Supporting Information

Efficient Synthesis of Bioactive Isoindolinone Derivatives Containing Continuous Quaternary Carbons by Intermolecular OH Transfer

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1. General information

All ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded on Brucker spectrometers in $CDCl_3$. Tetramethylsilane (TMS) served as an internal standard ($\delta = 0$) for ^{1}H NMR, and CD_3OD, CD_3CN or $CDCl_3$ was used as internal standard ($\delta = 49.0$, $\delta = 1.3$, 118.3 or $\delta = 77.0$) for ^{13}C NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). High-resolution mass spectrometry (HRMS) was performed on IonSpec FT-ICR mass spectrometer. Single crystal X-ray diffraction data were recorded on Bruker-AXS SMART APEX II single crystal X-ray diffractometer. Yields for all compounds were combined yields for all isomers unless otherwise indicated.

3-Hydroxyisoindolin-1-ones **3**[1] and diazo compounds[2] were prepared according to the literature methods. The benzyl alcohols were purchased from Sahn Chemical Technology Ltd and used without further purification. All reactions and manipulations were carried out under air atmosphere in a flame-dried or oven-dried flask containing magnetic stir bar. Dichloromethane (DCM), 1,2-dichloroethane (DCE), THF and toluene was distilled over calcium hydride. Solvents for the column chromatography were distilled before use.

Expression and purification of SARS-CoV-2 $3CL^{pro}$ was performed according to our previous methods.[3] The plasmids were transformed into BE21 (DE3) cells, *E. coli* was incubated and grown overnight as starter cultures. Then it was used to expand the culture at a 1:50 dilution, and then the cultures were further grown at 220 rpm, 37 °C until the OD600 reached 0.6-0.7. Protease expression was induced by addition of 0.3 mM IPTG, the cultures were incubated at 18 °C, 180 rpm for 16 h. Collected cells were sonicated in buffer (25 mM Tris, 150 mM NaCl, 20 mM imidazole, 1 mM DTT, pH 7.4) and the lysate was centrifuged at 4 °C for 30 min at 12000 rpm. 2 mL of Ni NTA agarose (GE Healthcare) was added to the supernatant for binding overnight. The miscellaneous proteins were eluted with a low concentration of imidazole, and the SARS-CoV-2 $3CL^{pro}$ was eluted with 300 mM

imidazole. SARS-CoV-2 $3CL^{pro}$ was dialyzed through a dialysis membrane with a truncated molecular weight of 10 kDa and stored in solution (25 mM HEPES, 150 mM NaCl, 1 mM DTT, pH 7.4) for experiments.

The in *vitro* SARS-CoV-2 $3CL^{pro}$ bioactivity was detected by our previous method.[3] The fiuorogenic peptide Dabcyl-KNSTLQSGLRK-Edans was synthesized (Genscript, Nanjing, China), then resuspended in DMSO at 10 mM and used as a substrate. For the measurement of inhibition ratio, SARS-CoV-2 $3CL^{pro}$ in the assay buffer (1×PBS, 1 mM EDTA, pH 7.4) was added to 96 well plate at a final concentration of 0.12 μM. Test compounds were prepared in assay buffer and then added to the wells for 30 min at 37 °C. Substrates were added at 20 μM to initiate the reaction for 20 min at 37 °C. The fluorescence (Excitation 340 nm, Emission 490 nm) was measured using a Cytation 5 plate reader (BioTek, USA). Data were processed through GraphPad Prism 8.0.

2. Optimization of reaction conditions

Scheme S1. Exploring the effect of varying the equivalent of H_2O on yield

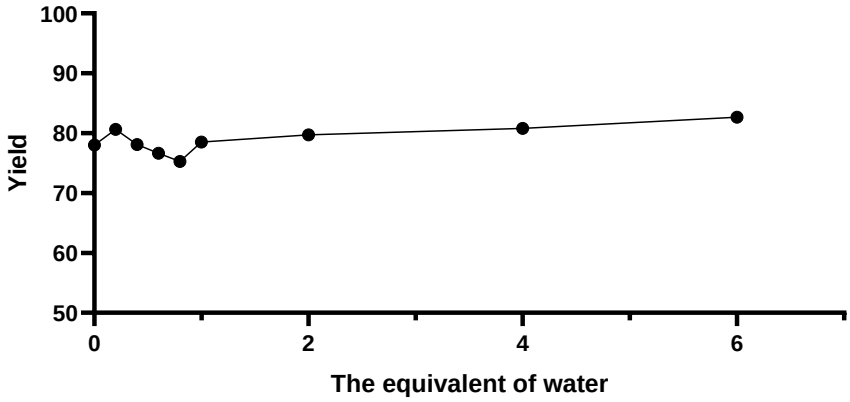
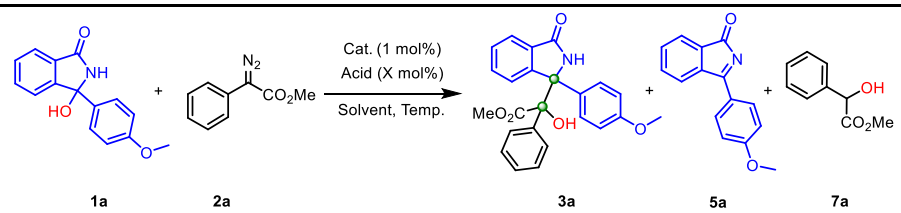


Table S1. Optimization of reaction conditions[a]

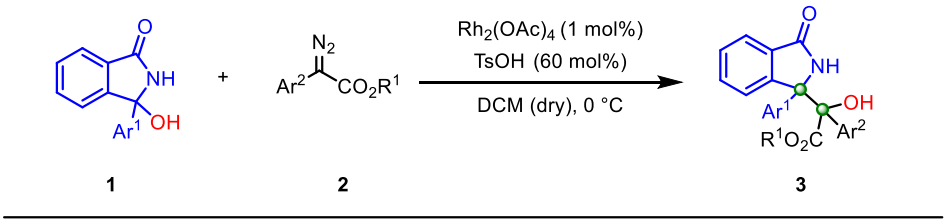


entry	temp. (°C)	catalyst	acid	solvent	x (mol%)	yield[b] (%)	dr[c]
1	25	$Rh_2(OAc)_4$	TsOH	DCM[d]	60	78	1:2
2	25	$Rh_2(OAc)_4$	TsOH	DCM	60	80	1:2
3	25	$[PdCl(\eta^3\text{-}C_3H_5)]_2$	TsOH	DCM	60	71	1:2
4	25	Rh_2(s-nttl)$_4$	TsOH	DCM	60	73	1:2
5	25	$Cu(OTf)_2$	TsOH	DCM	60	<5	1:2
6	25	$Rh_2(OAc)_4$	H_3PO_4	DCM	60	70	1:2
7	25	$Rh_2(OAc)_4$	CH_3SO_3H	DCM	60	73	1:2
8	25	$Rh_2(OAc)_4$	CF_3COOH	DCM	60	53	1:2
9	25	$Rh_2(OAc)_4$	CH_3COOH	DCM	60	64	1:2
10	-20	$Rh_2(OAc)_4$	TsOH	DCM	60	84	1:2
11	0	$Rh_2(OAc)_4$	TsOH	DCM	60	88	1:2
12	40	$Rh_2(OAc)_4$	TsOH	DCM	60	73	1:2
13	0	$Rh_2(OAc)_4$	TsOH	DCE	60	77	1:2
14	0	$Rh_2(OAc)_4$	TsOH	Toluene	60	74	1:2
15	0	$Rh_2(OAc)_4$	TsOH	THF	60	80	1:2
16	25	$Rh_2(OAc)_4$	TsOH	DCM	10	69	1:2
17	25	$Rh_2(OAc)_4$	TsOH	DCM	60	83	1:2
18	25	$Rh_2(OAc)_4$	TsOH	DCM	90	84	1:2
19	25	$Rh_2(OAc)_4$	TsOH	DCM	120	82	1:2

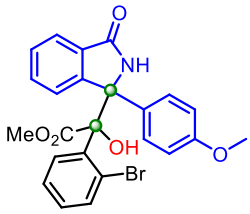
[a] Unless otherwise noted, all reactions were conducted on a 0.1 mmol scale of **1a**, **1a**:**2a** = 1:1.5 and solvents were of analytical reagent grade. Due to the lower reaction yield when **1a**:**2a** was in a 1:1 ratio after 4 hours, the equivalent of **2a** was increased to 1.5, allowing **1a** to be fully reacted within 4 hours. [b] Combined yield of *anti*- and *syn*-isomers after isolation. [c] The ratio of diastereomers (dr) was determined by ^{1}H NMR of the crude products. [d] The reaction of entry 1 proceeded with ultradry solvent.

3. Examples of unreactive substrates

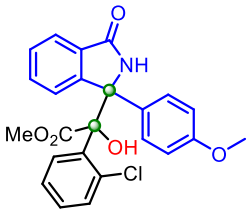
Scheme S2. Examples of unreactive substrates[a]



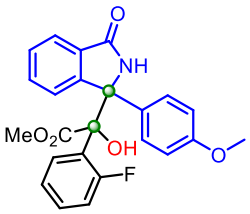
1 **2** **3**



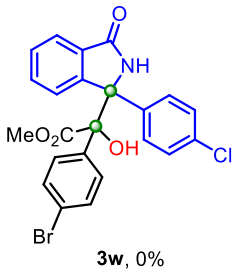
3t, 0%



3u, 0%



3v, 0%

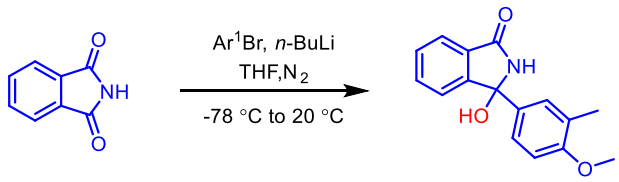


3w, 0%

[a] Unless otherwise noted, all reactions were conducted in the 2mL mixture solvent of **1** (0.3 mmol) and the catalyst, and **2** (0.45 mmol) was added dropwise by syringe pump at a flow rate of 1 mL/h at 0 °C.

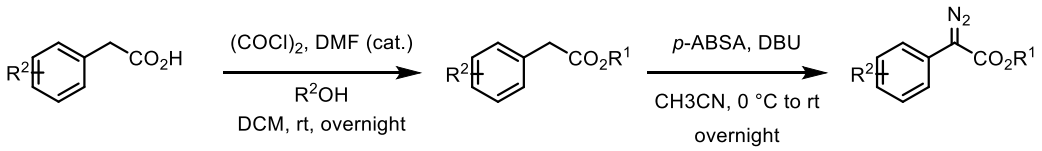
4. General procedure

4.1 General procedure for the synthesis of 3-Aryl-3-hydroxyisoindolin-1-ones[1]



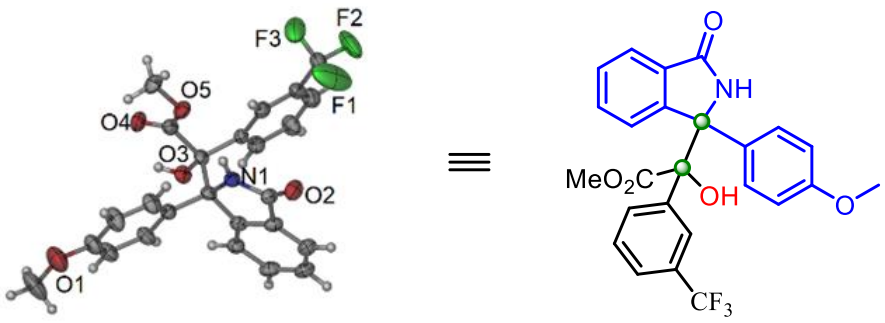
A solution of aryl bromide (3.0 equiv) in THF (50 mL) was taken in an oven-dried RB flask and cooled to –78 °C. To the solution was added drop wise *n*-butyllithium (3 equiv, 12 mL, 2.5 M in hexane, 30 mmol), and the mixture was stirred at –78 °C for 0.5 h. To the solution was added phthalimide (1 equiv, 10 mmol) and the mixture was stirred for further 15 min at –78 °C and for 4h at room temperature. Upon completion (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl solution. Then, aqueous solution was extracted with ethyl acetate (3 times). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The pure product was obtained by washing the crude product with CH_2Cl_2/hexane (1:3, v/v) as a solvent.

4.2 General procedure for the preparation of phenyl diazoester[2]



Under nitrogen, at room temperature, a round bottomed flask is charged with the phenylacetic acid (20 mmol, 1 equiv.), dry DCM (0.4 M), oxalyl chloride (1.5 equiv.). Then, DMF (1 or 2 drops) is added. The reaction is allowed to stir at room temperature for 2h. Then, the reaction temperature is cooled to 0 °C and an excess of alcohol (x mL) is added. The reaction is allowed to warm up to room temperature and to stir at this temperature overnight. Then, the reaction is quenched with a saturated aqueous solution of $NaHCO_3$, extracted with AcOEt (3x mL), dried with $MgSO_4$ and concentrated under reduced pressure. The solvent wasremoved and the crude product was obtained used directly in the next step. To a mixture of the crude product obtained above (20 mmol) and tosyl azide (*p*-ABSA) (30 mmol) in anhydrous CH_3CN (20 mL), 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) (30 mmol) was added slowly. The reaction mixture was stirred at room temperature for overnight. Upon complete consumption of the starting materials, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 × 30 mL), washed by brine. The combined extracts were dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (PE/EA, 50:1) to afford the phenyl diazoester.

5. Single crystal X-ray diffraction data of *anti*-3e (CDCC NO.: 2308679)

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Bond precision:   C-C = 0.0097 A          Wavelength=1.54184

Cell:             a=8.2517(2)     b=20.7292(7)         c=13.3563(5)
                  alpha=90        beta=102.561(3)      gamma=90
Temperature:      173 K

                  Calculated                  Reported
Volume            2229.93(13)                 2229.93(13)
Space group       P 21                        P 1 21 1
Hall group        P 2yb                       P 2yb
Moiety formula    C25 H20 F3 N O5             C25 H20 F3 N O5
Sum formula       C25 H20 F3 N O5             C25 H20 F3 N O5
Mr                471.42                      471.42
Dx,g cm-3         1.404                       1.404
Z                 4                           4
Mu (mm-1)         0.977                       0.977
F000              976.0                       976.0
F000'             979.67
h,k,lmax                                      9,24,15
Nref                                          6757
Tmin,Tmax         0.791,0.839                 0.488,1.000
Tmin'             0.717

Correction method= # Reported T Limits: Tmin=0.488 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness=                 Theta(max)= 67.066

R(reflections)= 0.0744( 5476)                wR2(reflections)=
                                             0.2167( 6757)
S = 1.097                  Npar= 619
```

Fig. S1 ORTEP diagram for the compound *anti*-**3e**. Thermal ellipsoids are shown at the 50% probability level.

The method for the crystal growth of *anti*-**3e** is as follows: *anti*-**3e** (15 mg) was stored in a 2.0 mL mixture of DCM/EA (v/v, 4:1) solvents in a refrigerator at 4 °C for five days, and 1.5 mL of an equal proportion of the mixed solution was continually added to the bottle. The bottle continued to be stored in under same conditions for three days.

6. References

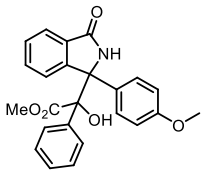
[1] (*a*) T. Nishimura, A. Noishiki, Y. Ebe and T. Hayashi, Hydroxorhodium/Chiral Diene Complexes as Effective Catalysts for the Asymmetric Arylation of 3-Aryl-3-hydroxyisoindolin-1-ones, *Angew. Chem. Int. Ed*., 2013, **52**, 1777−1780; (*b*) J. Sućˊ, I. Dokli and M. Gredičak, Chiral Brønsted acid-catalysed enantioselective synthesis of isoindolinone-derived N (acyl), S-acetals, *Chem. Commun*., 2016, **52**, 2071−2074; (*c*) Y. P. Ruan, M. D. Chen, M. Z. He, X. Zhou and P. Q. Huang, A Practical Two-Step Synthesis of 3-Alkyl-2, 3-dihydro-1*H*-isoindolin-1-ones, *Synth. Commun*., 2004, **34**, 853−861; (*d*) J. Q. Zhou, W. J. Sheng, J. H. Jia, Q. Ye, J. R. Gao and Y. X. Jia, Chiral phosphoric acid catalyzed asymmetric hydrogenolysis of racemic 3-aryl-3-hydroxyisoindolin-1-ones, *Tetrahedron Lett.*, 2013, **54**, 3082−3084; (*e*) A. Suneja, R. A. Unhale and V. K. Singh, Enantioselective hydrophosphonylation of in situ generated N-acyl ketimines catalyzed by BINOL-derived phosphoric acid, *Org. Lett.*, 2017, **19**, 476−479; (*f*) R. A. Unhale, N. Molleti, N. K. Rana, S. Dhanasekaran, S. Bhandary and V. K. Singh, Chiral phosphoric acid catalyzed enantioselective addition of thiols to in situ generated ketimines: Synthesis of N, S-ketals, *Tetrahedron Lett.*, 2017, **58**, 145−151.

[2] S. Thurow, A. A. G. Fernandes, Y. Quevedo-Acosta, M. F. de Oliveira, M. G. de Oliveira, I. D. Jurberg, Preparation of Organic Nitrates from Aryldiazoacetates and $Fe(NO_3)_3 \cdot 9H_2O$, *Org. Lett*., 2019, **21**, 6909−6913.

[3] R. Wang, Q. Hu, H. Wang, G. Zhu, M. Wang, Q. Zhang, Y. Zhao, C. Li, Y. Zhang, G. Ge, H. Chen and L. Chen, Identification of Vitamin K3 and its analogues as covalent inhibitors of SARS-CoV-2 $3CL^{pro}$, *Int. J. Biol. Macromol.*, 2021, **183**, 182−192.

7. Characterization data for the products 3

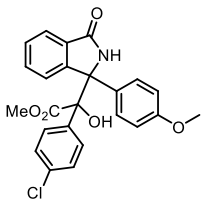
Methyl 2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)-2-phenylacetate (**3a**). White solid, *syn*/*anti* isomer (2:5) ratio.



3a
(*syn* : *anti* = 2:5)

Mixture of (*syn* : *anti* = 2:5) isomers of **3a** (88% yield): **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.35 (d, J = 7.9 Hz, 1H), 8.06 (d, J = 7.9 Hz, 2.5H), 7.84 (d, J = 9.0 Hz, 4.5H), 7.62 (t, J = 7.6 Hz, 1H), 7.57 – 7.52 (m, 3.5H), 7.47 – 7.42 (m, 3H), 7.40 – 7.32 (m, 7.5H), 7.20 (d, J = 7.7 Hz, 5H), 7.17 – 7.07 (m, 5.5H), 7.01 (t, J = 7.6 Hz, 5H), 6.85 (d, J = 9.0 Hz, 5H), 6.76 (d, J = 8.9 Hz, 2H), 3.75 (s, 7.5H), 3.74 (s, 3H), 3.70 (s, 7.5H), 3.55 (s, 3H). **^{13}C NMR** (100 MHz, Methanol-d_4) δ 174.6, 173.6, 172.3, 172.1, 171.5, 160.54, 160.48, 149.7, 148.8, 139.1, 133.9, 133.1, 132.6, 132.54, 132.48, 131.4, 130.9, 129.6, 129.5, 129.3, 129.2, 129.1, 128.5, 128.29, 128.26, 128.2, 128.1, 128.0, 123.8, 123.4, 114.4, 113.7, 85.3, 84.2, 73.8, 72.1, 55.63, 55.60, 53.1, 53.0. **HRMS(ESI)** Calcd. for $C_{24}H_{21}NNaO_5$ $(M + Na)^+$ 426.1312, found 426.1305.

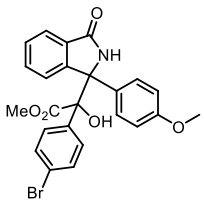
Methyl 2-(4-chlorophenyl)-2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)acetate (**3b**). White solid, *syn*/*anti* isomer (1:1) ratio.



3b
(*syn* : *anti* = 1:1)

Mixture of (*syn* : *anti* = 1:1) isomers of **3b** (83% yield): **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 8.23 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.91 (s, 1H), 7.79 (d, J = 8.9 Hz, 2H), 7.64 (d, J = 7.8 Hz, 2H), 7.56 (dd, J = 15.4, 7.1 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.42 – 7.33 (m, 6H), 7.23 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 5.01 (s, 1H), 4.87 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.56 (s, 3H). **^{13}C NMR** (100 MHz, Acetonitrile-d_3) δ 173.6, 172.8, 169.8, 169.6, 160.1, 160.0, 148.0, 147.5, 137.3, 137.2, 134.7, 134.6, 133.5, 132.5, 132.4, 130.8, 130.4, 130.0, 129.8, 129.6, 129.4, 129.3, 128.2, 127.9, 127.64, 127.62, 123.7, 123.2, 114.3, 113.7, 84.3, 83.3, 72.3, 70.6, 55.8, 53.9, 53.8. **HRMS(ESI)** Calcd. for $C_{24}H_{20}ClNNaO_5$ $(M + Na)^+$ 460.0922, found 460.0949.

Methyl 2-(4-bromophenyl)-2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)acetate (**3c**). White solid, *syn*/*anti* isomer (2:3) ratio.

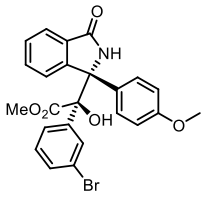


3c
(*syn* : *anti* = 2:3)

Mixture of (*syn* : *anti* = 2:3) isomers of **3c** (89% yield): **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.14 (d, J = 7.8 Hz, 1.5H), 8.06 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 7.76 (t, J = 8.4 Hz, 3.5H), 7.63 (t, J = 7.5 Hz, 1.5H), 7.55 – 7.47 (m, 3.5H), 7.37 – 7.32 (m, 7H), 7.23 (s, 3H), 7.18 (s, 4H), 7.03 (s, 1.5H), 6.85 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.7 Hz, 3H), 4.34 (s, 1.5H), 4.10 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (s, 4.5H), 3.57 (s, 4.5H). **^{13}C NMR** (100 MHz, Chloroform-d) δ 172.7, 172.3, 169.8, 169.4, 159.3, 159.2, 146.7, 146.3, 135.7, 135.5, 132.3, 131.9, 131.7, 131.3, 131.0, 130.7, 130.5, 129.2, 129.1, 129.0, 128.8, 128.7,

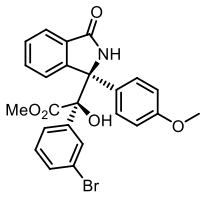
128.5, 128.3, 126.3, 126.0, 123.8, 123.3, 123.0, 113.7, 113.1, 83.4, 82.0, 70.6, 69.7, 55.2, 53.8. **HRMS(ESI)** Calcd. for $C_{24}H_{20}BrNNaO_5$ $(M + Na)^+$ 504.0417, found 504.0411.

Methyl 2-(3-bromophenyl)-2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)acetate (**3d**). White solid, *syn*/*anti* isomer (1:1) ratio.



anti-**3d**

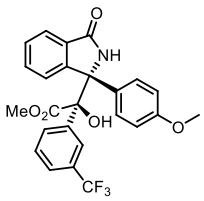
anti-**3d** (38% yield): **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 8.07 (d, J = 7.8 Hz, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.9 Hz, 2H), 7.58 (t, J = 7.0 Hz, 1H), 7.39 – 7.26 (m, 5H), 7.01 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 5.07 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H). **^{13}C NMR** (100 MHz, Acetonitrile-d_3) δ 173.4, 169.7, 168.7, 160.1, 147.9, 140.9, 132.43, 132.38, 132.0, 131.0, 129.8, 129.5, 129.3, 127.7, 126.8, 123.2, 121.7, 114.4, 84.3, 70.6, 55.8, 54.0. **HRMS(ESI)** Calcd. for $C_{24}H_{20}BrNNaO_5$ $(M + Na)^+$ 504.0417, found 504.0423.



syn-**3d**

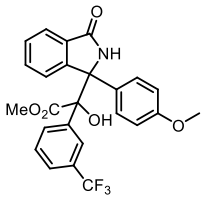
syn-**3d** (38% yield): **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 8.24 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 16.4, 8.7 Hz, 2H), 7.53 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 8.9 Hz, 3H), 7.35 (d, J = 8.2 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 8.9 Hz, 2H), 3.75 (s, 3H), 3.57 (s, 3H). **^{13}C NMR** (100 MHz, Acetonitrile-d_3) δ 172.2, 169.2, 159.7, 147.0, 140.4, 138.4, 133.1, 132.1, 131.7, 130.9, 130.4, 130.0, 129.8, 129.5, 127.3, 126.7, 123.3, 121.7, 82.9, 72.1, 55.5, 53.5. **HRMS(ESI)** Calcd. for $C_{24}H_{20}BrNNaO_5$ $(M + Na)^+$ 504.0417, found 504.0438.

Methyl 2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)-2-(3-(trifluoromethyl)phenyl)acetate (**3e**). White solid, *syn/anti* isomer (1:3) ratio.



anti-**3e**

anti-**3e** (38% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.09 (d, J = 7.8 Hz, 1H), 7.85 – 7.75 (m, 3H), 7.62 – 7.52 (m, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.39 – 7.32 (m, 2H), 7.22 (t, J = 7.9 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 4.16 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.6, 169.8, 159.5, 146.5, 137.5, 131.9, 131.3, 130.5, 130.04, 129.96, 129.7, 128.9, 128.4, 127.8, 126.4, 125.36 (q, J = 3.9 Hz), 124.17 (q, J = 3.6 Hz), 123.3, 113.9, 83.5, 69.9, 55.4, 54.0. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.84. **HRMS(ESI)** Calcd. for $C_{25}H_{20}F_3NNaO_5$ $(M + Na)^+$ 494.1186, found 494.1198.

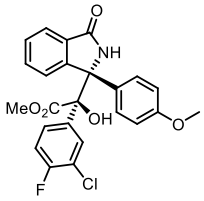


3e
(*syn* : *anti* = 1:1)

Mixture of (*syn* : *anti* = 1:1) isomers of **3e** (38% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H), 8.14 (dd, J = 7.5, 3.7 Hz, 2H), 7.83 – 7.77 (m, 3H), 7.73 (d, J = 6.8 Hz, 1H), 7.64 (t, J = 7.2 Hz, 2H), 7.57 (d, J = 7.7 Hz, 2H), 7.51 – 7.44 (m, 4H), 7.39 – 7.27 (m, 6H), 7.17 (t, J = 7.9 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 4.46 (s, 1H), 4.34 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.7, 172.2, 170.1, 159.43, 159.40, 146.5, 146.1, 137.64, 137.60, 132.5, 131.9, 131.8, 131.5, 130.5, 130.24, 130.17, 130.1, 129.92, 129.85, 129.6, 129.3, 129.2, 128.80, 128.75, 128.5, 128.3, 127.7, 126.5, 126.2, 125.45 (q, J = 3.6 Hz), 125.30, 125.21 (q, J = 3.7 Hz), 125.81 (q, J = 3.6 Hz), 124.22 (q, J = 3.7 Hz), 123.9, 123.2, 122.6, 122.5, 113.8, 113.3, 83.4, 82.4, 71.5, 70.2,

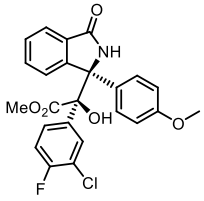
55.4, 55.3, 54.0, 53.9. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.70, -62.82. **HRMS(ESI)** Calcd. for $C_{25}H_{20}F_3NNaO_5$ $(M + Na)^+$ 494.1186, found 494.1204.

Methyl 2-(3-chloro-4-fluorophenyl)-2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)acetate (**3f**). White solid, *syn/anti* isomer (1:1) ratio.



anti-**3f**

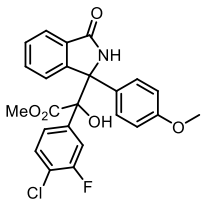
anti-**3f** (38.5% yield): **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 8.07 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 7.77 (d, *J* = 8.9 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.38 (d, *J* = 3.7 Hz, 2H), 7.32 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.94 (t, *J* = 8.9 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.08 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H). **^{13}C NMR** (100 MHz, Acetonitrile-d_3) δ 173.2, 169.7, 160.2, 159.6 (d, *J* = 1.2 Hz), 157.1, 147.7, 135.9 (d, *J* = 3.7 Hz), 132.5 (d, *J* = 8.0 Hz), 132.1, 130.5, 129.6, 129.3, 128.5 (d, *J* = 7.6 Hz), 127.6, 123.3, 119.9 (d, *J* = 17.7 Hz), 116.0 (d, *J* = 21.0 Hz), 114.4, 83.9, 70.7, 55.8, 54.1. **^{19}F NMR** (376 MHz, Acetonitrile-d_3) δ -118.10. **HRMS(ESI)** Calcd. for $C_{24}H_{19}ClFNNaO_5$ $(M + Na)^+$ 478.0828, found 478.0849.



syn-**3f**

syn-**3f** (38.5% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 (s, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.59 – 7.51 (m, 2H), 7.36 (dd, *J* = 16.2, 7.8 Hz, 2H), 7.28 (s, 1H), 6.83 (dd, *J* = 20.5, 8.7 Hz, 3H), 4.22 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.6, 159.3 (d, *J* = 23.6 Hz), 156.7, 146.5 (d, *J* = 2.5 Hz), 133.6 (d, *J* = 3.5 Hz), 131.9, 130.5 (d, *J* = 2.5 Hz), 129.8, 128.9, 128.5, 127.0, 126.9 (d, *J* = 7.6 Hz), 126.5, 123.4, 120.3 (d, *J* = 18.5 Hz), 115.5, 115.3, 113.9, 83.0, 70.1, 55.4, 54.1. **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -115.41. **HRMS(ESI)** Calcd. For $C_{24}H_{19}ClFNNaO_5$ $(M + Na)^+$ 478.0828, found 478.0849.

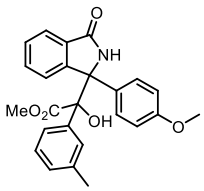
Methyl 2-(4-chloro-3-fluorophenyl)-2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)acetate (**3g**). White solid, *syn/anti* isomer (1:1) ratio.



3g
(*syn* : *anti* = 1:1)

Mixture of (*syn* : *anti* = 1:1) isomers of **3g** (78% yield): **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.36 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 9.5 Hz, 2H), 7.50 – 7.43 (m, 4H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 11.3 Hz, 1H), 7.20 (s, 2H), 7.14 – 7.06 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.55 (s, 3H). **^{13}C NMR** (100 MHz, Methanol-d_4) δ 173.7, 172.8, 172.3, 172.0, 160.6z8, 160.65, 159.5, 159.3, 157.1, 156.9, 149.0, 148.2, 140.8, 140.74, 140.70, 140.6, 133.7, 132.83, 132.75, 132.43, 132.41, 130.8, 130.7, 130.3, 130.1, 130.0, 129.7, 129.5, 128.4, 128.2, 125.4, 125.3, 125.02, 125.0, 124.0, 123.6, 121.7, 121.6, 121.5, 121.4, 117.3, 117.0, 116.9, 116.9, 116.6, 114.8, 114.7, 114.5, 113.9, 84.5, 83.5, 73.8, 72.0, 55.6, 53.5, 53.3. **^{19}F NMR** (376 MHz, Methanol-d_4) δ -117.78 (dd, *J* = 10.4, 7.2 Hz), -118.16 (d, *J* = 11.2 Hz), -118.43 (dd, *J* = 11.1, 7.3 Hz). **HRMS(ESI)** Calcd. for $C_{24}H_{19}ClFNNaO_5$ $(M + Na)^+$ 478.0828, found 478.0832.

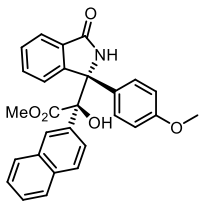
Methyl 2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)-2-(m-tolyl)acetate (**3h**). White solid, *syn/anti* isomer (10:31) ratio.



3h
(*syn* : *anti* = 10:31)

Mixture of (*syn* : *anti* = 10:31) isomers of **3h** (84% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 3.1H), 7.79 (d, *J* = 8.9 Hz, 6.2H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 6.9 Hz, 4.1H), 7.52 (t, *J* = 7.5 Hz, 4.1H), 7.48 – 7.43 (m, 4.1H), 7.32 (t, *J* = 7.4 Hz, 4H), 7.23 – 7.17 (m, 3.1H), 7.11 (d, *J* = 7.1 Hz, 2H), 7.03 – 7.00 (m, 3.1H), 6.95 – 6.94 (m, 9.3H), 6.84 (d, *J* = 8.9 Hz, 6.2H), 6.73 (d, *J* = 8.9 Hz, 2H), 4.29 (s, 1H), 4.00 (s, 3.1H), 3.79 – 3.74 (m, 21.6H), 3.54 (s, 3H), 2.24 (s, 3H), 2.10 (s, 9.3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.1, 172.9, 169.9, 169.5, 159.23, 159.16, 147.3, 146.8, 137.7, 137.1, 136.7, 136.6, 132.5, 131.8, 131.6, 131.53, 131.49, 129.6, 129.5, 129.4, 129.3, 129.1, 128.5, 128.3, 128.2, 128.0, 127.9, 127.5, 127.4, 126.4, 126.1, 124.3, 123.74, 123.70, 123.1, 113.8, 112.9, 84.1, 82.3, 70.5, 69.9, 55.3, 53.7, 53.6, 21.7, 21.5. **HRMS(ESI)** Calcd. for $C_{25}H_{23}NNaO_5$ $(M + Na)^+$ 440.1468, found 440.1475.

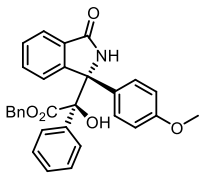
Methyl 2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)-2-(naphthalen-2-yl)acetate (**3i**). White solid, *syn/anti* isomer (1:5) ratio.



anti-**3i**

anti-**3i** (73% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 7.8 Hz, 1H), 7.84 – 7.80 (m, 2H), 7.71 – 7.66 (m, 3H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.43 – 7.32 (m, 4H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.88 – 6.84 (m, 2H), 4.09 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.1, 169.8, 159.3, 150.6, 147.2, 134.1, 133.0, 132.3, 131.7, 131.42, 131.39, 128.62, 128.59, 128.4, 127.5, 127.1, 126.7, 126.4, 126.2, 124.0, 123.3, 113.8, 84.2, 70.0, 55.4, 53.7. **HRMS(ESI)** Calcd. for $C_{28}H_{23}NNaO_5$ $(M + Na)^+$ 476.1468, found 476.1462.

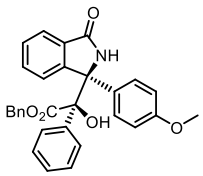
Benzyl 2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)-2-phenylacetate (**3j**). White solid, *syn/anti* isomer (1:1) ratio.



anti-**3j**

anti-**3j** (41% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.74 (dd, *J* = 9.6, 2.6 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.20 – 7.15 (m, 3H), 7.15 – 7.09 (m, 3H), 7.04 (t, *J* = 7.6 Hz, 2H), 6.77 (dd, *J* = 9.6, 2.6 Hz, 2H), 5.23 (d, *J* = 11.8 Hz, 1H), 5.11 (d, *J* = 11.8 Hz, 1H), 3.96 (s, 1H), 3.79 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.5, 169.7, 159.3, 147.2, 136.7, 134.0, 131.7, 131.4, 131.3, 129.2, 129.1, 128.9, 128.8, 128.6, 128.3, 127.5, 126.7, 126.4, 123.1, 113.8, 84.0, 69.7, 69.0, 55.3. **HRMS(ESI)** Calcd. for $C_{30}H_{25}NNaO_5$ $(M + Na)^+$ 502.1625, found 502.1607.

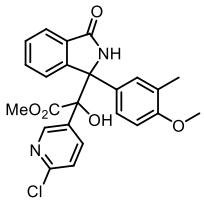
Benzyl 2-hydroxy-2-(1-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)-2-phenylacetate (**3j**). White solid, *syn/anti* isomer (1:1) ratio.



syn-**3j**

syn-**3j** (41% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.46 – 7.42 (m, 2H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.27 (s, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.18 – 7.15 (m, 2H), 7.13 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 9.0 Hz, 3H), 5.04 (d, *J* = 11.7 Hz, 1H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.29 (s, 1H), 3.75 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.2, 169.3, 159.2, 146.5, 136.9, 133.9, 132.4, 131.7, 129.43, 129.39, 129.3, 129.04, 129.01, 128.91, 128.85, 128.0, 127.2, 126.1, 123.8, 113.0, 82.2, 70.5, 69.2, 55.3. **HRMS(ESI)** Calcd. for $C_{30}H_{25}NNaO_5$ $(M + Na)^+$ 502.1625, found 502.1617.

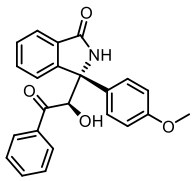
Methyl 2-(6-chloropyridin-3-yl)-2-hydroxy-2-(1-(4-methoxy-3-methylphenyl)-3-oxoisoindolin-1-yl)acetate (**3k**). White solid, *syn/anti* isomer (1:1) ratio.



3k
(*syn* : *anti* = 1:1)

Mixture of (*syn* : *anti* = 1:1) isomers of **3k** (73% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 9.00 (s, 1H), 8.44 – 8.37 (m, 2H), 8.28 – 8.17 (m, 2H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.81 – 7.73 (m, 3H), 7.64 (dd, *J* = 12.8, 6.4 Hz, 3H), 7.60 – 7.48 (m, 3H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 4.54 (s, 1H), 4.45 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.5, 171.9, 157.8, 152.2, 151.7, 151.5, 149.1, 148.7, 146.3, 145.9, 139.9, 138.3, 137.6, 132.5, 132.1, 132.0, 131.6, 131.5, 131.3, 130.3, 129.6, 129.4, 129.3, 129.1, 127.94, 127.89, 126.62, 126.59, 126.5, 126.3, 126.1, 125.8, 124.9, 123.9, 123.5, 123.0, 122.7, 109.7, 109.3, 82.1, 81.5, 72.0, 70.4, 55.4, 54.3, 54.0, 16.7, 16.6. **HRMS(ESI)** Calcd. for $C_{24}H_{21}ClN_2NaO_5$ $(M + Na)^+$ 475.1031, found 475.1059.

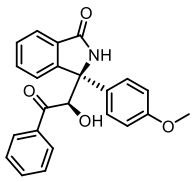
3-(1-hydroxy-2-oxo-2-phenylethyl)-3-(4-methoxyphenyl)isoindolin-1-one (**3l**). White solid, *syn/anti* isomer (1:1) ratio.



anti-**3l**

anti-**3l** (43.5% yield): **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 7.94 (d, *J* = 7.7 Hz, 2H), 7.71 (dd, *J* = 15.3, 7.6 Hz, 2H), 7.65 – 7.59 (m, 2H), 7.51 – 7.44 (m, 6H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.13 (s, 1H), 3.69 (s, 3H). **^{13}C NMR** (100 MHz, Acetonitrile-d_3) δ 200.1, 170.7, 160.0, 150.3, 136.9, 136.8, 134.8, 133.1, 133.0, 129.8, 129.6, 129.4, 127.5, 124.11, 124.06, 115.0, 74.1, 69.8, 55.8. **HRMS(ESI)** Calcd. for $C_{23}H_{19}NNaO_4$ $(M + Na)^+$ 396.1206, found 396.1223.

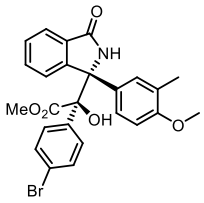
3-(1-hydroxy-2-oxo-2-phenylethyl)-3-(4-methoxyphenyl)isoindolin-1-one (**3l**). White solid, *syn/anti* isomer (1:1) ratio.



syn-**3l**

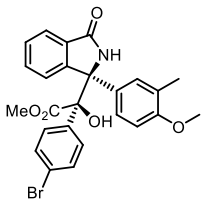
syn-**3l** (43.5% yield): **^{1}H NMR** (400 MHz, Acetonitrile-d_3) δ 7.59 (d, J = 8.7 Hz, 3H), 7.53 (d, J = 7.8 Hz, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.24 – 7.18 (m, 3H), 7.17 – 7.12 (m, 1H), 6.92 (d, J = 8.7 Hz, 2H), 6.15 (s, 1H), 3.76 (s, 3H). **^{13}C NMR** (100 MHz, Acetonitrile-d_3) δ 201.5, 170.1, 160.1, 148.3, 137.7, 133.7, 133.3, 132.7, 131.5, 129.4, 129.1, 129.0, 128.1, 125.7, 123.8, 114.8, 77.2, 70.4, 55.9. **HRMS(ESI)** Calcd. for $C_{23}H_{19}NNaO_4$ $(M + Na)^+$ 396.1206, found 396.1227.

Methyl 2-(4-bromophenyl)-2-hydroxy-2-(1-(4-methoxy-3-methylphenyl)-3-oxoisoindolin-1-yl)acetate (**3n**). White solid, *syn/anti* isomer (1:1) ratio.



anti-**3n**

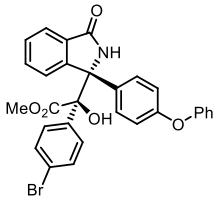
anti-**3n** (39% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.29 (s, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.60 – 7.49 (m, 3H), 7.34 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.7 Hz, 1H), 4.19 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.17 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 173.0, 170.2, 157.6, 146.9, 135.7, 131.7, 130.55, 130.51, 130.1, 129.6, 128.69, 128.65, 126.52, 126.48, 125.7, 123.3, 123.0, 109.6, 83.3, 70.0, 55.4, 53.9, 16.7. **HRMS(ESI)** Calcd. for $C_{25}H_{22}BrNNaO_5$ $(M + Na)^+$ 518.0574, found 518.0587.



syn-**3n**

syn-**3n** (39% yield): white solid. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.13 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.35 (s, 4H), 7.10 – 7.02 (m, 2H), 6.80 (s, 1H), 6.67 (d, J = 8.6 Hz, 1H), 4.29 (s, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.5, 169.4, 157.6, 146.4, 135.8, 132.3, 131.9, 131.0, 130.3, 129.22, 129.17, 128.4, 126.5, 126.2, 126.0, 123.9, 123.4, 109.1, 82.2, 70.7, 55.4, 53.9, 16.6. **HRMS(ESI)** Calcd. for $C_{25}H_{22}BrNNaO_5$ $(M + Na)^+$ 518.0574, found 518.0584.

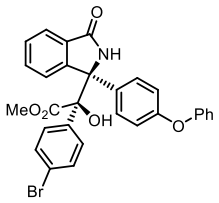
Methyl 2-(4-bromophenyl)-2-hydroxy-2-(3-oxo-1-(4-phenoxyphenyl)isoindolin-1-yl)acetate (**3o**). White solid, *syn/anti* isomer (1:1) ratio.



anti-**3o**

anti-**3o** (33.5% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.27 (d, J = 21.9 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.58 – 7.49 (m, 2H), 7.40 – 7.31 (m, 3H), 7.23 – 7.16 (m, 4H), 7.12 (t, J = 7.4 Hz, 1H), 6.97 (dd, J = 19.3, 8.4 Hz, 4H), 4.18 (d, J = 5.8 Hz, 1H), 3.83 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.8, 170.1, 157.5, 156.6, 146.6, 135.5, 133.3, 131.8, 131.5, 130.6, 130.0, 128.9, 128.8, 128.6, 126.5, 123.9, 123.4, 123.2, 119.6, 118.1, 83.4, 70.0, 54.0. **HRMS(ESI)** Calcd. for $C_{29}H_{22}BrNNaO_5$ $(M + Na)^+$ 566.0574, found 566.0535.

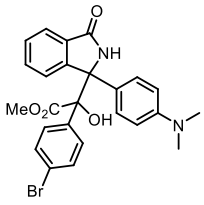
Methyl 2-(4-bromophenyl)-2-hydroxy-2-(3-oxo-1-(4-phenoxyphenyl)isoindolin-1-yl)acetate (**3o**). White solid, *syn/anti* isomer (1:1) ratio.



syn-**3o**

syn-**3o** (33.5% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.39 – 7.27 (m, 8H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.93 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.36 (s, 1H), 3.57 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.4, 169.4, 157.4, 156.6, 146.2, 135.7, 132.4, 132.1, 131.4, 131.2, 130.0, 129.6, 129.4, 129.1, 126.1, 124.0, 123.9, 123.5, 119.5, 117.6, 82.1, 70.6, 54.0. **HRMS(ESI)** Calcd. for $C_{29}H_{22}BrNNaO_5$ $(M + Na)^+$ 566.0574, found 566.0545.

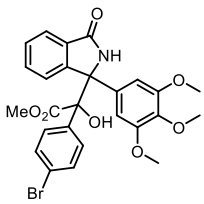
Methyl 2-(benzyloxy)-2-(4-bromophenyl)-2-(1-(4-(dimethylamino)phenyl)-3-oxoisoindolin-1-yl)acetate (**3p**). White solid, *syn/anti* isomer (2:3) ratio.



3p
(*syn* : *anti* = 2:3)

Mixture of (*syn* : *anti* = 2:3) isomers of **3p** (76% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 8.09 (d, *J* = 7.7 Hz, 1.5H), 7.87 (s, 1H), 7.77 (s, 1.5H), 7.66 (d, *J* = 9.0 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1.5H), 7.54 – 7.45 (m, 4H), 7.39 – 7.29 (m, 8H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.17 (dd, *J* = 9.0, 2.9 Hz, 5H), 6.65 (d, *J* = 9.0 Hz, 2H), 6.56 (d, *J* = 9.0 Hz, 3H), 4.32 (s, 1.5H), 4.11 (s, 1H), 3.79 (s, 3H), 3.58 (s, 4.5H), 2.93 (s, 6H), 2.91 (s, 9H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.9, 172.6, 150.1, 150.0, 147.1, 146.6, 136.0, 135.7, 132.5, 131.8, 131.6, 131.4, 130.9, 130.5, 129.3, 129.0, 128.8, 128.63, 128.55, 128.0, 126.4, 126.1, 125.6, 123.9, 123.4, 123.2, 123.0, 112.0, 111.4, 83.4, 82.3, 77.5, 69.9, 53.9, 53.8, 40.40, 40.37. **HRMS(ESI)** Calcd. for $C_{25}H_{24}BrN_2O_4$ $(M + H)^+$ 495.0914, found 495.0905.

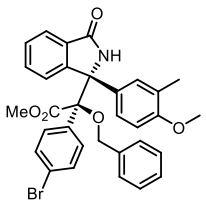
Methyl 2-(4-bromophenyl)-2-(1-(4-(dimethylamino)phenyl)-3-oxoisoindolin-1-yl)-2-hydroxyacetate (**3q**). White solid, *syn/anti* isomer (10:13) ratio.



3q
(*syn* : *anti* = 10:13)

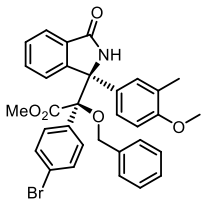
Mixture of (*syn* : *anti* = 10:13) isomers of **3q** (61% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 7.8 Hz, 1H), 8.05 (s, 1.3H), 8.03 (s, 1H), 7.75 (d, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1.3H), 7.59 – 7.52 (m, 2.6H), 7.52 – 7.47 (m, 2H), 7.41 (t, *J* = 8.3 Hz, 3.6H), 7.35 (d, *J* = 7.6 Hz, 2.3H), 7.21 – 7.12 (m, 7.2H), 6.53 (s, 2H), 4.31 (s, 1H), 4.10 (s, 1.3H), 3.86 – 3.81 (m, 15.6H), 3.80 (s, 3H), 3.69 (s, 6H), 3.57 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 172.7, 172.4, 171.7, 171.6, 170.0, 169.7, 153.0, 152.4, 146.5, 146.1, 138.1, 135.9, 135.7, 134.6, 132.6, 132.5, 132.0, 131.9, 131.5, 131.1, 130.7, 129.5, 129.3, 129.0, 128.6, 126.4, 126.1, 123.9, 123.43, 123.40, 123.3, 106.1, 104.7, 83.7, 82.2, 71.5, 70.2, 61.0, 56.4, 56.2, 53.98, 53.95. **HRMS(ESI)** Calcd. for $C_{26}H_{24}BrNNaO_7$ $(M + Na)^+$ 564.0628, found 564.0602.

Methyl 2-(benzyloxy)-2-(4-bromophenyl)-2-(1-(4-methoxy-3-methylphenyl)-3-oxoisoindolin-1-yl)acetate (**3r**). White solid, *syn/anti* isomer (1:1) ratio.



anti-**3r**

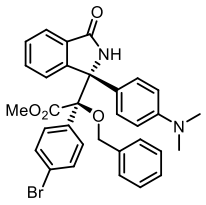
anti-**3r** (43% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.10 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.43 – 7.35 (m, 7H), 7.30 (d, J = 8.5 Hz, 2H), 7.20 (dd, J = 18.0, 8.6 Hz, 4H), 6.64 (d, J = 8.7 Hz, 1H), 4.69 (d, J = 11.1 Hz, 1H), 4.26 (d, J = 11.2 Hz, 1H), 3.79 (s, 3H), 3.41 (s, 3H), 2.13 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 169.8, 169.6, 157.5, 146.9, 137.8, 132.5, 131.8, 131.48, 131.45, 130.9, 130.5, 128.7, 128.6, 128.5, 127.8, 127.6, 127.1, 126.7, 125.5, 123.5, 123.3, 108.6, 89.7, 71.6, 69.0, 55.3, 52.1, 16.3. **HRMS(ESI)** Calcd. for $C_{32}H_{28}BrNNaO_5$ $(M + Na)^+$ 608.1043, found 608.1026.



syn-**3r**

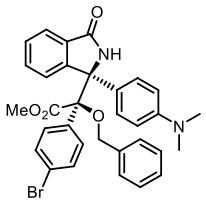
syn-**3r** (43% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.79 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.45 – 7.36 (m, 7H), 7.25 – 7.16 (m, 3H), 6.72 (d, J = 9.3 Hz, 3H), 4.91 (d, J = 10.9 Hz, 1H), 4.19 (d, J = 10.9 Hz, 1H), 3.79 (s, 3H), 3.62 (s, 3H), 2.15 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 171.8, 169.4, 157.6, 147.2, 138.1, 132.4, 131.9, 131.8, 131.3, 131.1, 129.4, 129.3, 128.8, 128.7, 128.3, 128.1, 126.9, 126.4, 125.1, 123.6, 123.4, 109.5, 91.9, 71.0, 70.4, 55.4, 52.5, 16.6. **HRMS(ESI)** Calcd. for $C_{32}H_{28}BrNNaO_5$ $(M + Na)^+$ 608.1043, found 608.1037.

Methyl 2-(benzyloxy)-2-(4-bromophenyl)-2-(1-(4-(dimethylamino)phenyl)-3-oxoisoindolin-1-yl)acetate (3s). White solid, *syn/anti* isomer (1:1) ratio.



anti-**3s**

anti-**3s** (41% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.04 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.43 – 7.30 (m, 10H), 7.23 (d, J = 8.4 Hz, 2H), 6.72 (s, 1H), 6.55 (d, J = 8.7 Hz, 2H), 4.66 (d, J = 11.2 Hz, 1H), 4.24 (d, J = 11.2 Hz, 1H), 3.42 (s, 3H), 2.92 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 170.0, 169.5, 150.7, 150.1, 138.0, 132.9, 131.9, 131.4, 131.0, 130.7, 129.6, 128.7, 128.6, 127.9, 127.7, 126.8, 124.4, 123.5, 123.4, 111.3, 90.0, 71.6, 69.2, 52.3, 40.4. **HRMS(ESI)** Calcd. for $C_{32}H_{29}BrN_2NaO_4$ $(M + Na)^+$ 607.1203, found 607.1212.

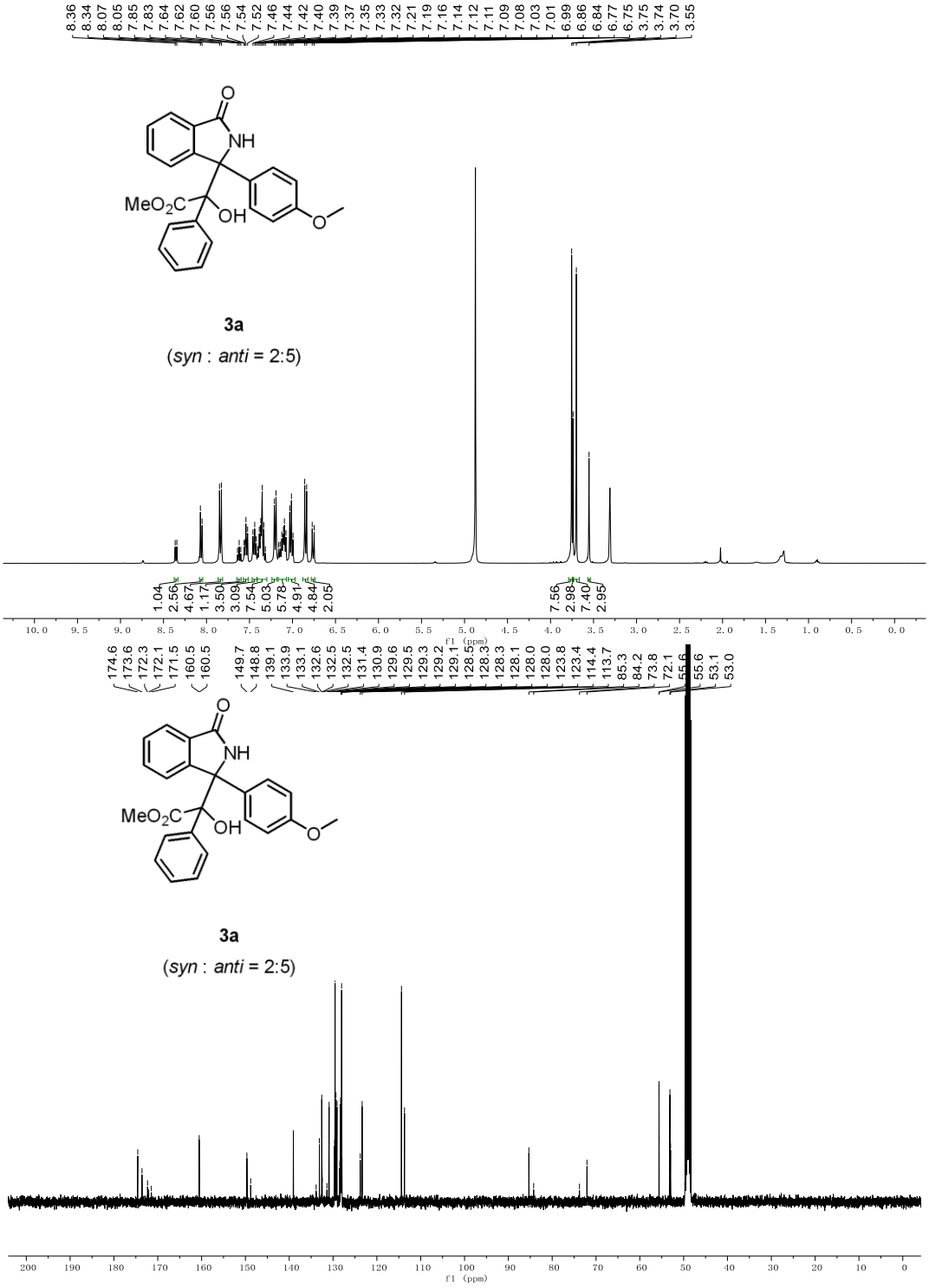


syn-**3s**

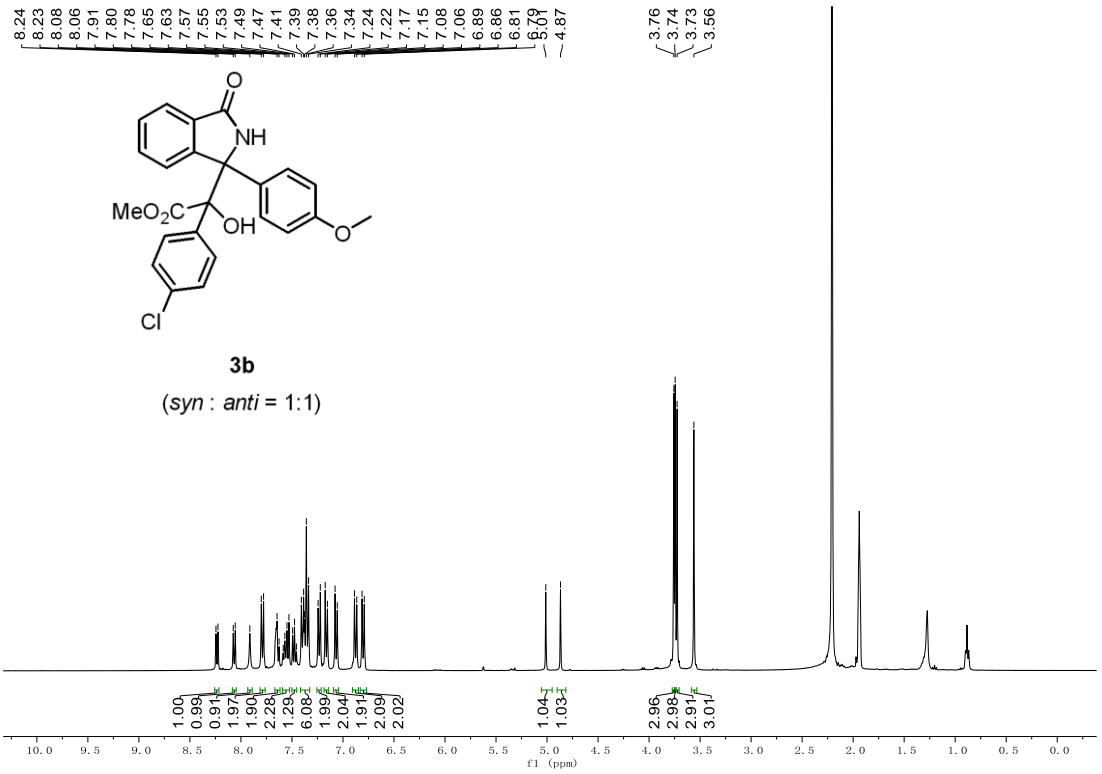
syn-**3s** (41% yield): **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 7.3 Hz, 1H), 7.46 – 7.33 (m, 7H), 7.22 (d, J = 9.6 Hz, 3H), 6.75 (s, 2H), 6.62 (d, J = 8.8 Hz, 2H), 4.95 (d, J = 11.0 Hz, 1H), 4.18 (d, J = 11.0 Hz, 1H), 3.63 (s, 3H), 2.92 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 171.8, 169.4, 150.1, 147.5, 138.2, 132.7, 131.9, 131.7, 131.0, 129.5, 128.63, 128.60, 128.3, 128.0, 127.6, 126.94, 126.91, 123.5, 123.3, 112.0, 92.1, 71.0, 70.2, 52.5, 40.4. **HRMS(ESI)** Calcd. for $C_{32}H_{30}BrN_2O_4$ $(M + H)^+$ 585.1383, found 585.1362.

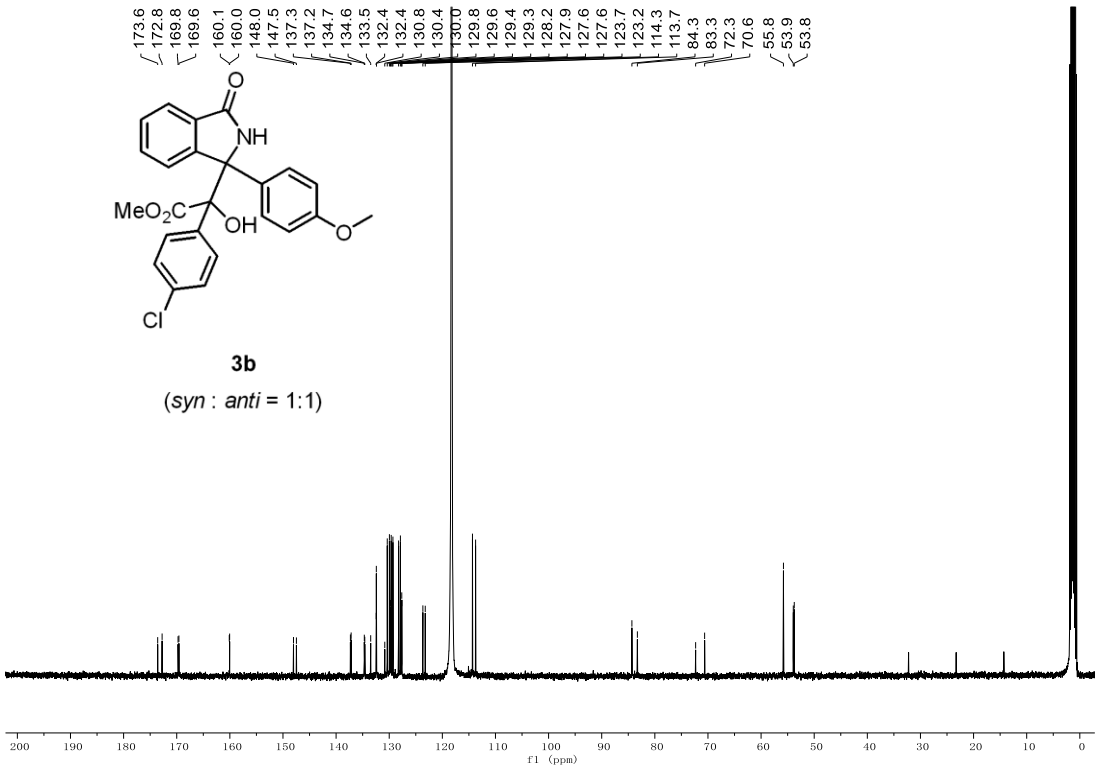
8. ^{1}H, ^{19}F and ^{13}C NMR spectra for products 3

^{1}H NMR (400 MHz, CD_3OD) and ^{13}C NMR (100 MHz, CD_3OD) spectra for 3a

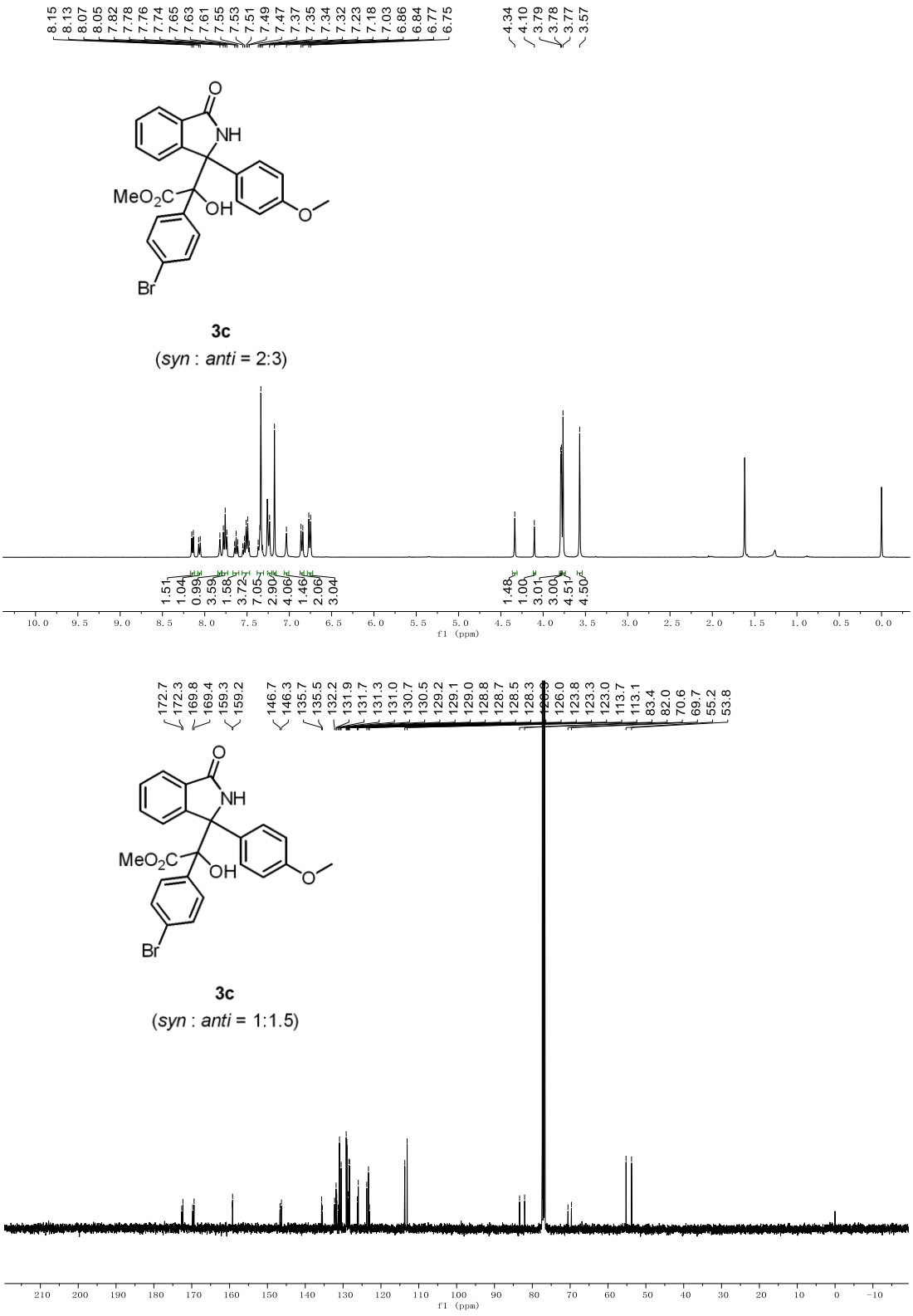


^{1}H NMR (400 MHz, CD_3CN) and ^{13}C NMR (100 MHz, CD_3CN) spectra for 3b

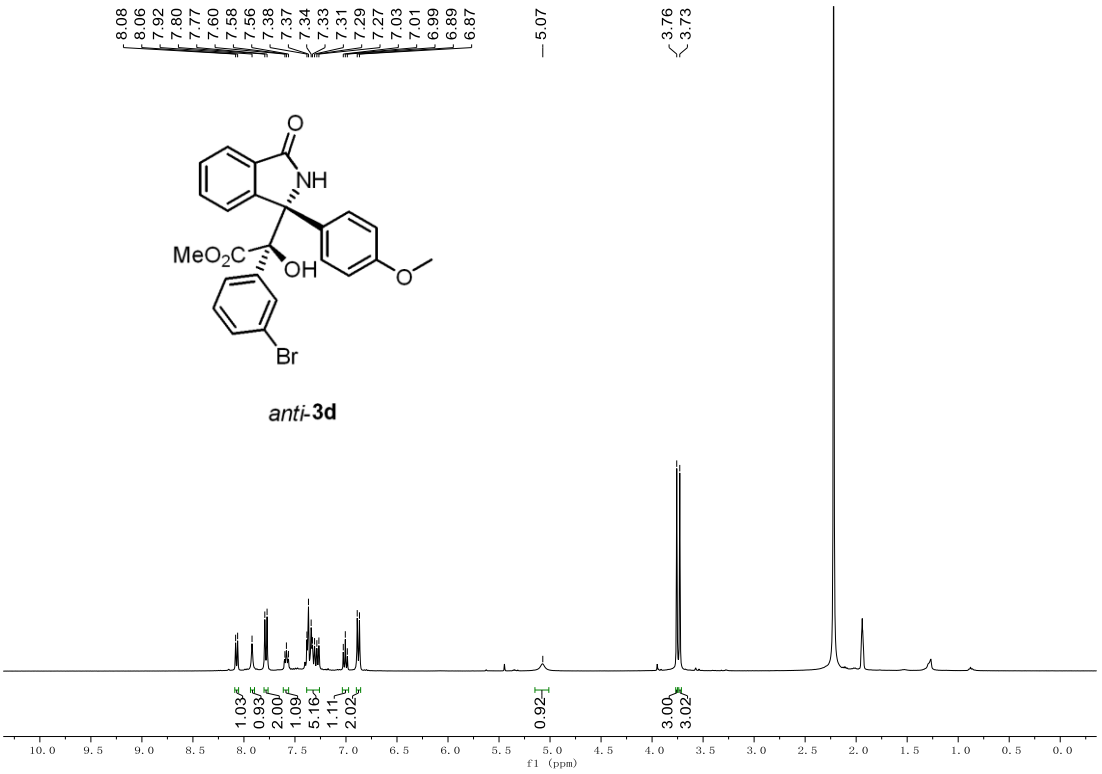


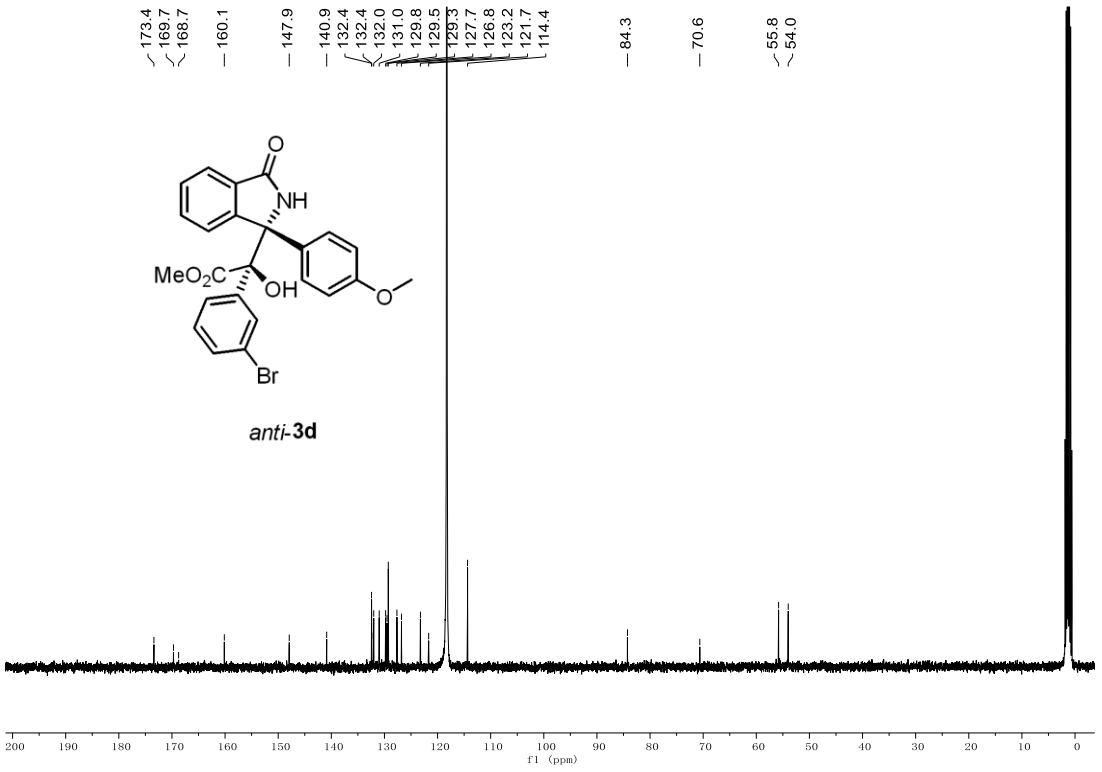


^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for 3c

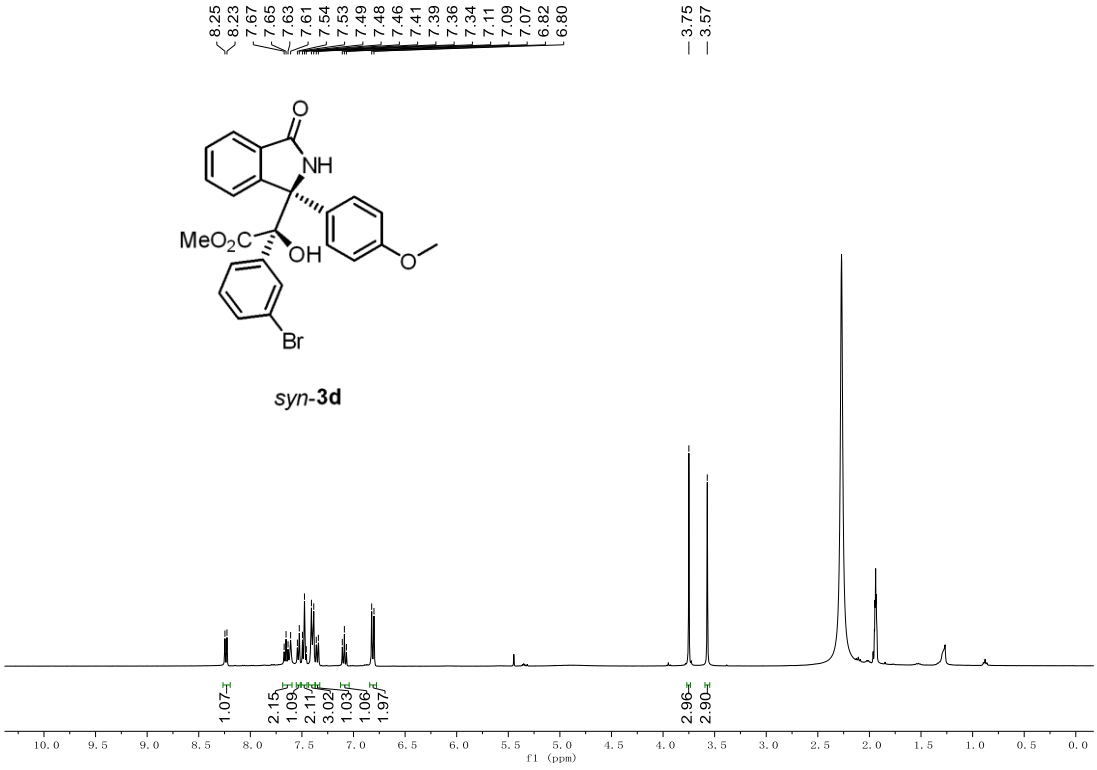


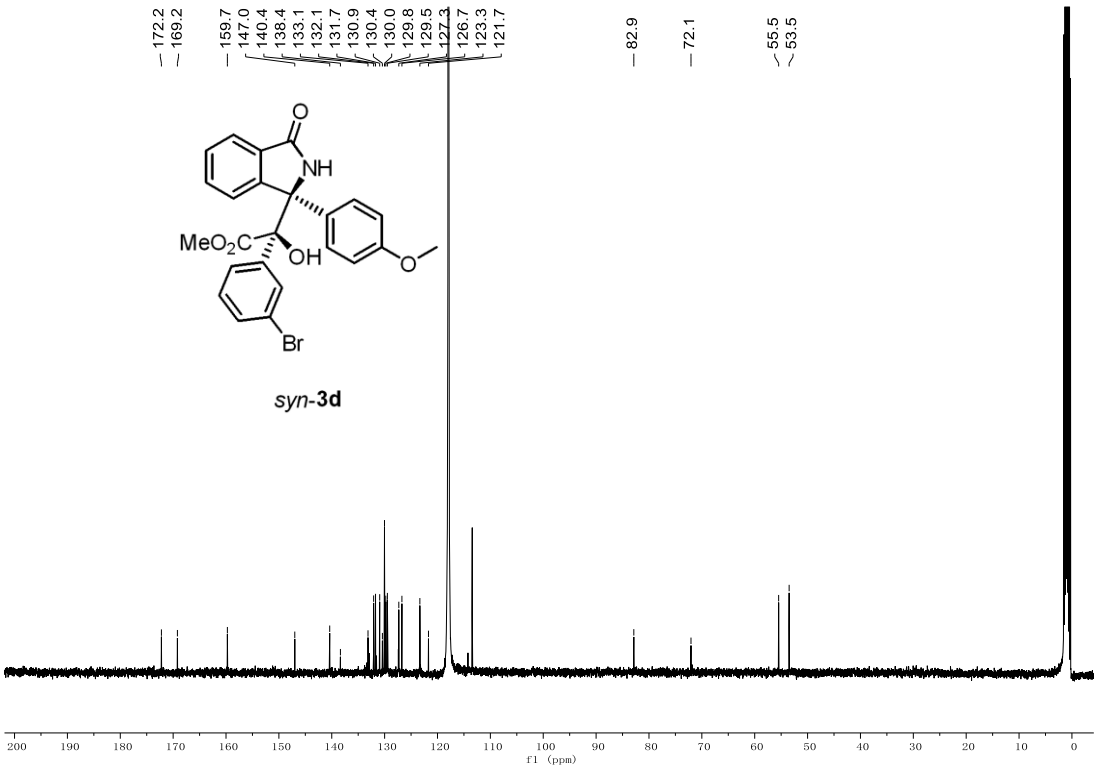
^{1}H NMR (400 MHz, CD_3CN) and ^{13}C NMR (100 MHz, CD_3CN) spectra for *anti*-3d



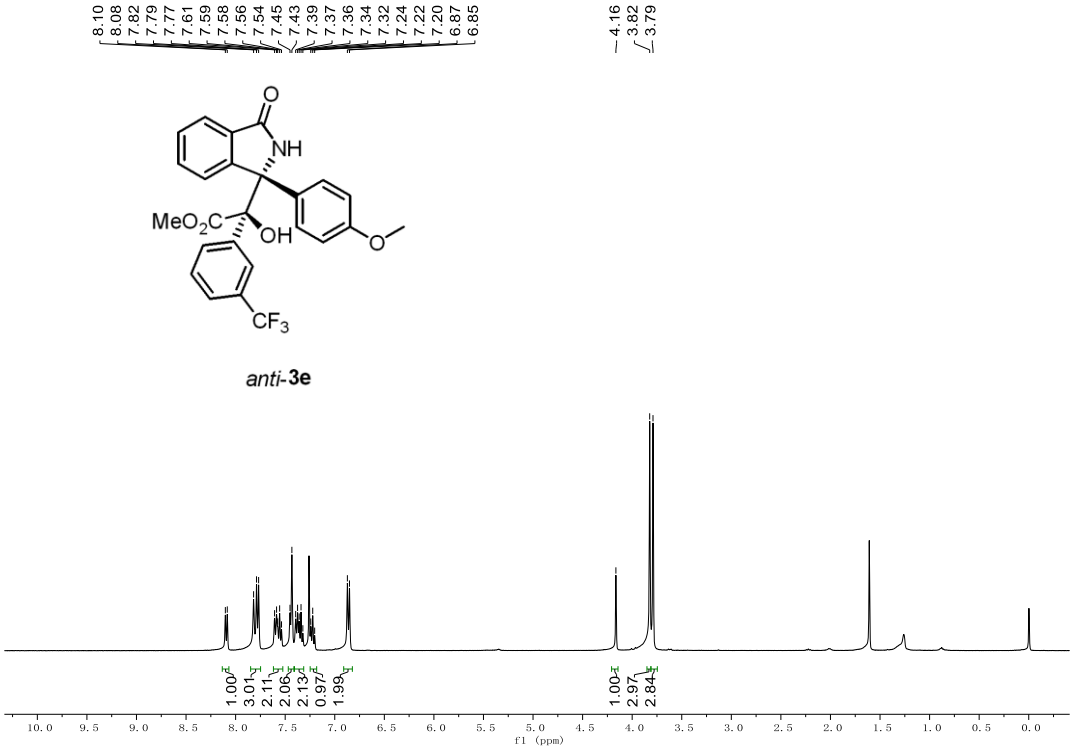


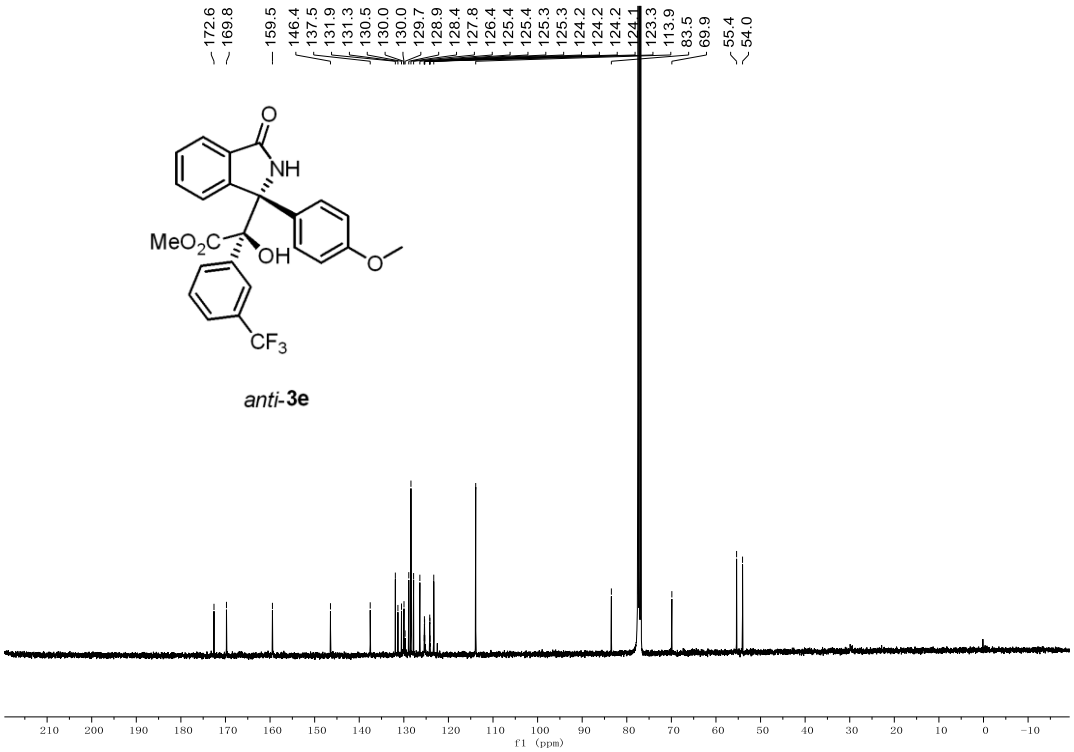
^{1}H NMR (400 MHz, CD_3CN) and ^{13}C NMR (100 MHz, CD_3CN) spectra for *syn*-3d

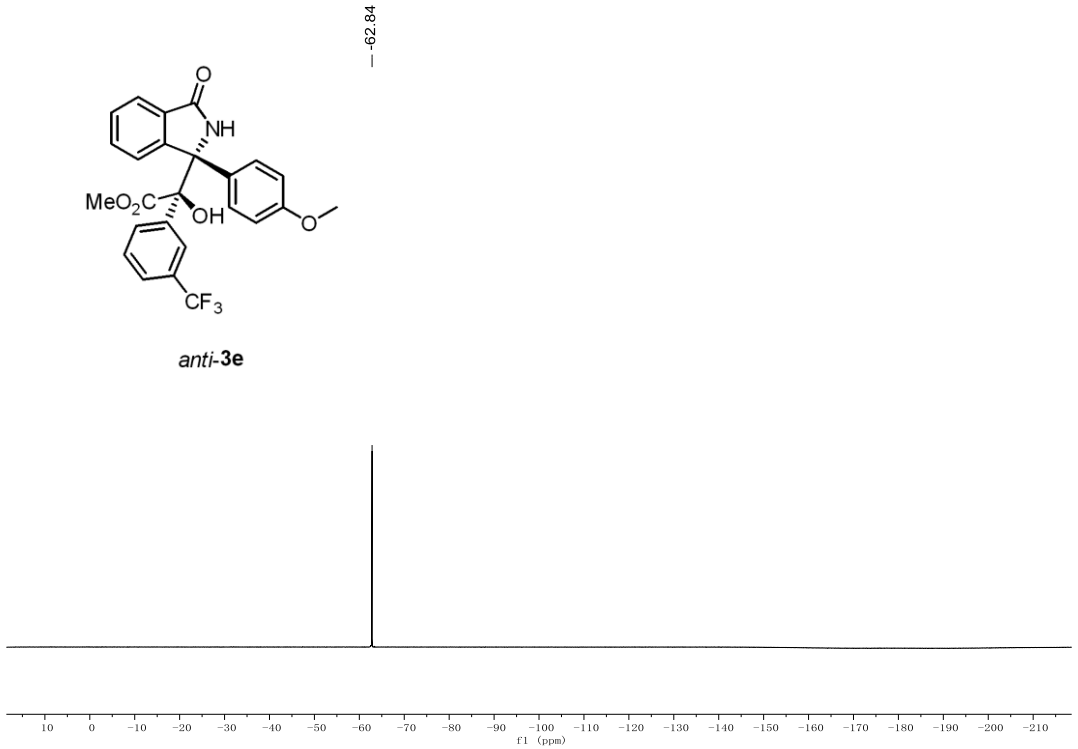




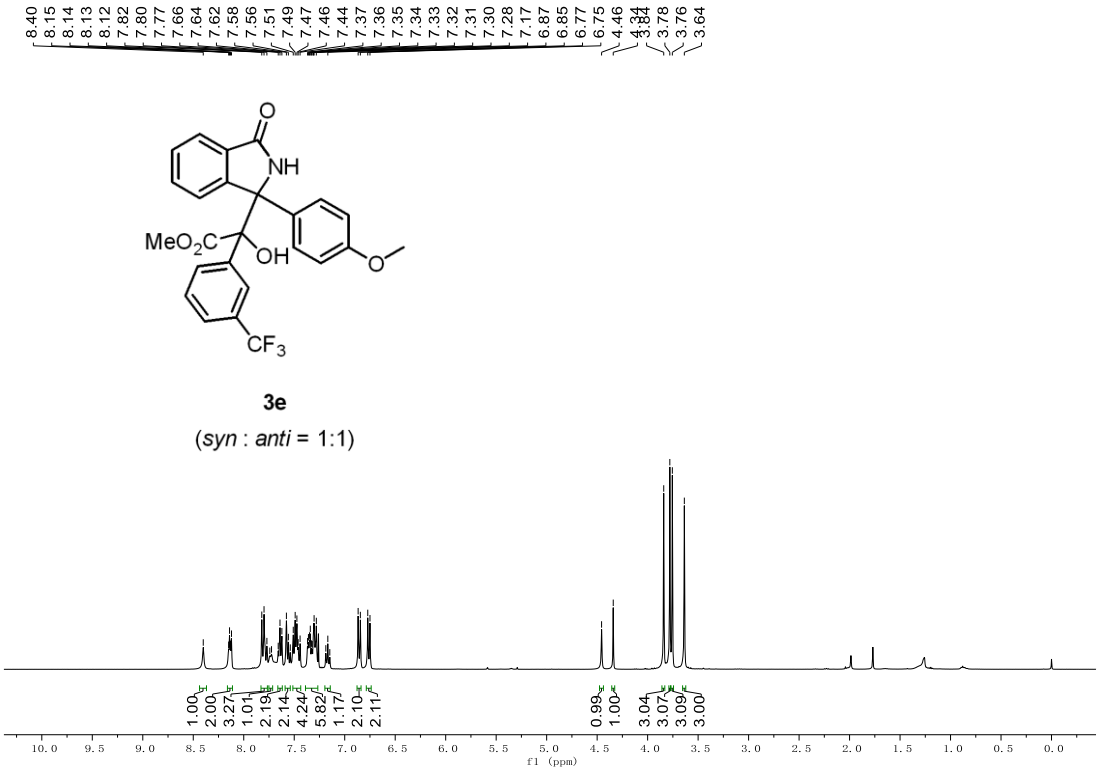
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$) and ^{19}F NMR (376 MHz, $CDCl_3$) spectra for *anti*-3e

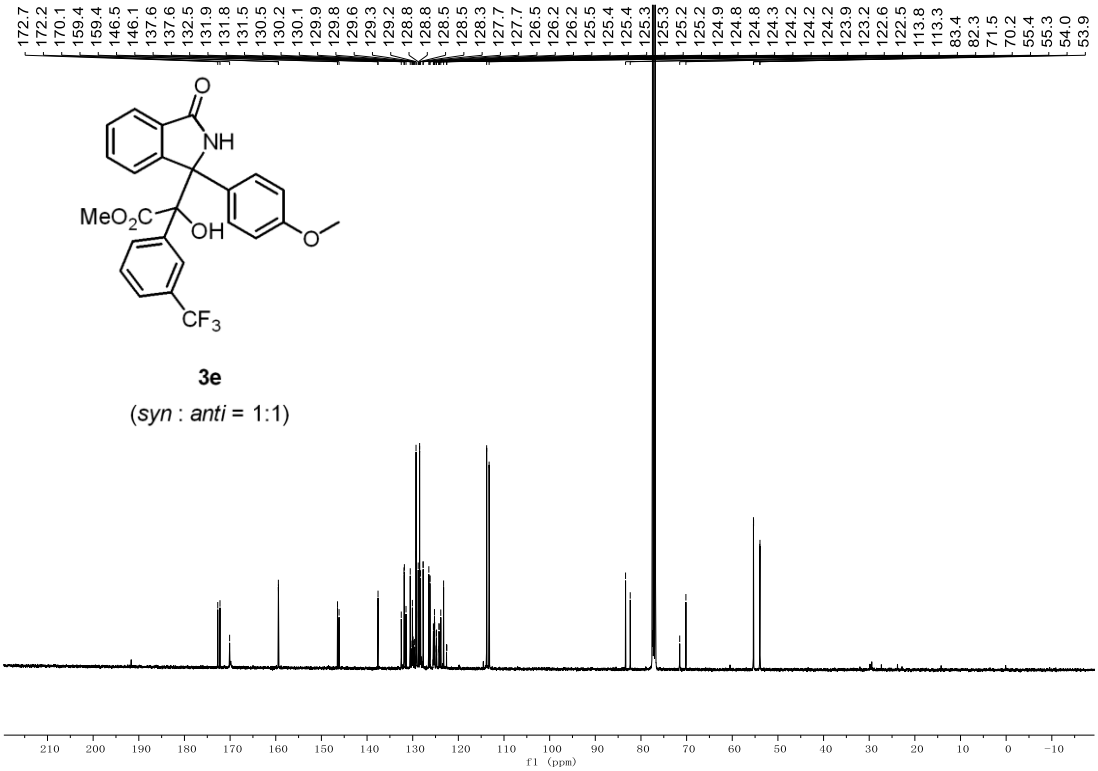






^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$) and ^{19}F NMR (376 MHz, $CDCl_3$) spectra for 3e




172.7
172.2
170.1
159.4
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146.1
137.6
137.6
132.5
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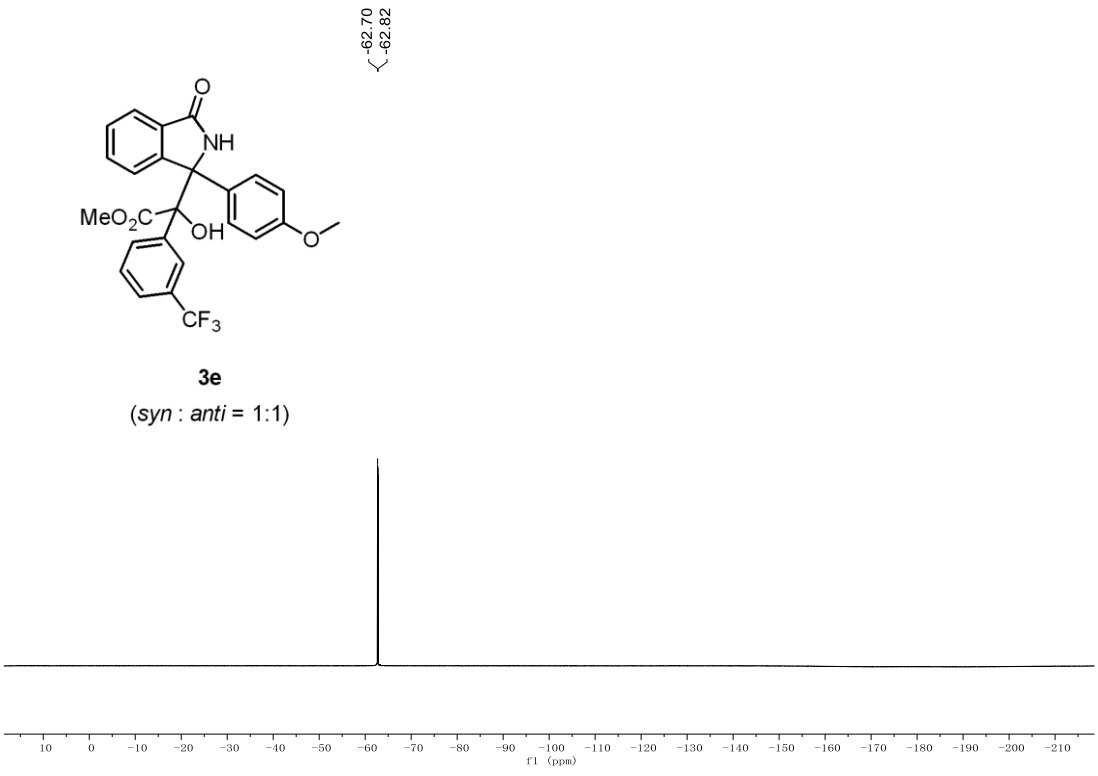
123.9
123.2
122.6
122.5
113.8
113.3
83.4
82.3
71.5
70.2
55.4
55.3
54.0
53.9
O
NH
MeO2C
OH
O
CF3
3e
(syn : anti = 1:1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-62.70
-62.82
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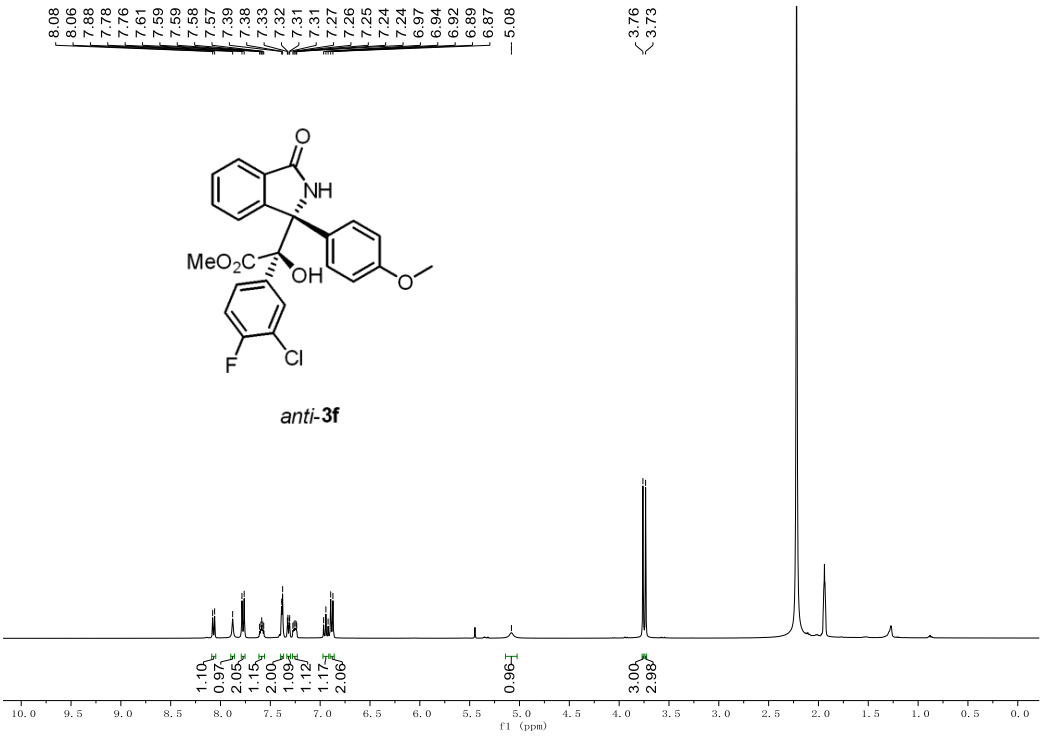
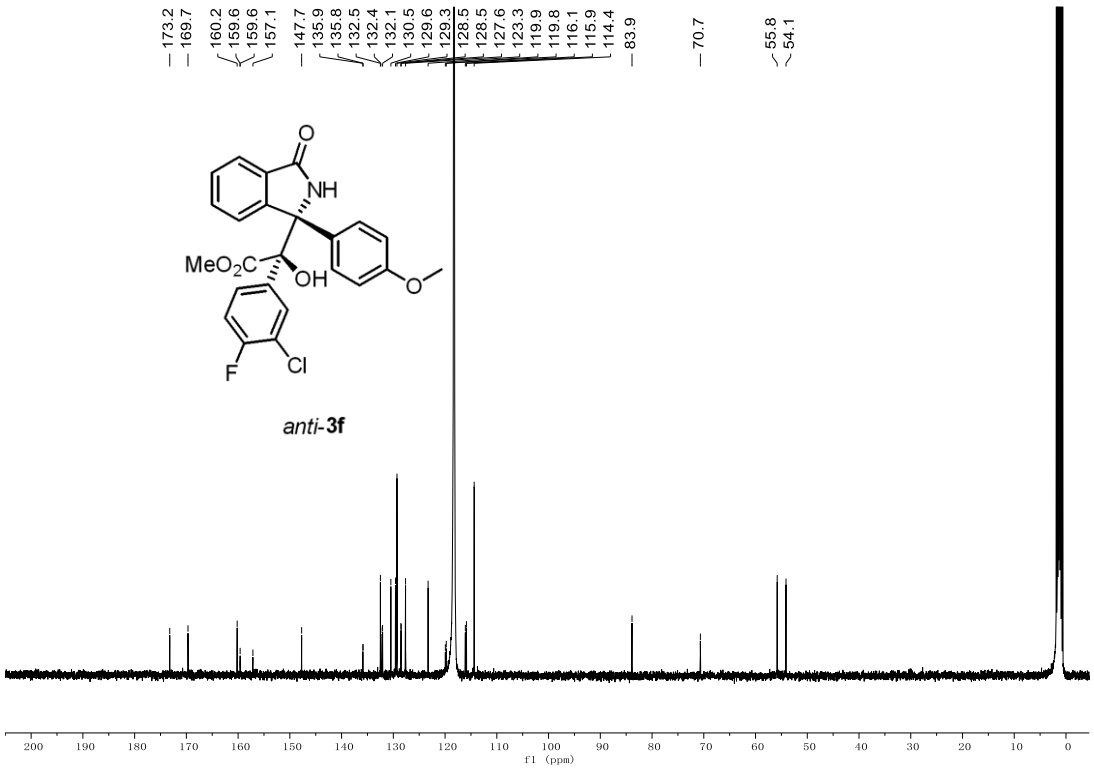
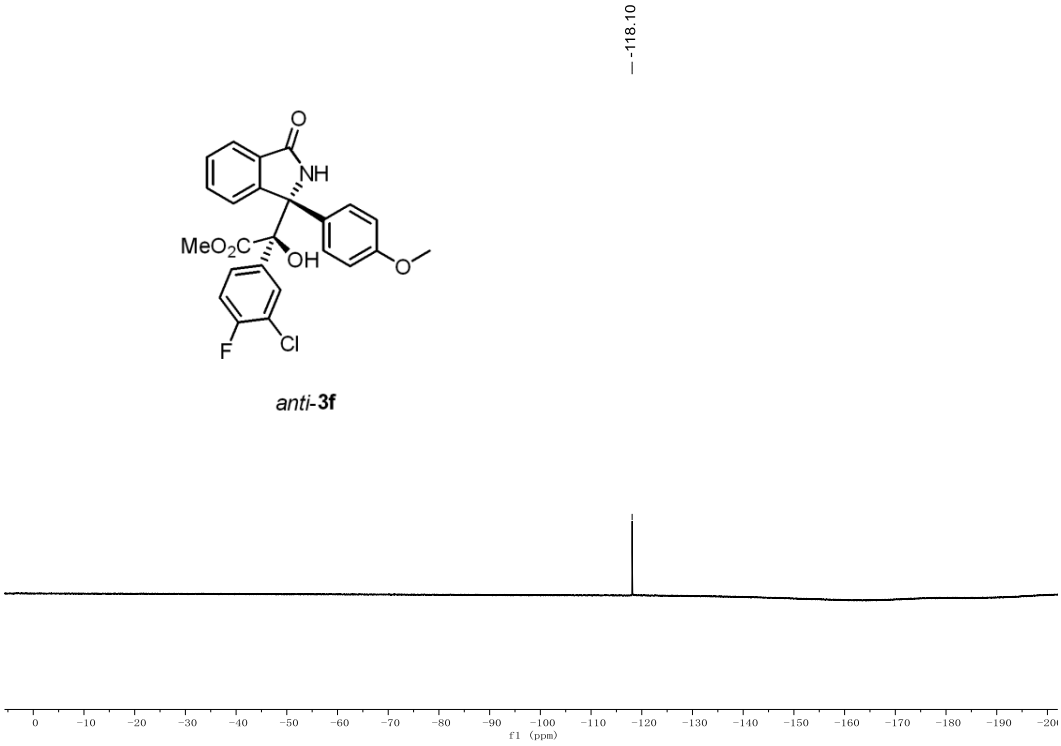
NH
MeO2C
OH
O
CF3
3e
(syn : anti = 1:1)
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

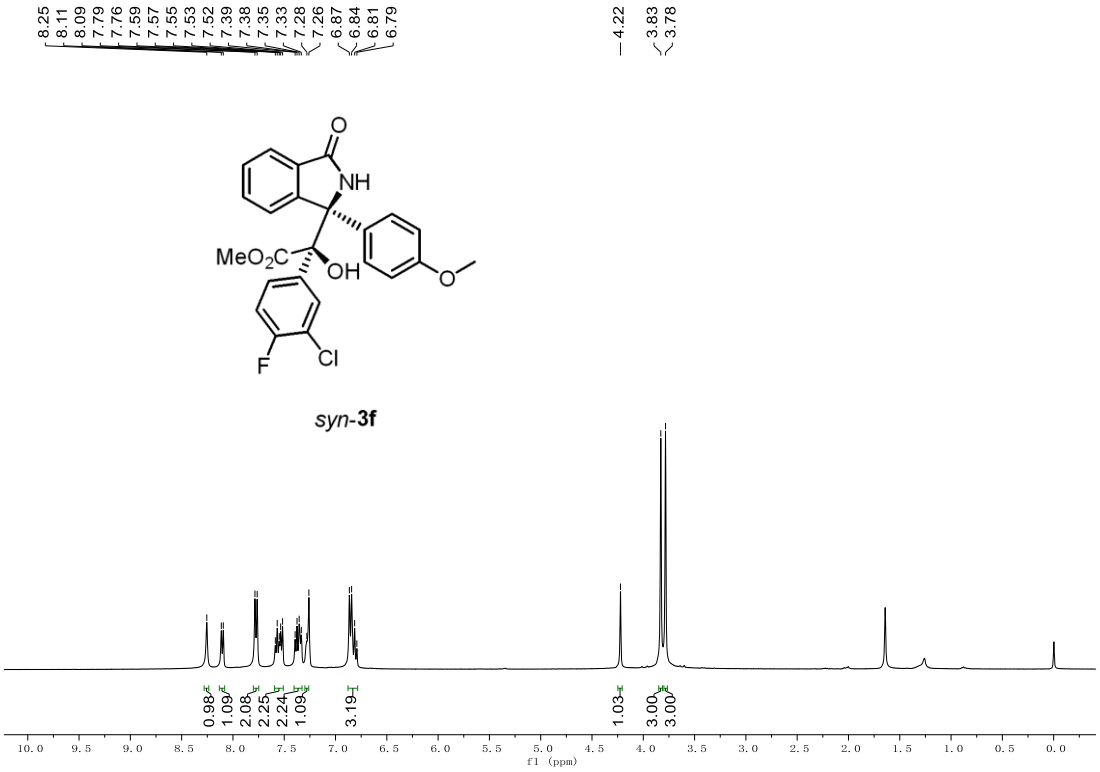
^{1}H NMR (400 MHz, CD_3CN), ^{13}C NMR (100 MHz, CD_3CN) and ^{19}F NMR (376 MHz, CD_3CN) spectra for *anti*-3f

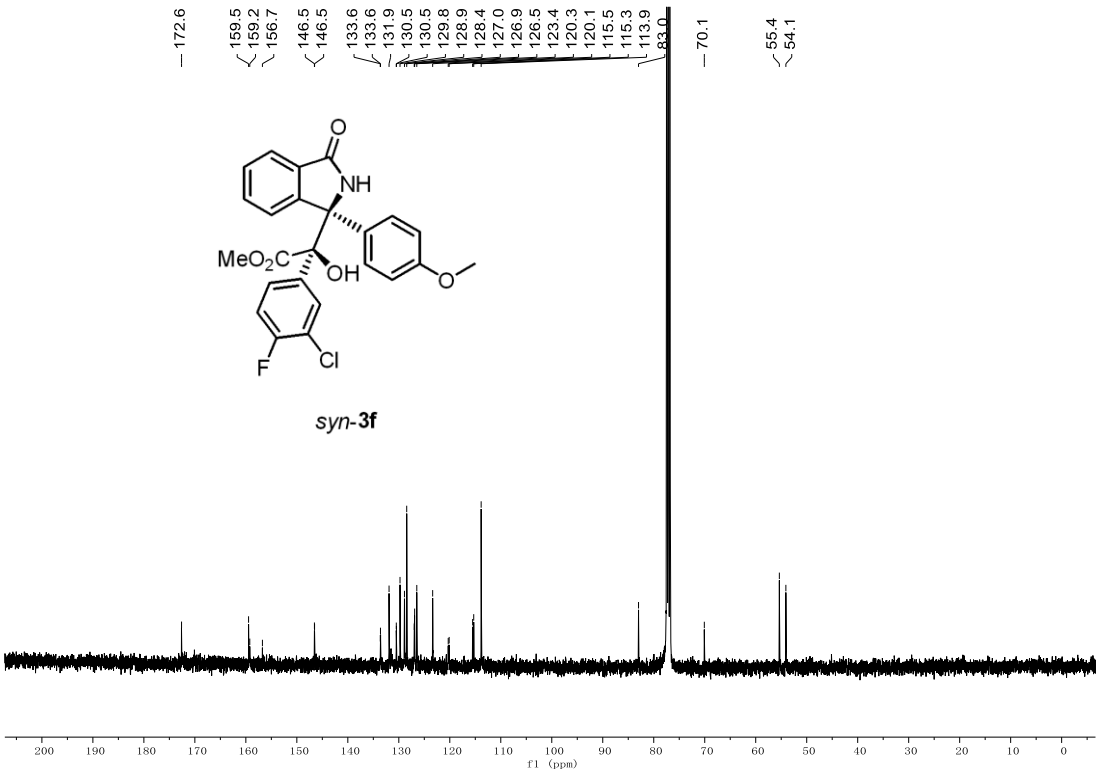






^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$) and ^{19}F NMR (376 MHz, $CDCl_3$) spectra for *syn*-3f




172.6
159.5
159.2
156.7
146.5
146.5
133.6
133.6
131.9
130.5
130.5
129.8
128.9
128.4
127.0
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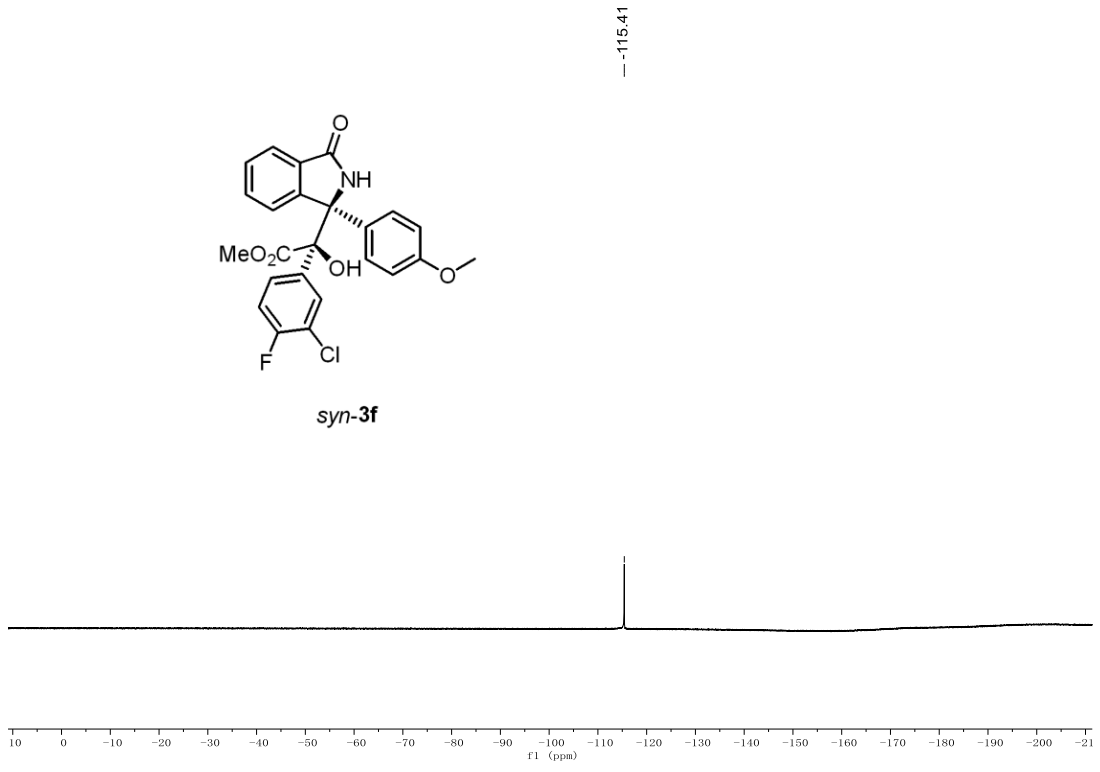
126.5
123.4
120.3
120.1
115.5
115.3
113.9
83.0
70.1
55.4
54.1
O
NH
MeO2C
OH
O
F
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

syn-**3f**


-115.41
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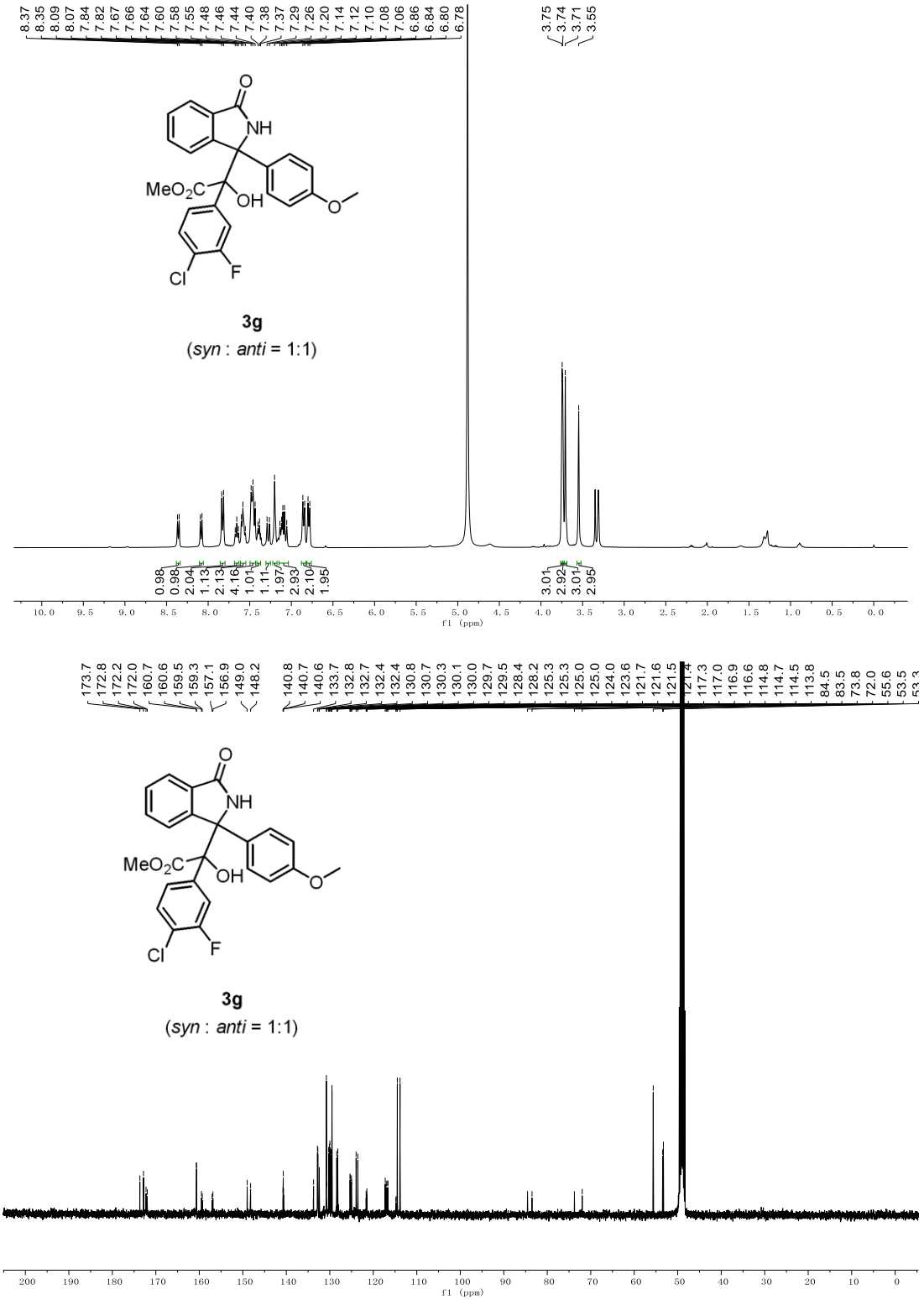
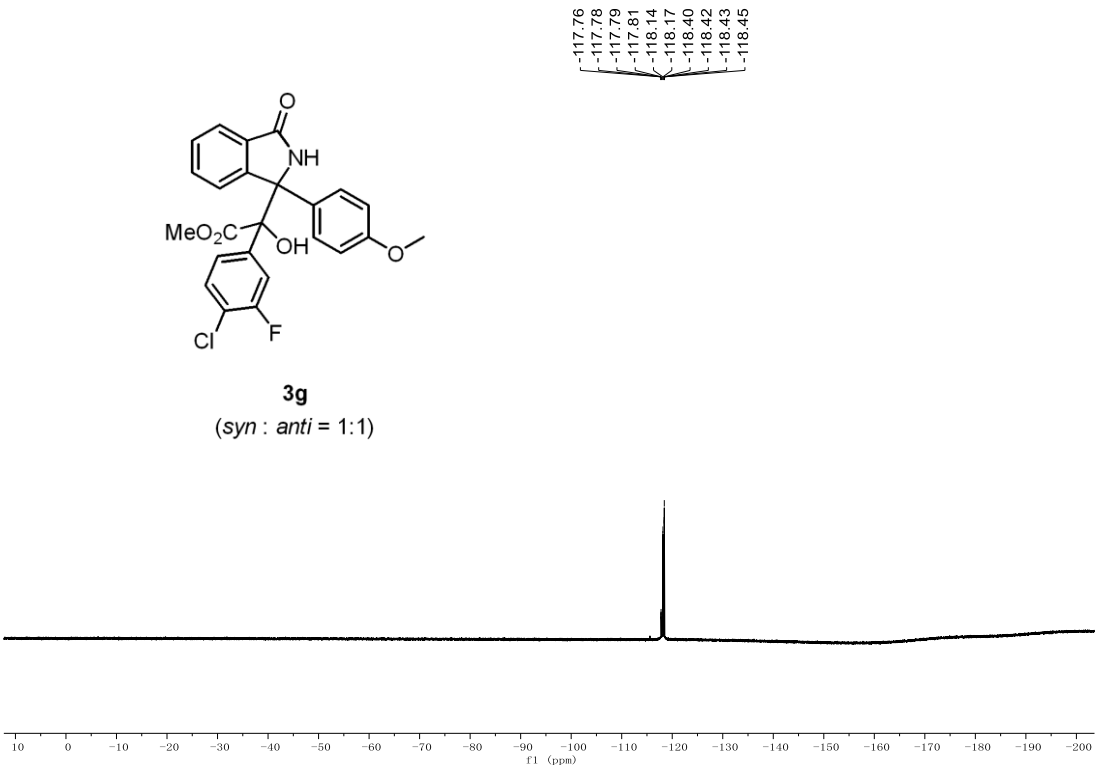
MeO2C
OH
O
F
Cl
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -21
f1 (ppm)

syn-**3f**

^{1}H NMR (400 MHz, CD_3OD), ^{13}C NMR (100 MHz, CD_3OD) and ^{19}F NMR (376 MHz, CD_3OD) spectra for 3g

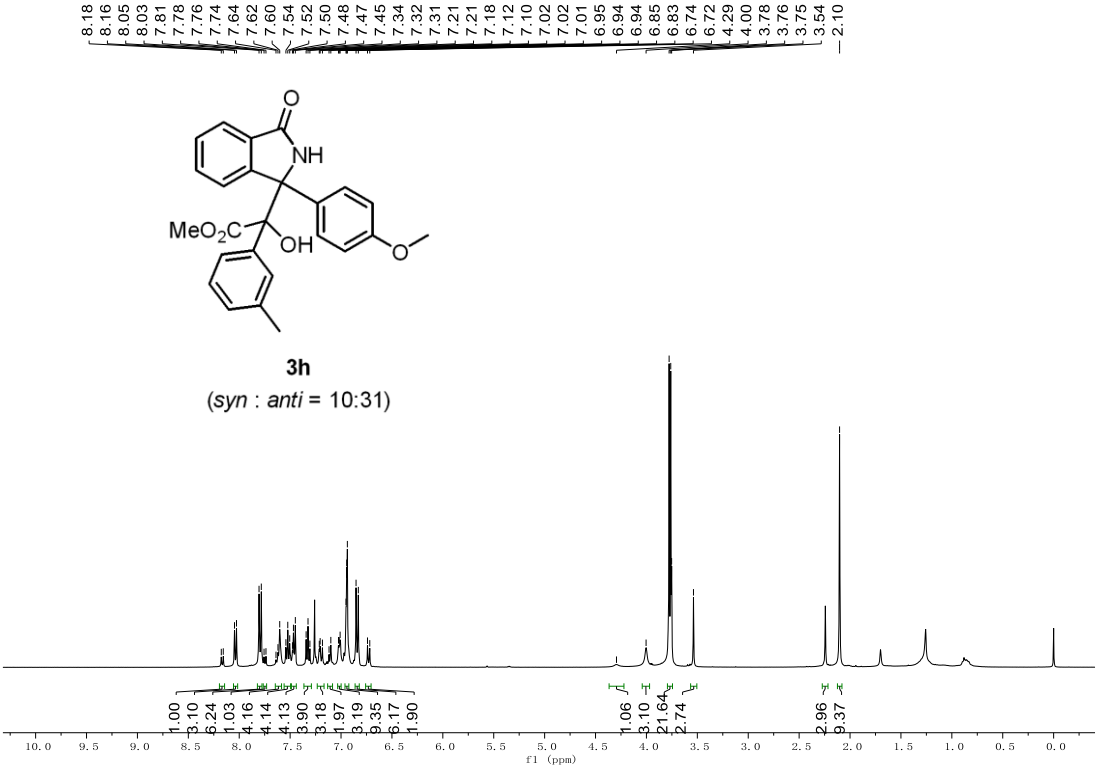




3g

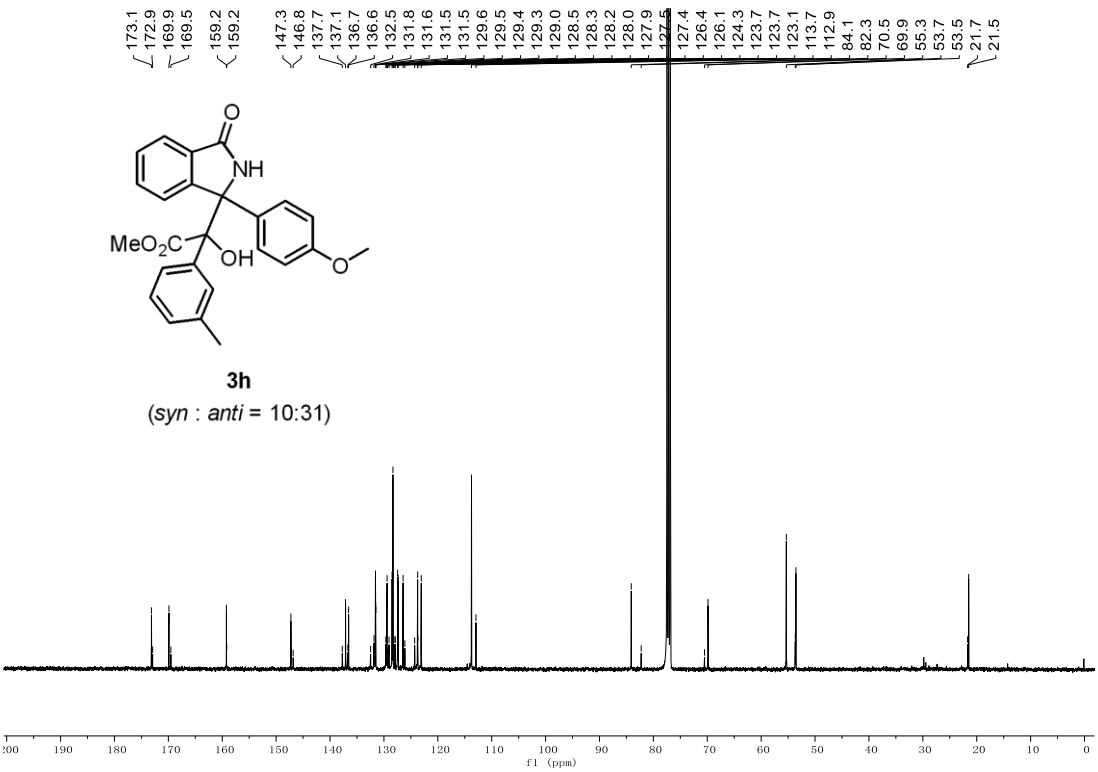
(*syn* : *anti* = 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for 3h

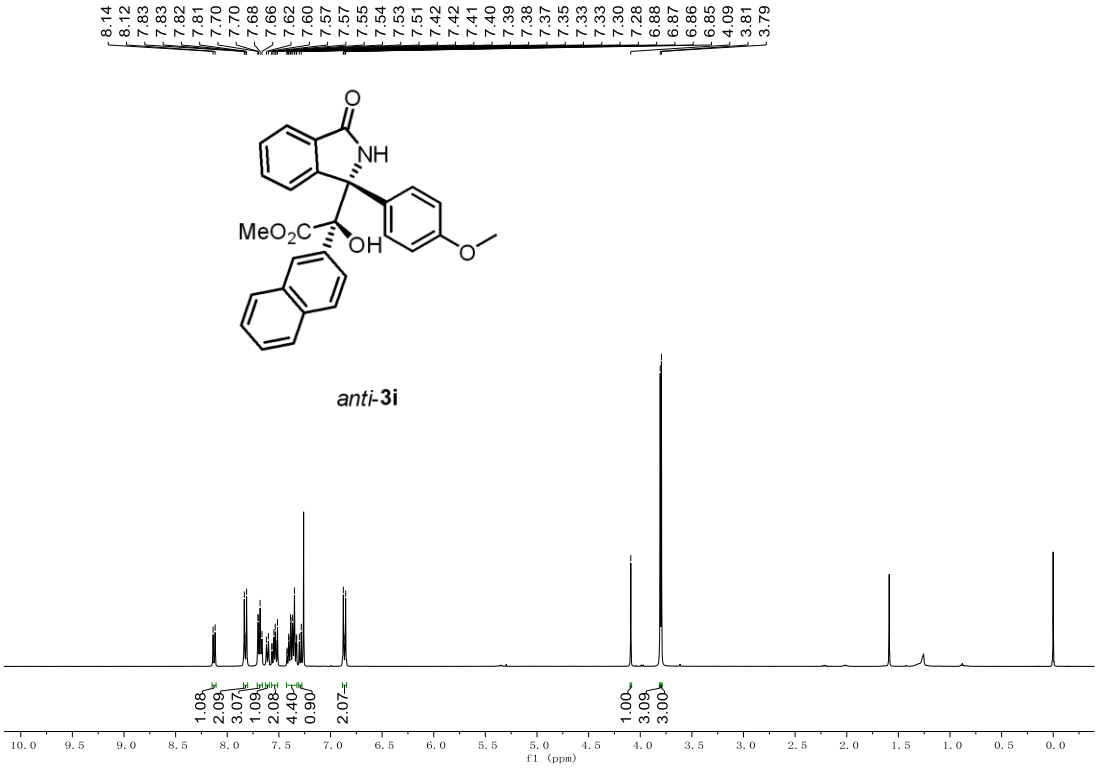


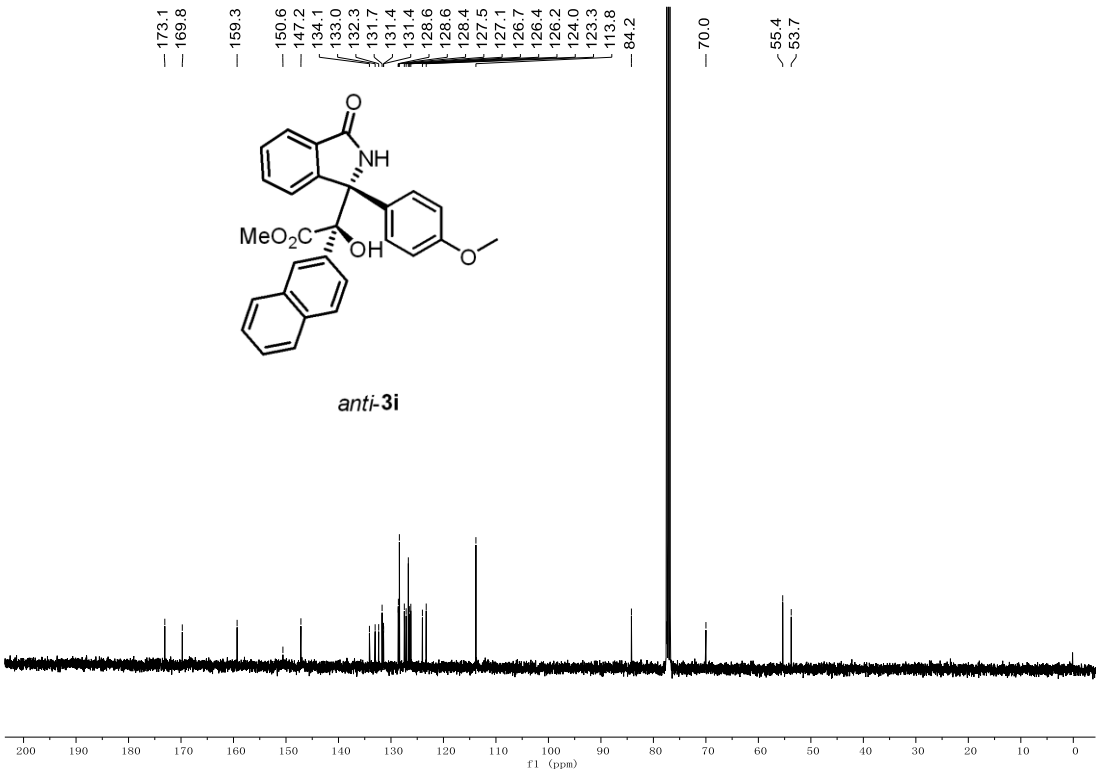
3h

(*syn* : *anti* = 10:31)

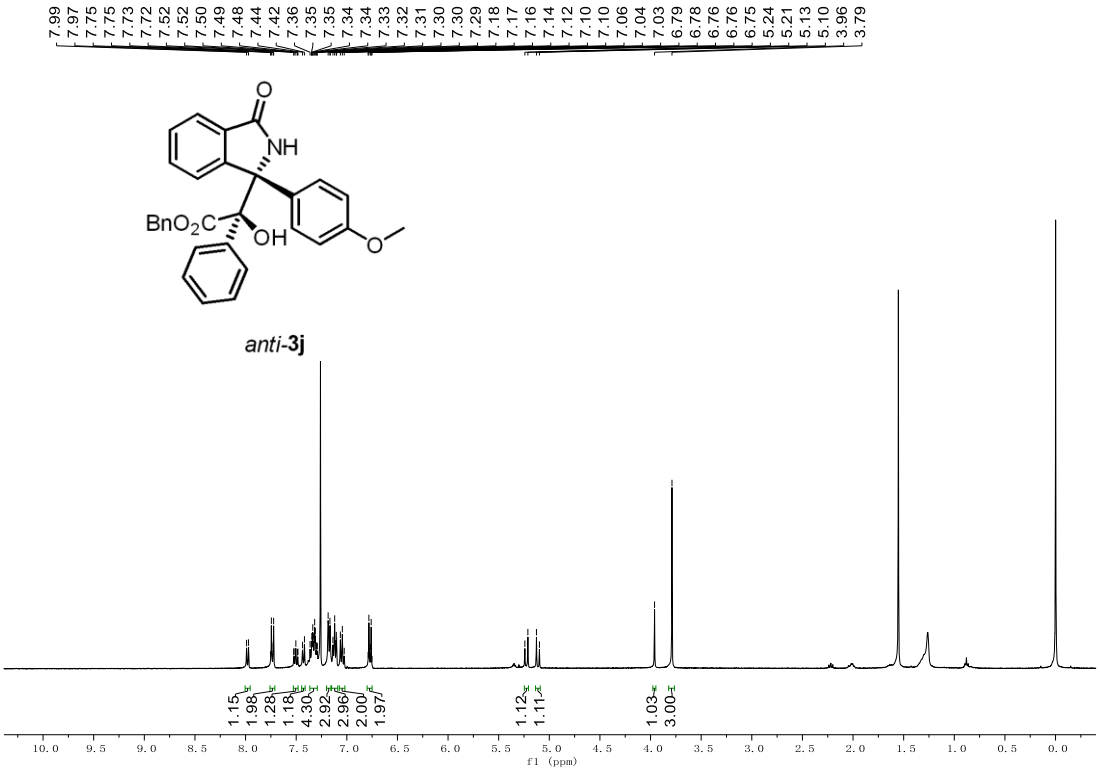


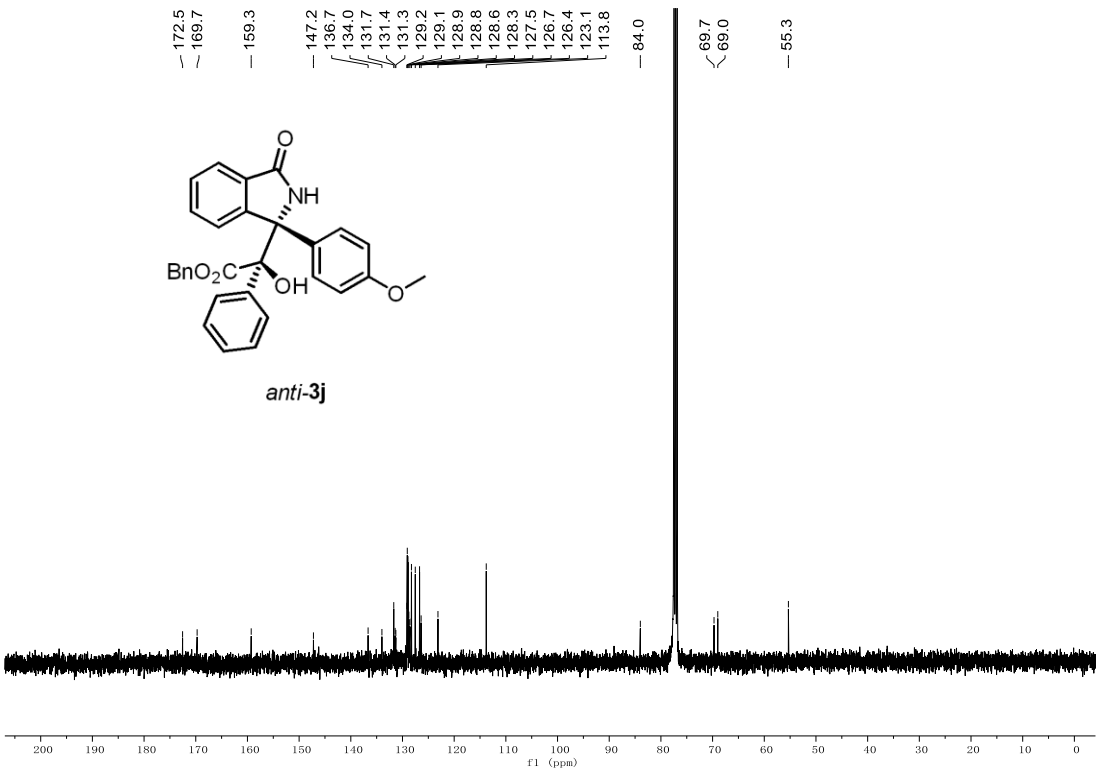
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *anti*-3i



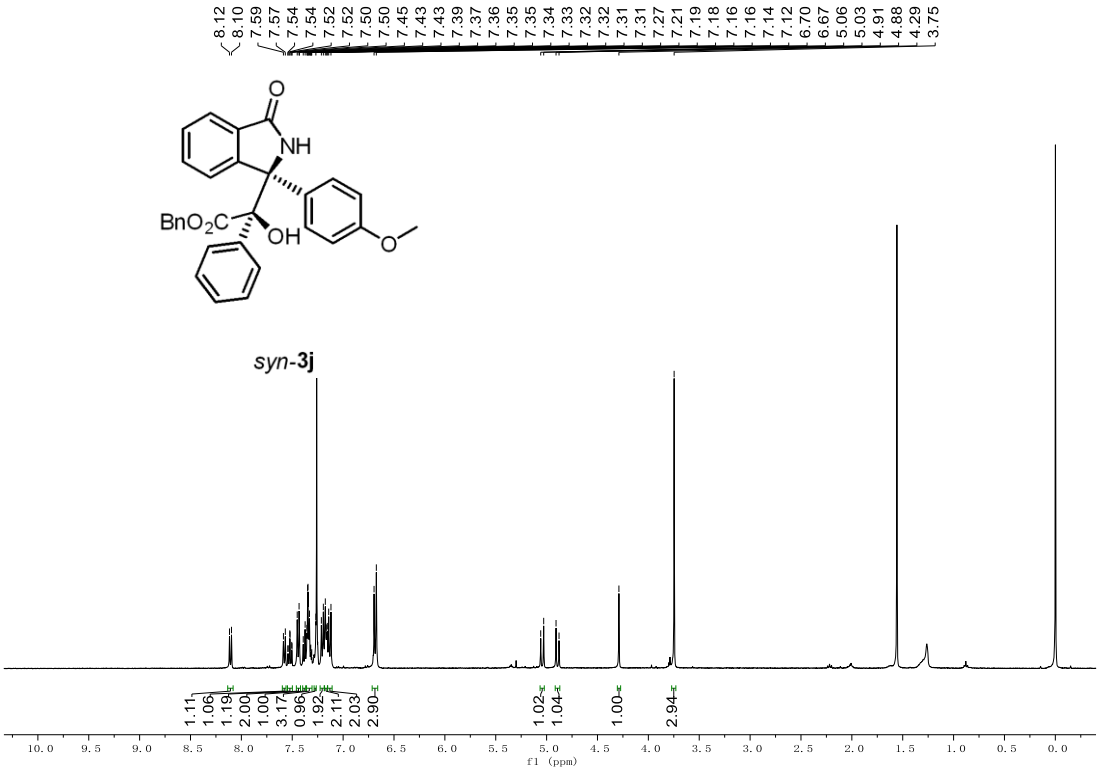


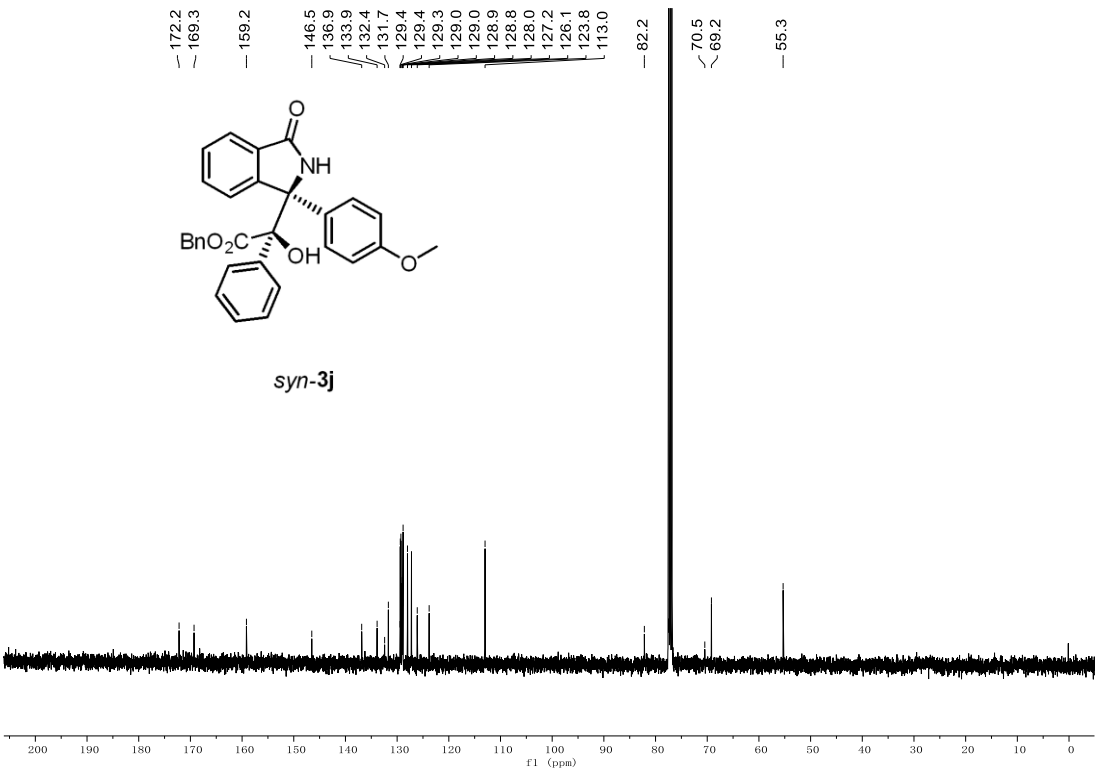
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *anti*-3j





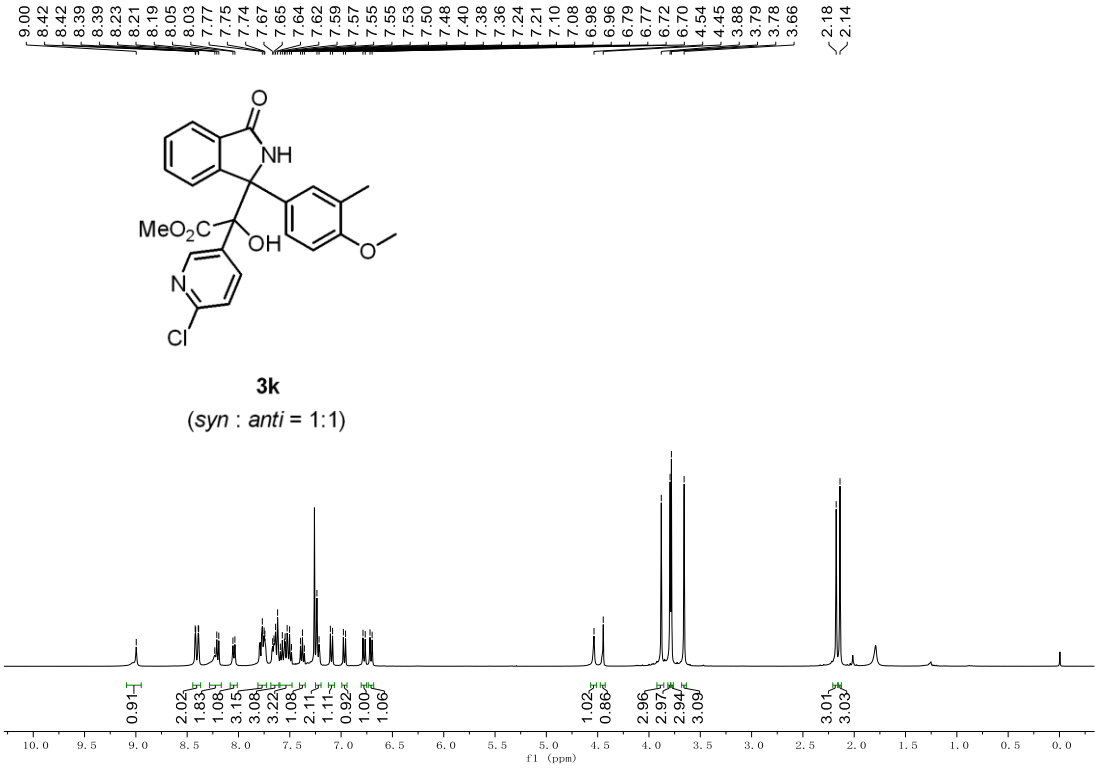
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *syn*-3j





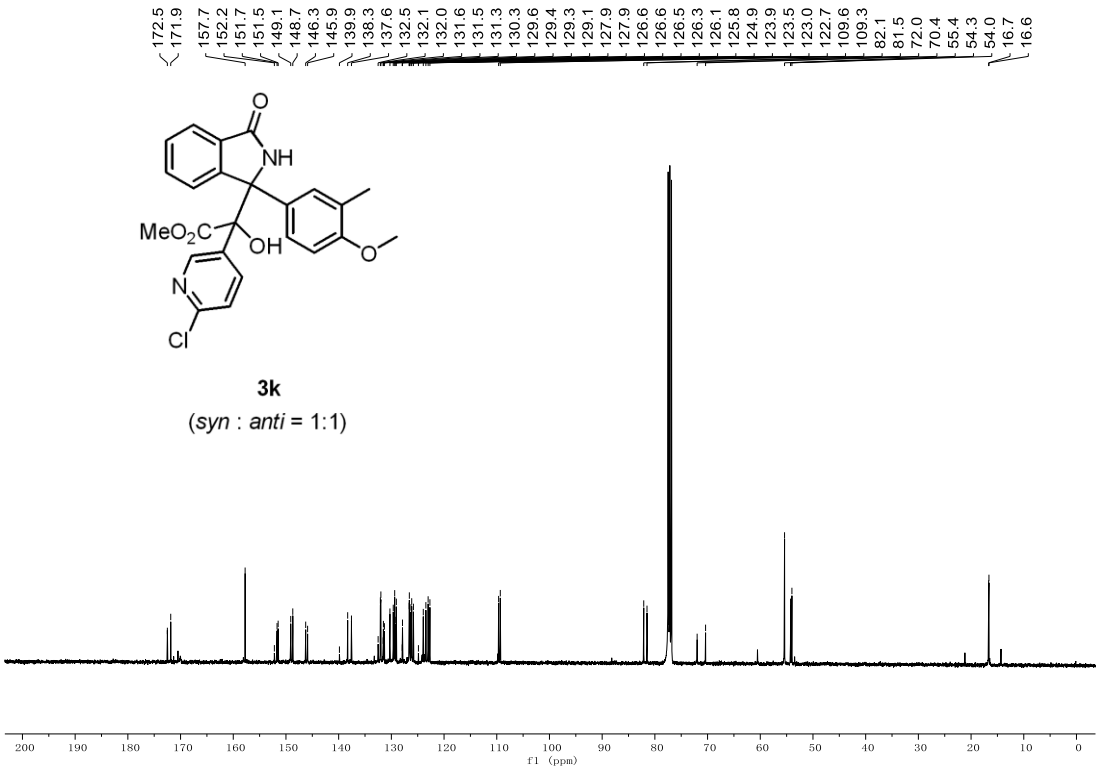
syn-**3j**

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for 3k

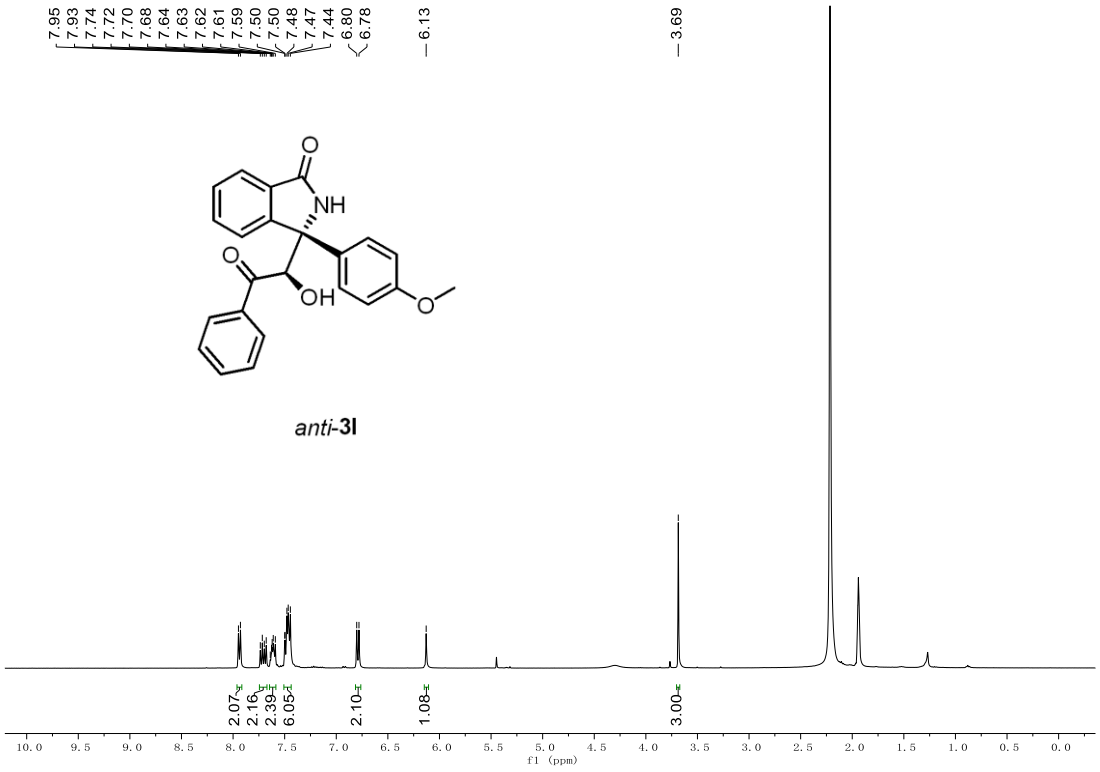


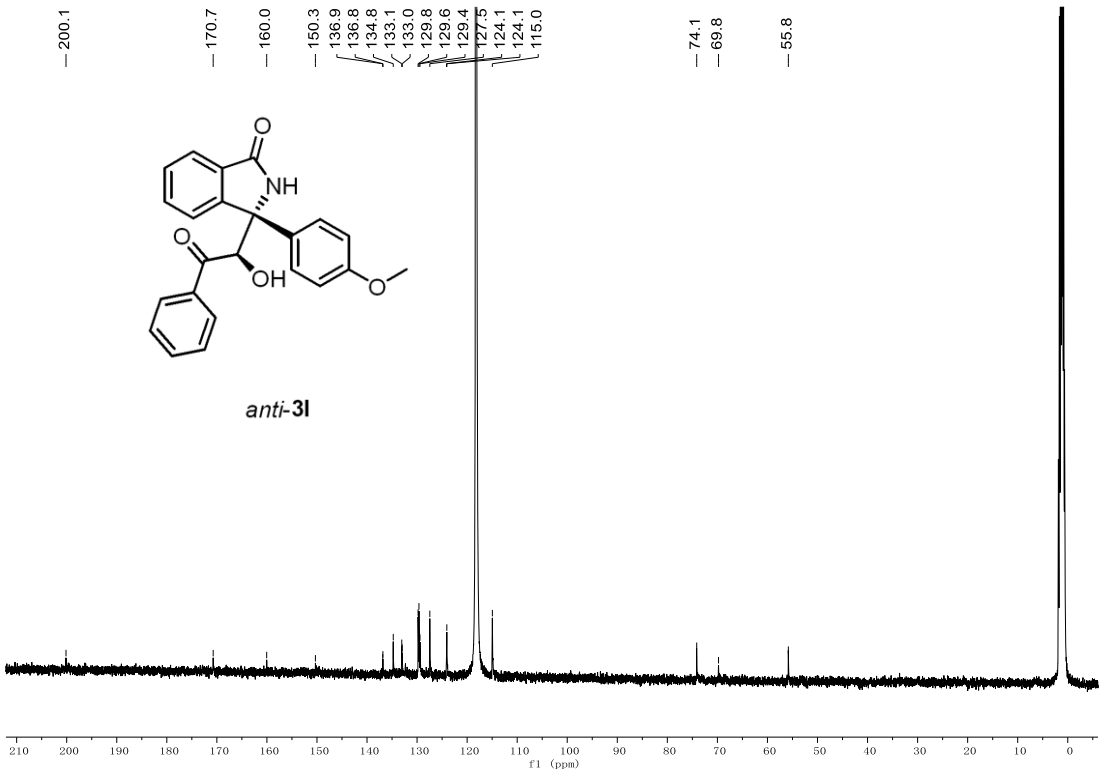
3k

(*syn* : *anti* = 1:1)

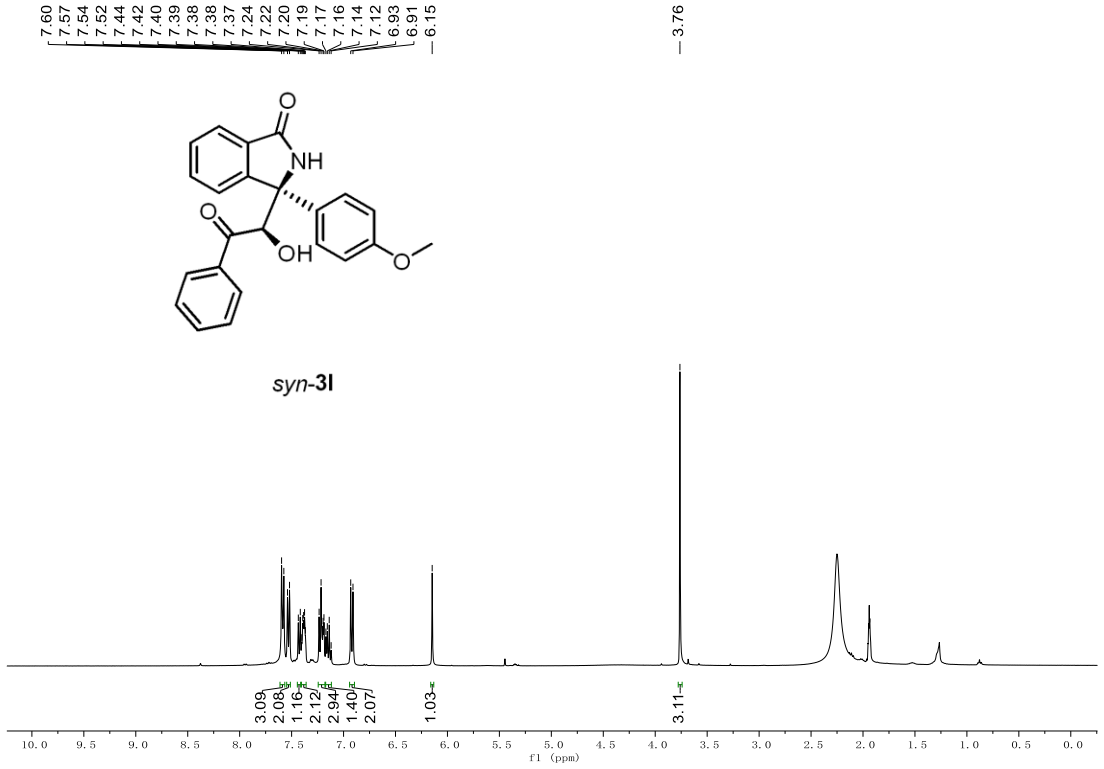


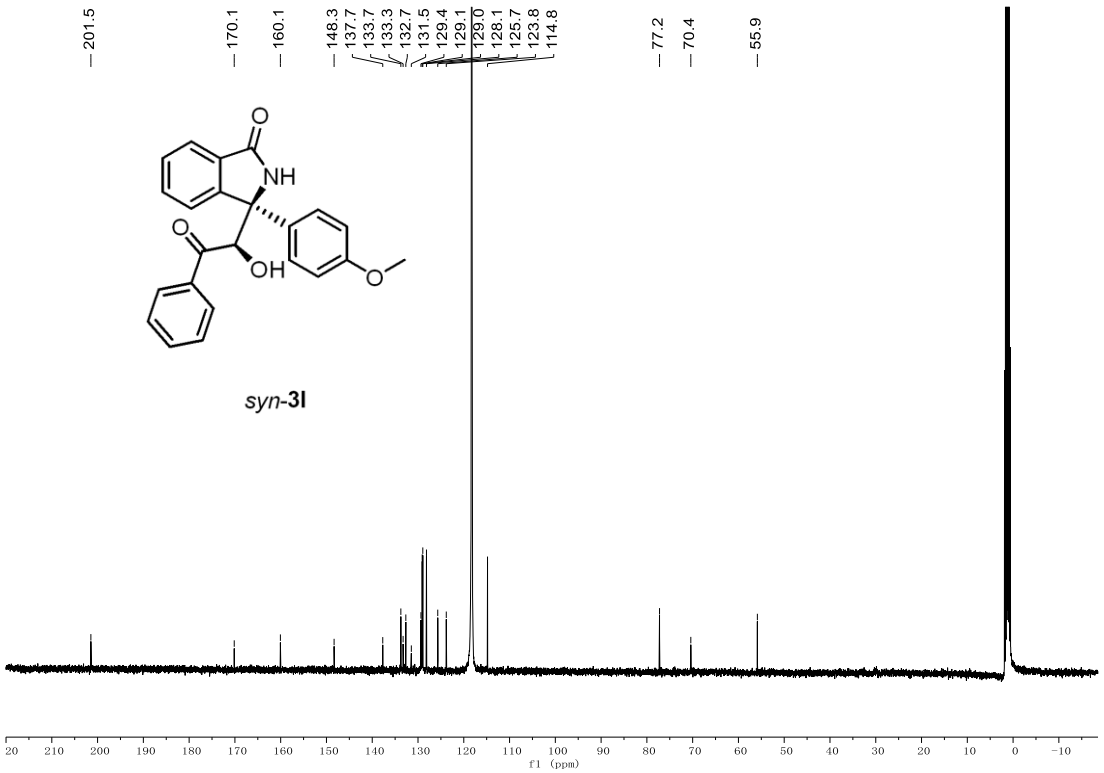
^{1}H NMR (400 MHz, CD_3CN) and ^{13}C NMR (100 MHz, CD_3CN) spectra for *anti*-3l





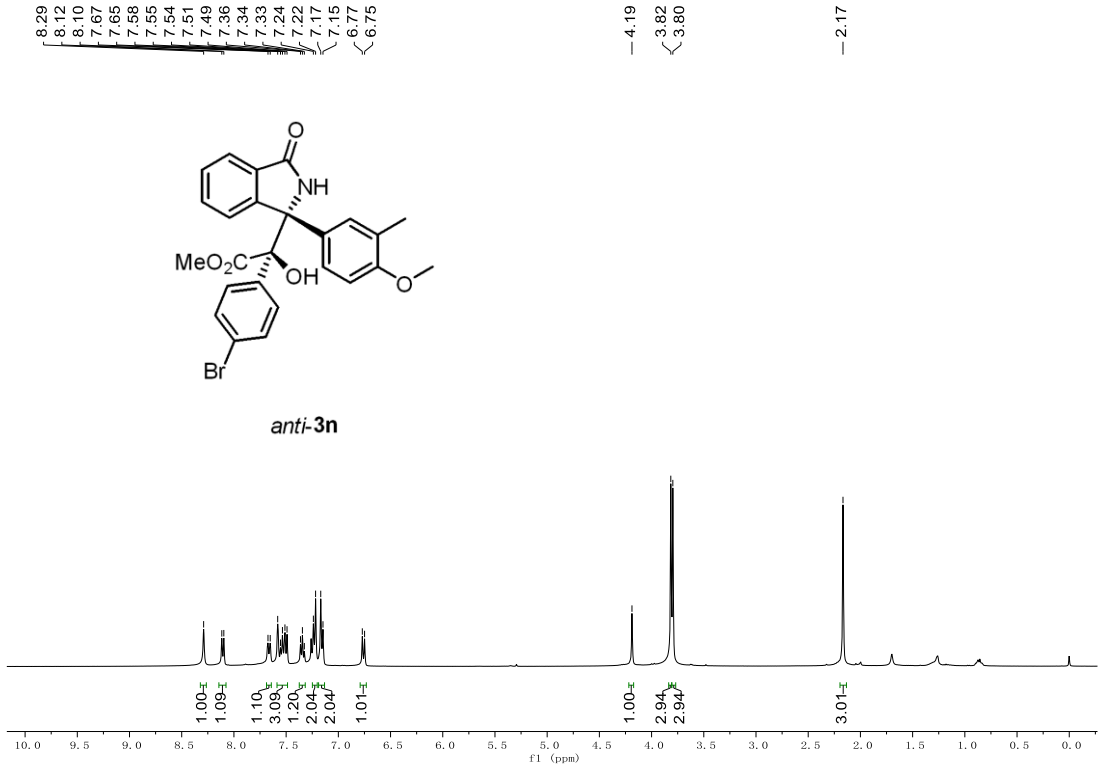
^{1}H NMR (400 MHz, CD_3CN) and ^{13}C NMR (100 MHz, CD_3CN) spectra for *syn*-3l



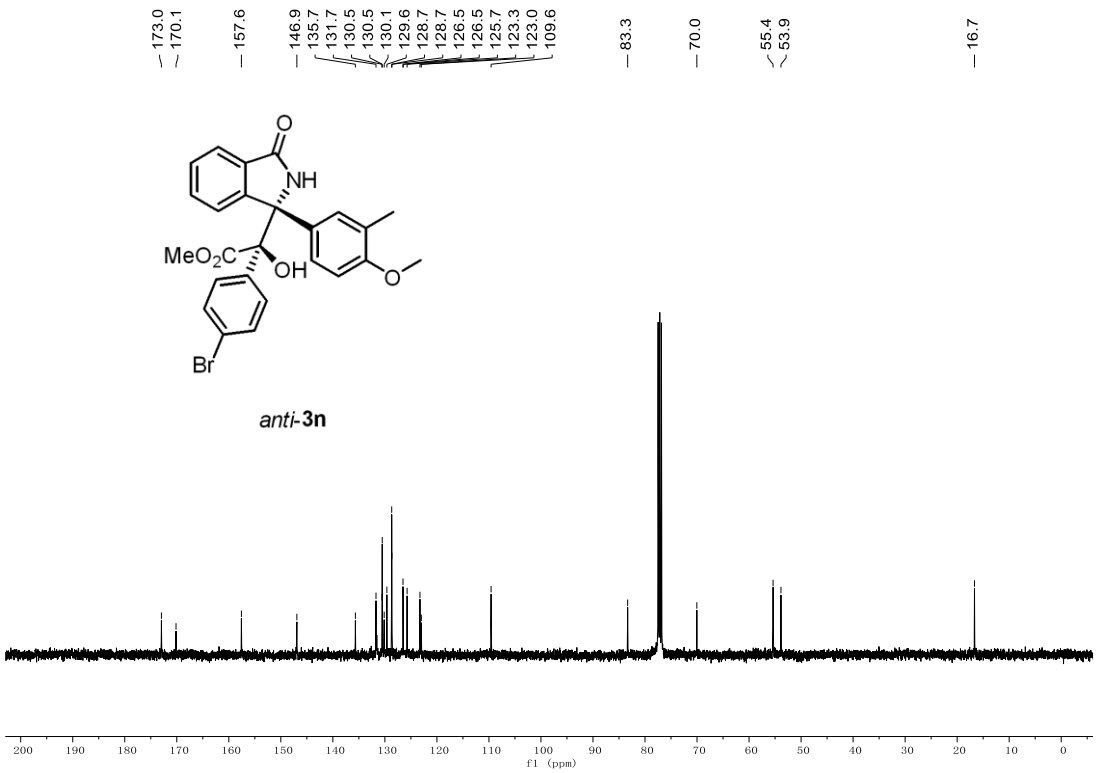


syn-**3l**

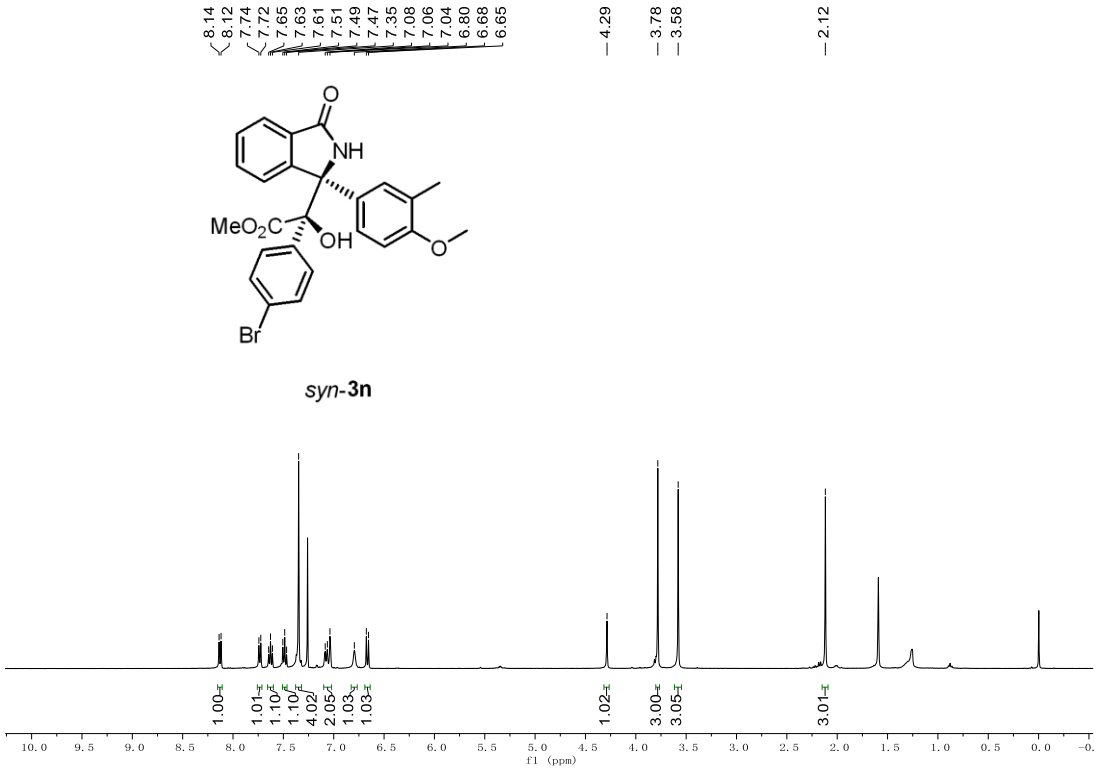
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *anti*-3n

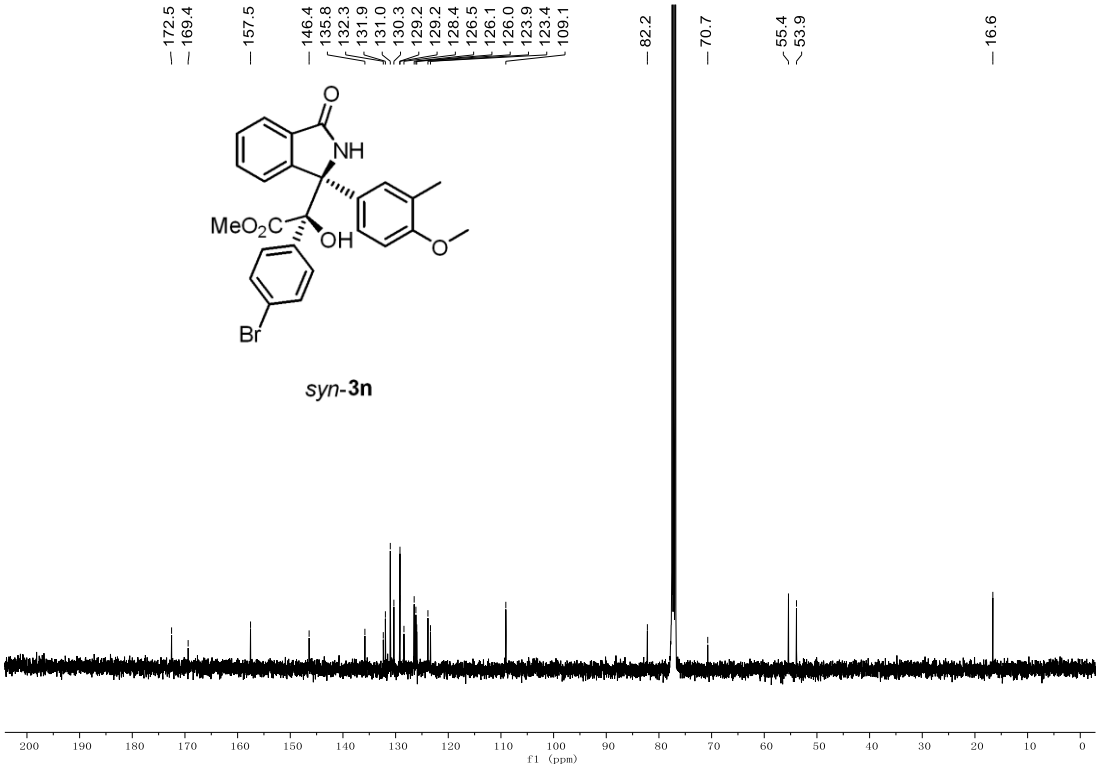


anti-**3n**



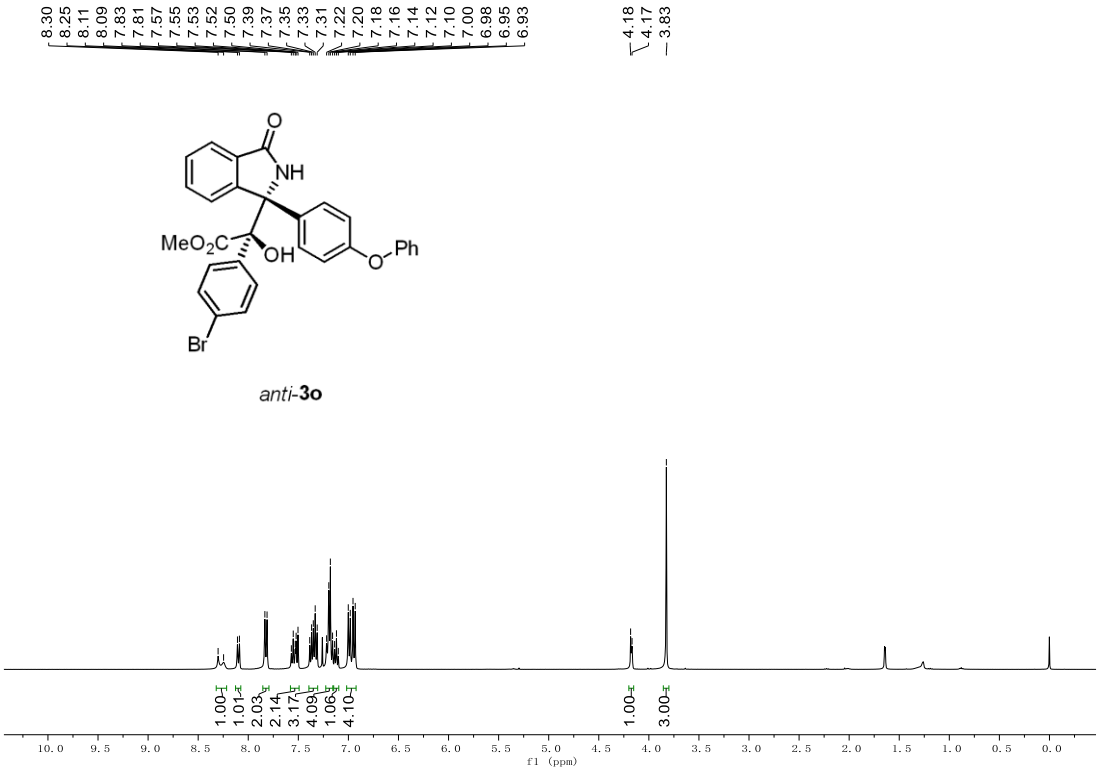
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *syn*-3n



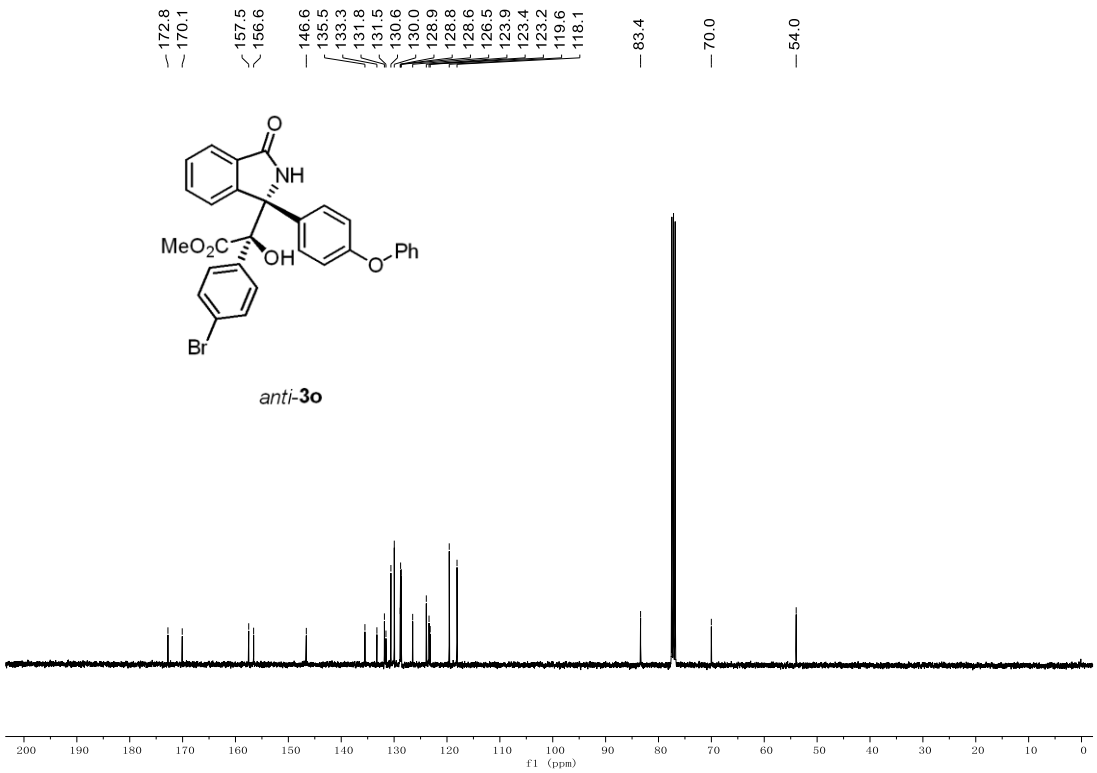


syn-**3n**

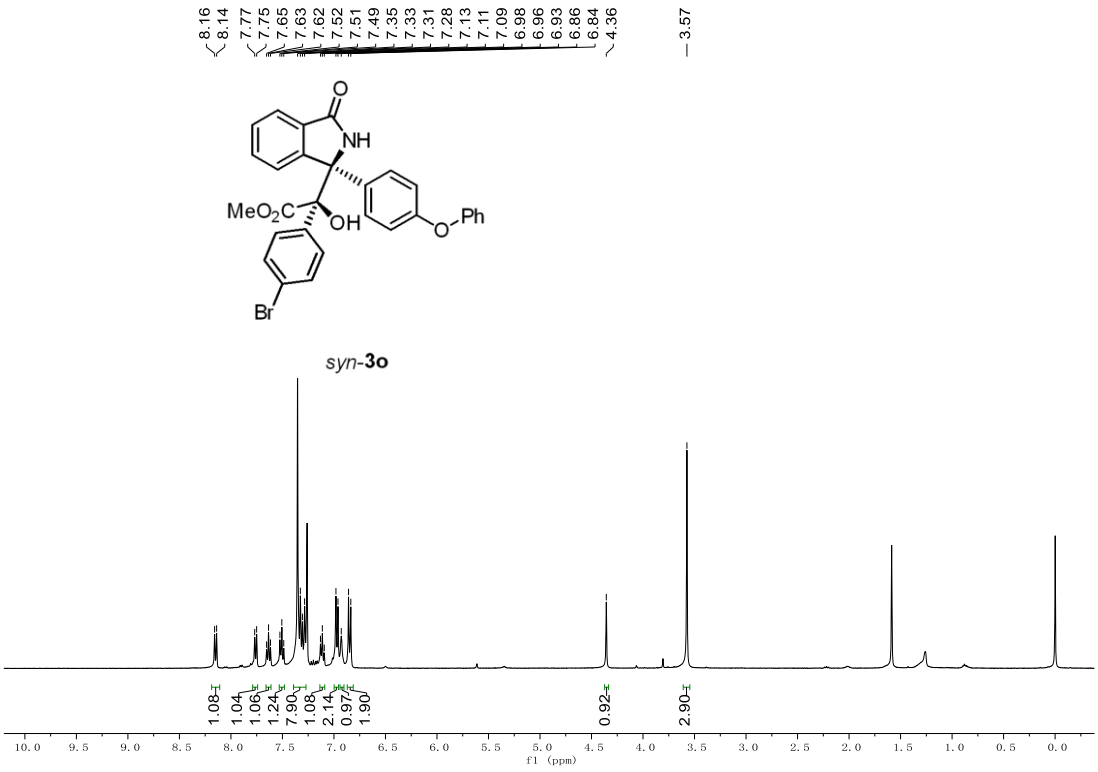
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *anti*-3o

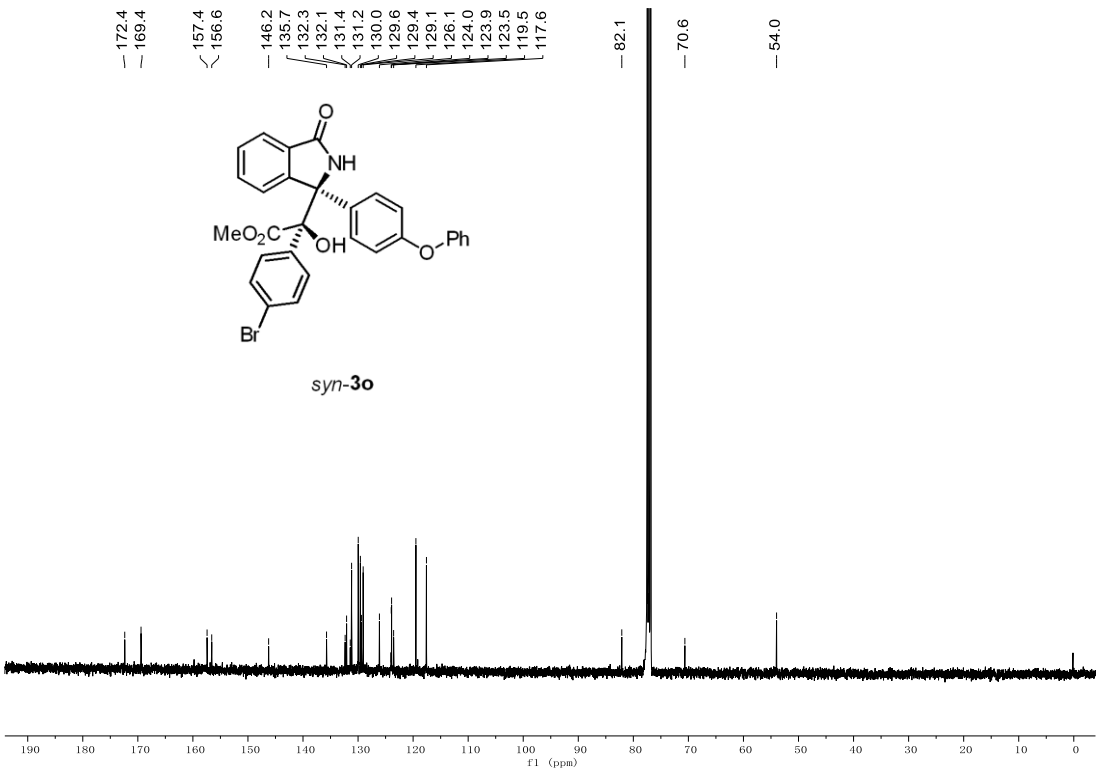


anti-**3o**



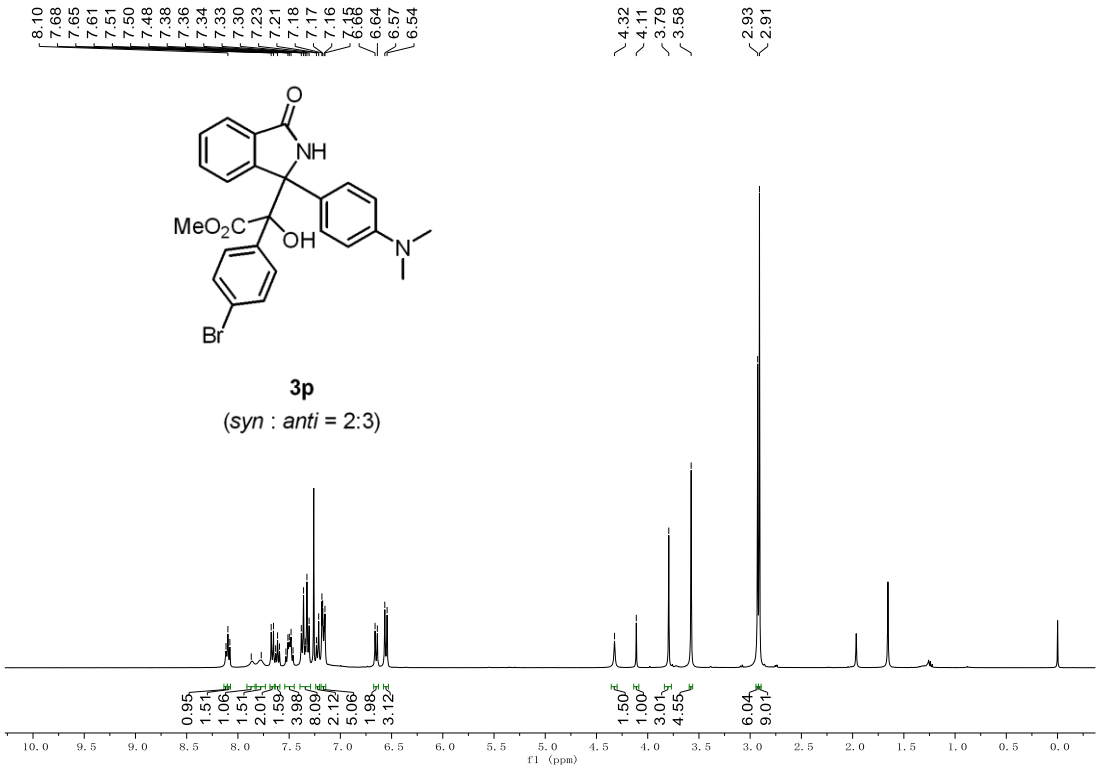
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *syn*-3o





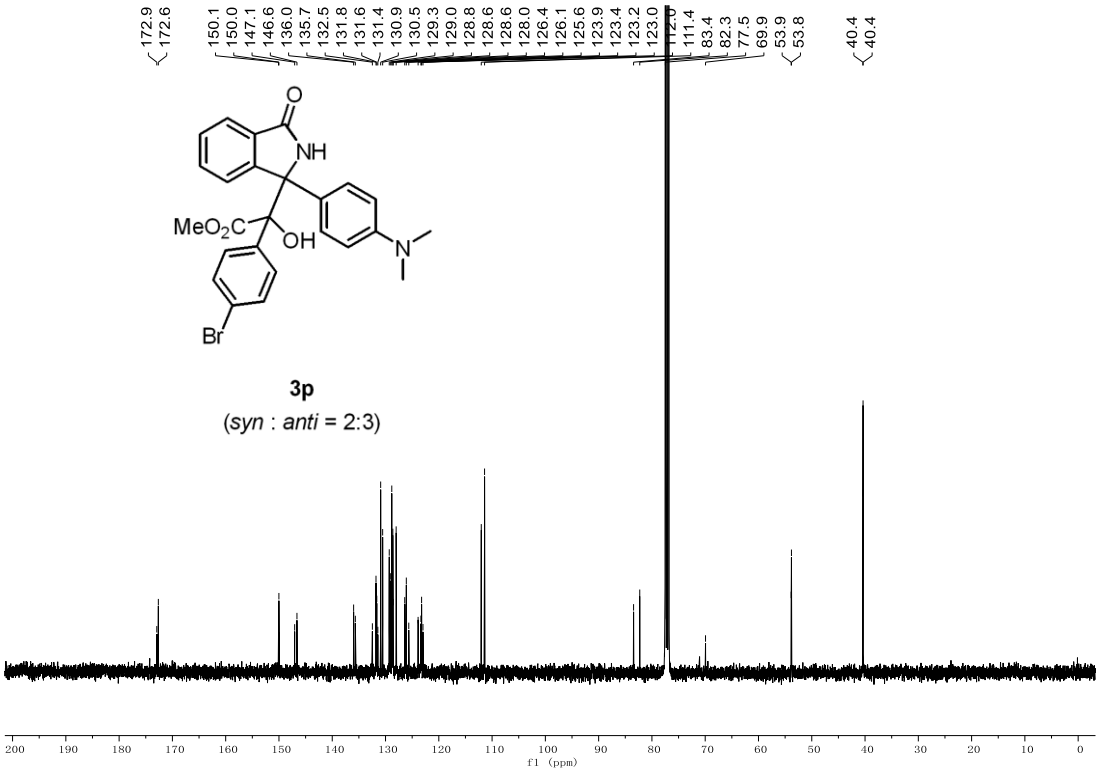
syn-**3o**

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for 3p

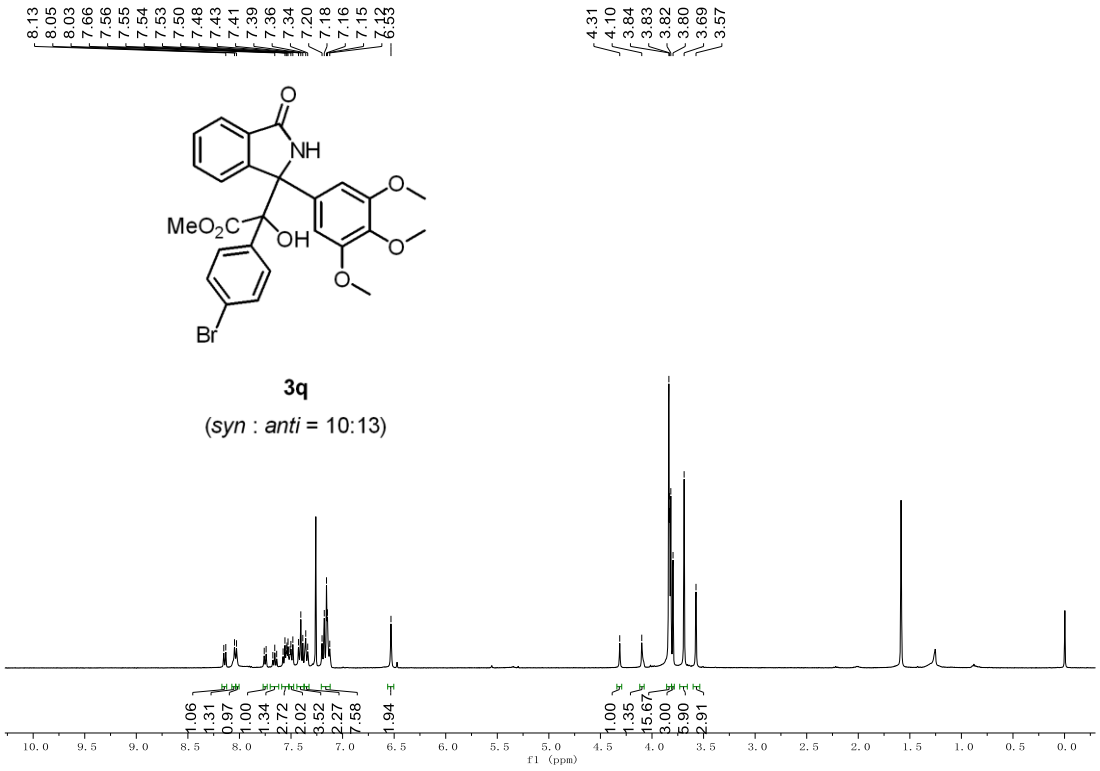


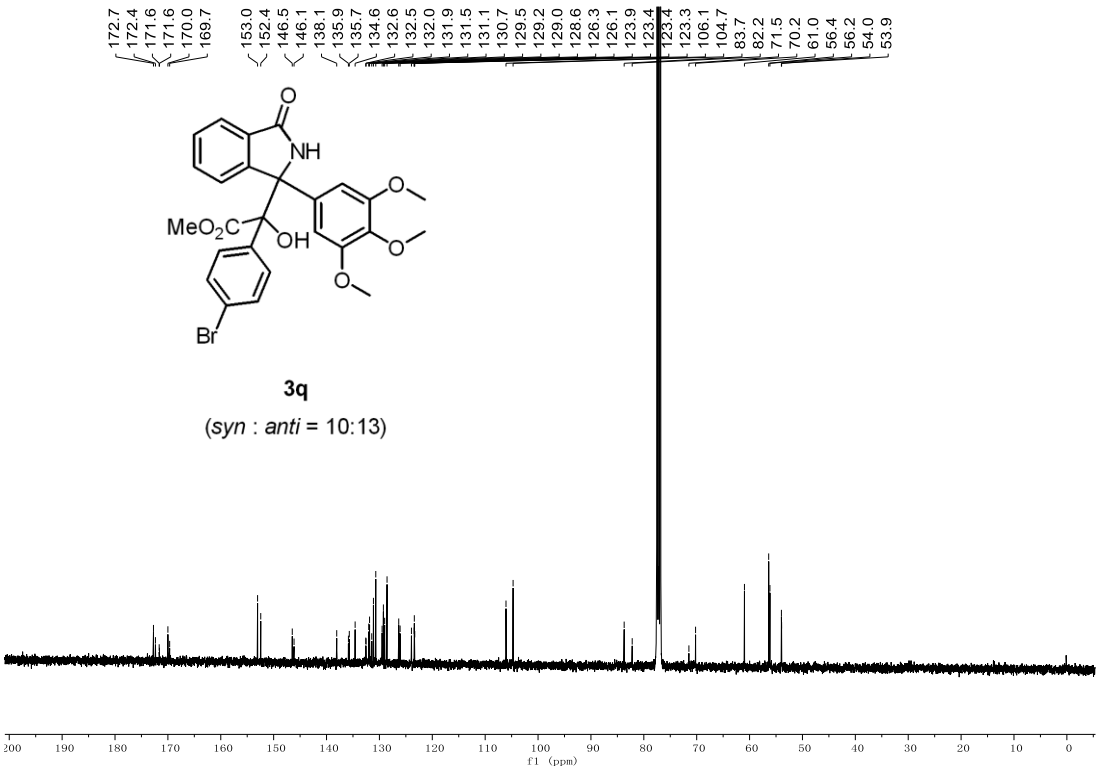
3p

(*syn* : *anti* = 2:3)

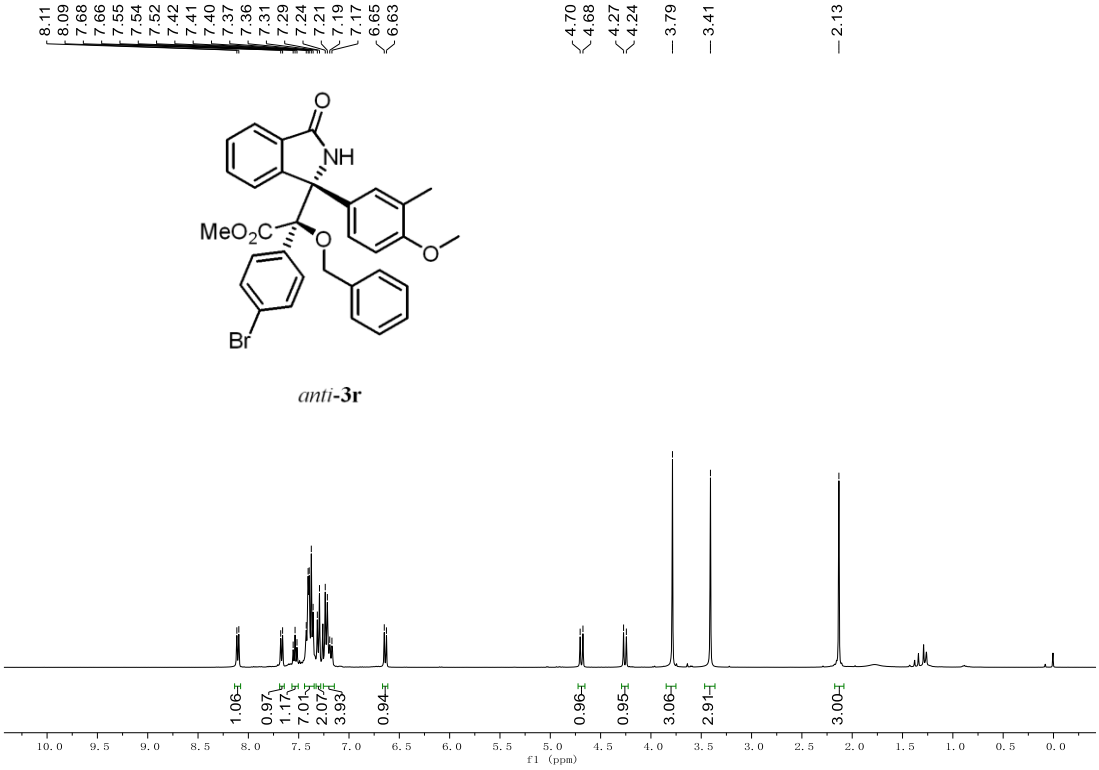


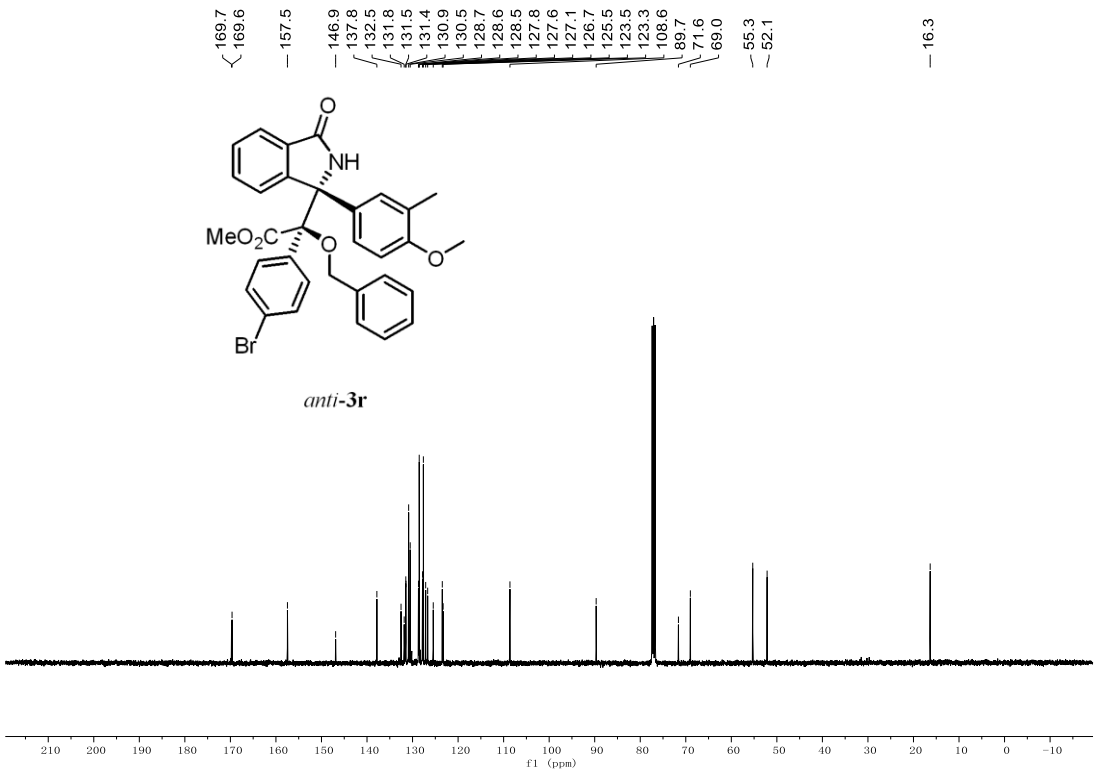
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for 3q



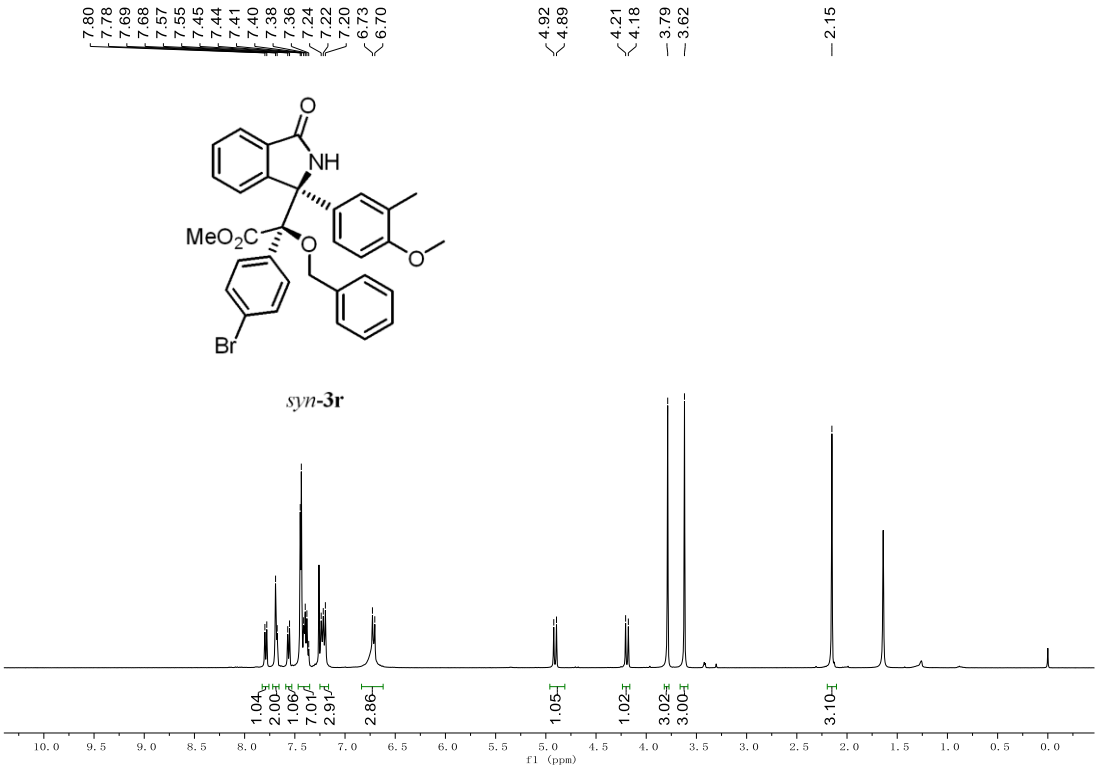


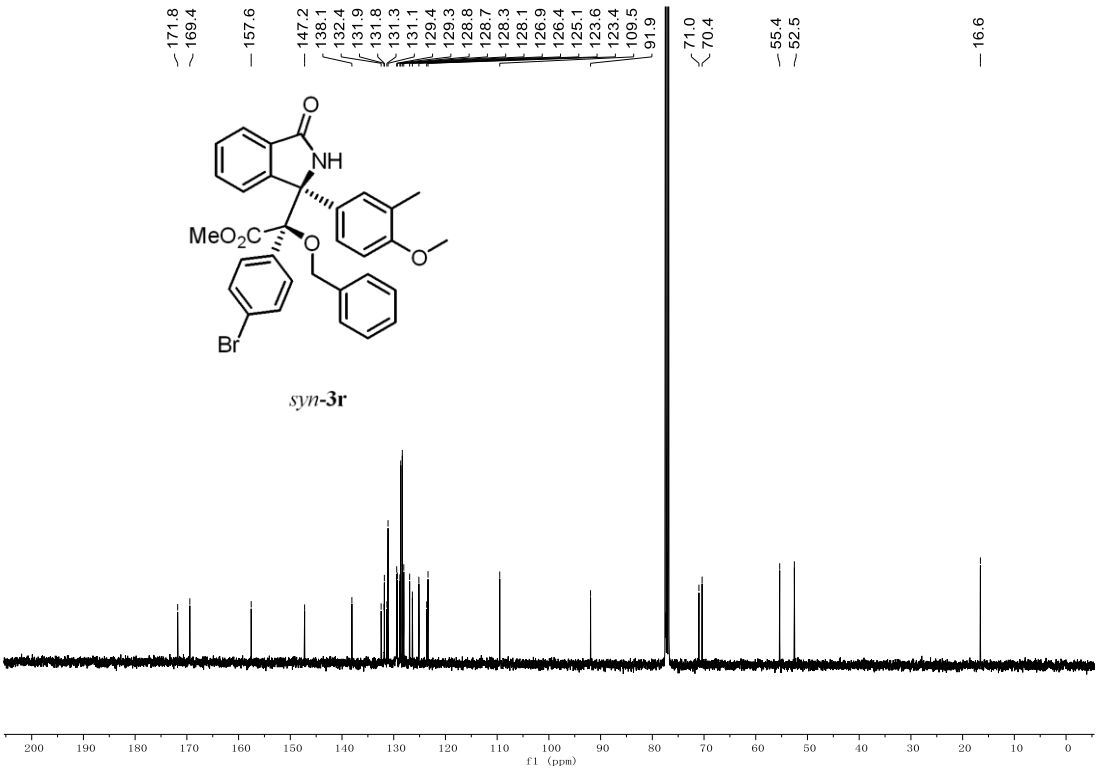
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *anti*-3r





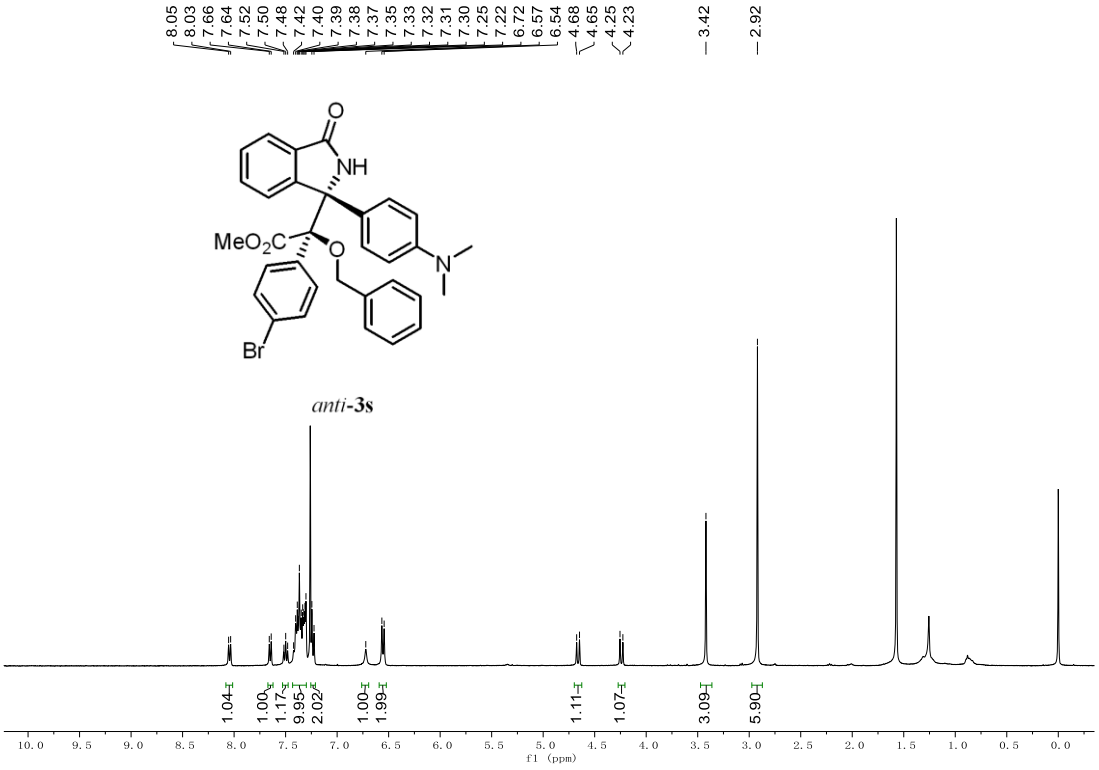
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *syn*-3r



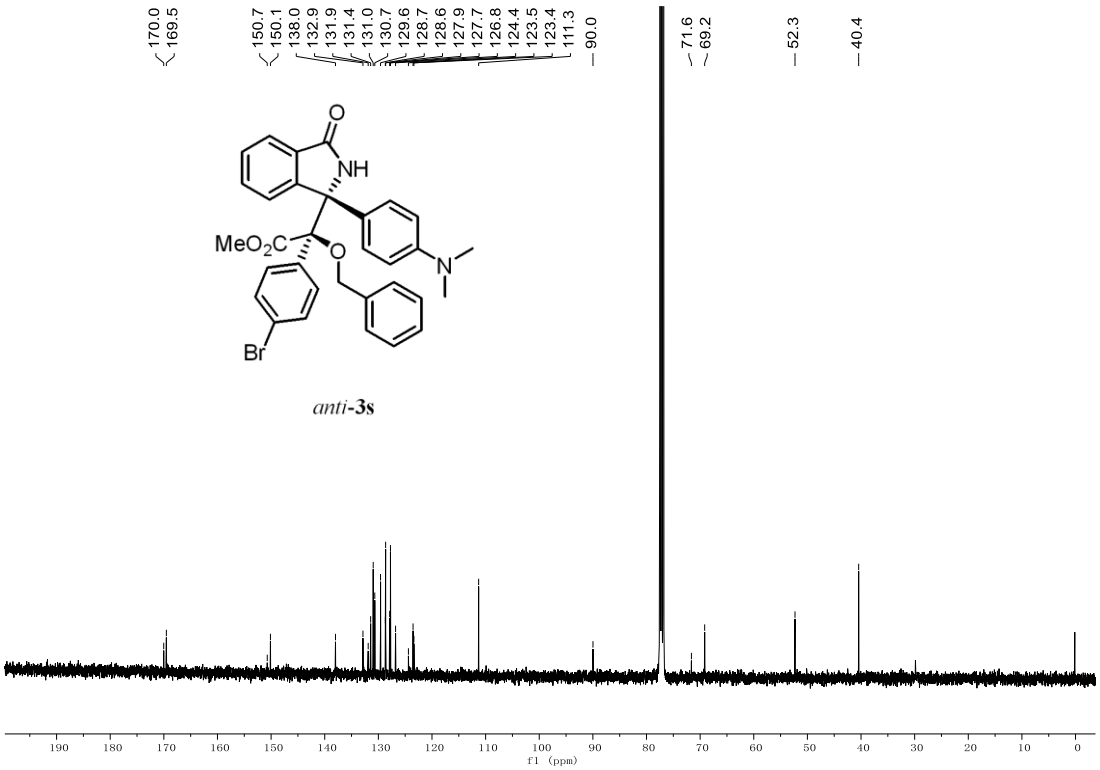


syn-**3r**

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *anti*-3s

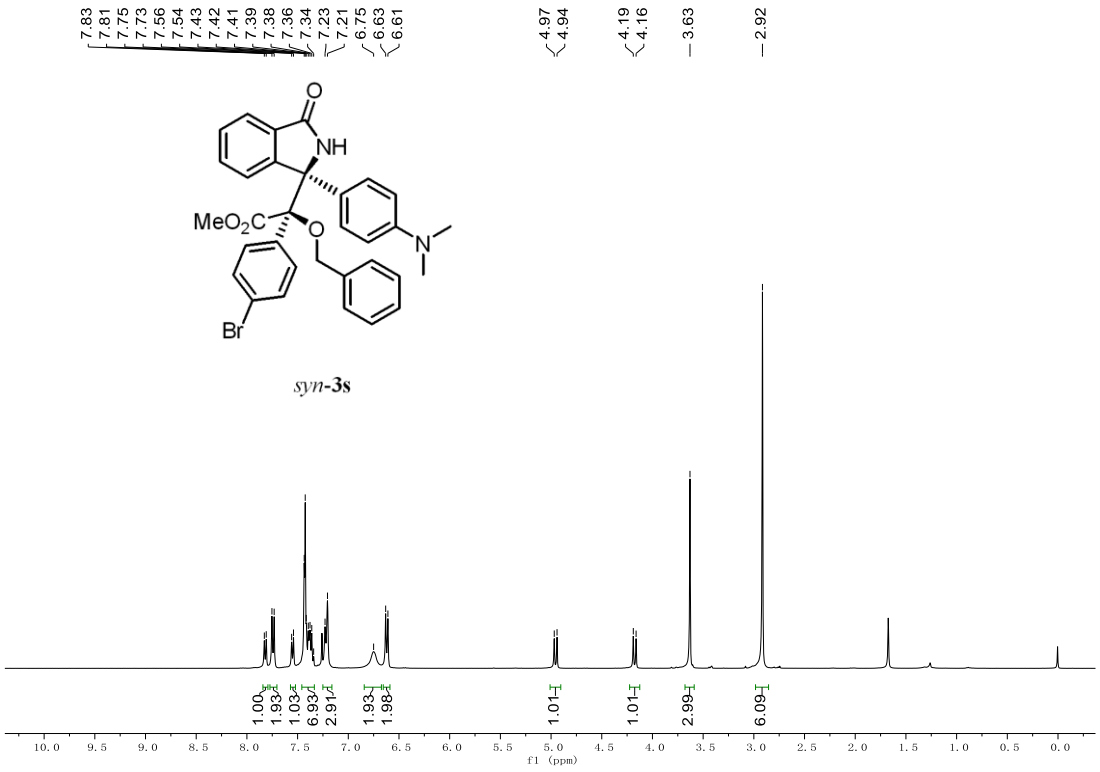


anti-**3s**

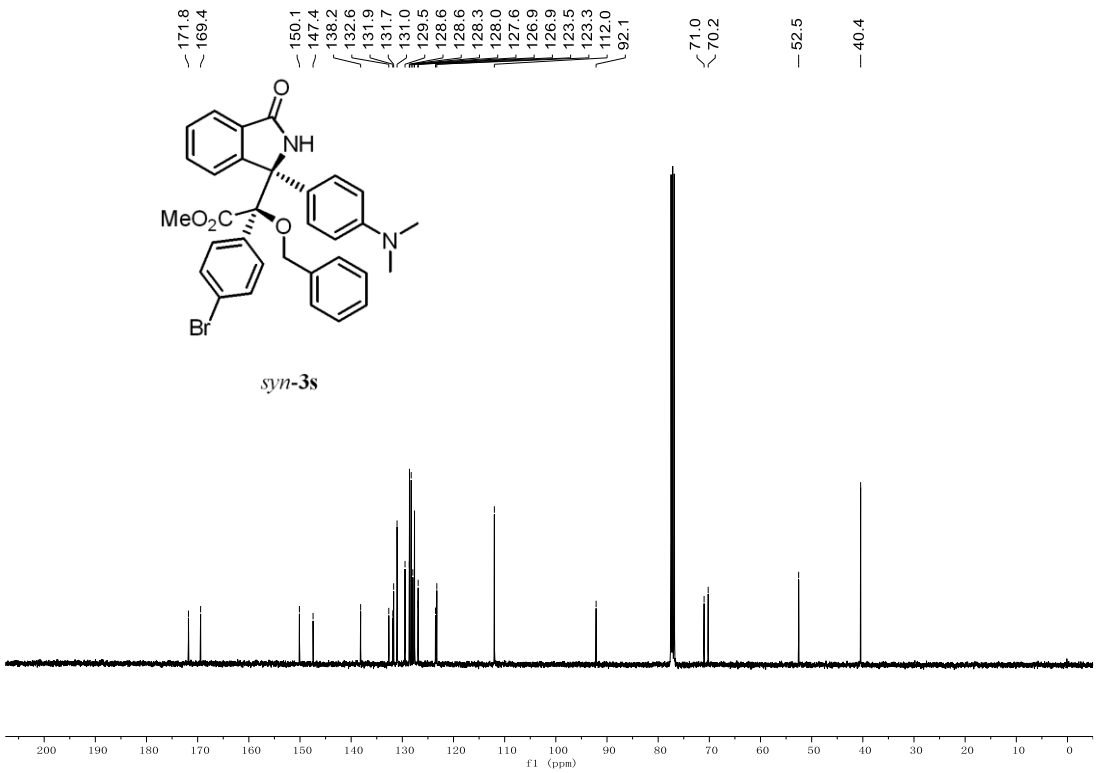


anti-**3s**

^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectra for *syn*-3s



syn-**3s**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127.6
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126.9
123.5
123.3
112.0
92.1
71.0
70.2
52.5
40.4
O
NH
MeO2C
O
N
Br
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

syn-**3s**