Electronic Supplementary Information

A visible-light-promoted aerobic C-H/C-N cleavage cascade to isoxazolidine skeletons

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Part I. General Information

Unless otherwise stated, reactions were performed under air. Solvents and reagents were used as received from suppliers unless otherwise stated. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR data were obtained on Bruker Advance III 400 MHz nuclear resonance spectrometers with $CDCl_3$ as solvents at ambient temperature. Chemical shifts were reported in units (ppm) by assigning chloroform residue in the ^{1}H NMR spectrum as 7.26 ppm. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet and m = multiplet), coupling constant (J values) in Hz and integration. Chemical shifts for ^{13}C NMR spectra were recorded in ppm from chloroform using the central peak of $CDCl_3$ (77.0 ppm) as the internal standard. Flash column chromatography was performed using 200-300 mesh silica or 200 -300 mesh neutral Al_2O_3 with the indicated solvent system according to standard techniques. Reactions were monitored by TLC on silica gel plates (GF254), and the analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm). Low resolution mass spectra were obtained using ThermoFisher Scientific LCQ FLEET mass spectrometer or Daojin (Japan) LC-MS 2020 spectrometer. High resolution mass spectra were obtained using an Agilent 6210 Series TOF LC-MS equipped with electrospray ionization (ESI) probe operating in positive ion mode. Melting points (mp) were determined with a digital electrothermal apparatus without further correction. The value of diastereoisomeric ratio was determined by ^{1}H NMR spectroscopy performed on Bruker Advance III 400 MHz nuclear resonance spectrometer.

The 1,2,3,4-tetrahydroisoquinoline and 7-methoxy-1,2,3,4-tetrahydroisoquinoline derivatives,[1] 6,7-dimethoxy-1,2,3,4-tedrahydroisoquinoline[2] were prepared according to literature procedures. The α-ketoesters were obtained according to the literature procedures.[3,4]

Part II. Optimization of Biomimetic Tandem Reaction Conditions

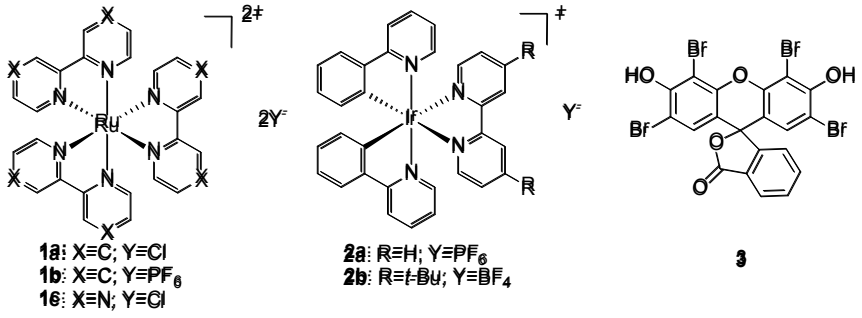
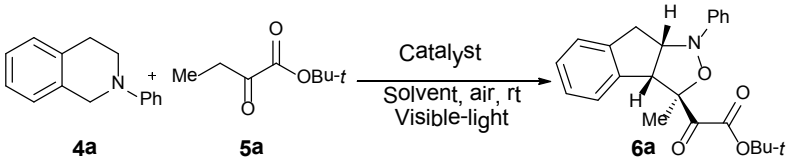


Table 1. Optimization of the biomimetic tandem reaction conditions.[a]

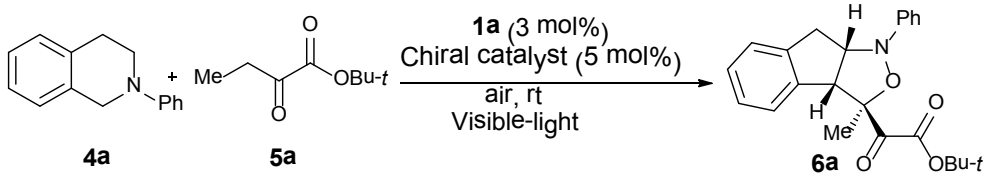


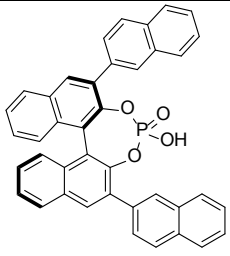
Entry	Catalyst (mol%)	Additive	Solvent	T/h	d.r.[b]	Yield (%)[c]
1	**1a** (3%)	-	MeOH	170	> 20:1	51
2	**1b** (3%)	-	MeOH	170	N.D.	trace
3	**1c** (3%)	-	MeOH	170	> 20:1	28
4	**2a** (3%)	-	MeOH	170	N.D.	trace
5	**2b** (3%)	-	MeOH	70	> 20:1	39
6	**2b** (1%)	-	MeOH	70	> 20:1	46
7	**3** (5%)	-	MeOH	170	-	N.P.
8	**1a** (3%)	4 Å MS (50 mg)	MeOH	120	N.D.	trace
9	**1a** (3%)	5 Å MS (50 mg)	MeOH	120	N.D.	trace
10	**1a** (3%)	DABCO (1.5 equiv)	MeOH	70	N.D.	trace
11	**1a** (3%)	DBU (1.5 euiqv)	MeOH	170	-	N.D.
12	**1a** (3%)	HOAc (10 mol%)	MeOH	120	> 20:1	56
13	**1a** (3%)	MsOH (10 mol%)	MeOH	120	> 20:1	55

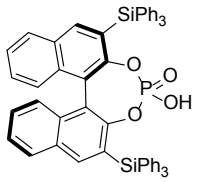
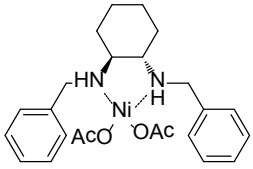
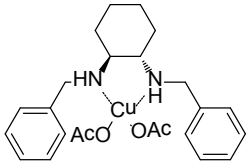
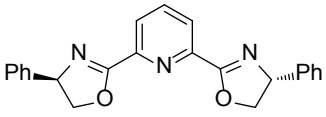
Entry	Catalyst (mol%)	Additive	Solvent	T/h	d.r.[b]	Yield (%)[c]
14	**1a** (3%)	TFA (10 mol%)	MeOH	120	> 20:1	47
15	**1a** (3%)	TfOH (10 mol%)	MeOH	70	> 20:1	60
16	**1a (3%)**	**TfOH (10 mol%)**	***i*-PrOH**	**70**	> 20:1	**63**
17	**1a** (3%)	TfOH (10 mol%)	EtOH	120	> 20:1	54
18	**1a** (3%)	TfOH (10 mol%)	MeCN	120	> 20:1	15
19	**1a** (3%)	TfOH (10 mol%)	DMF	70	N.D.	trace
20	**1a** (3%)	TfOH (10 mol%)	NMP	70	N.D.	trace
21	**1a** (3%)	TfOH (10 mol%)	DCM	70	-	N.P.
22	**1a** (3%)	TfOH (10 mol%)	1,4-dioxane	70	-	N.P.
23	**2b** (1%)	TfOH (10 mol%)	*i*-PrOH	70	> 20:1	48
24[d]	**1a** (3%)	TfOH (10 mol%)	*i*-PrOH	70	-	N.P.
25[e]	-	TfOH (10 mol%)	*i*-PrOH	70	N.D.	N.P.
26[f]	**1a** (3%)	TfOH (10 mol%)	*i*-PrOH	70	-	N.P.

[a]Reaction conditions: **4a** (0.1 mmol), **5a** (3.5 equiv), solvent (1.5 mL), catalyst **1-3** (1-5 mol%), additive, 5w blue LEDs (light-emitting diode strips, λ_{max} = 455 nm), ambient temperature, air. [b] Diastereoisomeric ratio as determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d]The reaction was performed under N_2 atmosphere. [e]The reaction was performed in the absence of any photocatalyst. [f] The reaction was performed in the dark.

Table 2 Exploration of the asymmetric version of the biomimetic tandem reaction conditions.[a]



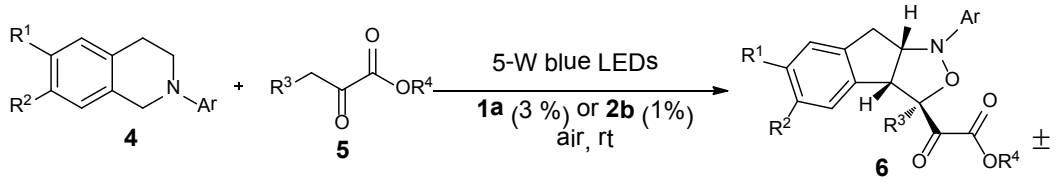
Entry	Chiral catalyst (5 mol%)	Solvent	Yield	ee[b]
1		*i*-PrOH	40	racemic

2		*i*-PrOH	45	racemic
3	*L*-Proline	*i*-PrOH	26	racemic
4		*i*-PrOH:MeCN=1:1	17	racemic
5		*i*-PrOH:MeCN=1:1	trace.	N.D.
6	 **(5%)** + **Au(OAc)$_3$ (5%)**	**MeCN**	**18**	**7**

[a]Reaction conditions: **4a** (0.1 mmol), **5a** (3.5 equiv), solvent (1.5 mL), **1a** (3 mol%), chiral catalyst (5 mol%), 5 W blue LEDs (light-emitting diode strips, λ_{max} = 455 nm), ambient temperature, air. [b] The enantiomeric excesses of **6a** were determined by chiral HPLC analysis under the conditions as follows: Chiralcel AD column, *i*-PrOH/hexane = 5/95, flow rate = 1.0 mL/min, λ = 210 nm.

Part III. General Experimental Details of Biomimetic Tandem Reactions and Characterization Data for Products

General procedure

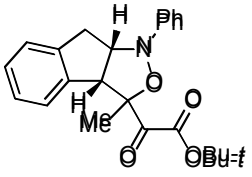


Method A: To the solution of α-ketoesters **5** (3.5 equiv) in *i*-PrOH (1.5 mL) was successively added TfOH (10 mol%) and $[Ru(bpy)_3 2Cl]\cdot 6H_2O$ **1a** (3 mol%, 0.003 mmol, 2.2 mg), followed by addition of tertiary amine **4** (0.1 mmol). Then, the reaction mixture was effectively stirred at ambient temperature by irradiation with 5 W blue LEDs under air. After the reaction finished, the reaction mixture was concentrated by rotary evaporation, and saturated $NaHCO_3$ (2.0 mL) was added into the residue. Then, the resulting aqueous solution was extracted with ethyl acetate (5.0 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and subjected to purification by flash chromatography on silica gel (petroleum ether 60-90:EtOAc, 50:1-10:1 v/v) to afford the resulting bicyclic isoxazolidines **6**.

Method B: To the solution of α-ketoesters **5a** (3.5 equiv) in MeOH (3.0 mL) was successively added TfOH (10 mol%) and $Ir(ppy)_2(dtbbpy)BF_4$ **2b** (1 mol%, 0.002 mmol, 1.7 mg), followed by addition of tertiary amine **4b-f** (0.2 mmol). Then, the reaction mixture was effectively stirred at ambient temperature by irradiation with 5 W blue LEDs under air. After the reaction finished, the reaction mixture was concentrated by rotary evaporation,

and saturated $NaHCO_3$ (2.0 mL) was added into the residue. Then, the resulting aqueous solution was extracted with ethyl acetate (5.0 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and subjected to purification by flash chromatography on silica gel (petroleum ether 60-90:EtOAc, 50:1-20:1 v/v) to afford the resulting bicyclic isoxazolidines **6**.

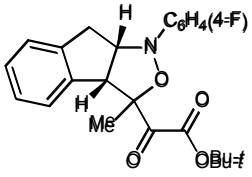
Characterization data of bicyclic isoxazolidines 6[5]



***tert*-Butyl 2-(3-methyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2-oxoacetate 6a.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and *tert*-butyl 2-oxobutanoate **5a** by irradiation with blue LEDs for 70 h, and purified by flash column chromatography as a white solid in 63% yield. When the reaction was carried out in 1 mmol scale, normal work-up can afford **6a** in 54% yield, d.r. > 20:1; mp. 113-115 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 15:1 v/v): R_f = 0.48.

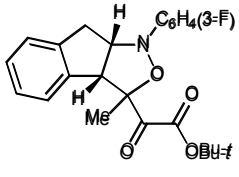
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33-7.18 (m, 5 H), 7.12-7.06 (m, 1 H), 7.04-6.94 (m, 3 H), 5.10-5.01 (m, 1 H), 4.74 (d, *J* = 8.0 Hz, 1H), 3.07-2.86 (m, 2 H), 1.41 (s, 3 H), 1.38 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.7, 163.4, 146.9, 143.2, 138.5, 128.7, 128.0, 126.6, 126.3, 124.7, 122.0, 116.4, 89.1, 84.1, 67.3, 59.3, 34.6, 27.9, 18.2; Dept^{135} NMR (100 MHz, $CDCl_3$): δ (ppm) = 128.7, 128.0, 126.6, 126.3, 124.7, 122.0, 116.4,

67.3, 59.3, 34.5, 27.9, 18.2; MS (ESI) *m/z:* 380.15 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NaNO_4$ $[M+Na]^+$: 402.1676; found: 402.1658.



***tert*-Butyl-2-(1-(4-fluorophenyl)-3-methyl-3,3a,8,8a-tetrahydro-1H-indeno[2,1-c]isoxazol-3-yl)-2-oxoacetate 6b.** The title compound was prepared according to the general method B described above using *N*-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline **4b** and *tert*-butyl 2-oxobutanoate **5a** by irradiation with blue LEDs for 90 h, and purified by flash column chromatography as a white solid in 48% yield. Method A: 170 h, 46% yield. d.r. > 20:1; mp. 134-136 ^oC; TLC (petroleum ether 60-90:ethyl acetate, 15:1 v/v): R_f = 0.53.

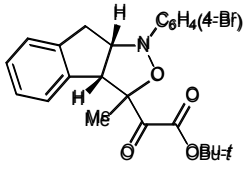
^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.25-7.19 (m, 3 H), 7.13-7.07 (m, 1 H), 7.03-6.94 (m, 4 H), 5.03-4.96 (m, 1H), 4.73 (d, *J* = 8.0 Hz, 1 H), 3.02-2.86 (m, 2 H), 1.40 (s, 3 H), 1.39(s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.5, 163.3, 158.3 (d, *J* = 139.2 Hz), 143.1 (d, *J* = 2.3 Hz), 143.0, 138.3, 128.1, 126.7, 126.3, 124.7, 117.8 (d, *J* = 7.6 Hz), 115.4 (d, *J* = 22.1 Hz), 89.2, 84.1, 67.8, 59.4, 34.2, 27.9, 18.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) = -121.9; MS (ESI) *m/z:* 398.05 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{23}H_{24}FNNaO_4$ $[M+Na]^+$: 420.1582; found: 420.1584.



***tert*-Butyl 2-(1-(3-fluorophenyl)-3-methyl-3,3a,8,8a-tetrahydro-1H -indeno-[2,1-c]isoxazol-3-yl)-2-oxoacetate 6c.** The title compound was prepared according to the general method B described above using *N*-(3-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline **4c** and *tert*-butyl 2-oxobutanoate **5a** by

irradiation with blue LEDs for 170 h, and purified by flash column chromatography as a white solid in 53% yield; d.r. > 20:1; mp. 118-120 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 20:1 v/v): R_f = 0.34.

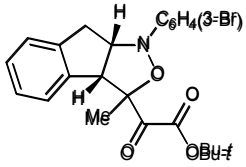
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.26-7.19 (m, 4 H), 7.15-7.09 (m, 1 H), 6.81-6.63 (m, 3 H), 5.07-4.98 (m, 1 H), 3.12-2.86 (m, 2 H), 1.41 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.4, 163.2 (d, $^{1}J_{C\text{-}F}$ = 242.5 Hz), 163.2 (O=C-O), 148.4 (d, $^{3}J_{C\text{-}F}$ = 9.8 Hz), 142.9, 138.2, 130.0 (d, $^{3}J_{C\text{-}F}$ = 9.6 Hz), 128.2, 126.7, 126.3, 124.7, 111.7 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 108.5 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz), 104.0 (d, $^{2}J_{C\text{-}F}$ = 26.3 Hz), 89.2, 84.3, 67.2, 59.2, 34.7, 27.9, 18.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) = -112.3; MS (ESI) *m/z:* 398.05 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{23}H_{24}FNNaO_4$ $[M+Na]^+$: 420.1582; found: 420.1584.



***tert*-Butyl 2-(1-(4-bromophenyl)-3-methyl-3,3a,8,8a-tetrahydro-1H-indeno-[2,1-c]isoxazol-3-yl)-2-oxoacetate 6d.** The title compound was prepared according to the general method B described above using *N*-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinoline **4d** and *tert*-butyl 2-oxobutanoate **5a** by irradiation with blue LEDs for 70 h, and purified by flash column chromatography as a white solid in 43% yield; d.r. > 20:1; mp. 168-170 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 20:1 v/v): R_f = 0.34.

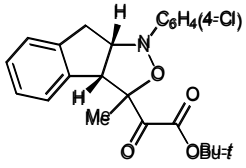
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44-7.35 (m, 2 H), 7.25-7.19 (m, 3 H), 7.15-7.07 (m, 1 H), 6.93-6.86 (m, 2 H), 5.05-4.97 (m, 1 H), 4.74 (d, *J* = 8.0 Hz, 1 H), 3.07-2.84 (m, 2 H), 1.40 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.4, 163.2, 145.9, 142.9,

138.2, 131.7, 128.2, 126.7, 126.3, 124.7, 118.0, 114.6, 89.3, 84.2, 67.3, 59.3, 34.5, 28.0, 18.2; MS (ESI) *m/z:* 460.08 ($M+H^+$, ^{81}Br); HRMS (ESI) *m/z* calcd for $C_{23}H_{24}{}^{79}BrNNaO_4$ $[M+Na]^+$: 480.0781; found: 480.0784.



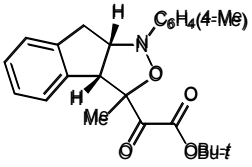
***tert*-Butyl 2-(1-(4-bromophenyl)-3-methyl-3,3a,8,8a-tetrahydro-1H -indeno-[2,1-c]isoxazol-3-yl)-2-oxoacetate 6e.** The title compound was prepared according to the general method B described above using *N*-(3-bromophenyl)-1,2,3,4-tetrahydroisoquinoline **4e** and *tert*-butyl 2-oxobutanoate **5a** by irradiation with blue LEDs for 170 h, and purified by flash column chromatography as a white solid in 41% yield; d.r. > 20:1; mp. 152-153 ^oC; TLC (petroleum ether 60-90:ethyl acetate, 20:1 v/v): $R_f = 0.28$.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.19-7.12 (m, 4 H), 7.11-7.00 (m, 3 H), 6.84-6.78 (m, 1 H), 4.99-4.91 (m, 1 H), 4.67 (d, *J* = 8.0 Hz, 1 H), 3.05-2.79 (m, 2 H), 1.35 (s, 9 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.3, 163.3, 148.0, 142.9, 138.2, 130.1, 128.2, 126.8, 126.3, 124.8, 122.8, 119.4, 114.6, 89.3, 84.4, 67.0, 59.2, 34.7, 27.9, 18.2; MS (ESI) *m/z:* 460.10 ($M+H^+$, ^{81}Br); HRMS (ESI) *m/z* calcd for $C_{23}H_{24}{}^{79}BrNNaO_4$ $[M+Na]^+$: 480.0781; found: 480.0784.



***tert*-Butyl 2-(1-(4-chlorophenyl)-3-methyl-3,3a,8,8a-tetrahydro-1H -indeno-[2,1-c]isoxazol-3-yl)-2-oxoacetate 6f.** The title compound was

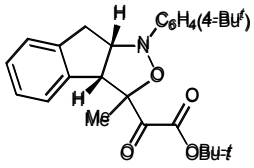
prepared according to the general method B described above using *N*-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline **4f** and *tert*-butyl 2-oxobutanoate **5a** by irradiation with blue LEDs for 60 h, and purified by flash column chromatography as a white solid in 50% yield; d.r. > 20:1; mp. 134-136 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 20:1 v/v): R_f = 0.33. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.27-7.19 (m, 5 H), 7.14-7.07 (m, 1 H), 6.98-6.92 (m, 2 H), 5.06-4.97 (m, 1 H), 4.74 (d, *J* = 8.0 Hz, 1 H), 3.07-2.84 (m, 2 H), 1.40 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.4, 163.2, 145.4, 142.9, 138.2, 128.8, 127.1, 126.7, 126.3, 124.7, 117.6, 89.3, 84.2, 67.4, 59.3, 34.5, 27.9, 18.2; MS (ESI) *m/z:* 414.25 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}ClNO_4$ $[M+H]^+$: 414.1467; found: 414.1469.



***tert*-Butyl 2-(3-methyl-1-(p-tolyl)-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2-oxoacetate 6g.** The title compound was prepared according to the general method A described above using *N* -(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline **4g** and *tert*-butyl 2-oxobutanoate **5a** by irradiation with blue LEDs for70 h, and purified by flash column chromatography as a white solid in 69% yield, d.r. > 20:1; mp. 117-119 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 15:1 v/v): R_f = 0.45.

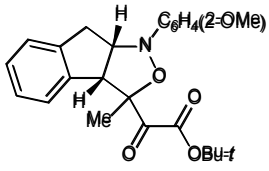
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.25-7.18 (m, 3 H), 7.11-7.06 (m, 3 H), 6.93-6.88 (m, 2 H), 5.05-4.98 (m, 1 H), 4.72 (d, *J* = 8.0 Hz, 1 H), 3.02-2.88 (m, 2 H), 2.30 (s, 3 H), 1.39 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.8, 163.4, 144.6, 143.3, 138.6, 131.4, 129.2, 128.0, 126.6, 126.3, 124.7, 116.5, 89.0, 84.0, 67.5, 59.3, 34.4, 27.9, 20.7,

18.2; MS (ESI) *m/z:* 394.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{24}H_{27}NNaO_4$ $[M+Na]^+$: 416.1832; found: 416.1835.



***tert*-Butyl2-(1-(4-*tert*-butylphenyl)-3-methyl-3,3a,8,8a-tetrahydro-1H-indeno-[2,1-c]isoxazol-3-yl)-2-oxoacetate 6h.** The title compound was prepared according to the general method A described above using *N*-(4-*tert*-butylphenyl)-1,2,3,4-tetrahydroisoquinoline **6h** and *tert*-butyl 2-oxobutanoate **5a** by irradiation with blue LEDs for 60 h, and purified by flash column chromatography as a white solid in 60% yield; d.r. > 20:1; mp. 134-136 °C; TLC (petroleum ether 60-90:ethyl acetate, 20:1 v/v): $R_f = 0.34$.

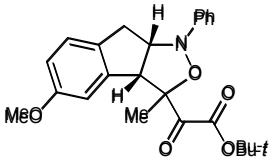
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.22-7.10 (m, 5 H), 7.06-7.00 (m, 1 H), 6.90-6.80 (m, 2 H), 5.00-4.90 (m, 1 H), 4.65 (d, *J* = 8.0 Hz, 1H), 3.00-2.83 (m, 2 H), 1.32 (s, 3 H), 1.31 (s, 9 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 199.7, 162.4, 143.8, 143.3, 142.3, 137.6, 126.9, 125.5, 125.3, 124.4, 123.6, 115.1, 88.0, 83.0, 66.3, 58.4, 33.5, 33.1, 30.4, 26.9, 17.2; MS (ESI) *m/z:* 436.42 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{27}H_{33}NNaO_4$ $[M+Na]^+$: 458.2302; found: 458.2310.



***tert*-Butyl2-(1-(2-methoxyphenyl)-3-methyl-3,3a,8,8a-tetrahydro-1H-indeno[2,1-c]isoxazol-3-yl)-2-oxoacetate 6i.** The title compound was prepared according to the general method A described above using *tert*-butyl 2-oxobutanoate **5a** and *N* -(2-methoxyphenyl)-1,2,3,4-

tetrahydroisoquinoline **6i** and by irradiation with blue LEDs for 170 h, and purified by flash column chromatography as a light yellow oil in 52% yield, d.r. > 20:1; TLC (petroleum ether 60-90:ethyl acetate, 10:1 v/v): $R_f = 0.53$.

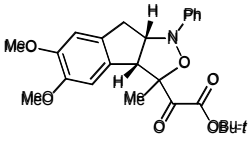
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.30-7.16 (m, 4 H), 7.09-6.98 (m, 2 H), 6.95-6.84 (m, 2 H), 5.44-5.35 (m, 1 H), 4.70 (d, *J* = 8.0 Hz, 1 H), 3.83 (s, 3 H), 2.88 (dd, *J* = 17.2, 5.2 Hz 1H), 2.69 (dd, *J* = 17.2, 8.8, Hz, 1 H), 1.43 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 201.0, 163.7, 147.7, 143.7, 139.0, 136.1, 127.8, 126.4, 124.6, 123.4, 120.9, 118.8, 111.3, 88.0, 83.7, 66.6, 59.7, 55.8, 33.7, 27.7, 18.0; MS (ESI) *m/z:* 410.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{24}H_{27}NNaO_5$ $[M+Na]^+$: 432.1781; found: 432.1769.



***tert*-Butyl 2-(5-methoxy-3-methyl-1-phenyl-3,3a,8,8a-tetrahydro -1H-indeno[2,1-c]iso-xazol-3-yl)-2-oxoacetate 6j.** The title compound was prepared according to the general method A described above using *tert*-butyl 2-oxobutanoate **5a** and 7-methoxy-*N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4j** by irradiation with blue LEDs for 120 h, and purified by flash column chromatography as a white solid in 65% yield, d.r. > 20:1; mp. 147-149 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 10:1 v/v): $R_f = 0.50$.

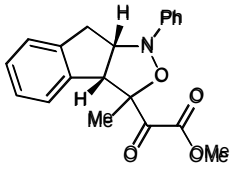
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.31-7.25 (m, 2 H), 7.03-6.93 (m, 4 H), 6.82-6.76 (m, 2 H), 5.09-5.02 (m, 1 H), 4.68 (d, *J* = 8.0 MHz, 1 H), 3.80 (s, 3 H), 2.99-2.79 (m, 2 H), 1.43 (s, 3 H), 1.38 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.8, 163.4, 158.8, 146.9, 139.9, 135.1, 128.7, 125.3, 121.9, 116.4, 114.5, 111.2, 89.1, 84.1, 68.0, 59.5, 55.5,

33.7, 27.9, 18.3; MS (ESI) *m/z:* 410.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{24}H_{27}NNaO_5$ $[M+Na]^+$: 432.1781; found: 432.1769.



***tert*-Butyl 2-(5,6-dimethoxy-3-methyl-1-phenyl-3,3a,8,8a-tetra-hydro-1H-indeno[2,1-c]isoxazol-3-yl)-2-oxoacetate 6k.** The title compound was prepared according to the general method A described above using *tert*-butyl 2-oxobutanoate **5a** and 6,7-dimethoxy-*N*-phenyl-1,2,3,4-tetrahydroisoquinoline **6k** by irradiation with blue LEDs for 120 h, and purified by flash column chromatography as a yellow solid in 60% yield, d.r. > 20:1; mp. 139-141 °C; TLC (petroleum ether 60-90:ethyl acetate, 10:1 v/v): R_f = 0.28.

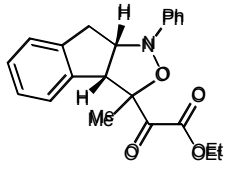
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.32-7.25 (m, 2 H), 7.04-6.94 (m, 3 H), 6.74 (s, 1 H), 6.60 (s, 1 H), 5.10-5.00 (m, 1 H), 4.65 (d, J = 8.0 Hz, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 2.99-2.82 (m, 2 H), 1.42 (s, 3 H), 1.38 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 201.1, 163.4, 149.6, 148.4, 146.9, 135.0, 129.8, 128.7, 121.9, 116.4, 118.9, 107.3, 89.1, 84.1, 67.9, 59.6, 56.2, 55.9, 34.6, 27.9, 18.3; MS (ESI) *m/z:* 440.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{25}H_{29}NNaO_6$ $[M+Na]^+$: 462.1887; found: 462.1878.



Methyl 2-(3-methyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2-oxoacetate 6m. The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and methyl 2-oxobutanoate **5b** by irradiation with

blue LEDs for 70 h, and purified by flash column chromatography as a white solid in 54% yield, d.r. > 20:1; mp. 108-110 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 15:1 v/v): R_f = 0.38.

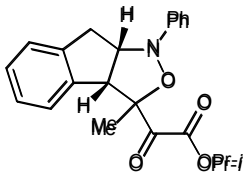
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.34-7.20 (m, 5 H), 7.15-7.07 (m, 1 H), 7.01-6.92 (m, 3 H), 5.10-5.00 (m, 1 H), 4.74 (d, *J* = 8.0 Hz, 1 H), 3.73 (s, 3 H), 3.10 (dd, *J* = 17.2, 8.4 Hz, 1 H), 2.94 (dd, *J* = 17.2, 5.2 Hz, 1 H), 1.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.5, 164.2, 146.6, 143.1, 138.2, 128.9, 128.1, 126.7, 126.3, 124.7, 122.0, 116.1, 89.3, 66.6, 59.5, 52.5, 34.6, 17.8; MS (ESI) *m/z:* 338.25 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{20}H_{19}NNaO_4$ $[M+Na]^+$: 360.1206; found: 360.1205.



Ethyl 2-(3-methyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno[2,1-c] isoxazol-3-yl)-2-oxoacetate 6n. The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and ethyl 2-oxobutanoate **5c** with blue LEDs for 120 h, and purified by flash column chromatography as a white solid in 68% yield, d.r. > 20:1; mp. 89-91 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 15:1 v/v): R_f = 0.45.

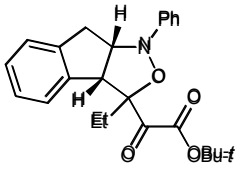
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.32-7.18 (m, 5 H), 7.13-7.07 (m, 1 H), 7.00-6.94 (m, 3 H), 5.09-5.02 (m, 1 H), 4.74 (d, *J* = 8.0 Hz, 1 H), 4.26-4.13 (m, 2 H), 3.07 (dd, *J* = 17.2, 8.4 Hz, 1 H), 2.93 (dd, *J* = 17.2, 5.6 Hz, 1 H), 11.43 (s, 3 H), 1.09 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.7, 164.0, 146.6, 143.2, 138.2, 128.8, 128.1, 126.7, 126.3, 124.7, 122.0, 116.1, 89.3, 66.7, 62.0, 59.5, 34.6, 17.9, 13.9; MS (ESI) *m/z:*

352.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NNaO_4$ $[M+Na]^+$: 374.1363; found: 374.1371.



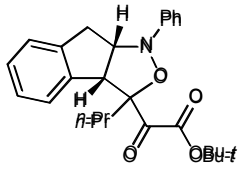
***iso*-Propyl 2-(3-methyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2-oxoacetate 6o.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and isopropyl 2-oxobutanoate **5d** by irradiation with blue LEDs for 100 h, and purified by flash column chromatography as a white solid in 62% yield, d.r. > 20:1; mp. 92-94 ^oC; TLC (petroleum ether 60-90:ethyl acetate, 15:1 v/v): $R_f = 0.41$.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33-7.19 (m, 5 H), 7.14-7.06 (m, 1 H), 7.02-6.93 (m, 3 H), 5.12-5.02 (m, 2 H), 4.75 (d, *J* = 8.0 Hz, 1 H), 3.11-2.88 (m, 2 H), 1.43 (s, 3 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 0.95 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.9, 163.7, 146.6, 143.2, 138.3, 128.8, 128.1, 126.6, 126.3, 124.7, 122.0, 116.2, 89.2, 70.2, 66.9, 59.4, 34.6, 21.7, 21.3, 18.0; MS (ESI) *m/z:* 366.33 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{22}H_{23}NNaO_4$ $[M+Na]^+$: 388.1519; found: 388.1489.



***tert*-Butyl 2-(3-ethyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2-oxoacetate 6p.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and *tert*-butyl 2-oxopentanoate **5e** by irradiation with blue

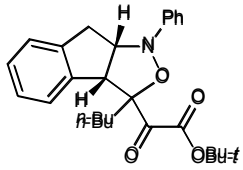
LEDs for 120 h, and purified by flash column chromatography as a white solid in 56% yield, d.r. > 20:1; mp. 109-111 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 25:1 v/v): R_f = 0.39. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35-7.27 (m, 3 H), 7.24-7.19 (m, 2 H), 7.13-7.07 (m, 1 H), 7.05-6.93 (m, 3 H), 5.05-4.97 (m, 1 H), 4.70 (d, *J* = 8.0 Hz, 1 H), 3.08-2.89 (m, 2 H), 1.87-1.64 (m, 2 H), 1.36 (s, 9 H), 0.96 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.5, 163.2, 147.0, 143.2, 138.4, 128.7, 128.1, 126.7, 126.1, 124.7, 121.9, 116.3, 92.4, 83.9, 67.3, 60.2, 34.8, 27.9, 25.1, 8.8; MS (ESI) *m/z:* 394.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{24}H_{27}NNaO_4$ $[M+Na]^+$: 416.1832; found: 416.1835.



***tert*-Butyl 2-oxo-2-(1-phenyl-3-propyl-3,3a,8,8a-tetrahydro-1H -indeno[2,1-c]isoxazol-3-yl)-acetate 6q.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and *tert*-butyl 2-oxohexanoate **5f** by irradiation with Blue LEDs for 170 h, and purified by flash column chromatography as a white solid in 43% yield, d.r. > 20:1; mp. 92-93 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 25:1 v/v): R_f = 0.39.

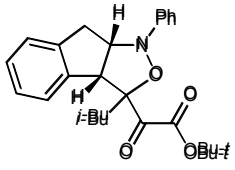
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.32-7.26 (m, 3 H), 7.25-7.19 (m, 2 H), 7.14-7.07 (m, 1 H), 7.04-6.94(m, 3 H), 5.06-4.96 (m, 1 H), 4.70 (d, *J* = 8.4 Hz, 1 H), 3.07-2.89 (m, 2 H), 1.77-1.38 (m, 4 H), 1.35 (s, 9 H), 0.85 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.6, 163.1, 146.9, 143.2, 138.5, 128.7, 128.1, 126.7, 126.1, 124.7,

121.9, 116.3, 92.1, 83.9, 67.2, 60.4, 34.7, 33.9, 27.9, 17.8, 14.3; MS (ESI) *m/z:* 408.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{25}H_{30}NO_4$ $[M+H]^+$: 408.2169; found: 408.2195.



***tert*-Butyl 2-(3-butyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2-oxo-acetate 6r.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and *tert*-butyl 2-oxoheptanoate **5g** by irradiation with blue LEDs for 170 h, and purified by flash column chromatography as a white solid in 40% yield, d.r. > 20:1; mp. 97-99 °C; TLC (petroleum ether 60-90:ethyl acetate, 25:1 v/v): $R_f = 0.48$.

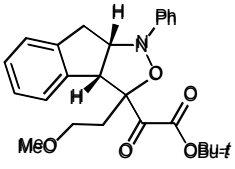
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33-7.18 (m, 5 H), 7.13-7.07 (m, 1 H), 7.04-6.93 (m, 3 H), 5.05-4.97 (m, 1 H), 4.71 (d, *J* = 8.0 Hz, 1 H), 3.08-2.88 (m, 2 H), 1.88-1.64 (m, 2 H), 1.47-1.17 (m, 13 H), 0.84 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.5, 163.1, 146.9, 143.2, 138.5, 128.7, 128.1, 126.7, 126.1, 124.7, 121.9, 116.3, 92.1, 83.9, 67.2, 60.2, 34.7, 31.5, 27.9, 26.4, 23.0, 13.8; MS (ESI) *m/z:* 444.42 ($M+Na^+$); HRMS (ESI) *m/z* calcd for $C_{26}H_{31}NNaO_4$ $[M+Na]^+$: 444.2145; found: 444.2126.



***tert*-Butyl 2-(3-isobutyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2-oxo-acetate 6s.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and *tert*-butyl 5-methyl-2-oxohexanoate **5h** by

irradiation with blue LEDs for 170 h, and purified by flash column chromatography as a white solid in 35% yield, d.r. > 20:1; mp. 109-111 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 25:1 v/v): R_f = 0.45.

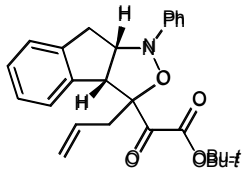
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.25-7.12 (m, 5 H), 7.07-7.00 (m, 1 H), 6.98-6.86 (m, 3 H), 4.94-4.85 (m, 1 H), 4.51 (d, *J* = 8.0 Hz, 1 H), 3.02-2.83 (m, 2 H), 1.85 (dd, *J* = 14.6, 4.8 Hz, 1 H), 1.76-1.63(m, 1 H), 1.27 (s, 9 H), 1.18 (dd, *J* = 14.6, 8.0 Hz, 1 H), 0.85 (d, *J* = 6.4 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 201.7, 162.7, 147.1, 143.1, 138.4, 128.7, 128.1, 126.7, 126.5, 124.7, 121.9, 116.3, 92.2, 83.9, 67.0, 62.7, 41.5, 34.8, 27.9, 24.8, 24.6, 23.5; MS (ESI) *m/z:* 444.42 ($M+Na^+$); HRMS (ESI) *m/z* calcd for $C_{26}H_{31}NNaO_4$ $[M+Na]^+$: 444.2145; found: 444.2126.



***tert*-Butyl 2-(3-(2-methoxyethyl)-1-phenyl-3,3a,8,8a-tetrahydro-1H -indeno[2,1-c]iso- xazol-3-yl)-2-oxoacetate 6t.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and *tert*-butyl 5-methoxy-2-oxopentanoate **5i** by irradiation with blue LEDs for 170 h, and purified by flash column chromatography as a yellow oil in 28% yield, d.r. > 20:1; TLC (petroleum ether 60-90:ethyl acetate, 10:1 v/v): R_f = 0.45.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.41-7.34 (m, 1 H), 7.32-7.20 (m, 4 H), 7.12-7.07 (m, 1 H), 7.06-7.95 (m, 3 H), 5.00-4.92 (m, 1 H), 4.67 (d, *J* =8.4 Hz, 1 H), 3.61-3.52 (m, 1 H), 3.44-3.36 (m, 1 H), 3.24 (s, 3 H), 3.11-2.89 (m, 2 H), 2.29-2.20 (m, 1 H), 1.75-1.67 (m,

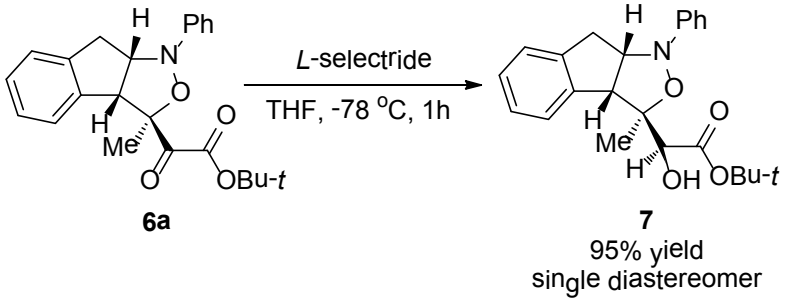
1 H), 1.38 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 198.3, 161.5, 147.0, 143.1, 138.2, 128.7, 128.2, 126.8, 126.5, 124.7, 122.0, 116.4, 89.9, 83.6, 68.0, 67.1, 61.5, 58.5, 34.9, 33.4, 27.9; MS (ESI) *m/z:* 446.33 ($M+Na^+$); HRMS (ESI) *m/z* calcd for $C_{25}H_{29}NNaO_5$ $[M+Na]^+$: 446.1938; found: 446.1954.



***tert*-Butyl 2-(3-allyl-1-phenyl-3,3a,8,8a-tetrahydro-1H-indeno [2,1-c]isoxazol-3-yl)-2 -oxoacetate 6u.** The title compound was prepared according to the general method A described above using *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **4a** and *tert*-butyl 2-oxohex-5-enoate **5j** by irradiation with blue LEDs for 170 h, and purified by flash column chromatography as a yellow oil in 52% yield, d.r. > 20:1; TLC (petroleum ether 60-90:ethyl acetate, 25:1v/v): R_f = 0.51. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.37-7.19 (m, 5 H), 7.15-7.07 (m, 1 H), 7.05-6.96 (m, 3 H), 5.83-5.69 (m, 1 H), 5.13-4.94 (m, 3 H), 4.72 (d, *J* = 8.0 Hz, 1 H), 3.10-2.90 (m, 2 H), 2.59 (dd, *J* = 14.8, 6.8 Hz, 1 H); 2.44 (dd, *J* = 14.8, 6.8 Hz, 1 H), 1.36 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 199.4, 162.7, 146.9, 143.2, 138.1, 131.2, 128.7, 128.2, 126.7, 126.4, 124.8, 122.0, 119.0, 116.4, 91.2, 84.0, 67.4, 60.4, 36.5, 34.8, 27.9; MS (ESI) *m/z:* 406.10 ($M+H^+$); HRMS (ESI) *m/z* calcd for $C_{25}H_{27}NNaO_4$ $[M+Na]^+$: 428.1832; found: 428.1801.

Part IV. Further Application of Bicyclic Isoxazolidine 6a

1. Synthesis of α-hydroxy isoxazolidine ester 7



6a **7**

95% yield

single diastereomer

The mixture of **6a** (0.5 mmol) in 5 mL THF was cooled at -78 °C and a 1.0 *M L*-selectride solution in THF was added (2.0 equiv). After being stirred for 1 h, the reaction mixture was quenched with saturated NH_4Cl aq. and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and filtered. After removal of solvents, the residue was purified by flash column chromatography (petroleum ether 60-90:EtOAc = 15:1 to 10:1 as eluent) to afford **7** in 95% yield as single diastereomer.

White solid, mp. 81-83 °C; TLC (petroleum ether 60-90:ethyl acetate, 10:1v/v): R_f = 0.27;

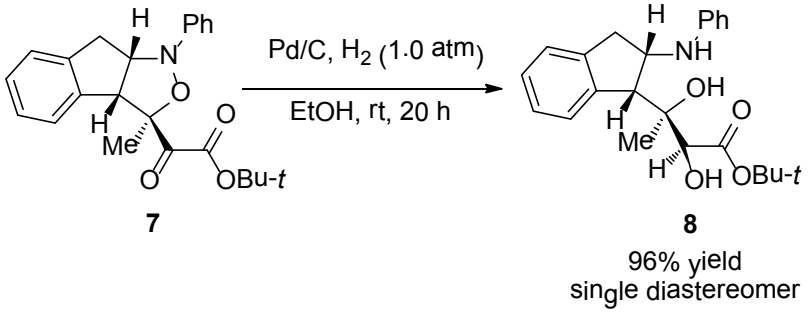
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33-7.27 (m, 2 H), 7.23-7.11 (m, 4 H), 7.05-6.93 (m, 3 H), 5.00-4.93 (m, 1 H), 4.66 (d, *J* = 8.4 Hz, 1 H), 4.30 (s, 1 H), 3.17-2.94 (m, 2 H), 1.50 (s, 9 H), 1.07 (s, 3 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.4, 147.9, 142.7, 140.2, 128.8, 127.7, 126.7, 125.6, 124.8, 121.5, 115.9, 85.9, 82.8, 75.9, 68.6, 58.2, 35.6, 28.1, 18.7;

MS (ESI) *m/z:* 382.25 ($M+H^+$);

HRMS (ESI) *m/z* calcd for $C_{23}H_{28}NO_4$ $[M+H]^+$: 382.2013; found: 382.2010.

2. Synthesis of α,β-dihydroxy-δ-amino acid derivative 8



10% Pd/C (30 mg) was added to a solution of **7** (0.3 mmol) in ethanol (5.0 mL) at room temperature under an atmosphere of hydrogen balloon (1.0 atm). The reaction mixture was stirred at room temperature for 20 hours, and then the mixture was filtered through Celite. The resulting organic filtrate was evaporated under reduced pressure to furnish the α,β-dihydroxy-δ-amino acid derivative **8** as a colorless oil in 96% yield.

TLC (petroleum ether 60-90:ethyl acetate, 10:1v/v): R_f = 0.21;

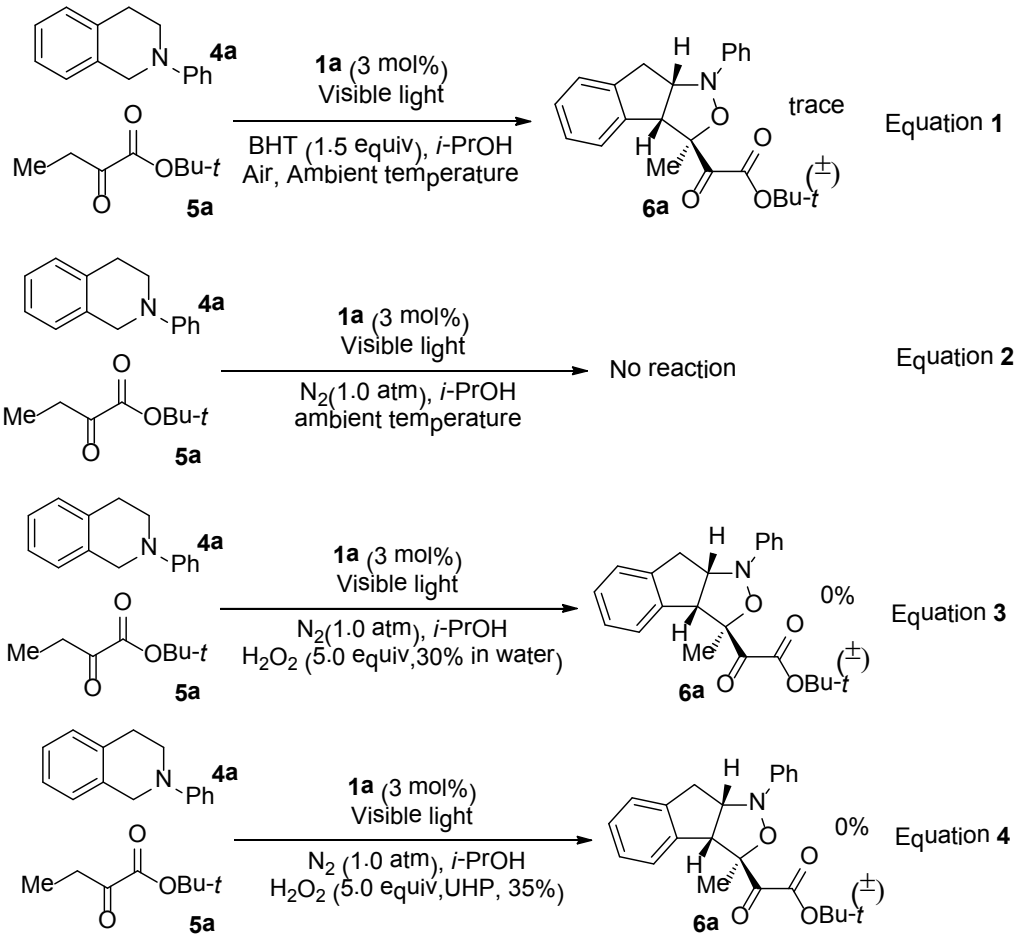
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.53-7.45 (m, 1 H), 7.25-7.15 (m, 5 H), 6.77-6.66 (m, 3 H), 4.54-4.46 (m, 1 H), 4.29 (s, 1 H), 3.86 (d, *J* = 6.8 Hz, 1 H), 3.24-3.08 (m, 2 H), 1.51 (s, 9 H), 1.35 (s, 3 H);

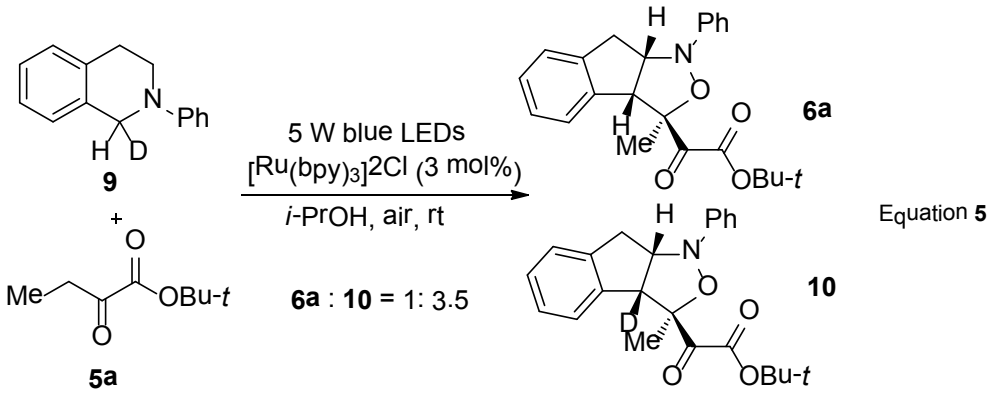
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 172.1, 147.4, 142.1, 141.5, 129.4, 127.2, 126.51, 126.49, 125.2, 117.9, 113.6, 83.4, 74.3, 59.1, 51.8, 39.7, 28.1, 21.6;

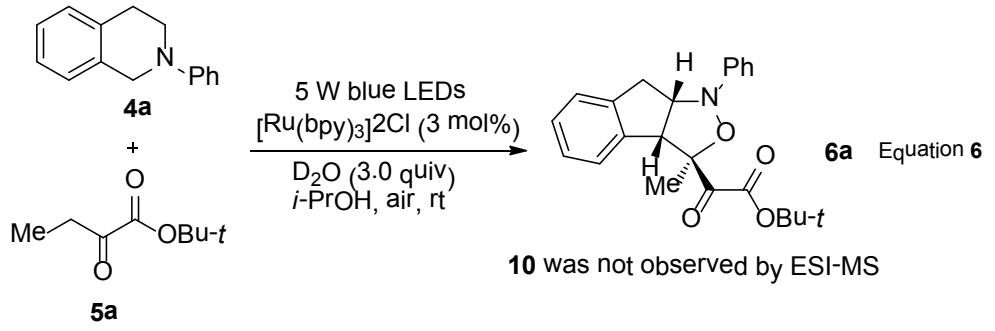
MS (ESI) *m/z:* 384.42($M+H^+$);

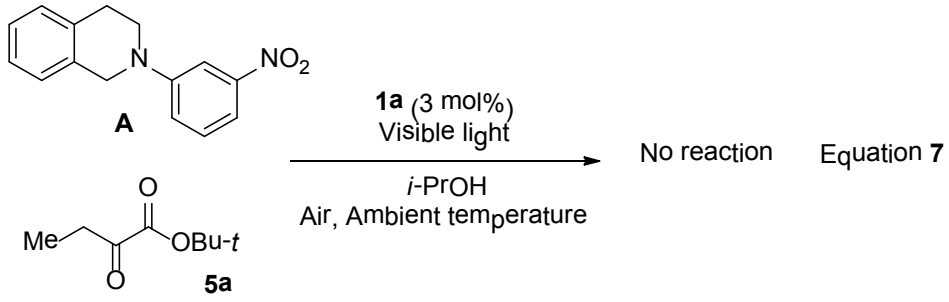
HRMS (ESI) *m/z* calcd for $C_{23}H_{30}NO_4$ $[M+H]^+$: 384.2169; found: 384.2170.

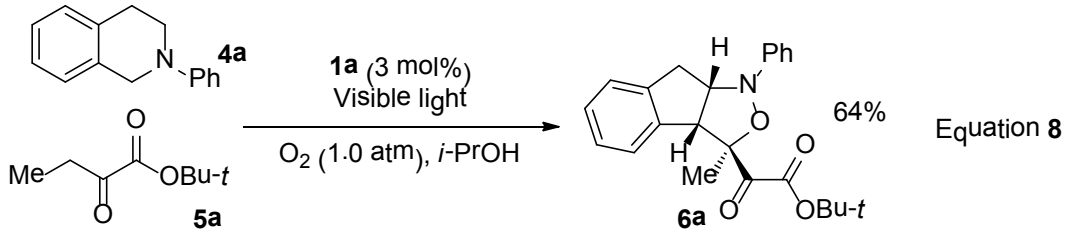
Part V. Experiments on Radical Inhibitions and Mechanistic Study











In Equation **1**, when the antioxidant BHT (2,6-di-*tert*-butyl-4-methylphenol) was added into the reaction system, the reaction speed was dramatically decreased and only trace product **6a** could be detected. In Equation **1**, when the tandem reaction was carried out under nitrogen atmosphere, **6a** could not be obtained. In Equation **3** and **4**, when the tandem

reaction was still carried out under nitrogen atmosphere but with H_2O_2 (5.0 equiv) as oxidant, we could also not observe the desired product **6a**, resulting in the oxidation of the amine to its N-O complex. In Equation **5**, the isotope labeling study was also investigated by the reaction of deuterated *N*-phenyl-1,2,3,4-tetrahydroisoquinoline **9** with *tert*-butyl 2-oxobutanoate **5a**, demonstrating that only one hydrogen atom in the α benzylic position was grabbed and the abstraction of hydrogen was 3.5 times faster than deuterium. Then, we tried to add D_2O (3.0 equiv) into the tandem reaction of **4a** and **5a** (Equation **6**), and only the normal product **6a** could be obtained, suggesting that no hydrogen of the product **6a** comes from water in air or solvent. Interestingly, when the tertiary amine **A** was used under the standard reaction conditions, the reaction was halted (Equation **7**). The reason for this may be that nitrobenzene is an oxidative quencher of $Ru(bpy)_3^{2+}$*, and thus the amine **A** here is an oxidant.

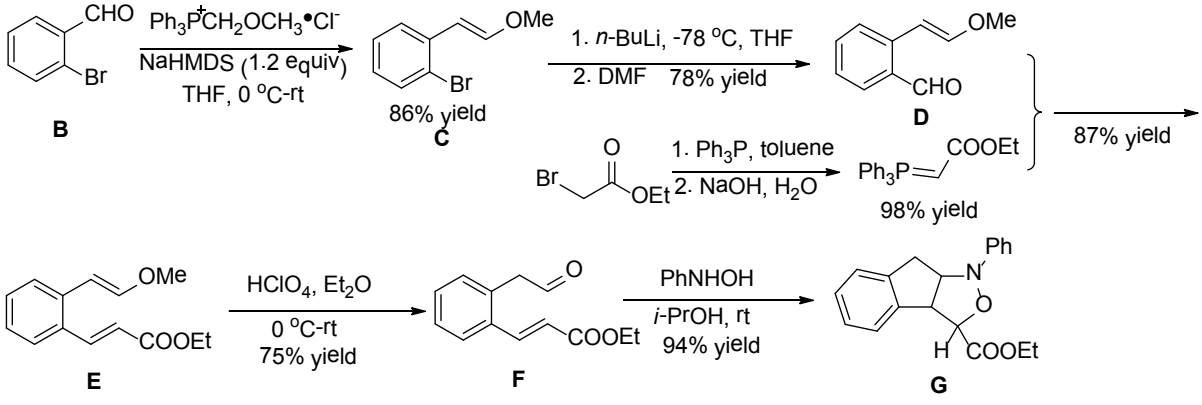


Figure 1: The step by step strategy to construct bicyclic isoxazolidine **S8**.

Synthesis of C[6,7]

To the stirred solution of (methoxymethyl)triphenylphosphonium chloride (3.77 g, 11 mmol, 1.1 equiv.) in 20 mL THF was added NaHMDS (12 mmol, 2 M in THF) dropwise at 0 ^{o}C for 30 min. When the mixture was stirred under nitrogen atmosphere for another 2 h, a solution of **B** (10 mmol) in THF was added dropwise to the reaction mixture. After 10 min at 0 ^{o}C, the reaction mixture was warmed to room temperature and stirred for another 2 h. When it was finished, the yellow solution was quenched with saturated NH_4Cl (5 mL) and the solvent was evaporated. Subsequently, *n*-hexane was added into the residue and the mixture was filtered to remove the triphenylphosphine oxide. The filtrate was washed with saturated Na_2CO_3, H_2O and brine. The organic layer was dried over Na_2SO_4, and the crude product was subjected to column chromatography on silica gel to give **C** in 86% yield as the mixture of *E* and *Z* isomers. The ^{1}H NMR data are accorded with the literature.

Synthesis of D[6,8]

To a stirred mixture of **C** (4 mmol) in THF (10 mL) was added *n*-BuLi (1.2 equiv, 2.5 M in THF) dropwise at -78 ^{o}C under nitrogen atmosphere. After stirring at -78 ^{o}C for another 2 h, anhydrous DMF (1.5 equiv) was added to give a light yellow solution. One hour later, water was added into the reaction mixture, and extracted with diethyl ether, dried over anhydrous Na_2SO_4, and the combined organic layers were concentrated. The crude product was eluted through a column chromatography on silica gel to afford **D** in 78% yield as the mixture of *E* and *Z* isomers. The ^{1}H NMR data are accorded with the literature.

Synthesis of E[9]

To the solution of **D** (2 mmol) in DCM (5 mL) was added ylide (1.1 equiv) at room temperature, and the reaction mixture was stirred for 12 hours. When the reaction finished (monitored by TLC), the organic solvent was evaporated under reduced pressure, and *n*-hexane was added to the residue. The filtrate was washed with saturated Na_2CO_3, H_2O and brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was subjected to column chromatography on silica gel to furnish the **E** in 87% yield as the mixture of *E* and *Z* isomers. The ^{1}H NMR data are accorded with the literature.

Synthesis of F[10]

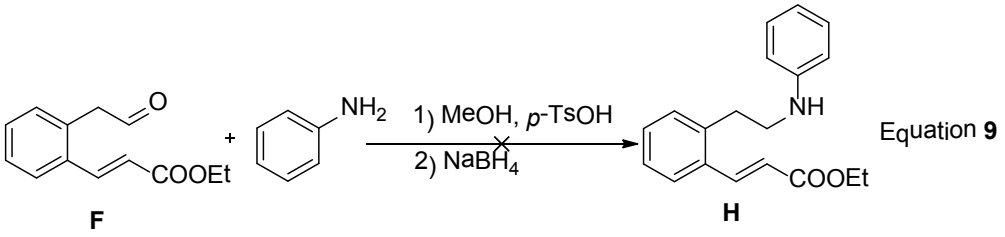
$HClO_4$ (1.5 mL, 70% in water) was added dropwise to a stirring solution of **E** (1 mmol) in 15 mL diethyl ether at 0 ºC. After 10 minutes, the cooling bath was removed and stirring continued until the reaction proceeds to completion (about 45 min). The mixture was diluted with water (20 mL) and extracted with ethyl acetate. The combined organic layers were washed with saturated Na_2CO_3, brine, dried with Na_2SO_4, filtered and concentrated to afford compound **F** in 75% yield for next step without purification. The ^{1}H NMR data are accorded with the literature.

Synthesis of G

N-phenylhydroxylamine (0.6 mmol) was added into a solution of **F** (0.5 mmol) in 3.0 mL *i*-PrOH, and the reaction mixture was stirred at room temperature for 8 hours. When the reaction was finished (monitored by TLC), the mixture was evaporated under reduced pressure, and the resulting residue was subjected to column chromatography on silica gel to

afford the bicyclic isoxazolidine **G** as a white solid in 94% yield. mp. 58-60 ^{o}C; TLC (petroleum ether 60-90:ethyl acetate, 5:1v/v): R_f = 0.63.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.43- 7.18 (m, 6 H), 7.15-7.09 (m, 2 H), 7.04-6.97 (m, 1 H), 4.65-4.54 (m, 3 H), 4.34-4.20 (m, 2 H), 3.34-3.12 (m, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 170.4, 148.7, 141.8, 141.5, 128.8, 128.1, 127.4, 125.1, 124.5, 122.4, 116.5, 82.2, 67.6, 61.6, 58.8, 37.1, 14.2; MS (ESI) *m/z:* 332.42 ($M+Na^+$); HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NNaO_3$ $[M+Na]^+$: 332.1257; found: 332.1254.



F **H** Equation **9**

Much to our surprise, when we tried to prepare the corresponding secondary amine **H** which can be further undergo the oxidation and cyclization under our biomimetic reaction condition, the **F** was decomposed as soon as the aniline was added.

References:

1 Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968.

2 K. Okano, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2006**, *128*, 7136.

3 A. Nakamura, S. Lectard, D. Hashizume, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4036.

4 D. Shi, Y. Xie, H. Zhou, C. Xia, H. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 1248.

5 The vicinal coupling constants J for H^7-H^{15} ($^3J_{7\text{-}15}$ = 8.0 Hz) matched well with the crystal structure and the similar known compounds, see: Rudolf Huisgen, R. G., H. Seidl, H. Hauck, *Chem. Ber.* **1968**, *101*, 2559.

6 P. Chua, B. Tan, L. Yang, X. Zeng, D. Zhu, G. Zhang, *Chem. Commun.* **2010**, *46*, 7611.

7 K. Uchida, S. Yokoshima, T. Kan, T. Fukuyama. *Org. Lett.* **2006**, *8*, 5311

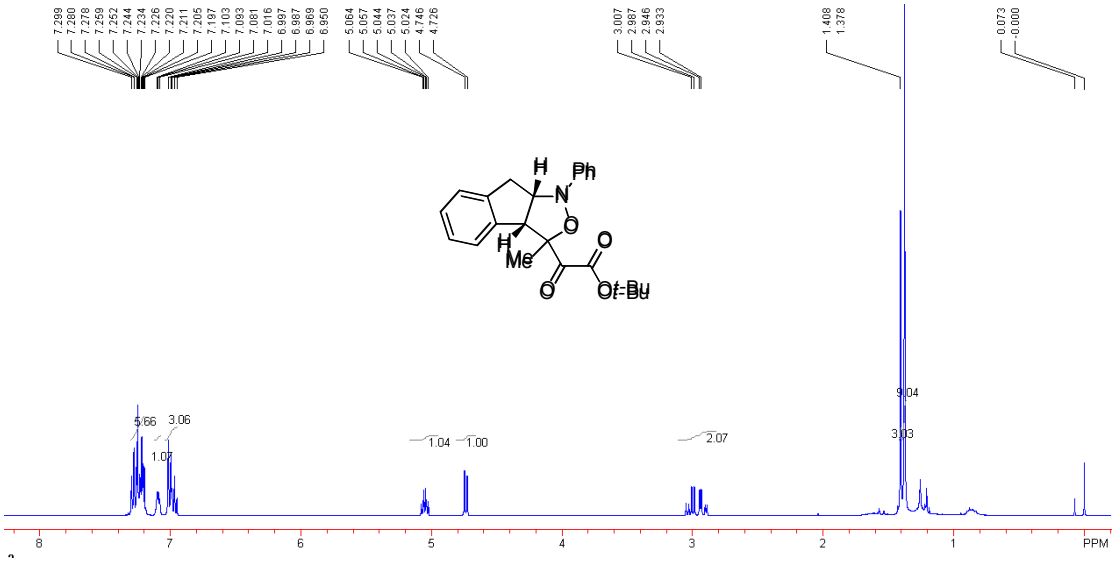
8 M.-Y. Lin, A. Das, R.-S. Liu. *J. Am. Chem. Soc.* **2006**, *128*, 9340

9 B. Tan, D. Zhu, L. Zhang, P. J. Chua, X. Zeng, G. Zhong, *Chem. Eur. J.* **2010**, *16*, 3842

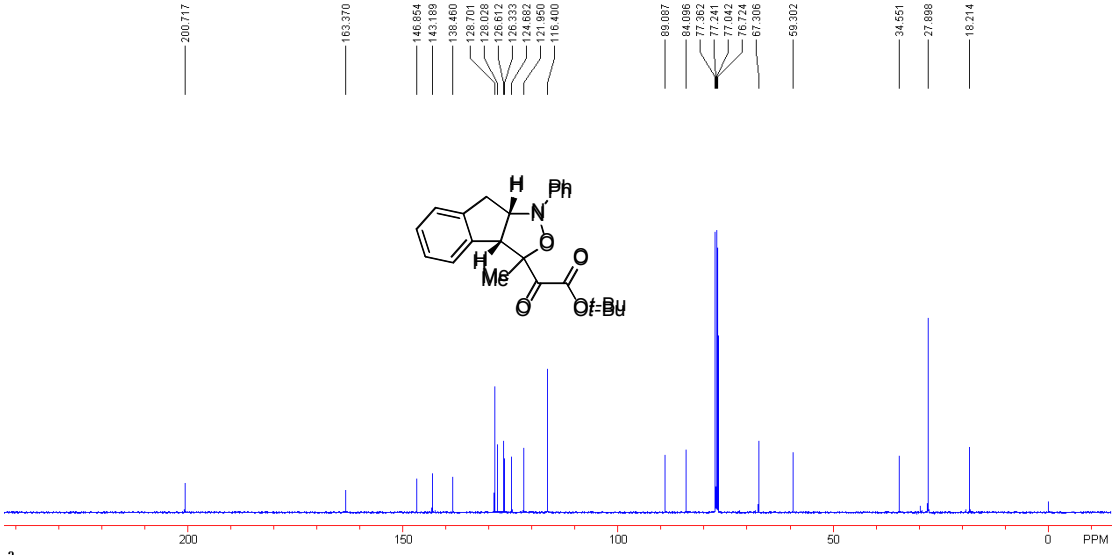
10 F. Richter, M. Bauer, C. Perez, C. Maichle-Mössmer, M. E. Maier. *J. Org. Chem.* **2002**, *67,* 2474.

Part VI. ^{1}H NMR, ^{13}C NMR, MS and Chiral HPLC Spectra

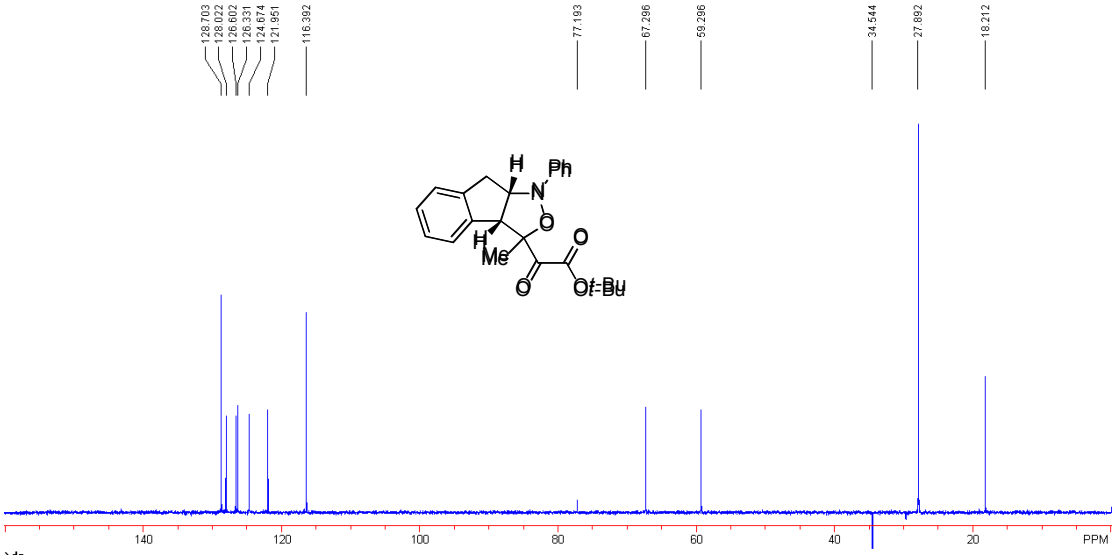
The ^{1}H NMR spectrum of **6a**



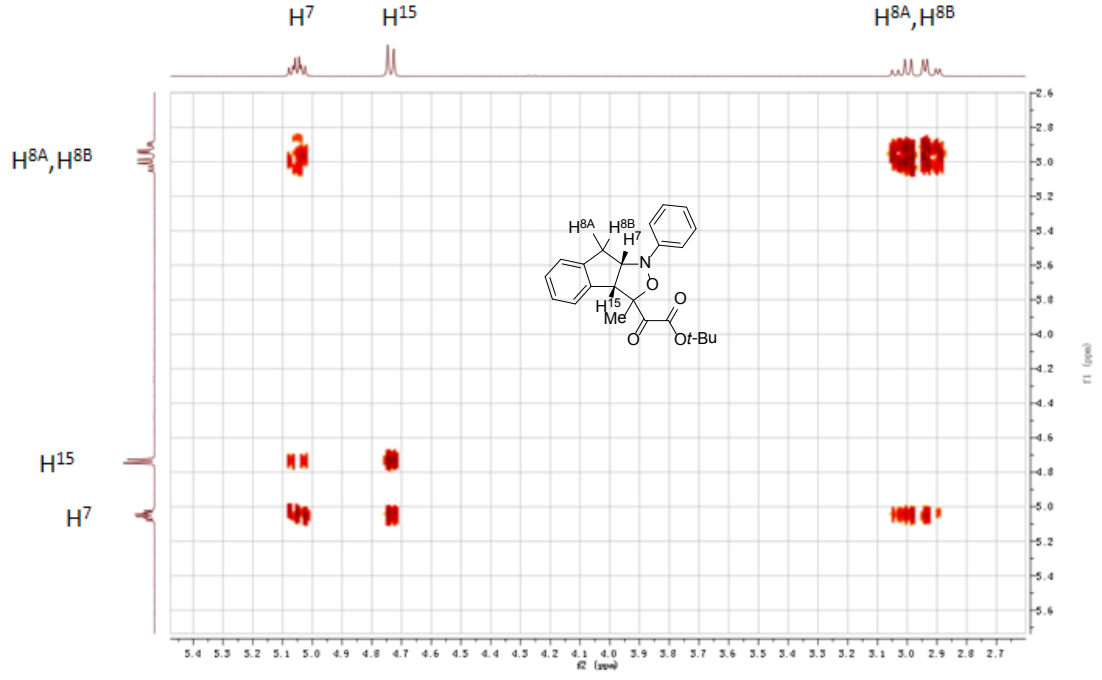
The ^{13}C NMR spectrum of **6a**



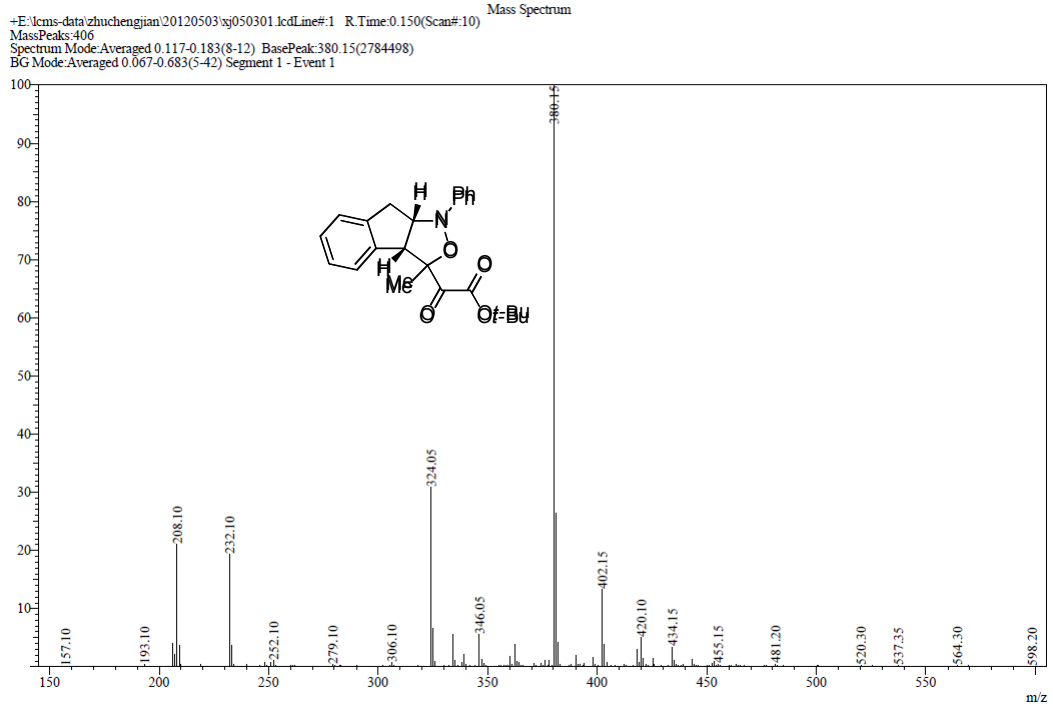
The Dept^{135} NMR spectrum for **6a**



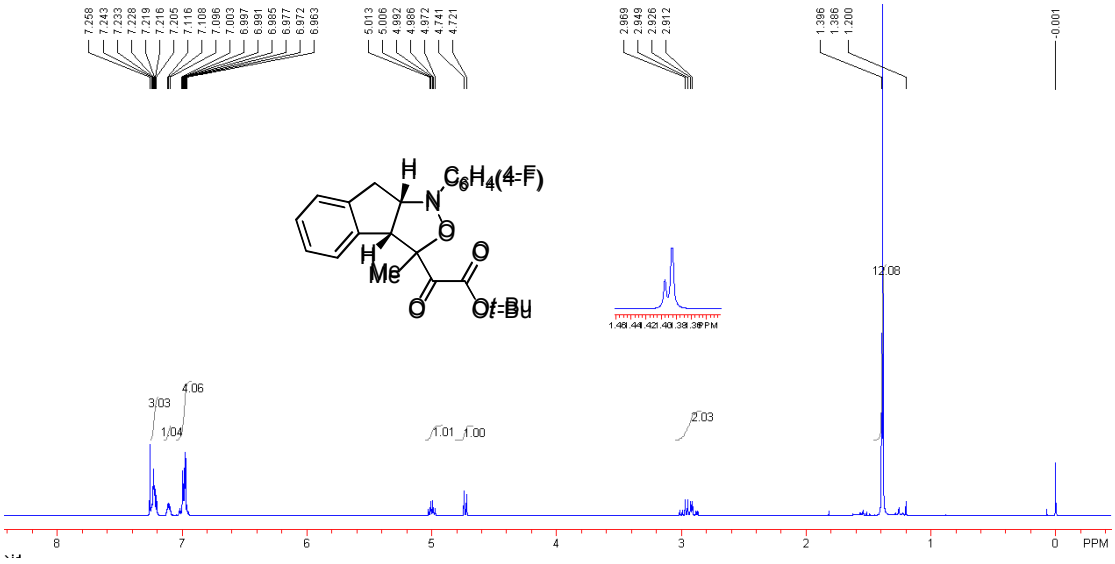
The H-H cosy spectrum of **6a**



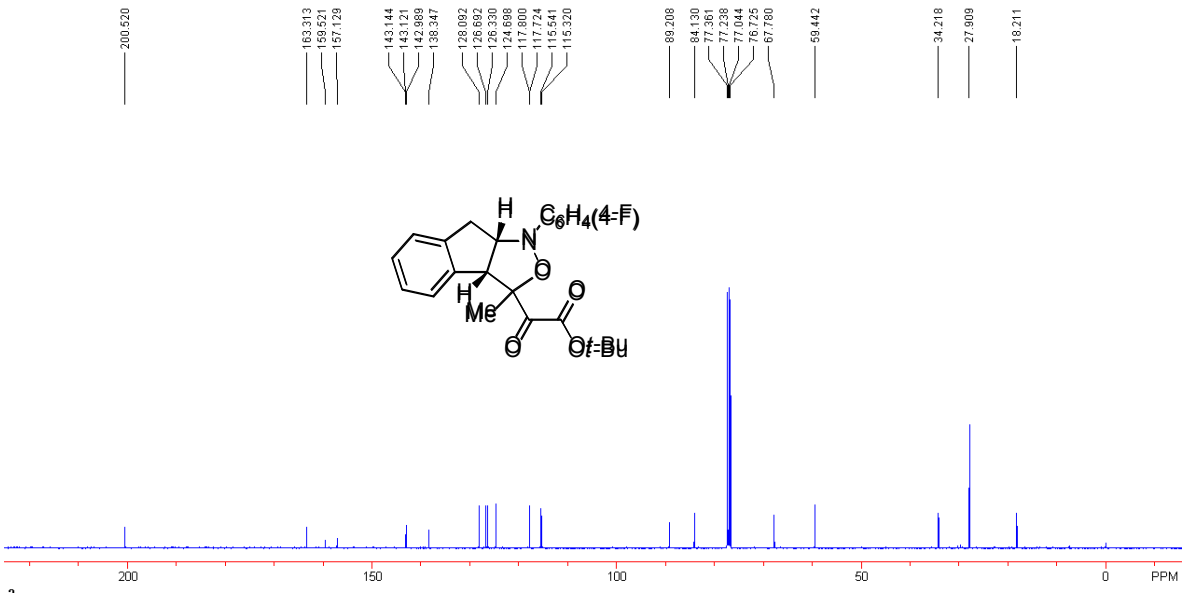
The MS(ESI) spectrum of **6a**



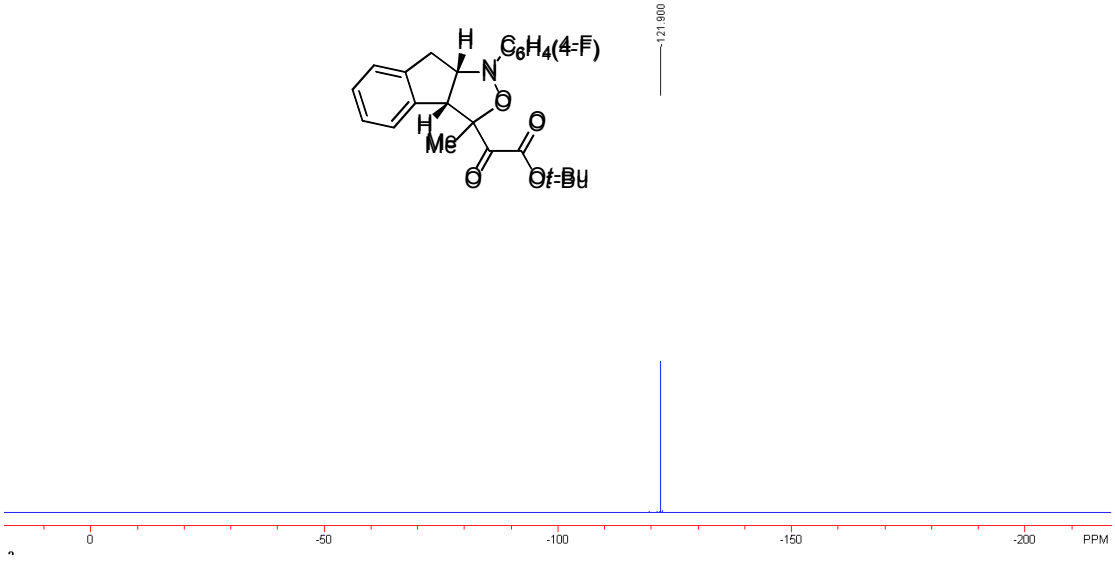
The ^{1}H NMR spectrum of **6b**



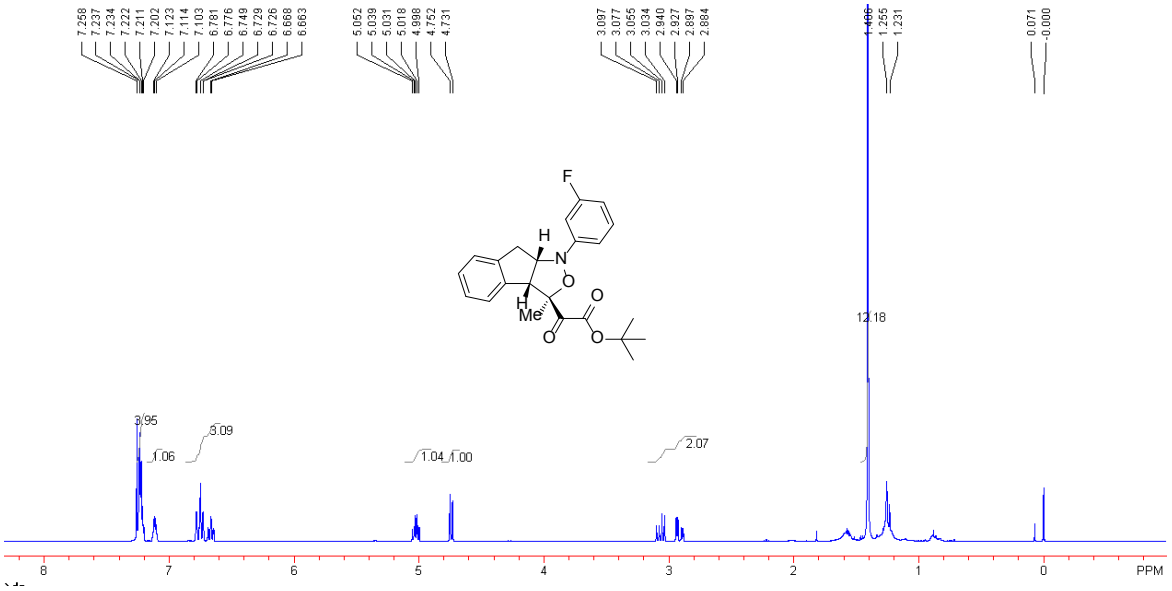
The ^{13}C NMR spectrum of **6b**



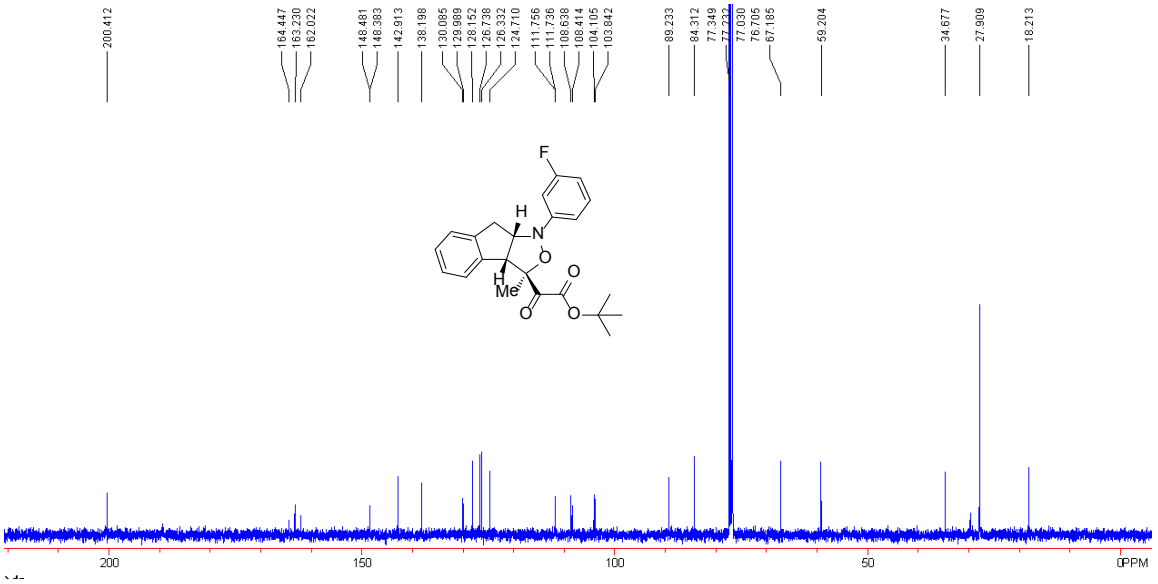
The ^{19}F NMR spectrum of **6b**



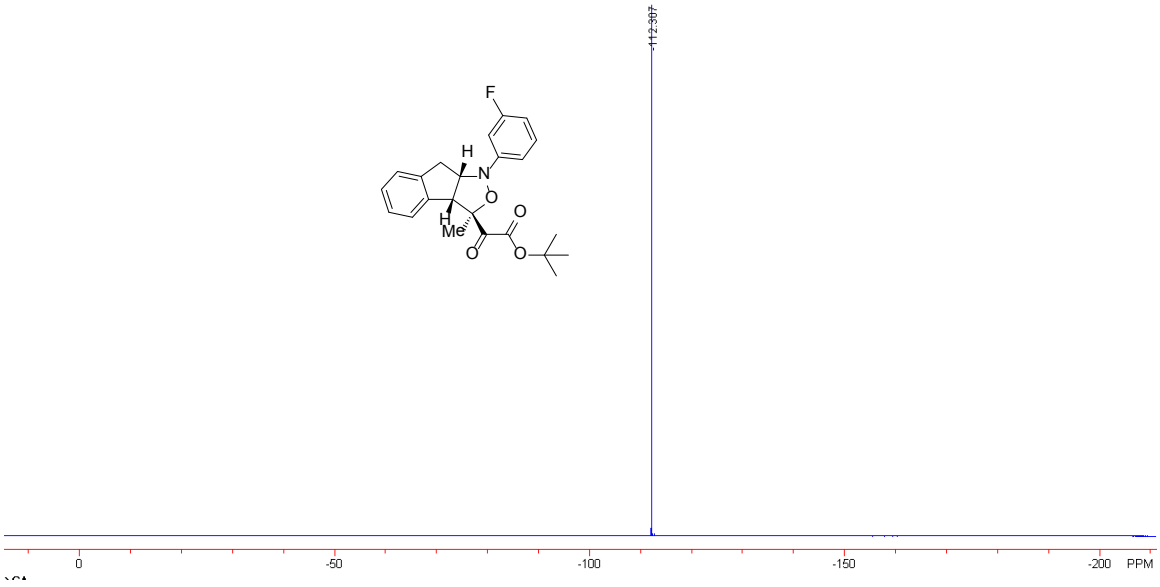
The ^{1}H NMR spectrum of **6c**



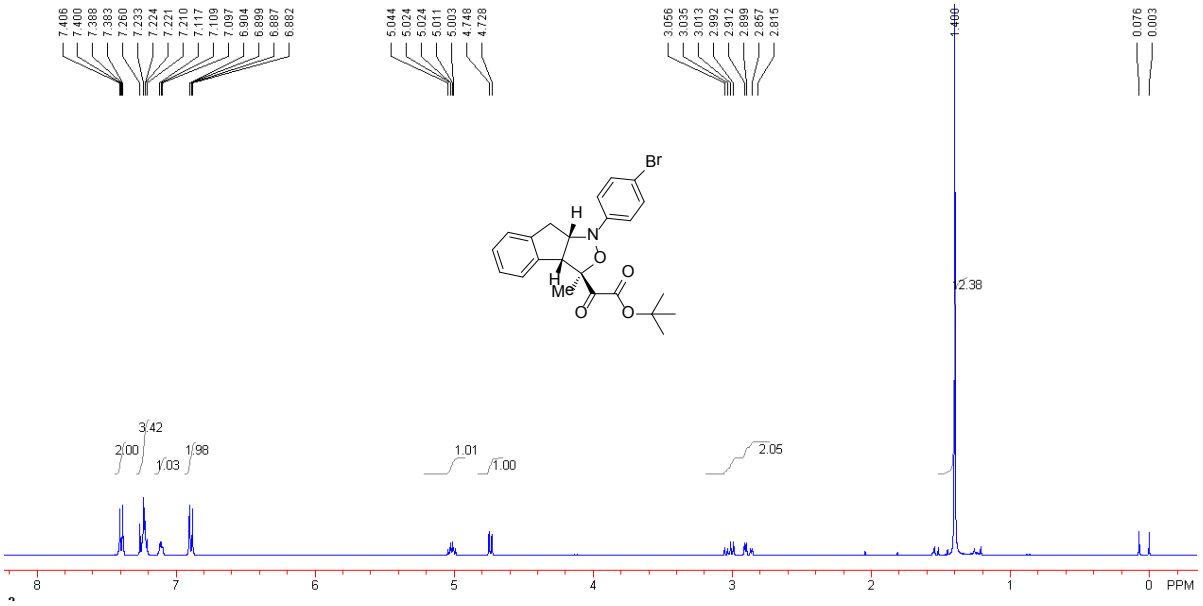
The ^{13}C NMR spectrum of **6c**



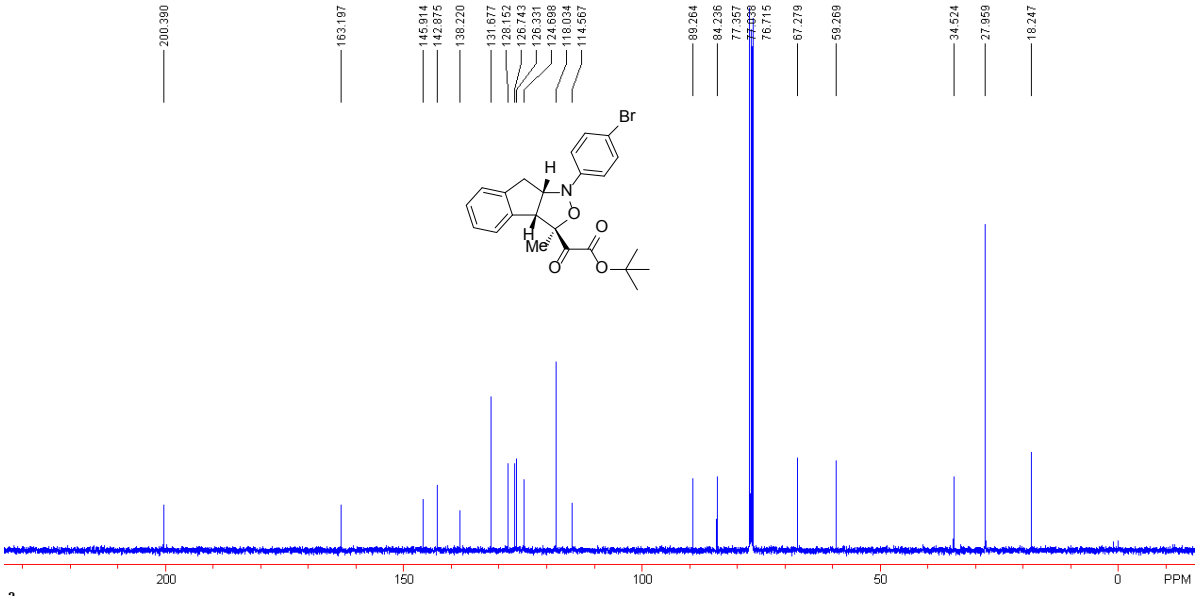
The ^{19}F NMR spectrum of **6c**



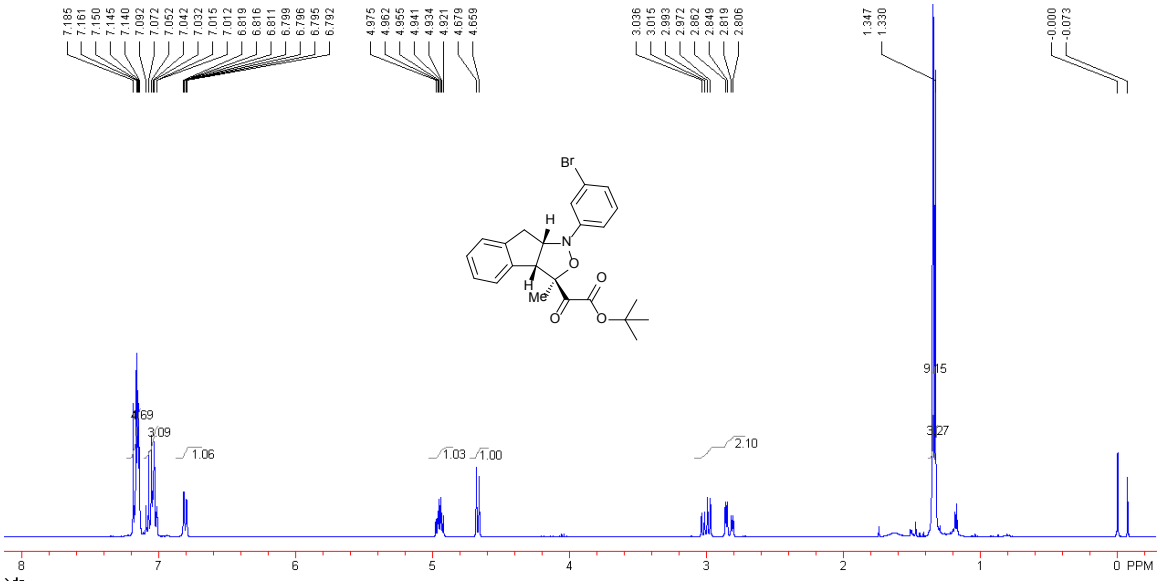
The ^{1}H NMR spectrum of **6d**



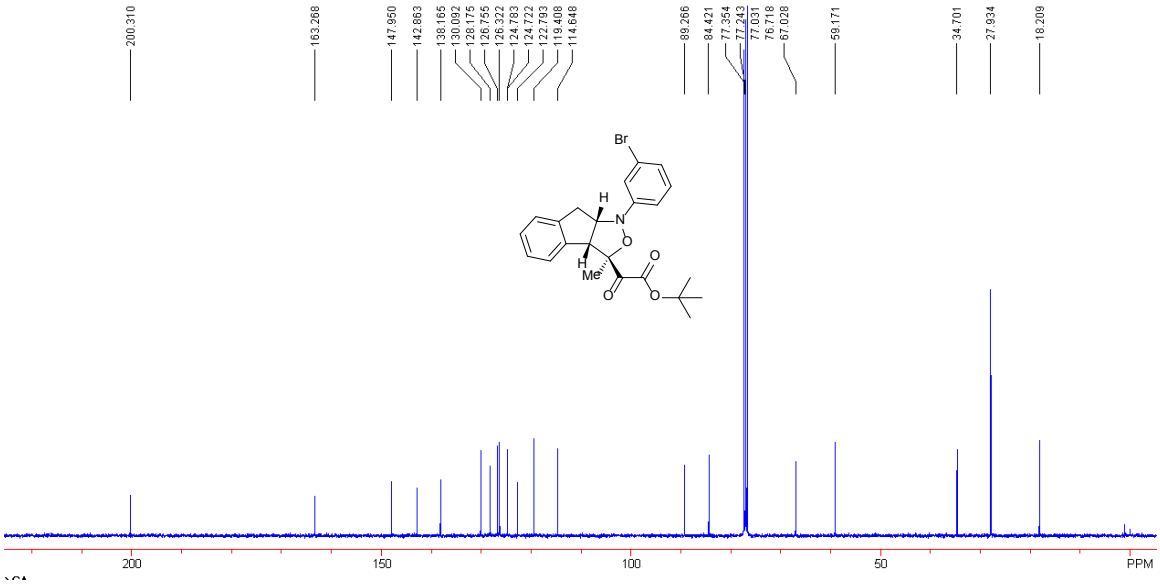
The ^{13}C NMR spectrum of **6d**



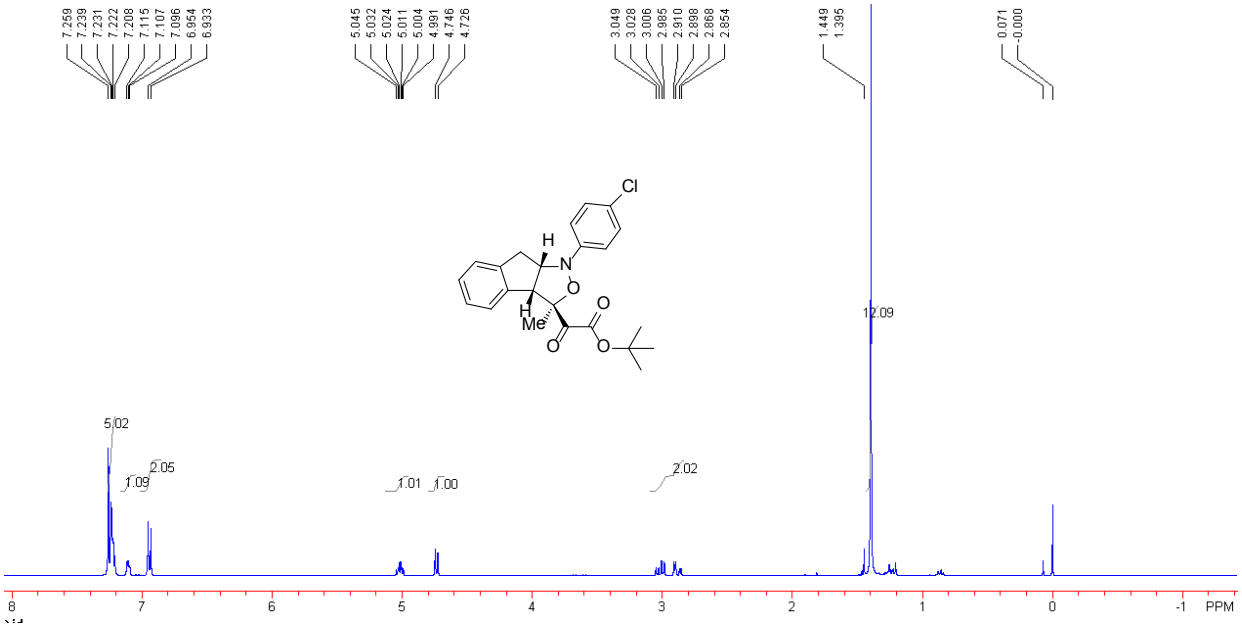
The ^{1}H NMR spectrum of **6e**



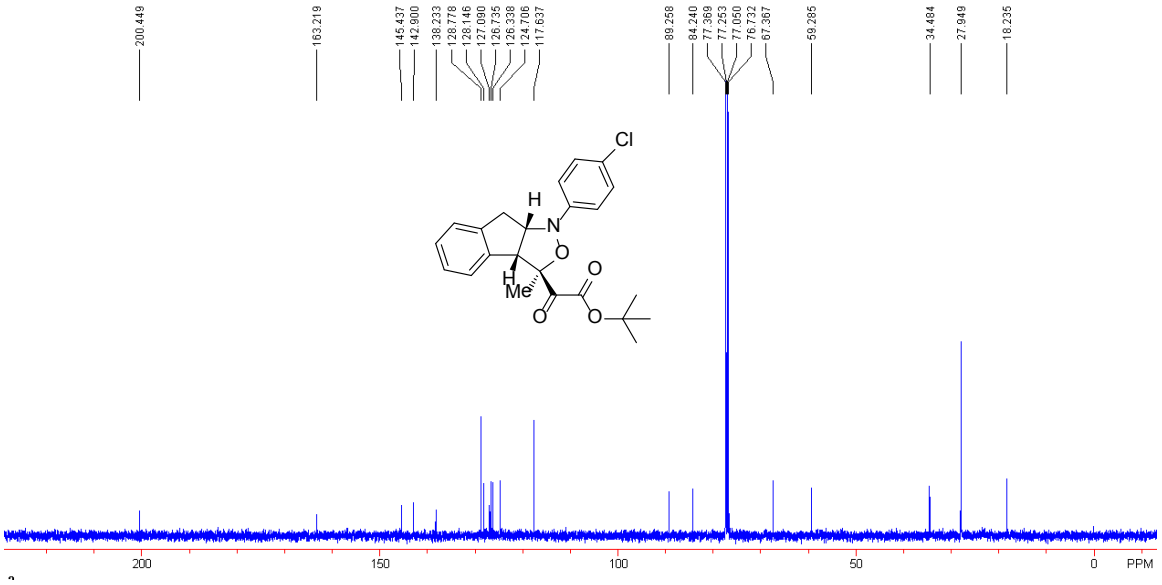
The ^{13}C NMR spectrum of **6e**



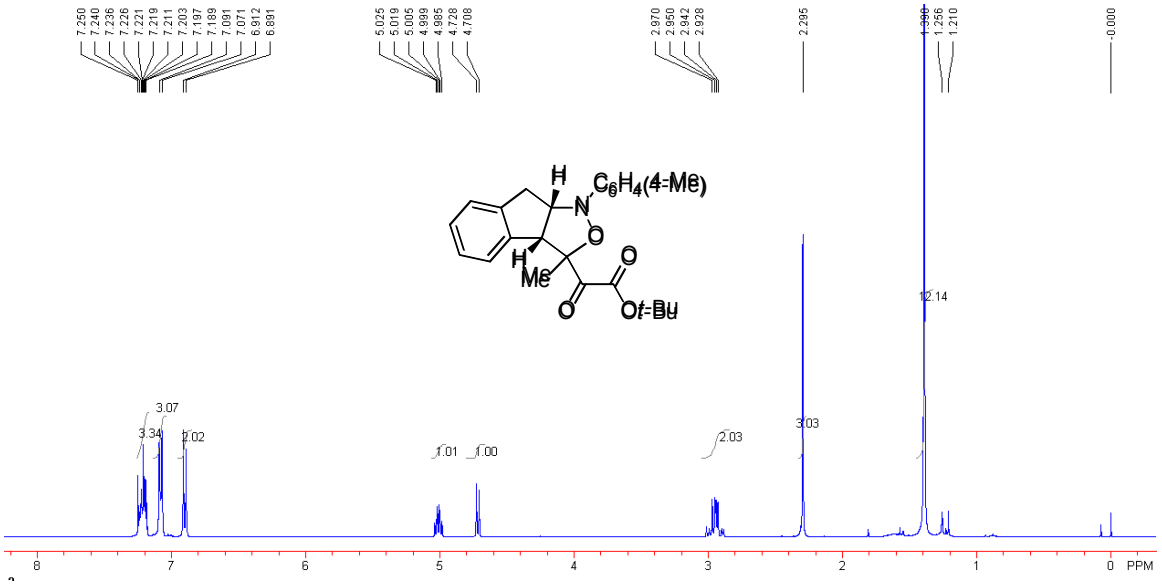
The ^{1}H NMR spectrum of **6f**



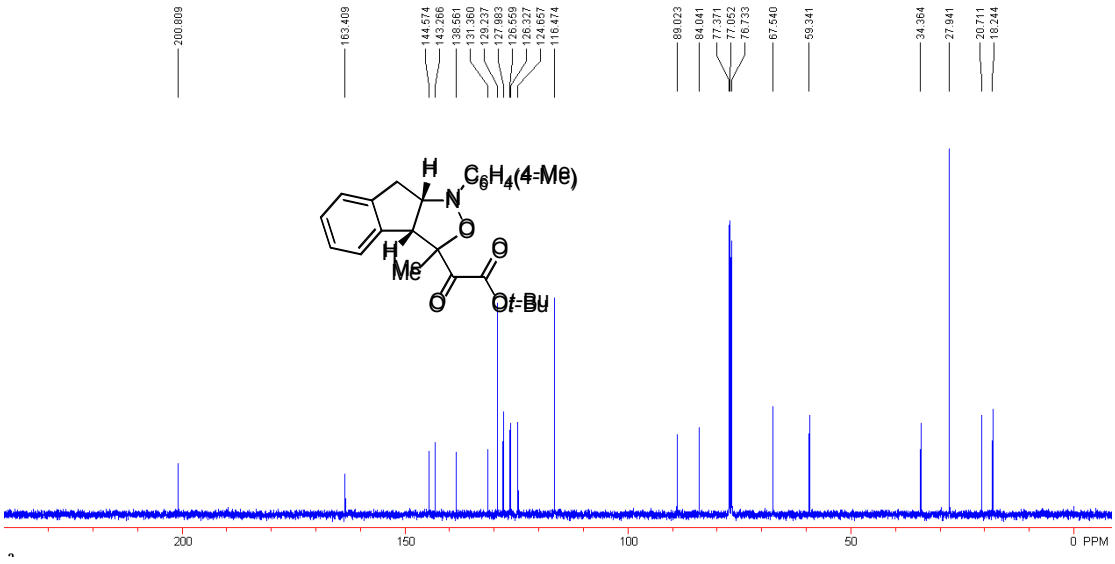
The ^{13}C NMR spectrum of **6f**



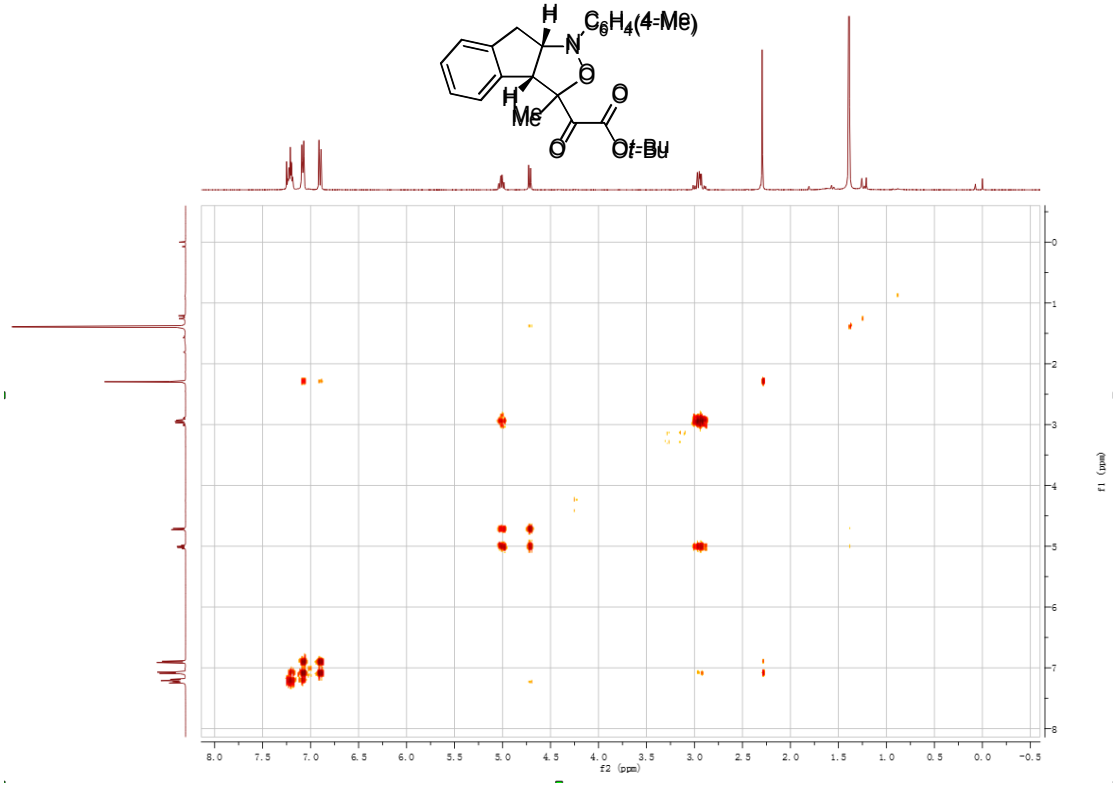
The ^{1}H NMR spectrum of **6g**



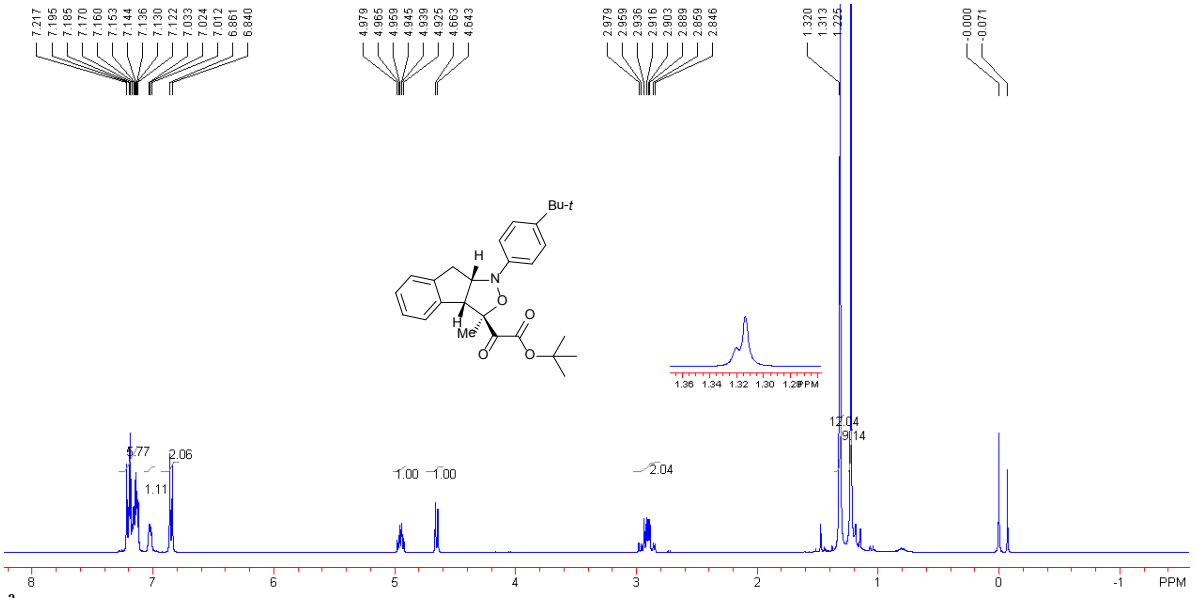
The ^{13}C NMR spectrum of **6g**



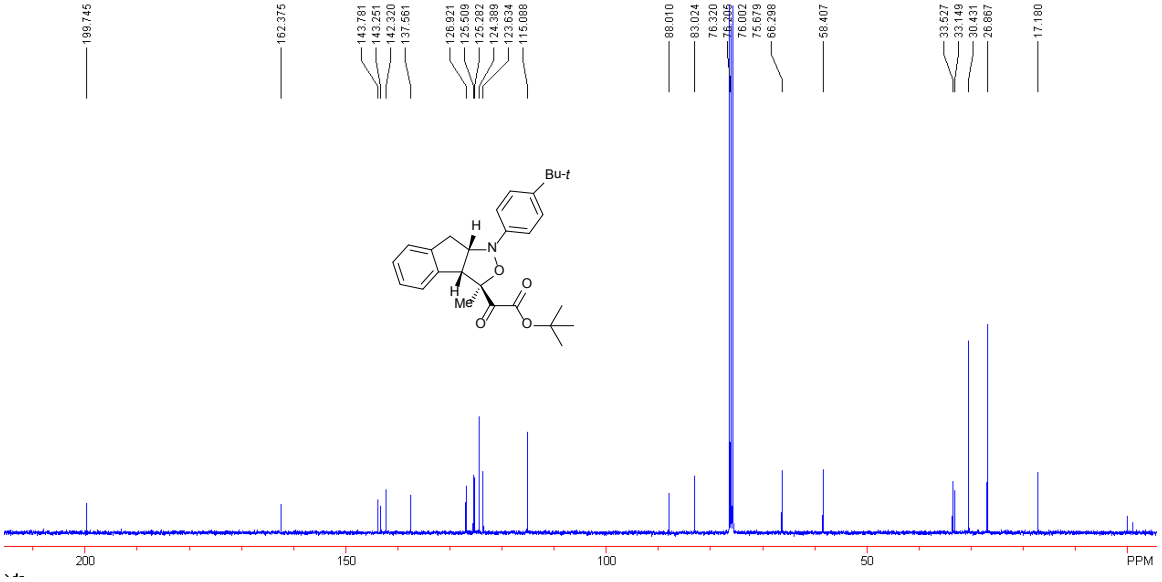
The H-H cosy spectrum of **6g**



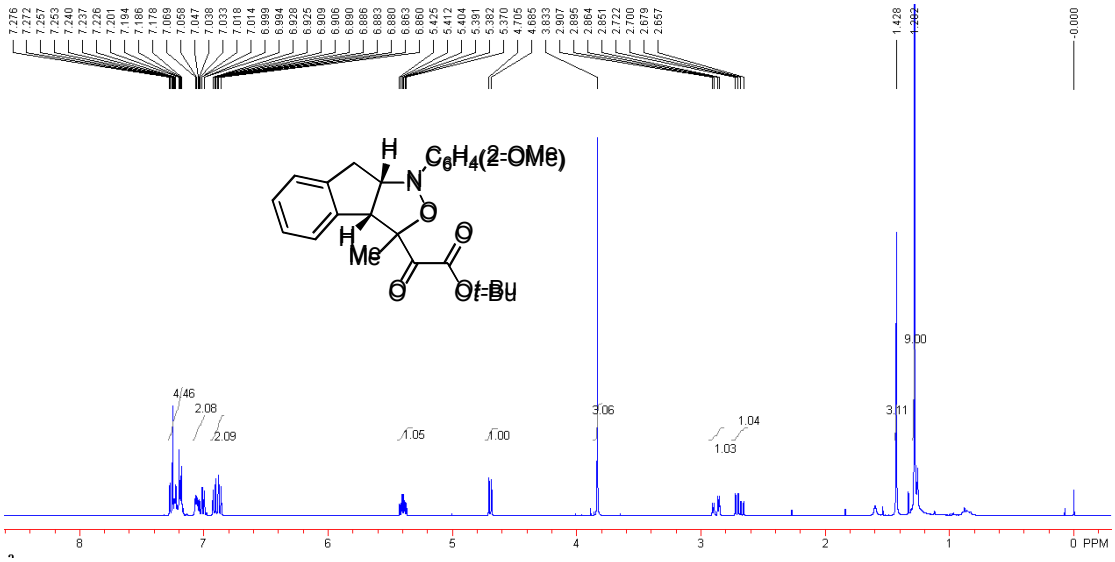
The ^{1}H NMR spectrum of **6h**



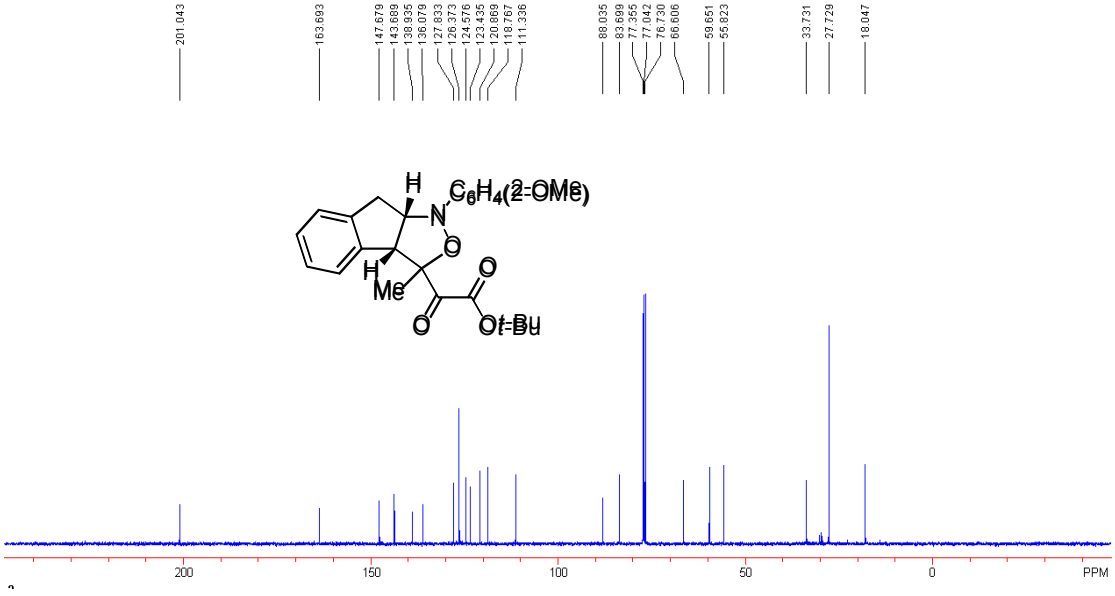
The ^{13}C NMR spectrum of **6h**



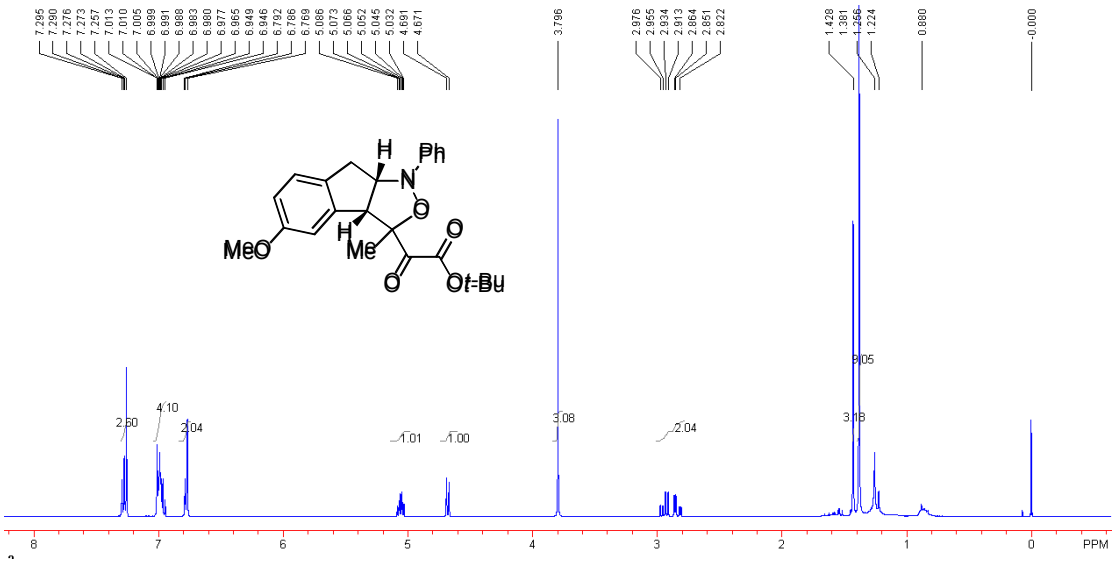
The ^{1}H NMR spectrum of **6i**



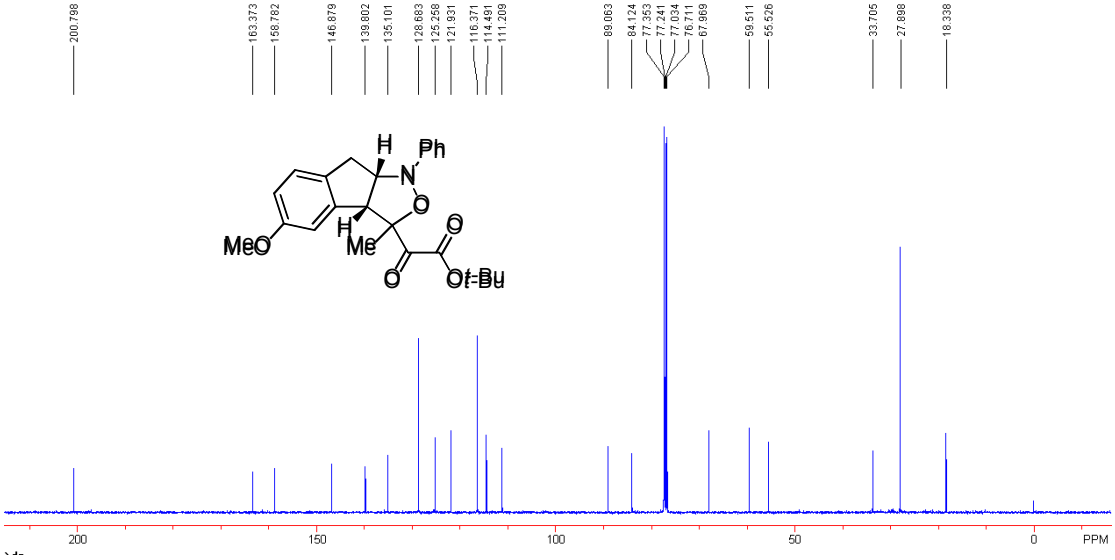
The ^{13}C NMR spectrum of **6i**



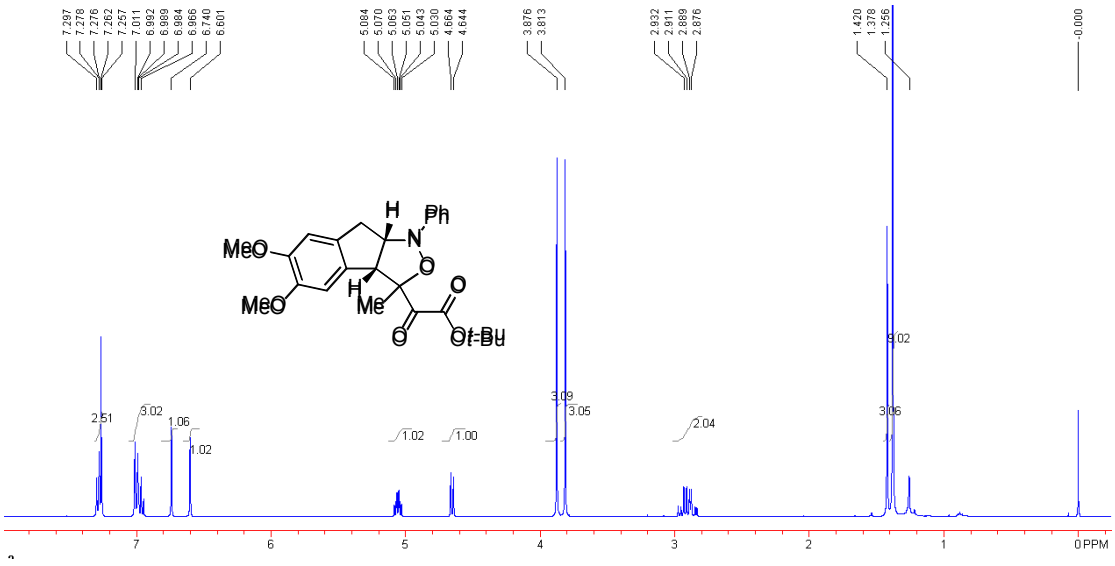
The ^{1}H NMR spectrum of **6j**



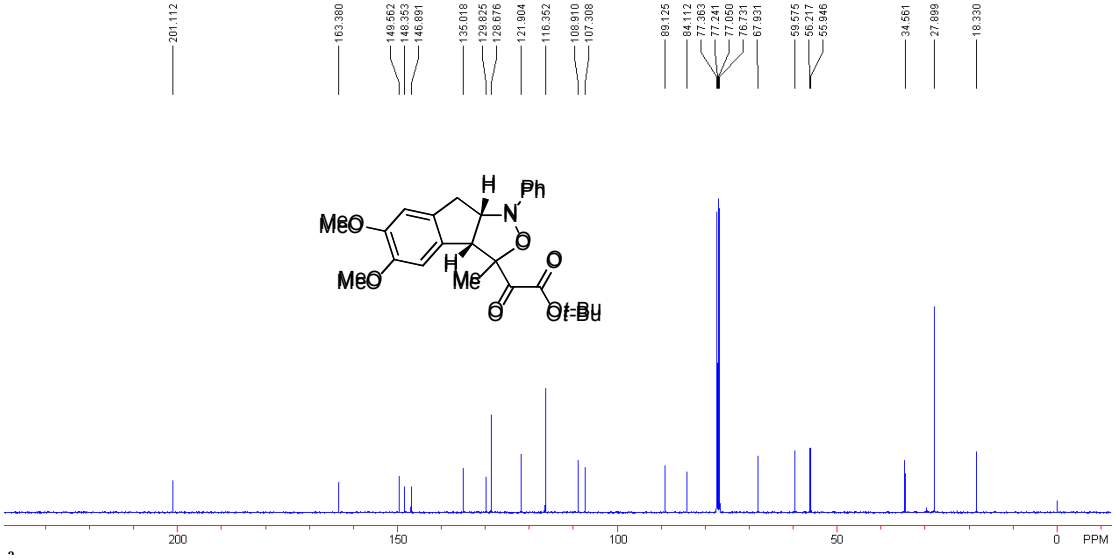
The ^{13}C NMR spectrum of **6j**



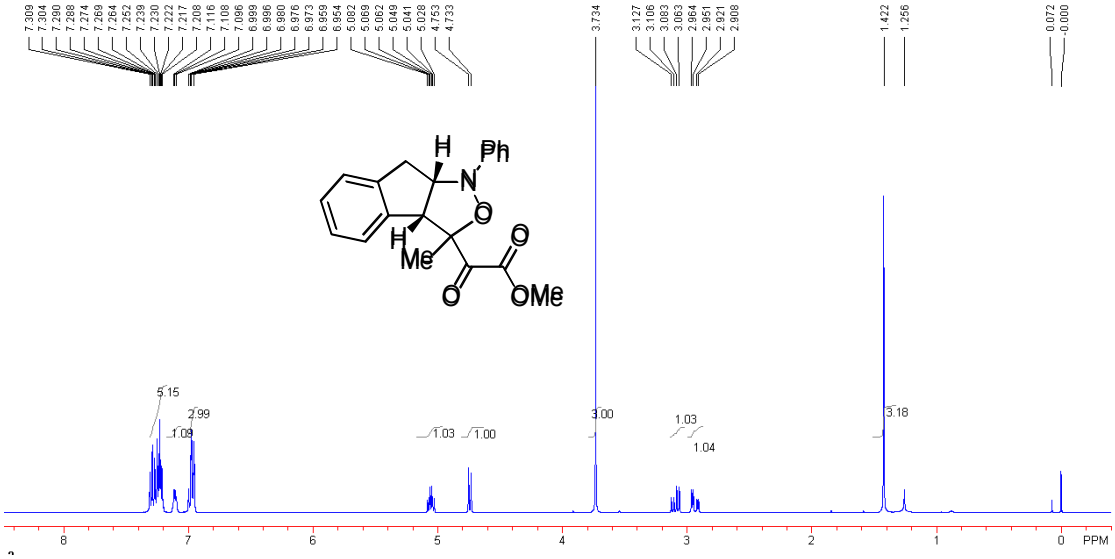
The ^{1}H NMR spectrum of **6k**



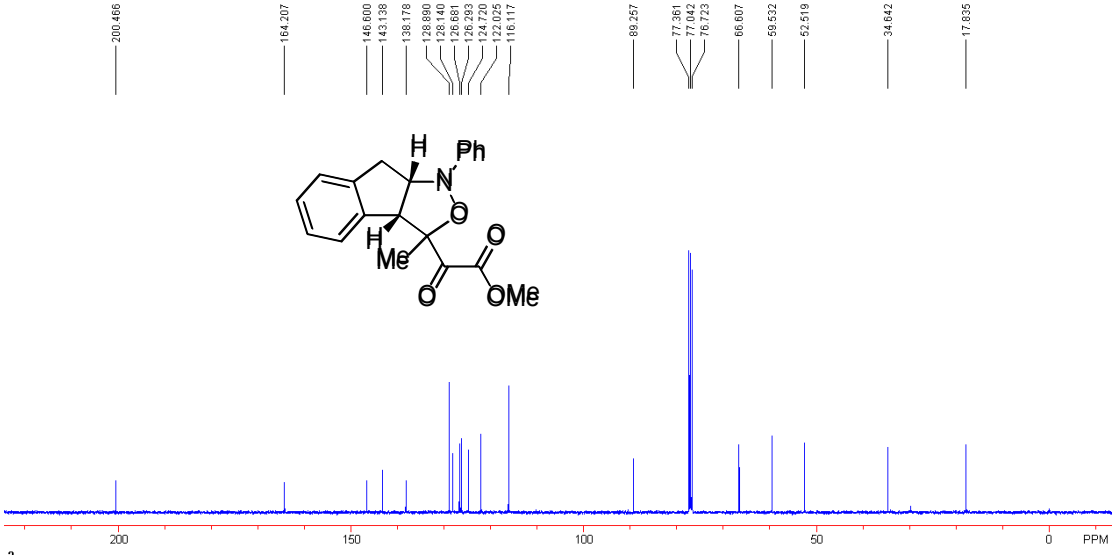
The ^{13}C NMR spectrum of **6k**



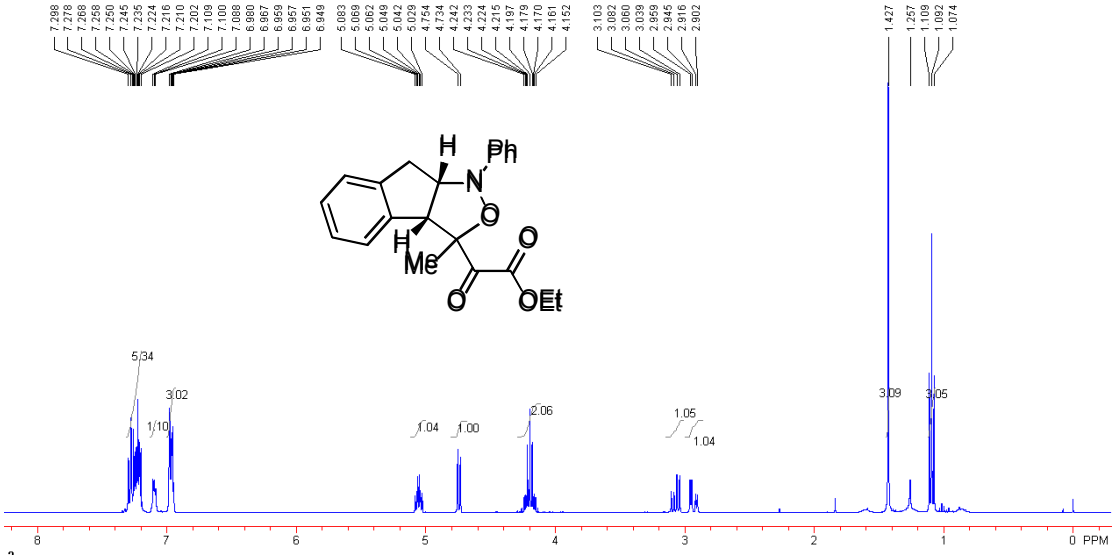
The ^{1}H NMR spectrum of **6m**



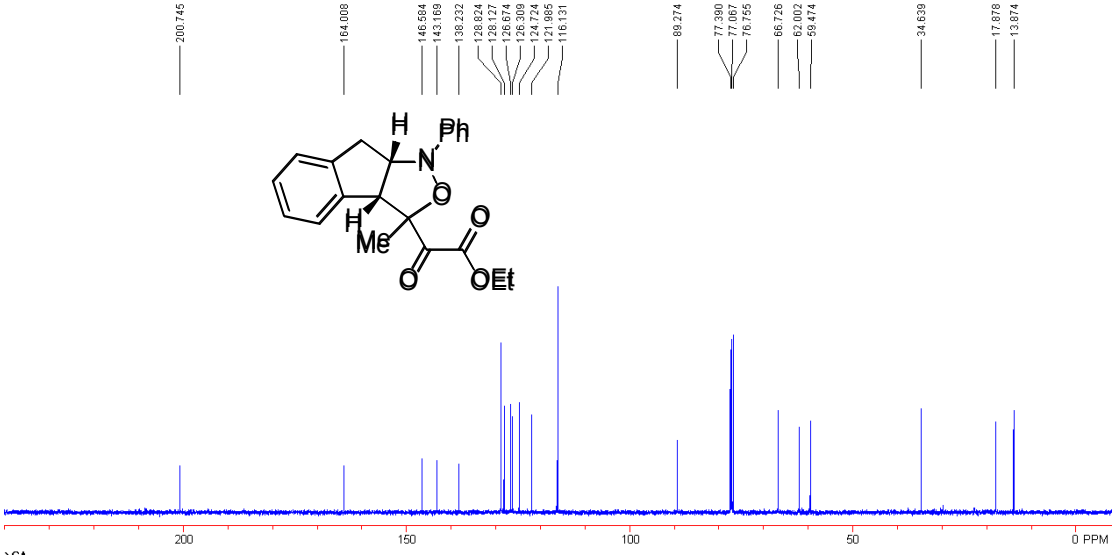
The ^{13}C NMR spectrum of **6m**



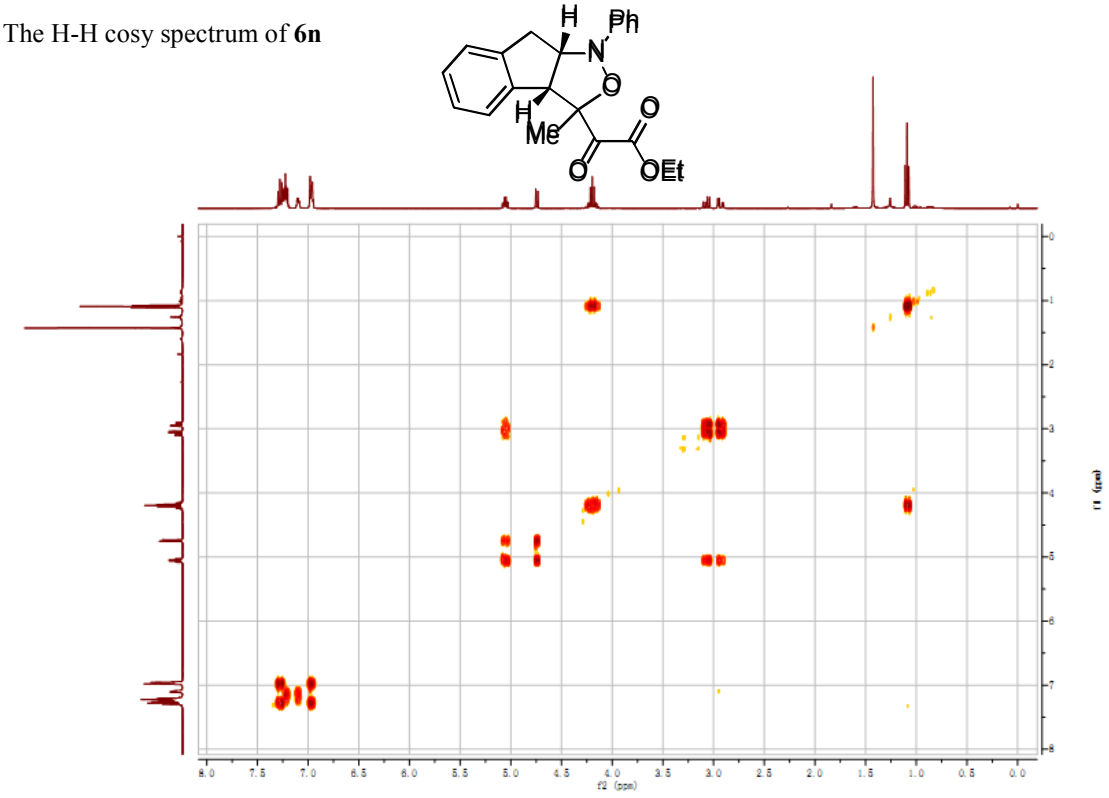
The ^{1}H NMR spectrum of **6n**



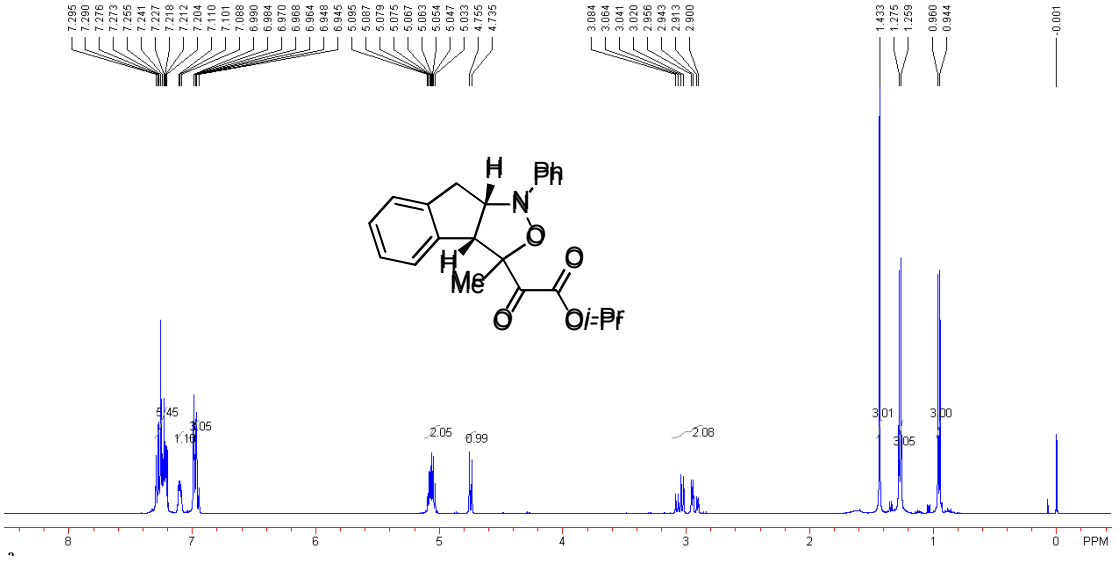
The ^{13}C NMR spectrum of **6n**



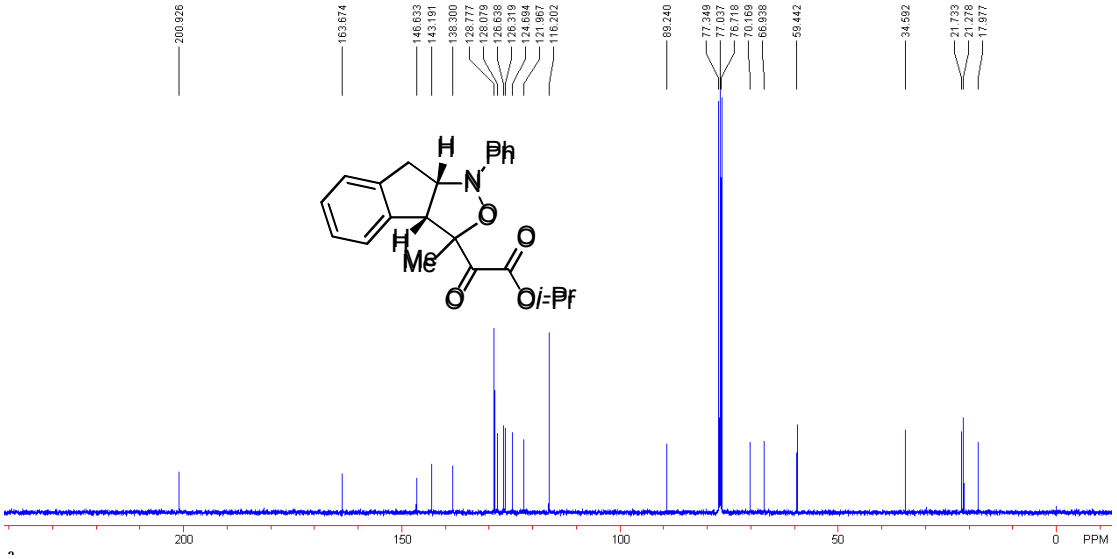
The H-H cosy spectrum of **6n**



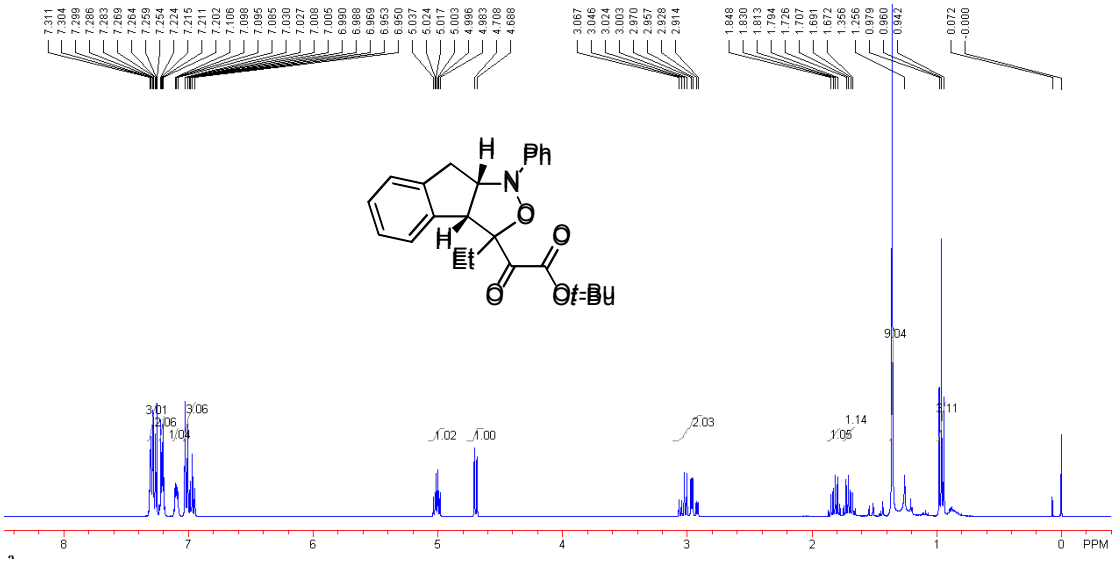
The ^{1}H NMR spectrum of **6o**



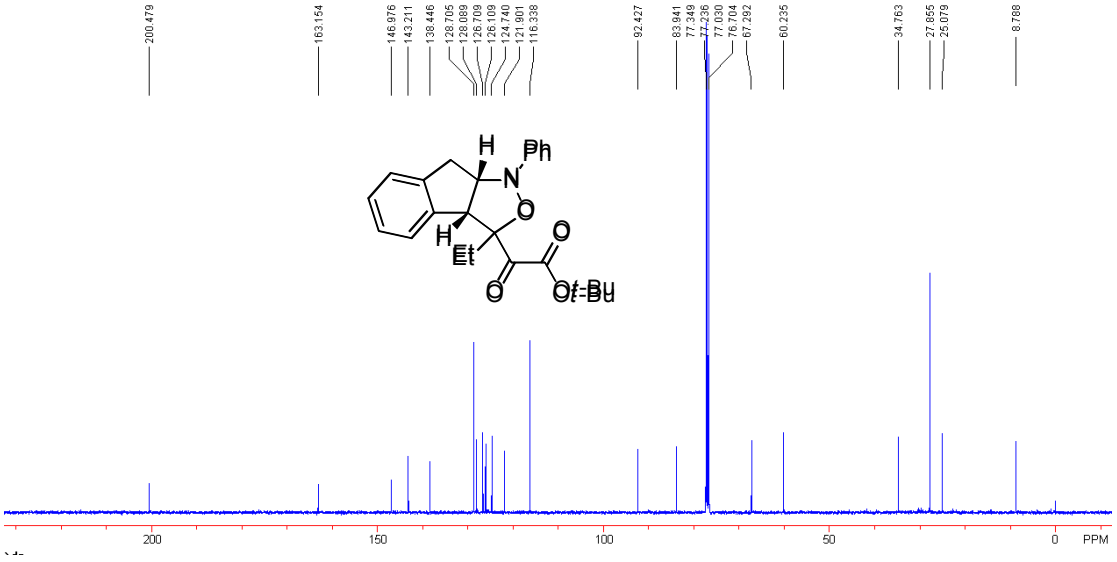
The ^{13}C NMR spectrum of **6o**



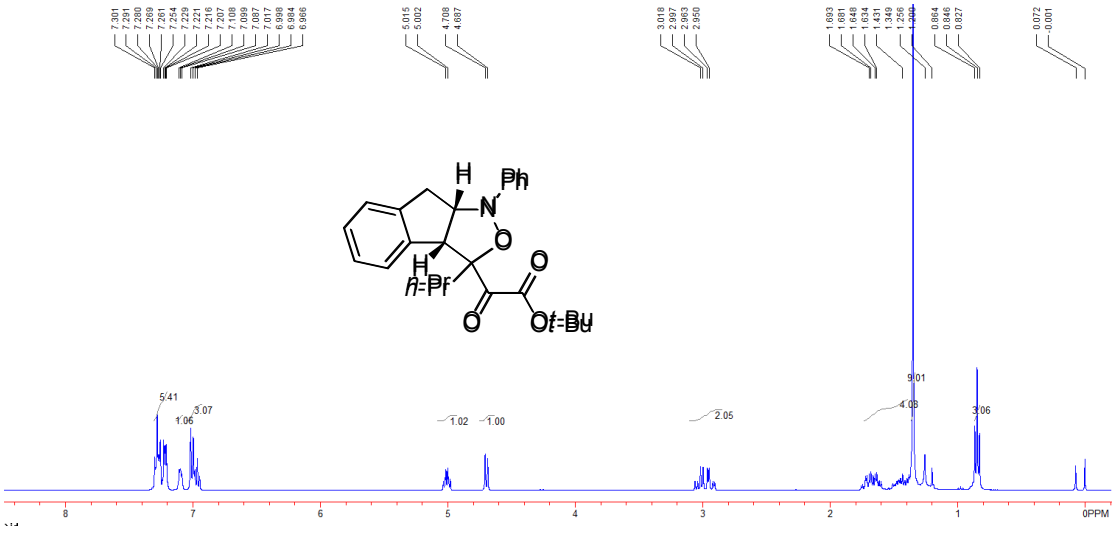
The ^{1}H NMR spectrum of **6p**



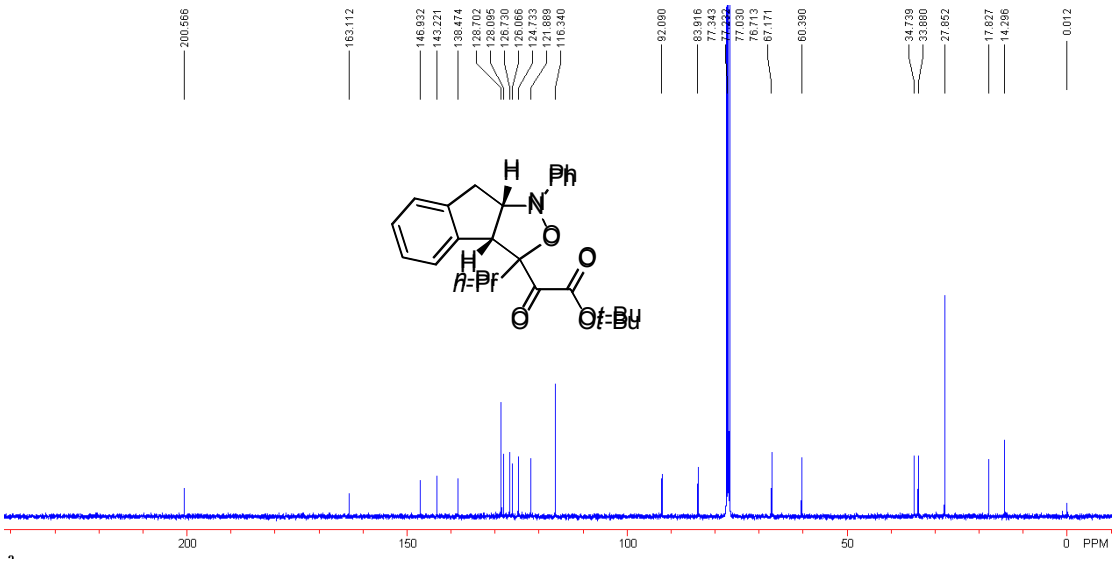
The ^{13}C NMR spectrum of **6p**



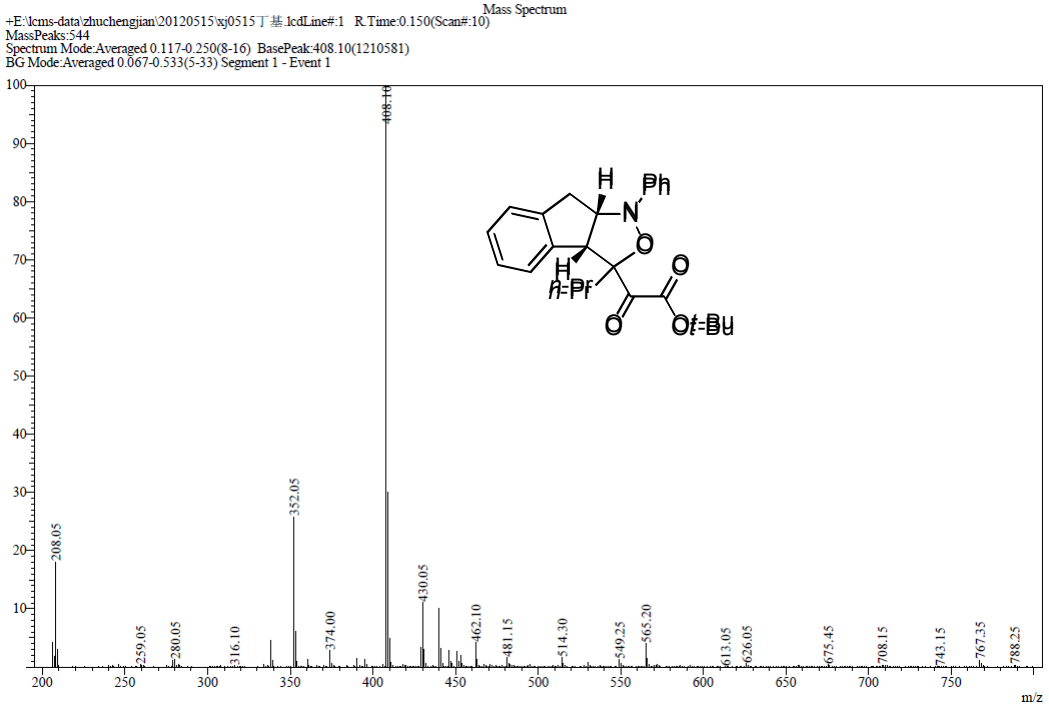
The ^{1}H NMR spectrum of **6q**



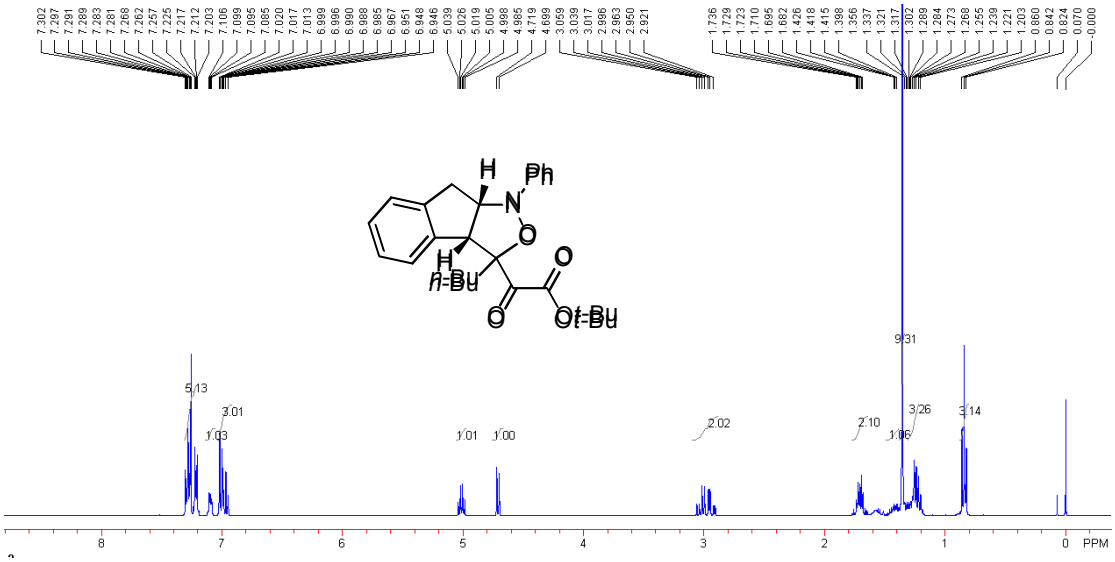
The ^{13}C NMR spectrum of **6q**



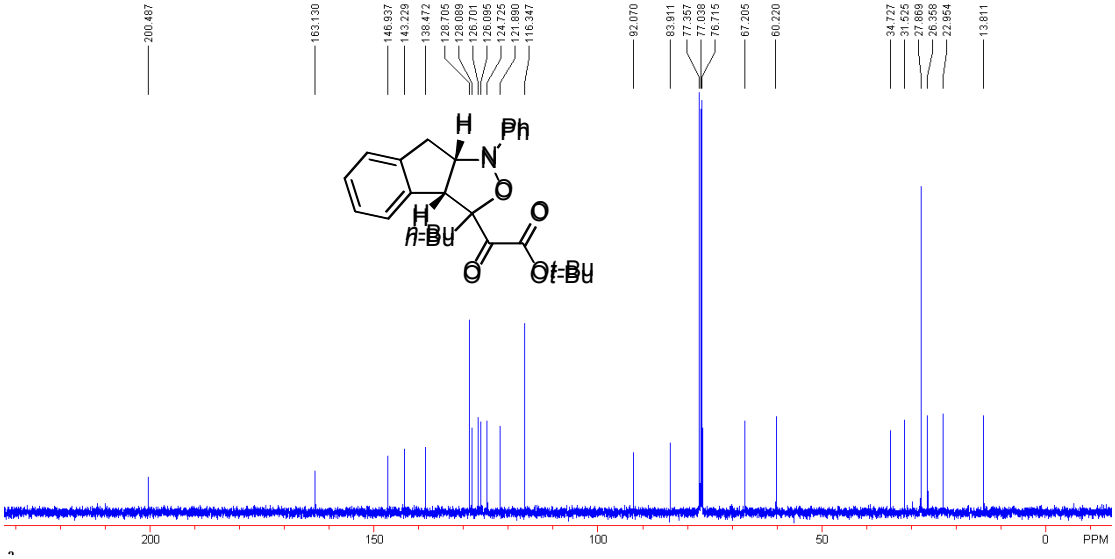
The MS(ESI) spectrum of **6q**



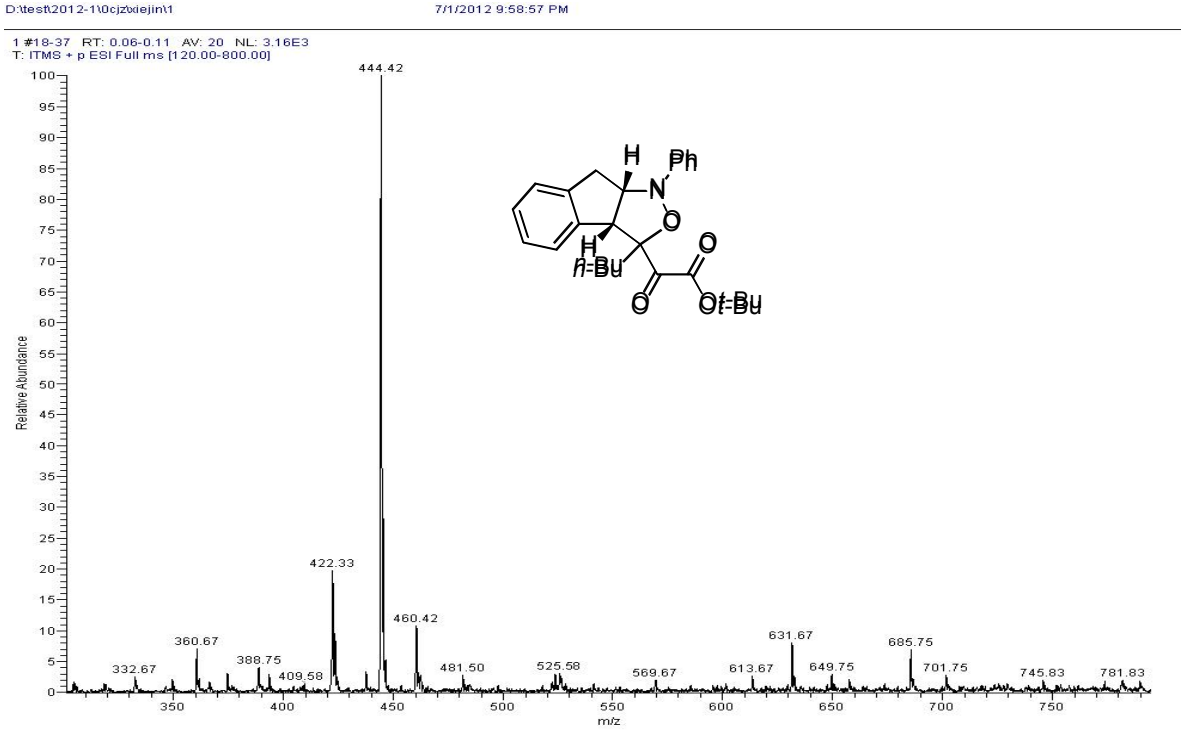
The ^{1}H NMR spectrum of **6r**



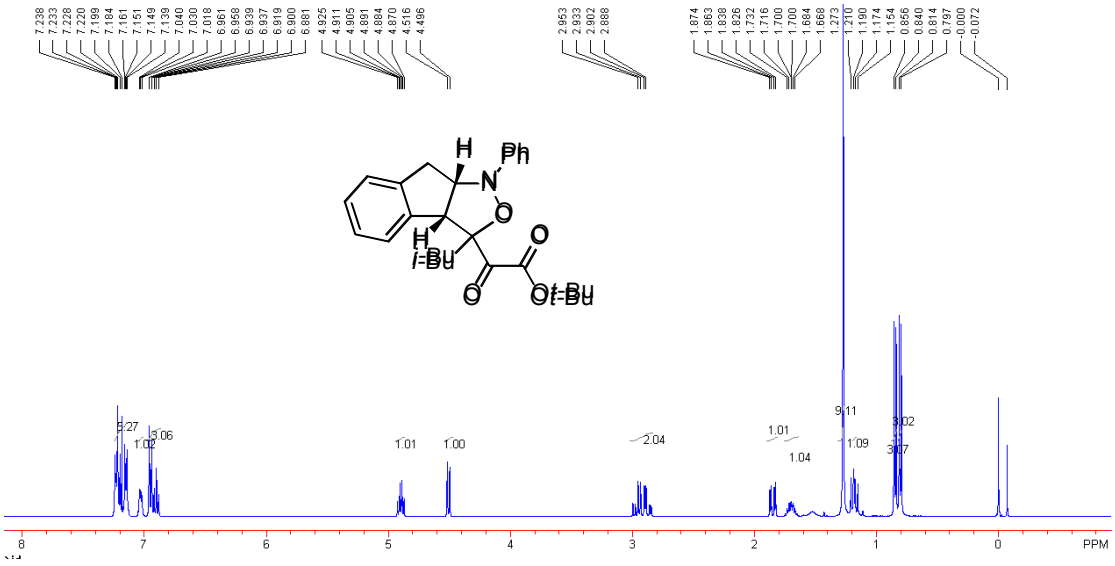
The ^{13}C NMR spectrum of **6r**



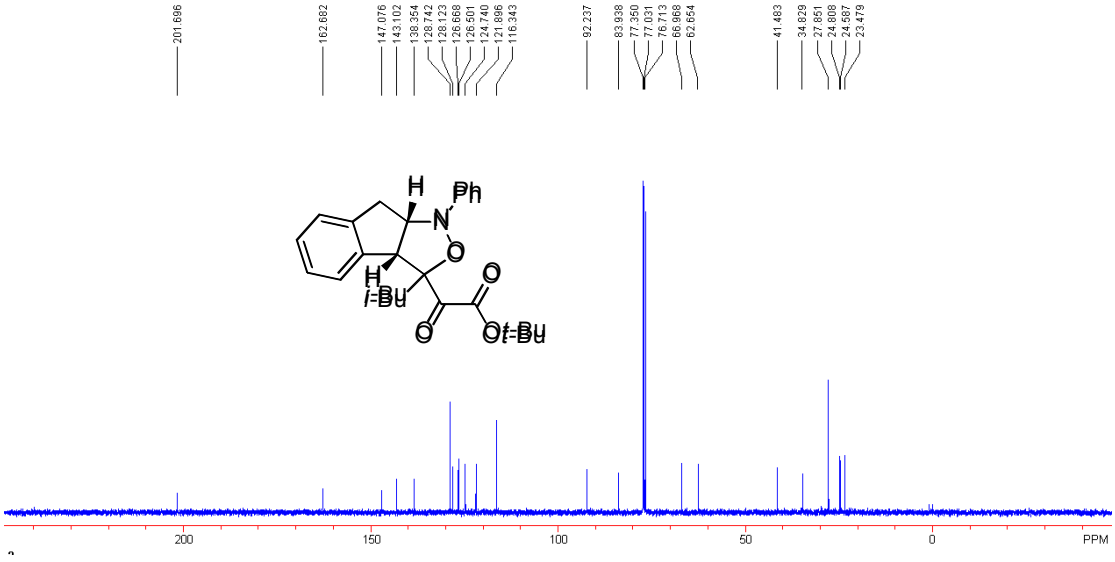
The MS (ESI) spectrum of **6r**



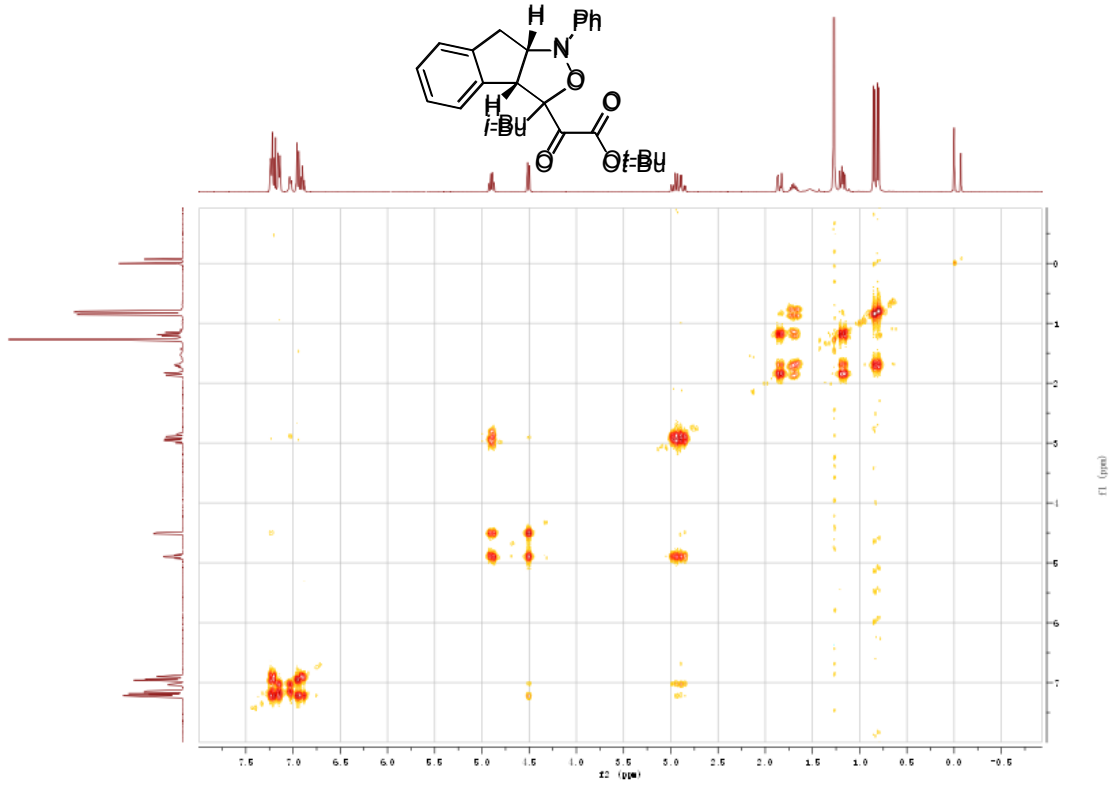
The ^{1}H NMR spectrum of **6s**



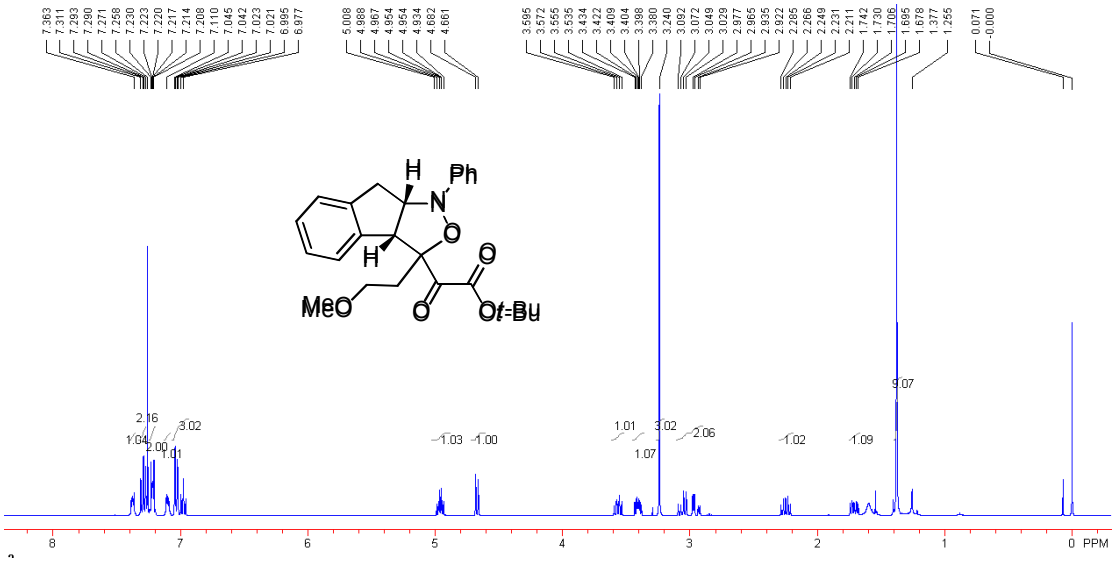
The ^{13}C NMR spectrum of **6s**



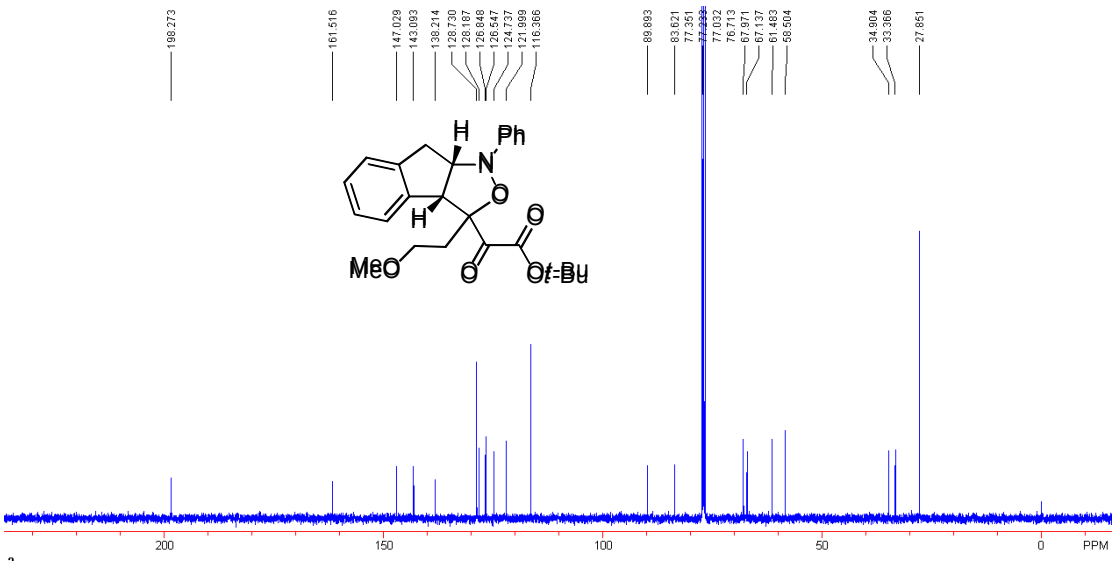
The H-H cosy spectrum of **6s**



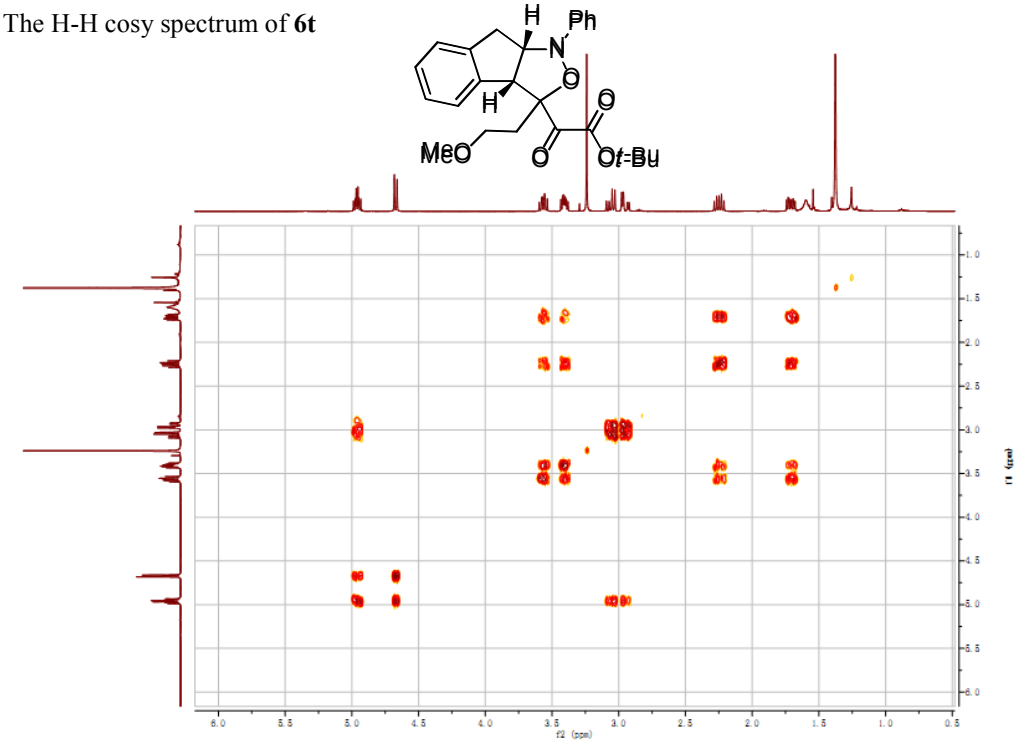
The ^{1}H NMR spectrum of **6t**



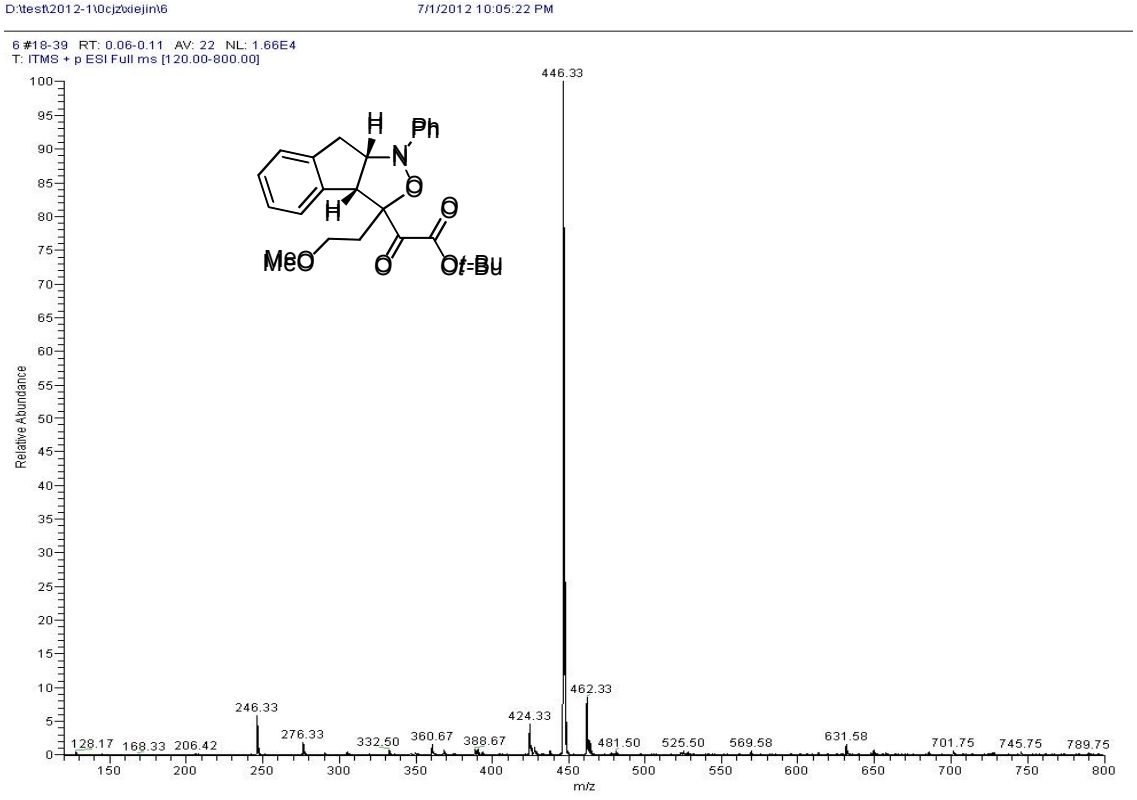
The ^{13}C NMR spectrum of **6t**



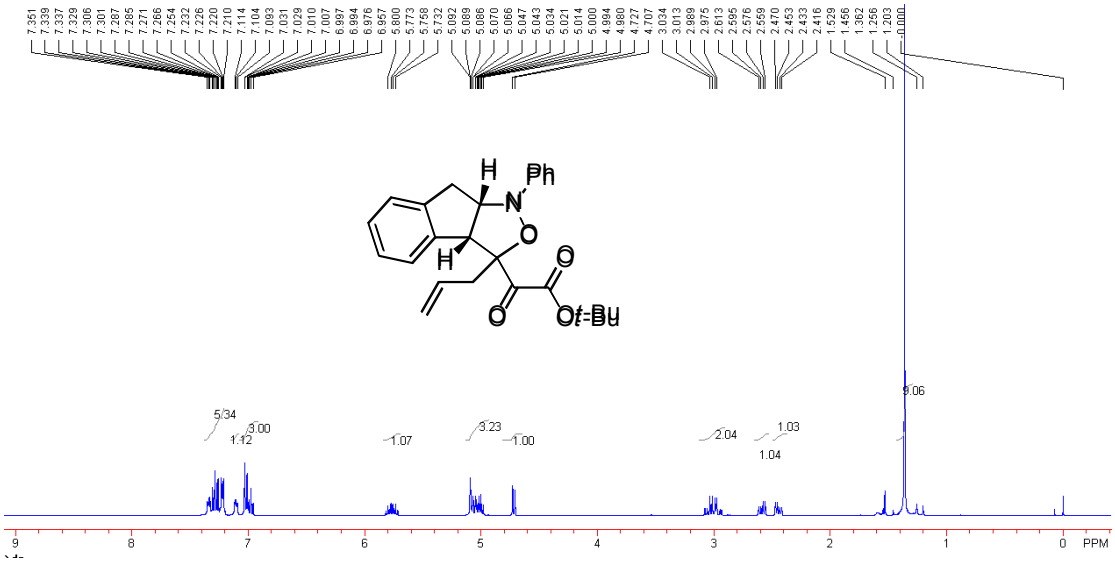
The H-H cosy spectrum of **6t**



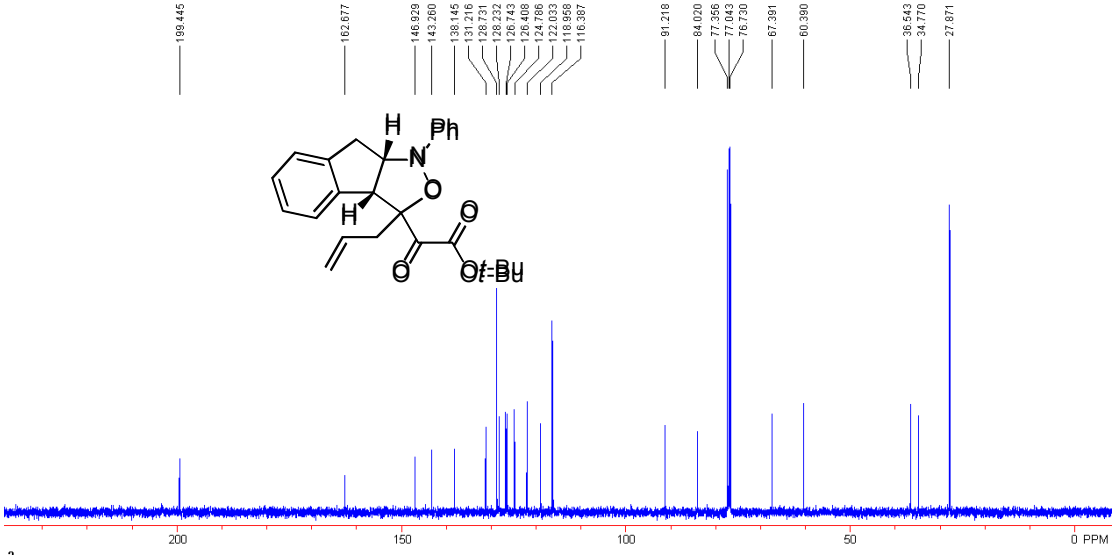
The MS(ESI) spectrum of **6t**



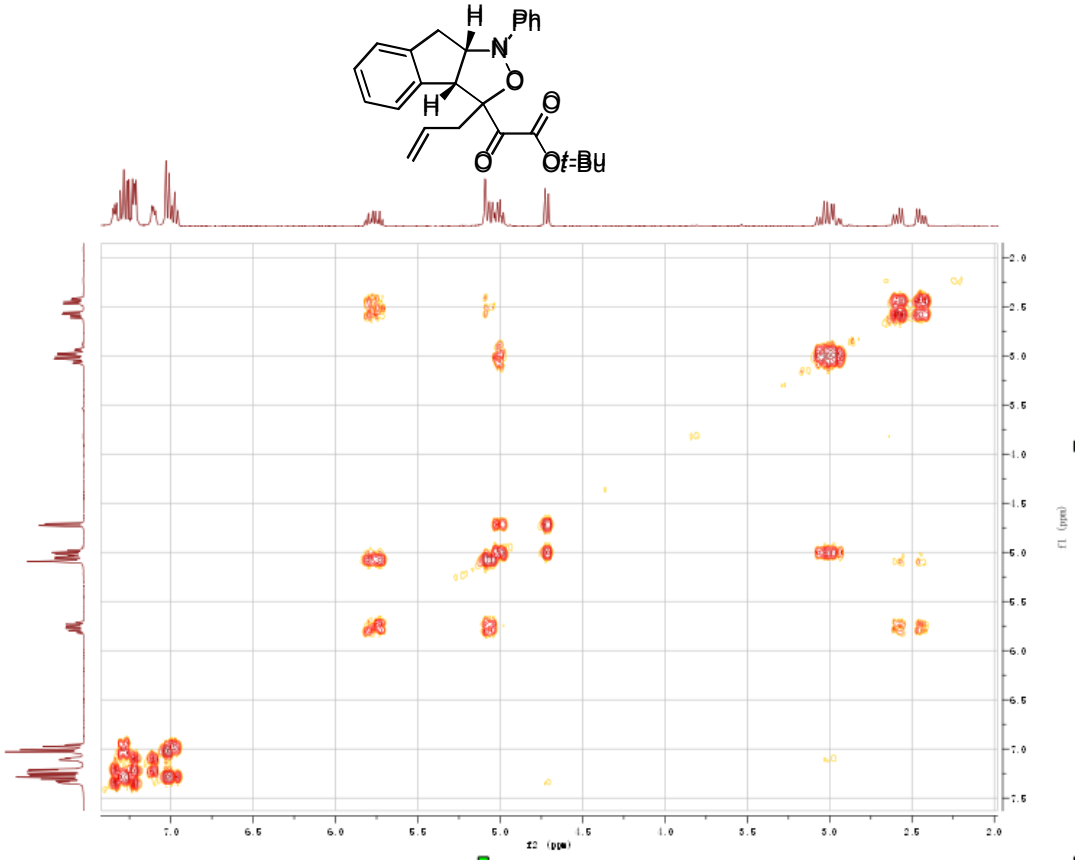
The ^{1}H NMR spectrum of **6u**



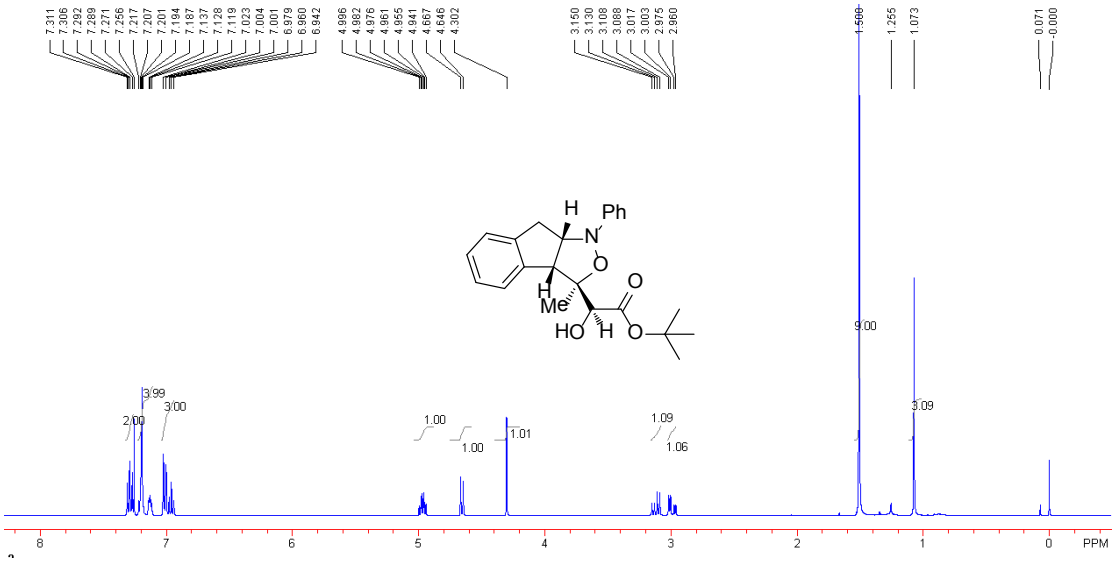
The ^{13}C NMR spectrum of **6u**



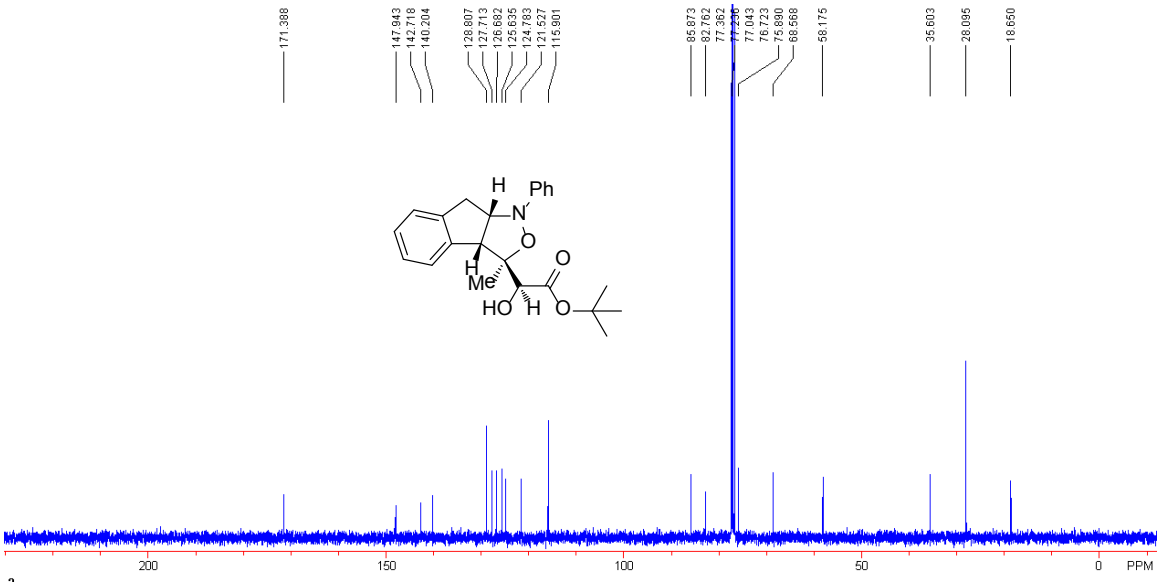
The H-H cosy spectrum of **6u**



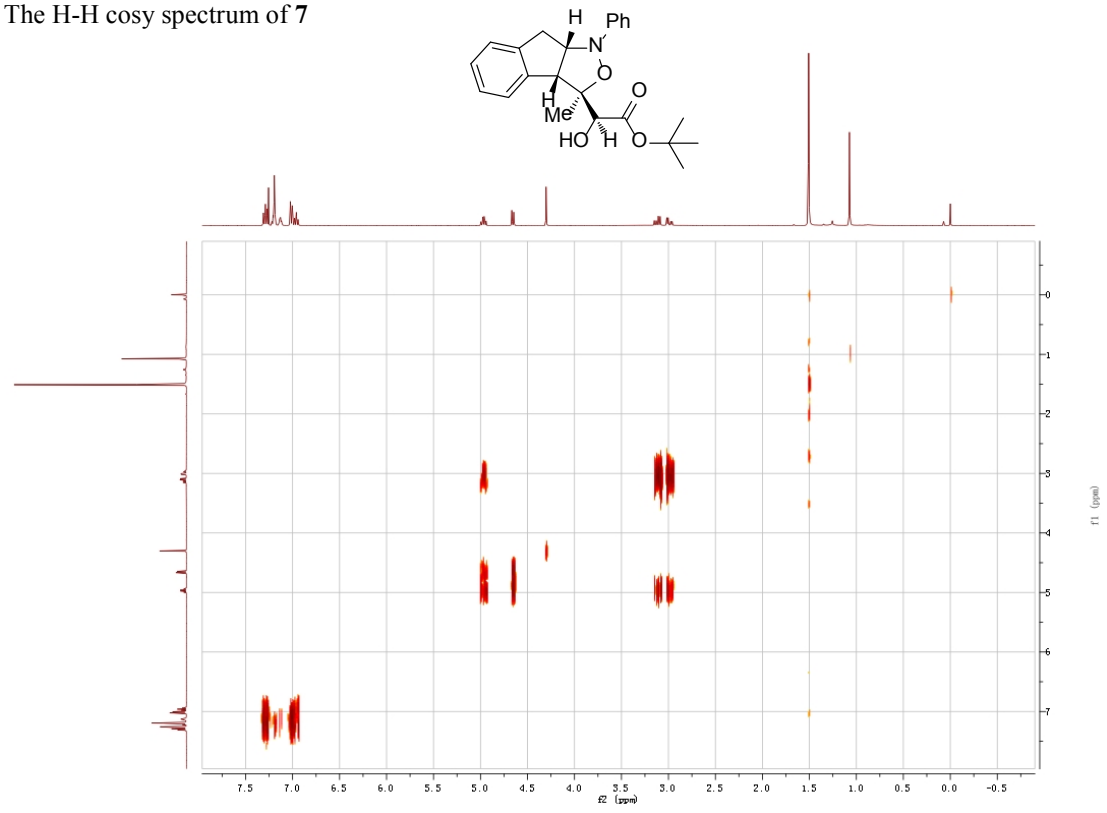
The ^{1}H NMR spectrum of **7**



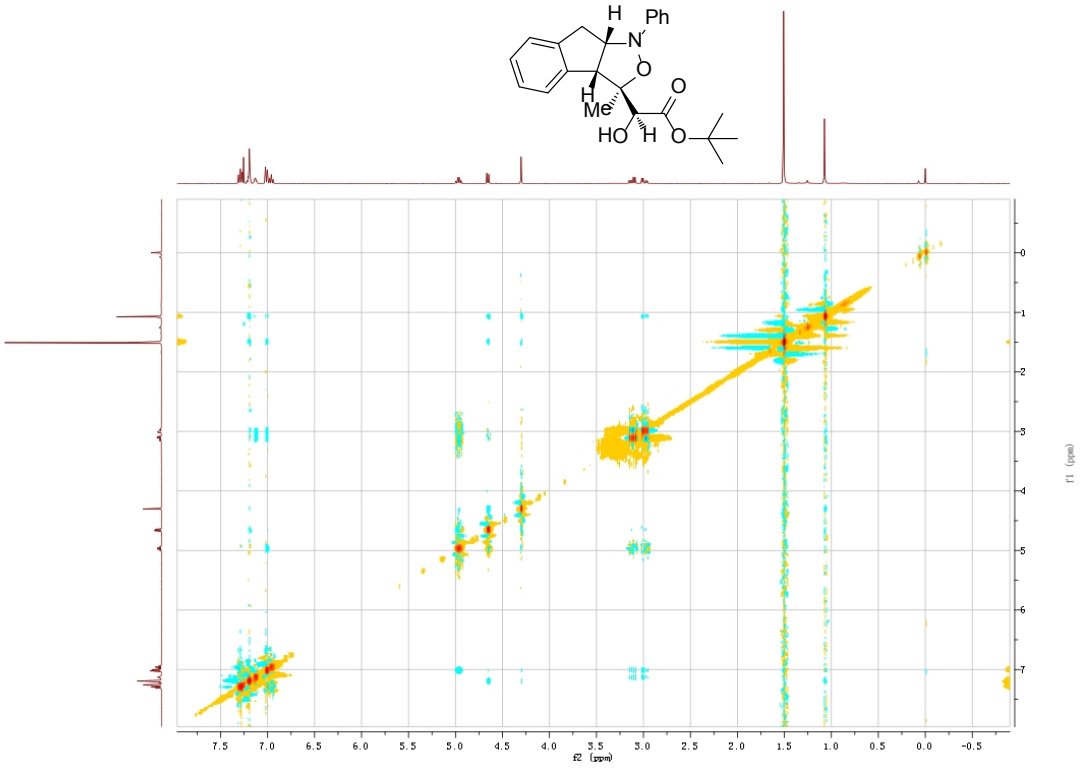
The ^{13}C NMR spectrum of **7**



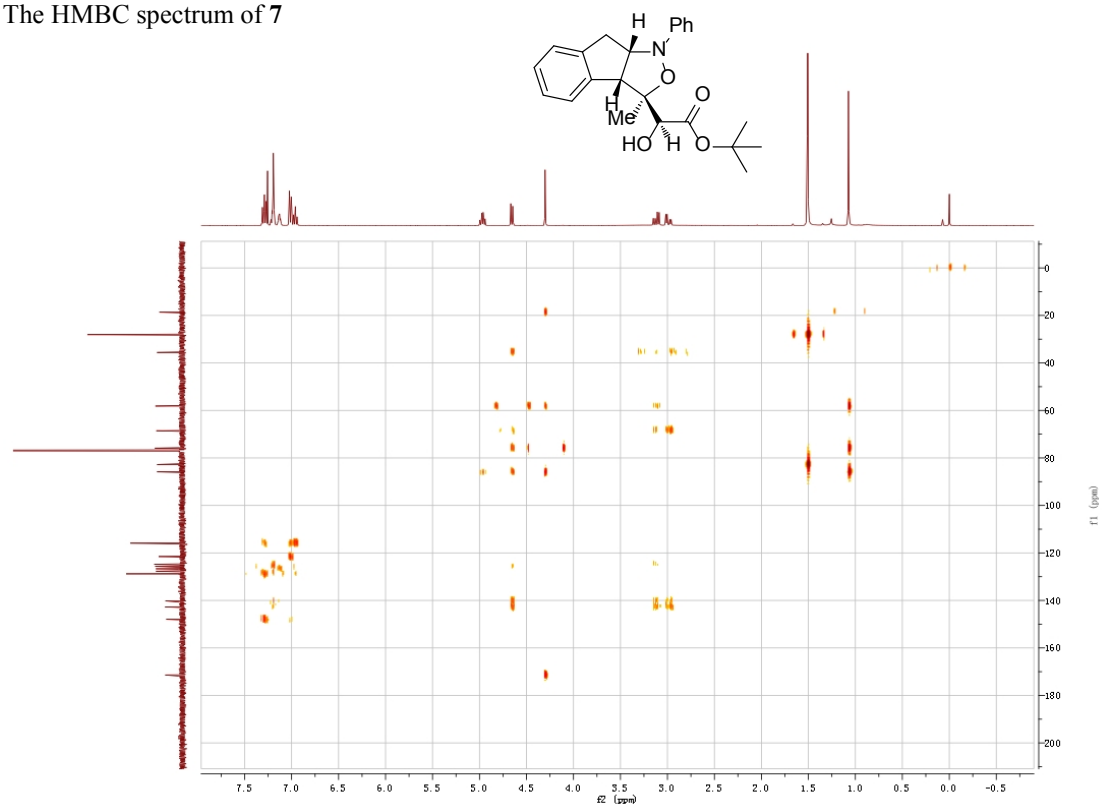
The H-H cosy spectrum of **7**



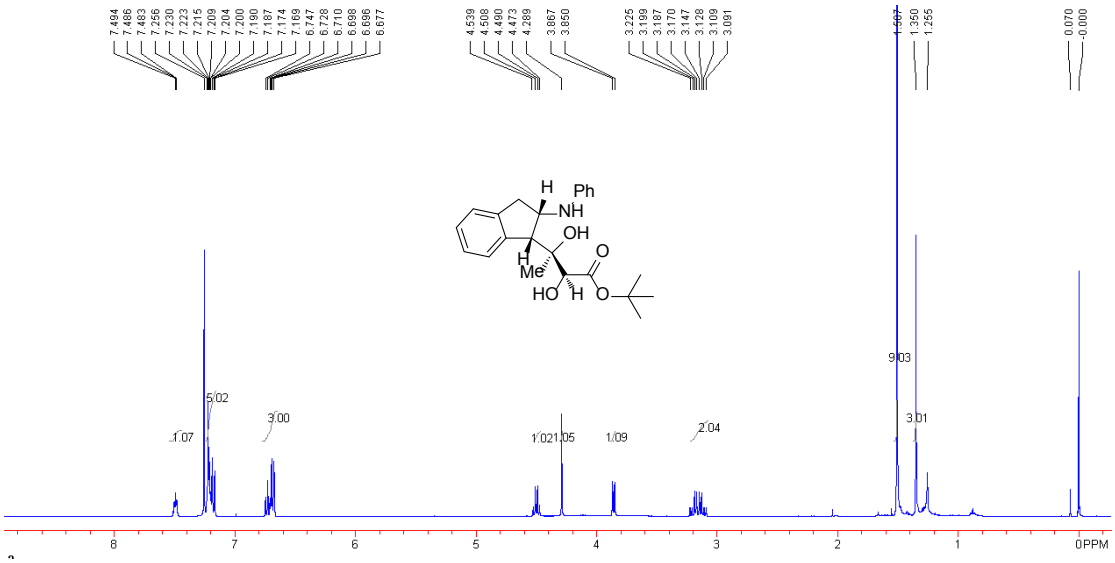
The noesy spectrum of **7**



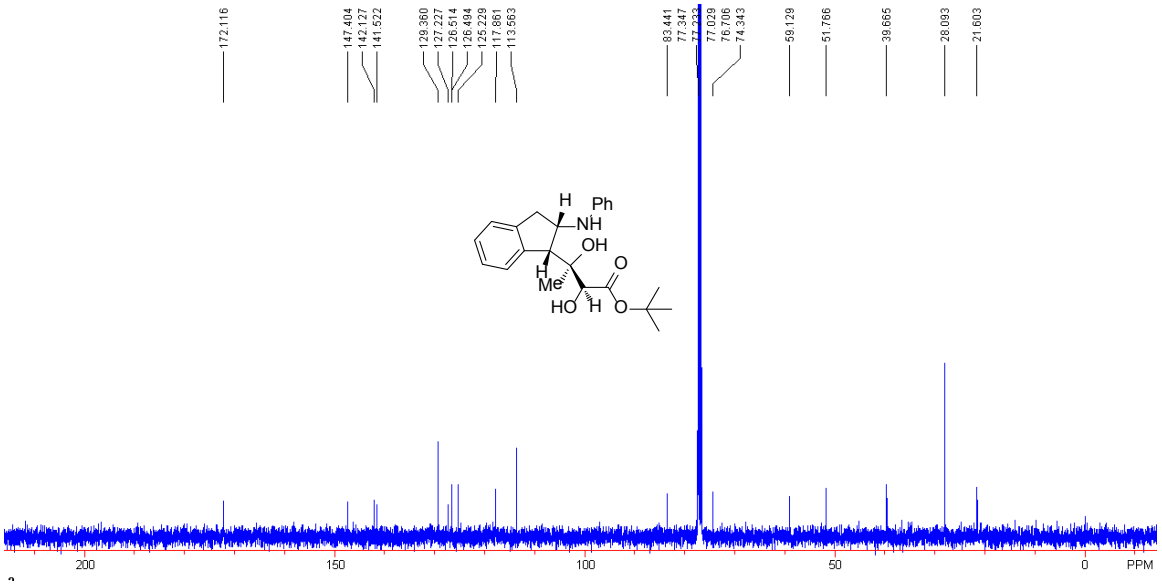
The HMBC spectrum of **7**



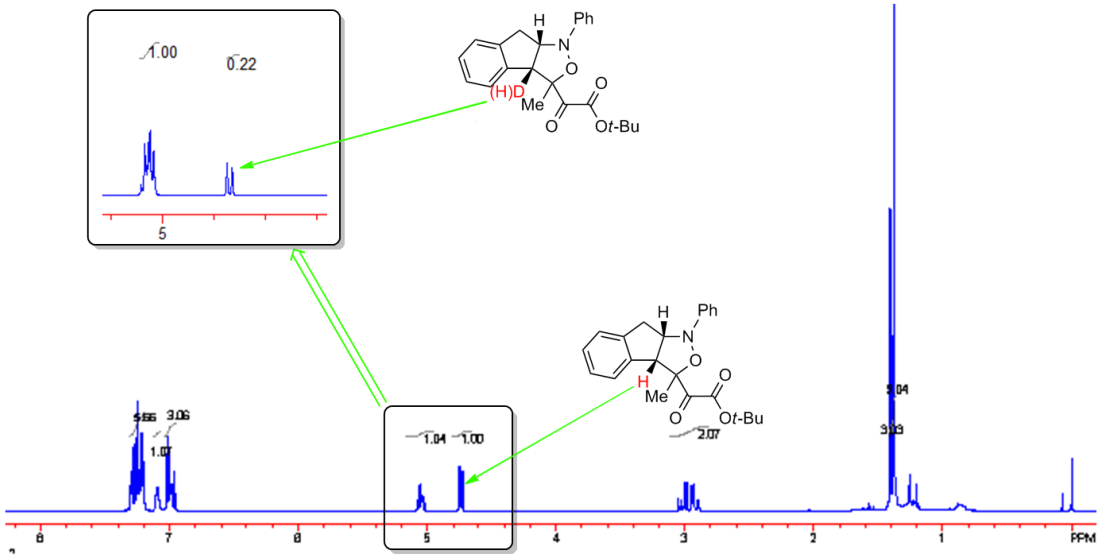
The ^{1}H NMR spectrum of **8**



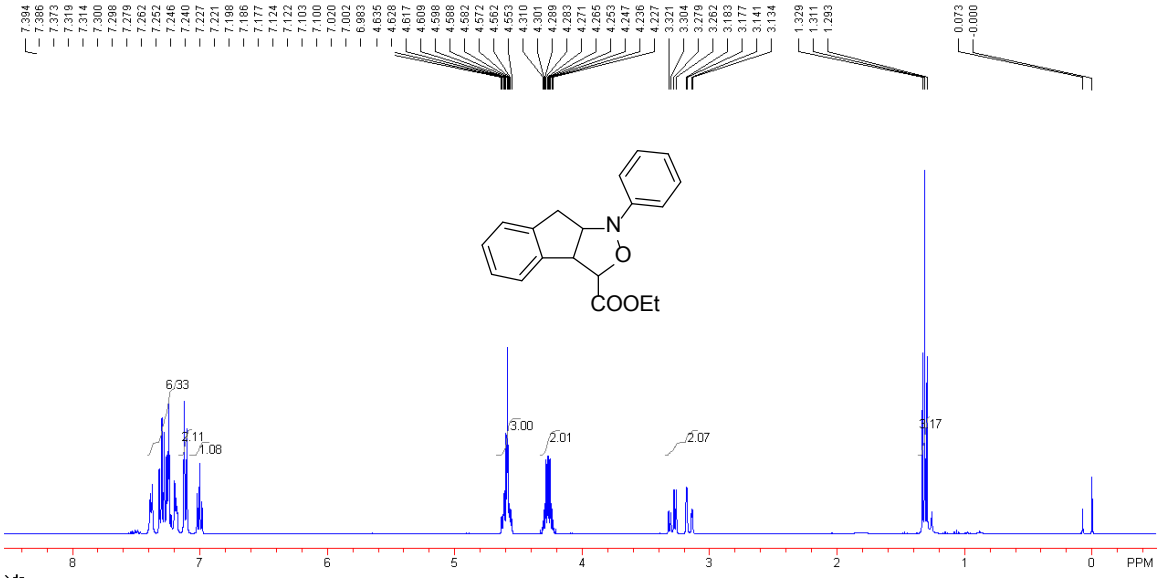
The ^{13}C NMR spectrum of **8**



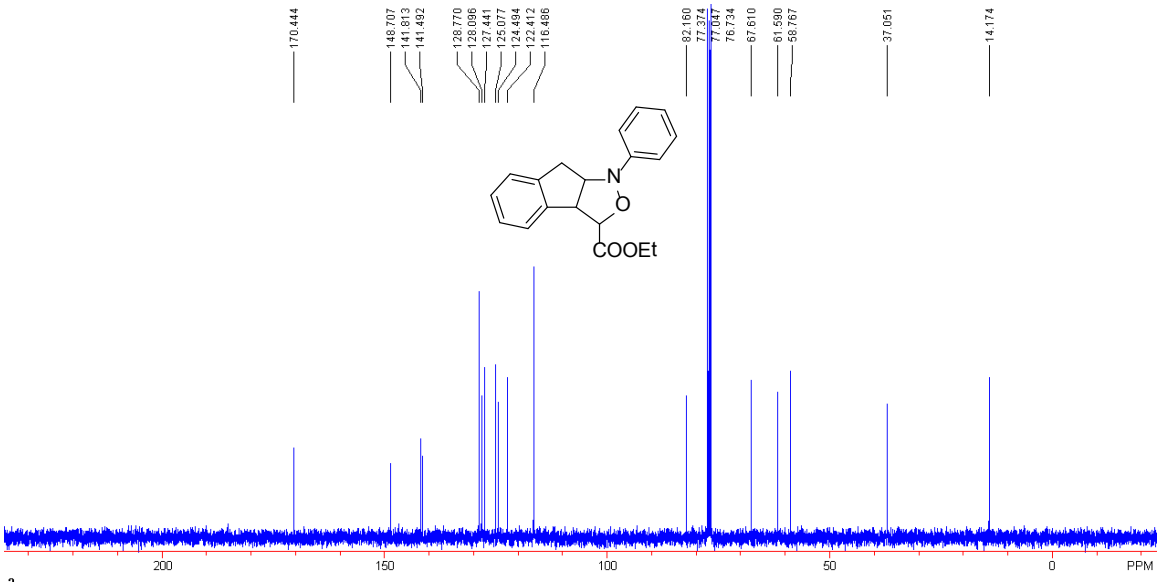
The ^{1}H NMR of labling expeiment (**6a** and **10**)



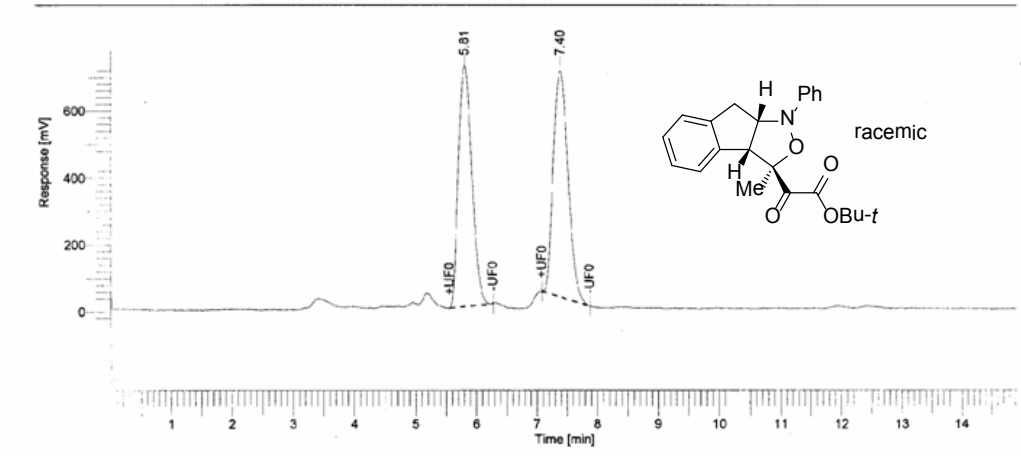
The ^{1}H spectrum of **G**



The ^{13}C spectrum of **G**



The HPLC trace of racemic product **6a**



色谱分析报告

分析结果

Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	Area/Height [s]
1	5.812	11096726.87	718655.48	49.21	49.21	15.4410
2	7.395	11452759.59	675998.53	50.79	50.79	16.9420
		22549486.47	1.39e+06	100.00	100.00	

The HPLC trace of product **6a** catalyzed by chiral ligand with metal (ee= 7%)

Software Version	: 6.3.2.0646	Date	: 2012-5-1 13:54:44
Operator	: manager	Sample Name	:
Sample Number	:	Study	:
AutoSampler	: NONE	Rack/Vial	: 0/0
Instrument Name	: PE LC	Channel	: A
Instrument Serial #	: None	A/D mV Range	: 1000
Delay Time	: 0.00 min	End Time	: 8.81 min
Sampling Rate	: 10.0000 pts/s		
Sample Volume	: 1.000000 ul	Area Reject	: 0.000000
Sample Amount	: 1.0000	Dilution Factor	: 1.00
Data Acquisition Time	: 2012-5-1 13:25:41	Cycle	: 1

Raw Data File : E:\Xie Jin\raw\xj 2012 0501 Au-Ru.raw
Result File : E:\Xie Jin\result\xj 2012 0501 Au-Ru.rst [Editing in Progress]
Inst Method : E:\Xie Jin\method\AD-95-5-1.0-210-1200-120 from E:\Xie Jin\raw\xj 2012 0501 Au-Ru.raw
Proc Method : E:\Xie Jin\method\AD-95-5-1.0-210-1200-120 from E:\Xie Jin\result\xj 2012 0501 Au-Ru.rst [Editing in Progress]
Calib Method : E:\Xie Jin\method\AD-95-5-1.0-210-1200-120 from E:\Xie Jin\result\xj 2012 0501 Au-Ru.rst [Editing in Progress]
Report Format File: C:\PenExe\TcWS\Ver6.3.2\Examples\HPLC REPORT SJT 01.rpt
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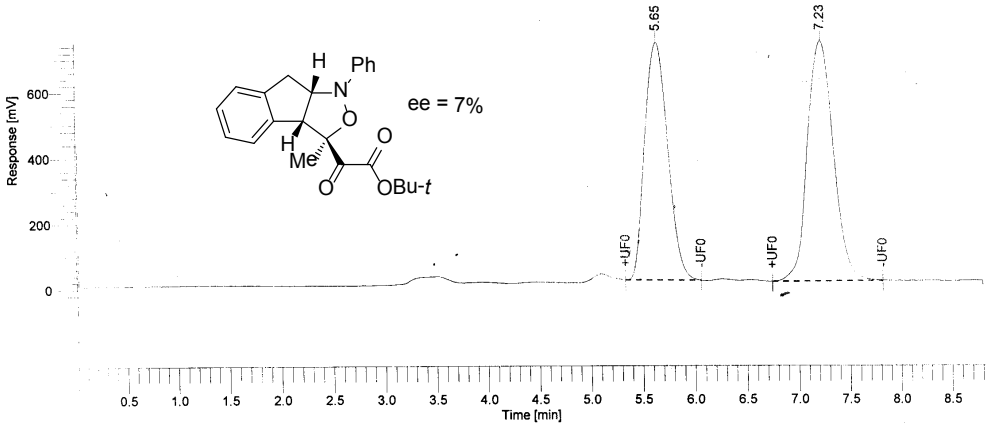

HPLC REPORT

HPLC REPORT

Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]	Norm. Area [%]	Raw Amount	Adjusted Amount
1		5.648	11108631.05	721763.13	46.47	46.47	11.1086	11.1086
2		7.230	12794820.89	727069.51	53.53	53.53	12.7948	12.7948
			23903451.94	1.45e+06	100.00	100.00	23.9035	23.9035

Missing Component Report

Component	Expected Retention (Calibration File)

All components were found

ANALYSIZED BY DATE

Part VII. X-ray structure analysis of bicyclic isoxazolidine 6a

Table 3. Crystal data and structure refinement for **6a (**CCDC 892907)

Identification Code	20120509B
CCDC deposition number	CCDC 892907
Empirical formula	$C_{23}H_{25}NO_4$
Formula weight	379.44
Crystallization Solvent	propan-2-ol
Data Collection	
Temperature	296 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space Group	P2(1)/c
Unit cell dimensions	a = 18.485(12) Å α = 90.00 b = 5.944(3) Å β = 92.841(13) c = 18.057(12) Å γ = 90.00
Volume	1982(2) $Å^3$
Z	4
Density (calculated)	1.272 mg/m^3
Absorption coefficient	0.087
F(000)	808
Crystal size, color, habit	0.28 x 0.16 x 0.16 mm, colorless, rod-like
Theta range for data collection	2.56-22.81 ^{o}
Index ranges	-21≤h≤21, -6 ≤k≤7, -21≤l≤21
Reflections collected	9500
Independent reflections	3353
Reflections with I > 2(Fo)	1681
Absorption correction	'multi-scan'
Max. and min. transmission	0.9863, 0.9761
Structure Solution and Refinement	
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	1681/0/257
Goodness-of-fit on F2	1.027
Final R indices [I > 2 sigma(I)]	R1 = 0.0684, wR2 = 0.1592
R indices (all data)	R1 = 0.1235, wR2 = 0.1862
Largest diff. peak and hole	0.247 / -0.283 $eÅ^{-3}$

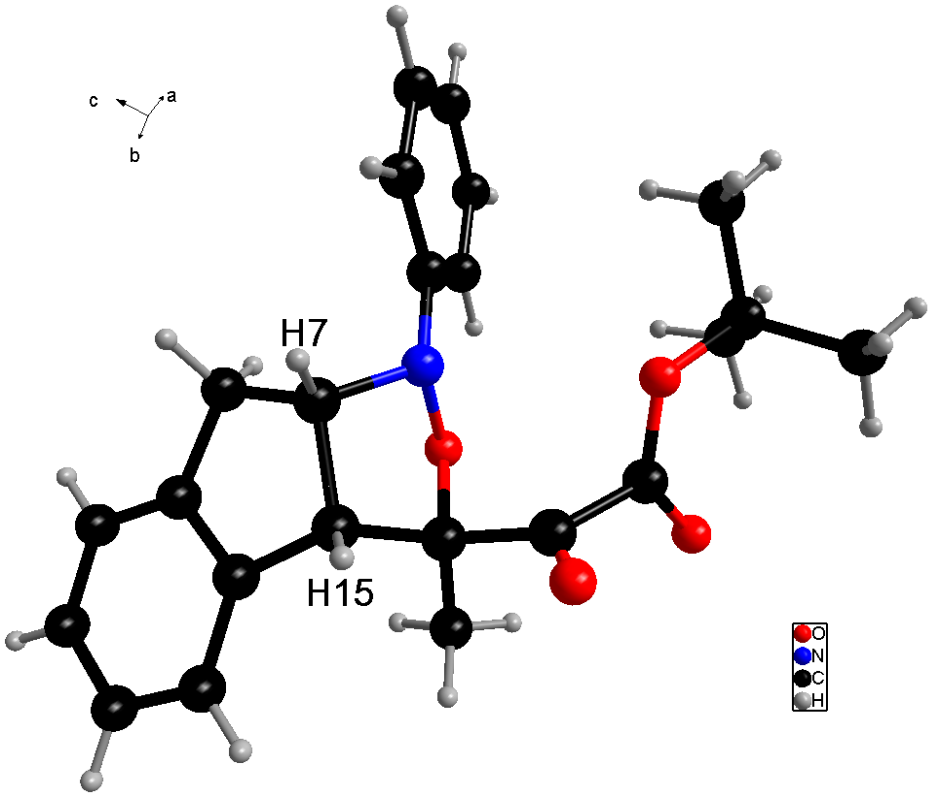

Figure 2. Single X-ray structure of **6a**