

Supplementary Materials: Organocatalytic, Asymmetric [2+2+2] Annulation to Construct Six-Membered Spirocyclic Oxindoles with Six Continuous Stereogenic Centers

Zhi-Long Li, Chao Liu, Rui Tan, Zhi-Ping Tong and Yan-Kai Liu

Table S1. Screening of reaction conditions [a].

Acid: A₁ R = 4-NO₂ A₂ R = H A₃ R = 4-OMe A₄ R = 2-F Base: B₁ = Ethyldiisopropylamine B₂ = Triethylamine B₃ = Triethylenediamine B₄ = K₂CO₃							
Entry	Solvent	Acid	Base	t ₁ [h]	t ₂ [h]	Yield [b] [%]	ee [c] [%]
1	MeCN	A ₁	B ₁	12	12	81	93
2	MeCN	A ₂	B ₁	16	12	76	93
3	MeCN	A ₃	B ₁	16	12	79	93
4	MeCN	A ₄	B ₁	12	12	81	93
5	MeCN	A ₁	B ₂	12	12	84	97
6	MeCN	A ₁	B ₃	12	10	84	97
7	MeCN	A ₁	B ₄	12	6	77	97
8	MeCN	A ₁	B ₅	12	24	67	98
9	MeCN	A ₁	B ₆	12	48	65	99
10	Toluene	A ₁	B ₂	24	12	88	93
11	CH ₂ Cl ₂	A ₁	B ₂	24	12	75	97
12	Et ₂ O	A ₁	B ₂	36	12	85	95
13	THF	A ₁	B ₂	36	12	75	97
14	EtOH	A ₁	B ₂	2	12	75	95
15	DMF	A ₁	B ₂	36	12	trace	–
16	EtOH with 5% H ₂ O	A ₁	B ₂	1	12	82	97
17	EtOH with 10% H ₂ O	A ₁	B ₂	2	12	82	96
18	EtOH with 20% H ₂ O	A ₁	B ₂	12	12	87	97
19	EtOH with 5% H ₂ O and 10% Cat	A ₁	B ₂	1	12	83	97
20	EtOH with 5% H ₂ O and 5% Cat	A ₁	B ₂	3	12	88	98
21	EtOH with 5% H ₂ O and 1% Cat	A ₁	B ₂	72	12	80	93

Notes: [a] Unless noted otherwise, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst **Cat.** (0.02 mmol), and acid **A** (0.02 mmol) in 0.4 mL of solvent at room temperature for specified time (t₁), and then **3a** (0.12 mmol) and base (0.04 mmol) were added to react for another time (t₂); [b] Isolated yield of **4a**; [c] Determined by HPLC analysis on chiral column; dr > 20:1 as determined by ¹H NMR spectroscopic and HPLC analysis.

1. The Confirmation of Absolute Configuration

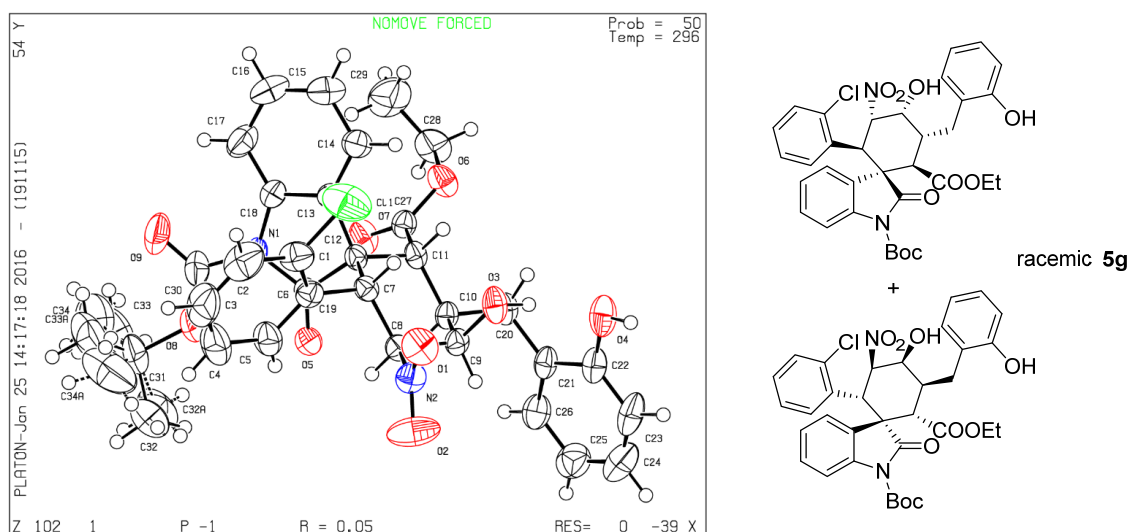


Figure S1. Crystal data for racemate compounds **5g** (CCDC 1468094 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre).

Table S2. The information of crystal of racemate compound **5g**.

Bond Precision:	C–C = 0.0035 Å	Wavelength = 0.71073	
Cell:	a = 11.4531(9)	b = 11.770(1)	c = 13.6961(11)
	alpha = 106.493(3)	beta = 90.763(3)	gamma = 108.221(2)
Temperature:	296 K		

Table S3. The information of crystal of racemate compound **5g**.

Parameter	Calculated	Reported
Volume	1671.0(2)	1670.9(2)
Space group	P-1	P-1
Hall group	–P 1	–P 1
Moiety formula	C ₃₄ H ₃₅ Cl N ₂ O ₉	C ₃₄ H ₃₅ Cl N ₂ O ₉
Sum formula	C ₃₄ H ₃₅ Cl N ₂ O ₉	C ₃₄ H ₃₅ Cl N ₂ O ₉
Mr	651.09	651.09
D _x , g cm ^{–3}	1.294	1.294
Z	2	2
Mu (mm ^{–1})	0.170	0.170
F ₀₀₀	684.0	684.0
F ₀₀₀ '	684.65	
h,k,lmax	14,15,17	14,15,17
Nref	7737	7705
Tmin,Tmax	0.973,0.983	0.696,0.746
Tmin'	0.957	

Table S4. The information of crystal of racemate compound **5g**.

Correction method = # Reported T Limits: Tmin = 0.696 Tmax = 0.746 AbsCorr = MULTI-SCAN	
Data completeness = 0.996	Theta(max) = 27.581
R(reflections) = 0.0476(3049)	wR2(reflections) = 0.1083(7705)
S = 0.844	Npar = 452

2. NMR Spectra and HPLC Traces

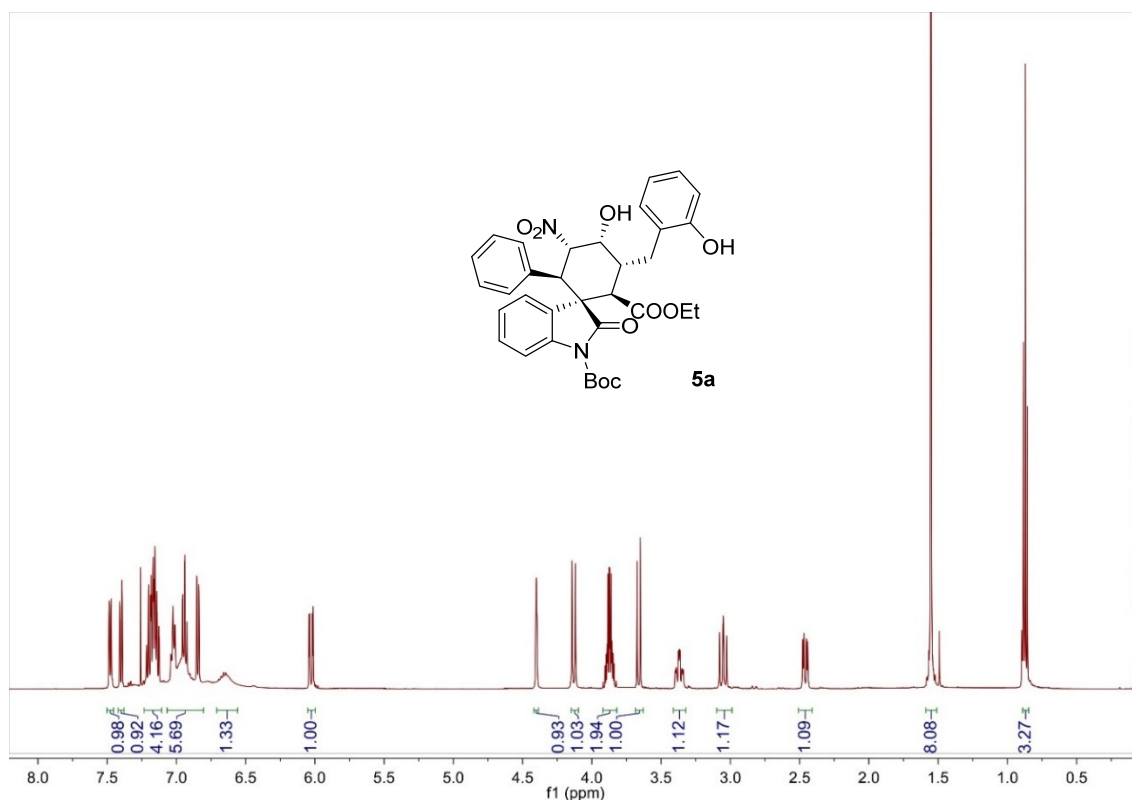


Figure S2. ^1H NMR spectrum (CDCl₃, 500 MHz) of **5a**.

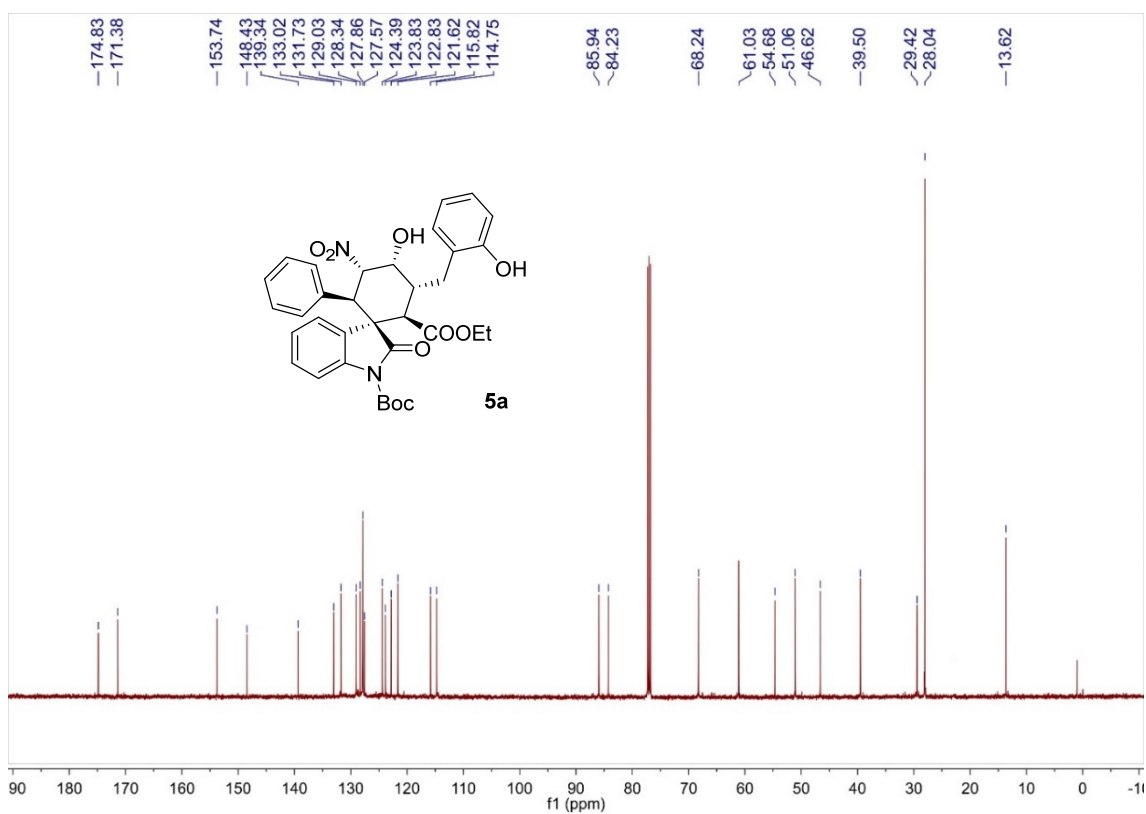


Figure S3. ^{13}C NMR spectrum (CDCl₃, 125 MHz) of **5a**.

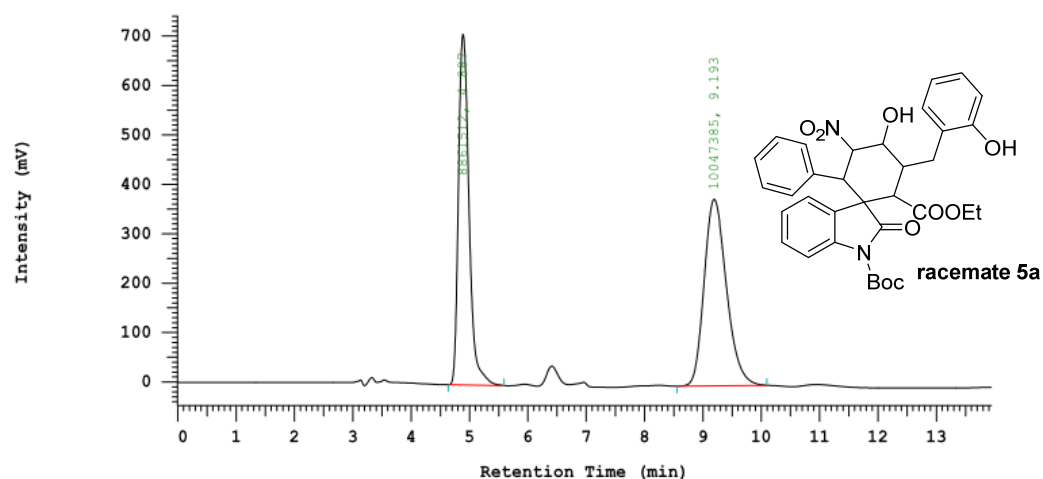


Figure S4. The HPLC profiles of racemate 5a

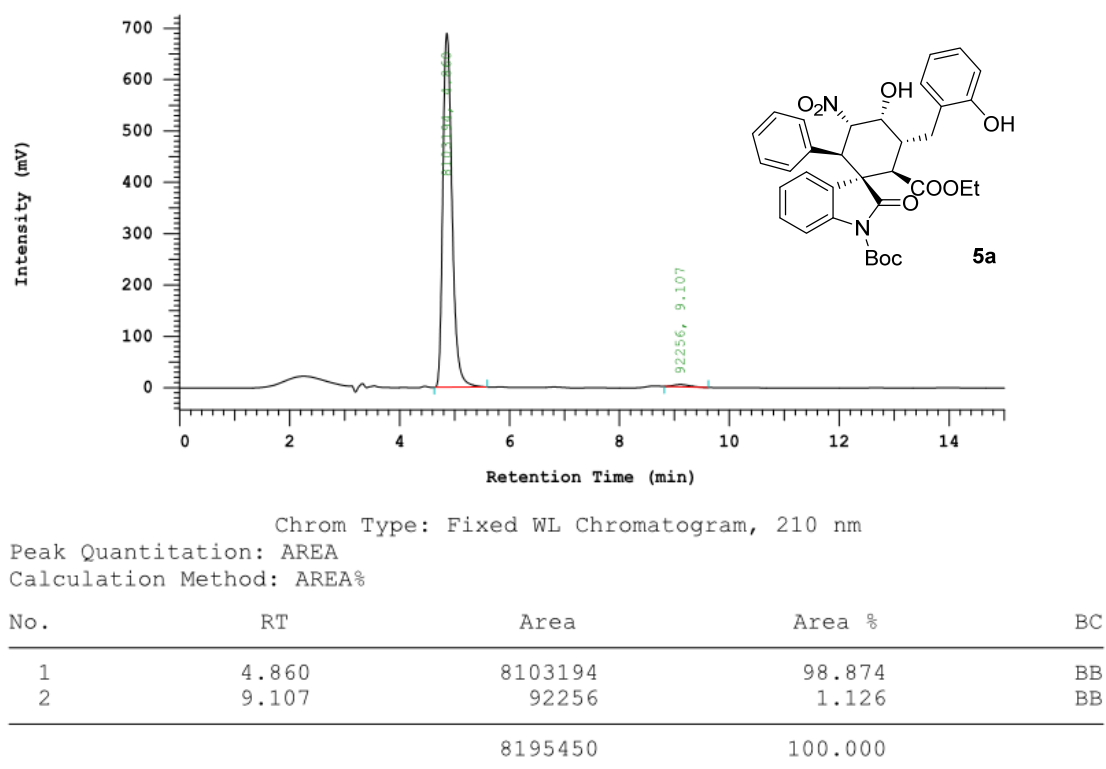


Figure S5. The HPLC profiles of 5a.

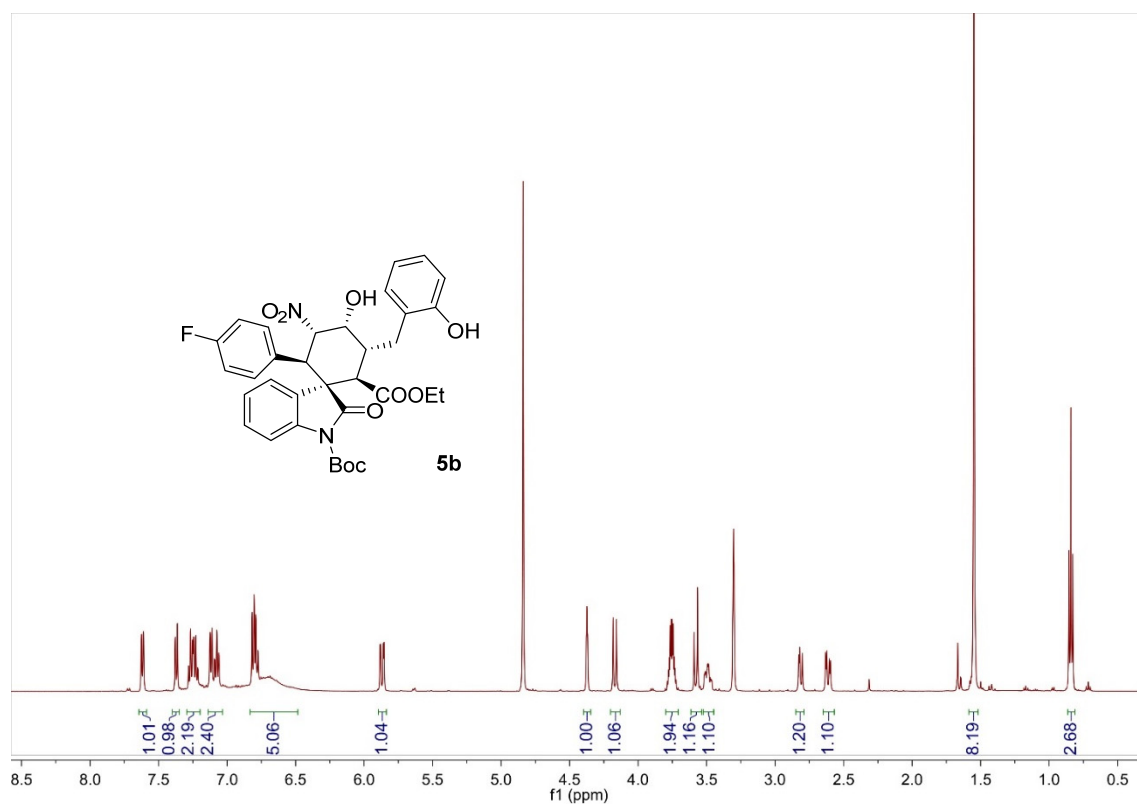


Figure S6. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5b**.

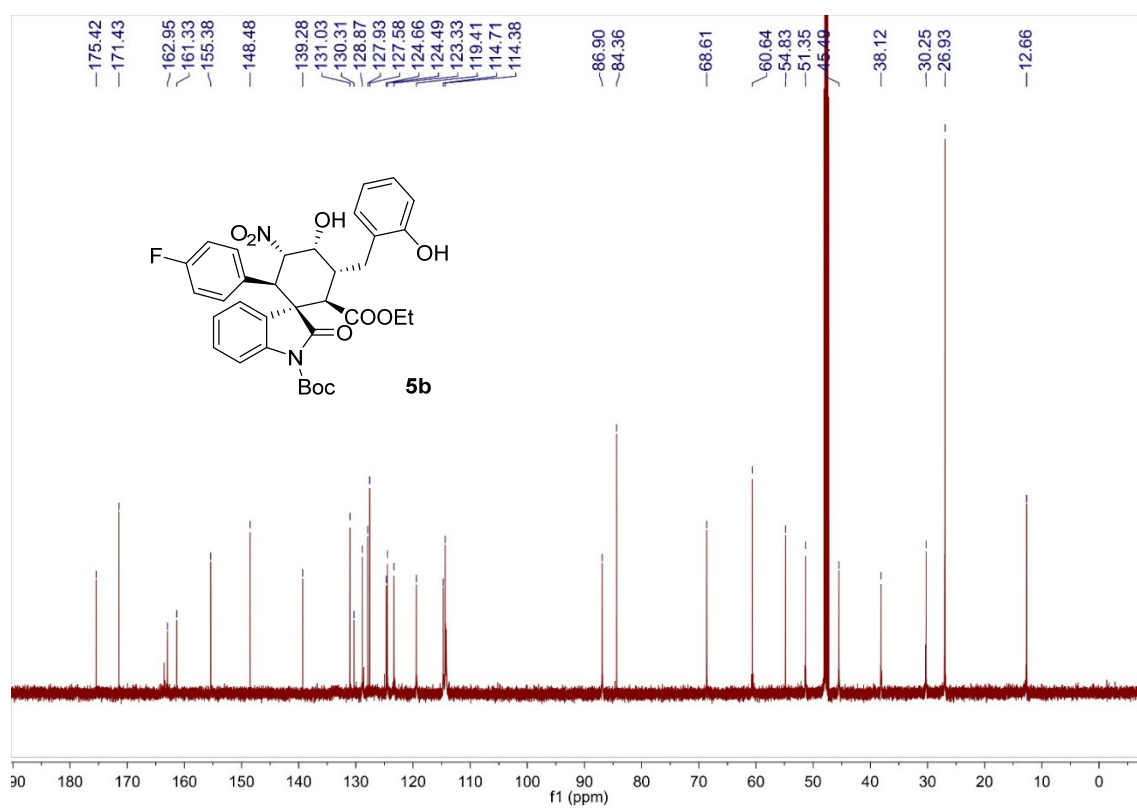
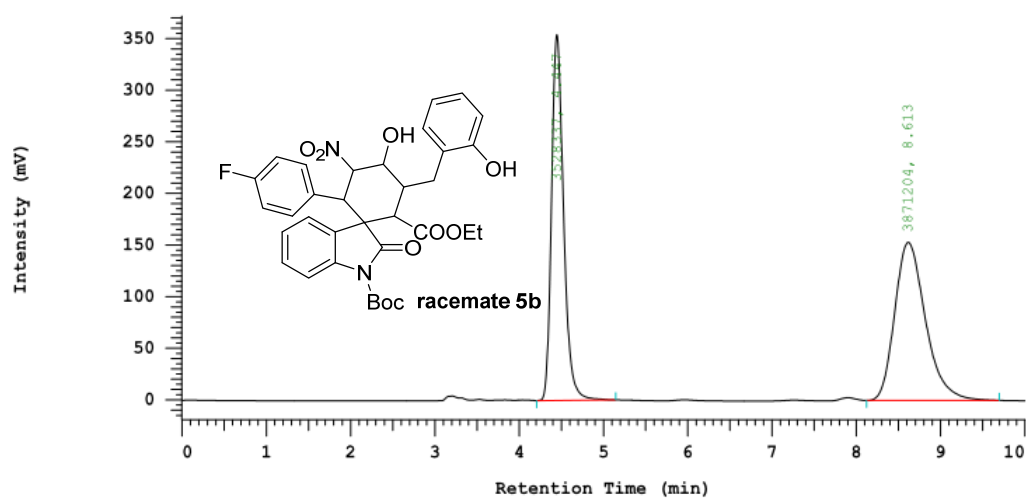


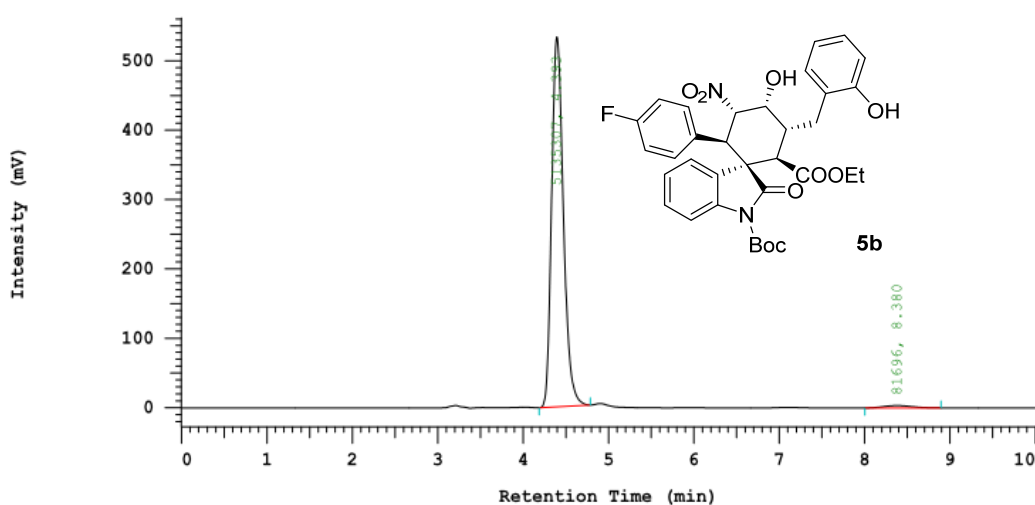
Figure S7. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5b**.



Chrom Type: Fixed WL Chromatogram, 210 nm
 Peak Quantitation: AREA
 Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	4.447	3528337	47.683	BB
2	8.613	3871204	52.317	BB
		7399541	100.000	

Figure S8. The HPLC profiles of racemate 5b.



Chrom Type: Fixed WL Chromatogram, 210 nm
 Peak Quantitation: AREA
 Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	4.393	5135307	98.434	BB
2	8.380	81696	1.566	BB
		5217003	100.000	

Figure S9. The HPLC profiles of 5b.

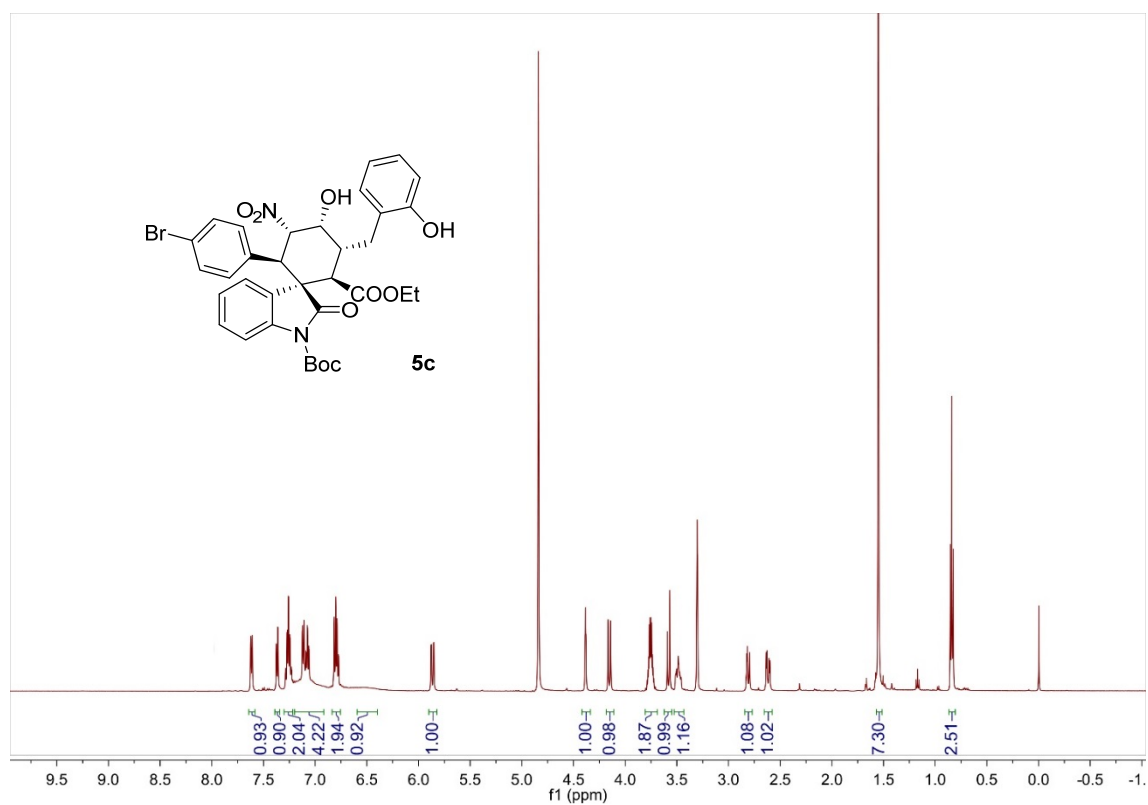


Figure S10. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5c**.

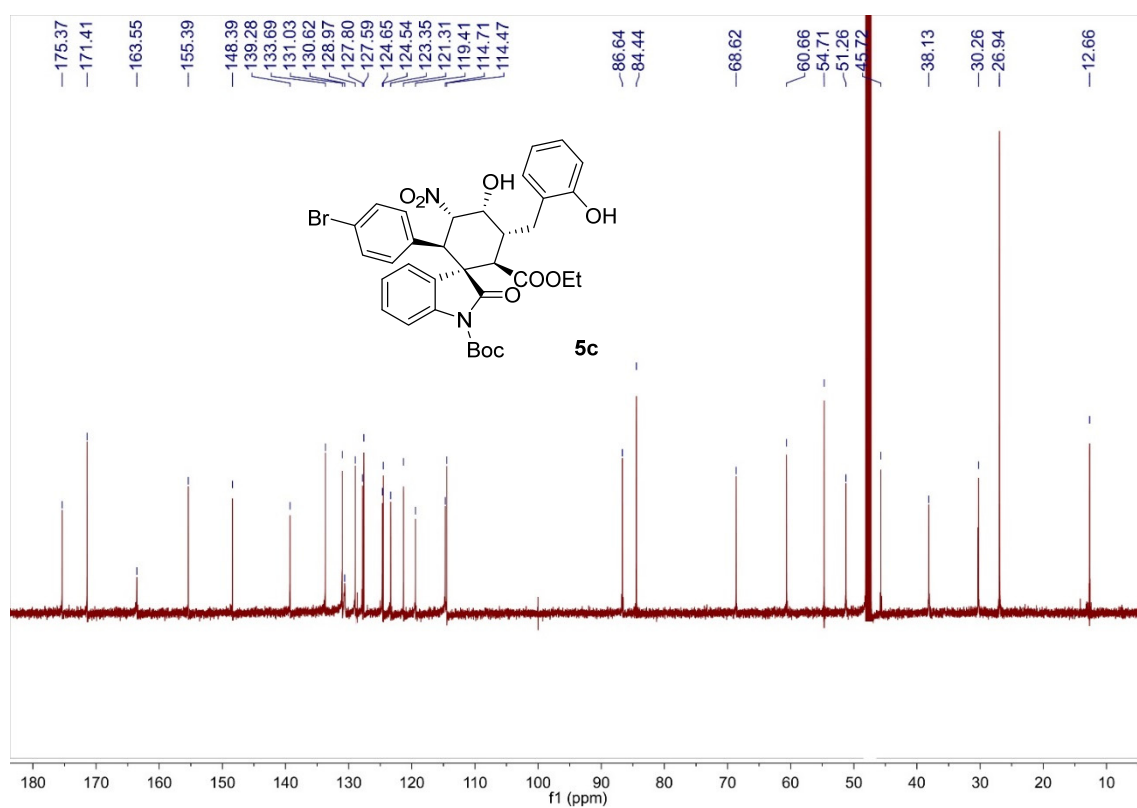


Figure S11. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5c**.

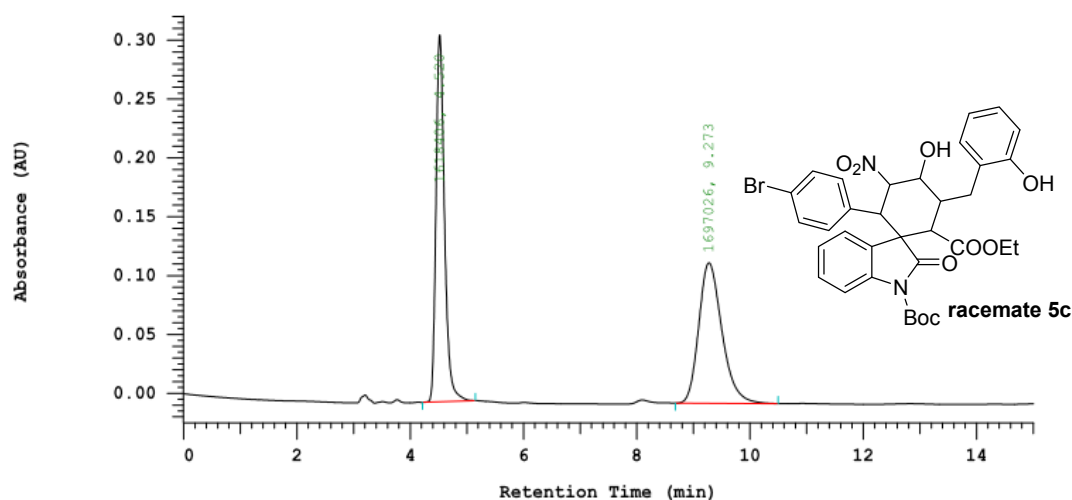


Figure S12. The HPLC profiles of racemate 5c.

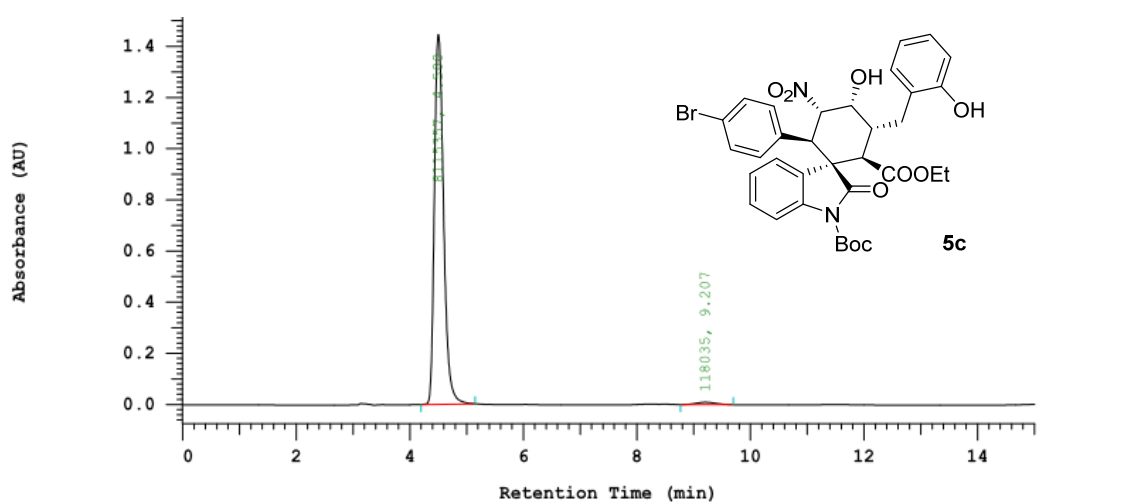


Figure S13. The HPLC profiles of 5b.

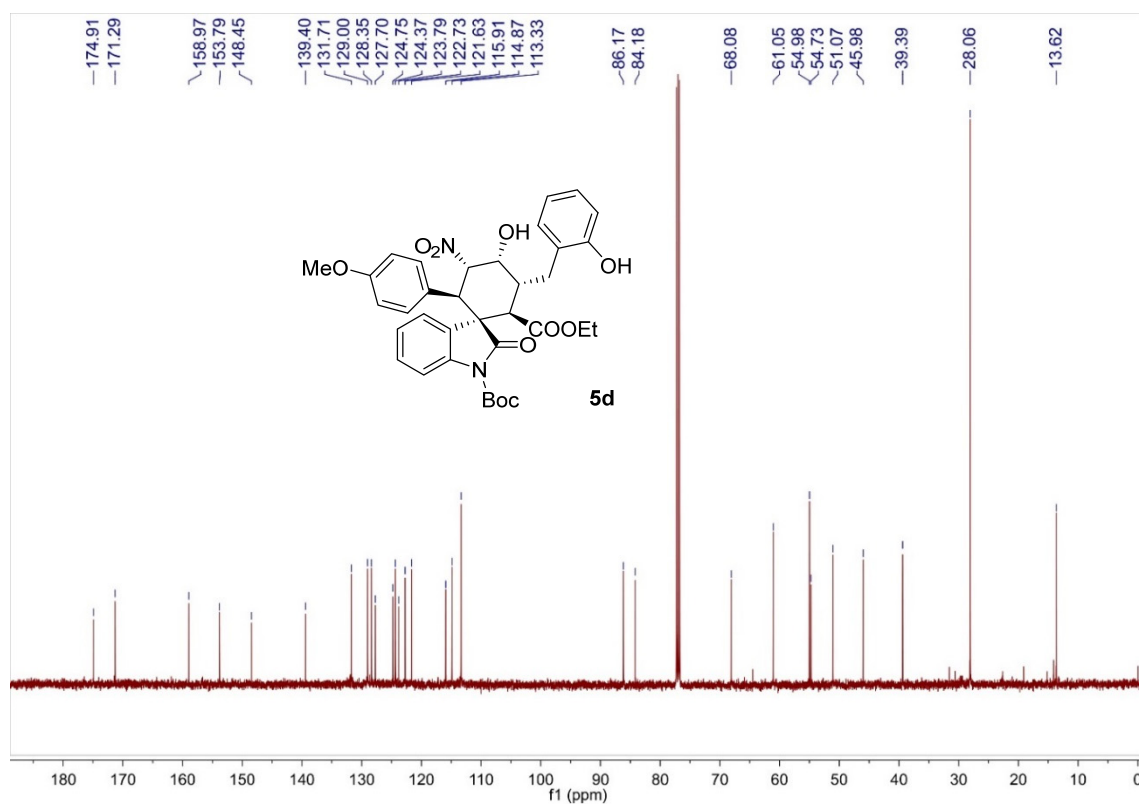


Figure S14. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5d**.

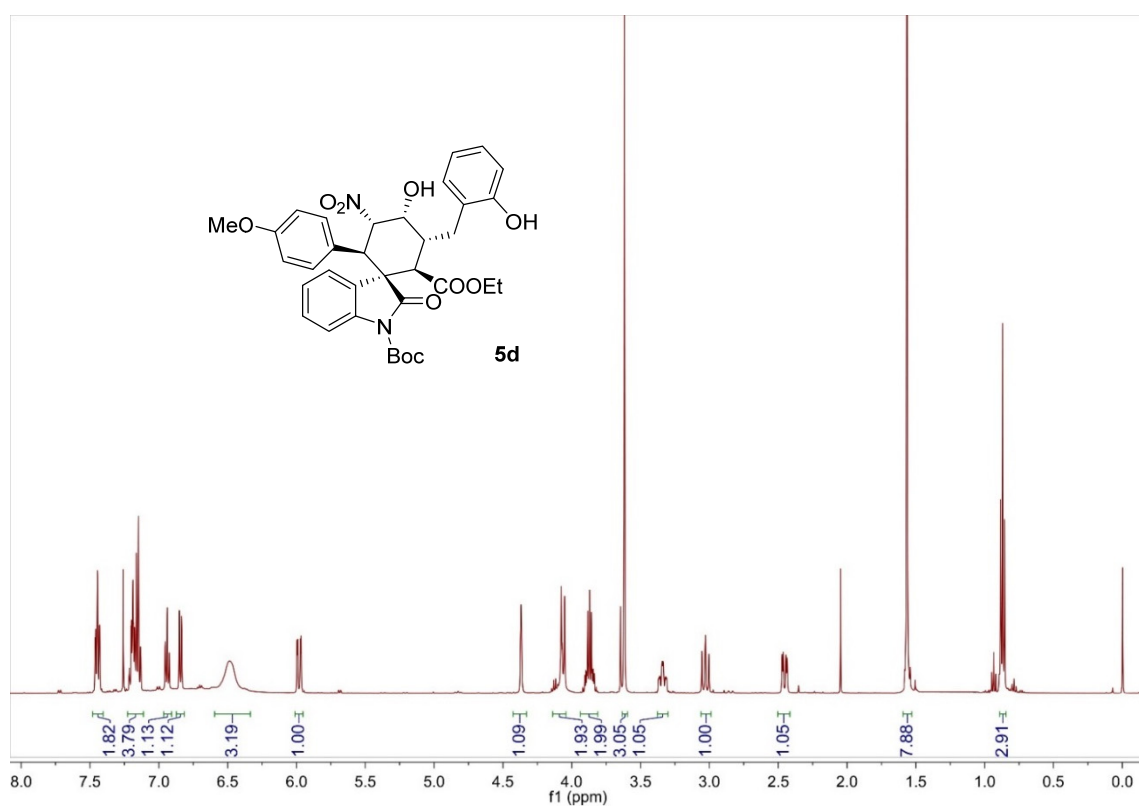
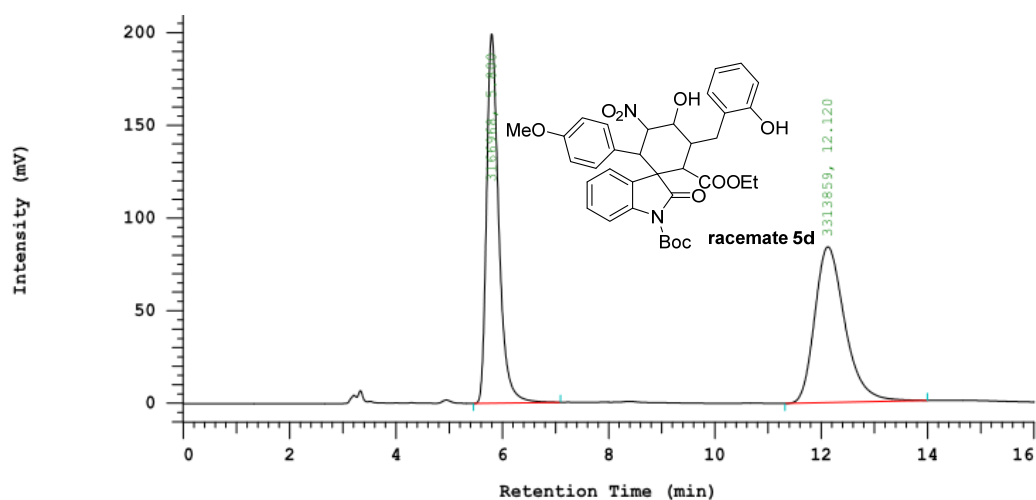


Figure S15. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5c**.



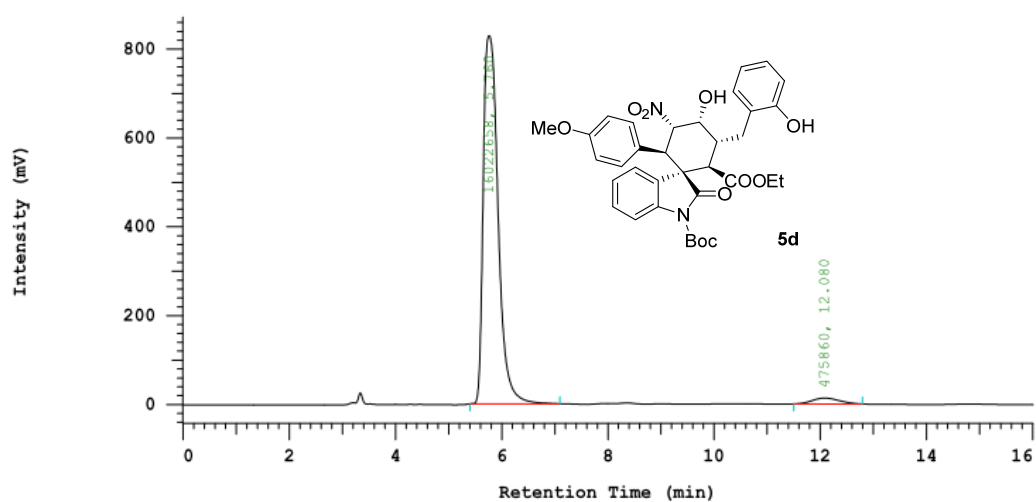
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	5.800	3166968	48.867	BB
2	12.120	3313859	51.133	BB
		6480827	100.000	

Figure S16. The HPLC profiles of racemate 5d.



Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	5.760	16022658	97.116	BB
2	12.080	475860	2.884	BB
		16498518	100.000	

Figure S17. The HPLC profiles of 5d.

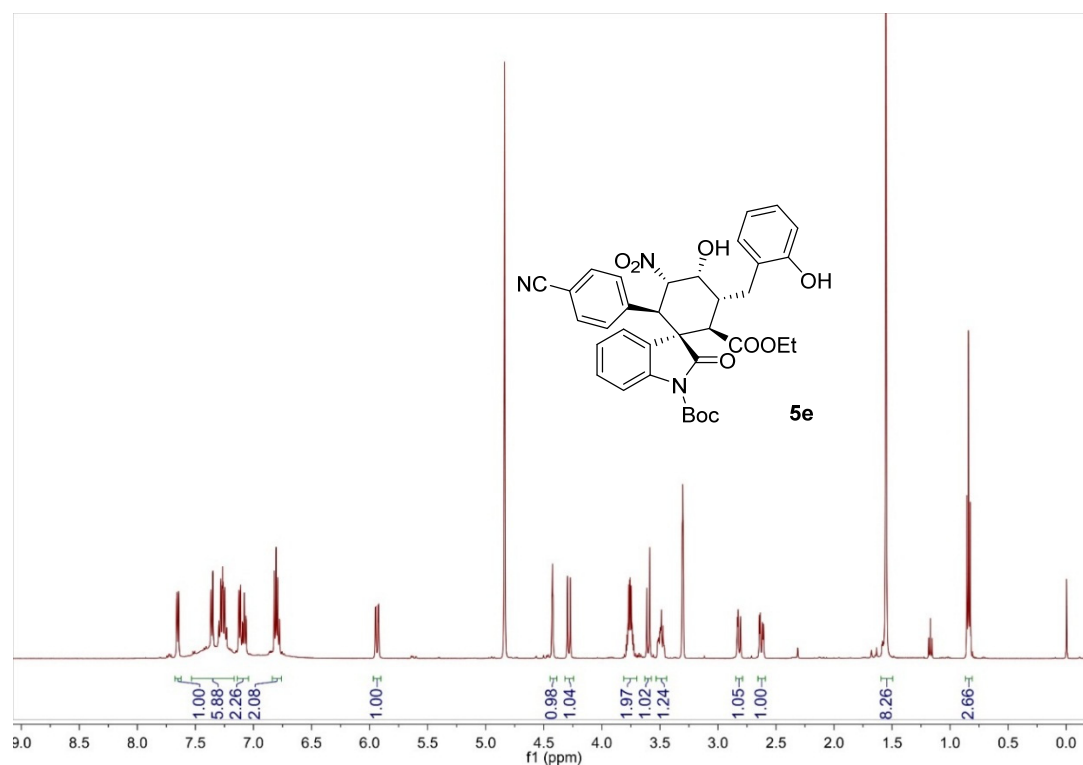


Figure S18. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5e**.

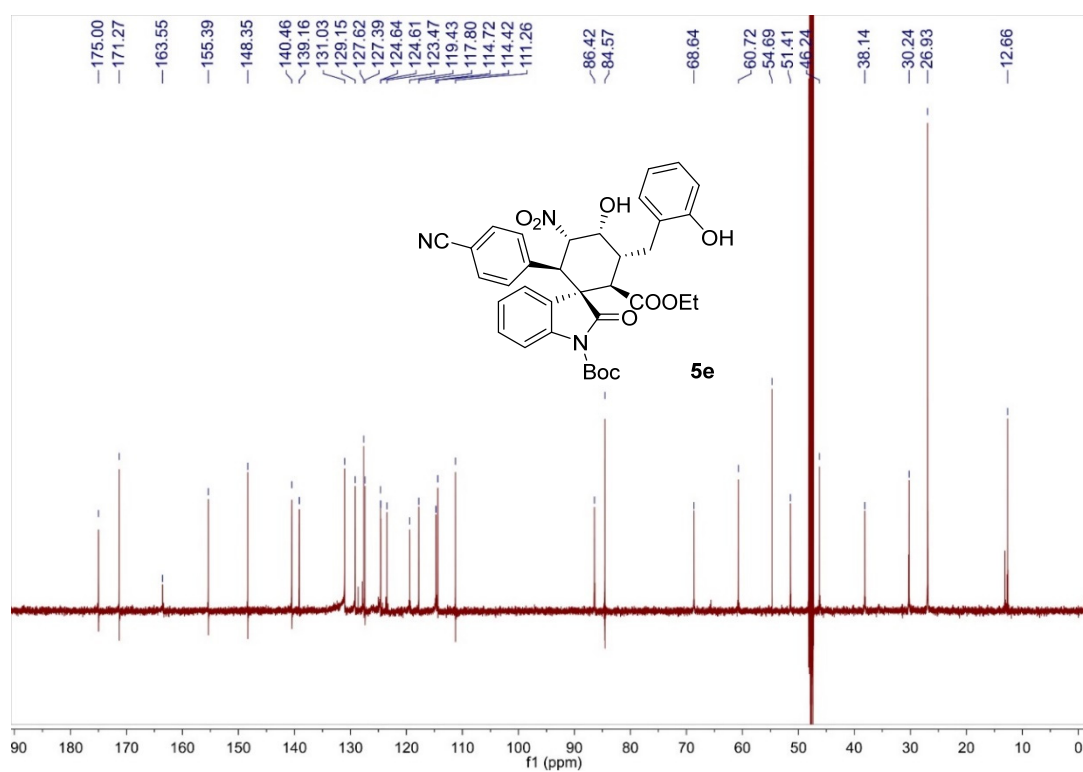


Figure S19. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5e**.

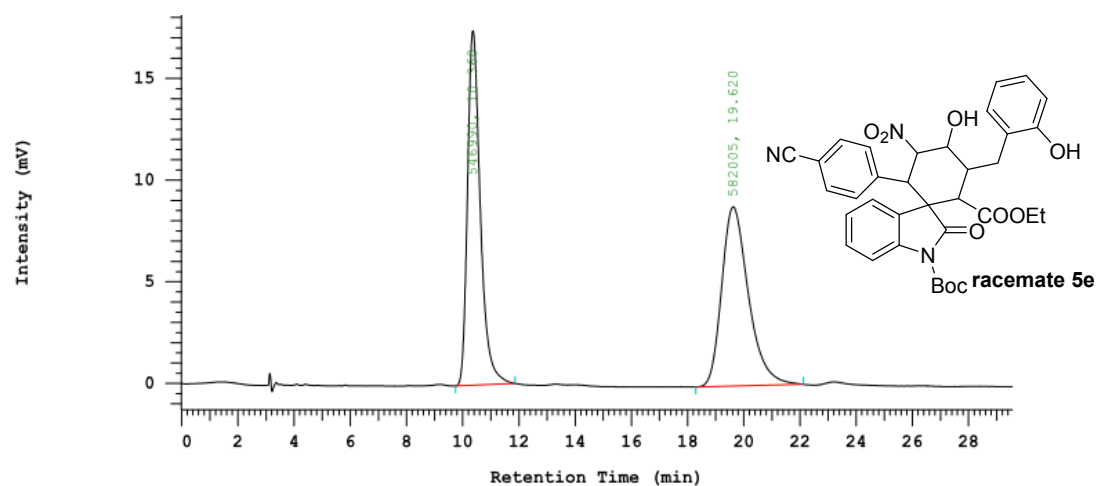


Figure S20. The HPLC profiles of racemate 5e.

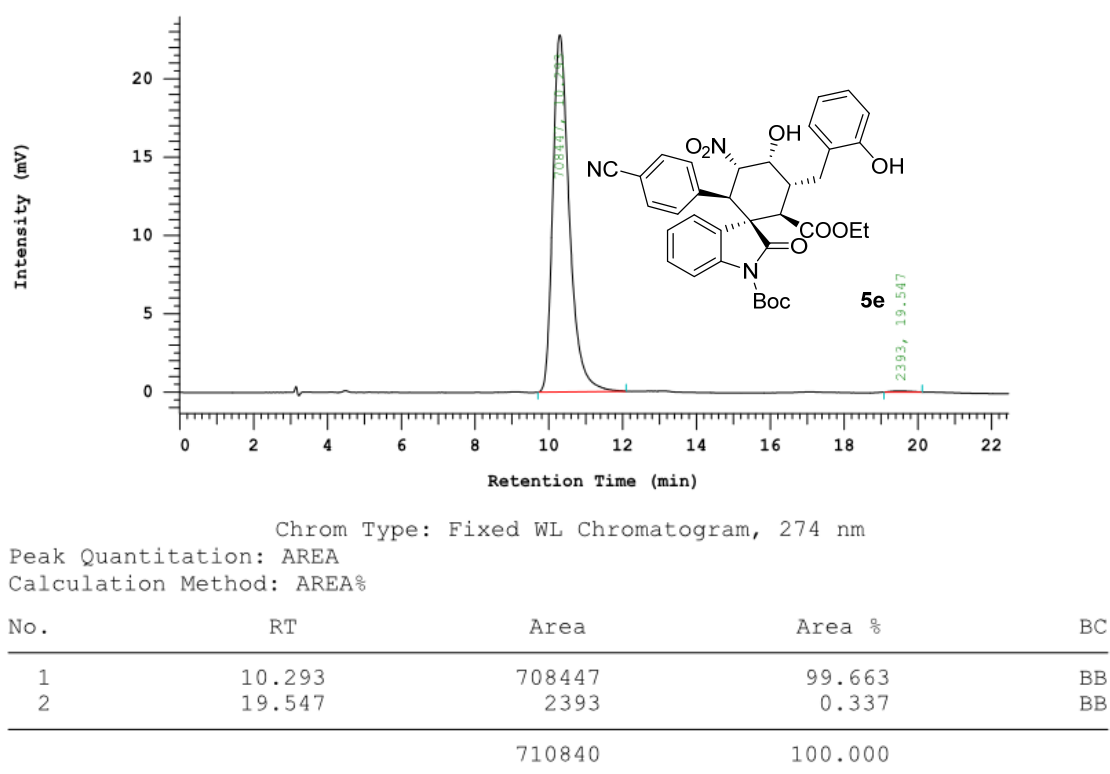


Figure S21. The HPLC profiles of 5e.

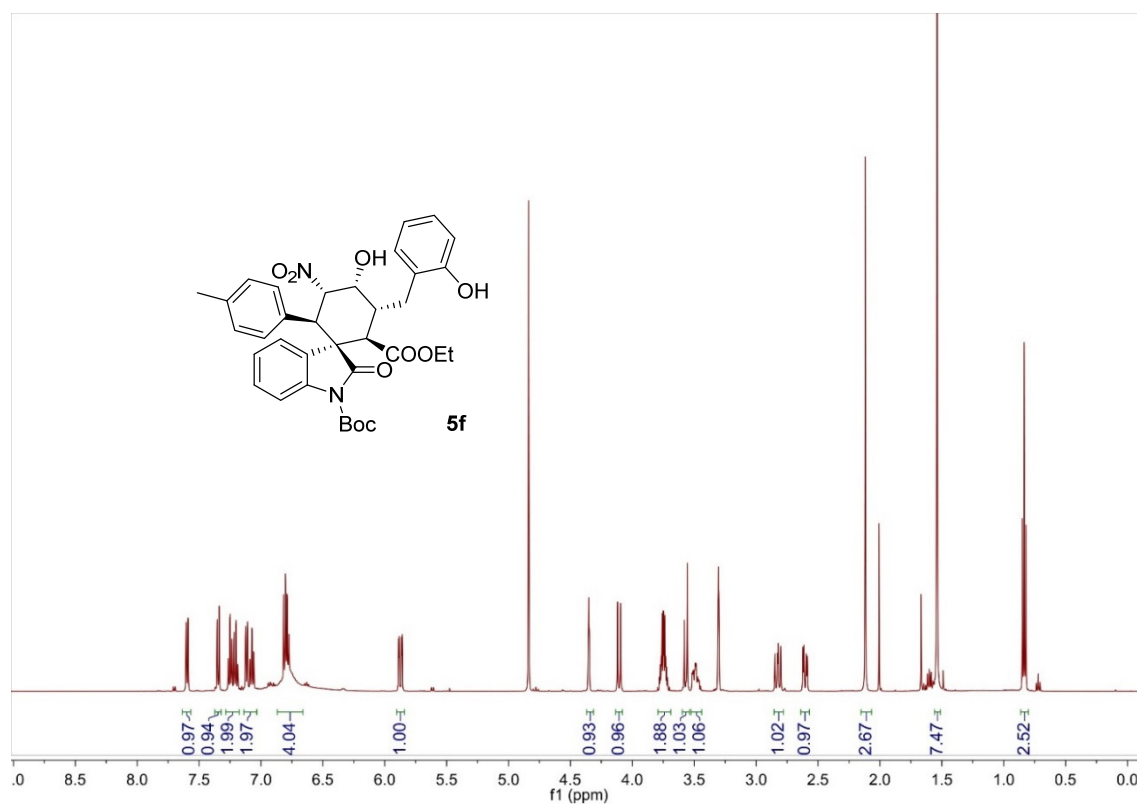


Figure S22. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5f**.

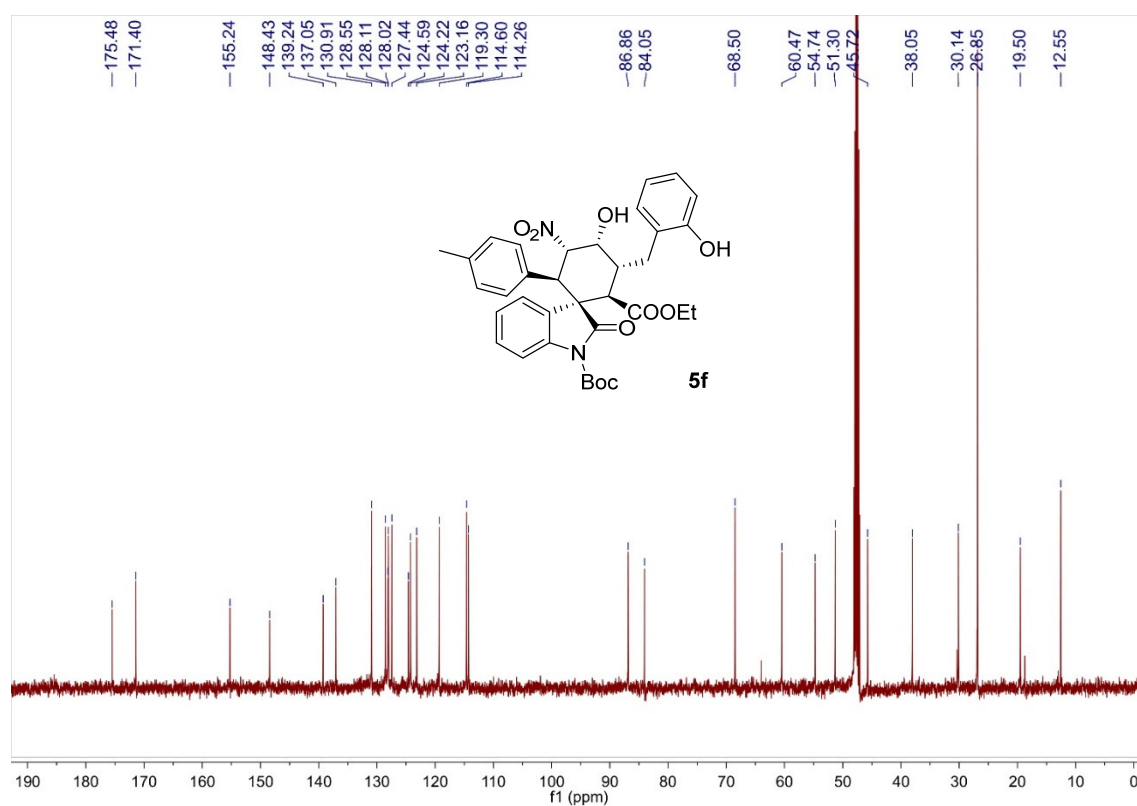
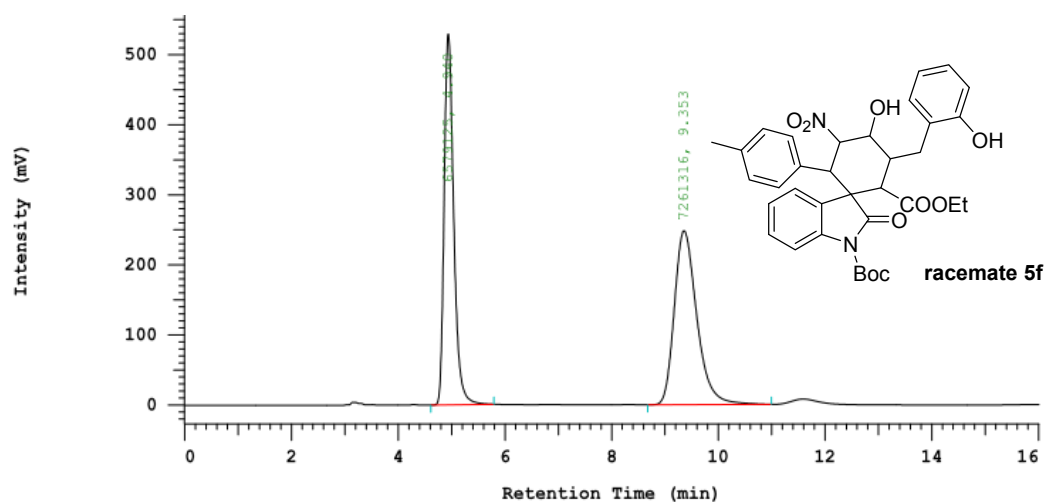


Figure S23. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5f**.



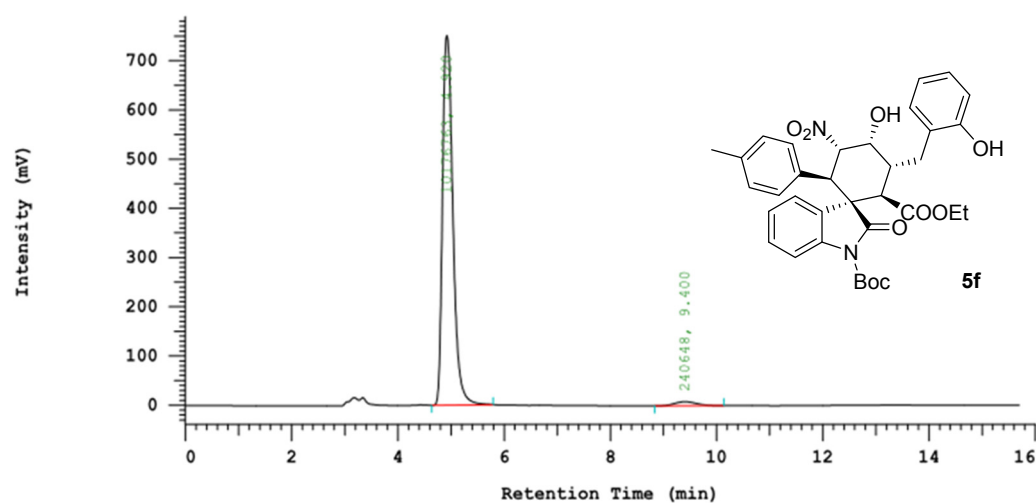
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	4.940	6579125	47.536	BB
2	9.353	7261316	52.464	BB
		13840441	100.000	

Figure S24. The HPLC profiles of racemate 5f.



Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	4.920	10176763	97.690	BB
2	9.400	240648	2.310	BB
		10417411	100.000	

Figure S25. The HPLC profiles of 5f.

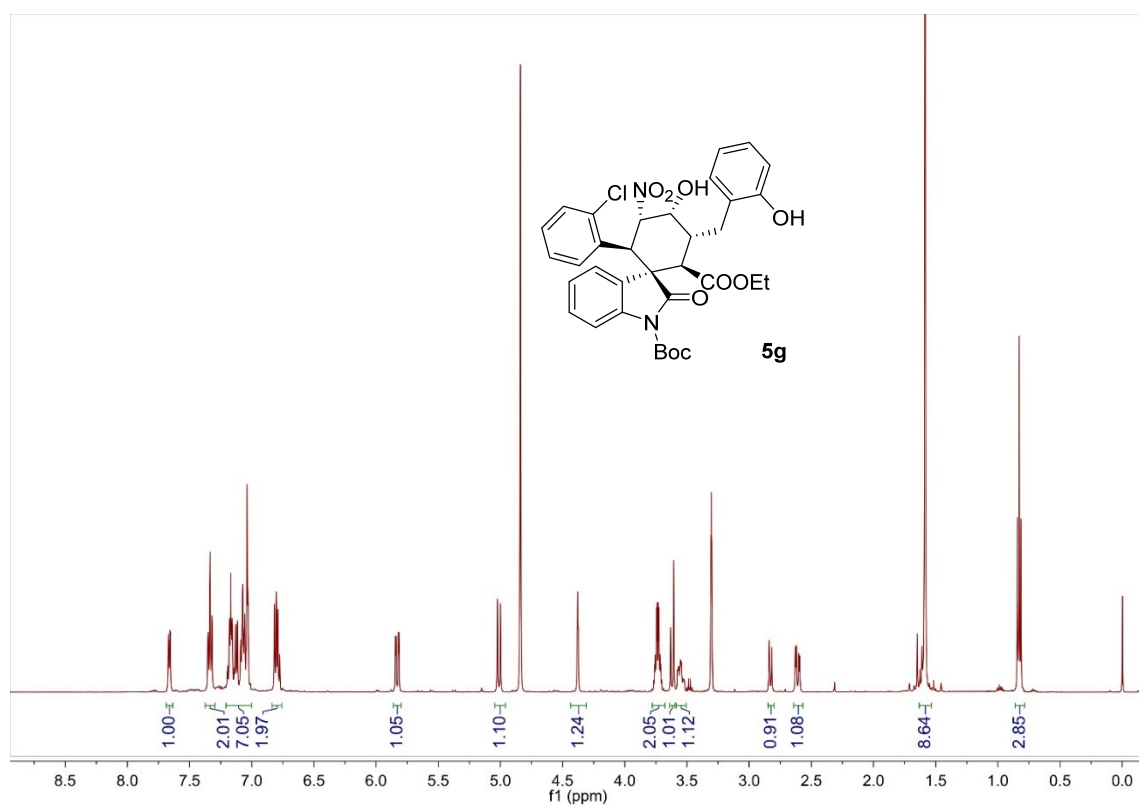


Figure S26. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5g**.

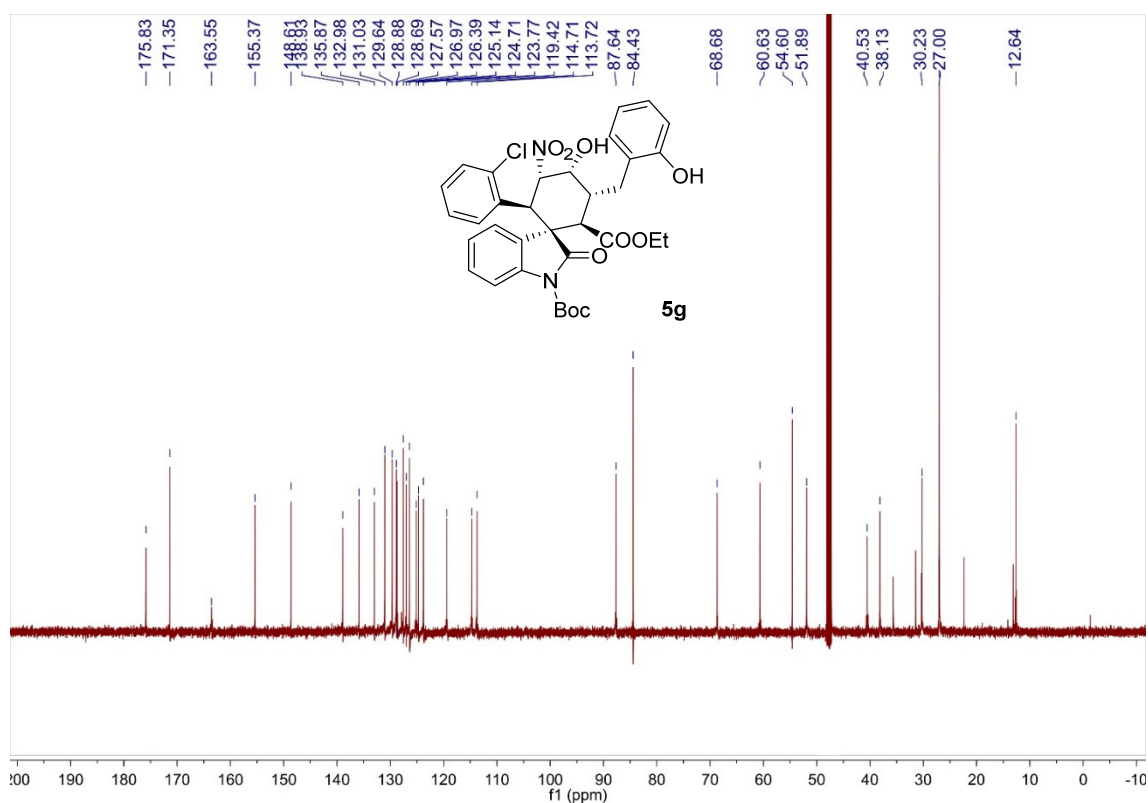
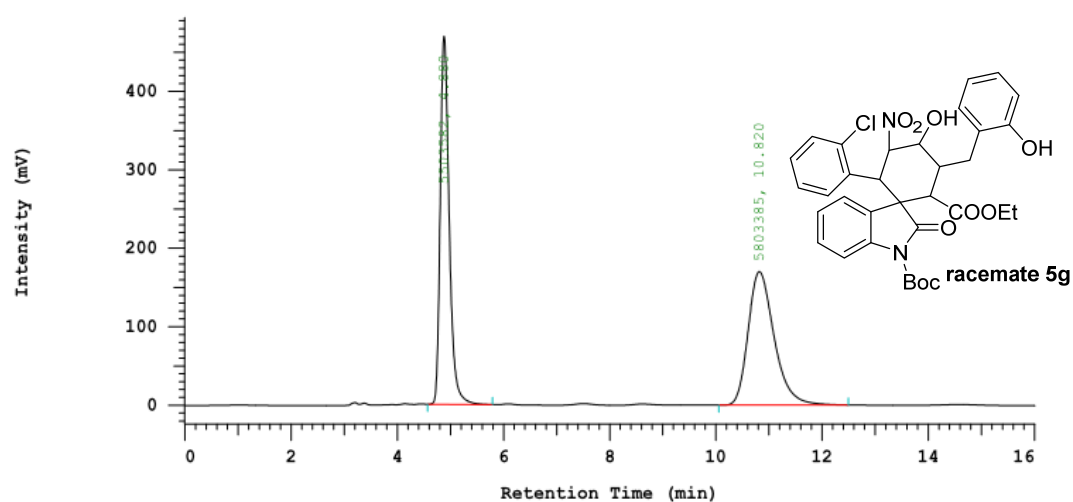
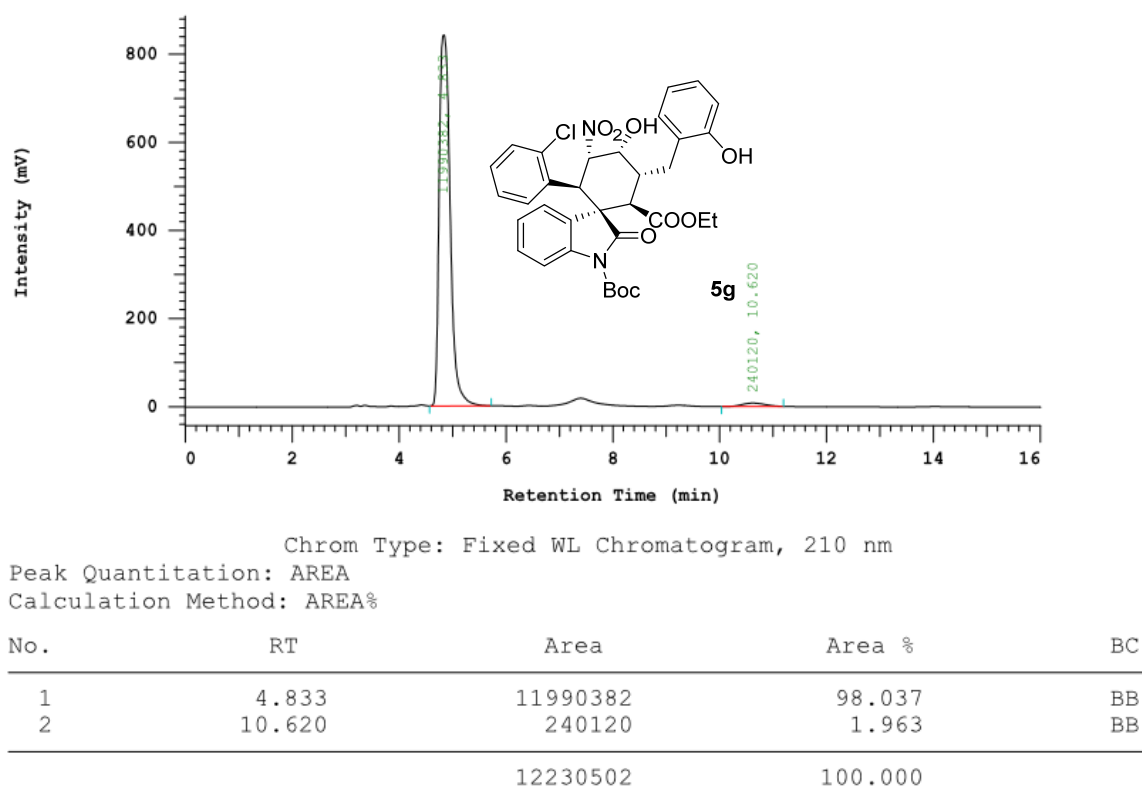


Figure S27. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5g**.

Figure S28. The HPLC profiles of racemate **5g**.Figure S29. The HPLC profiles of **5g**.

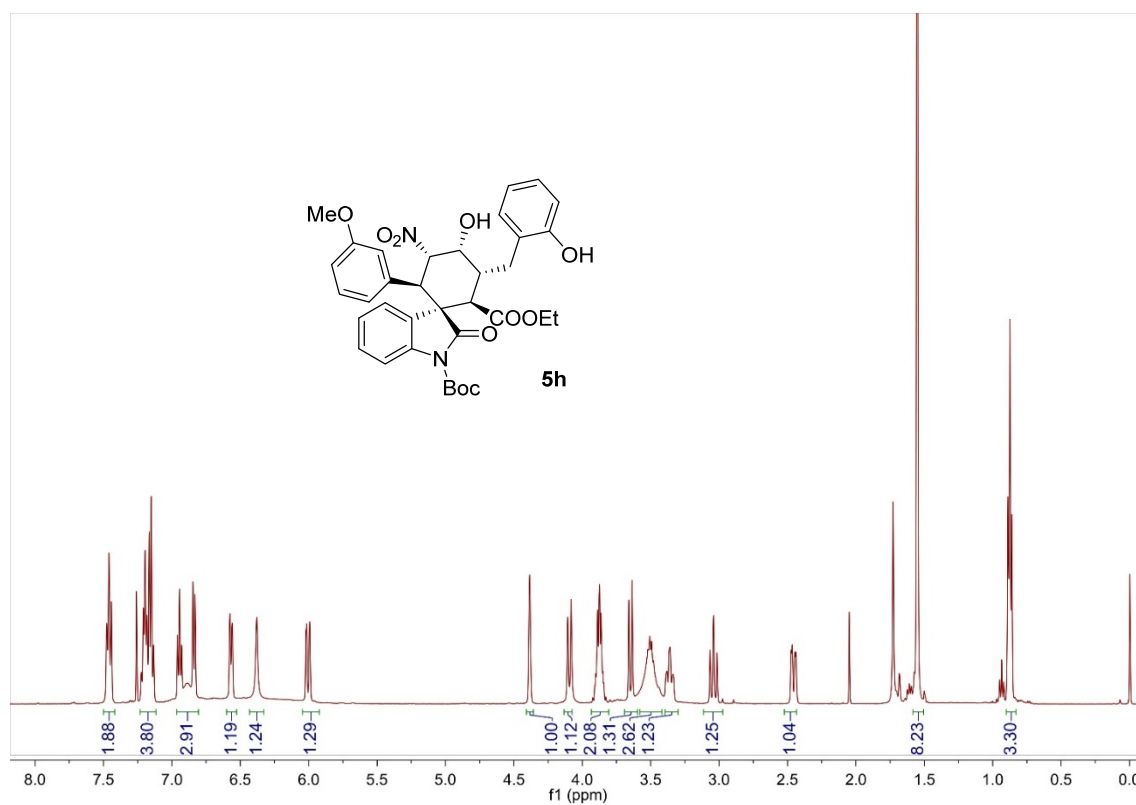


Figure S30. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5h**.

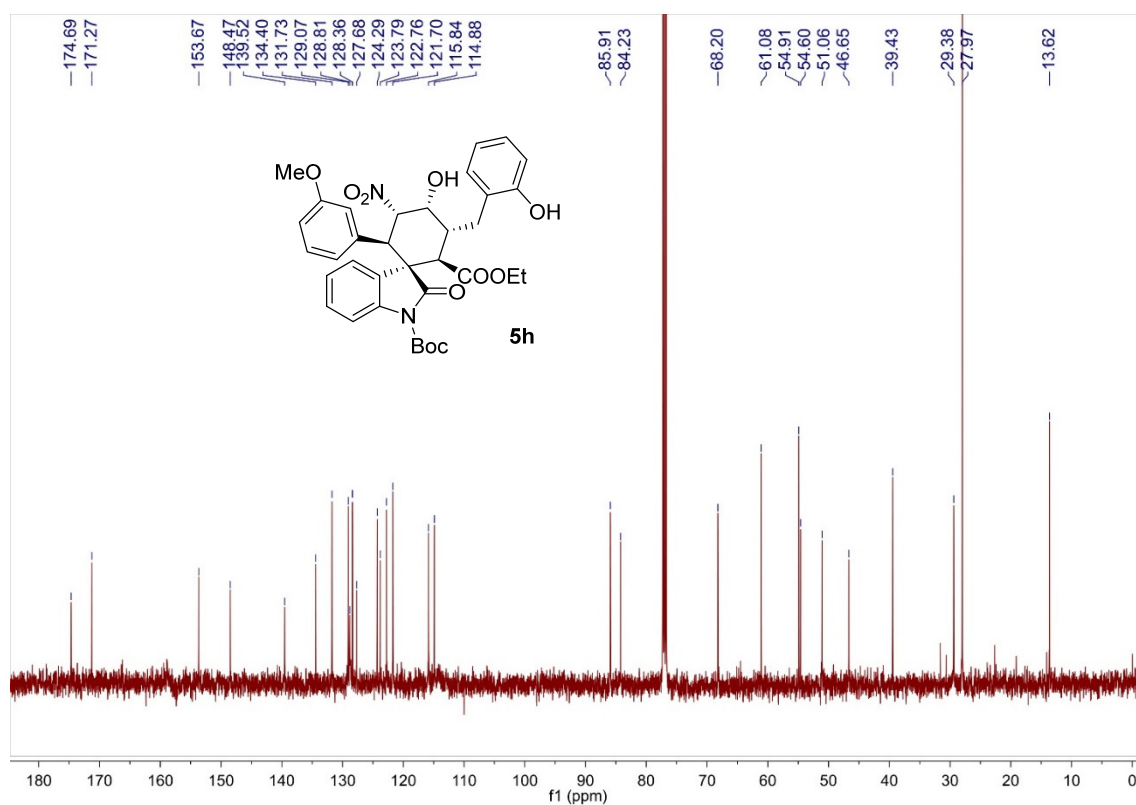
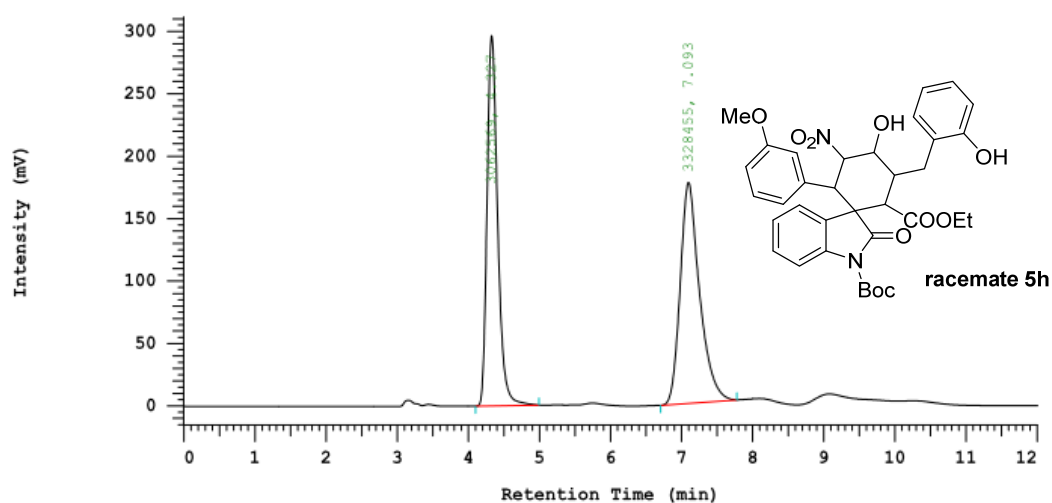


Figure S31. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5h**.



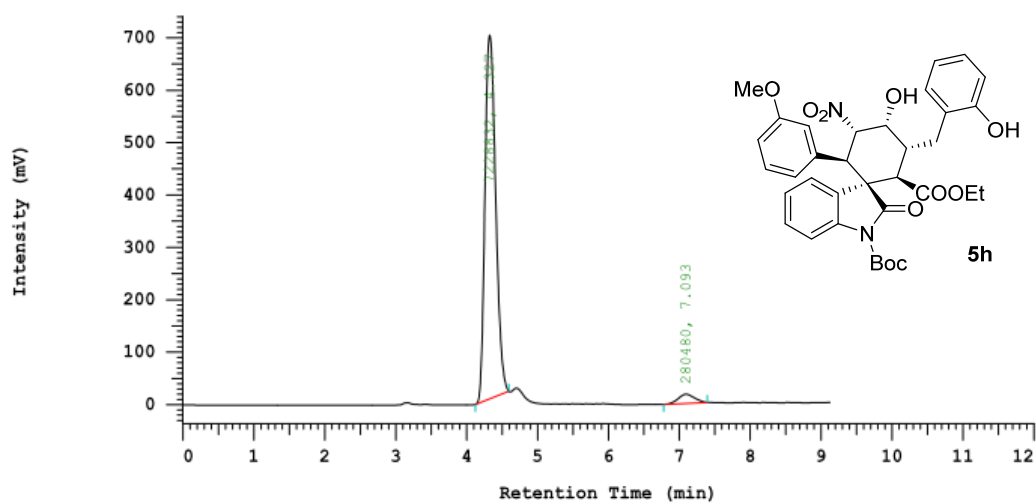
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	4.327	3062569	47.920	BB
2	7.093	3328455	52.080	BB
		6391024	100.000	

Figure S32. The HPLC profiles of racemate 5h.



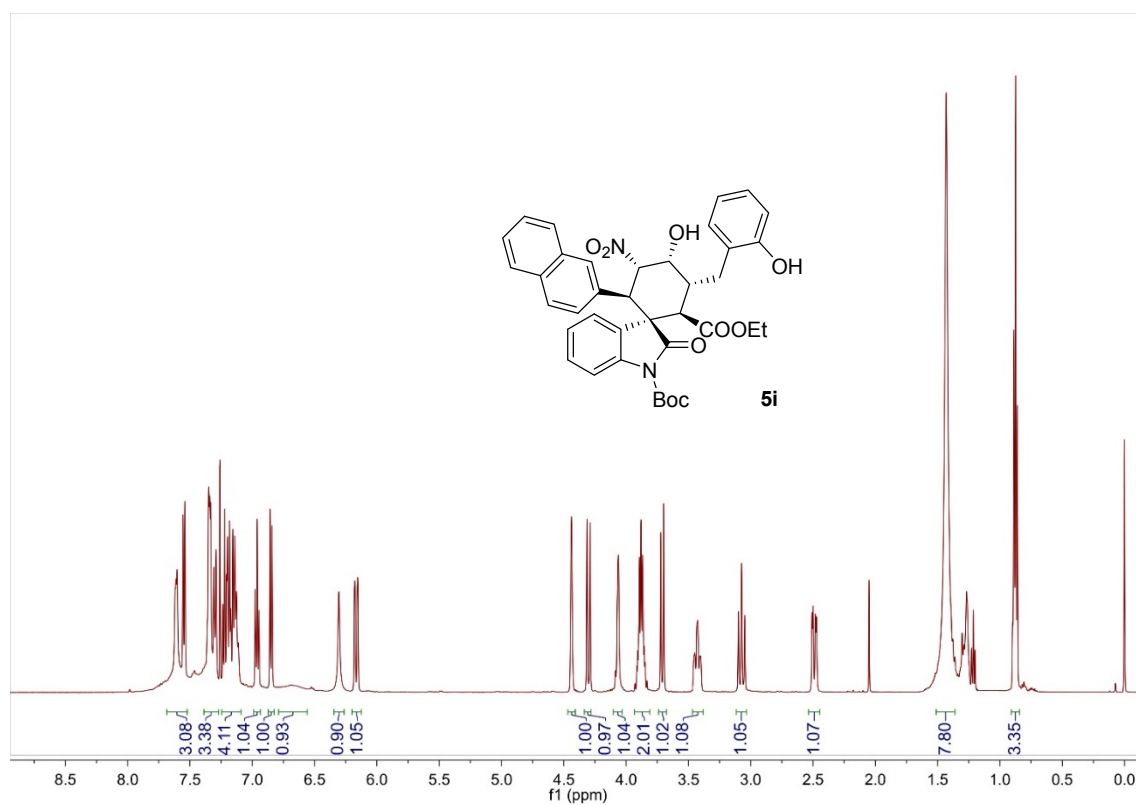
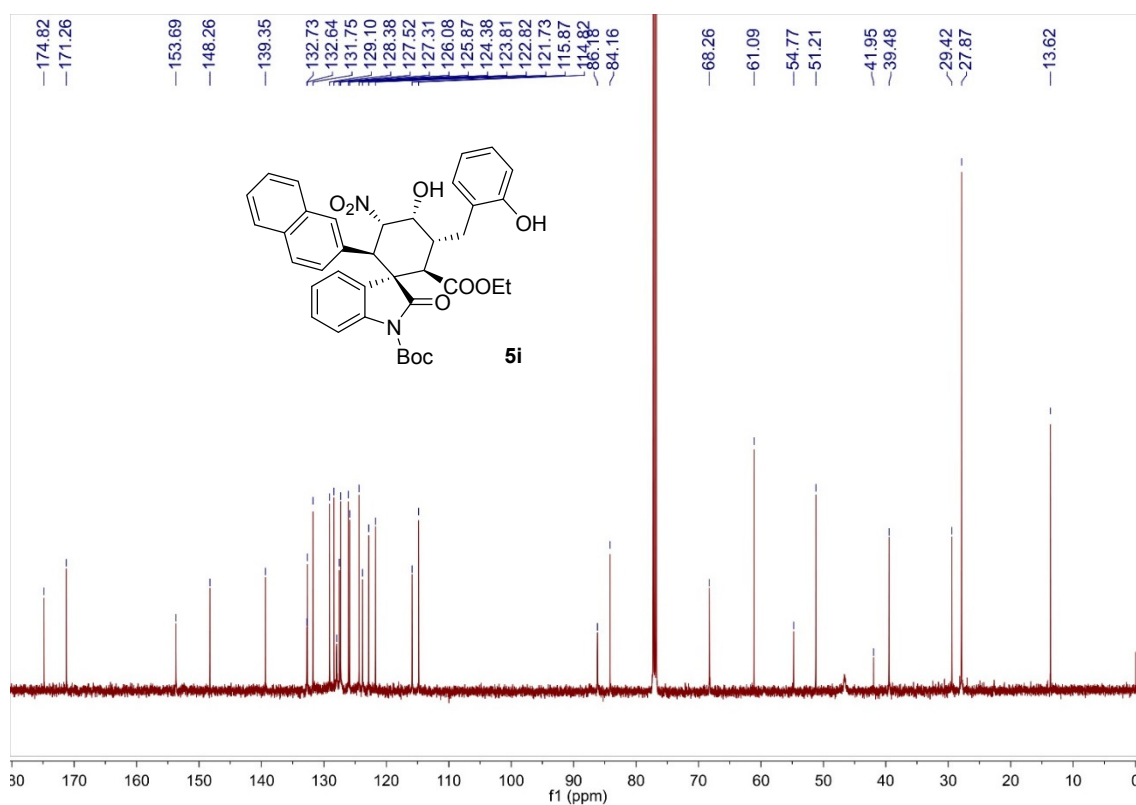
Chrom Type: Fixed WL Chromatogram, 210 nm

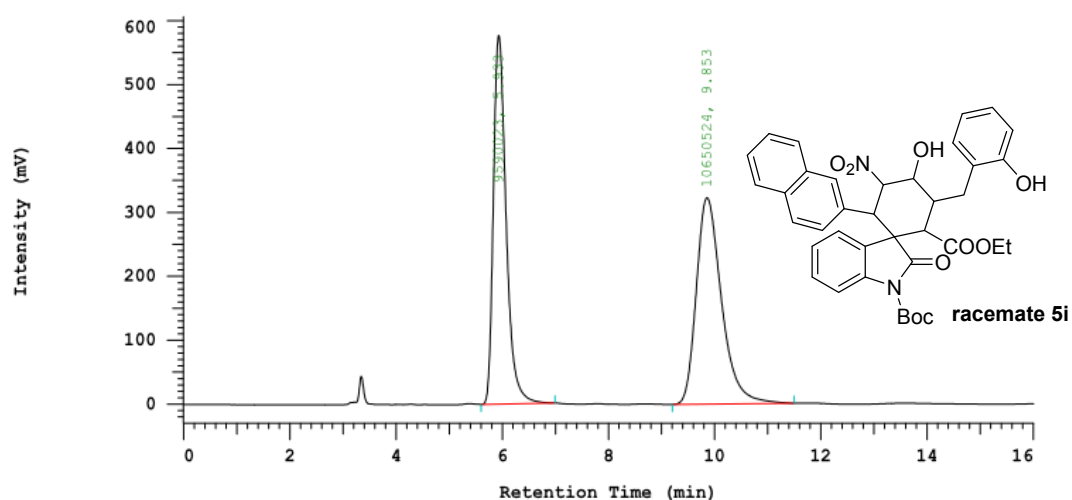
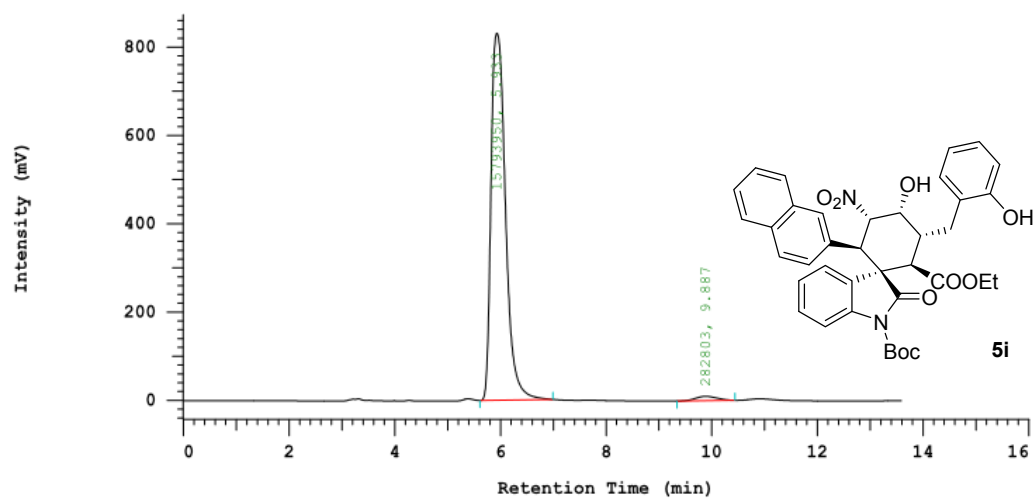
Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	4.327	7228832	96.265	BB
2	7.093	280480	3.735	BB
		7509312	100.000	

Figure S33. The HPLC profiles of 5h.

Figure S34. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5i**.Figure S35. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5i**.

Figure S36. The HPLC profiles of racemate **5i**.Figure S37. The HPLC profiles of **5i**.

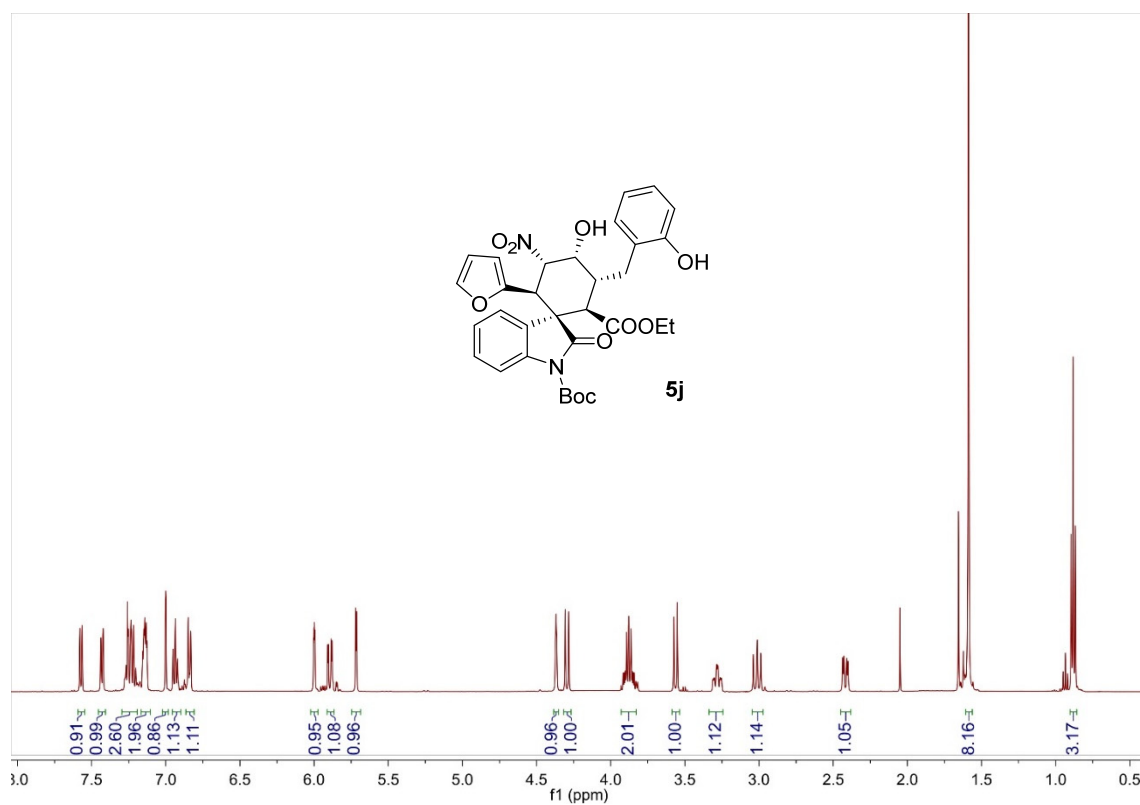


Figure S38. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5j**.

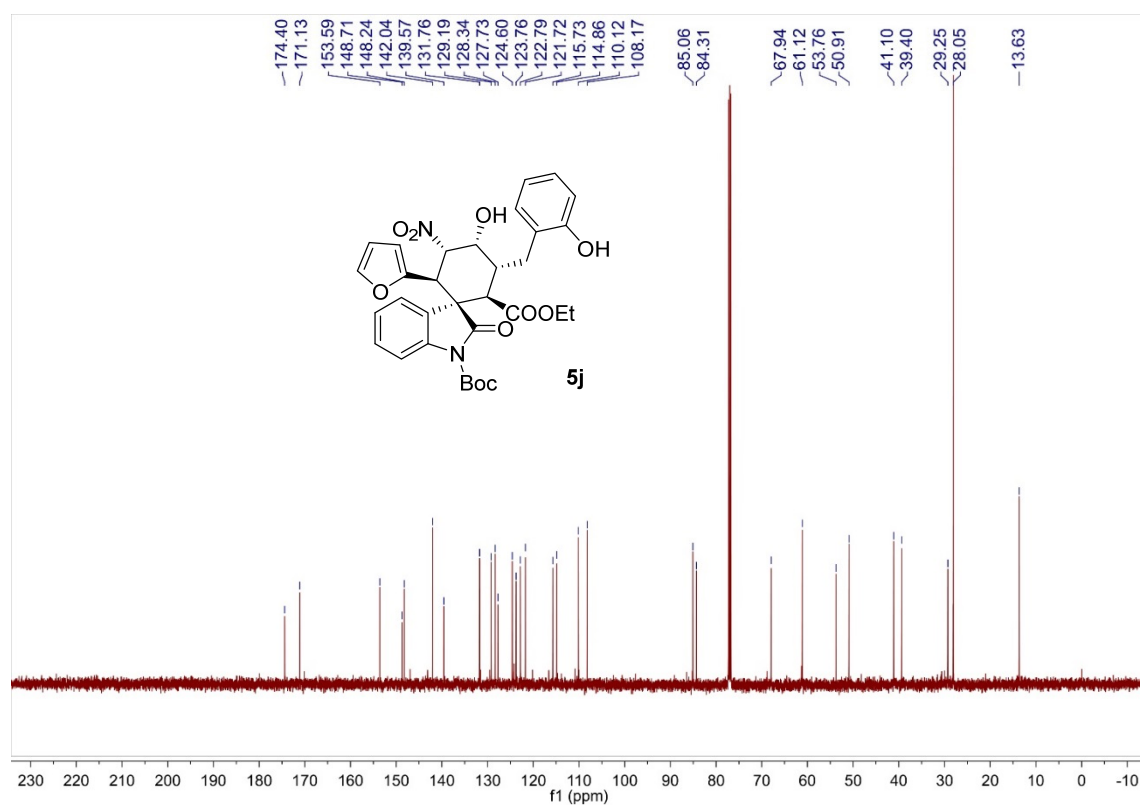


Figure S39. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5j**.

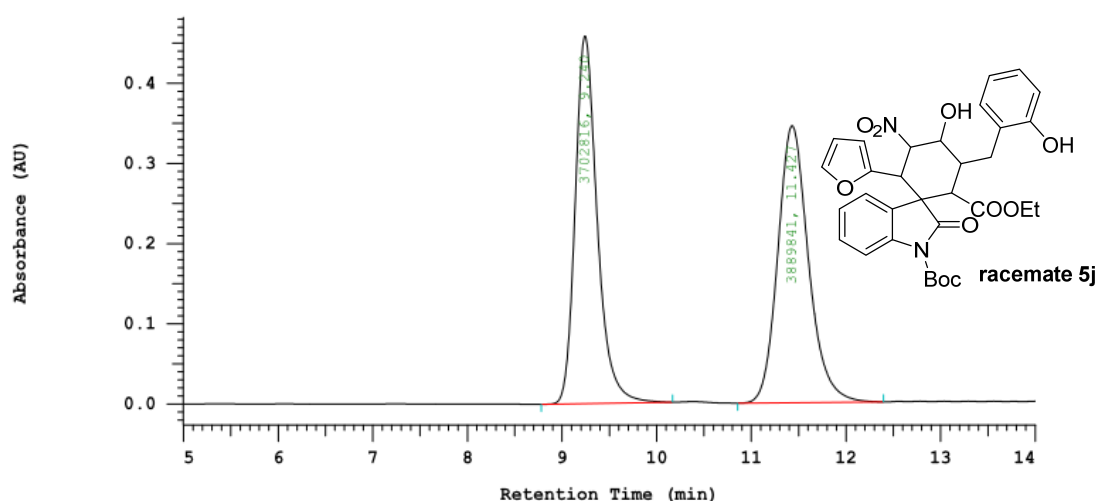


Figure S40. The HPLC profiles of racemate 5j.

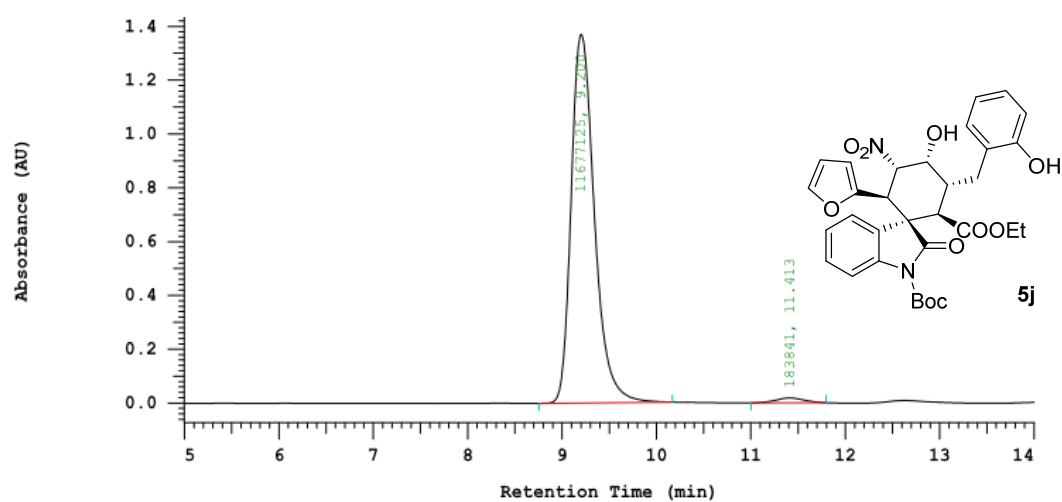


Figure S41. The HPLC profiles of 5j.

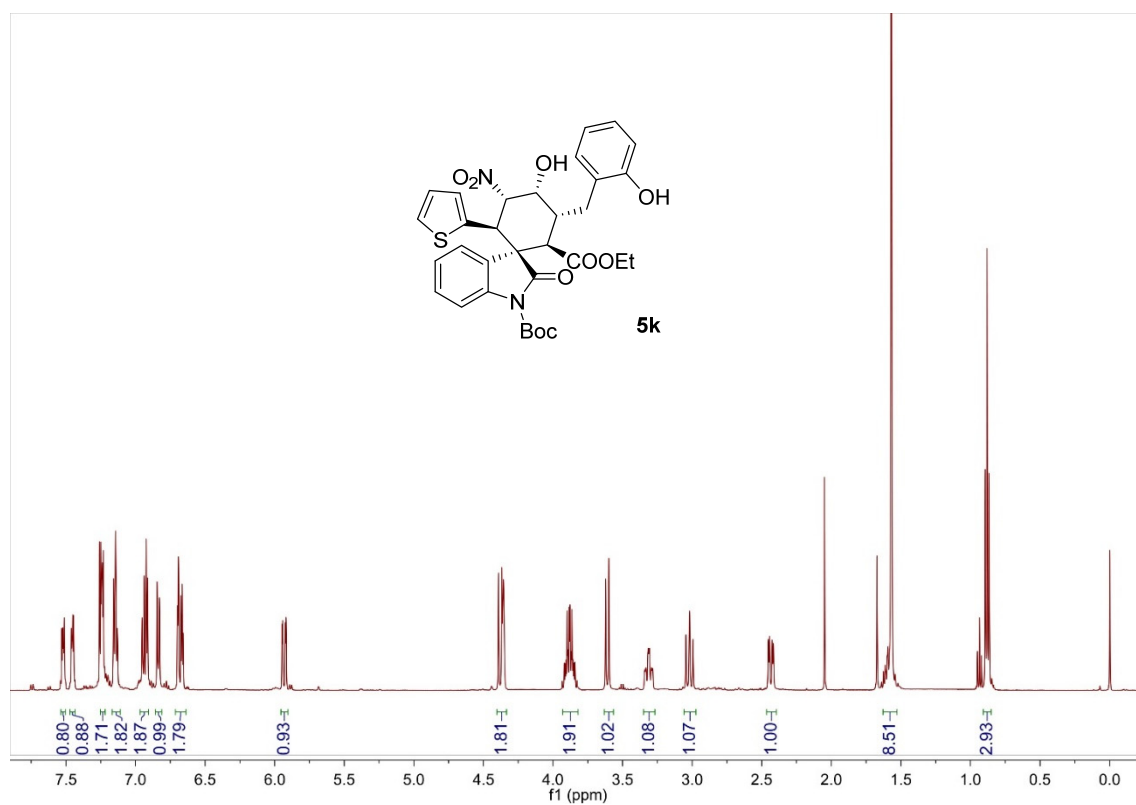


Figure S42. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5k**.

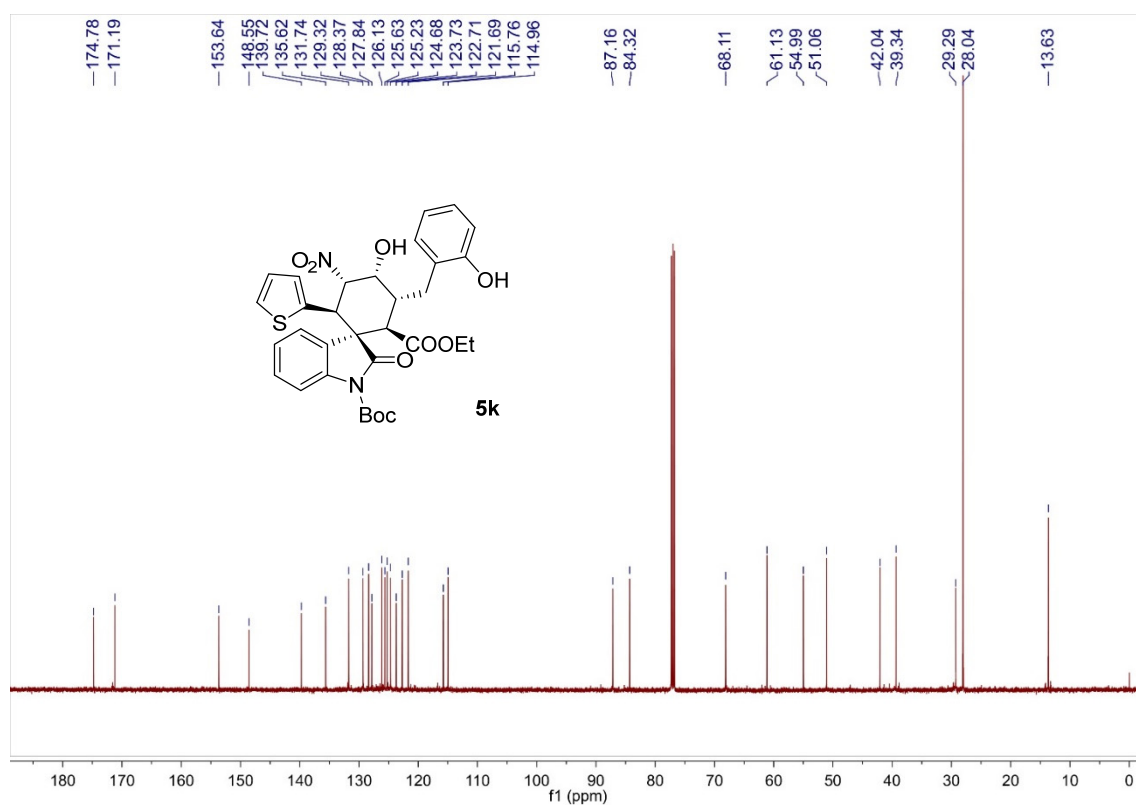
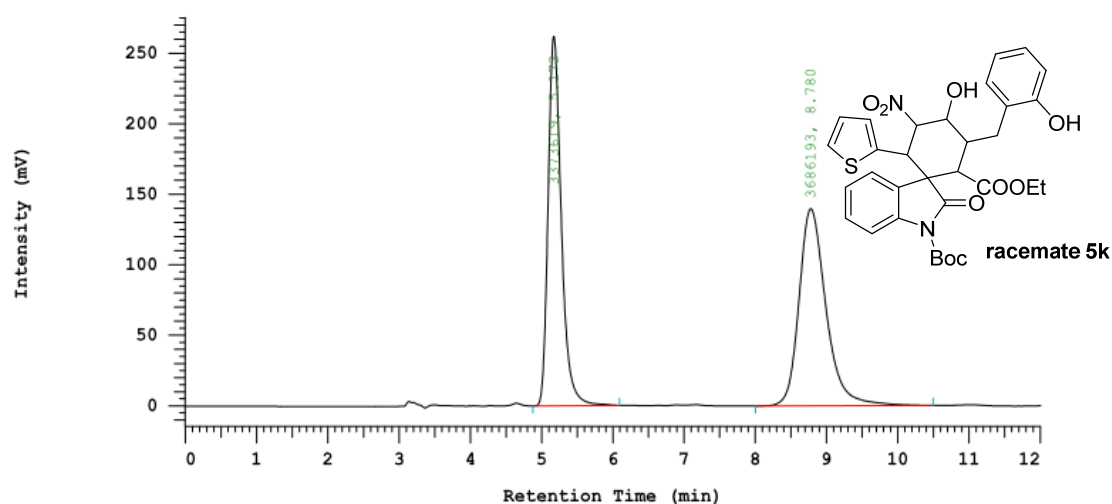


Figure S43. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5k**.



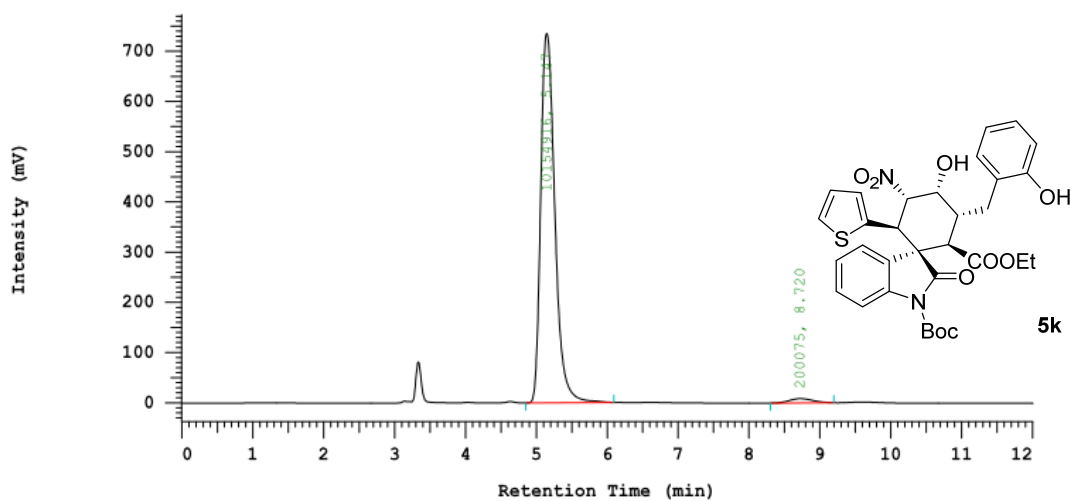
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	5.173	3373619	47.786	BB
2	8.780	3686193	52.214	BB
		7059812	100.000	

Figure S44. The HPLC profiles of racemate 5k.



Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	5.147	10154916	98.068	BB
2	8.720	200075	1.932	BB
		10354991	100.000	

Figure S45. The HPLC profiles of 5k.

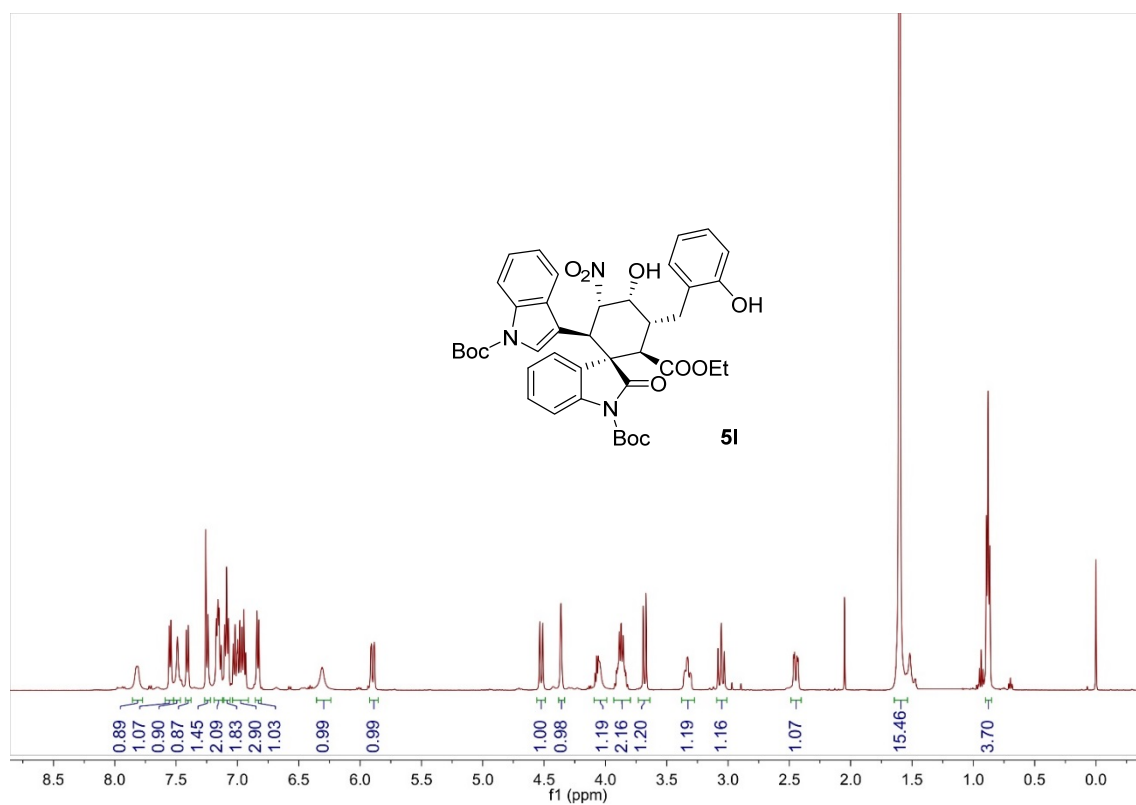


Figure S46. ¹H NMR spectrum (CDCl₃, 500 MHz) of **51**.

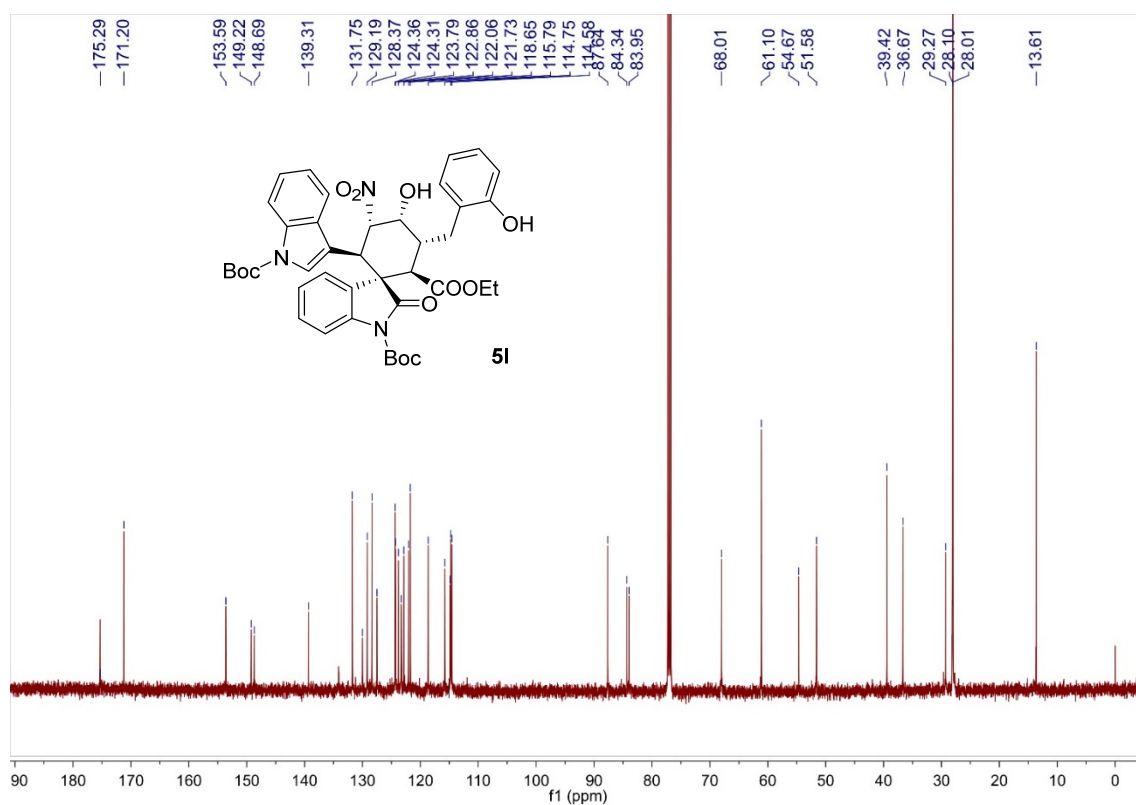


Figure S47. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **51**.

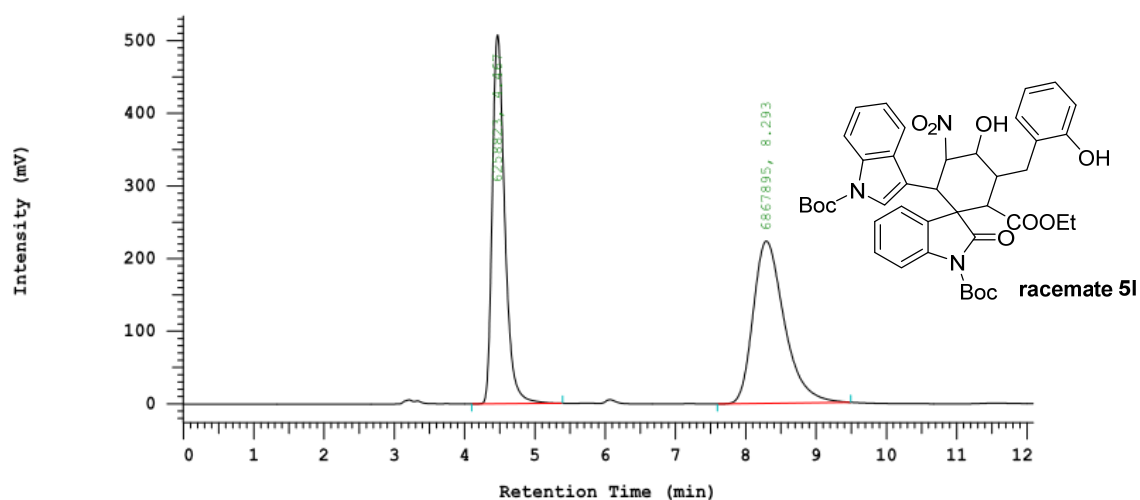


Figure S48. The HPLC profiles of racemate 5I.

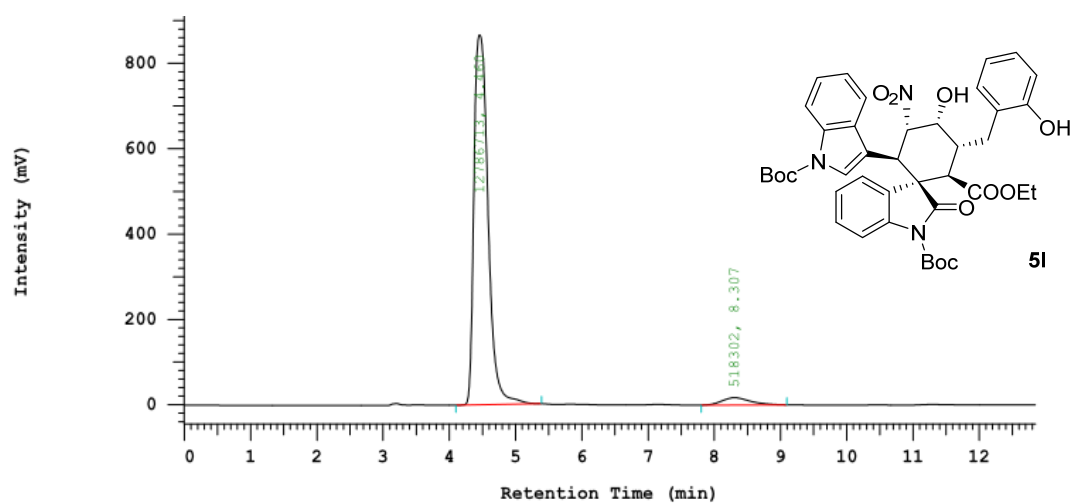


Figure S49. The HPLC profiles of 5I.

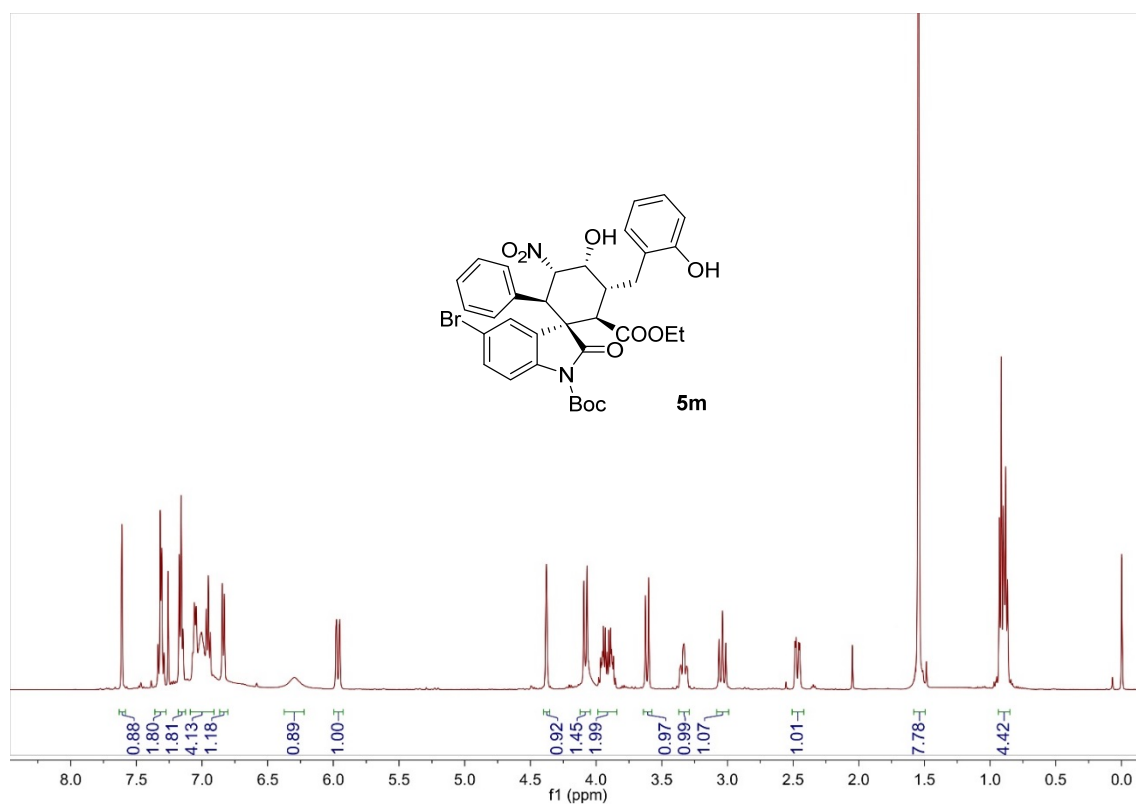


Figure S50. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5m**.

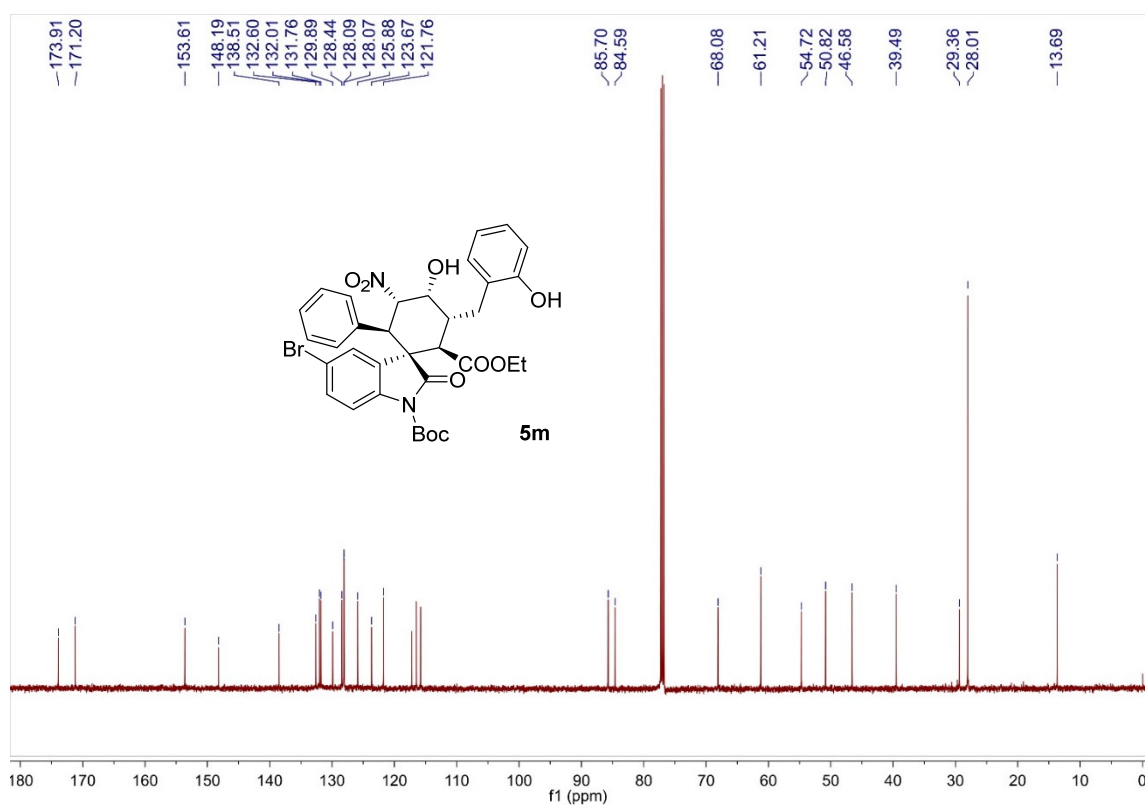


Figure S51. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5m**.

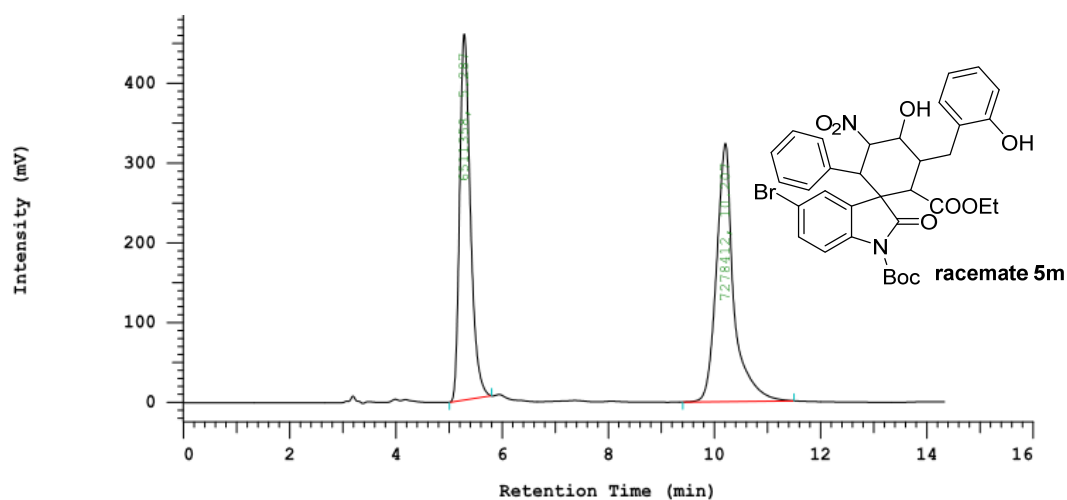


Figure S52. The HPLC profiles of racemate 5m.

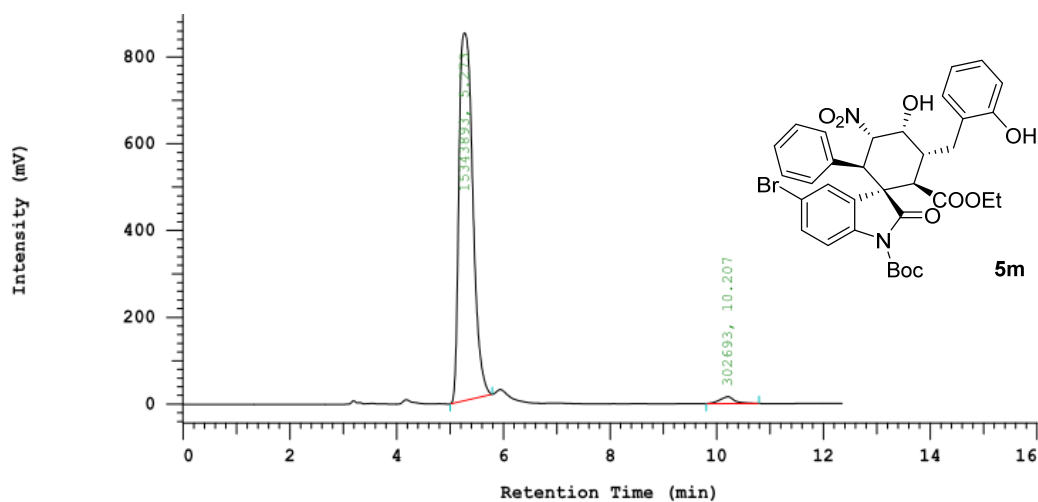


Figure S53. The HPLC profiles of 5m.

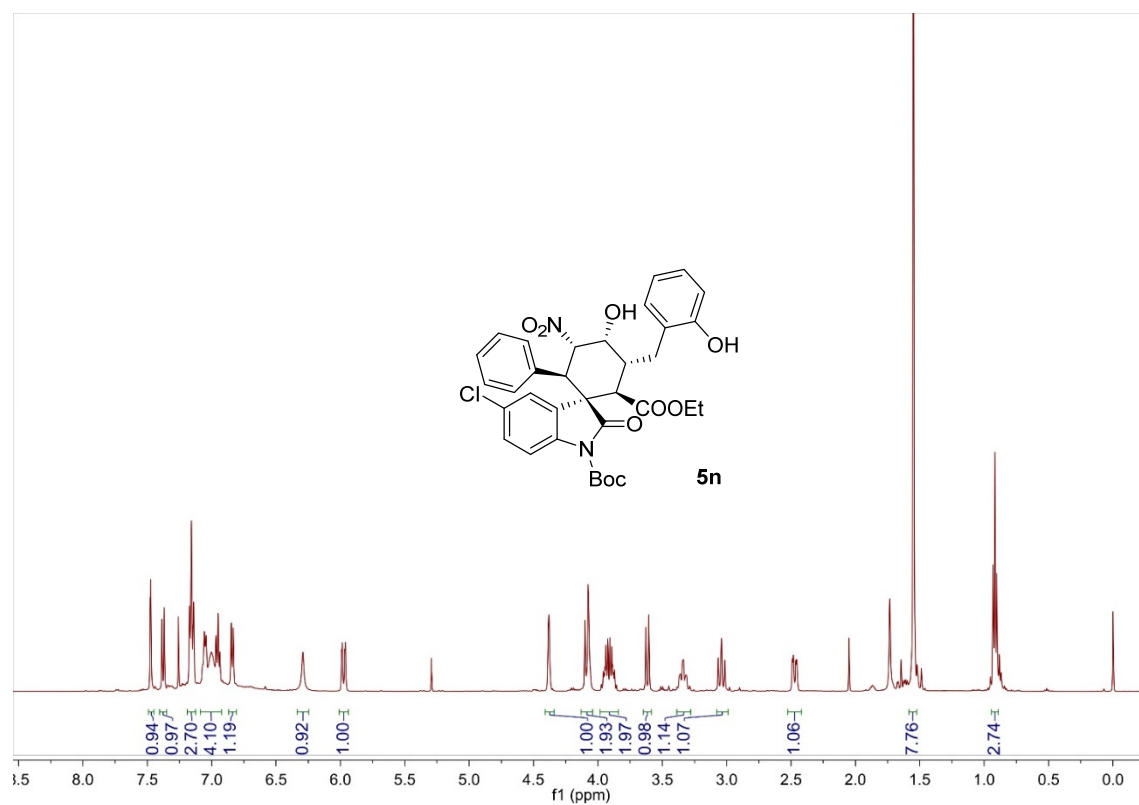


Figure S54. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5n**.

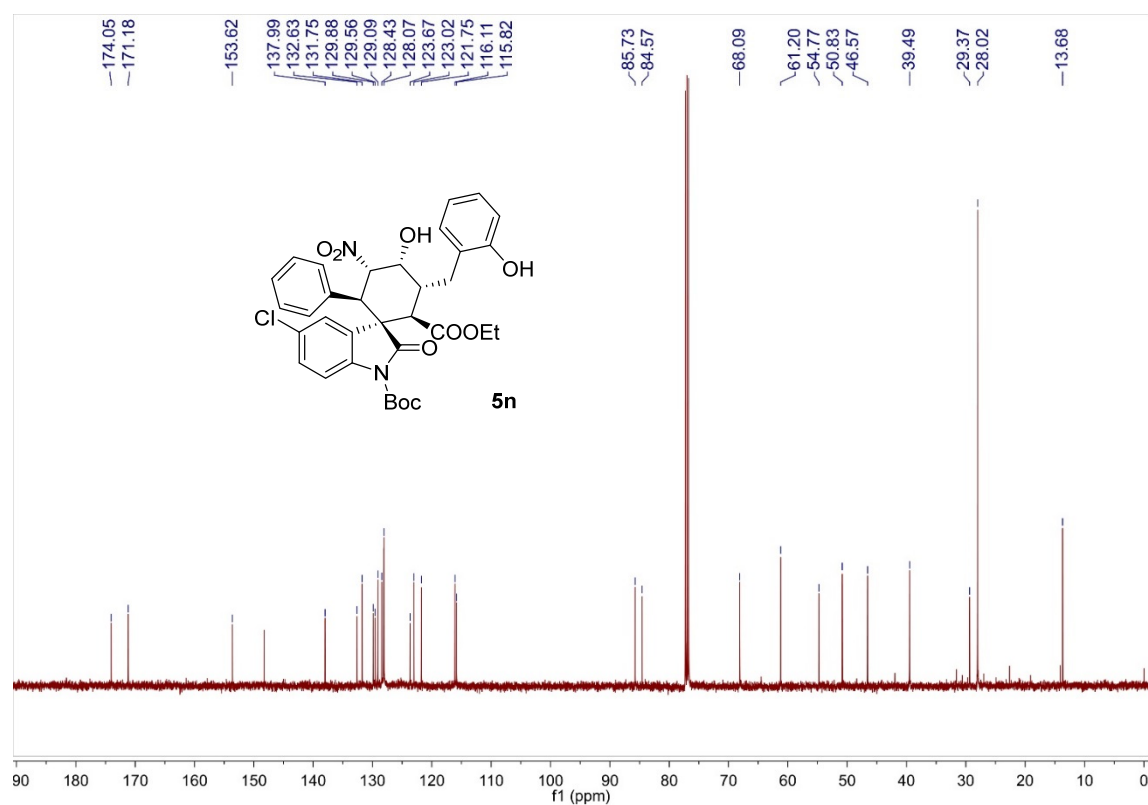


Figure S55. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5n**.

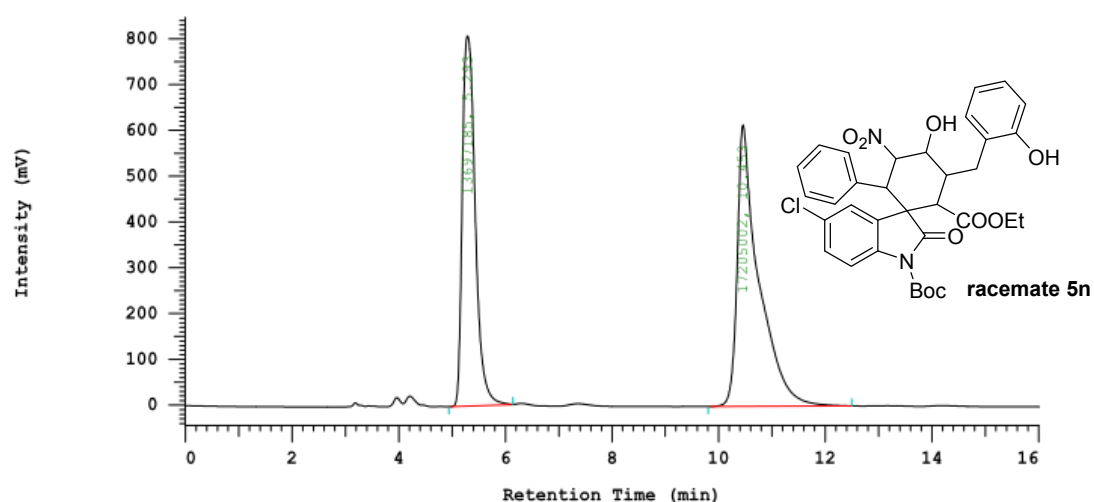


Figure S56. The HPLC profiles of racemate 5n.

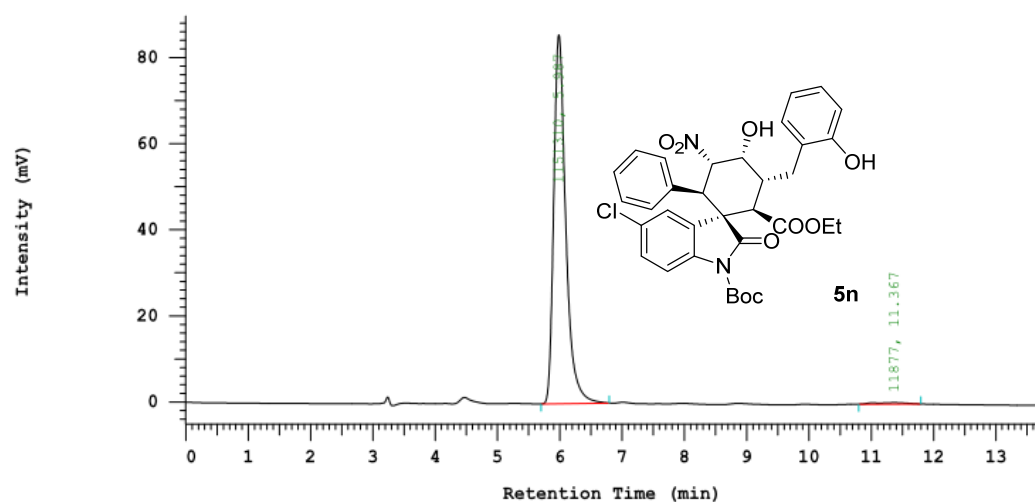


Figure S57. The HPLC profiles of 5n.

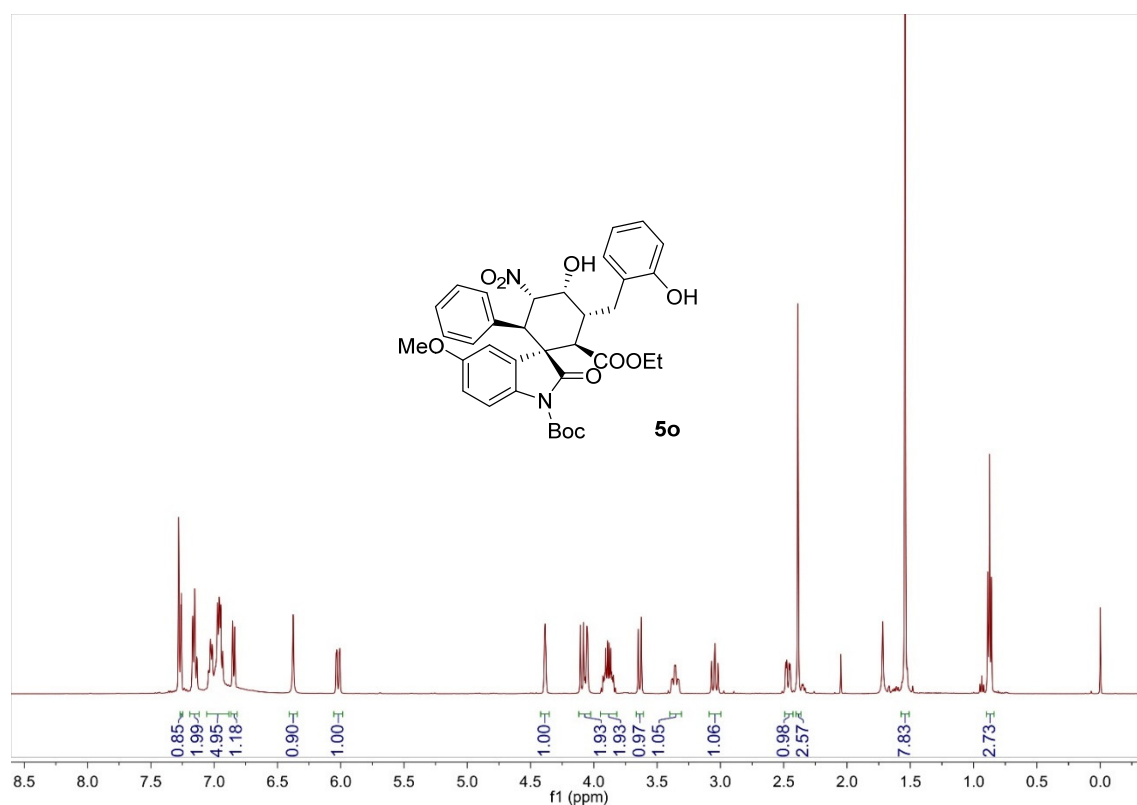


Figure S58. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5o**.

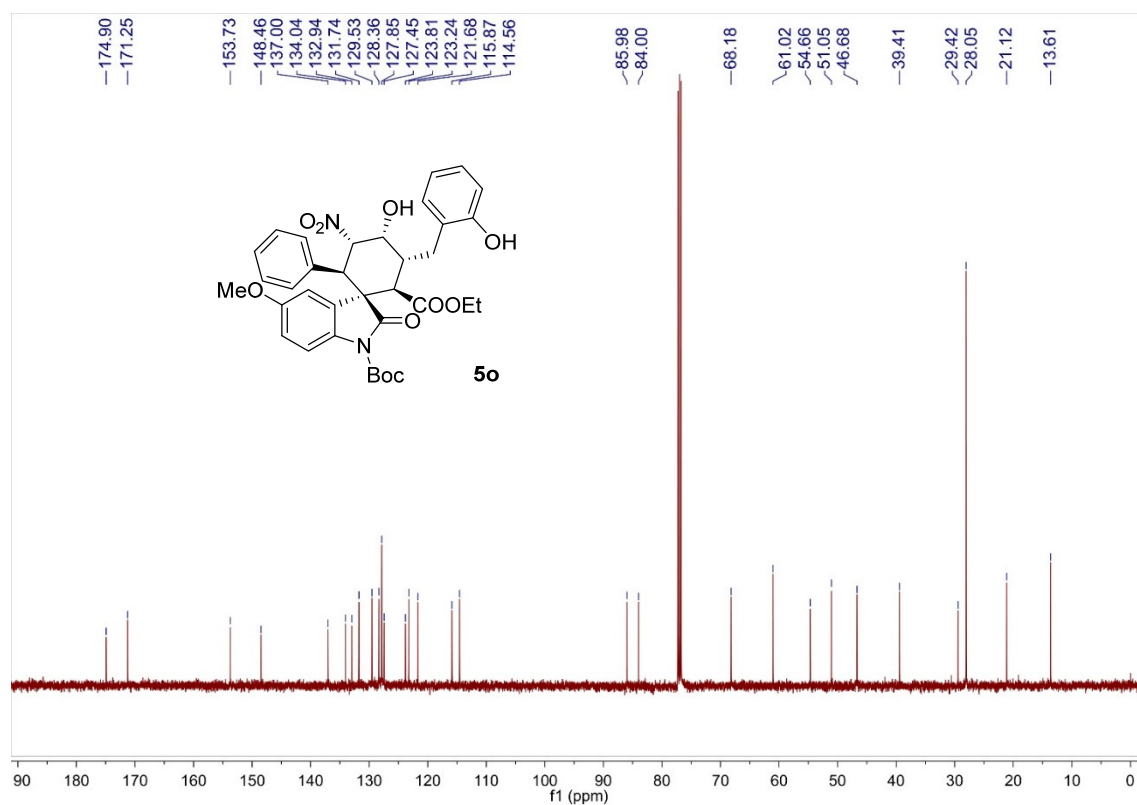


Figure S59. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5o**.

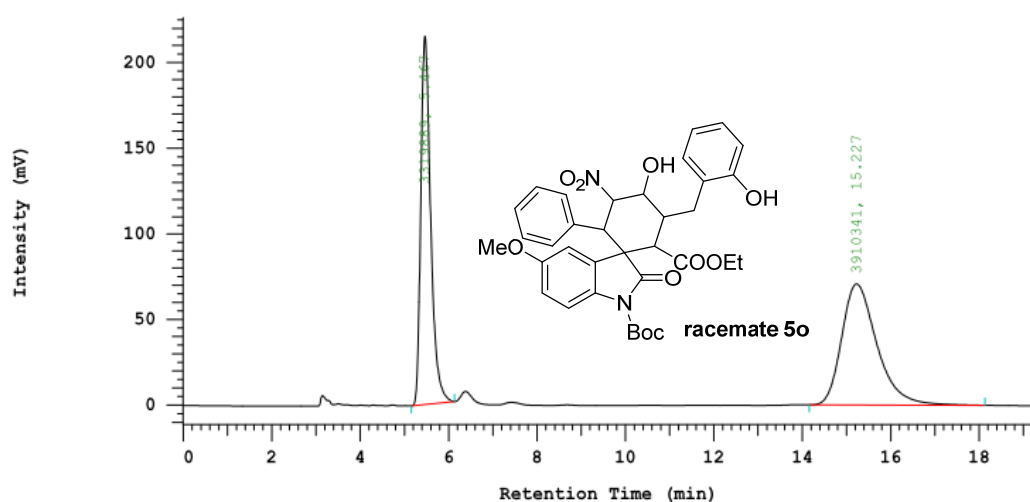


Figure S60. The HPLC profiles of racemate 5n.

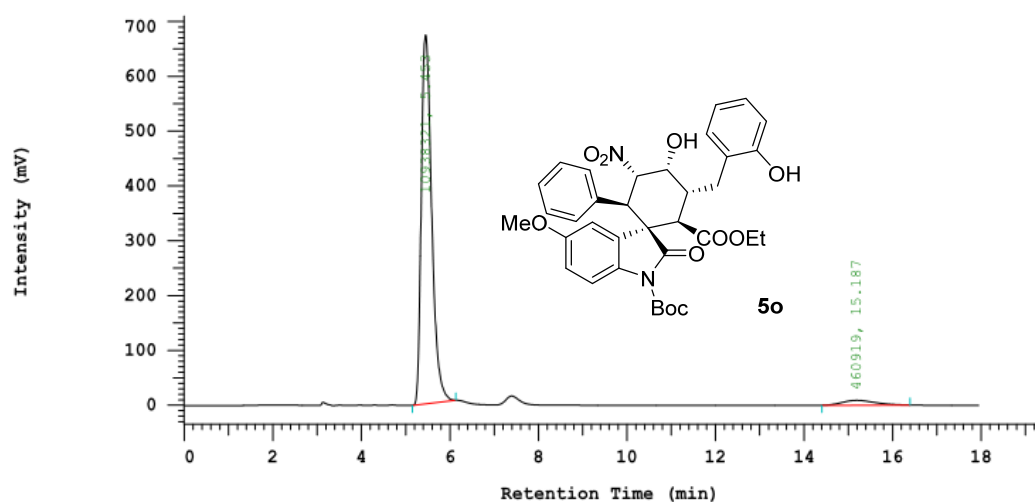


Figure S61. The HPLC profiles of 5n.

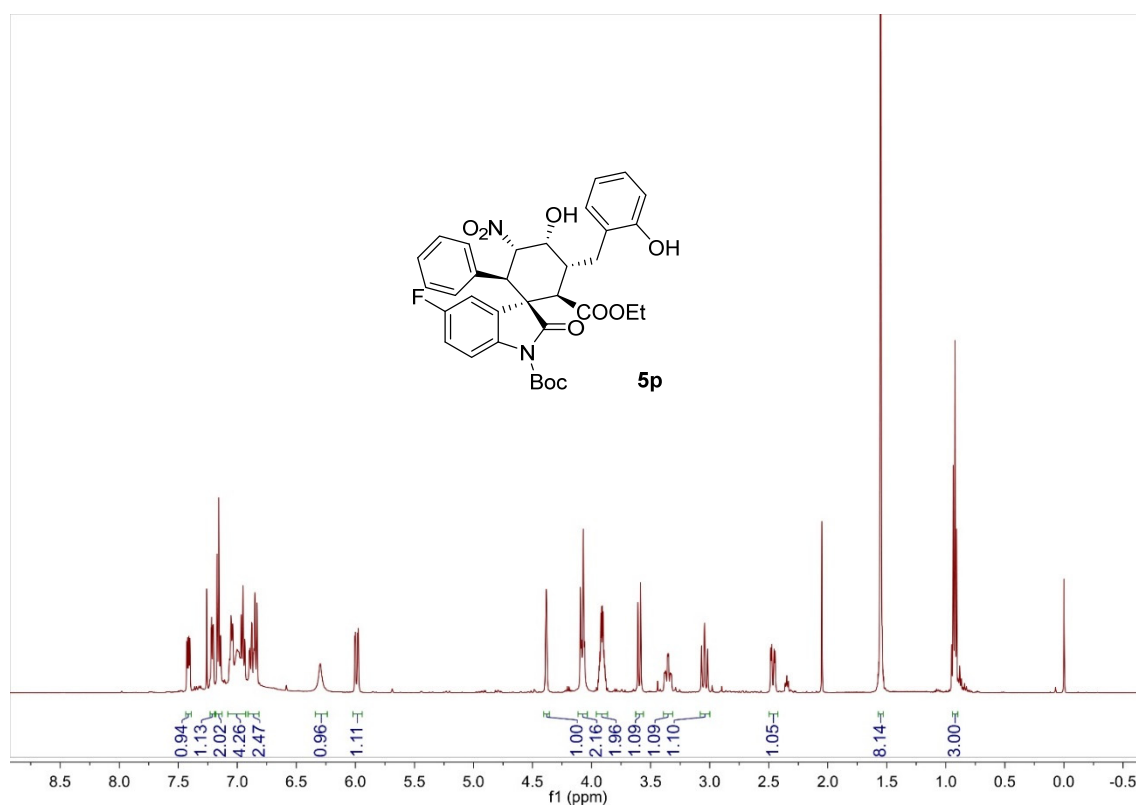


Figure S62. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5p**.

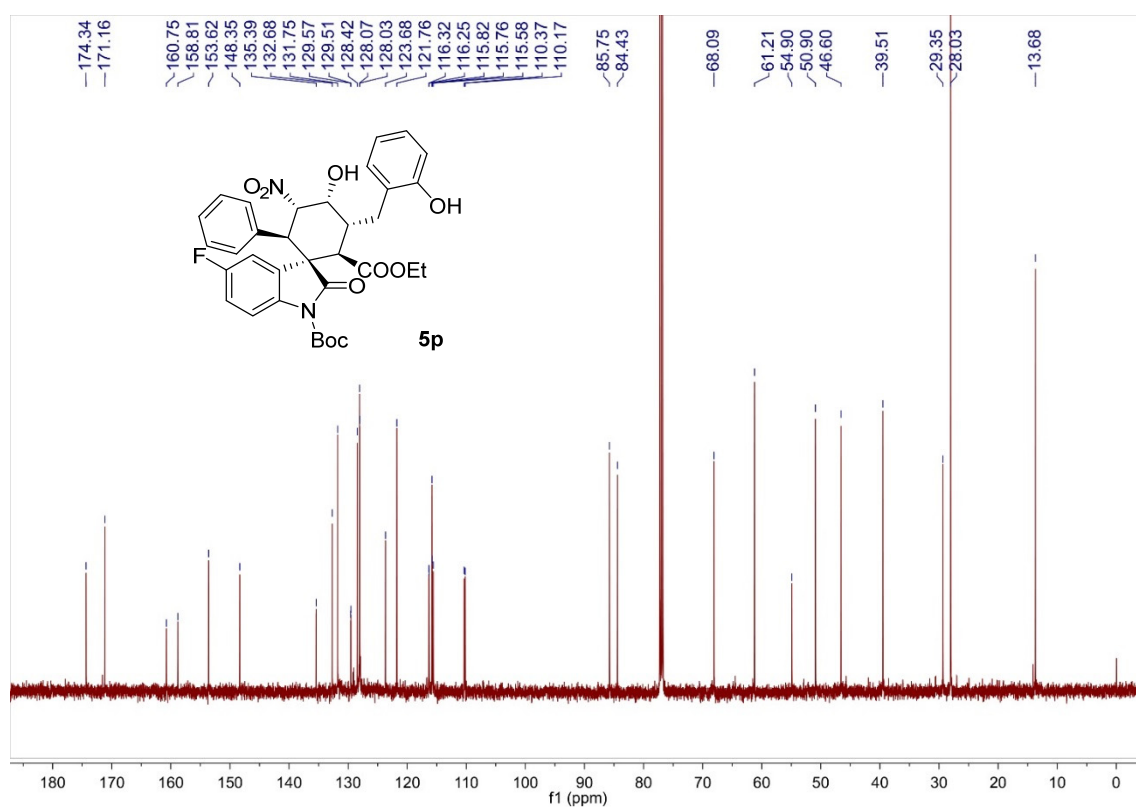
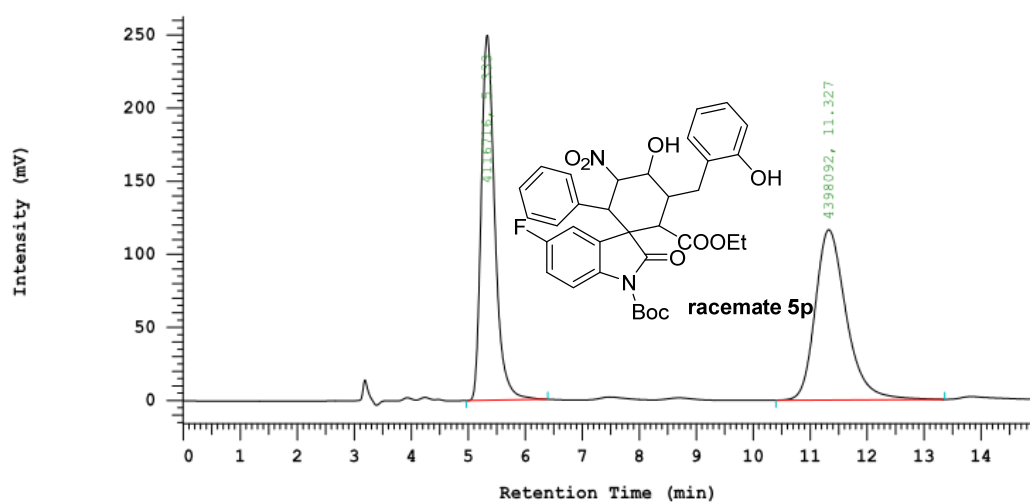


Figure S63. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5p**.



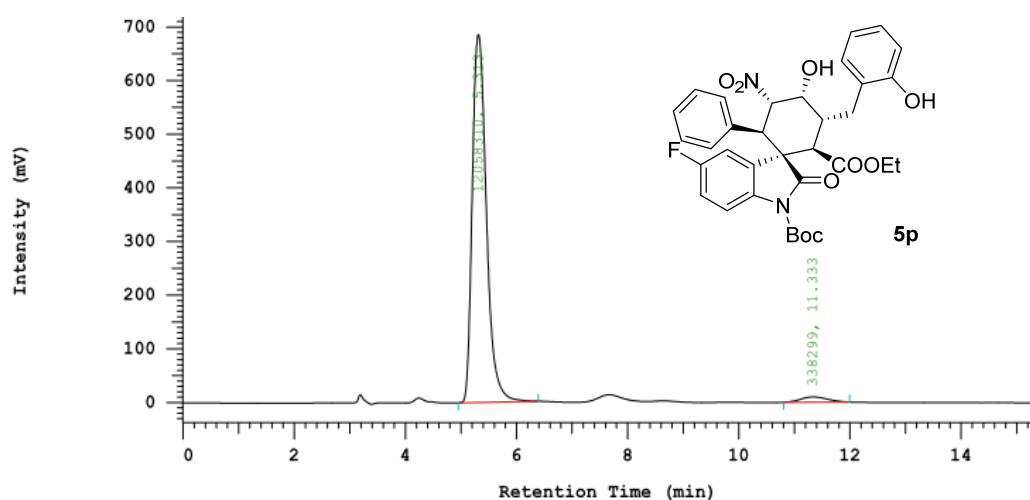
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	5.333	4116716	48.348	BB
2	11.327	4398092	51.652	BB
		8514808	100.000	

Figure S64. The HPLC profiles of racemate 5p.



Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	5.313	12058310	97.271	BB
2	11.333	338299	2.729	BB
		12396609	100.000	

Figure S65. The HPLC profiles of 5p.

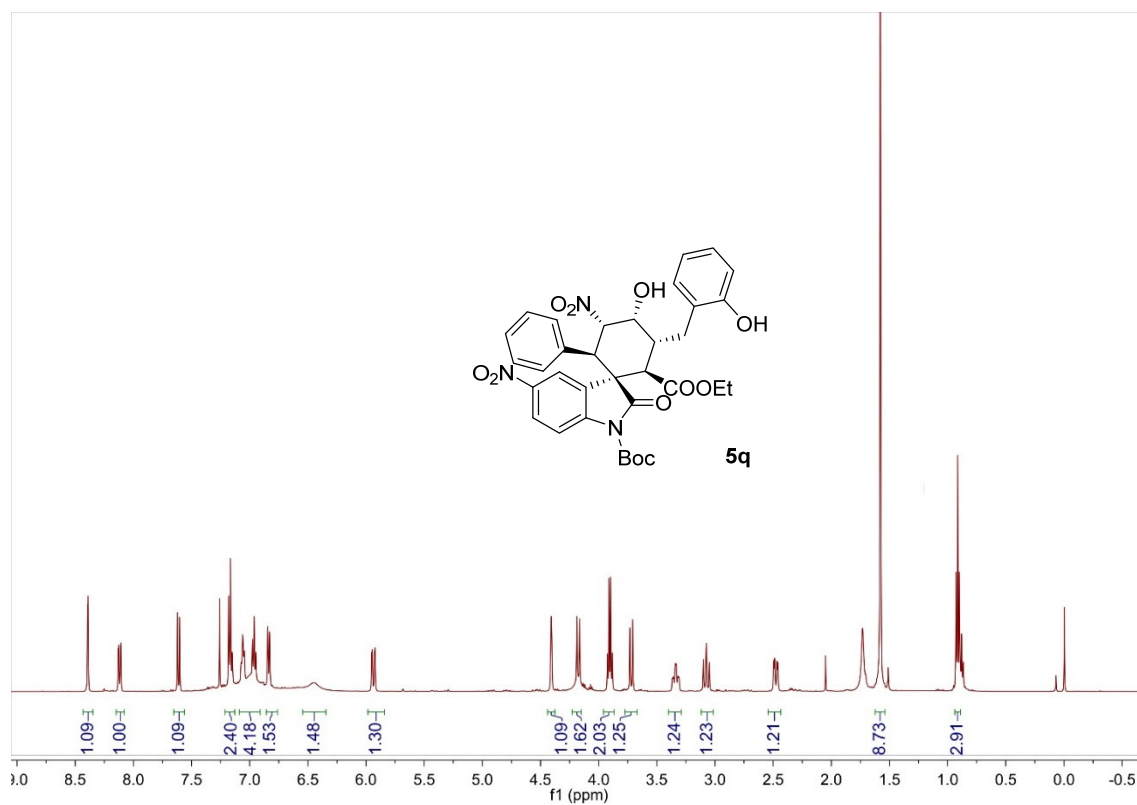


Figure S66. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5q**.

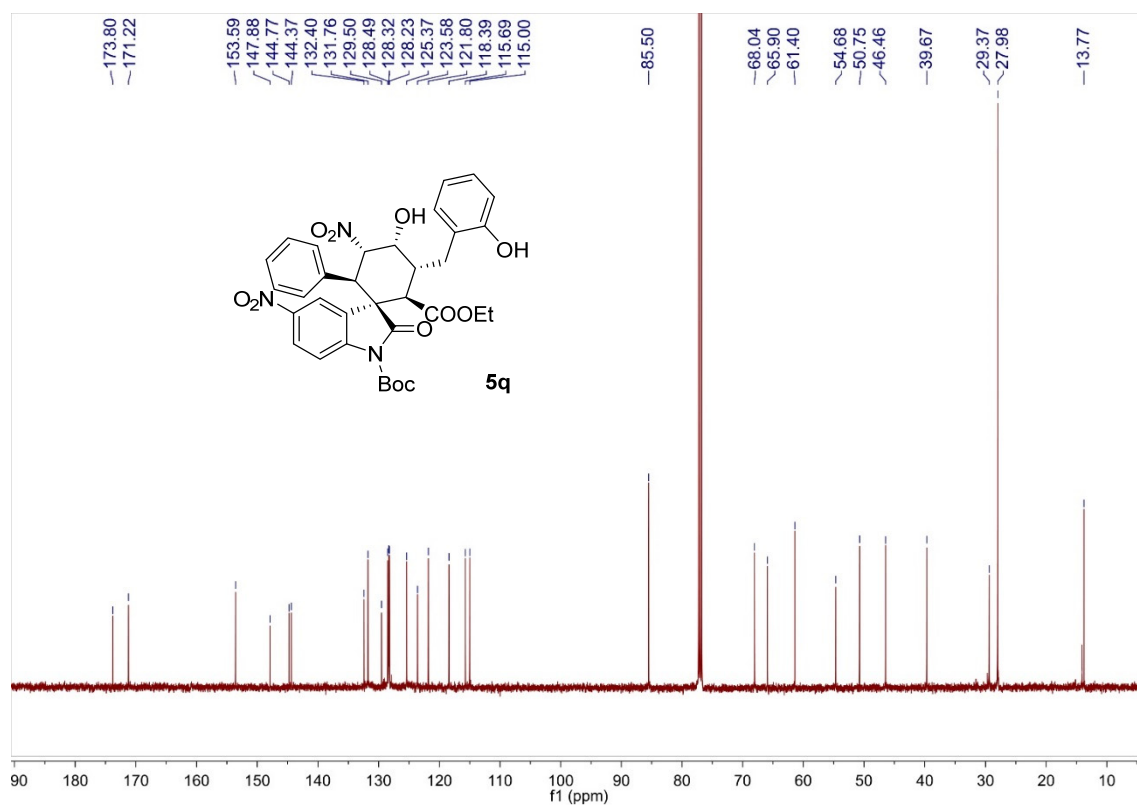
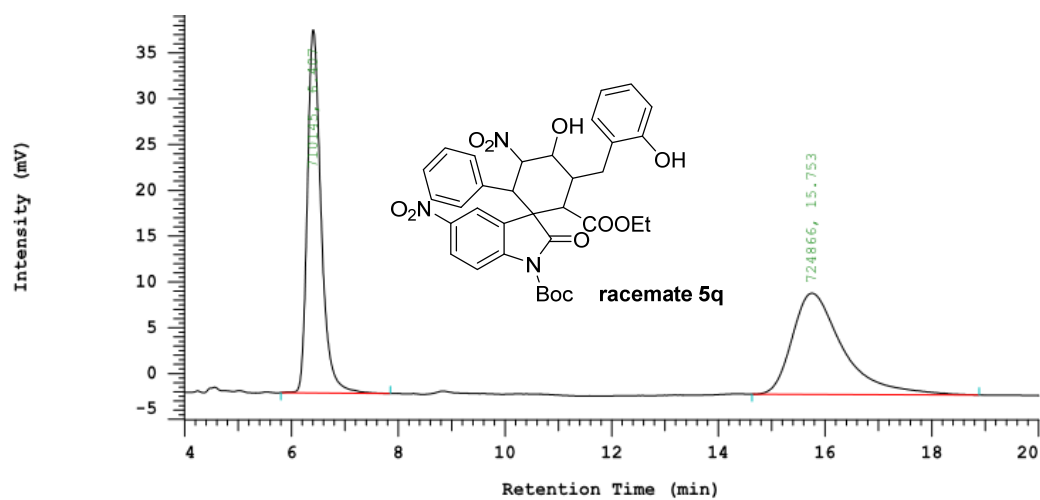


Figure S67. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5q**.



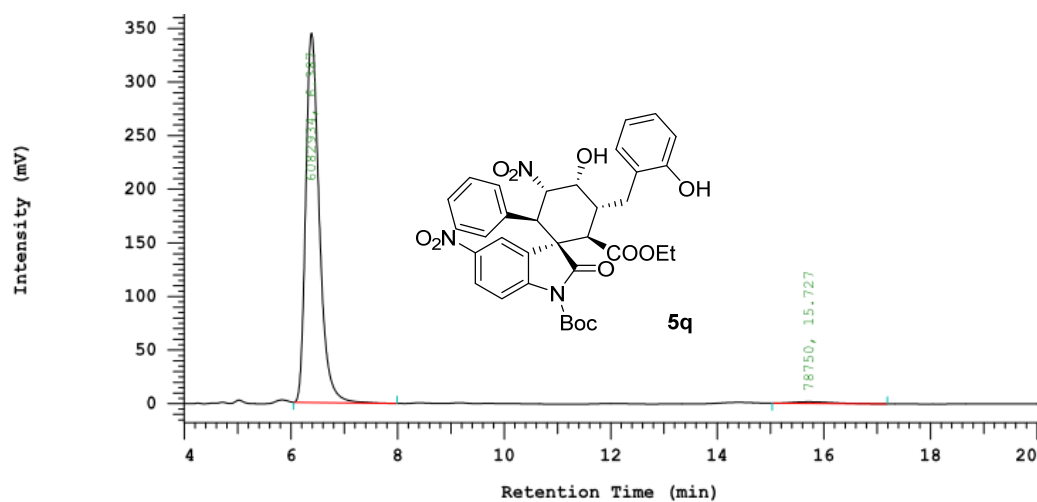
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	6.407	710145	49.487	BB
2	15.753	724866	50.513	BB
		1435011	100.000	

Figure S68. The HPLC profiles of racemate 5q.



Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	6.387	6082934	98.722	BB
2	15.727	78750	1.278	BB
		6161684	100.000	

Figure S69. The HPLC profiles of 5q.

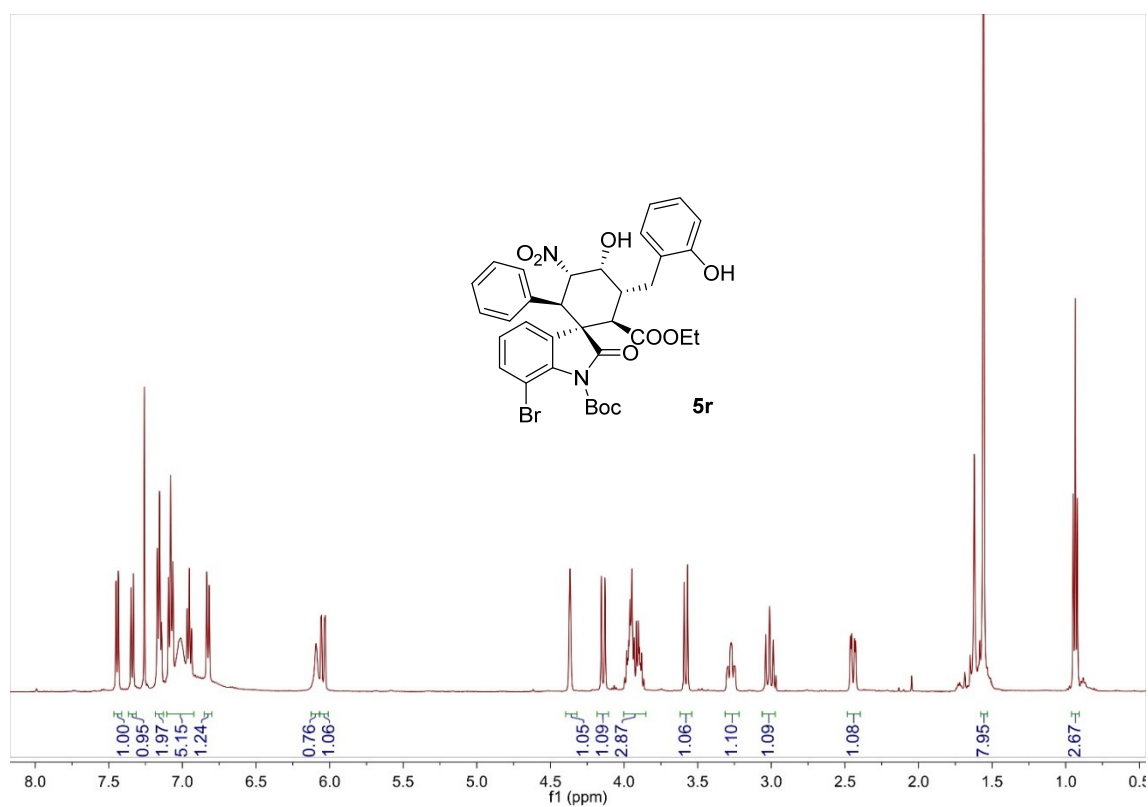


Figure S70. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5r**.

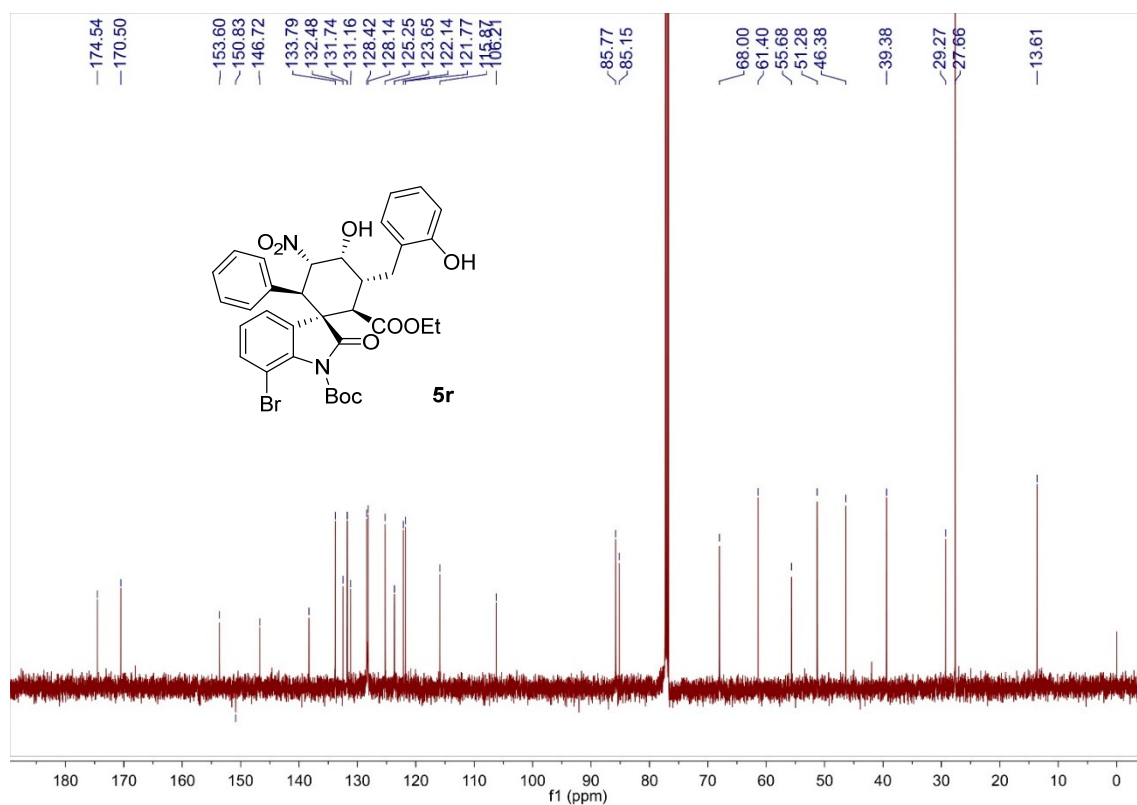


Figure S71. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5r**.

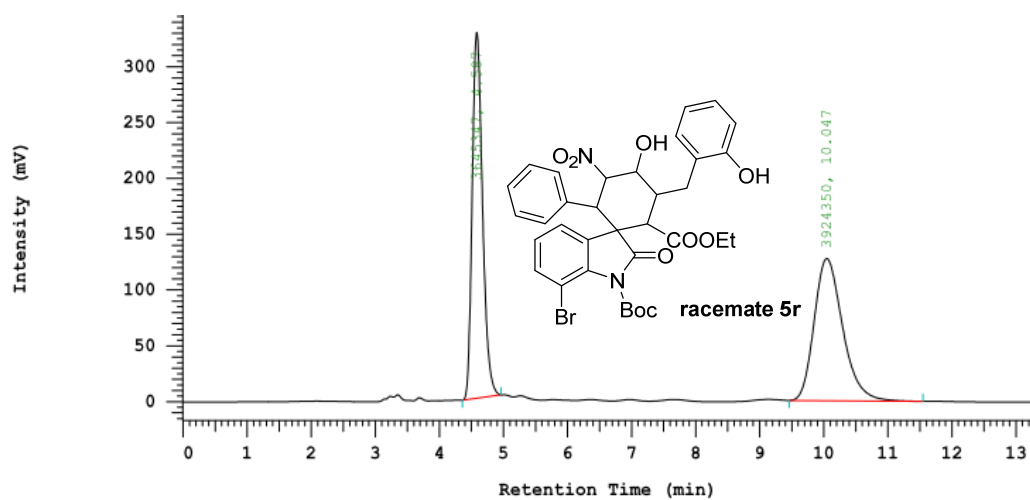


Figure S72. The HPLC profiles of racemate 5r.

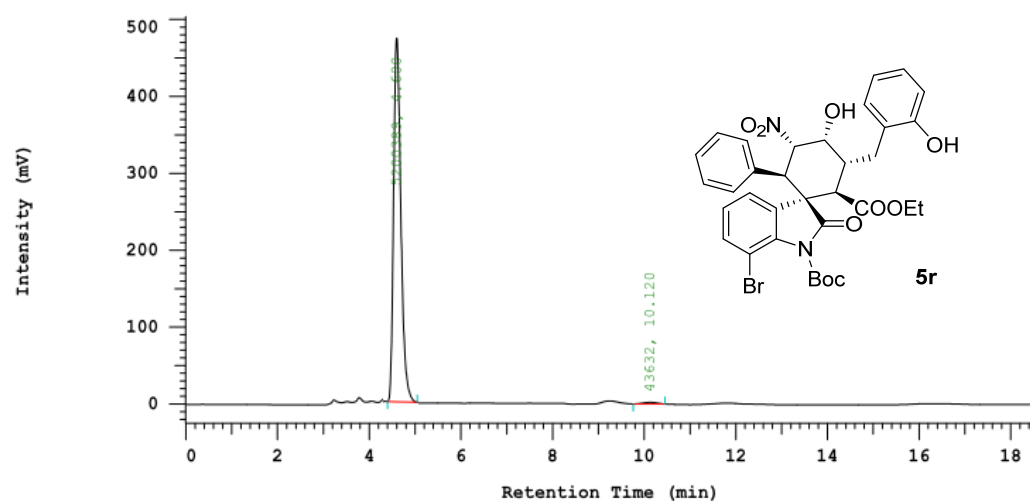


Figure S73. The HPLC profiles of 5r.

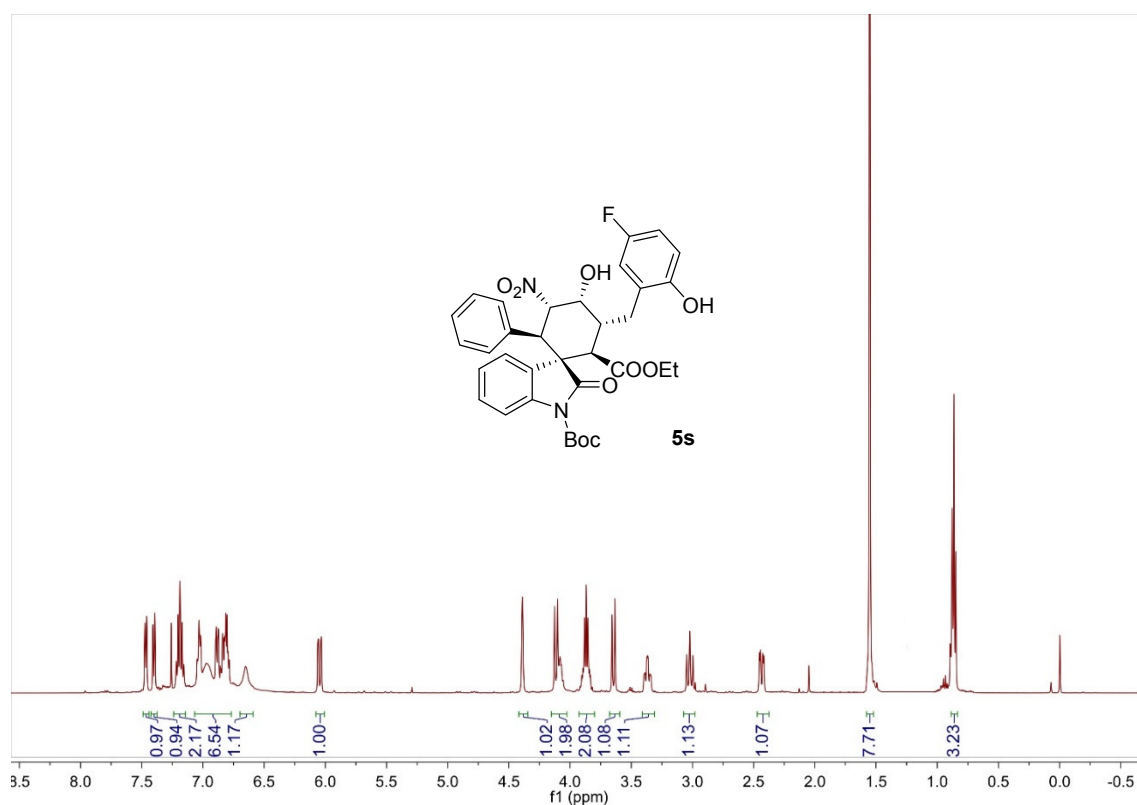


Figure S74. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5s**.

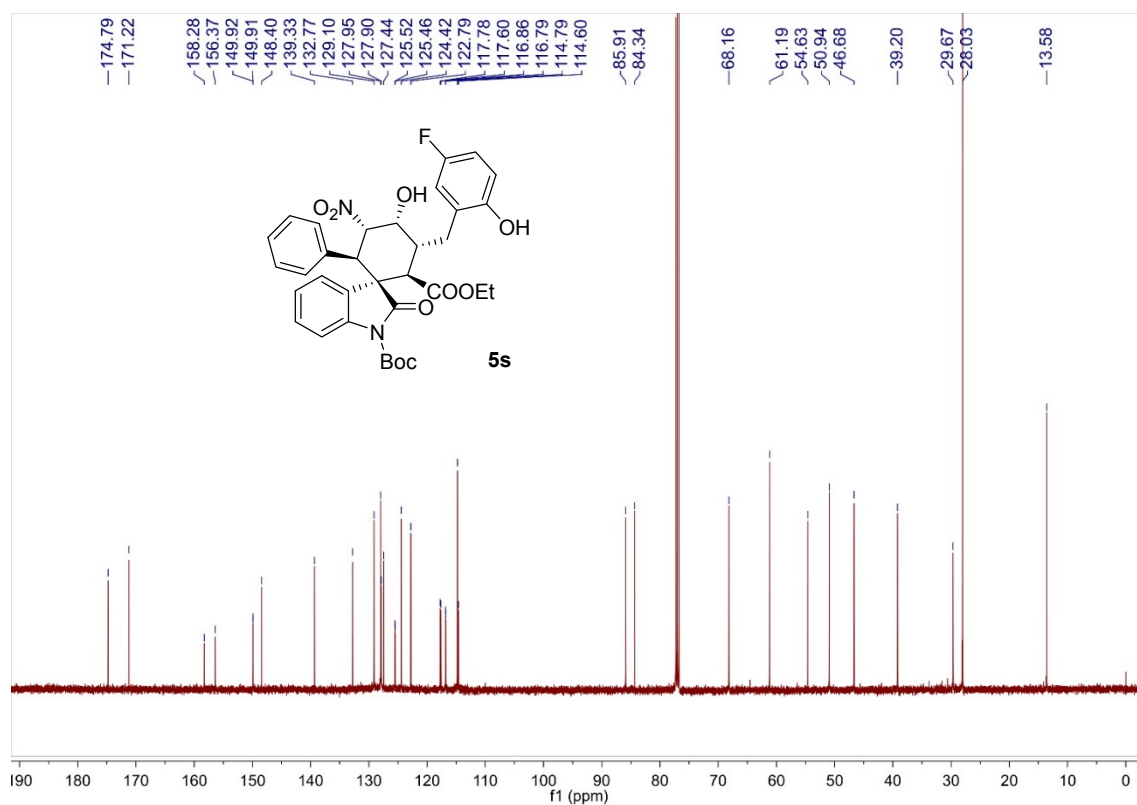
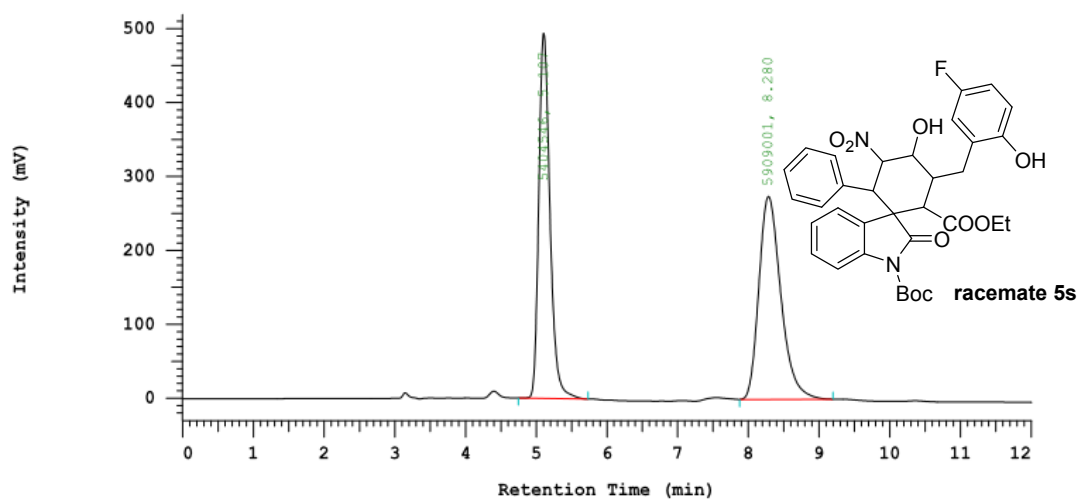


Figure S75. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5s**.



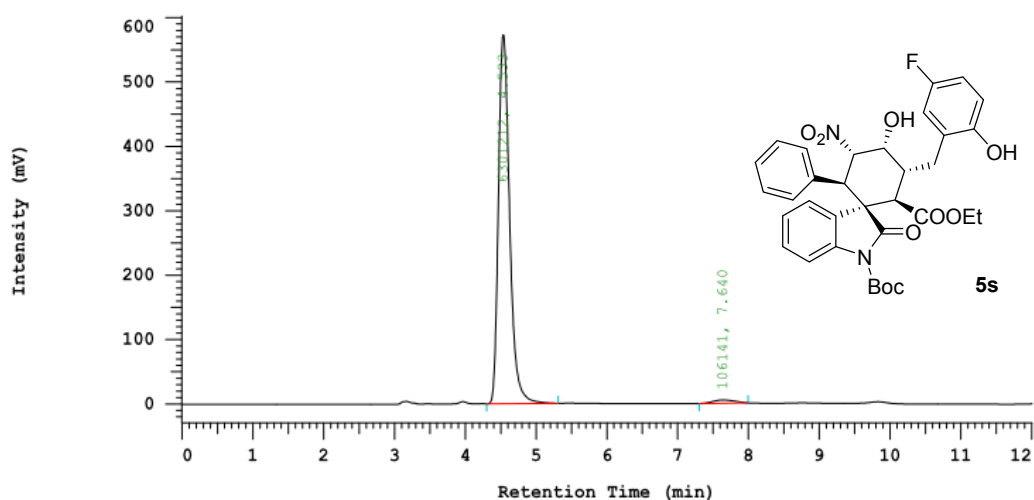
Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	5.107	5404546	47.771	BB
2	8.280	5909001	52.229	BB
		11313547	100.000	

Figure S76. The HPLC profiles of racemate 5s.



Chrom Type: Fixed WL Chromatogram, 210 nm

Peak Quantitation: AREA

Calculation Method: AREA%

No.	RT	Area	Area %	BC
1	4.533	6301212	98.343	BB
2	7.640	106141	1.657	BB
		6407353	100.000	

Figure S77. The HPLC profiles of 5s.

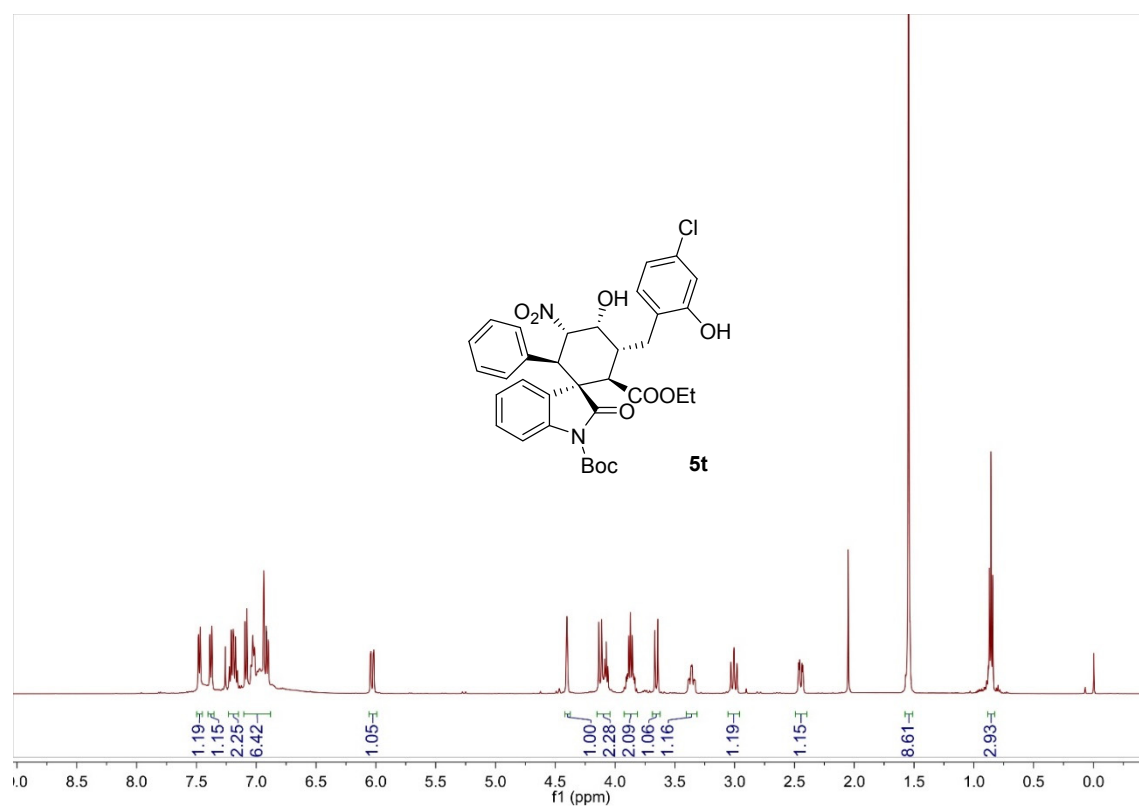


Figure S78. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5t**.

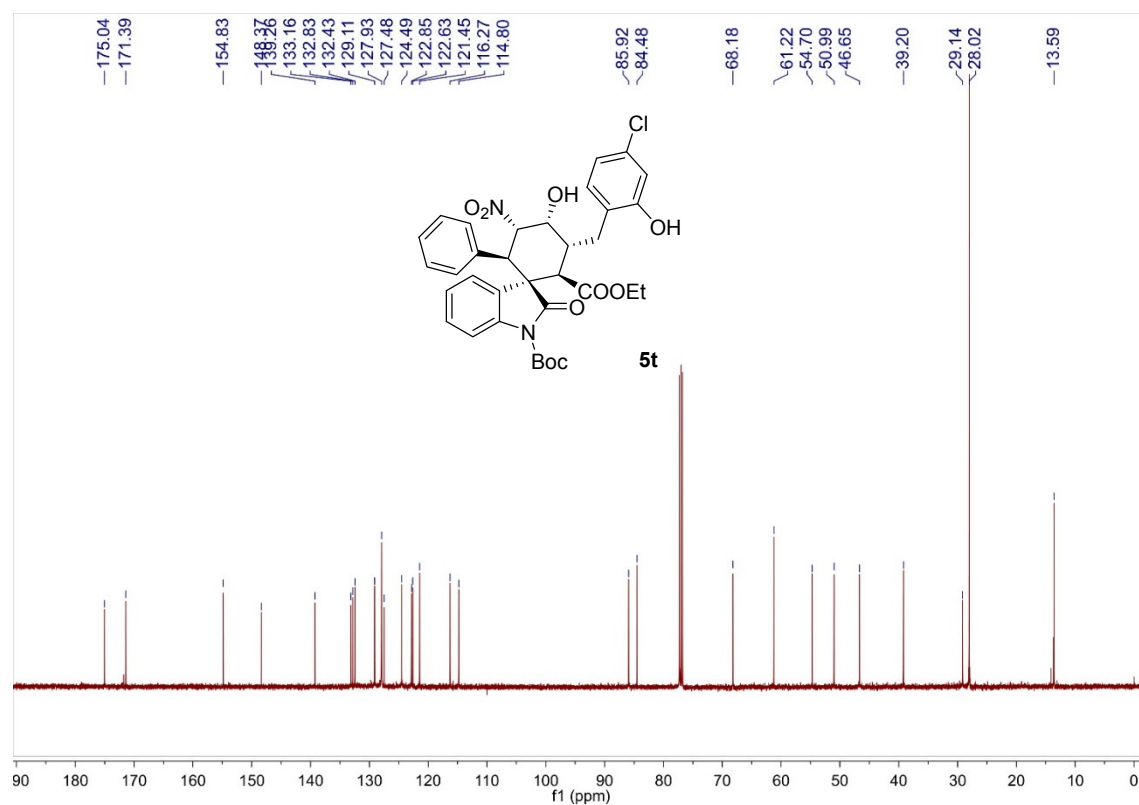
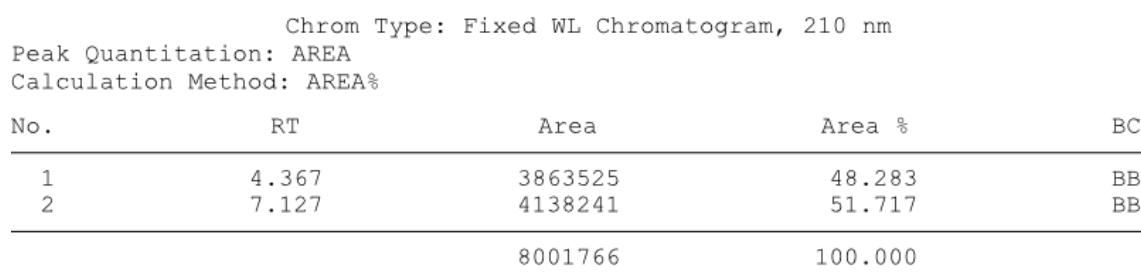


Figure S79. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5t**.



The figure displays an HPLC chromatogram of compound **5t**. The y-axis represents Intensity (mV) from 0 to 700, and the x-axis represents Retention Time (min) from 0 to 11. A major peak is observed at 4.564 minutes, with a baseline integration value of 280039. A minor peak is visible at 7.113 minutes, with a baseline integration value of 303457. The chemical structure of **5t** is shown to the right, featuring a complex polycyclic core with a Boc-protected nitrogen, a nitro group (O₂N), a hydroxyl group (OH), a chlorophenyl group (3-chloro-4-hydroxyphenyl), and an ethyl ester group (COOEt).

Chrom Type: Fixed WL Chromatogram, 210 nm				
Peak Quantitation: AREA				
Calculation Method: AREA%				
No.	RT	Area	Area %	BC
1	4.360	7580779	96.151	BB
2	7.113	303457	3.849	BB
		7884236	100.000	

Figure S81. The HPLC profiles of **5t**.

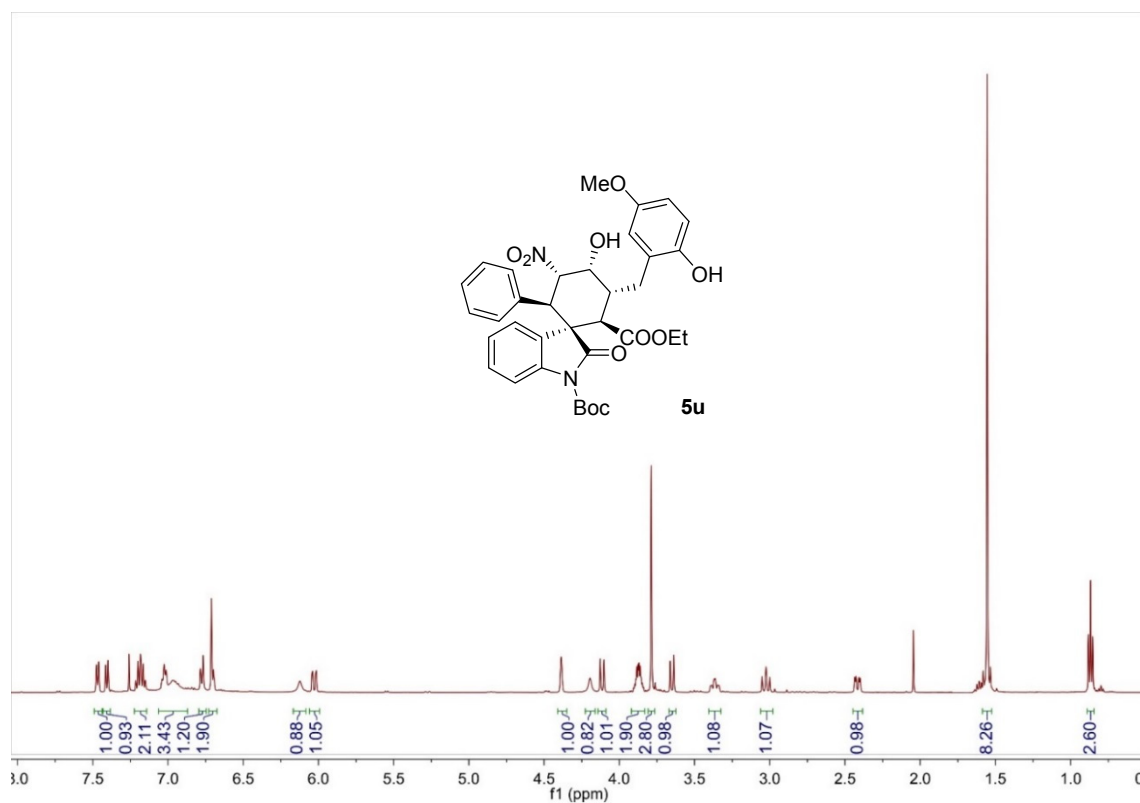


Figure S82. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5u**.

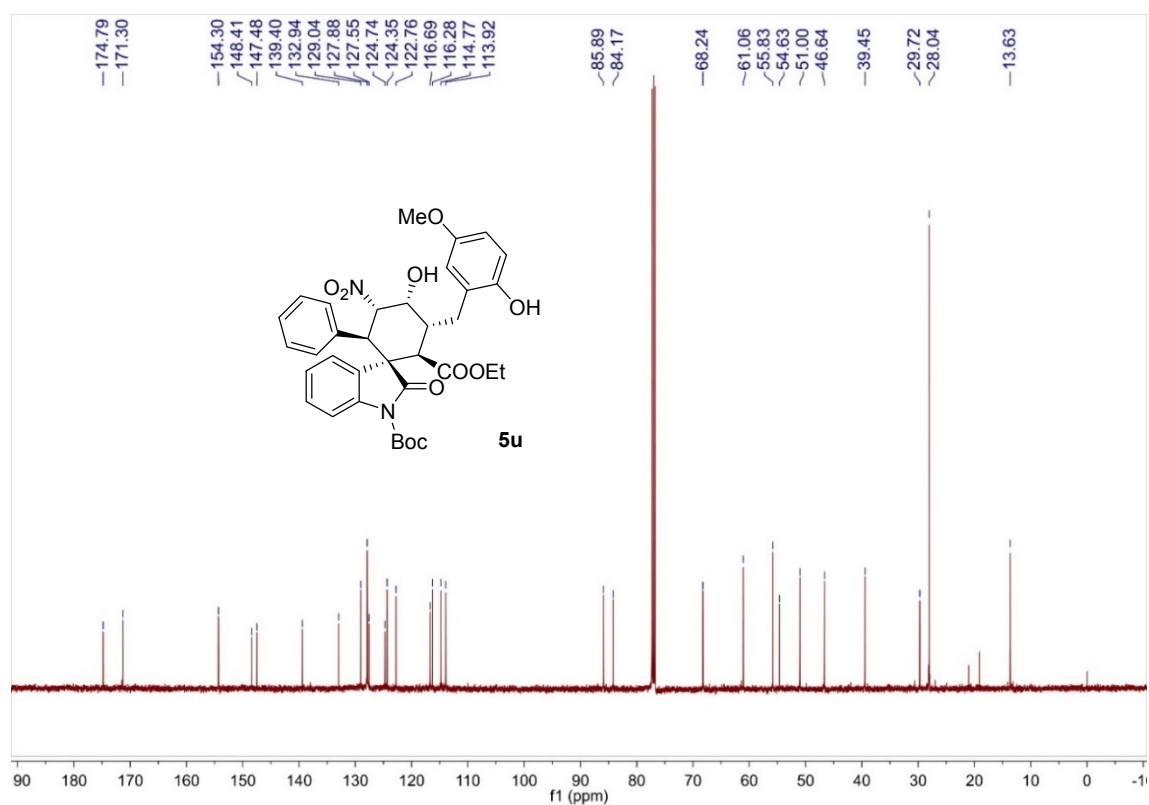


Figure S83. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5u**.

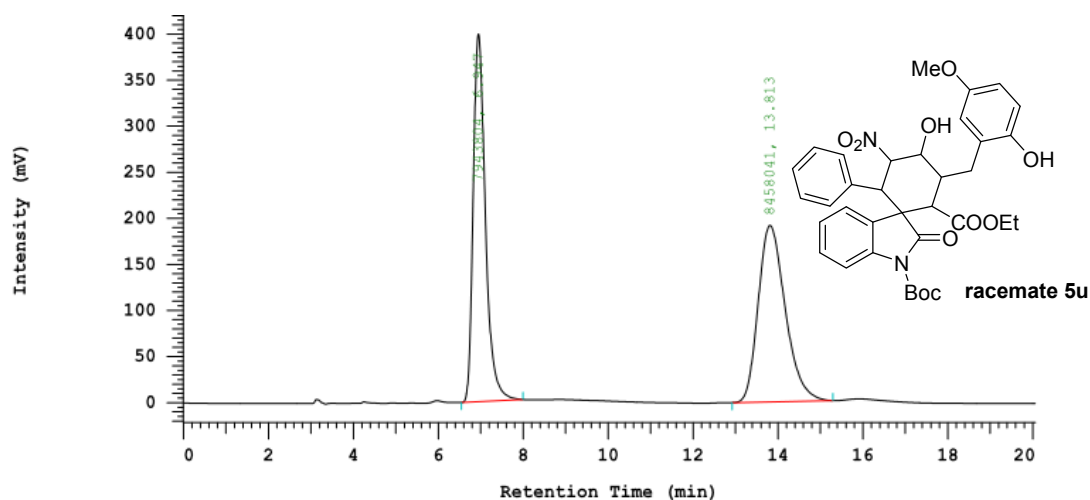


Figure S84. The HPLC profiles of racemate 5u.

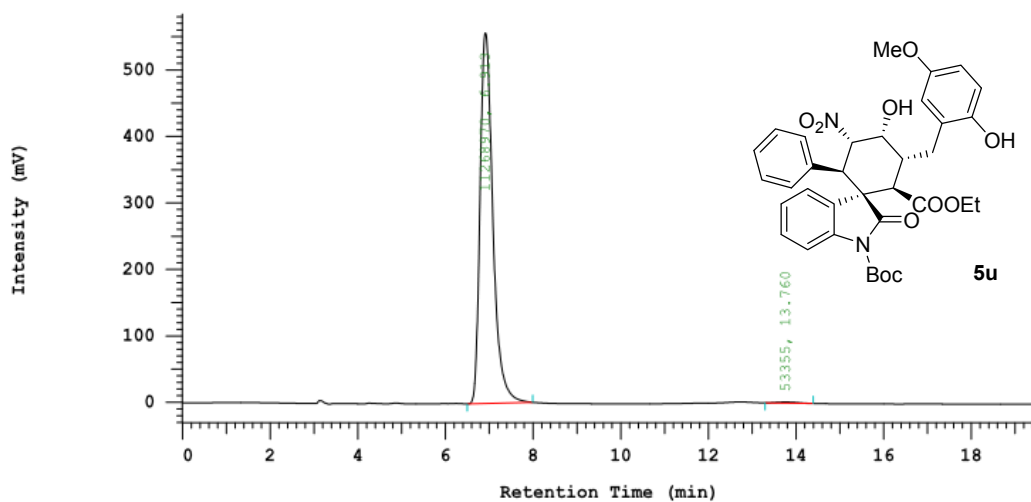


Figure S85. The HPLC profiles of 5u.

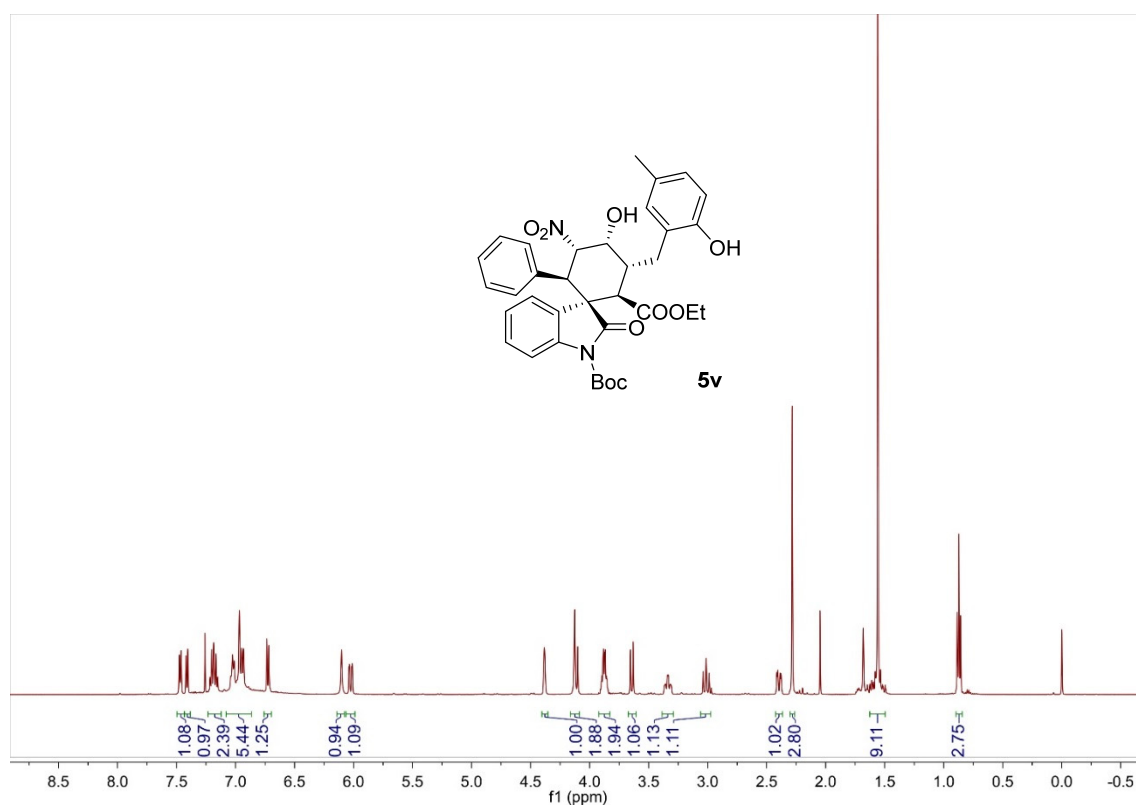


Figure S86. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5v**.

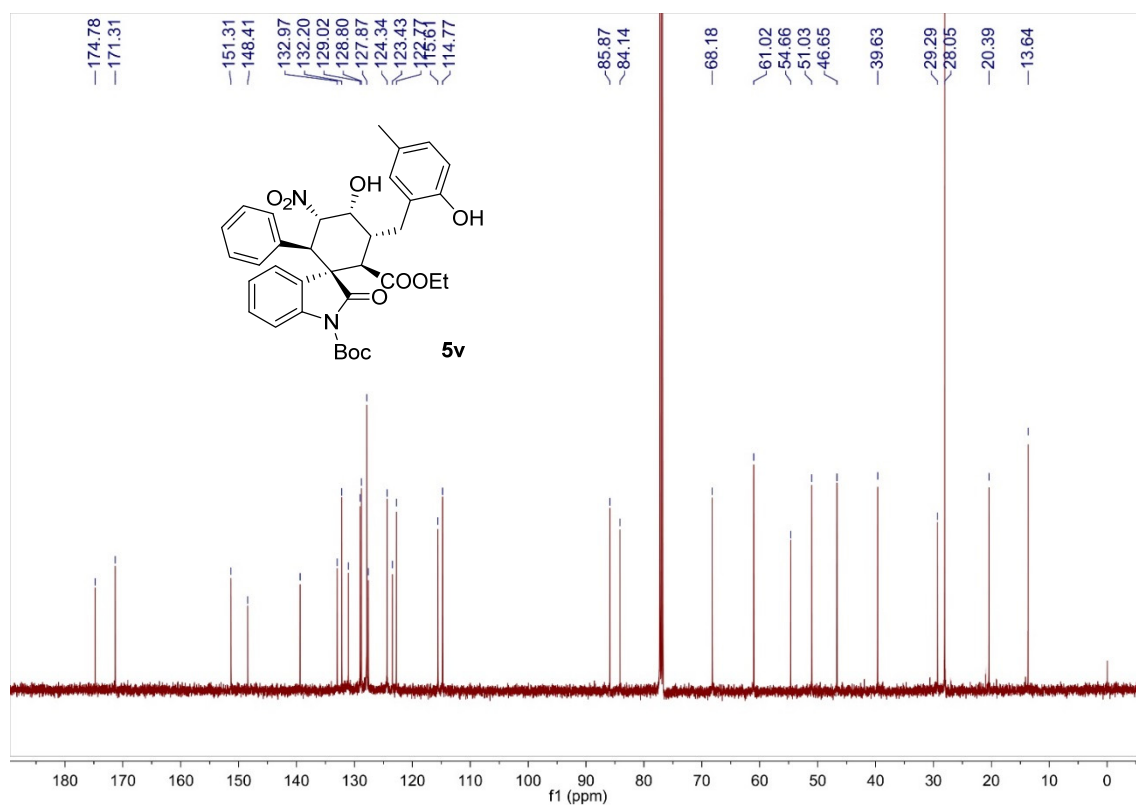


Figure S87. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5v**.

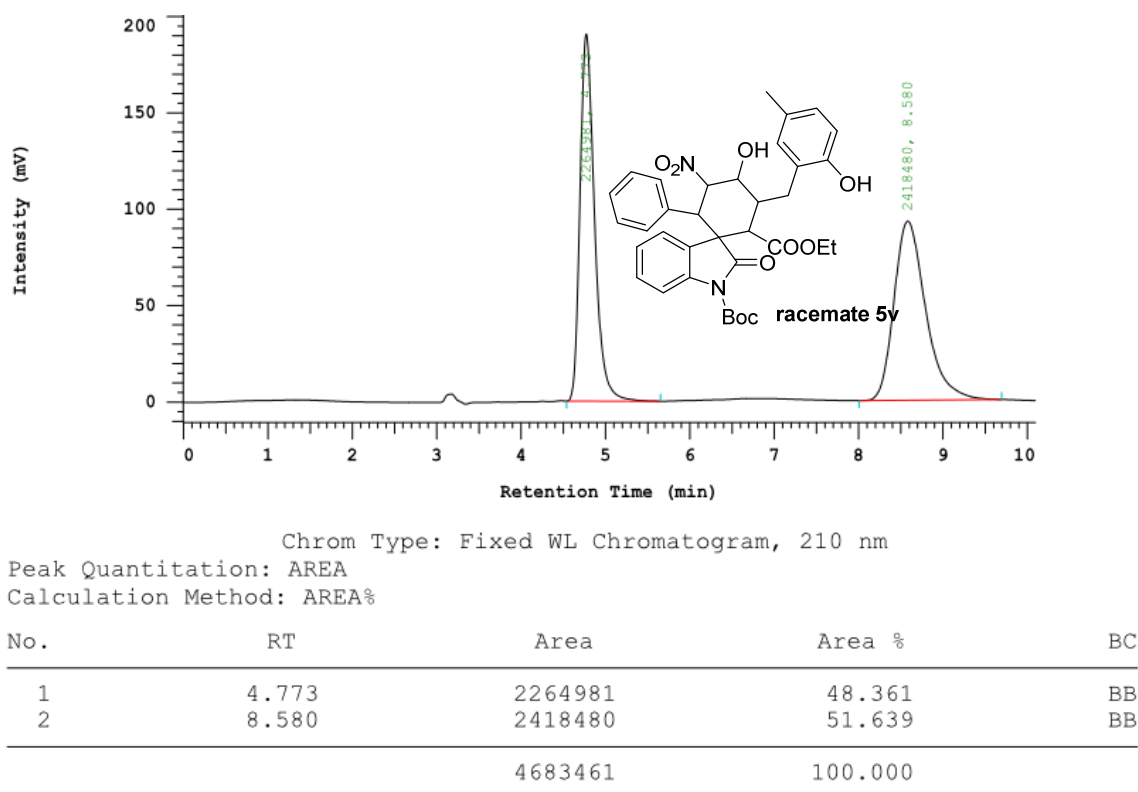


Figure S88. The HPLC profiles of racemate 5v.

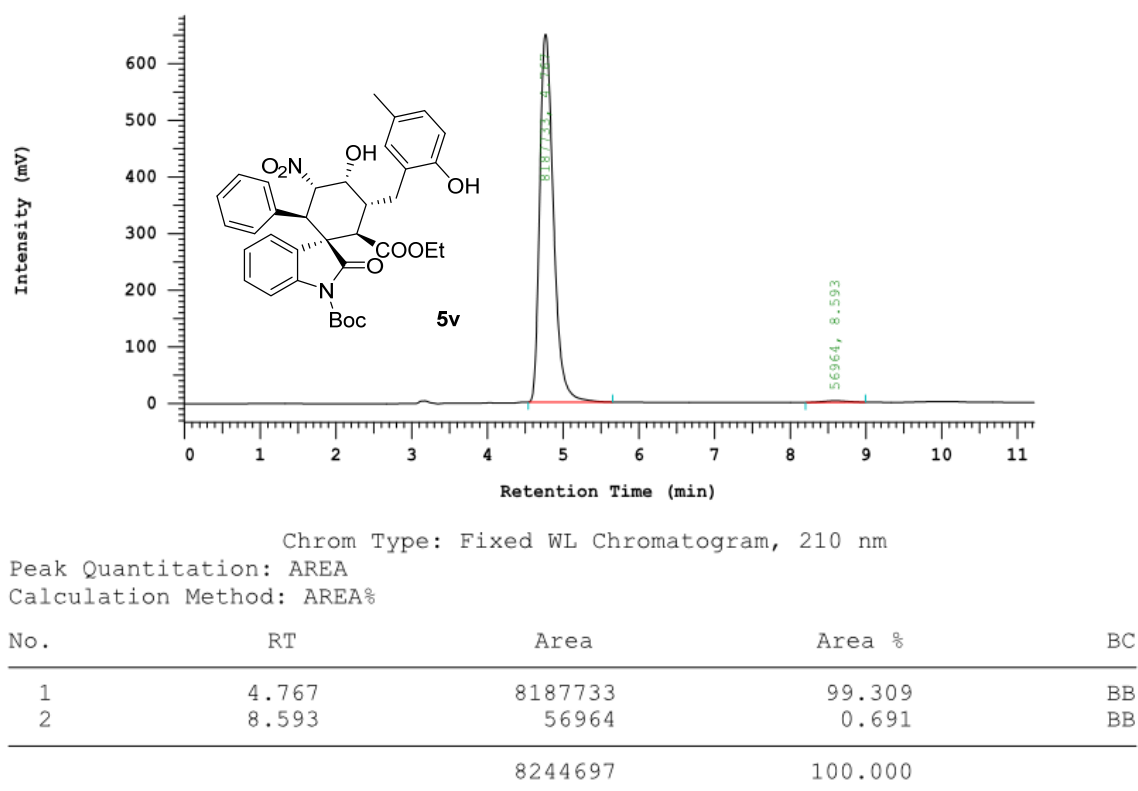


Figure S89. The HPLC profiles of 5v.

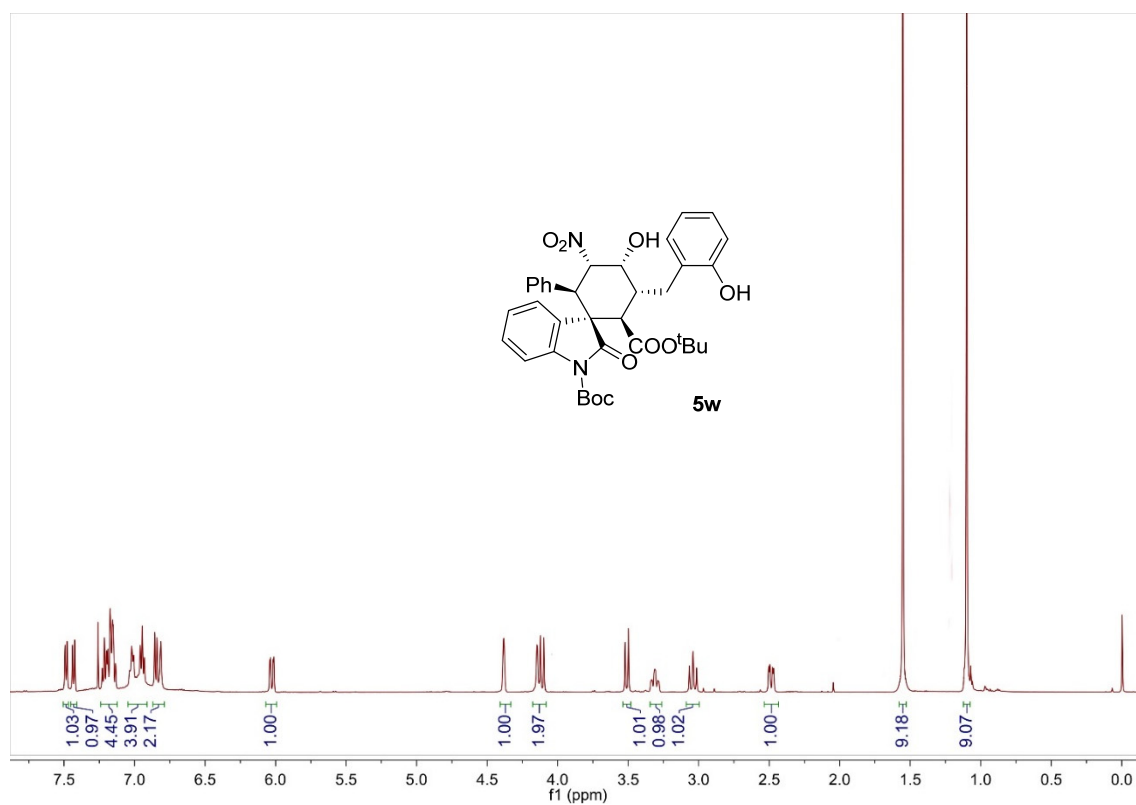


Figure S90. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5w**.

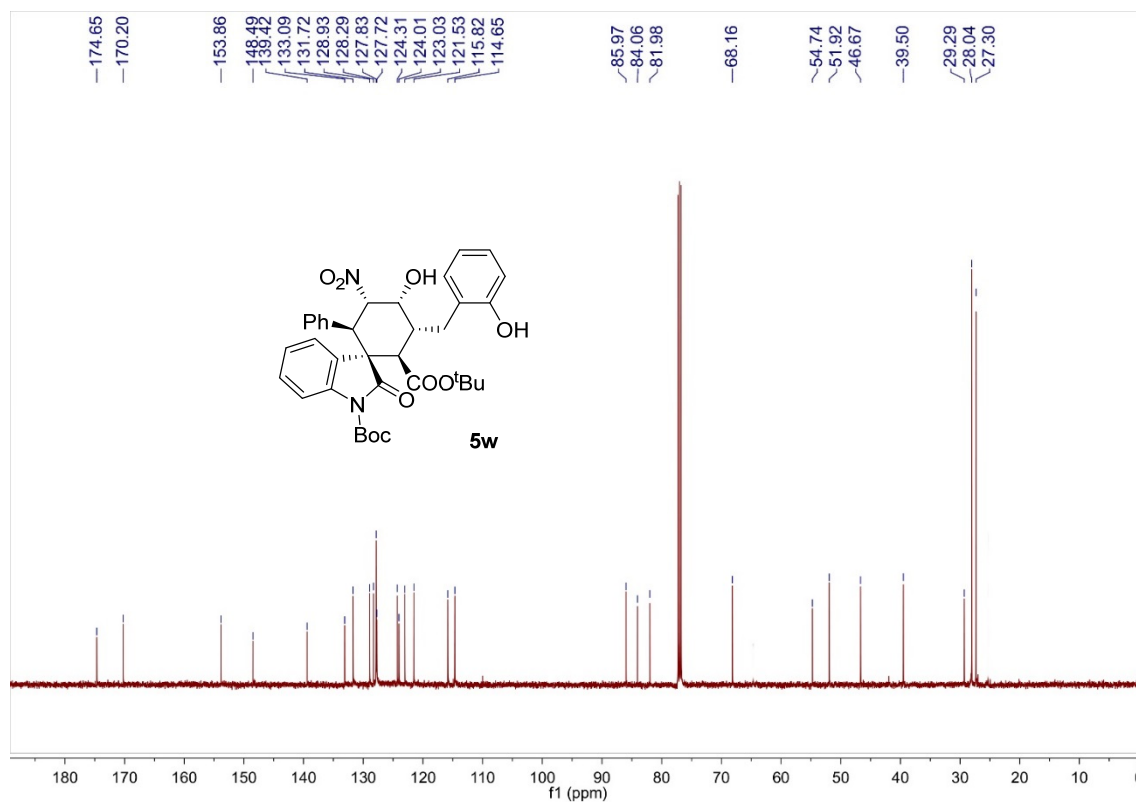


Figure S91. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5w**.

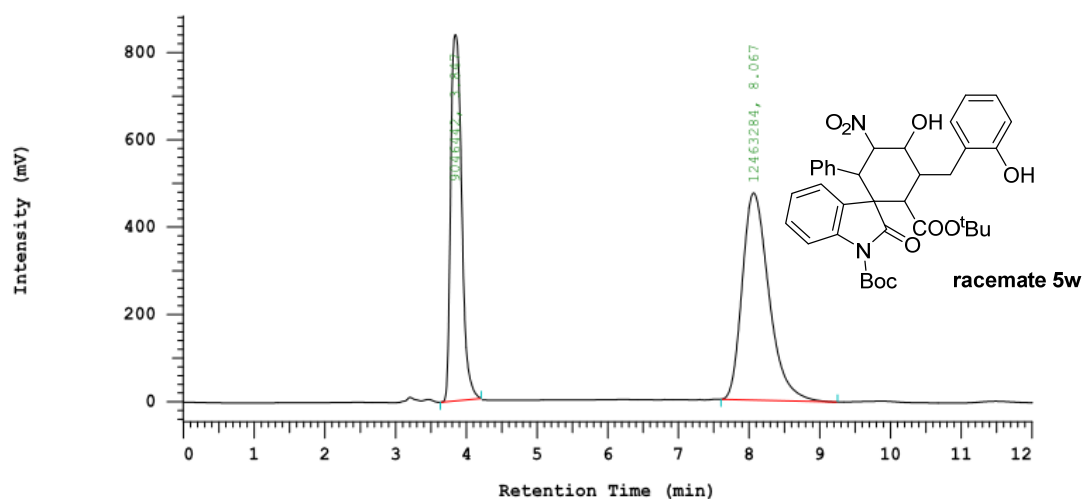


Figure S92. The HPLC profiles of racemate 5w.

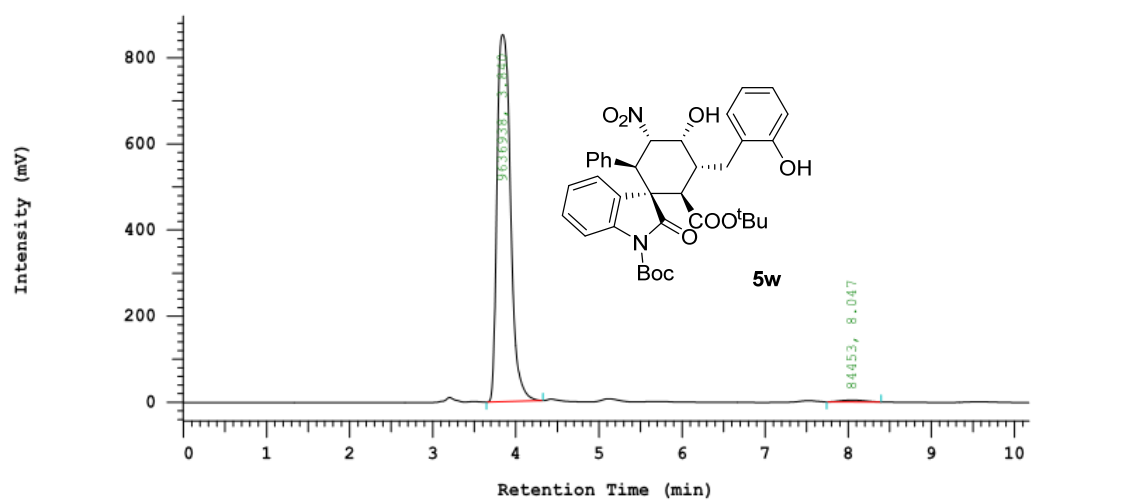


Figure S93. The HPLC profiles of 5w.

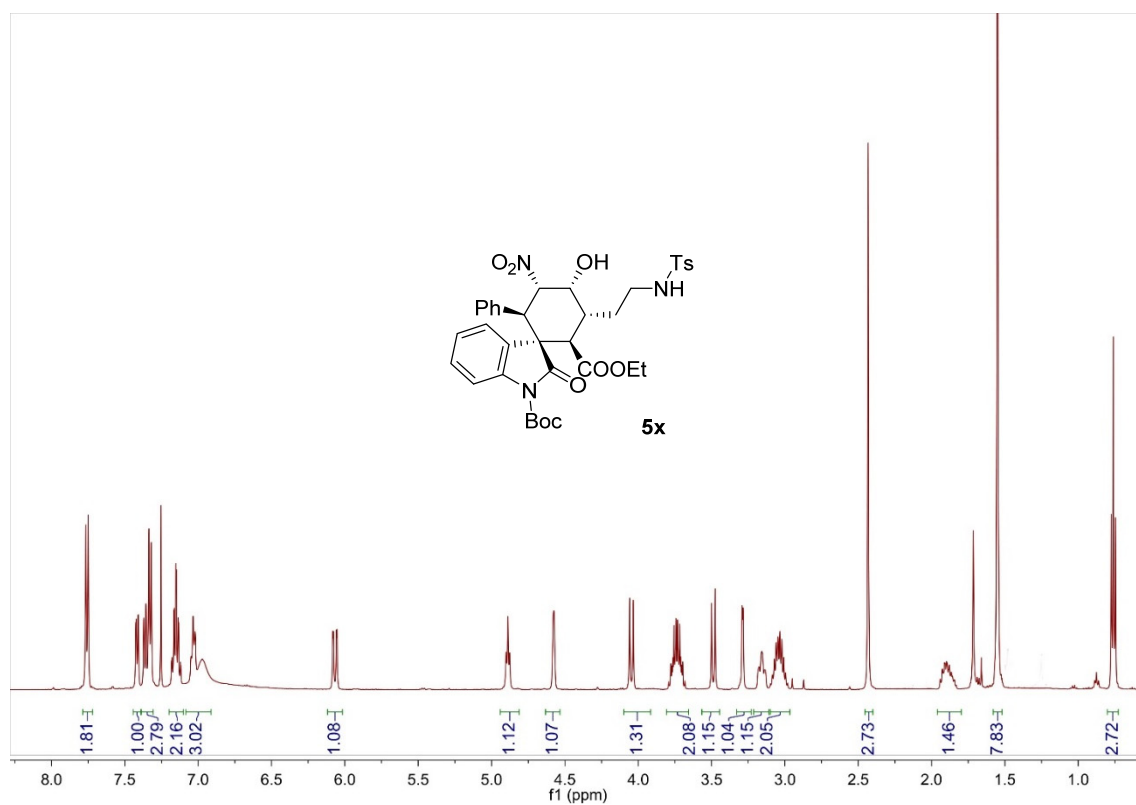


Figure S94. ¹H NMR spectrum (CDCl₃, 500 MHz) of **5x**.

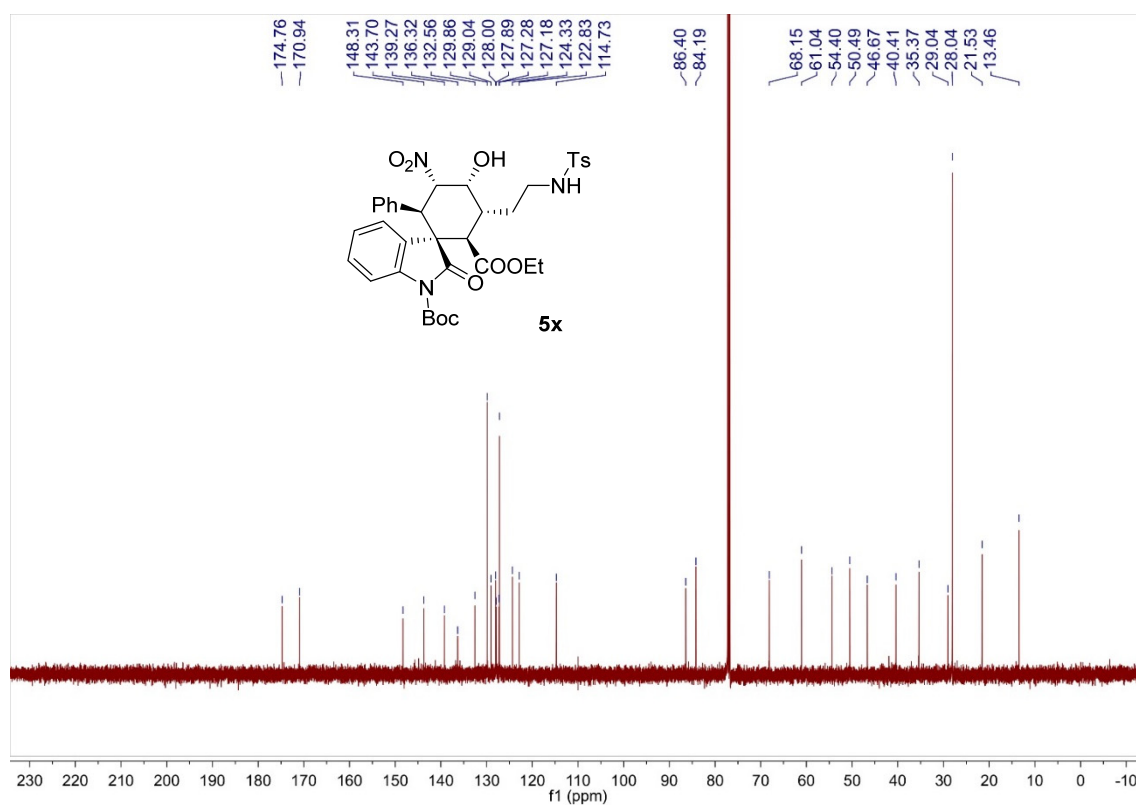


Figure S95. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **5x**.

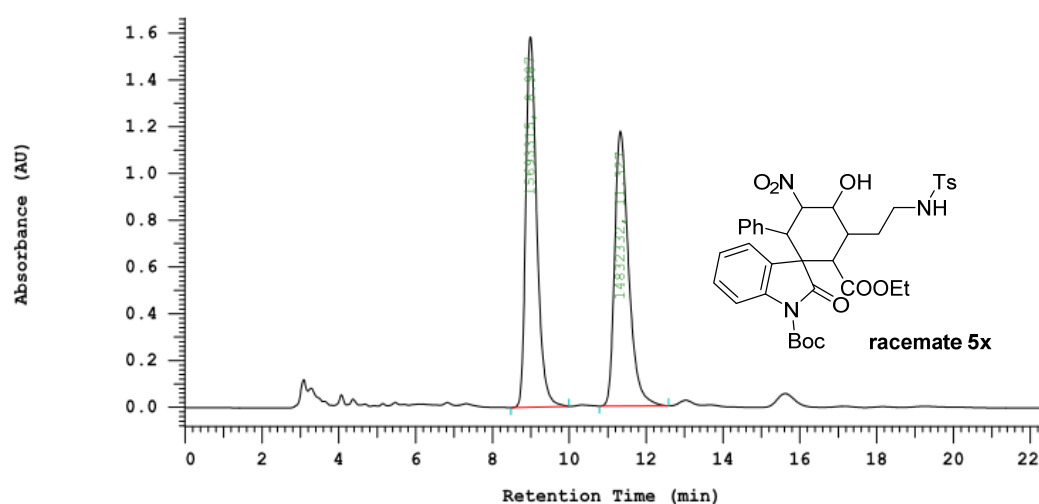


Figure S96. The HPLC profiles of racemate 5x.

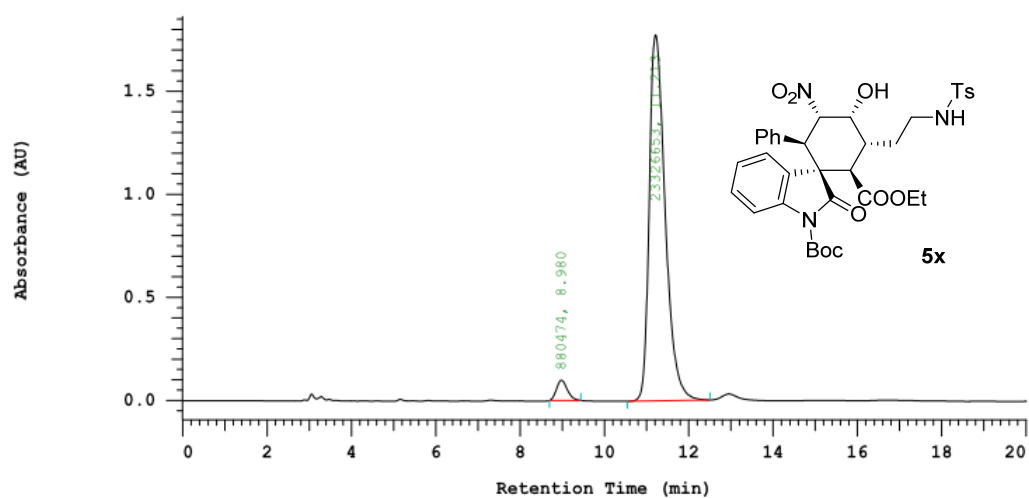


Figure S97. The HPLC profiles of 5x.

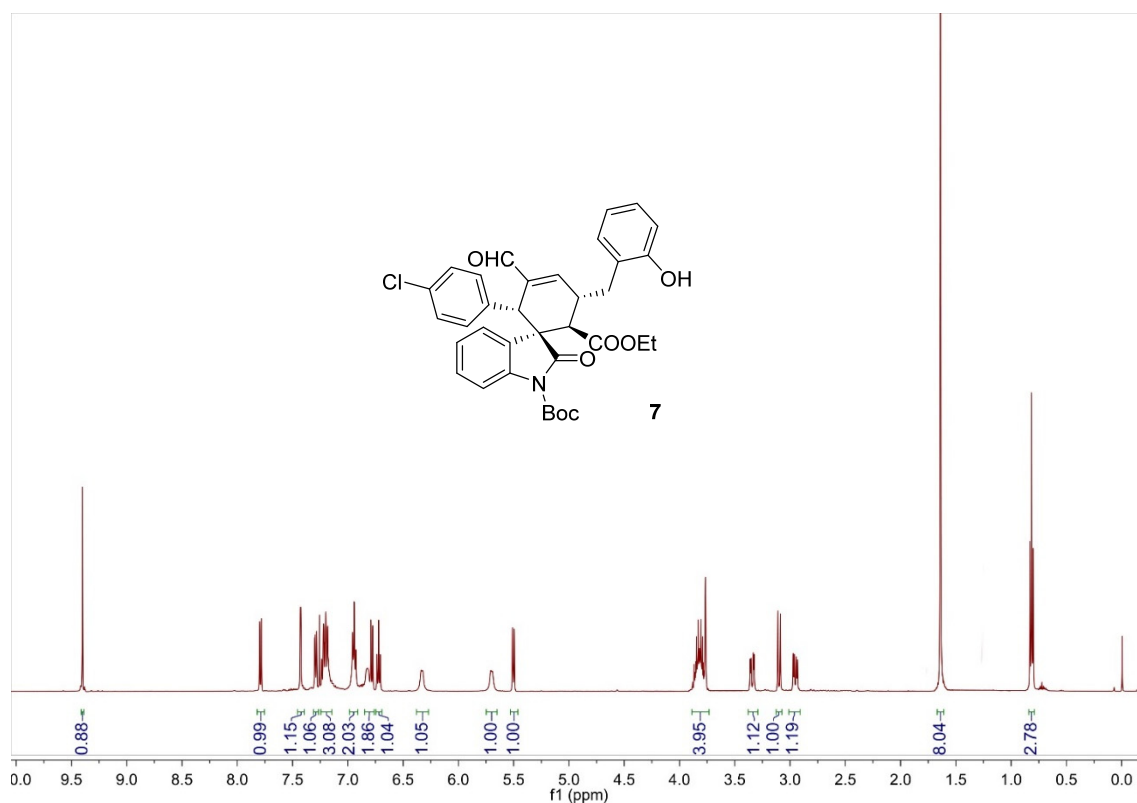


Figure S98. ¹H NMR spectrum (CDCl₃, 500 MHz) of **7**.

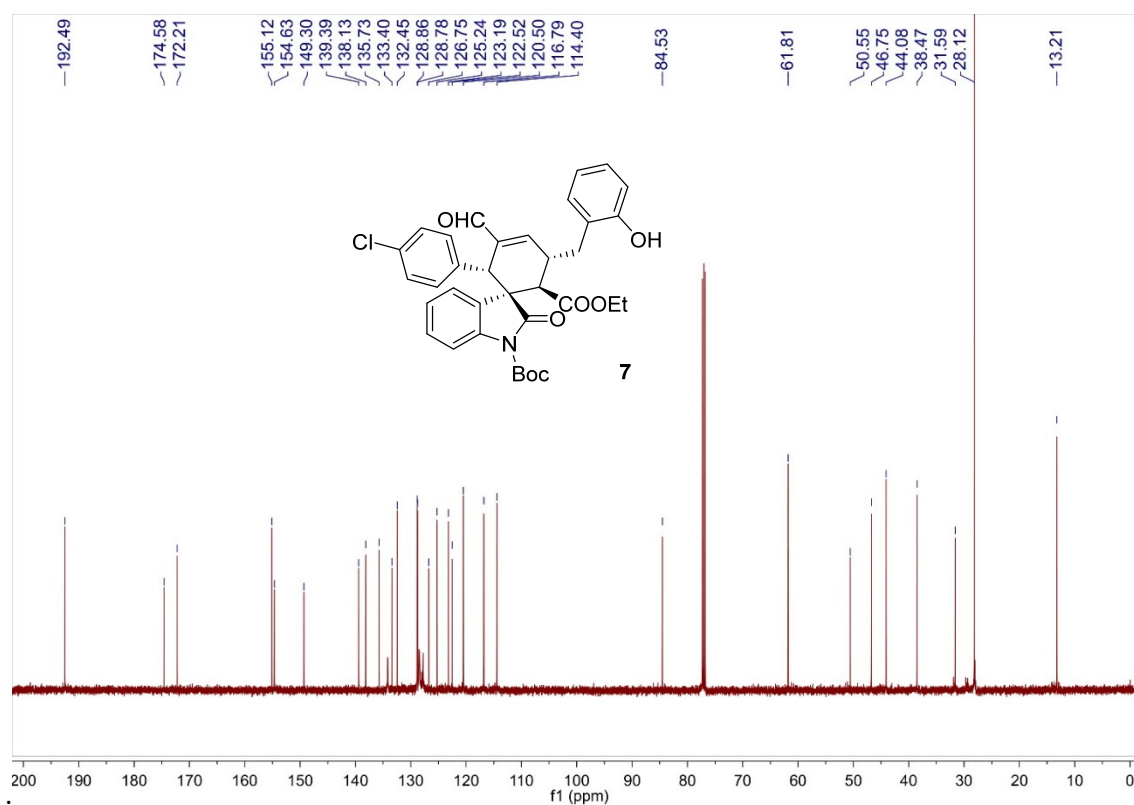


Figure S99. ¹³C NMR spectrum (CDCl₃, 125 MHz) of **7**.

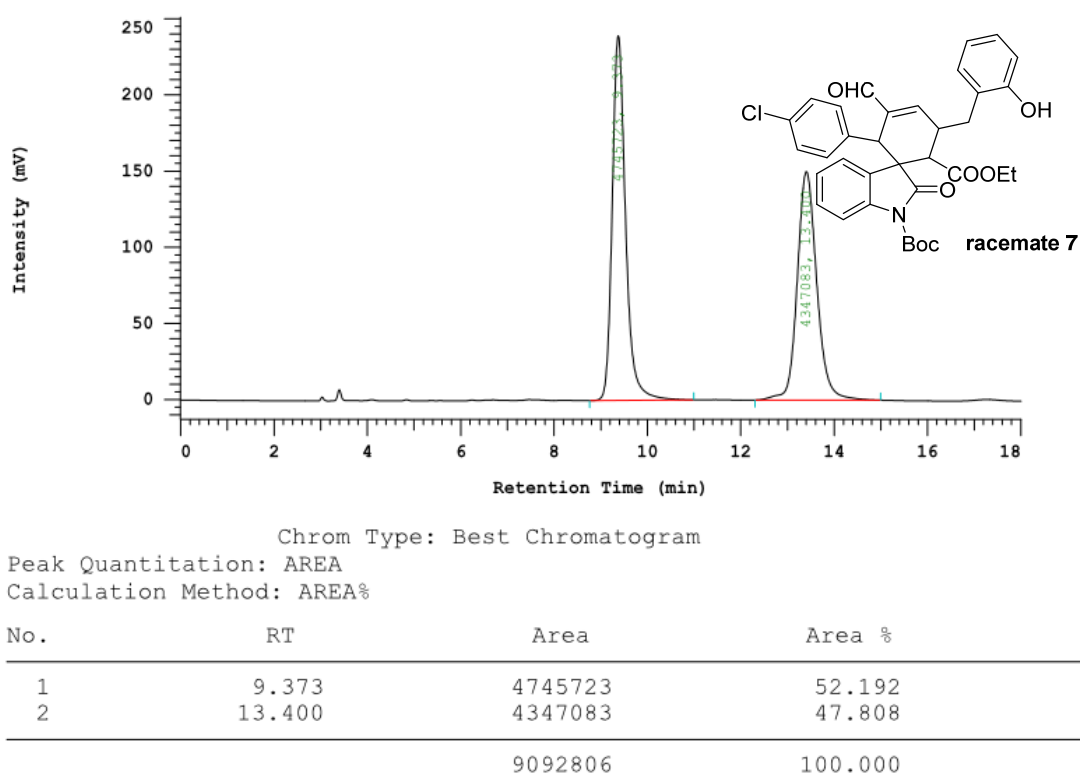


Figure S100. The HPLC profiles of racemate 7.

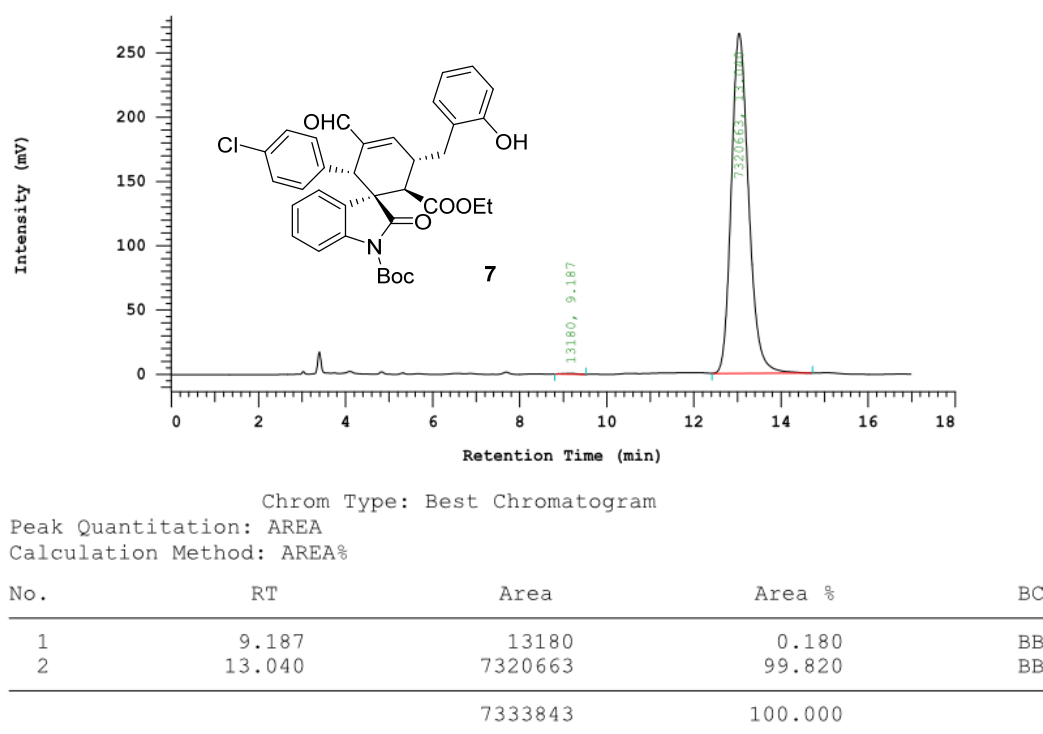


Figure S101. The HPLC profiles of racemate 7.

