6.7 min and 7.9 min (Chiralcel AD-H, λ = 254 nm, 30% iPrOH/hexanes, flow rate = 1.0 mL/min).

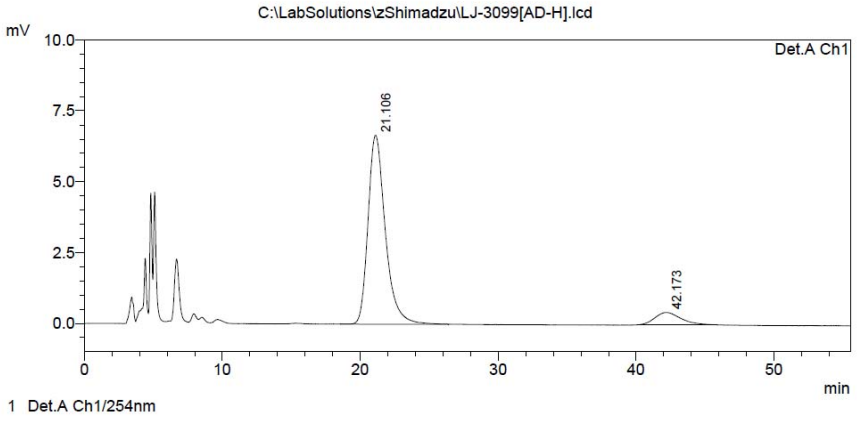


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.704	359910	16074	12.195	33.570
2	7.877	269007	9629	9.115	20.111
3	20.970	1176749	13819	39.873	28.862
4	41.835	1145595	8359	38.817	17.458
Total		2951261	47881	100.000	100.000

(Racemic **3v**)



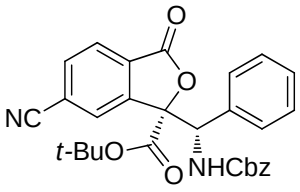
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.106	580175	6662	91.118	93.902
2	42.173	56556	433	8.882	6.098
Total		636730	7094	100.000	100.000

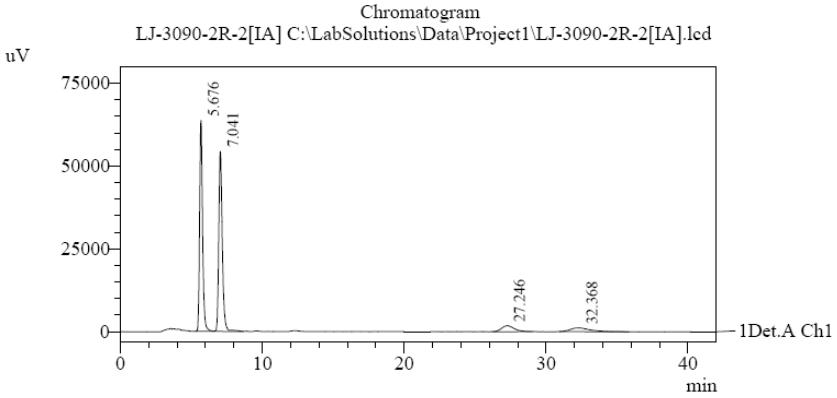
(Enantiomerically enriched **3v**)

(*R*)-*tert*-Butyl 1-((*S*)-(benzyloxycarbonylamino)(phenyl)methyl)-6-cyano-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3w**)



3w

A yellow foam; diastereomeric ratio was 87:13; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.69 (d, *J* = 4.2 Hz, 2H), 7.40 – 7.29 (m, 5H), 7.18 – 7.04 (m, 3H), 7.02 (d, *J* = 3.6 Hz, 2H), 6.07 (d, *J* = 10.1 Hz, 1H), 5.73 (d, *J* = 10.2 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 5.02 (d, *J* = 12.2 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.16, 164.73, 155.18, 145.71, 135.87, 133.95, 129.26, 128.97, 128.63, 128.54, 128.45, 128.30, 128.09, 127.85, 127.10, 126.58, 117.78, 117.16, 89.24, 85.83, 67.41, 60.30, 27.69; HRMS (ESI) m/z calcd for $C_{29}H_{26}N_2O_6$ $[M+Na]^+$ 521.1683, found 521.1707; the ee value of the major isomer was 83%, t_R (major) = 27.2 min and 32.3 min, t_R (minor) = 5.7 min and 7.0 min (Chiralcel IA, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



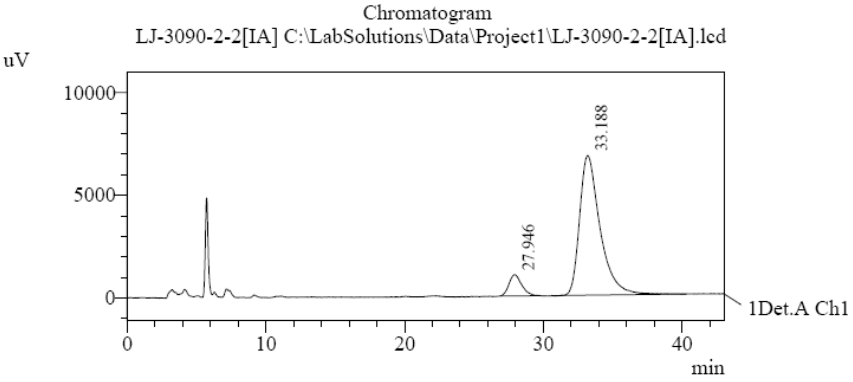
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.676	926116	63613	44.238	52.642
2	7.041	941347	54254	44.965	44.897
3	27.246	113090	1827	5.402	1.512
4	32.368	112946	1147	5.395	0.949
Total		2093498	120841	100.000	100.000

(Racemic **3w**)



1 Det.A Ch1 / 254nm

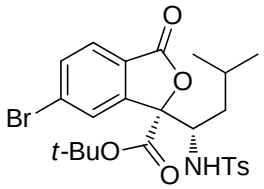
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.946	65707	1035	8.615	13.203
2	33.188	696989	6802	91.385	86.797
Total		762697	7837	100.000	100.000

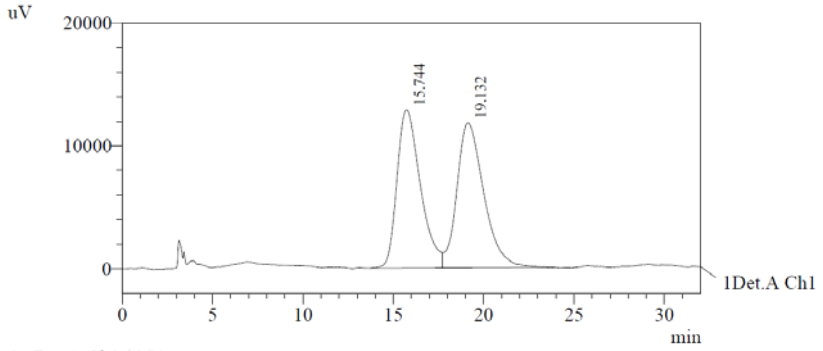
(Enantiomerically enriched **3w**)

(*R*)-*tert*-Butyl- 6-bromo-1-((*S*)-3-methyl-1-(4-methylphenylsulfonamido)butyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3x**)



3x

A light yellow oil; diastereomeric ratio was 70:30; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.71 (s, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.17 (td, *J* = 9.8 Hz, 3.5 Hz, 1H), 2.40 (s, 3H), 1.39 (s, 9H), 1.16 – 0.71 (m, 3H), 0.71 (t, *J* = 6.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.77, 166.23, 147.33, 143.35, 138.78, 134.07, 129.74, 129.57, 127.22, 127.05, 126.62, 124.47, 88.58, 85.29, 57.52, 41.08, 27.70, 23.96, 23.24, 21.49, 21.42; $[\alpha]_D^{rt}$ = -29.8 (c = 0.85, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{25}H_{30}BrNO_6S$ $[M+Na]^+$ 574.0869, found 574.0886; the ee value of the major isomer was 62%, t_R (major) = 27.2 min and 32.3 min, t_R (minor) = 15.7 min and 19.1 min (Chiralcel IA, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



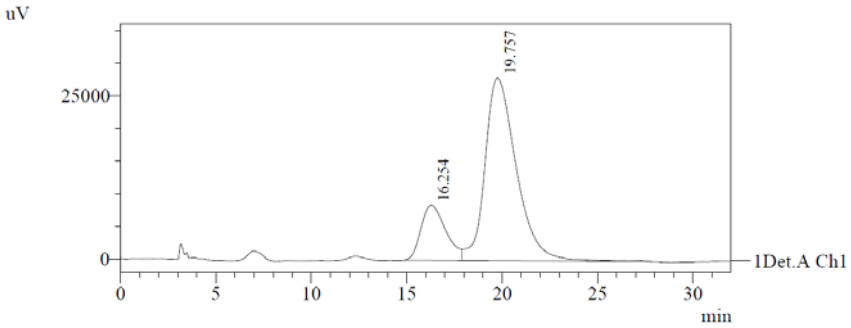
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.744	1165405	12897	48.747	52.167
2	19.132	1225320	11825	51.253	47.833
Total		2390725	24722	100.000	100.000

(Racemic **3x**)



1 Det.A Ch1 / 254nm

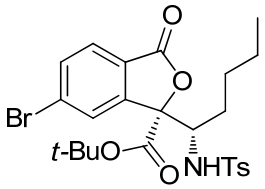
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.254	765880	8429	19.239	23.137
2	19.757	3214920	28001	80.761	76.863
Total		3980799	36430	100.000	100.000

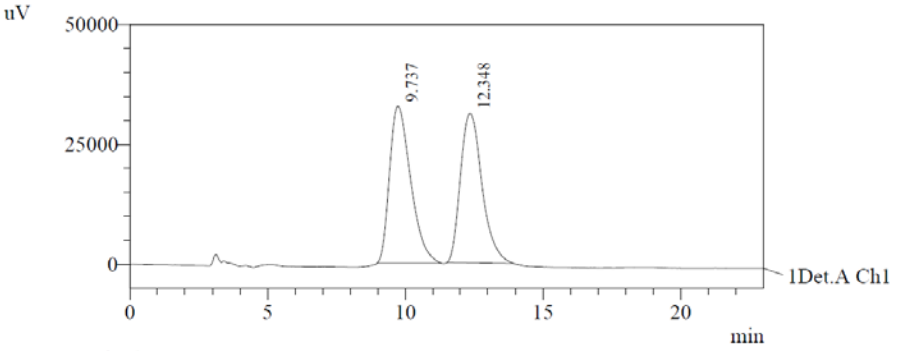
(Enantiomerically enriched **3x**)

(*R*)-*tert*-Butyl-6-bromo-1-((*S*)-1-(4-methylphenylsulfonamido)pentyl)-3-oxo-1,3-dihydroisobenzofuran-1-carboxylate (**3y**)



3y

A light yellow oil; diastereomeric ratio was 63:37; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.74 – 7.64 (m, 4H), 7.25 (d, *J* = 8.5 Hz, 2H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.14 – 4.04 (m, 1H), 2.40 (s, 3H), 1.40 (s, 9H), 1.35 – 1.27 (m, 2H), 1.04 – 0.82 (m, 4H), 0.61 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.83, 166.13, 147.32, 143.41, 138.77, 134.08, 129.79, 129.61, 127.19, 127.06, 126.70, 124.33, 88.55, 85.29, 59.22, 31.09, 27.86, 27.69, 22.27, 21.46, 13.55; $[\alpha]_D^{rt}$ = -27.4 (c = 0.80, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{25}H_{30}BrNO_6S$ $[M+Na]^+$ 574.0869, found 574.0882; the ee value of the major isomer was 55%, t_R (major) = 9.7 min and 12.3 min, (Chiralcel OD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).



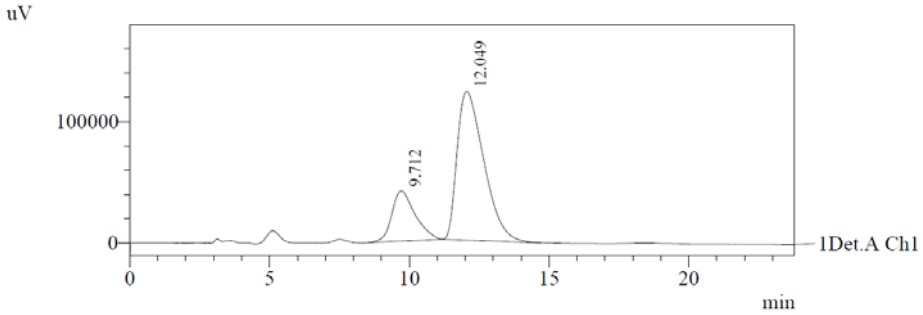
1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.737	1753971	32827	50.734	51.314
2	12.348	1703246	31146	49.266	48.686
Total		3457217	63974	100.000	100.000

(Racemic **3y**)



1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.712	2399841	41366	22.742	25.243
2	12.049	8152846	122503	77.258	74.757
Total		10552686	163869	100.000	100.000

(Enantiomerically enriched **3y**)

References

[1] X. Han, J. Kwiatkowski, F. Xue, K-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7604.

[2] J. Luo, L-W. Xu, A. S. H. Robyn, Y. Lu, *Org. Lett.* **2009**, *11*, 437.

[3] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967.

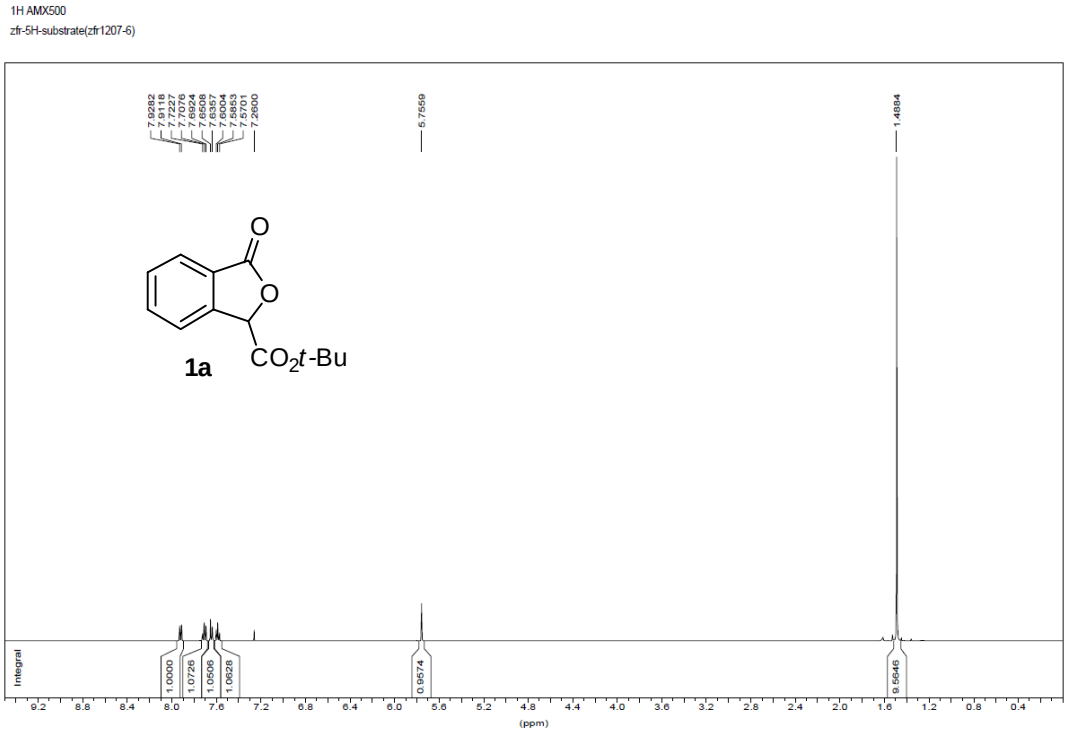
[4] Q. Zhu, Y. Lu, *Angew. Chem. Int. Ed.* **2010**, *49*, 7753.

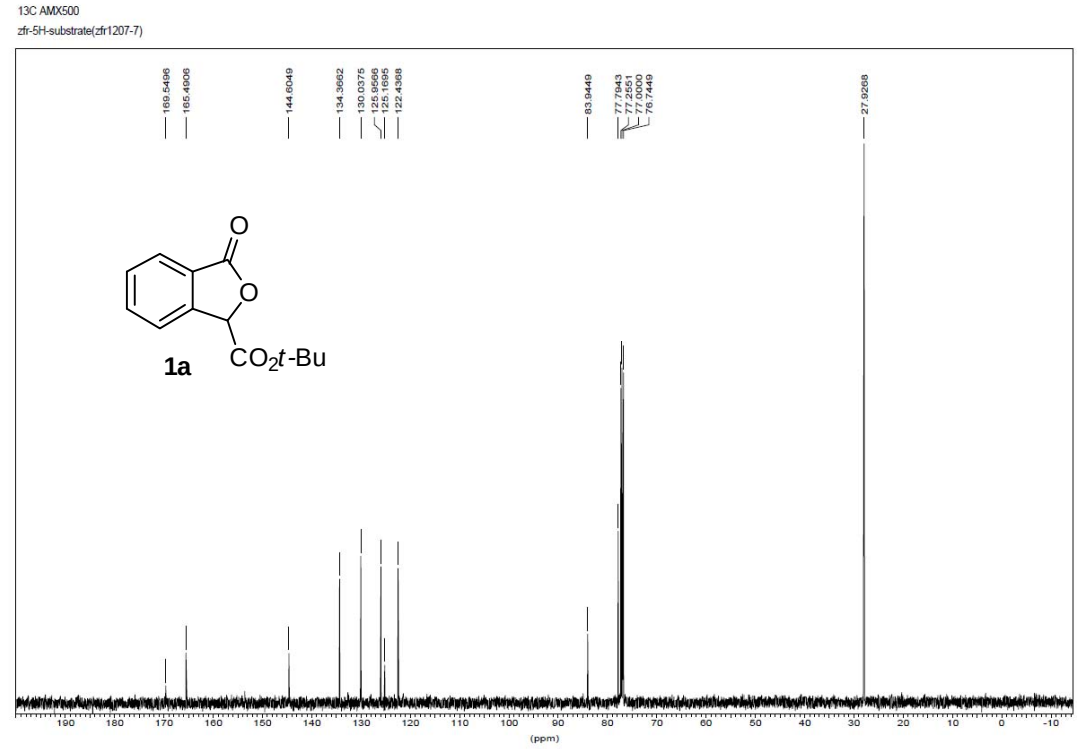
[5] A. L. Tilman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191.

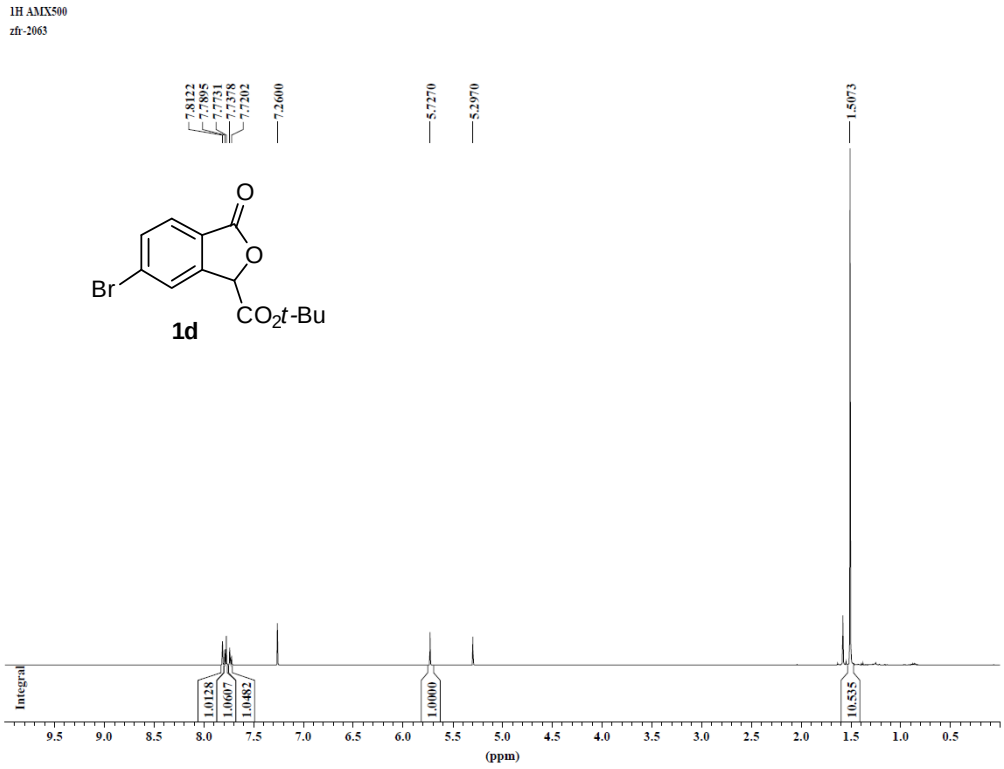
[6] D.-J. Dong, H.-H. Li, S.-K. Tian, *J. Am. Chem. Soc.* **2010**, *132*, 5018.

[7] F. Chemla, V. Hebbe, J.-F. Normant, *Synthesis*. **2000**, *1*, 75.

H. NMR Spectra of Products



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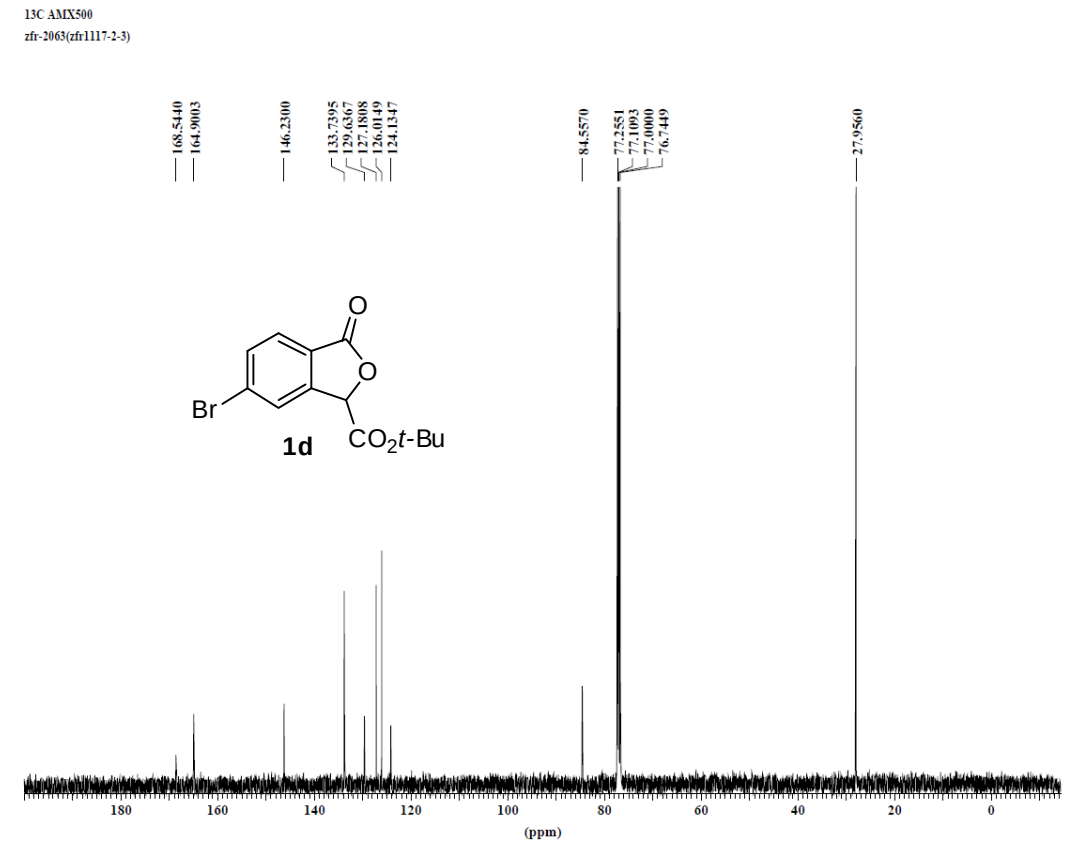
7.7895
7.7731
7.7378
7.7202
7.2600
5.7270
5.2970
1.5073
Br
O
O
CO2t-Bu
1d
Integral
1.0128
1.0607
1.0482
1.0000
10.535
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)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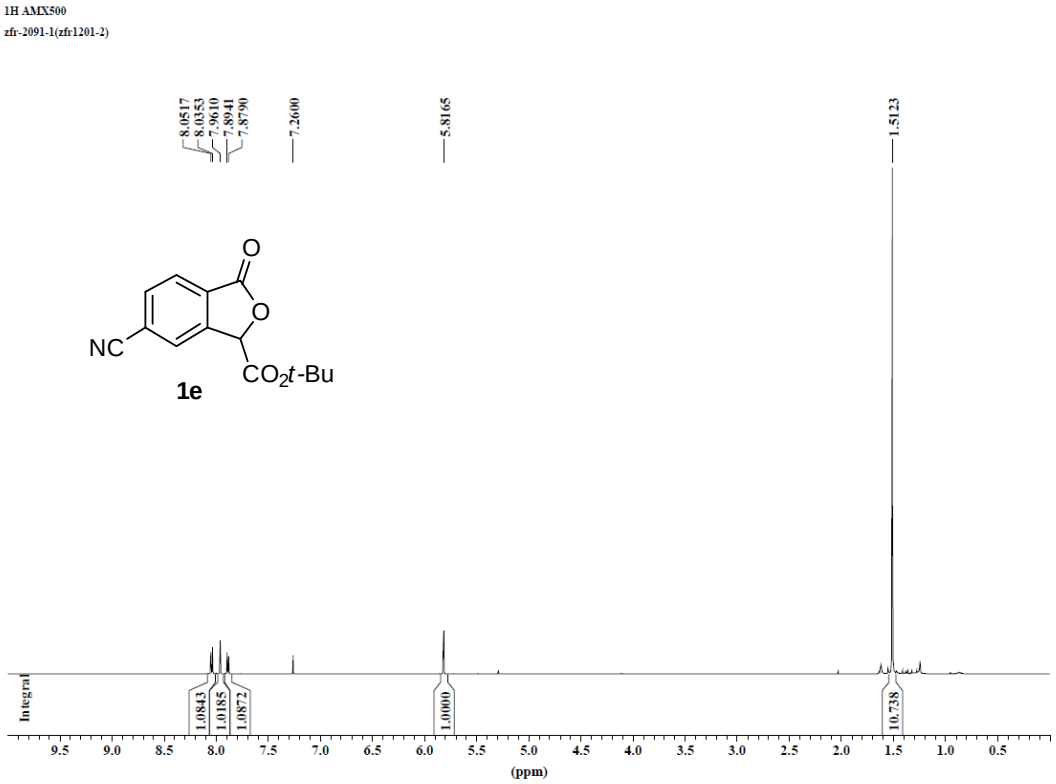
168.5440
164.9003
146.2300
133.7395
129.6367
127.1808
126.0149
124.1347
84.5570
77.2551
77.1093
77.0000
76.7449
27.9560
Br
O
O
CO2t-Bu
1d
180 160 140 120 100 80 60 40 20 0
(ppm)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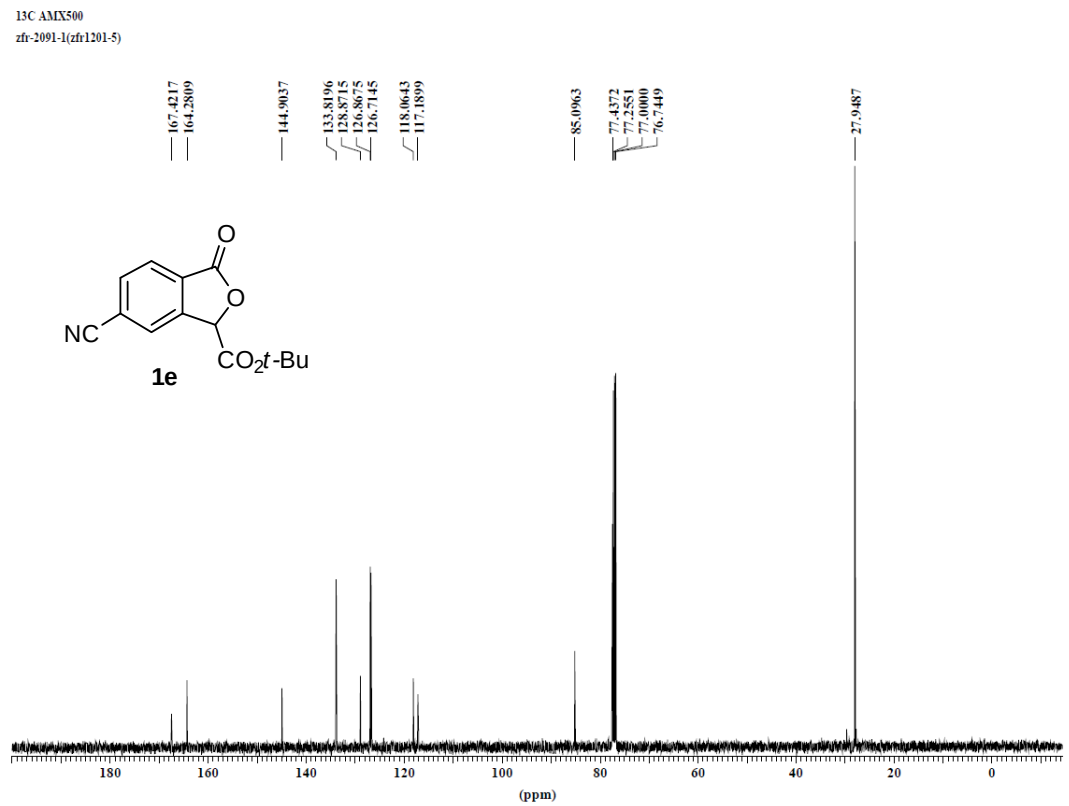
8.0517
8.0353
7.9610
7.8941
7.8790
7.2600
5.8165
1.5123
O
O
NC
CO2t-Bu
1e
Integral
1.0843
1.0185
1.0872
1.0000
10.738
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)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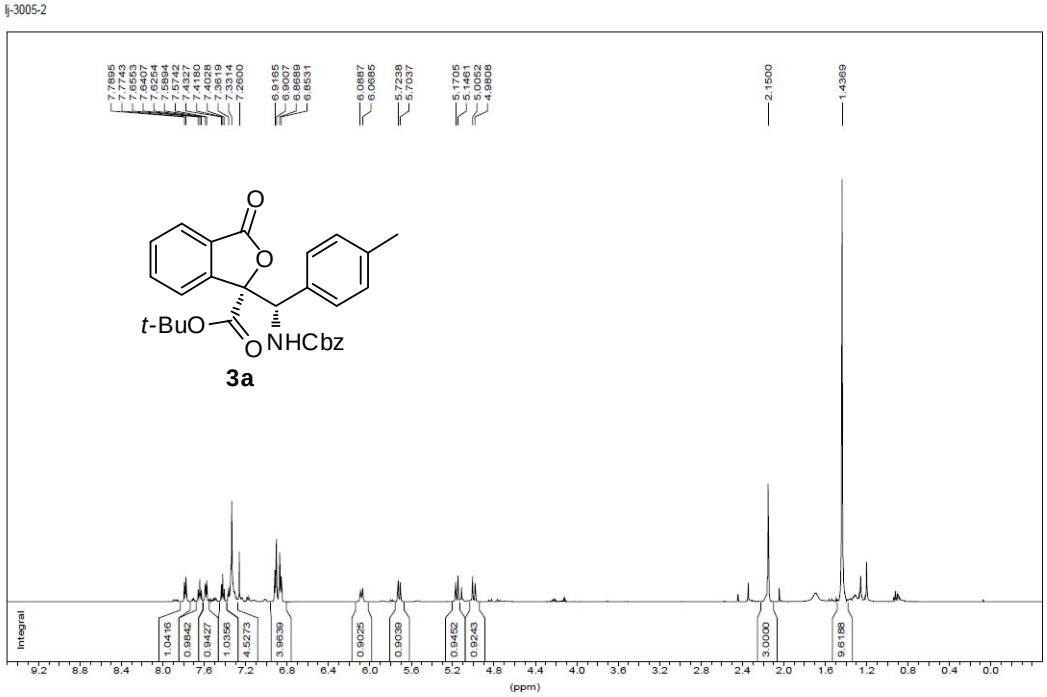
144.9037
133.8196
128.8715
126.8675
126.7145
118.0643
117.1899
85.0963
77.4372
77.2551
77.0000
76.7449
27.9487
O
O
NC
CO2t-Bu
1e
180 160 140 120 100 80 60 40 20 0
(ppm)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7.6407
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7.5894
7.5742
7.4327
7.4180
7.4028
7.3819
7.3314
7.2900
6.9165
6.9007
6.8689
6.8531
6.0887
6.0685
5.7238
5.7037
5.1705
5.1461
5.0952
4.9808
2.1500
1.4369
t-BuO
O
NHCbz
3a
Integral
1.0416
0.9842
0.9427
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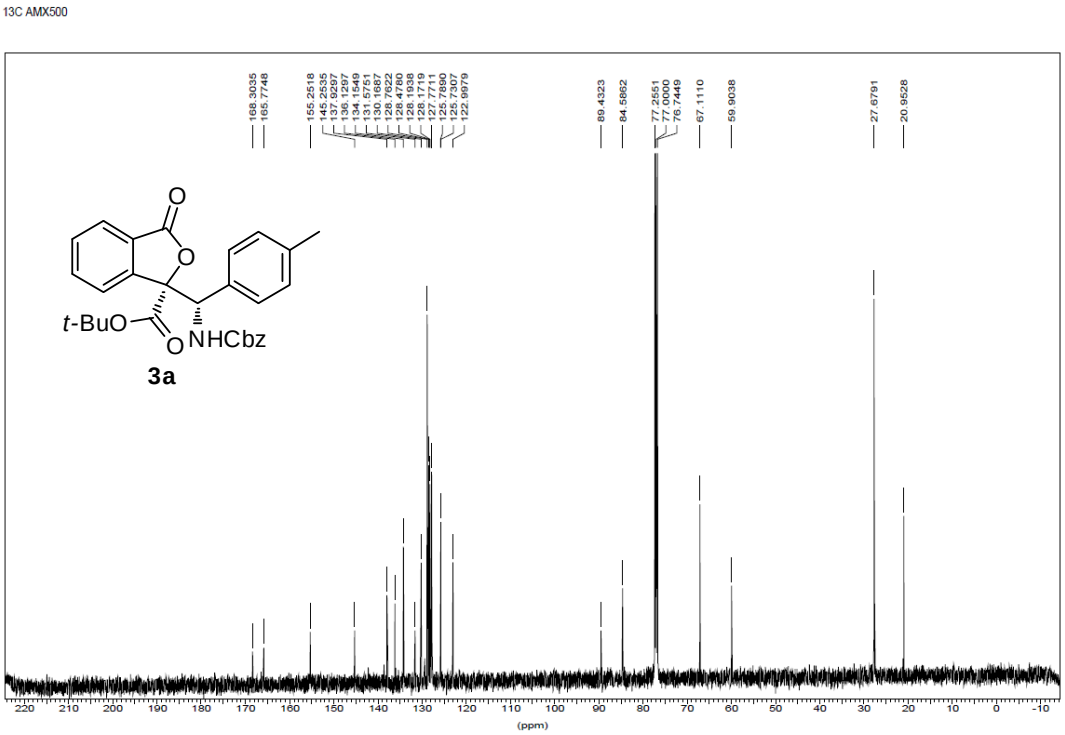
9.6188
(ppm)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145.2535
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134.4549
131.5741
130.1687
128.7622
128.4780
128.3188
128.1719
127.7711
125.7890
125.7707
122.9979
89.4323
84.5862
77.2551
77.0000
76.7449
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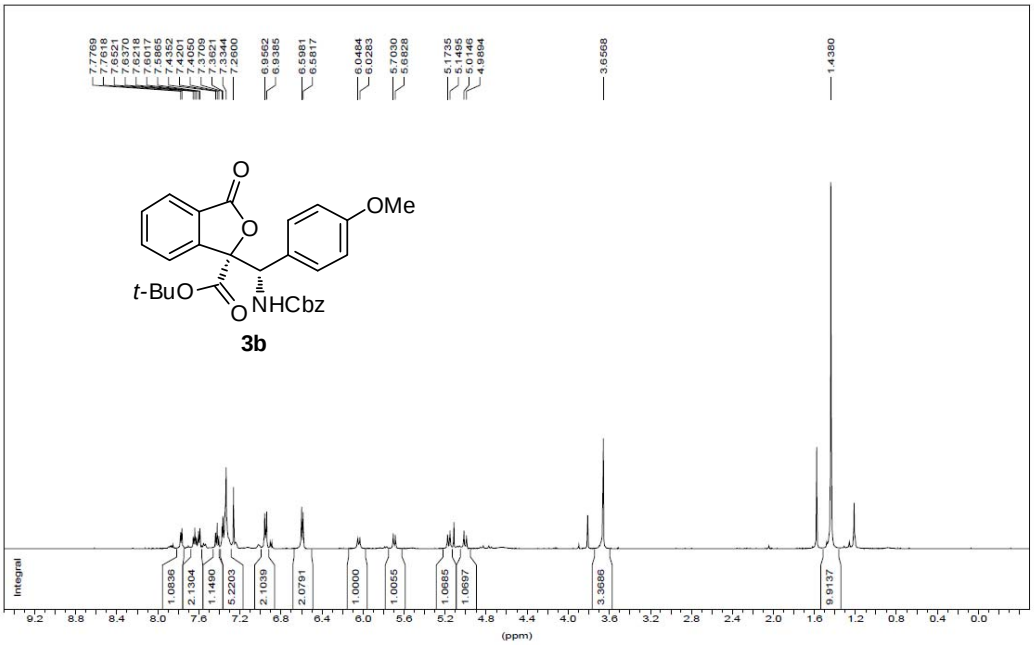
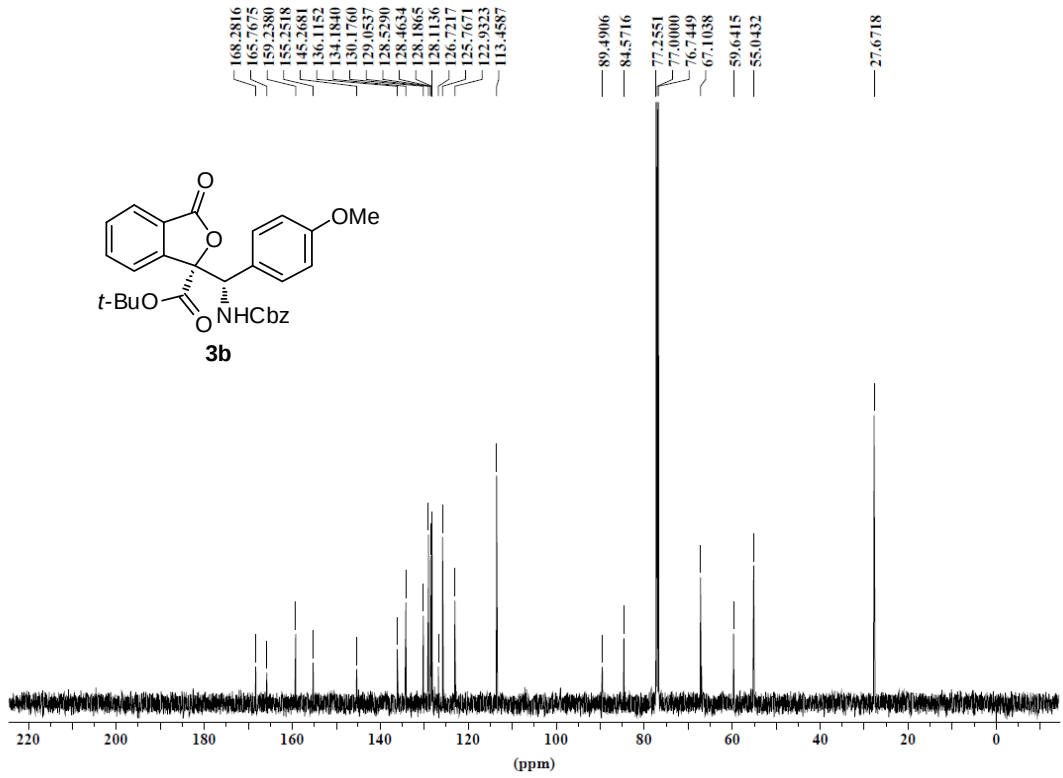
27.6791
20.9528
t-BuO
O
NHCbz
3a
(ppm)

1H AMX500 lj-4-OMe



13C AMX500 4-OMe



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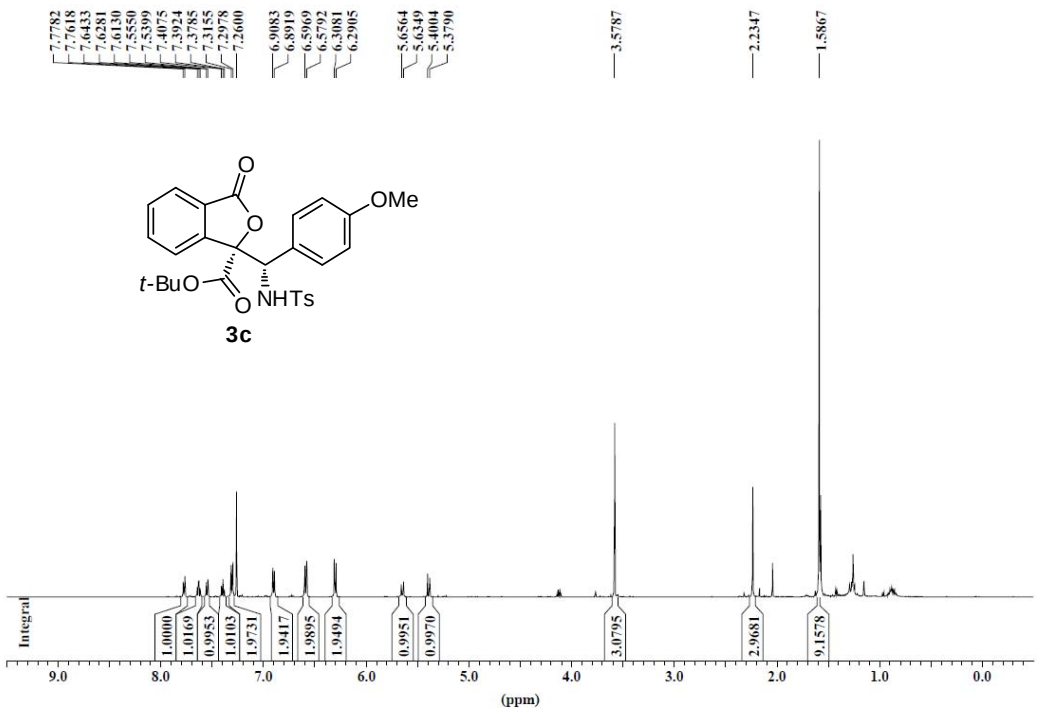

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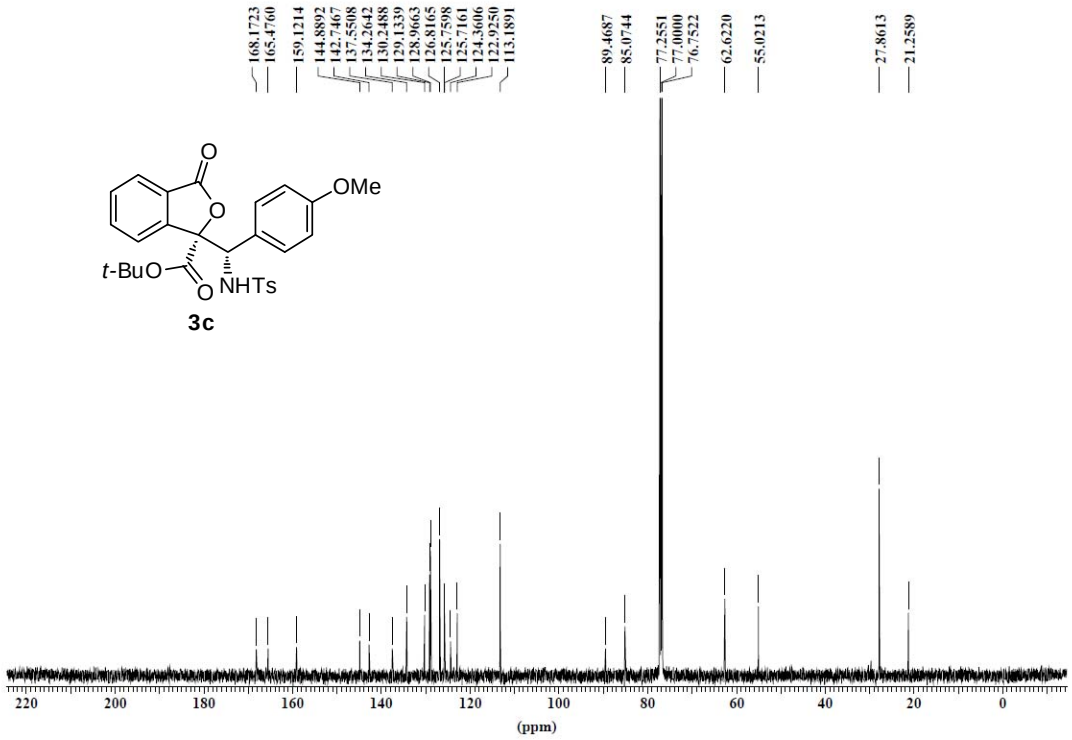
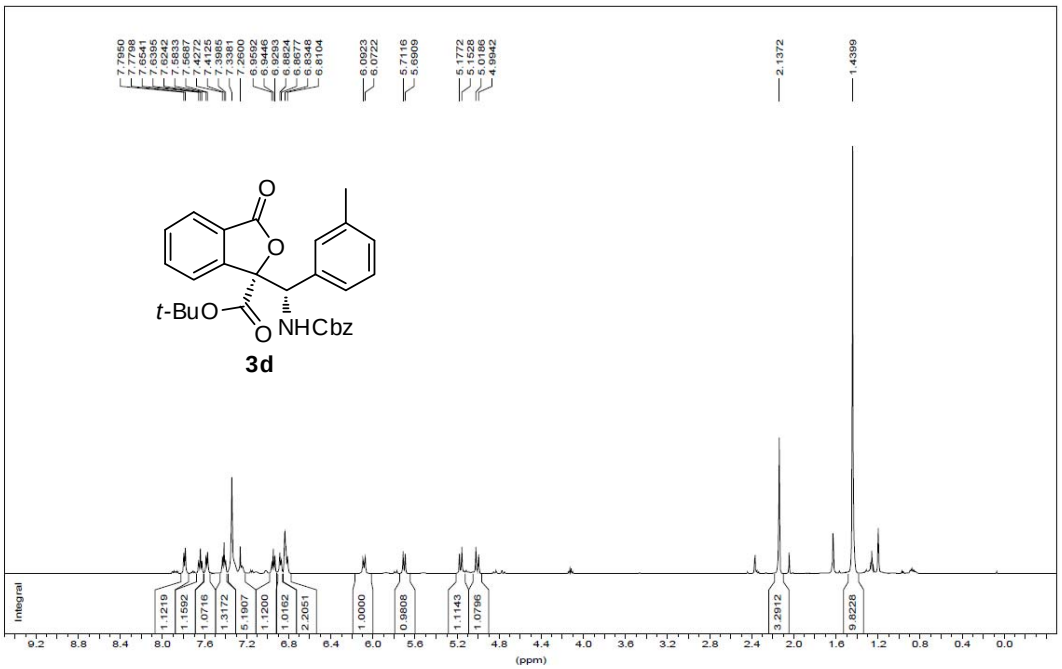


lj-3074-2



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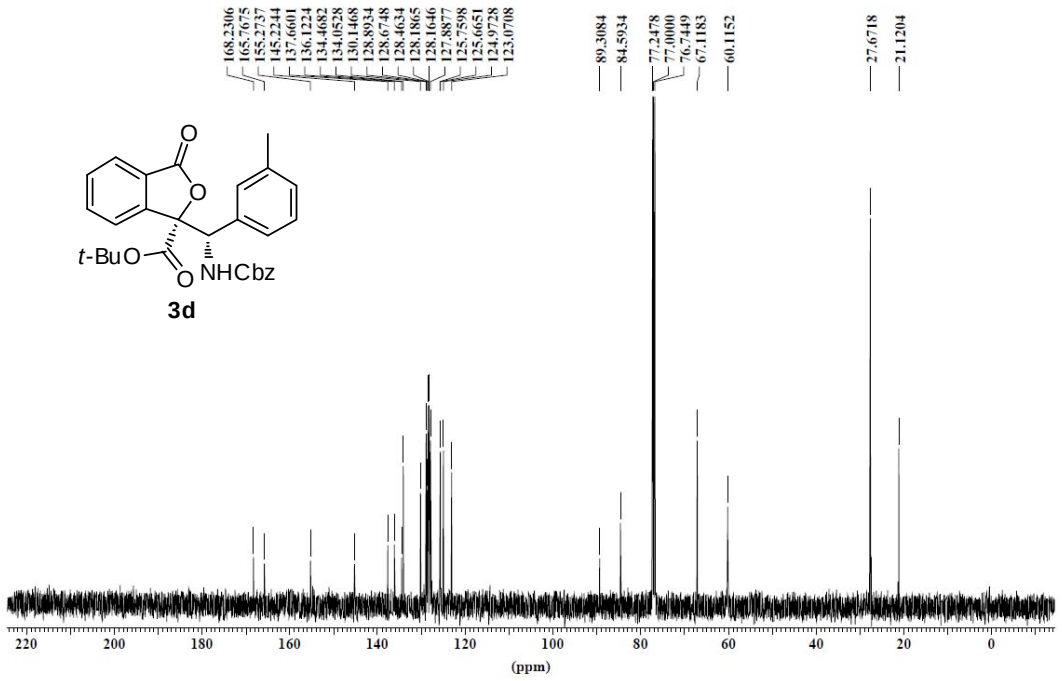

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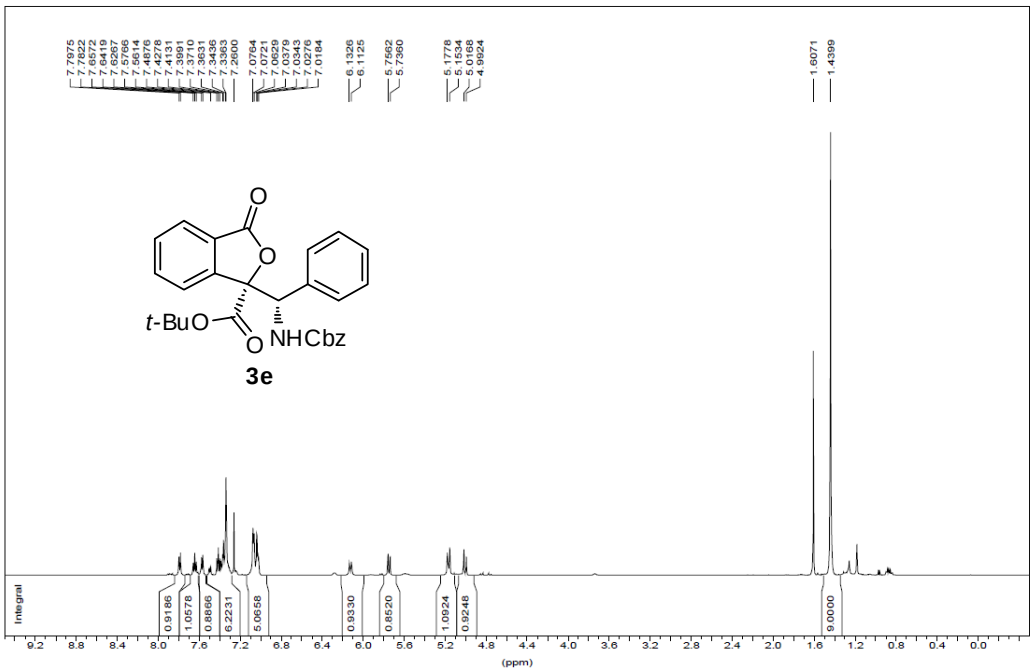
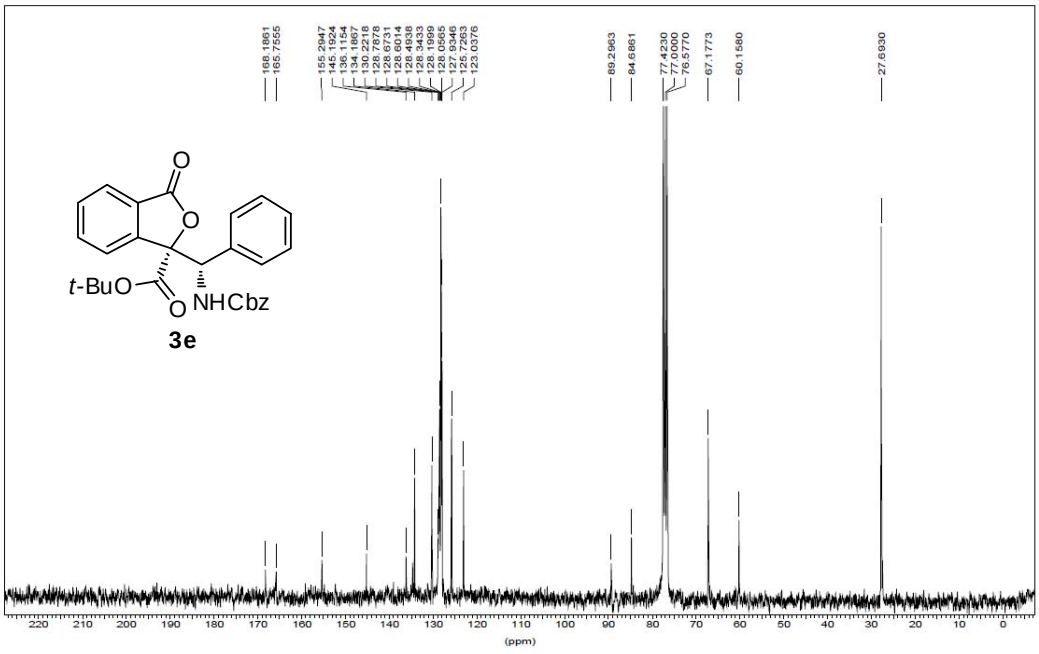
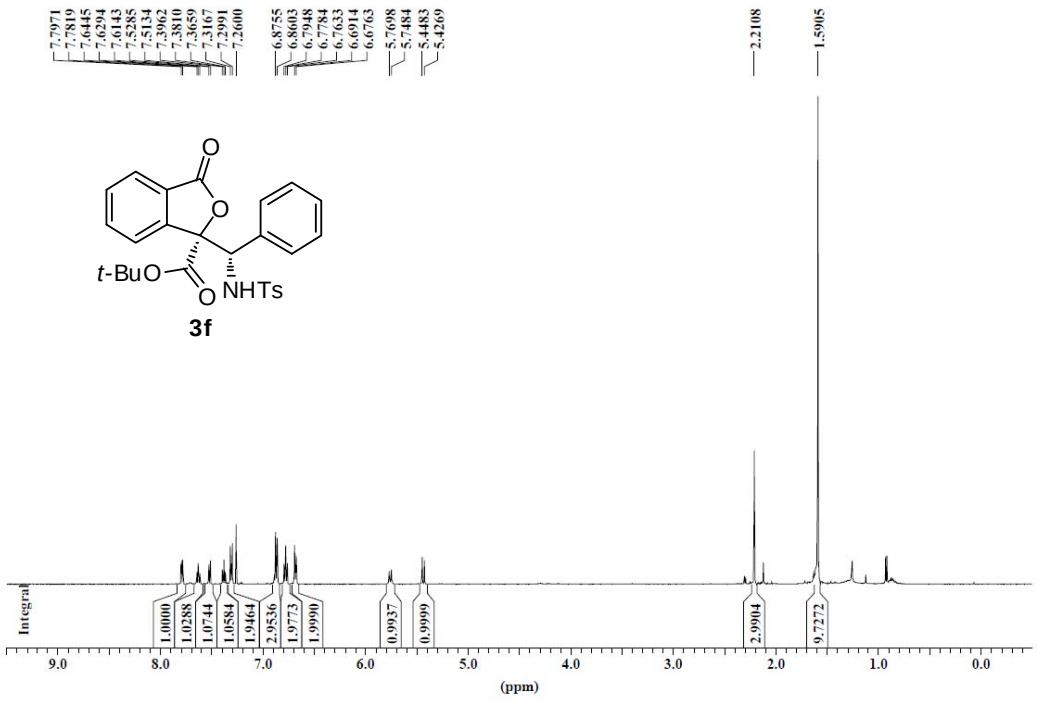


lj-3076-1

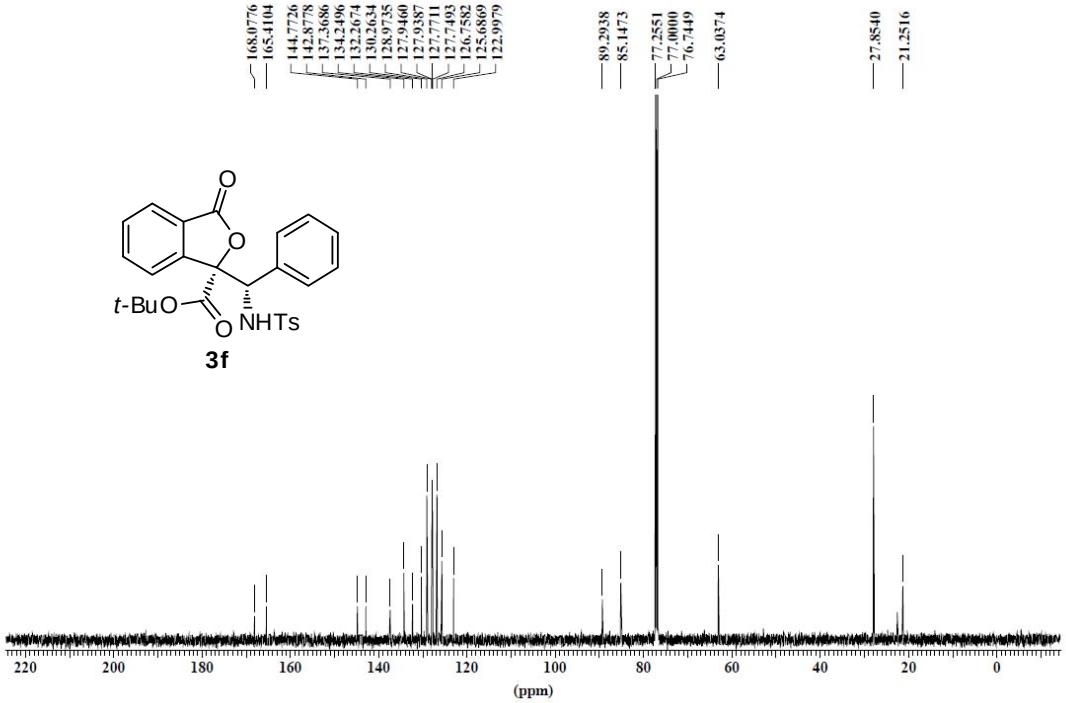


1H AMX500 lj-3131



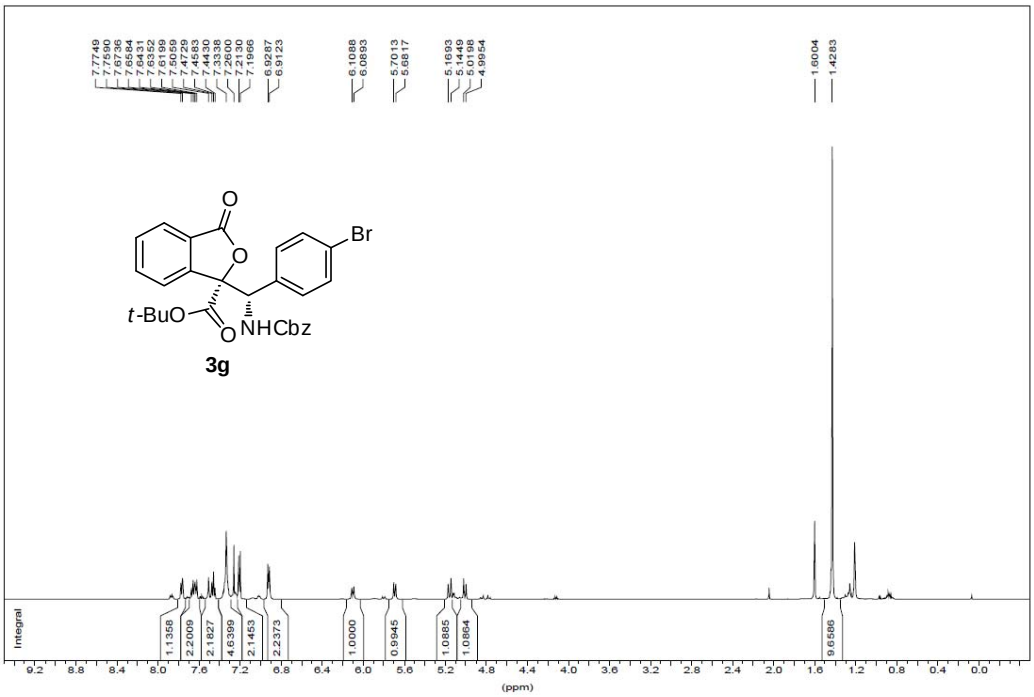
3f

13C AMX500 lj-3131



3f

lj-4-Br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7.6199
7.6059
7.4729
7.4583
7.4430
7.3338
7.2000
7.2130
7.1966
6.9287
6.9123
6.1088
6.0893
5.7013
5.6817
5.1693
5.1449
5.0198
4.9954
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1.4283
Br
O
O
t-BuO
O
NHCbz
3g
Integral
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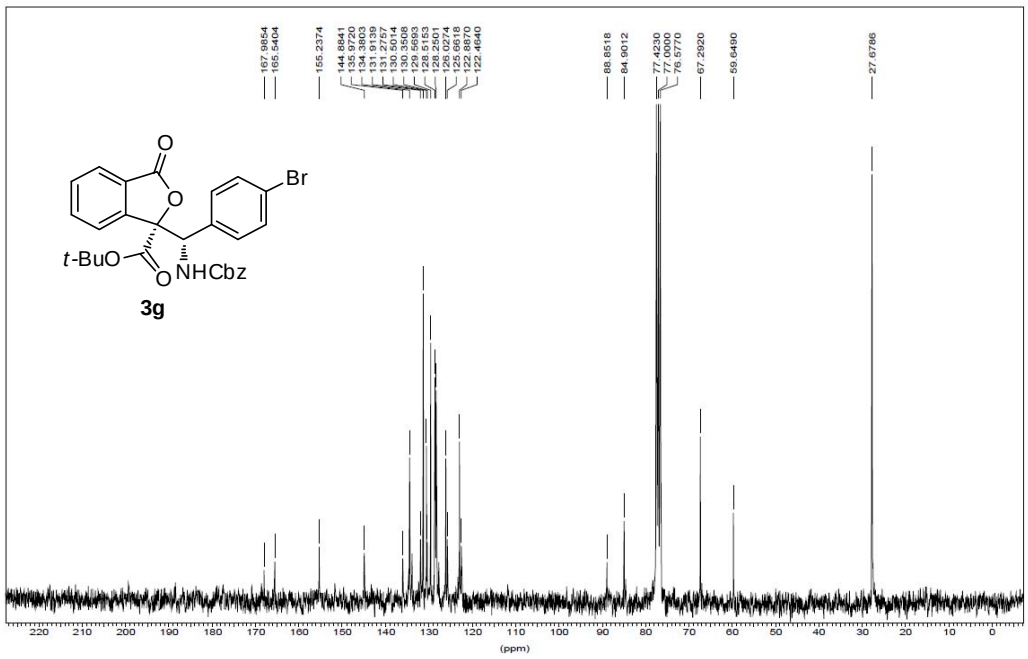
1.0864
9.6586
(ppm)

lj-4-Br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88.8518
84.9012
77.4230
77.0000
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27.6786
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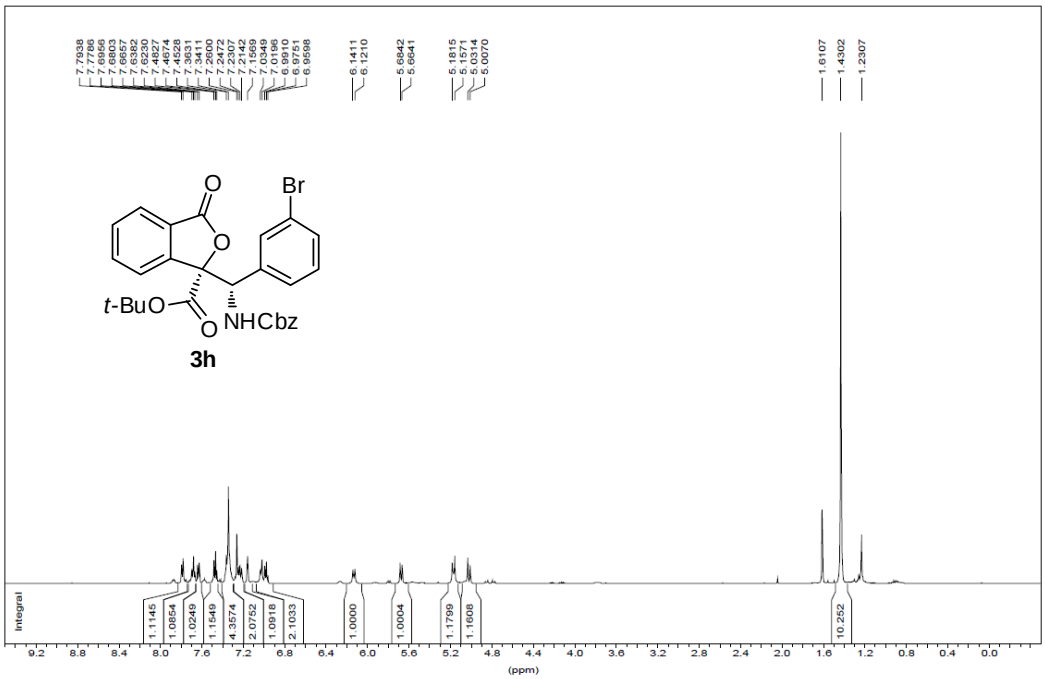
O
O
t-BuO
O
NHCbz
3g
(ppm)

lj-3061 ag



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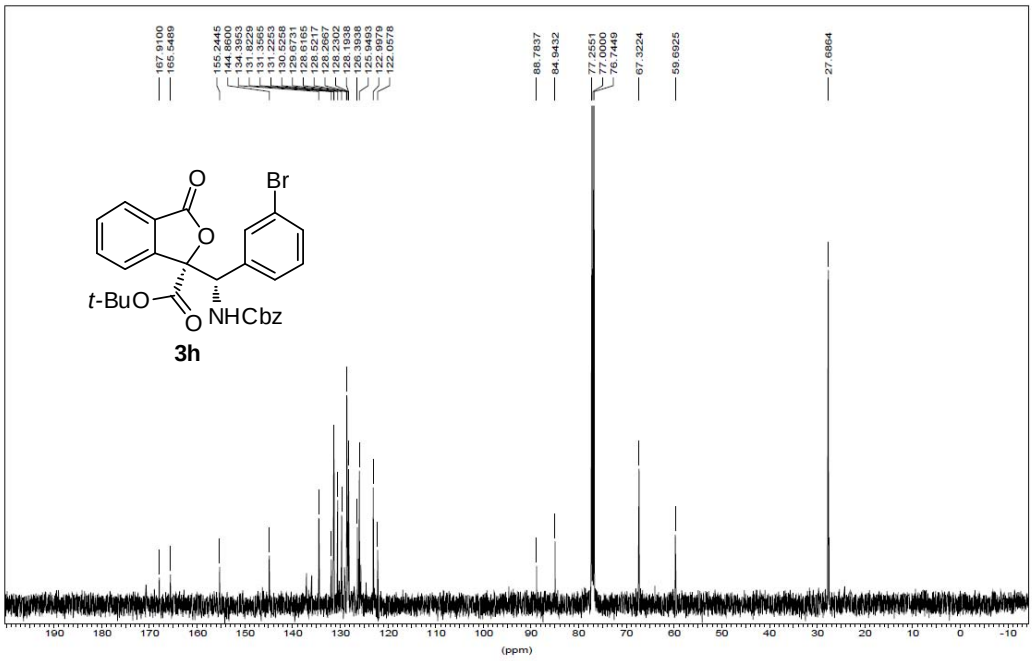

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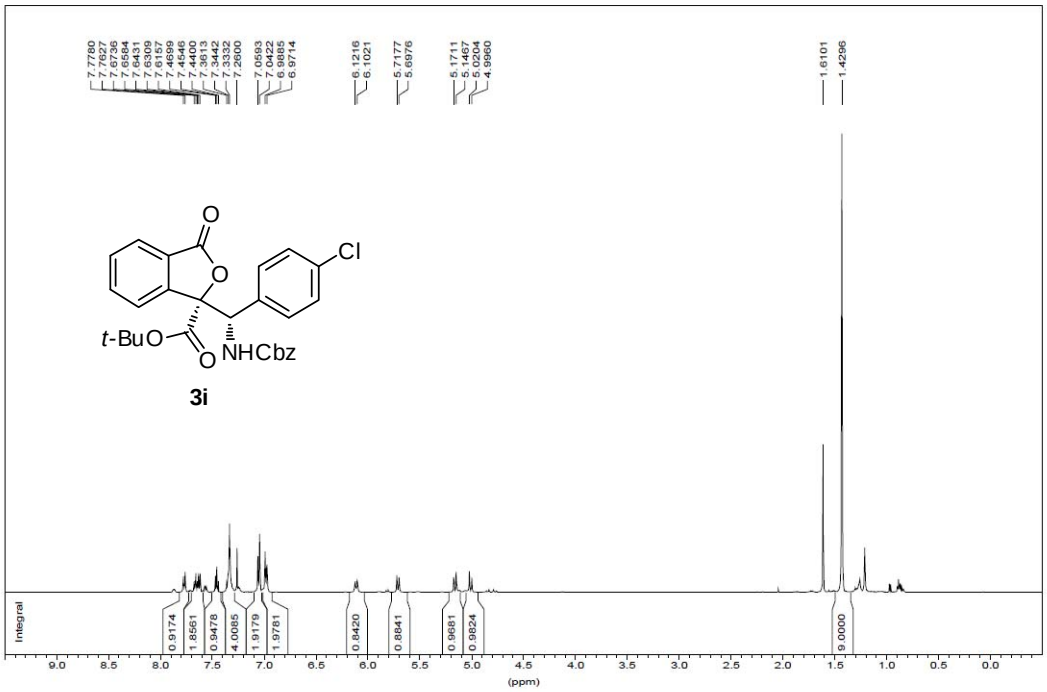
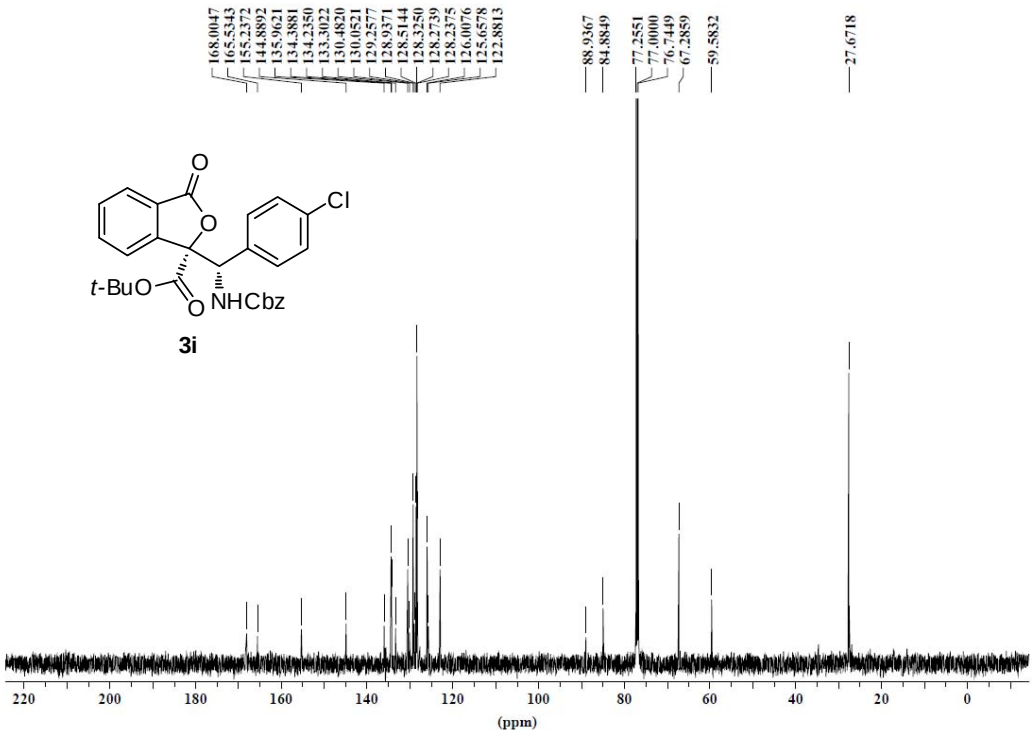


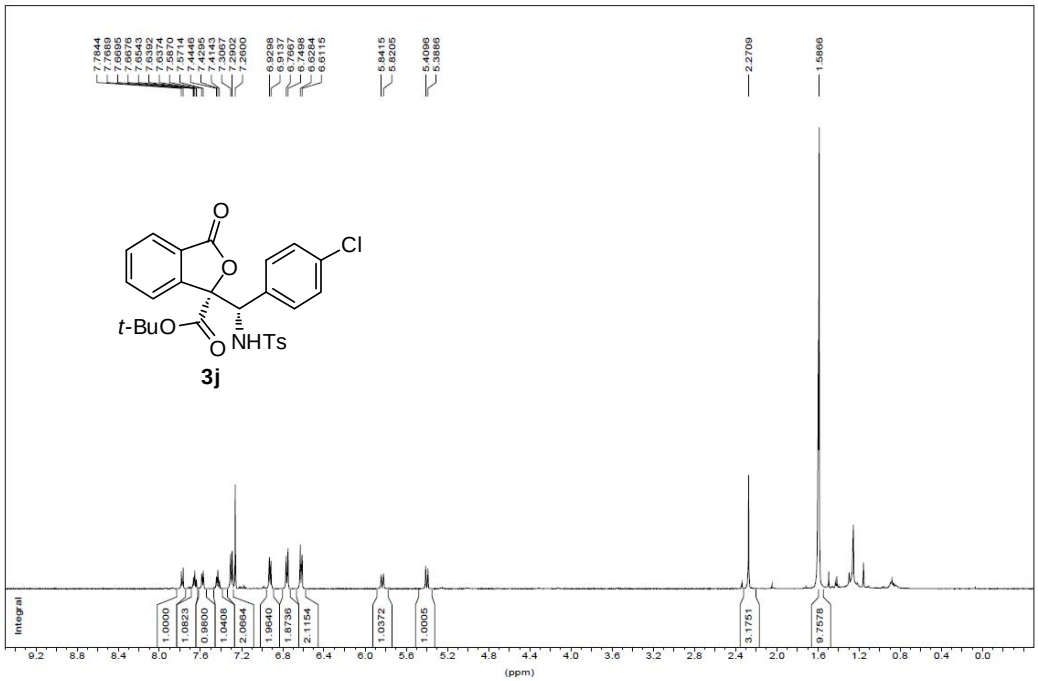
3i

13C AMX500 lj-3076-2

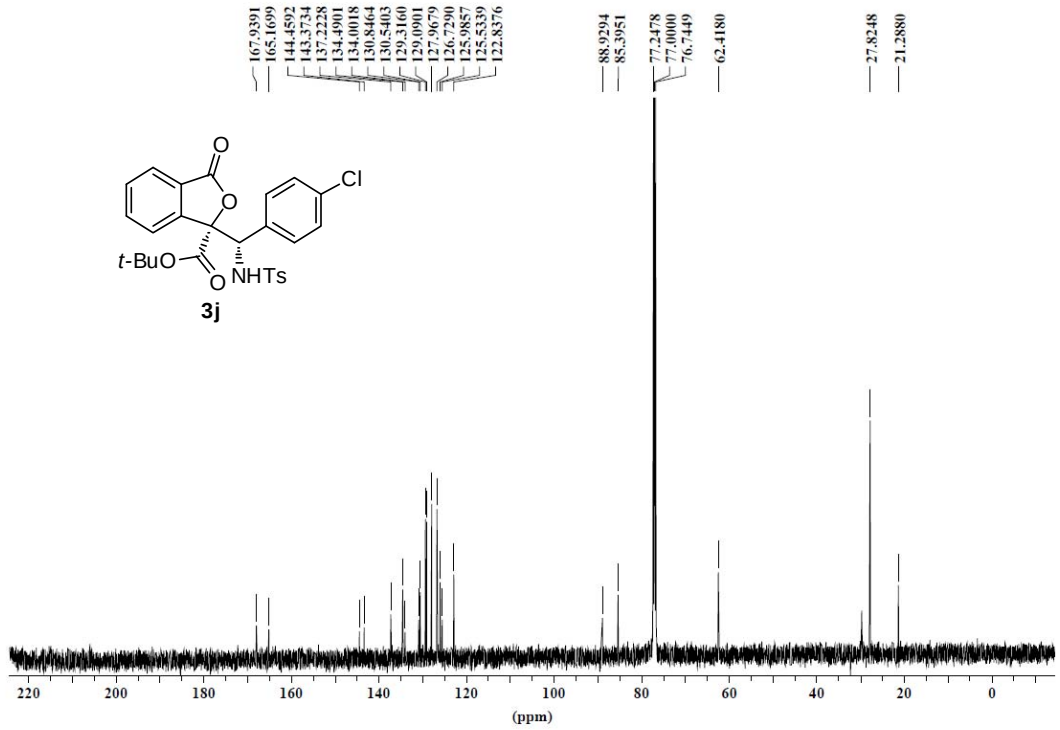


3i

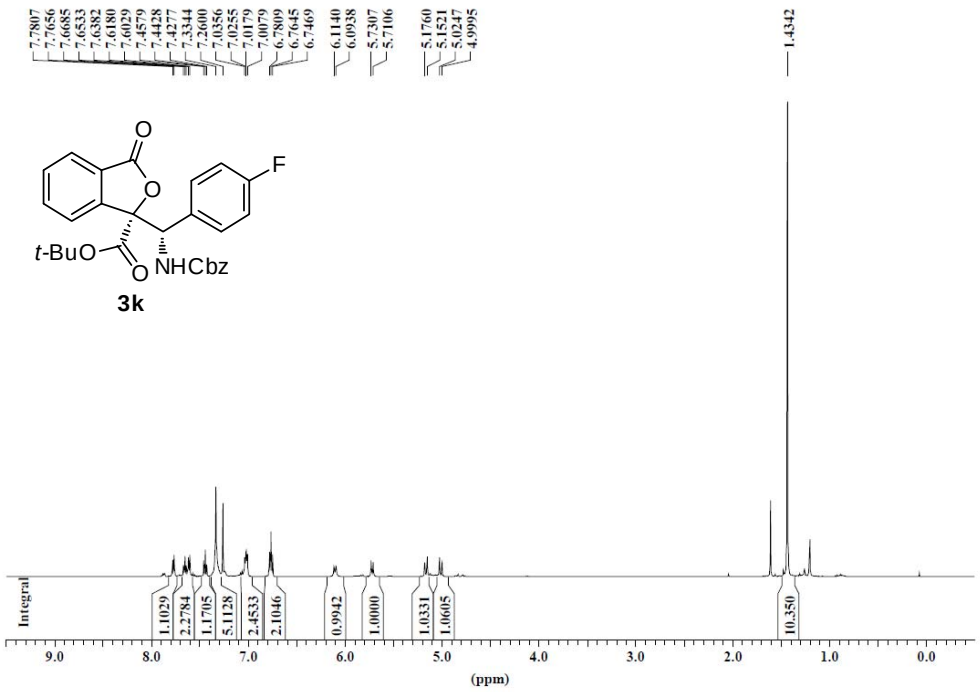
lj-Ts



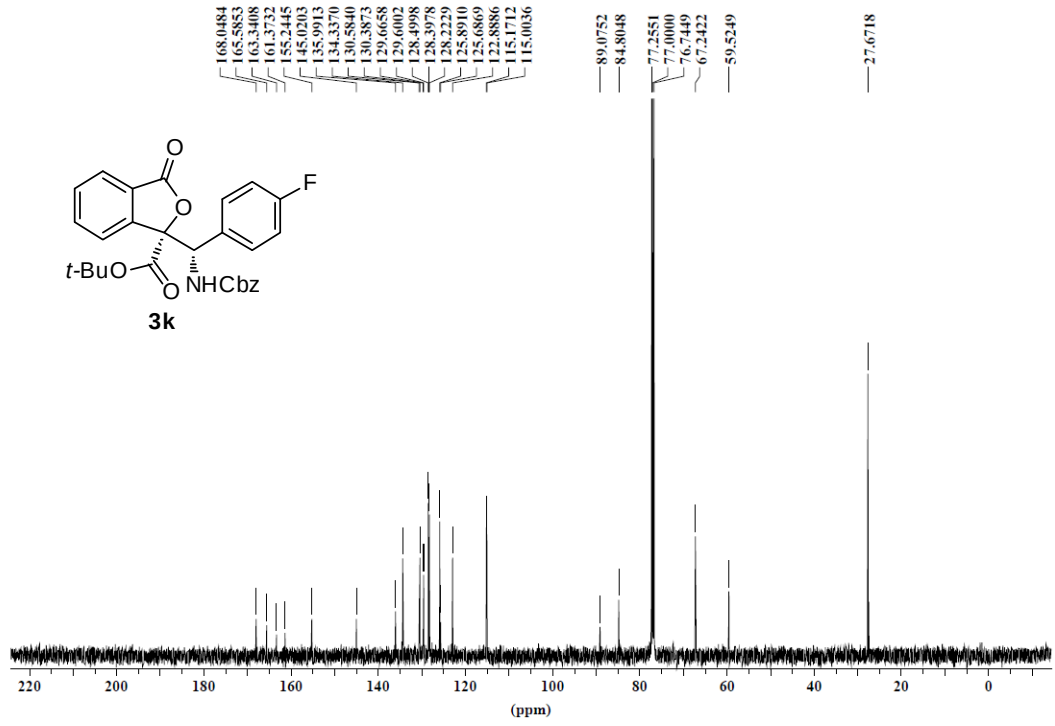
13C AMX500 lj-Cl-Ts



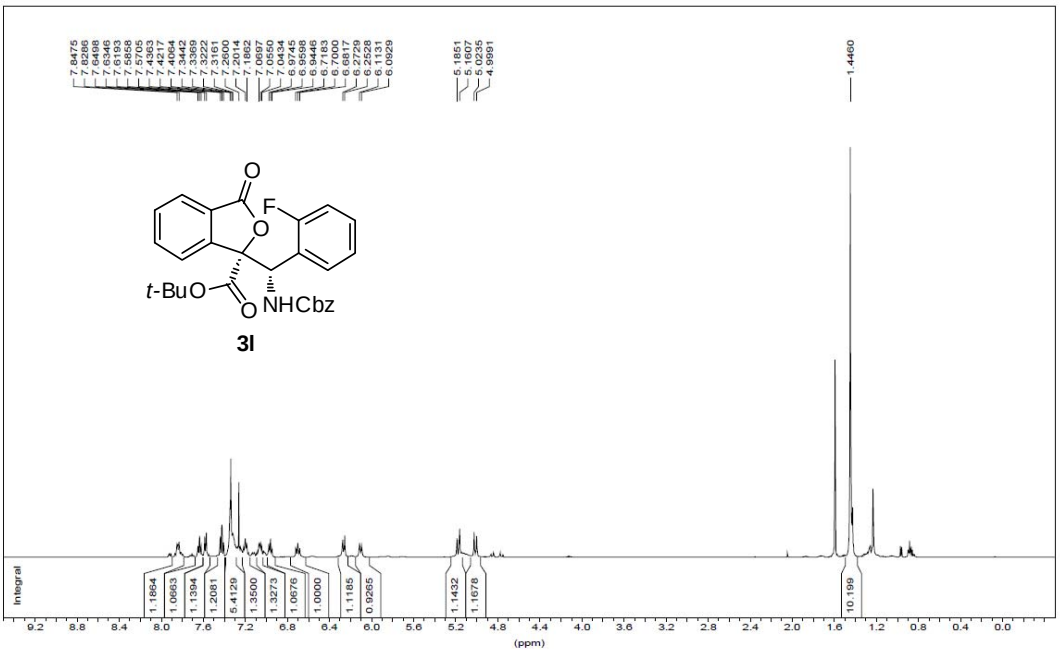
1H AMX500 4-F



13C AMX500 4-F



lj-3084-1



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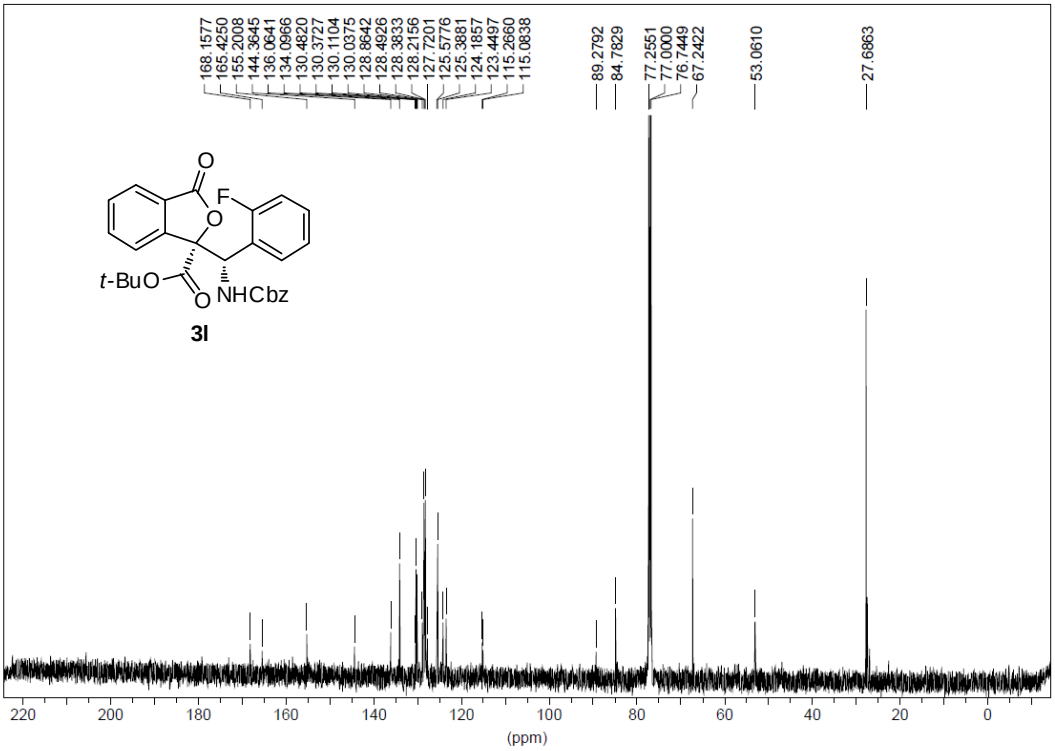
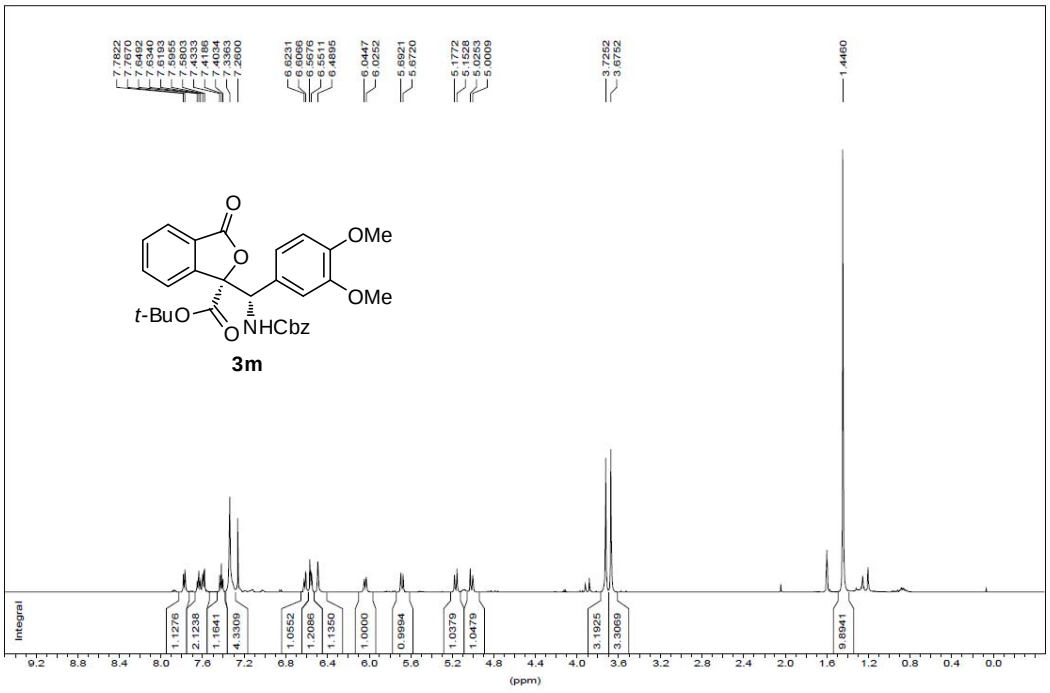
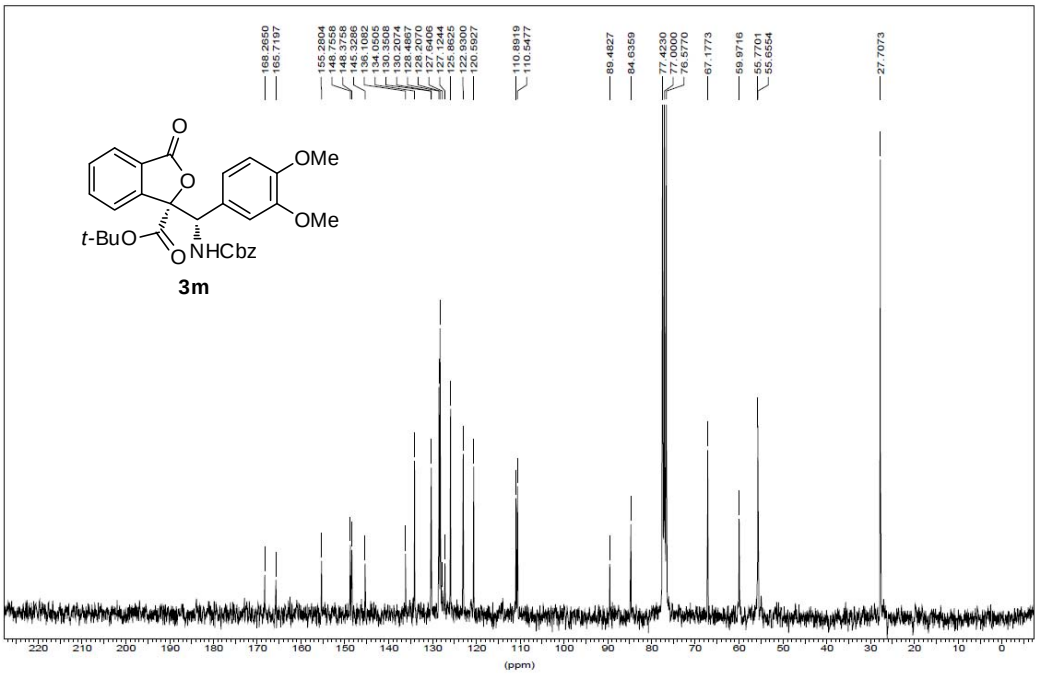
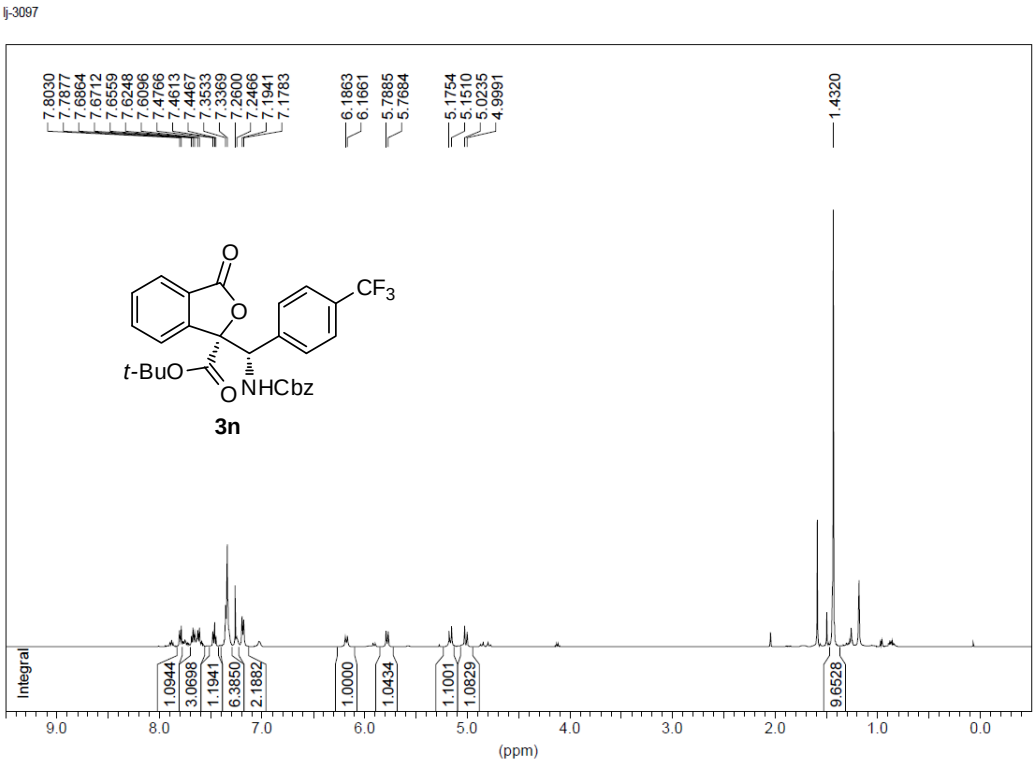


lj-3,4-OMe



lj-3,4-OMe

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7.7877
7.6864
7.6712
7.6559
7.6248
7.6096
7.4766
7.4613
7.4467
7.3533
7.3369
7.2600
7.2466
7.1941
7.1783
6.1863
6.1661
5.7885
5.7684
5.1754
5.1510
5.0235
4.9991
1.4320
O
O
CF3
t-BuO
O
NHCbz
3n
Integral
1.0944
3.0698
1.1941
6.3850
2.1882
1.0000
1.0434
1.1001
1.0829
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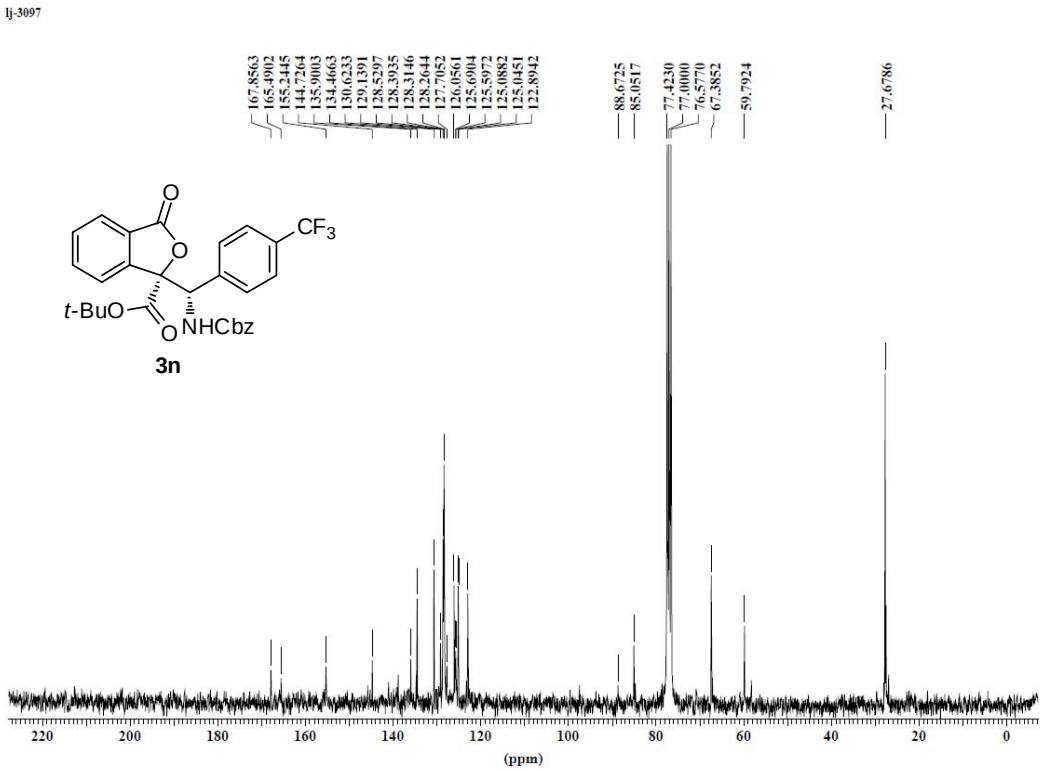
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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155.2445
144.7264
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129.1391
128.5397
128.3935
128.3146
128.2644
127.7052
126.0561
125.6904
125.5972
125.0882
125.0451
122.8942
88.6725
85.0517
77.4230
77.0000
76.5770
67.3852
59.7924
27.6786
O
O
CF3
t-BuO
O
NHCbz
3n
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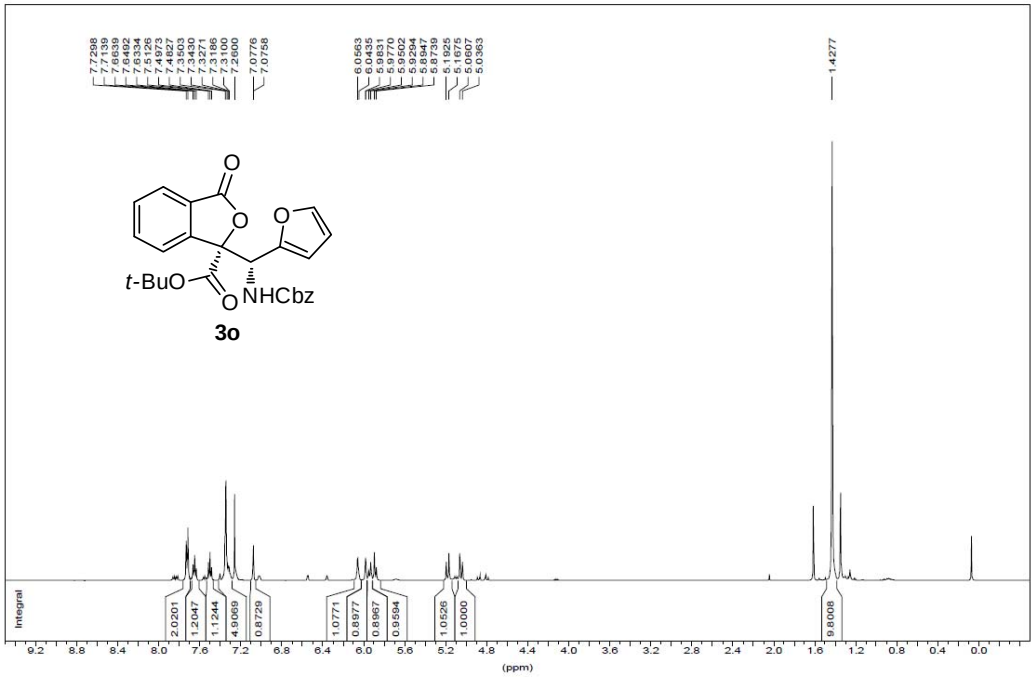
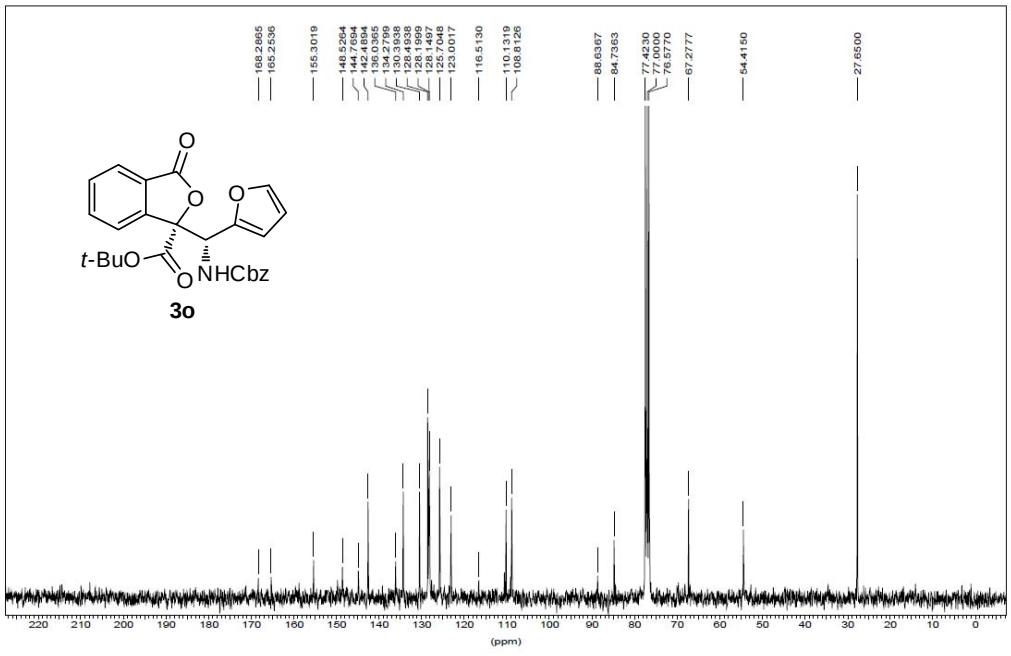
200
180
160
140
120
100
80
60
40
20
0
(ppm)

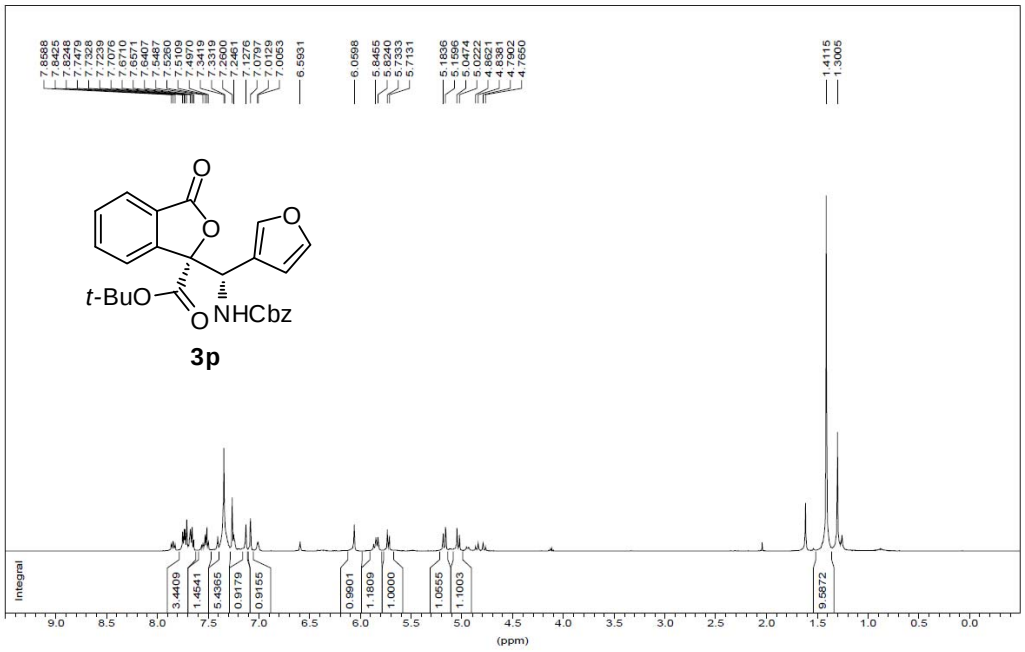
lj-2-furanyl



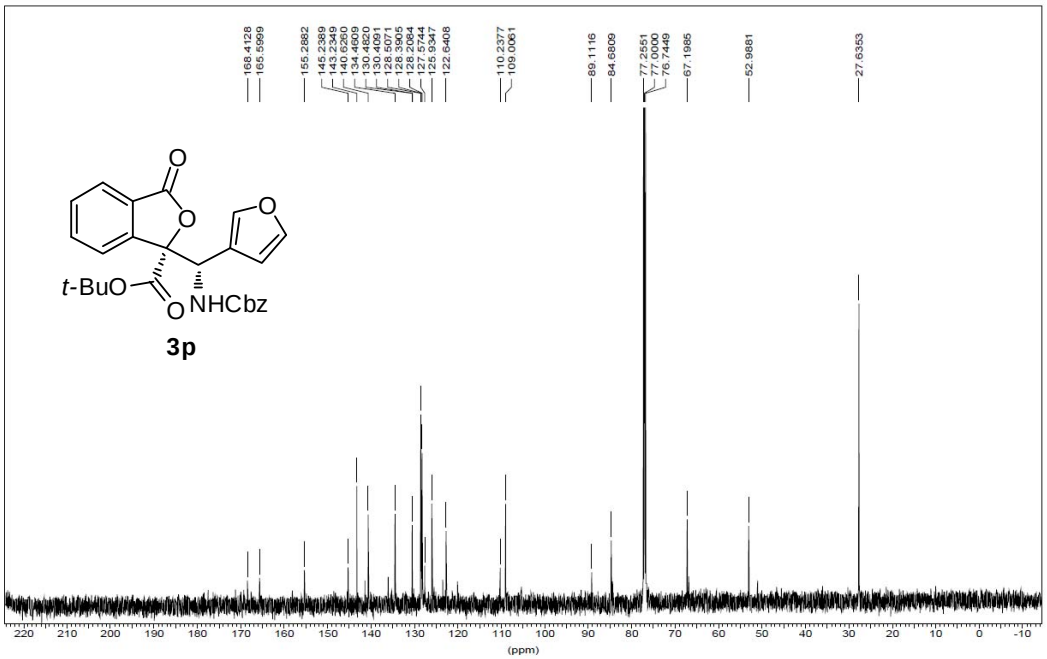
lj-2-furan 13C



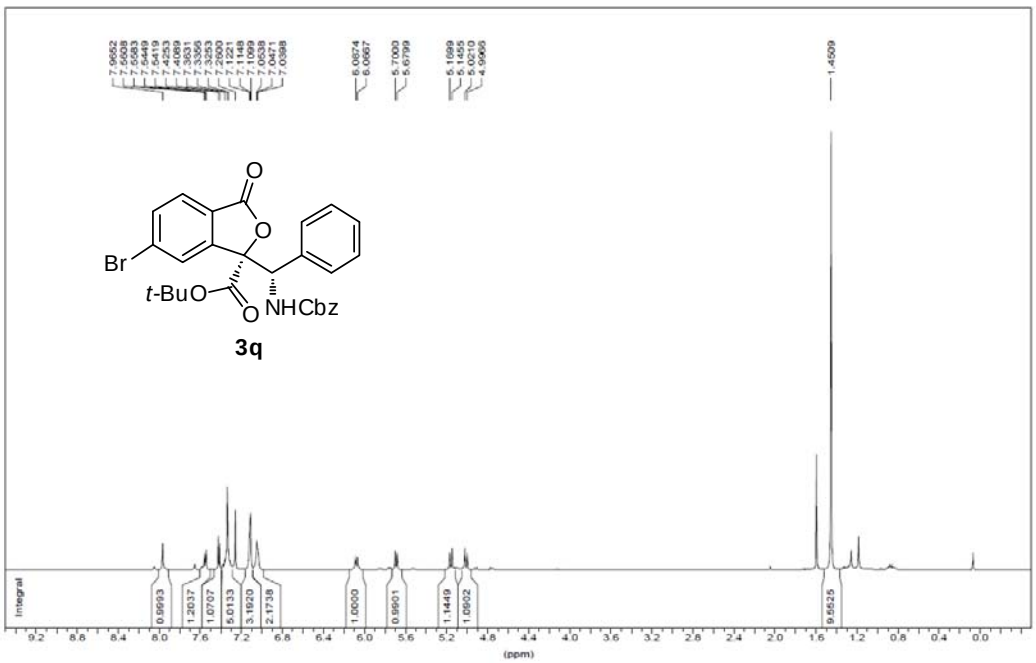
1H AMX500 3-furan



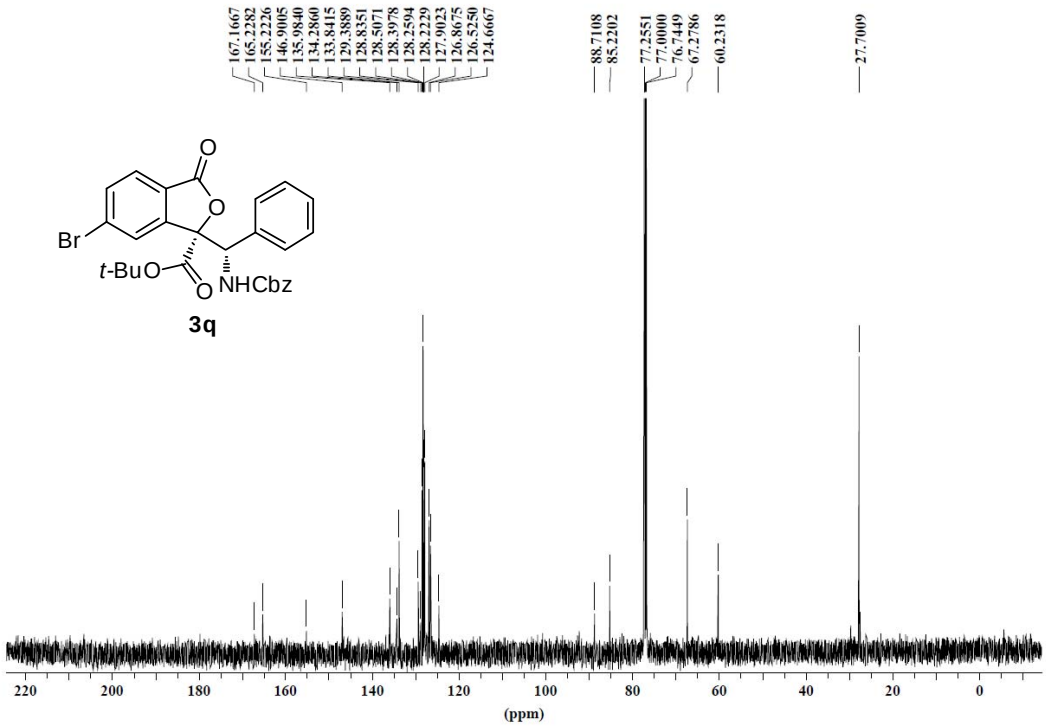
13C AMX500 lj-3-furan



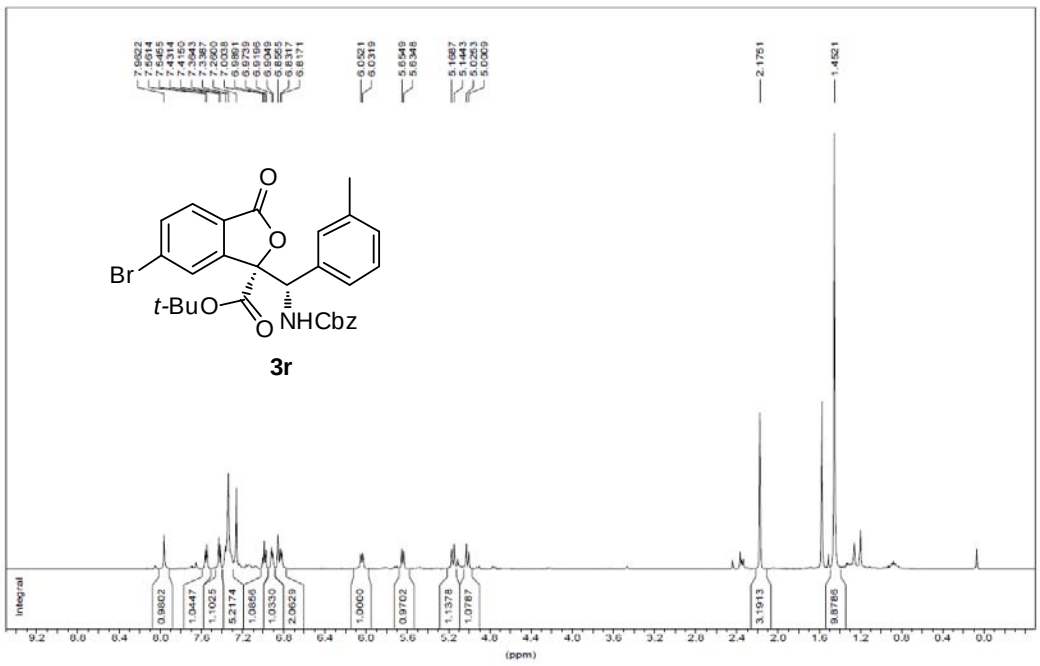
lj-3090-1



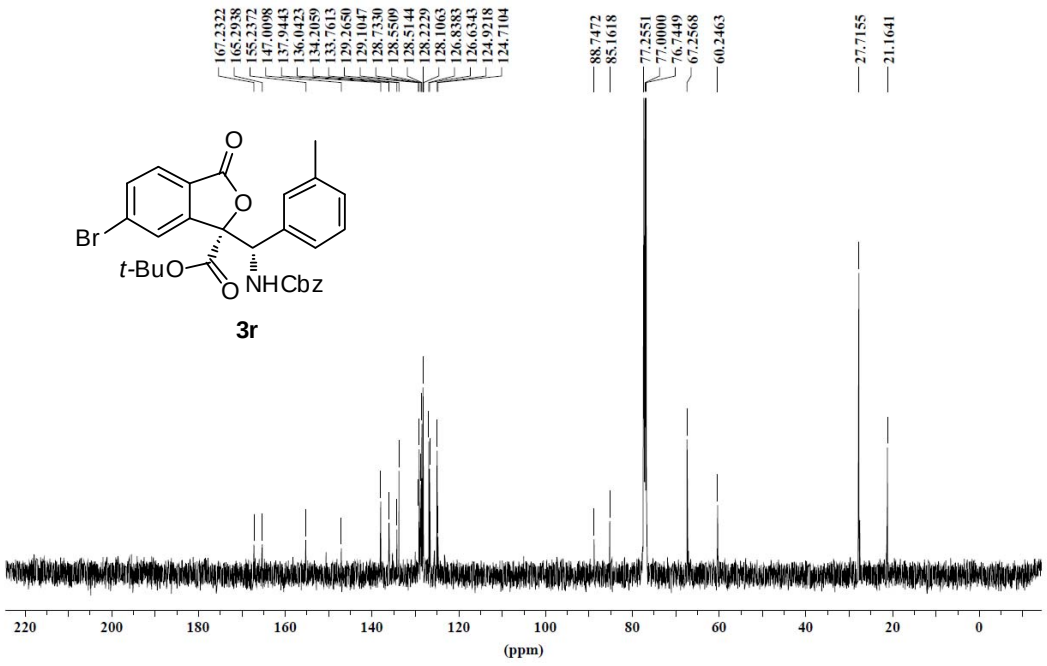
13C AMX500 lj-3090-1

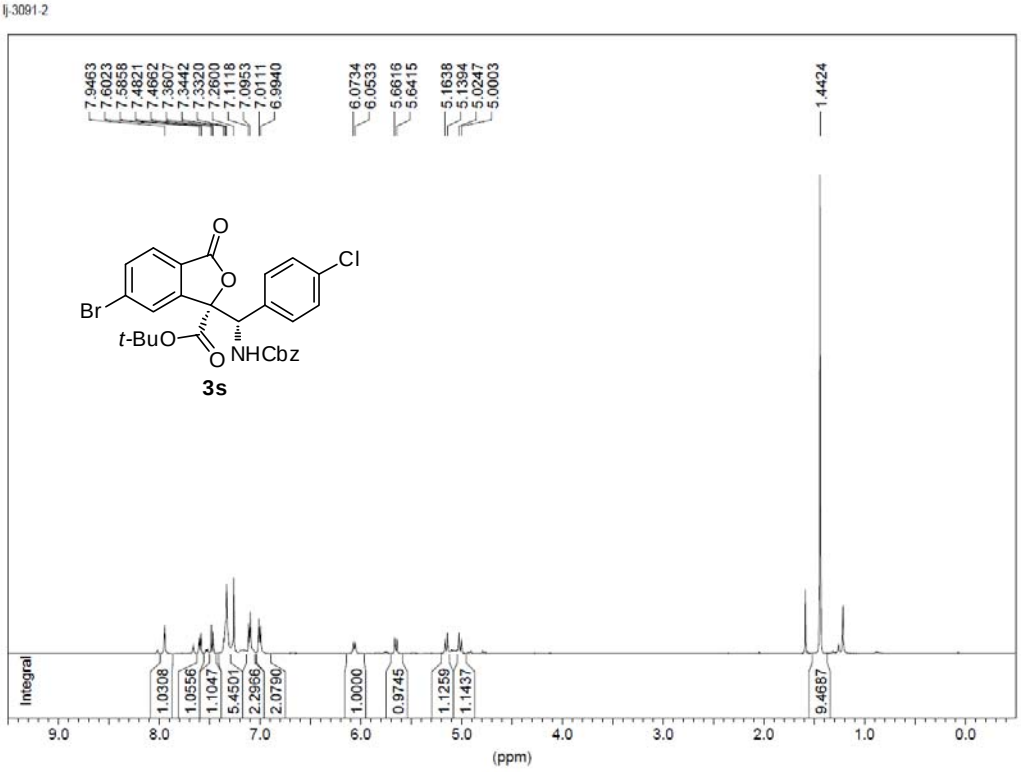


lj-3091-1



13C AMX500 lj-3091-1

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7.3607
7.3442
7.3320
7.2600
7.1118
7.0953
7.0111
6.9940
6.0734
6.0533
5.6616
5.6415
5.1638
5.1394
5.0247
5.0003
1.4424
Br
O
O
Cl
t-BuO
O
NHCbz
3s
Integral
1.0308
1.0556
1.1047
5.4501
2.2966
2.0790
1.0000
0.9745
1.1259
1.1437
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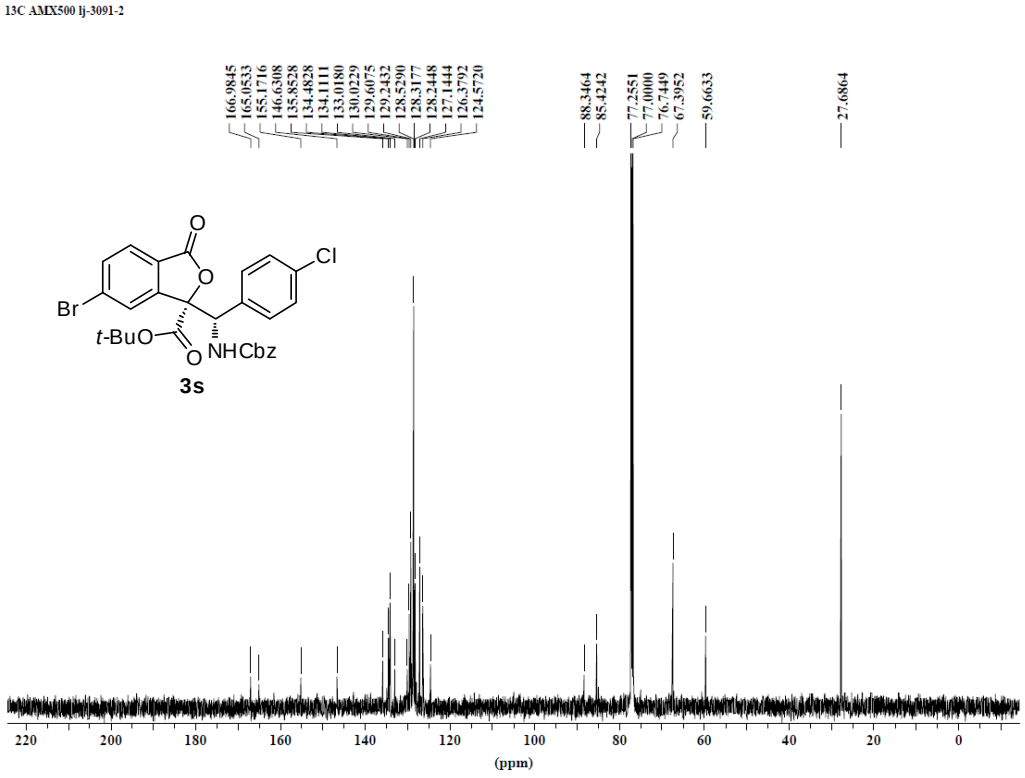
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)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146.6308
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134.1111
133.0180
130.0229
129.6075
129.2432
128.5290
128.3177
128.2448
127.1444
126.3792
124.5720
88.3464
85.4242
77.2551
77.0000
76.7449
67.3952
59.6633
27.6864
Br
O
O
Cl
t-BuO
O
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3s
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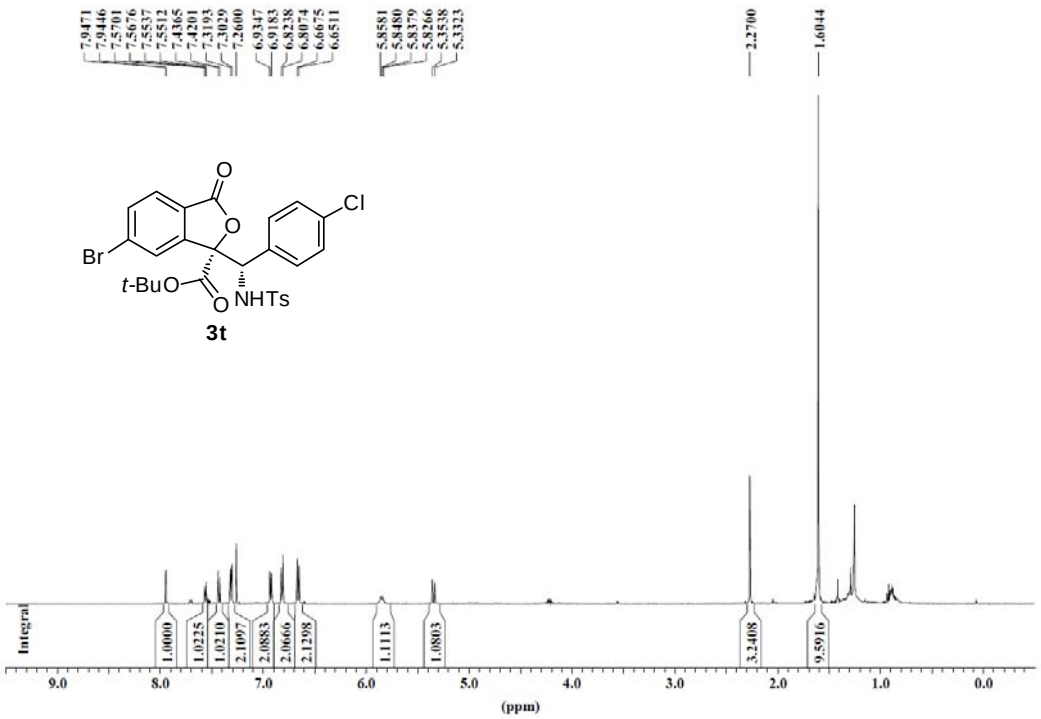
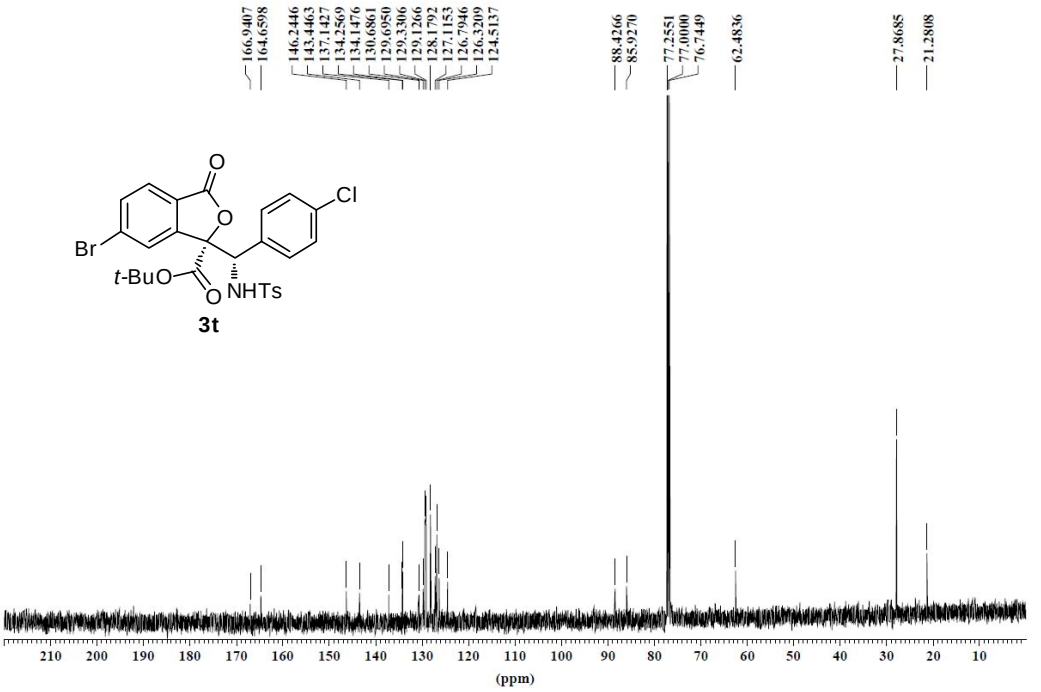
160
140
120
100
80
60
40
20
0
(ppm)

1H AMX500 lj-3129



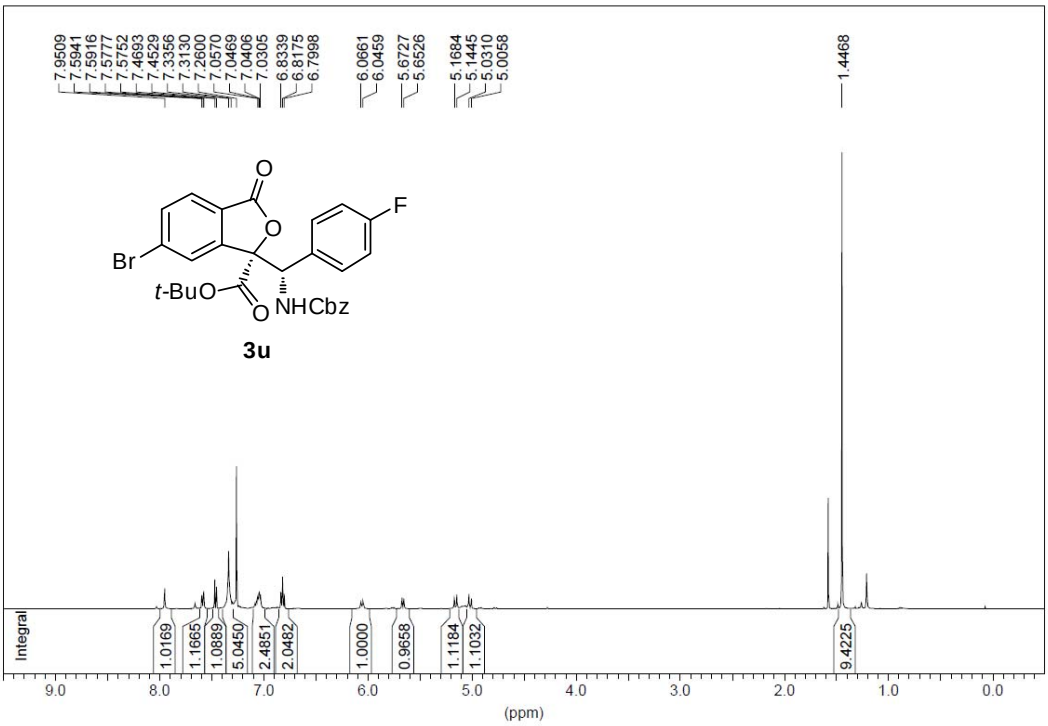
3t

13C AMX500 lj-3129



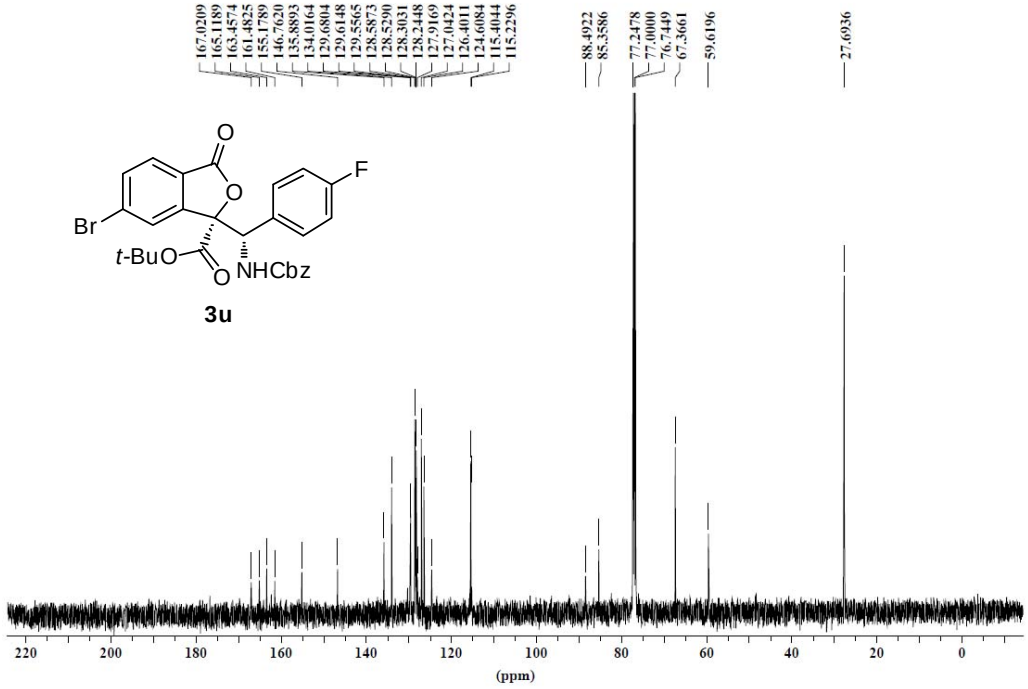
3t

1H AMX500 lj-3092



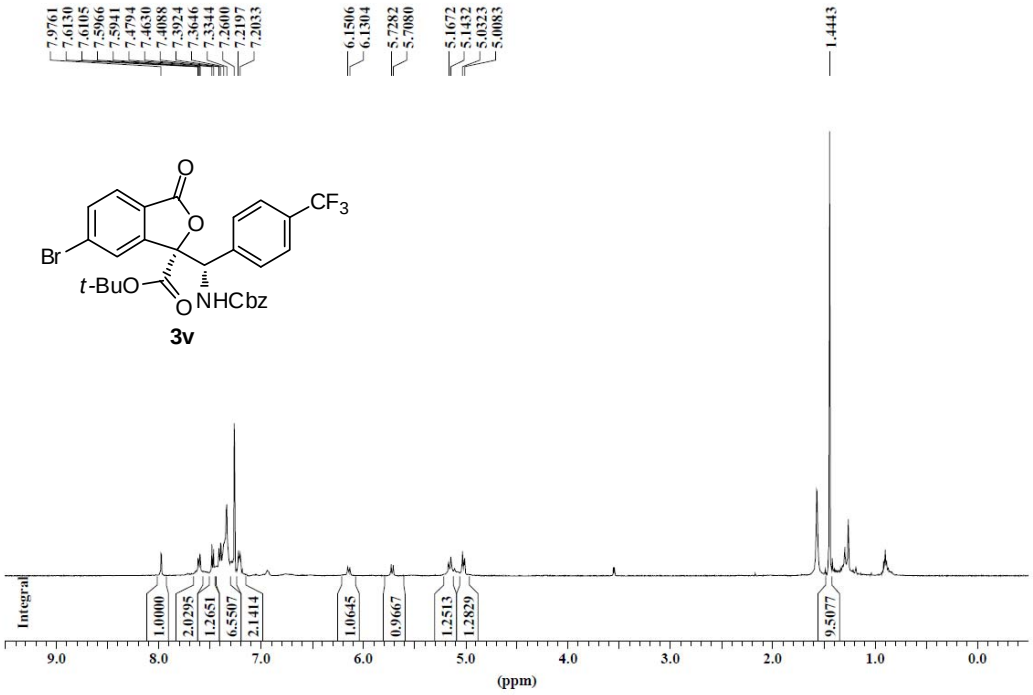
3u

13C AMX500 lj-3092



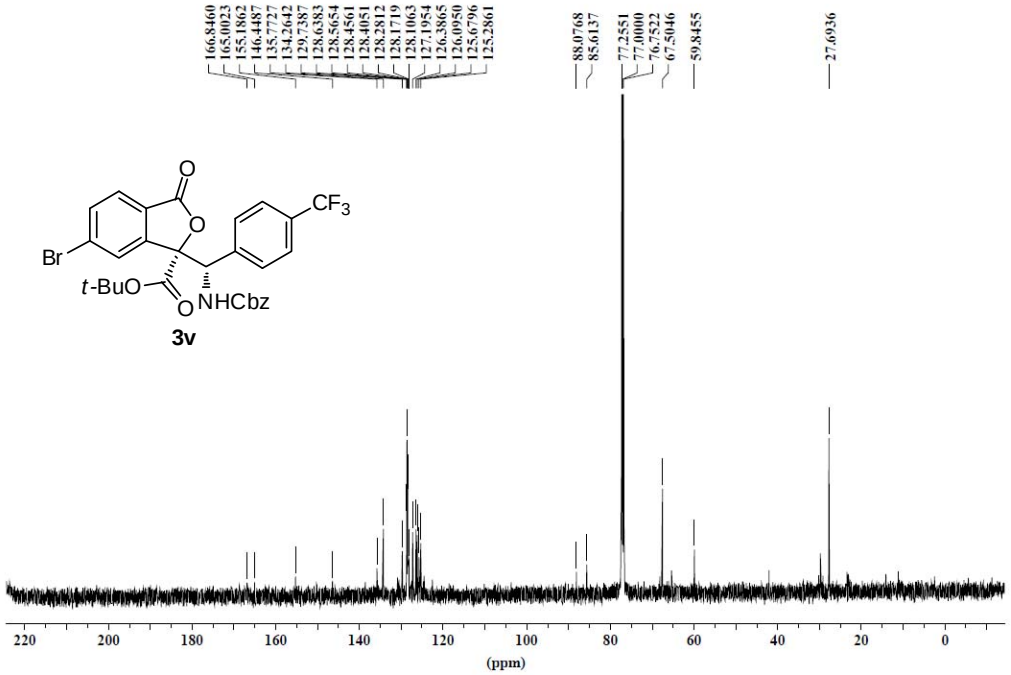
3u

1H AMX500 lj-3099



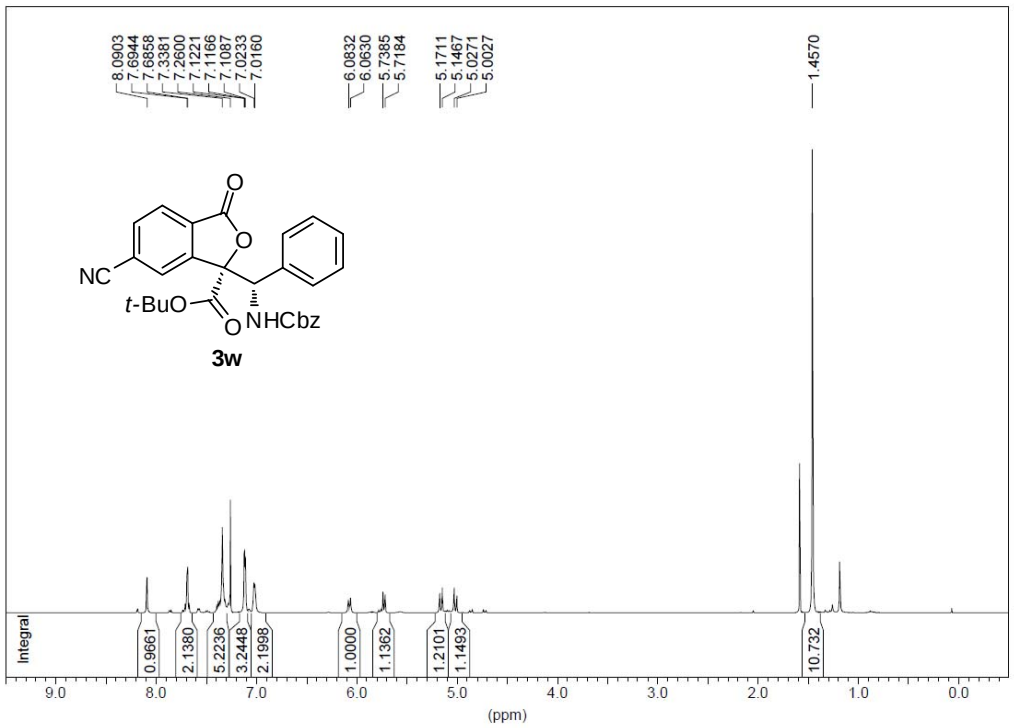
3v

13C AMX500 lj-3099

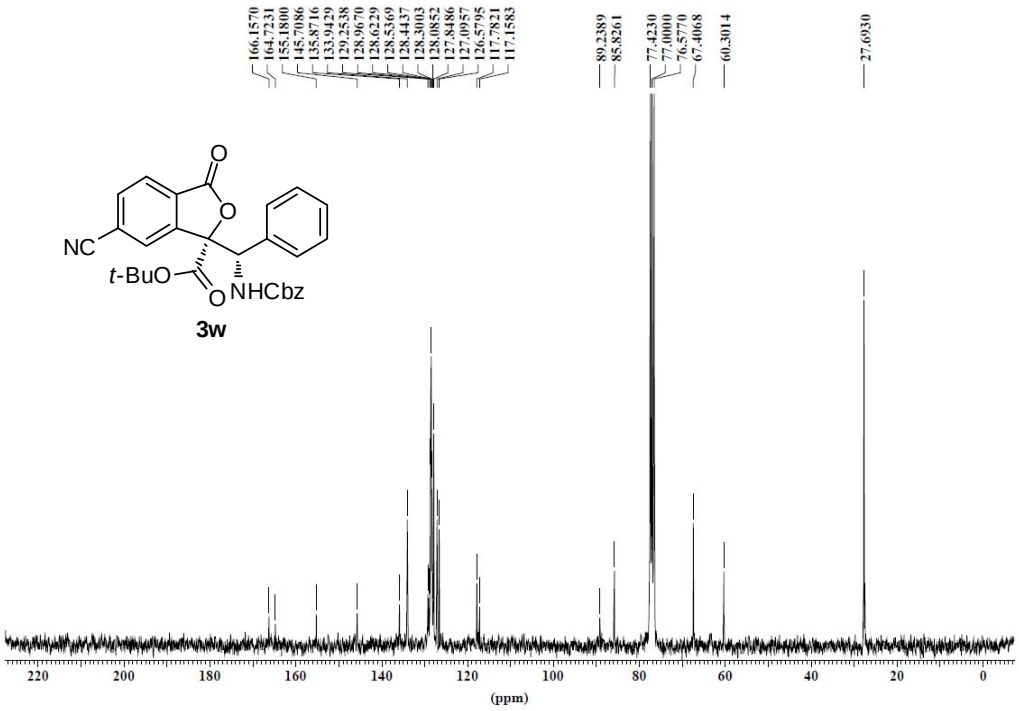


3v

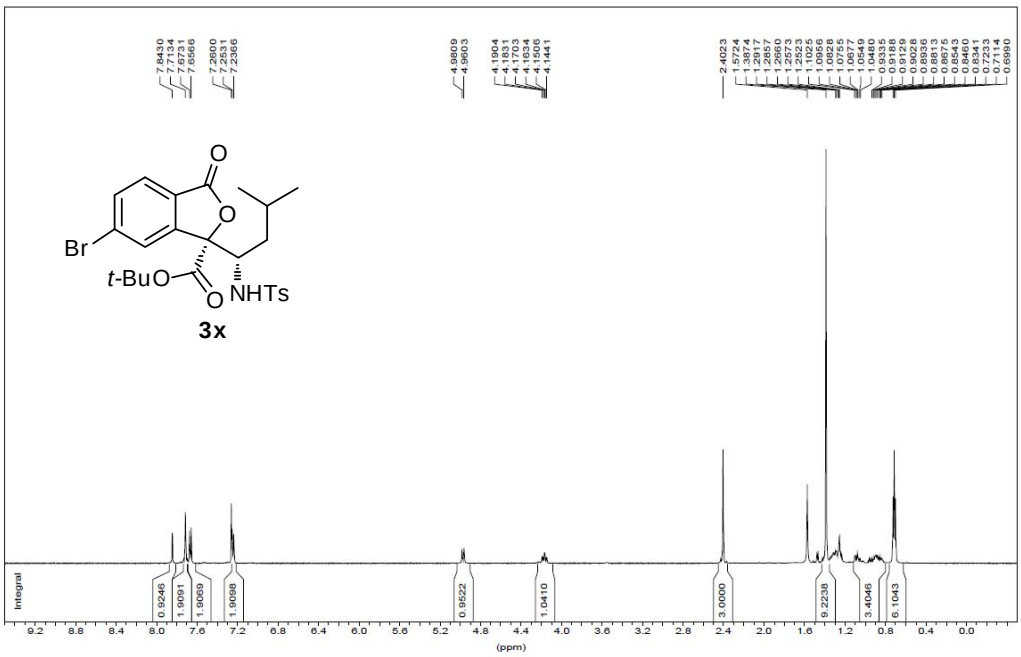
lj-3090-2



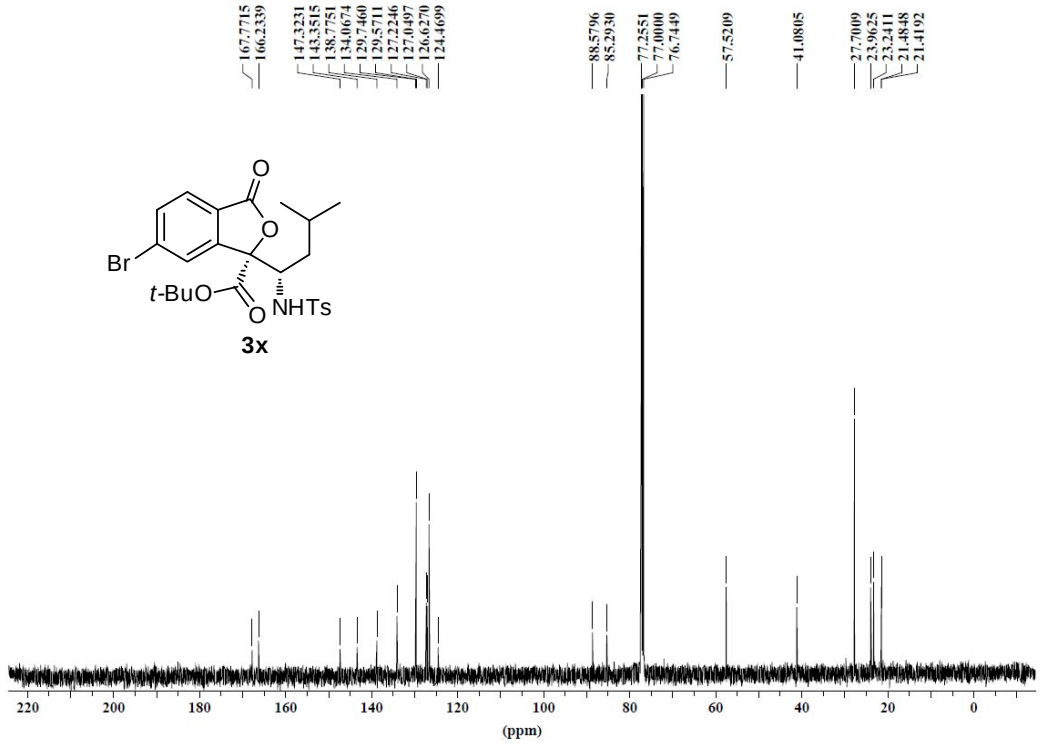
lj-3090-2



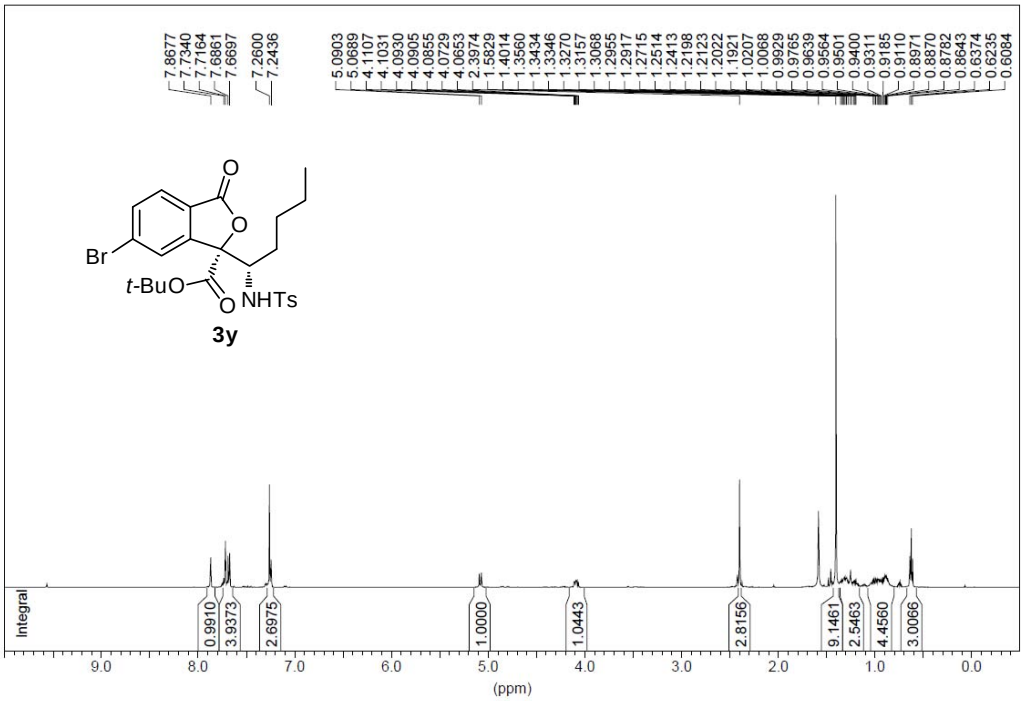
lj-3128



13C AMX500 lj-3128



1H AMX500 lj-3126-2-P1



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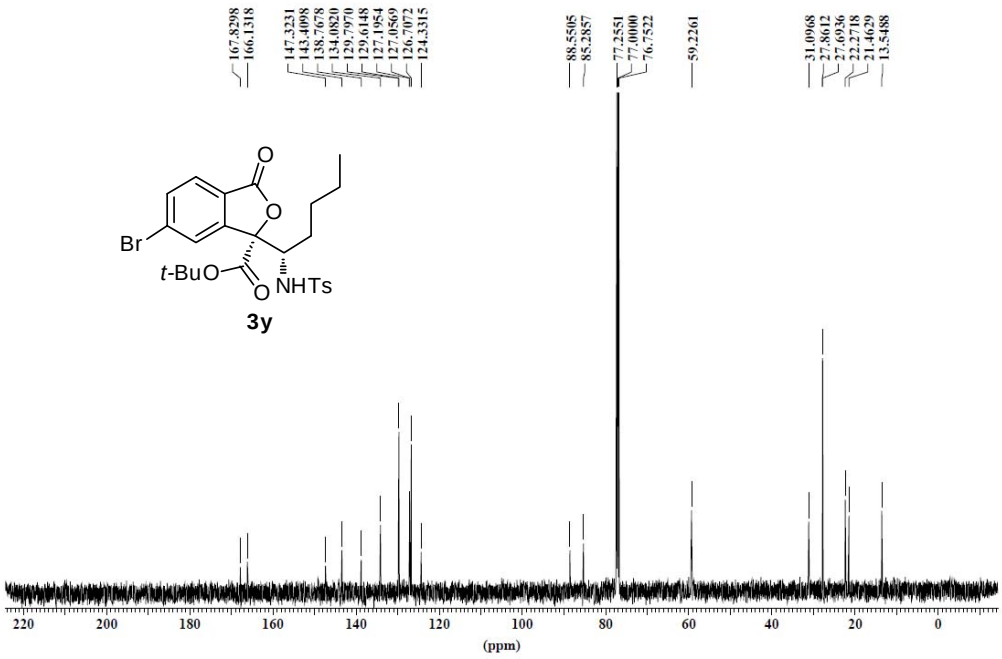
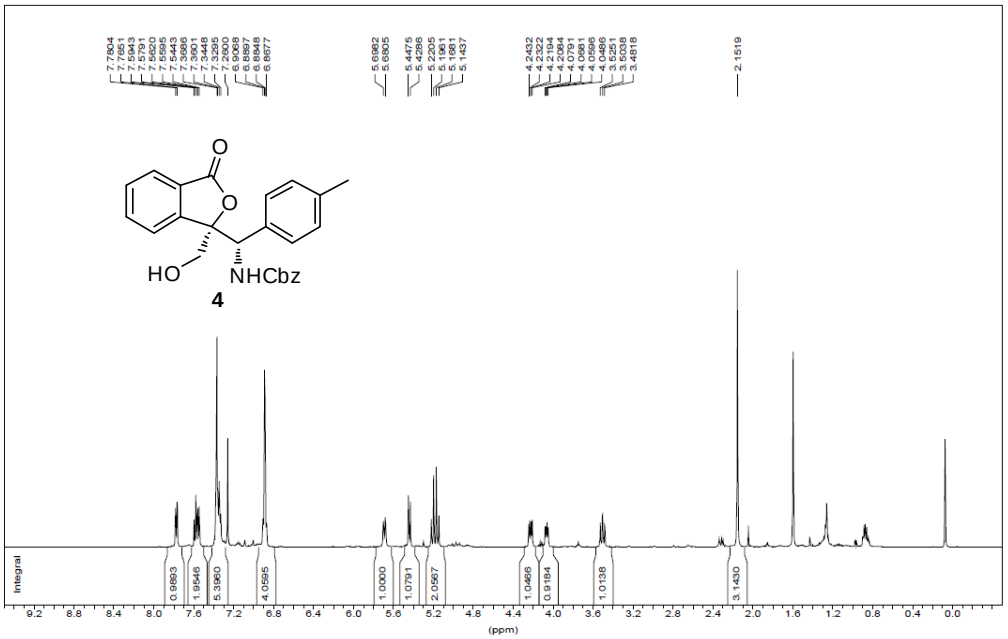
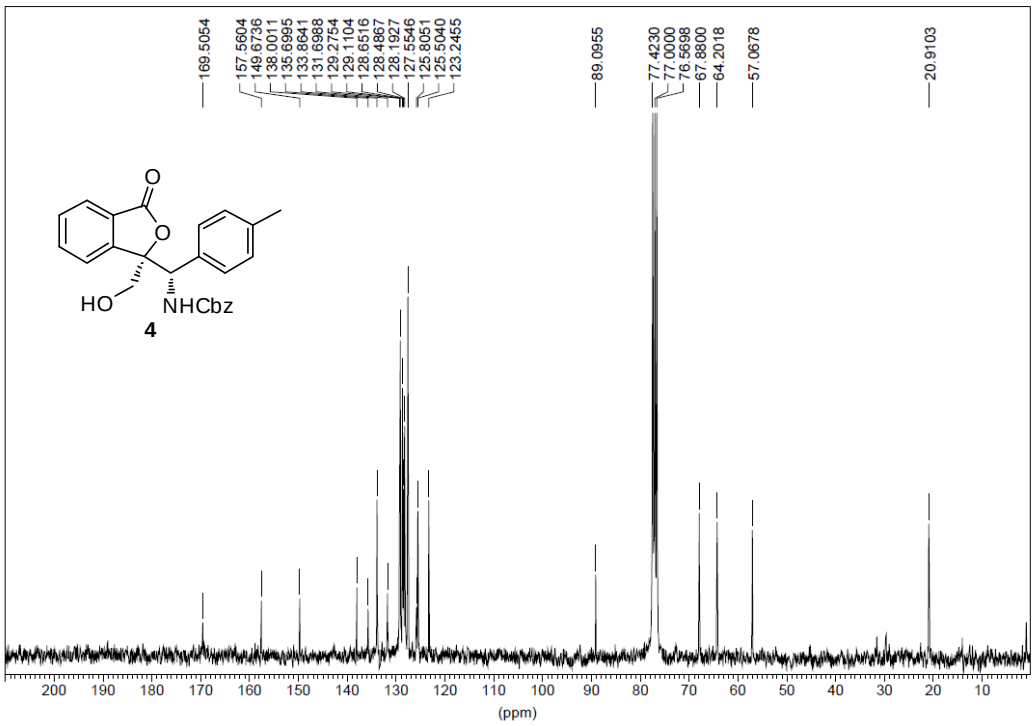


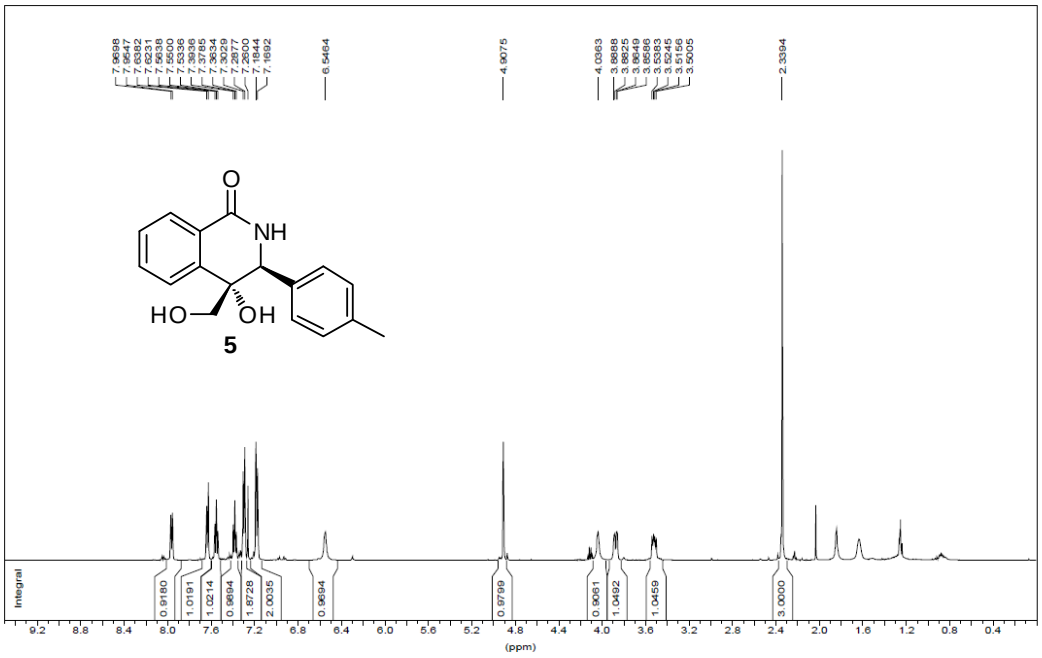
lj-reduction to OH



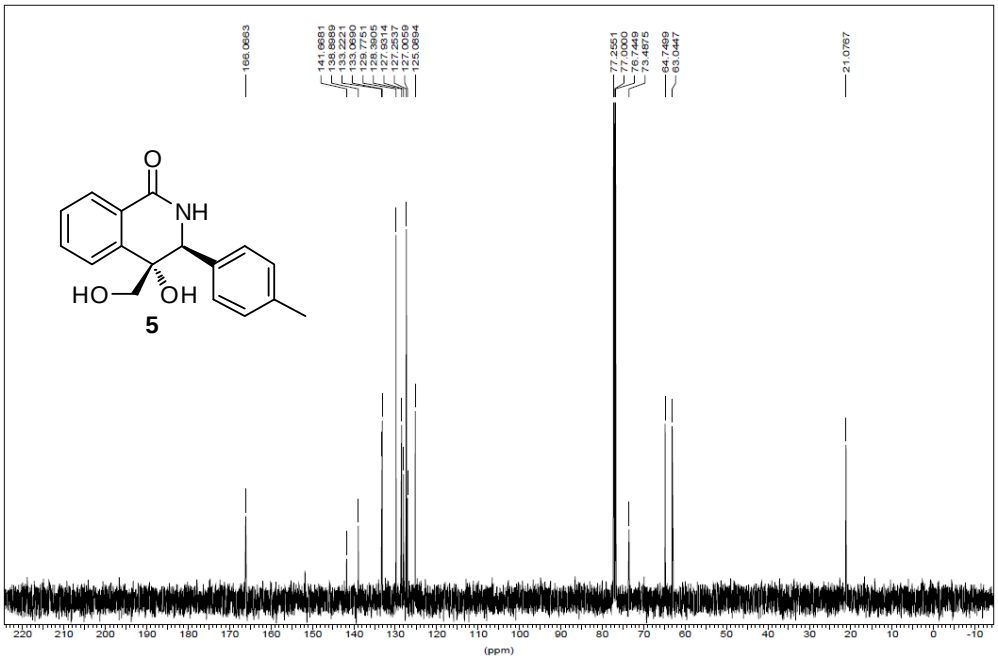
lj-OH



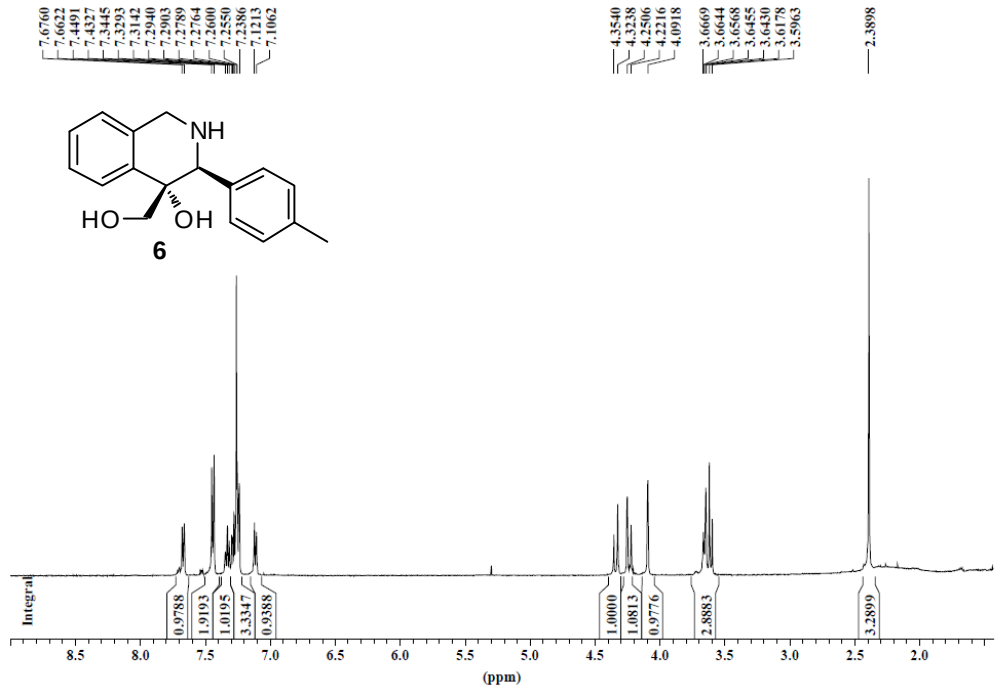
1H AMX500 lj-3021 p



13C AMX500 lj-3021 p



1H AMX500



13C AMX500 lj-3123