Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

First example of quinine-squaramide catalyzed enantioselective addition of diphenyl phosphite to ketimines derived from isatins

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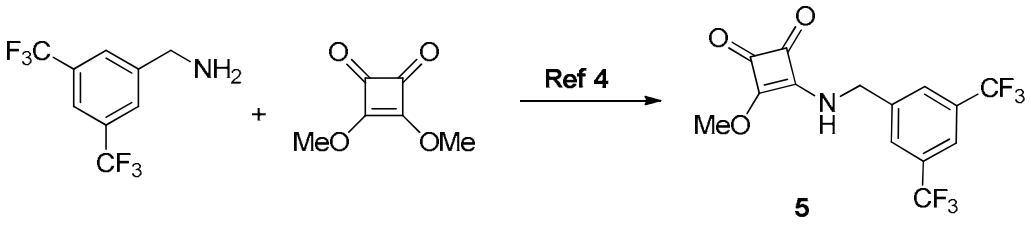
Contents

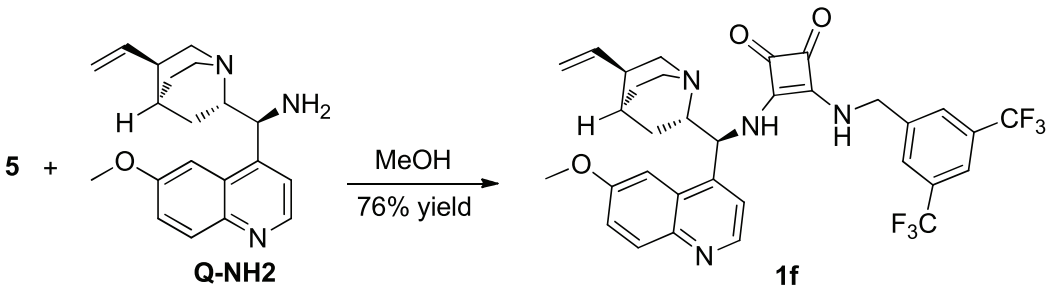
1. General Remarks

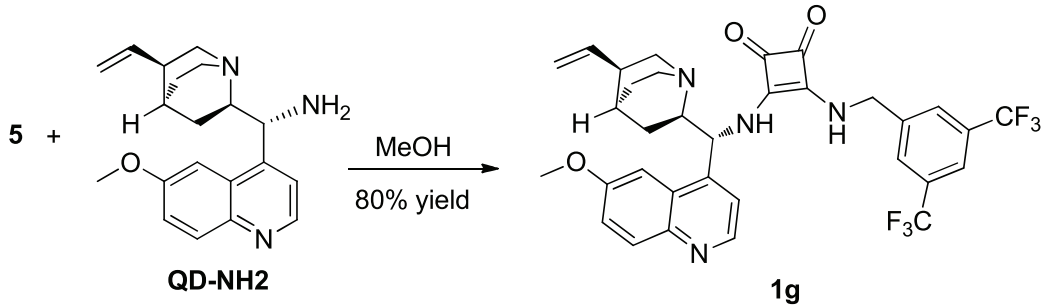
All the solvents were dried according to standard procedures. The reactions were carried out under nitrogen atmosphere. The isatin derivatives were purchased from commercial sources and used as such. The isatin derived ketimines were prepared according to previously reported procedure.1 Diphenyl phosphite was purchased from Sigma Aldrich and used without any purification. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase (Chiralpak AD-H and Chiralpak IC column) using mixture of hexane-isopropyl alcohol as eluent. Racemic samples were prepared by performing the reaction in the presence of triethyl amine as catalyst. All the compounds were purified by column chromatography on 100-200 mesh silica gel using hexane-ethyl acetate as eluent. All the reactions were monitored by TLC analysis. ^{1}H NMR spectra were recorded on 500 MHz or 300 MHz instruments using $CDCl_3$ as solvent and TMS as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz or 125 MHz using $CDCl_3$ as solvent and reference. Optical rotation was recorded on Perkin Elmer-343 polarimeter. Absolute configuration of the product was determined by single crystal X-ray analysis. Based on the stereochemistry of **4b,** the relative configuration of all the products were determined.

All quinine, quinidine were purchased from Sigma Aldrich. Catalysts **1b** and **1c** were prepared according to the literature procedure.[2] Ligands **1d** and **1e** were prepared according to the previously reported procedures.[3] The catalysts **1f** and **1g** were also prepared based on previous procedures.[4]

2. Procedure for the preparation of catalysts **1f** and **1g**.







To a solution of **5** (2.2 mmol) in methanol (20 mL) was added a solution of amine (2.0 mml) in methanol (4 mL). The resulting solution was allowed to stir at room temperature for 24h and the white precipitate of **1f** or **1g** was filtered with cold methanol and dried under vacum to obtain the squaramide catalysts **1f or 1g.**

Catalyst **1f**

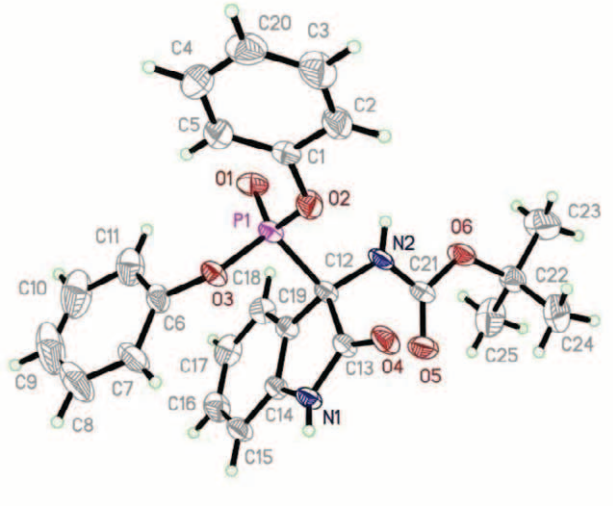
Yield 76%, white solid; ^{1}H NMR ($CDCl_3$ + DMSO-d6, 500 MHz) δ: 0.70-0.78 (m, 1H), 1.50-1.72 (m, 4H), 2.34 (br s, 1H), 2.60-2.80 (m, 2H), 3.30 (d, J = 10.1 Hz, 1H), 3.33 (d, J = 10.1 Hz, 1H), 3.47 (br s, 1H), 4.01 (s, 3H), 4.88 (d, J = 3.05 Hz, 2H), 5.00-5.08 (m, 2H), 5.84 (m, 1H), 6.14 (br s, 1H), 7.34 (d, J = 3.7 Hz, 1H), 7.38 (d, J = 0.9 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.50 (br s, 1H); 7.79 (s, 3H), 7.82 (br s, 1H), 8.00 (d, J = 9.2 Hz, 1H), 8.74 (d, J = 4.4 Hz, 1H); ^{13} C NMR ($CDCl_3$ + DMSO-d6,75 MHz) δ: 25.3, 26.3, 26.5, 45.5, 54.8, 55.1, 58.7, 100.3, 113.5, 118.0, 120.2, 120.3, 121.4, 123.8, 126.8, 127.2, 130.2, 130.4, 130.7, 140.4, 142.9, 143.6, 146.2, 157.3, 166.3, 181.6, 182.0; HRMS (ESI) m/z: calculated mass for $C_{33}H_{31}N_4O_3F_6$ $[M+H]^+$ = 645.2294; found 645.2291.

Catalyst **1g**

Yield 80%, pale yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.80-1.02 (m, 1H), 1.10 (m, 1H), 1.32-1.68 (m, 4H), 2.20 (m, 1H), 2.60-2.90 (m, 3H), 3.00-3.40 (m, 1H), 3.88 (s, 3H), 4.68 (q, J =

15.8 Hz, 2H), 5.07 (d, J = 10.6 Hz, 1H), 5.12 (d, J = 17.3 Hz, 1H), 5.82 (m, 1H), 6.13 (br s, 1H), 7.26-7.52 (m, 5 H), 7.61-7.80 (m, 3H), 7.95 (d, J = 9.1 Hz, 1H), 8.53 (d, J = 4.5 Hz, 1H); ^{13} C NMR ($CDCl_3$, 75 MHz) δ: 24.8, 26.0, 27.0, 38.6, 46.2, 46.3, 18.8, 55.3, 59.8, 101.1, 114.5, 120.9, 124.5, 127.4, 128.7, 129.4, 131.2, 131.7, 133.1, 139.8, 140.4, 144.2, 147.0, 157.9, 166.4, 167.9, 181.9, 182.6; HRMS (ESI) m/z: calculated mass for $C_{33}H_{31}N_4O_3F_6$ $[M+H]^+$ = 645.2294; found 645.2290.

3. ORTEP diagram of compound **4b**



The crystal data of **4b** have been deposited in CCDC with number 960126. $C_{25}H_{25}N_2O_6P$, M = 480.44, colorless needle, 0.18 x 0.08 x 0.05 mm^3, orthorhombic, space group P212121 (No. 19), a = 8.901(2), b = 12.206(3), c = 22.343(6) Å, V = 2427.3(11) $Å^3$, Z = 4, Dc = 1.315 g/cm^3, F000 = 1008, CCD Area Detector, MoKα radiation, λ = 0.71073 Å, T = 294(2)K, $2\theta_{max}$ = 50.0º, 21588 reflections collected, 4267 unique (R_{int} = 0.0865). Final G*oo*F = 1.048, R1 = 0.0685, wR2 = 0.1684, R indices based on 3790 reflections with I>2σ(I) (refinement on F^2), 318 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.156 mm^{-1}. Absolute structure parameter = 0.01(17).

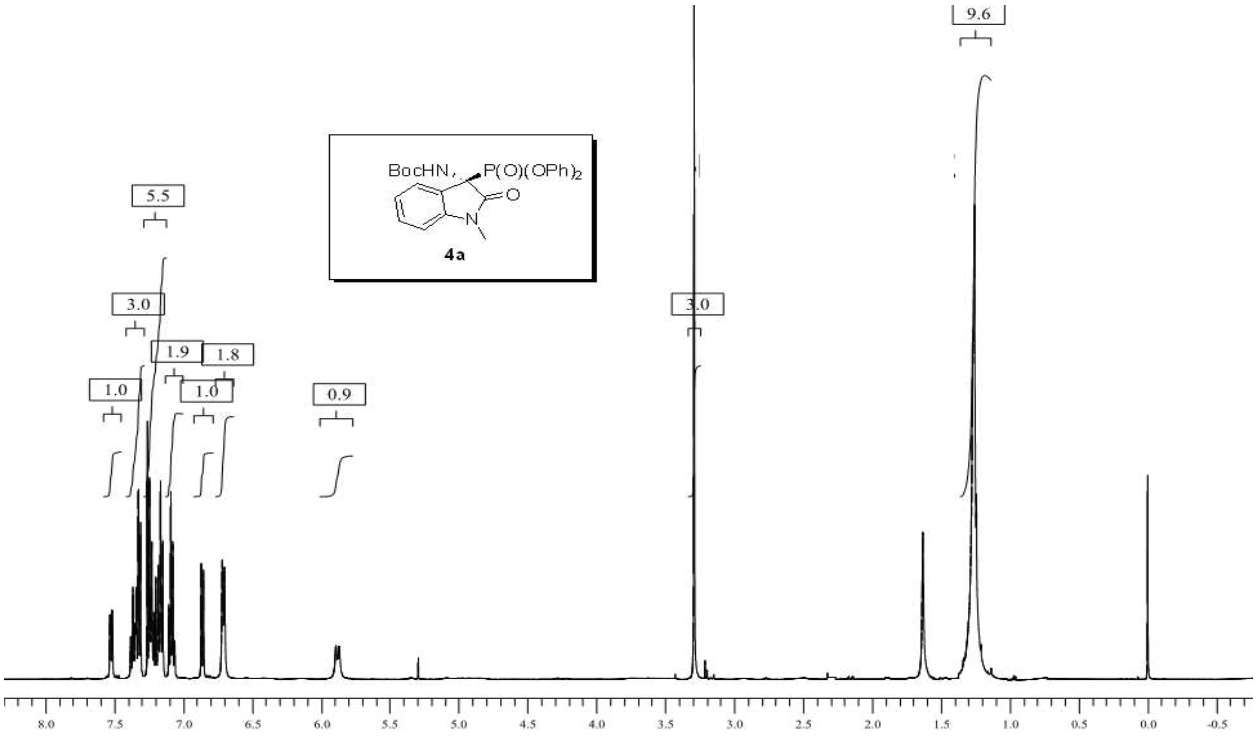
4. References

1. W. Yan, D. Wang, J. Feng, P. Li, D. Zhao, R. Wang, *Org. Lett.* 2012, **14**, 2512

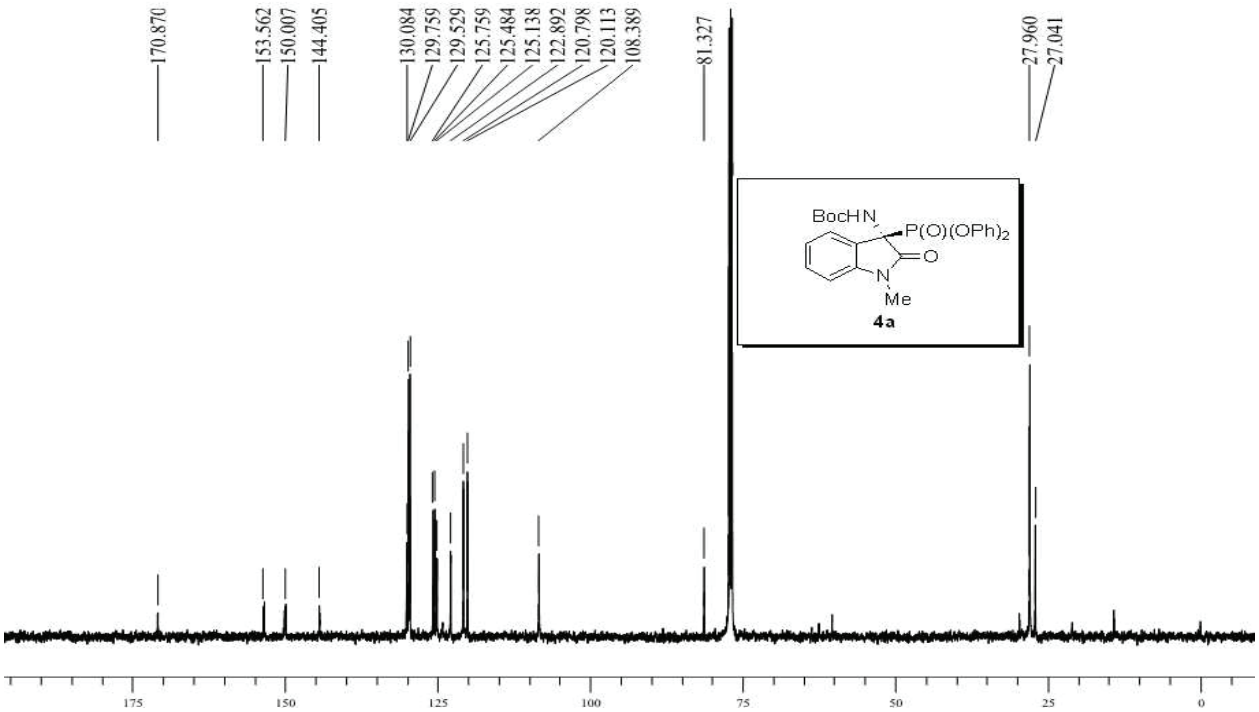
2. H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.,* 2004, **126**, 9906.

3. B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org Lett*. 2005, **7,** 1976.

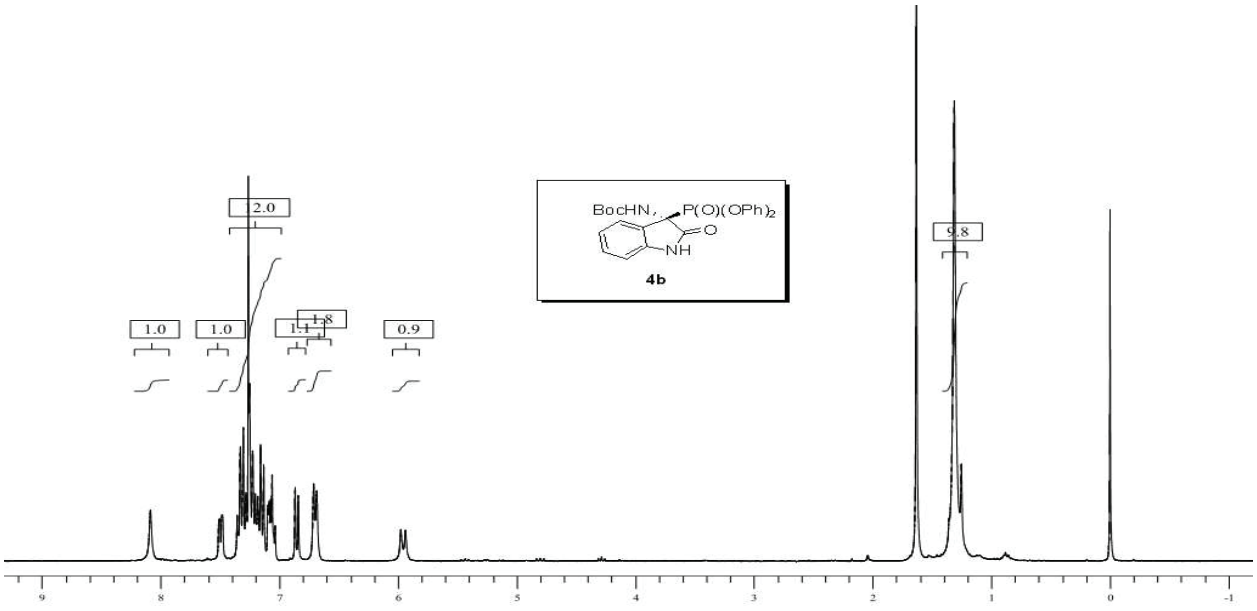
4. J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc*. 2008, **130**, 14416.



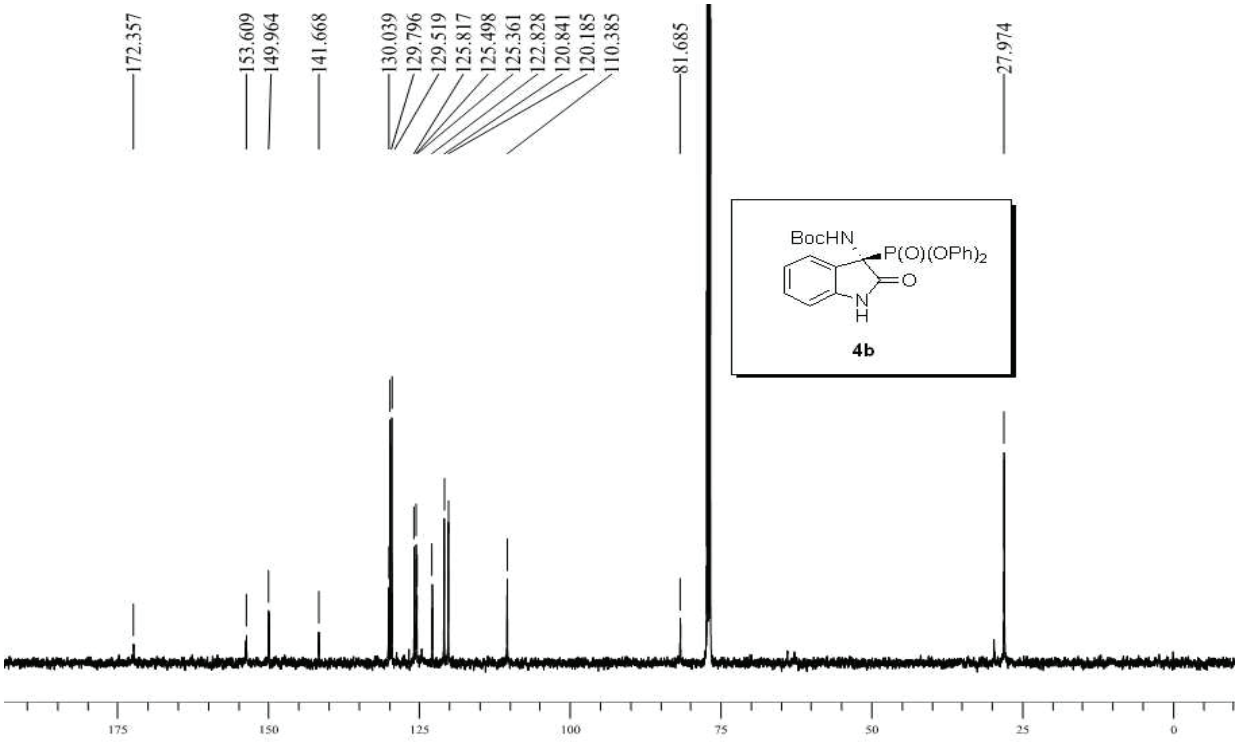
^{1}H NMR of Compound **4a** ($CDCl_3$, 300 MHz)



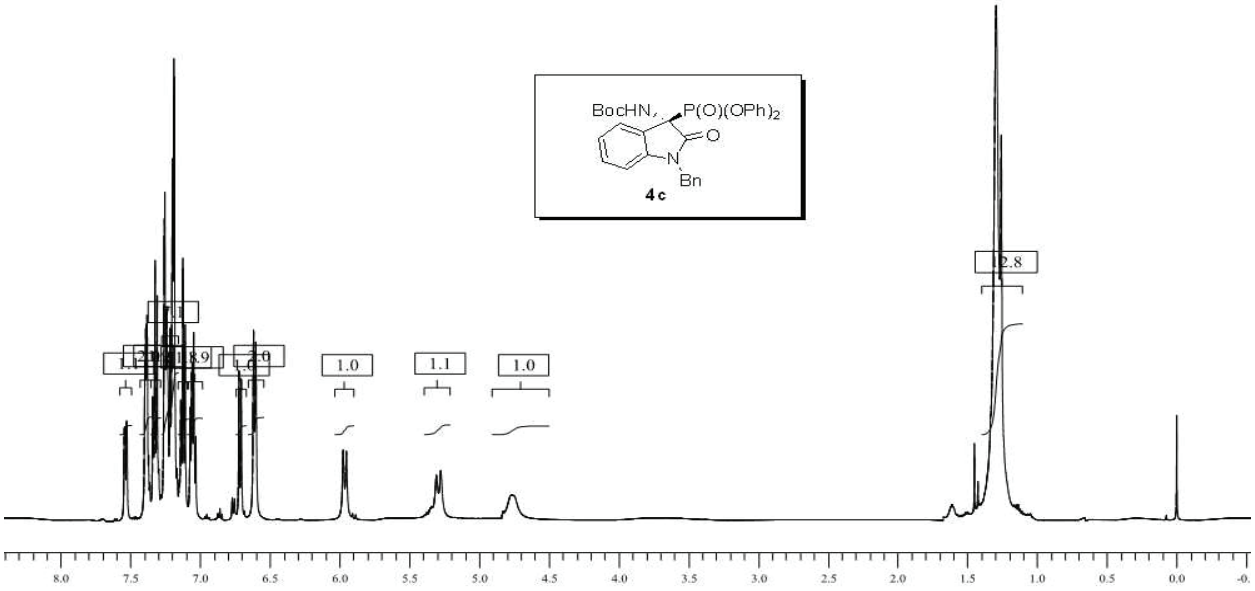
^{13}C NMR of Compound **4a** ($CDCl_3$, 75 MHz)



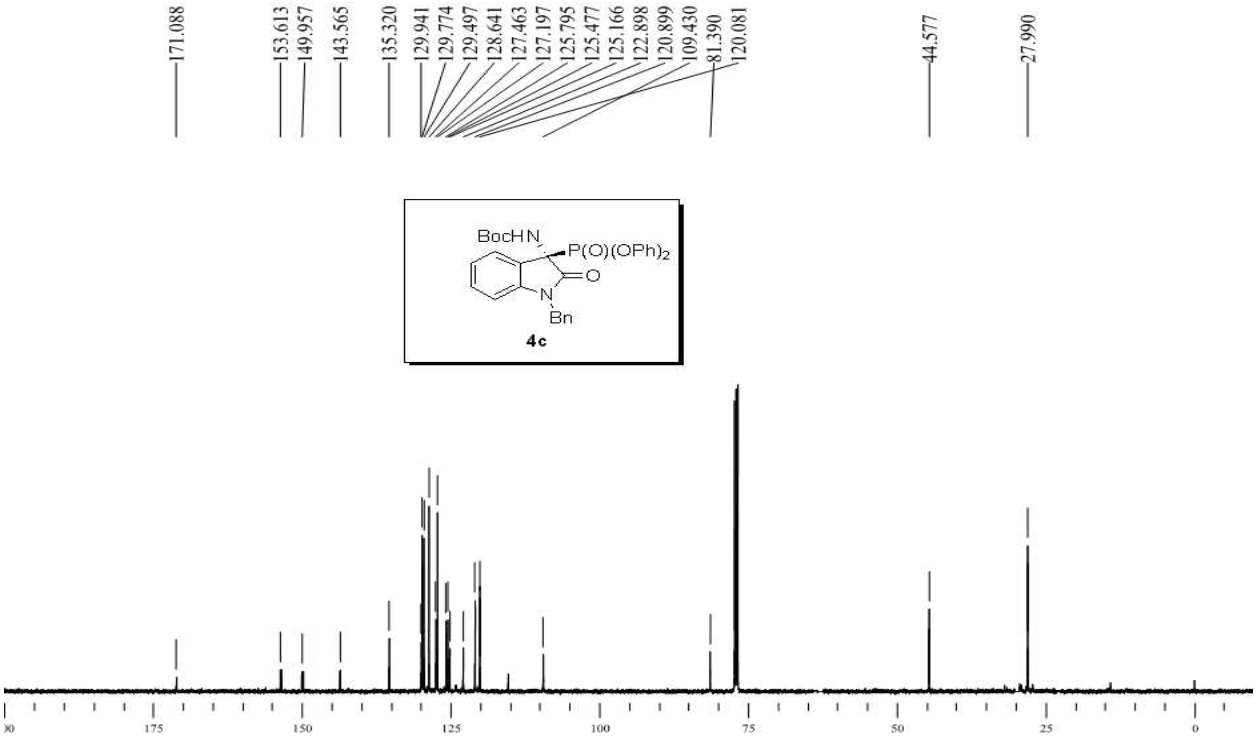
^{1}H NMR of Compound **4b** ($CDCl_3$, 300 MHz)



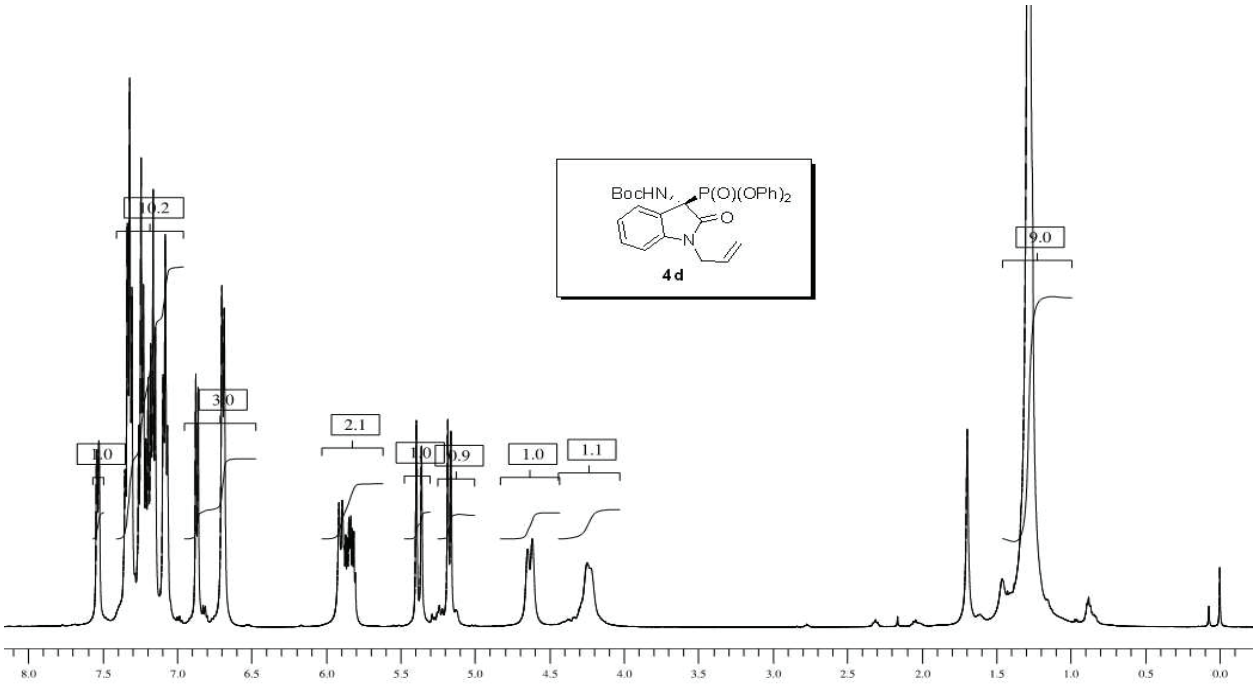
^{13}C NMR of Compound **4b** ($CDCl_3$, 75 MHz)



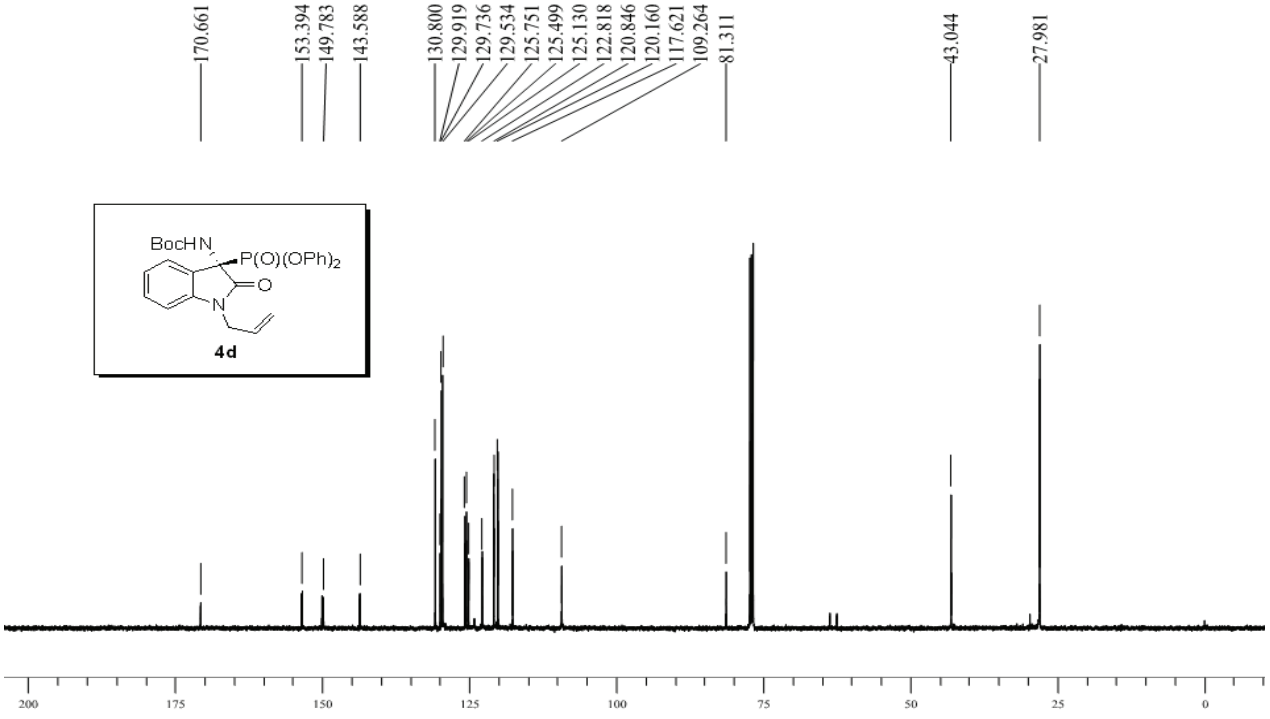
^{1}H NMR of Compound **4c** ($CDCl_3$, 300 MHz)



^{13}C NMR of Compound **4c** ($CDCl_3$, 75 MHz)



^{1}H NMR of Compound **4d** ($CDCl_3$, 300 MHz)



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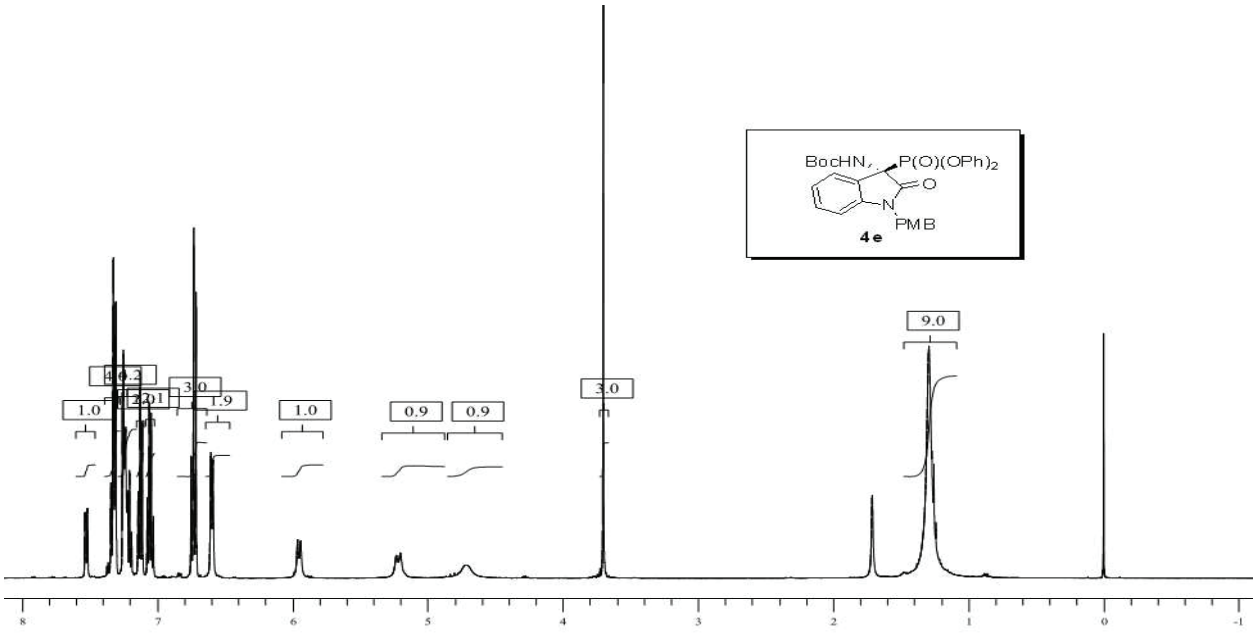

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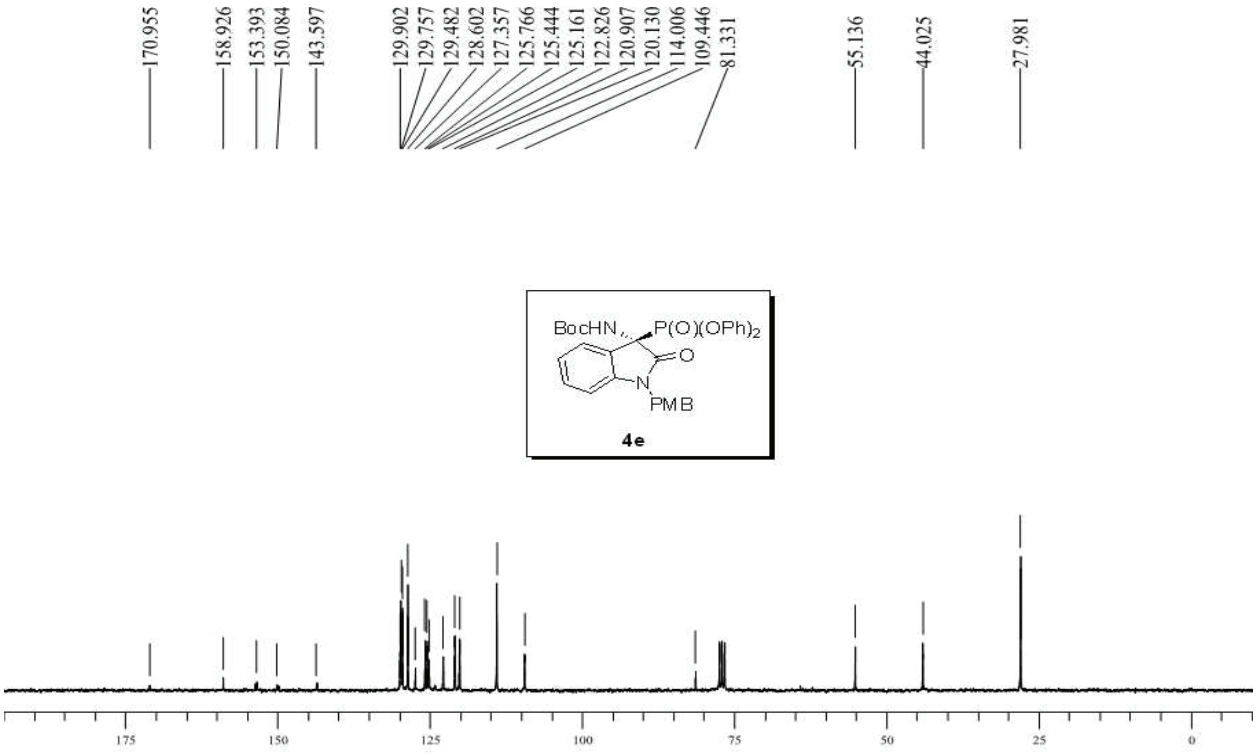
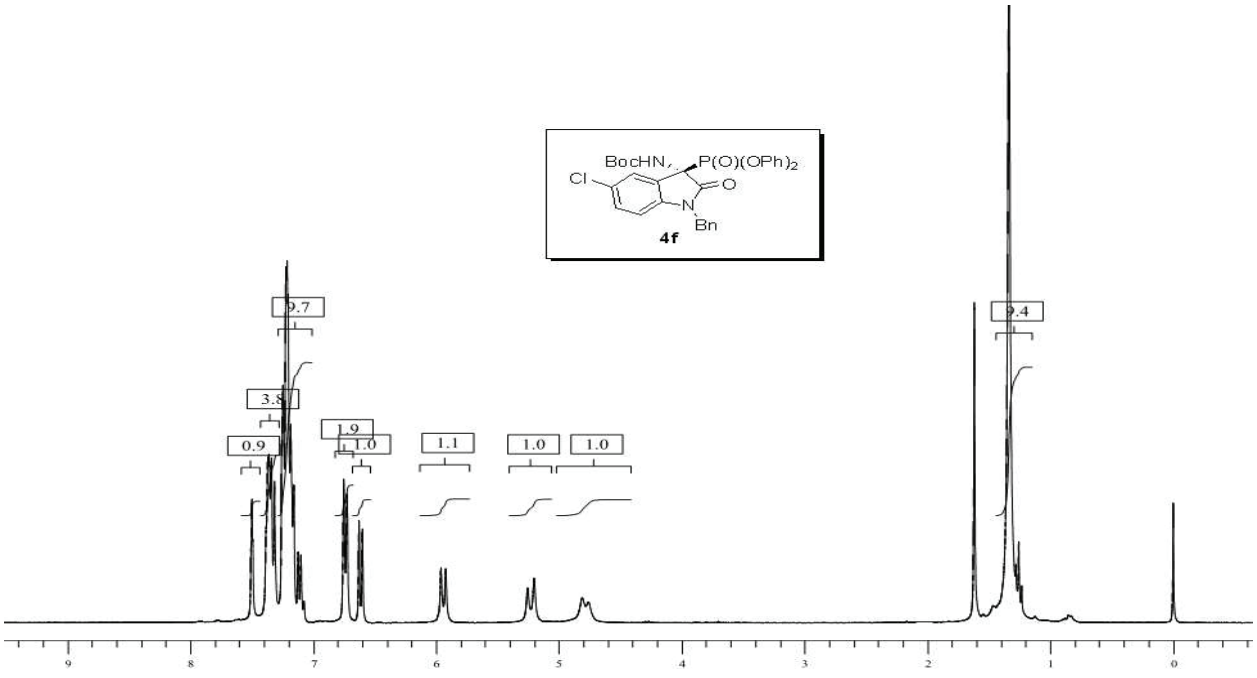
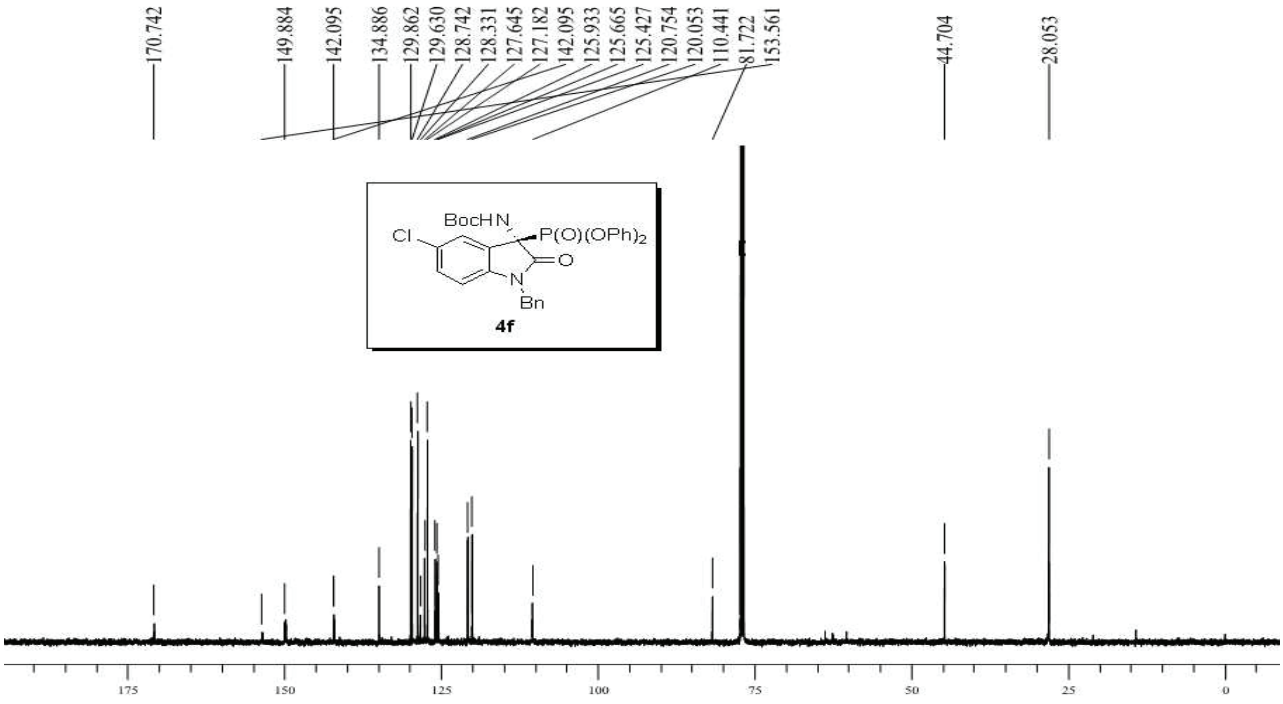


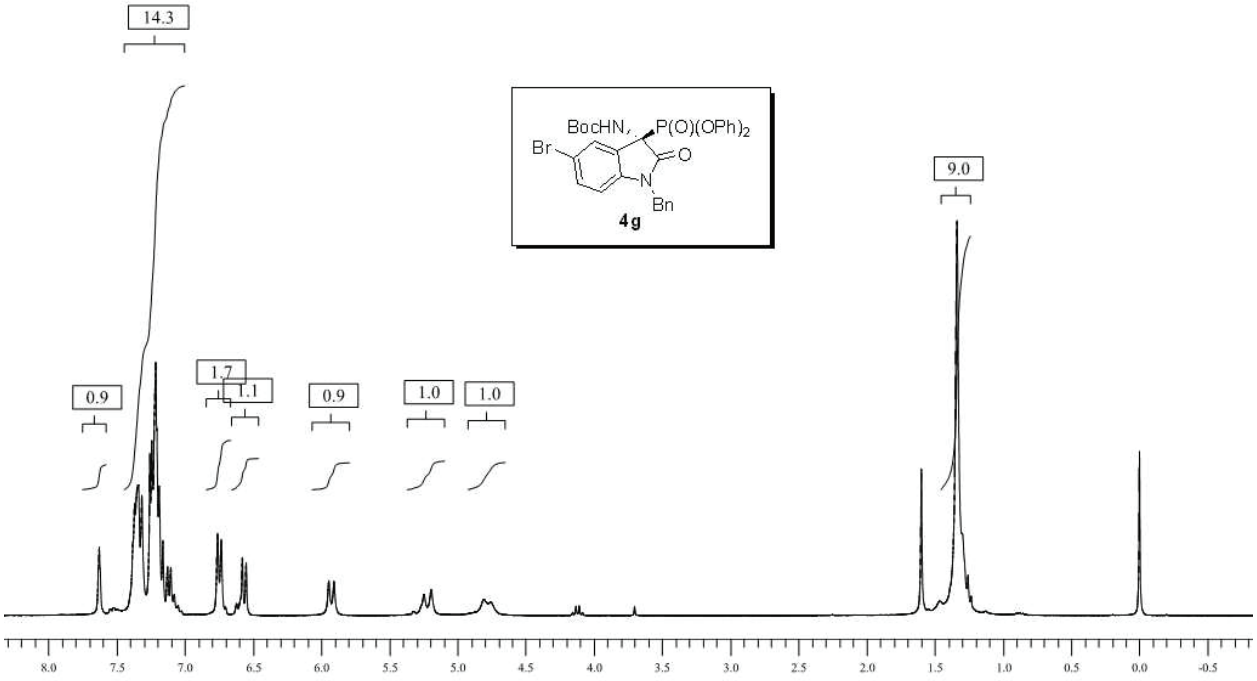
^{13}C NMR of Compound **4e** ($CDCl_3$, 75 MHz)



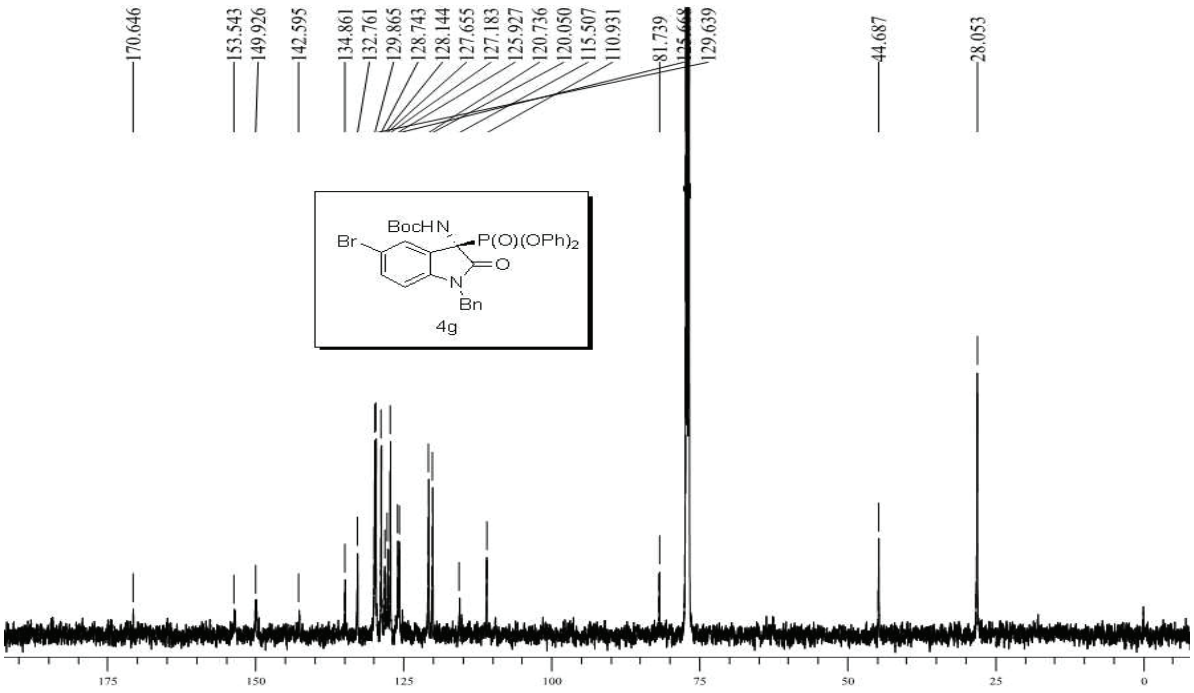
^{1}H NMR of Compound **4f** ($CDCl_3$, 300 MHz)



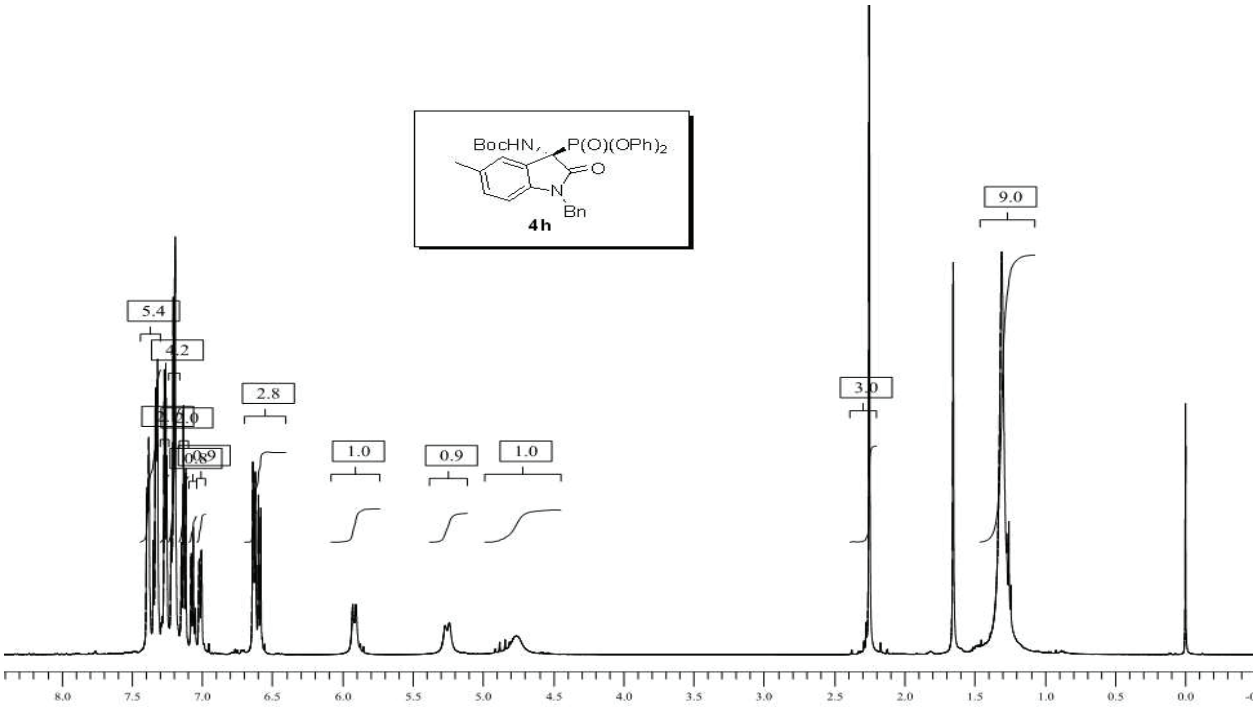
^{13}C NMR of Compound **4f**($CDCl_3$, 75 MHz)



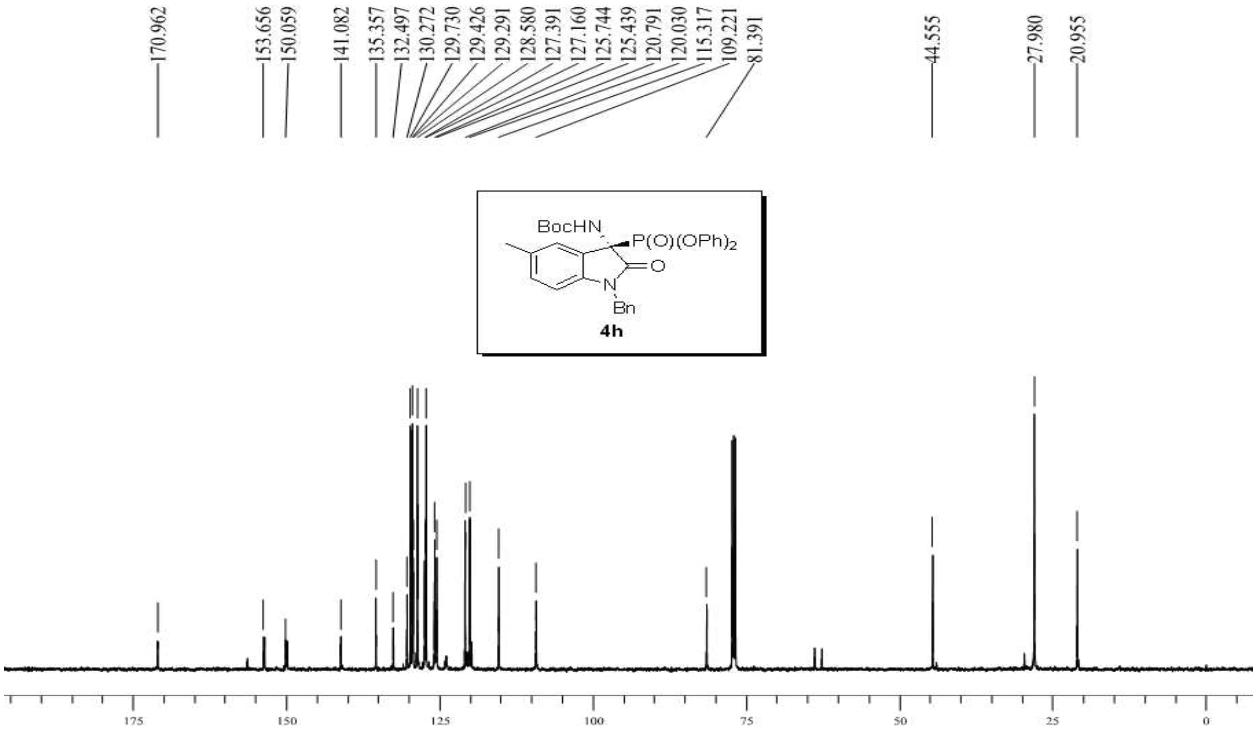
^{1}H NMR of Compound **4g** ($CDCl_3$, 300 MHz)



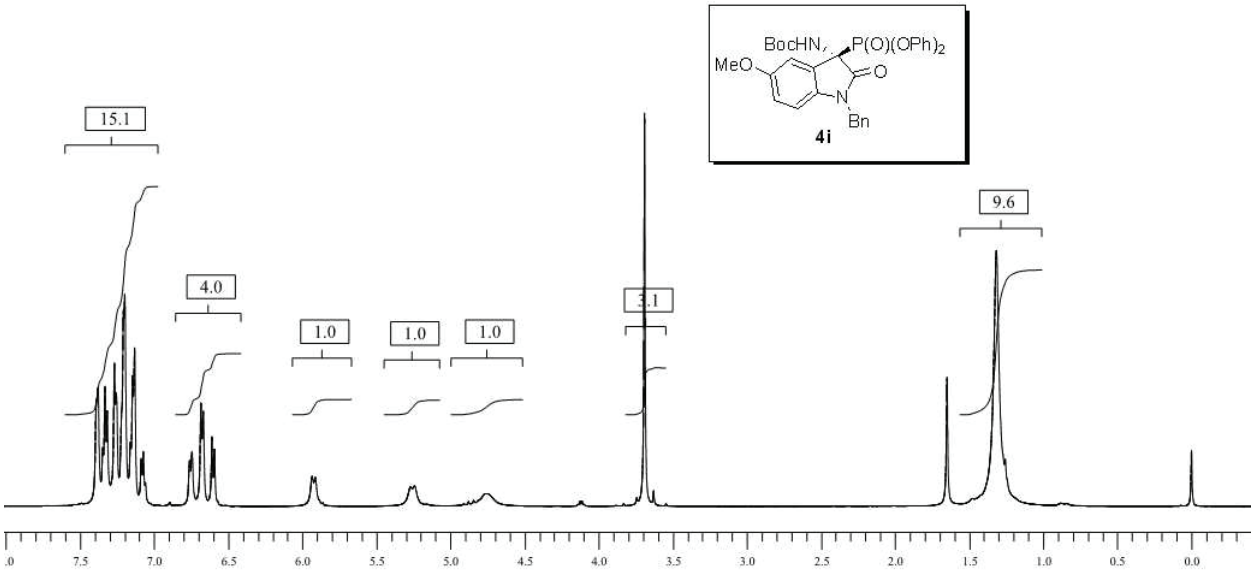
^{13}C NMR of Compound **4g** ($CDCl_3$, 75 MHz)



^{1}H NMR of Compound **4h** ($CDCl_3$, 300 MHz)



^{13}C NMR of Compound **4h** ($CDCl_3$, 75 MHz)



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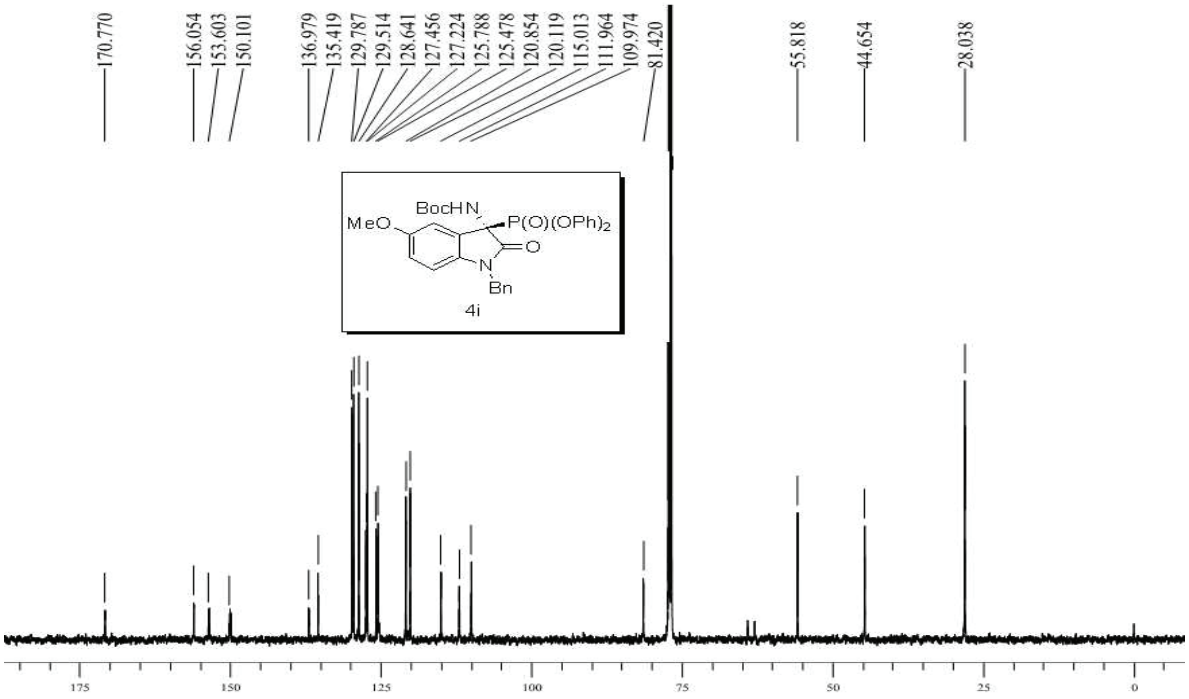

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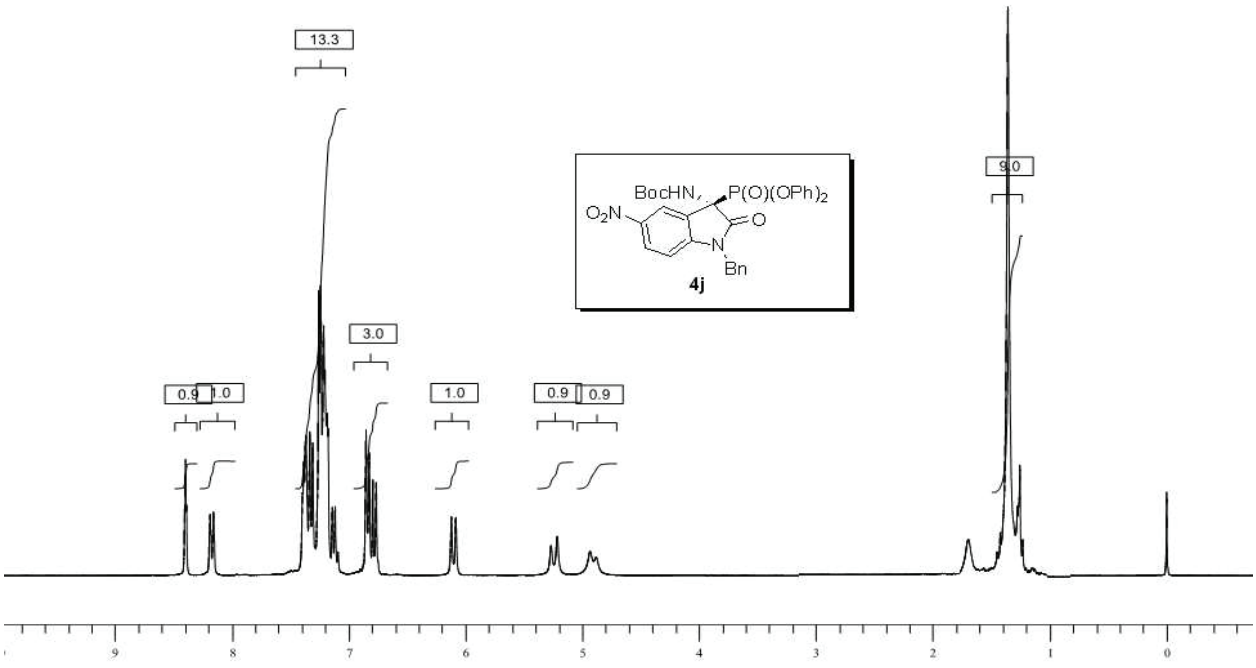

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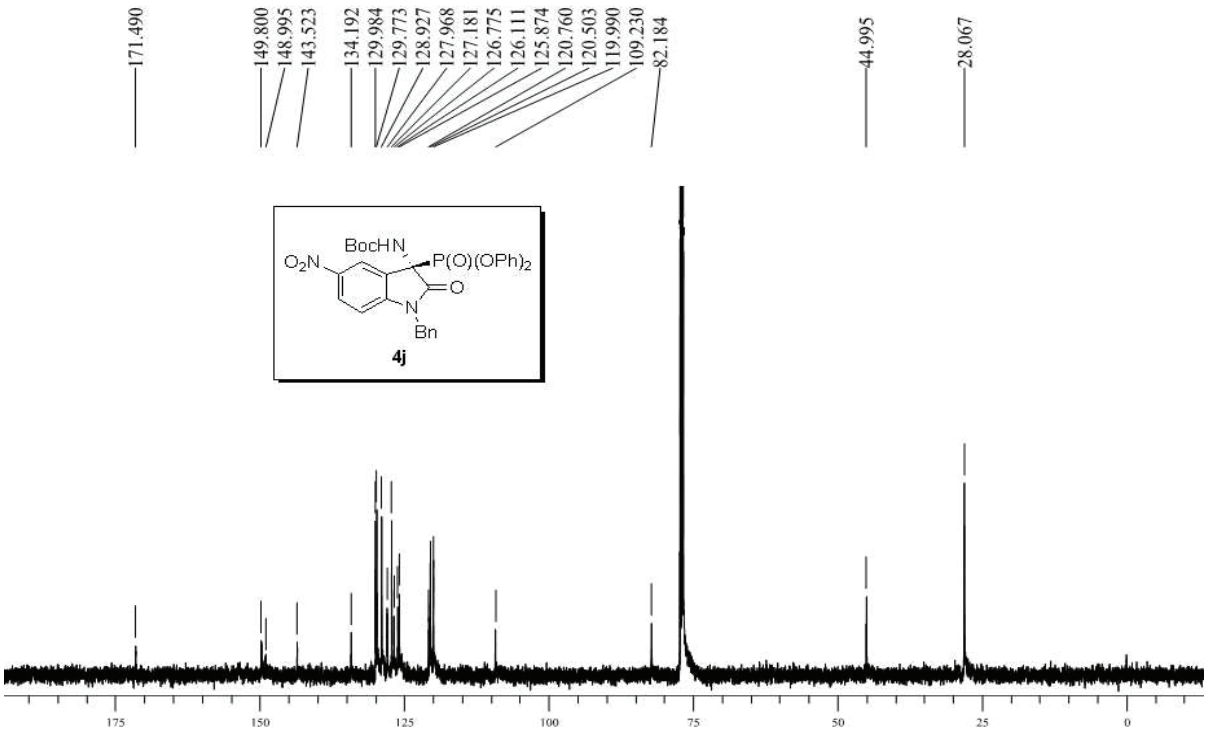

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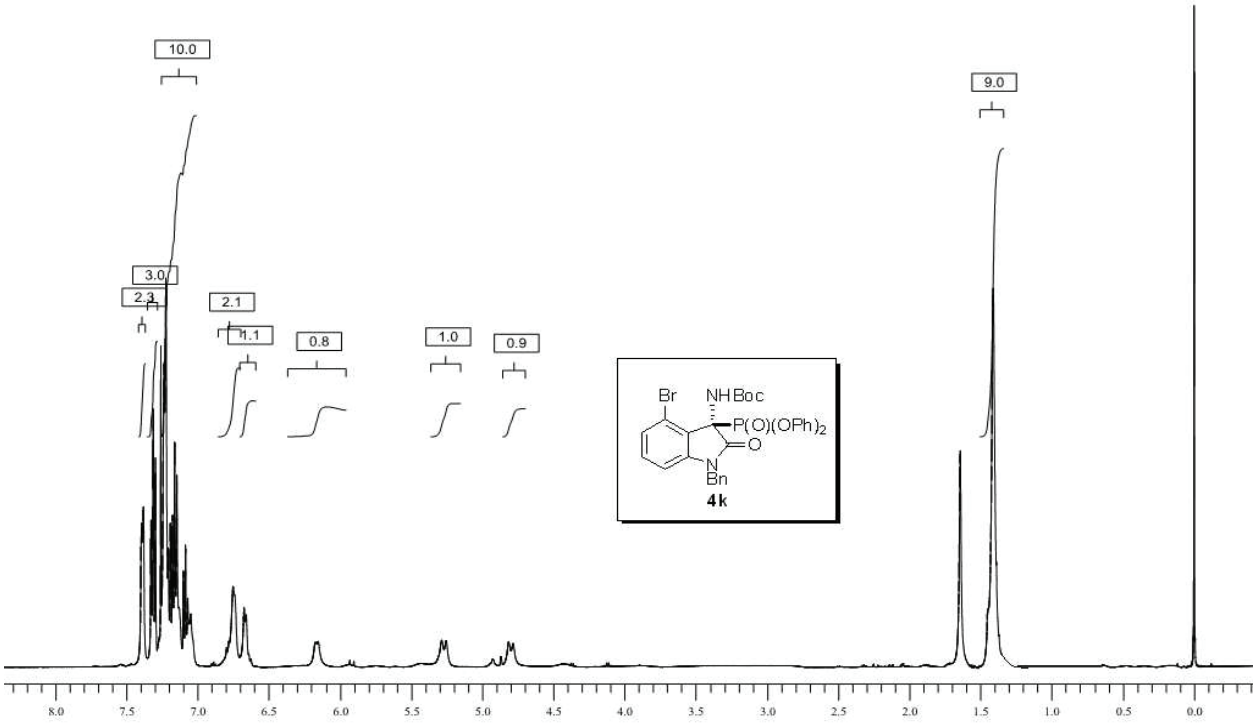

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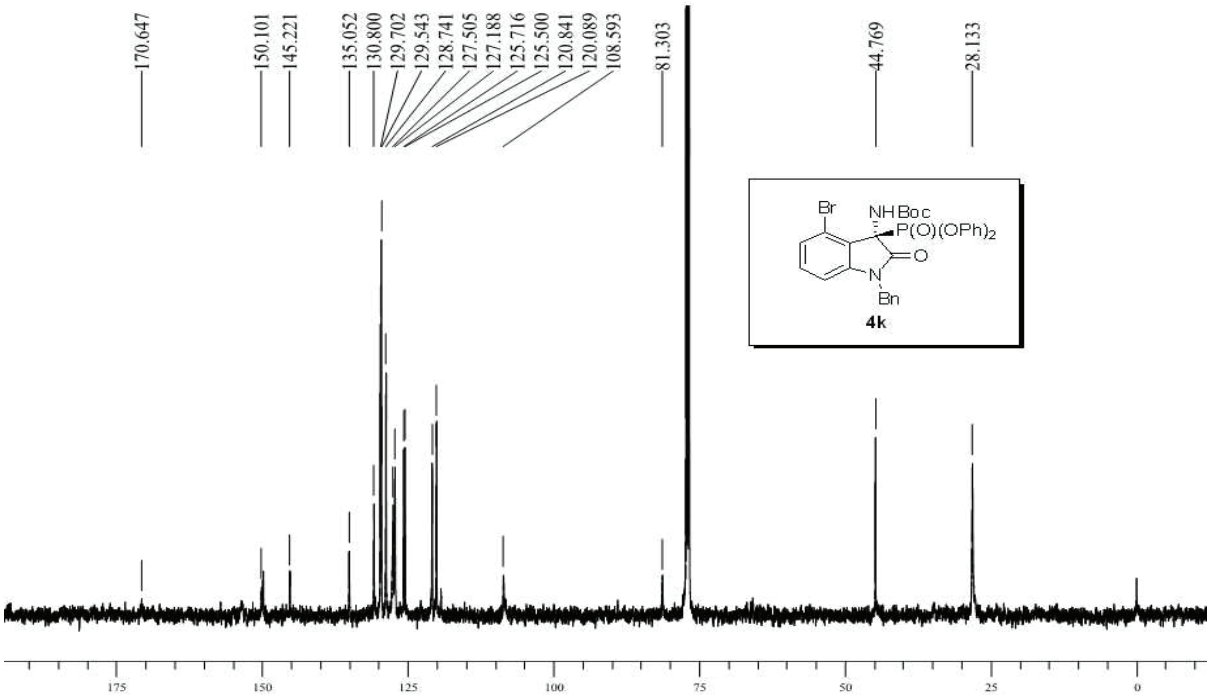

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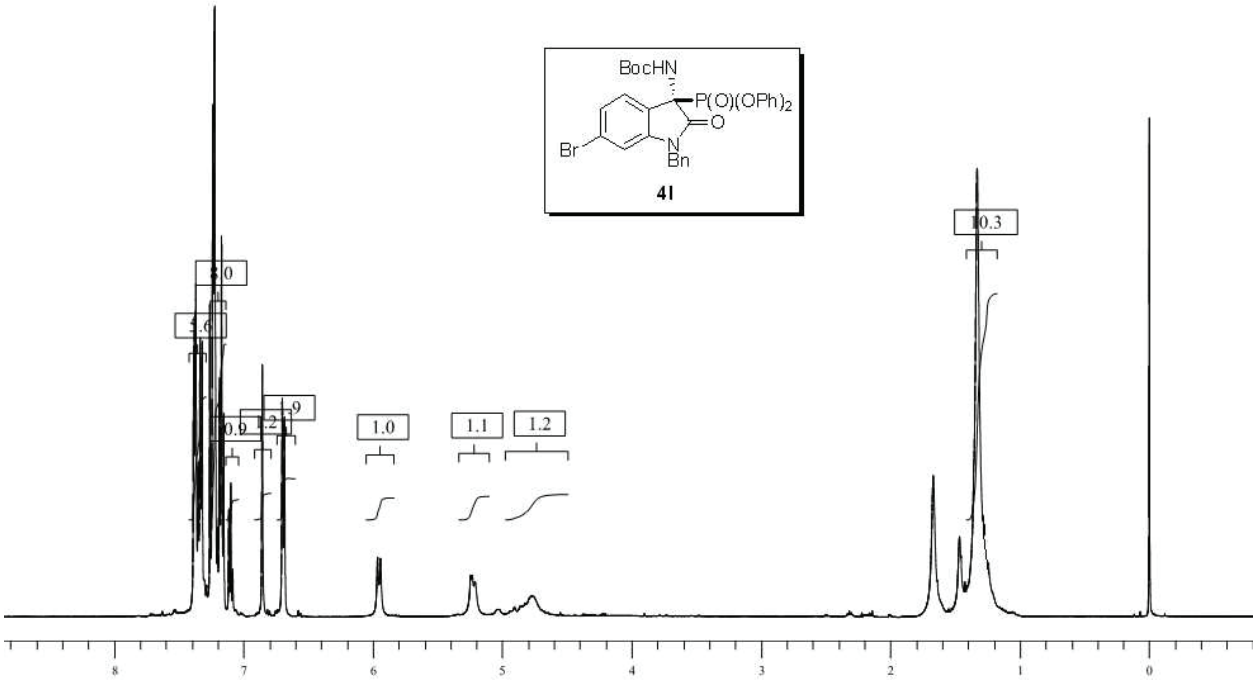
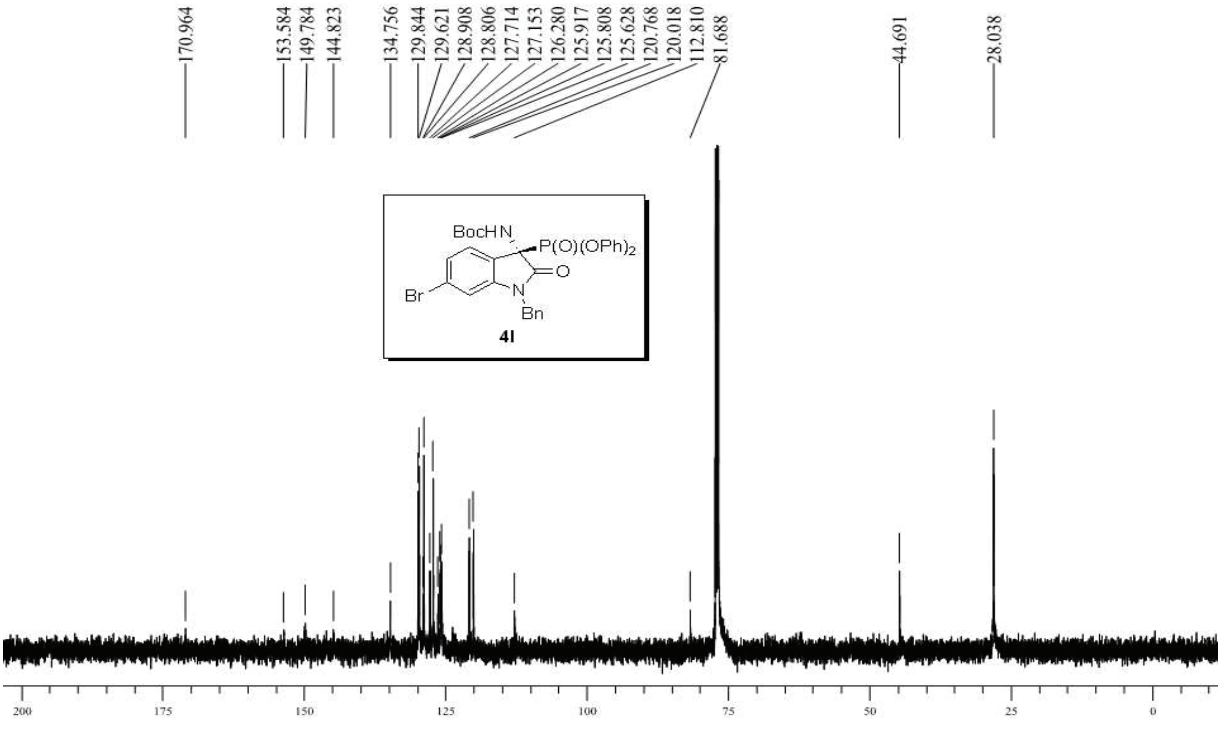
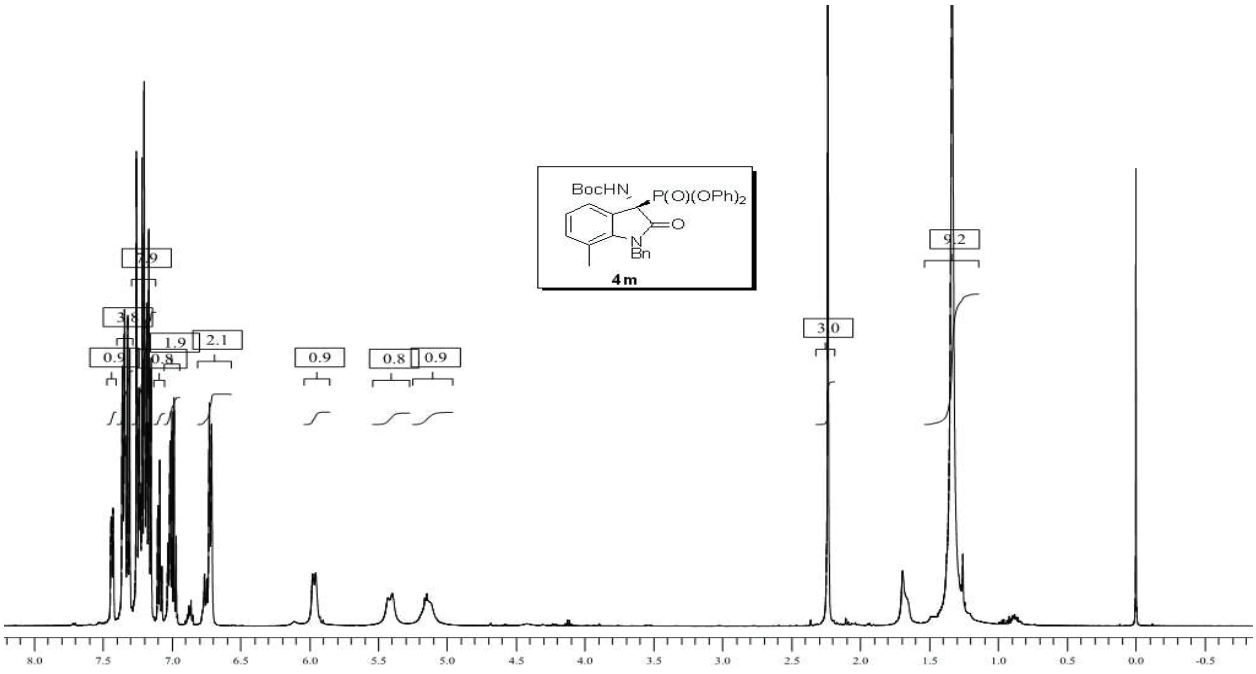


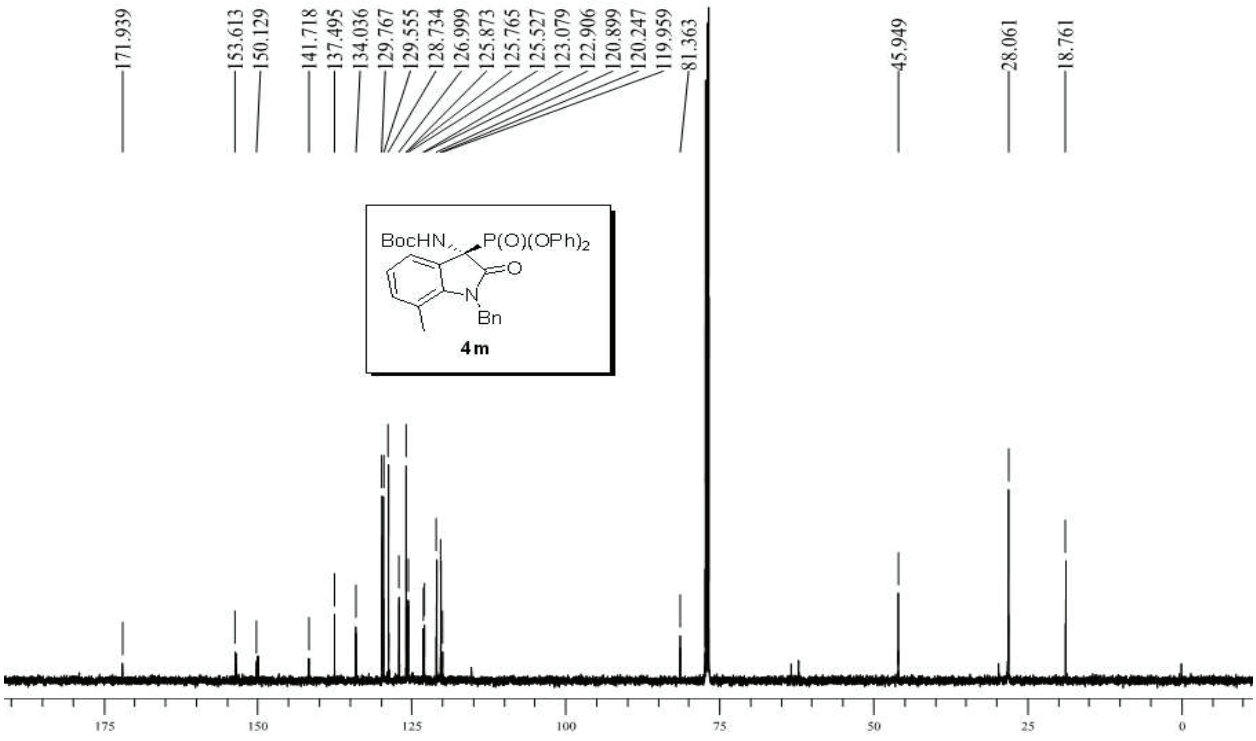
^{1}H NMR of Compound **4l** ($CDCl_3$, 300 MHz)



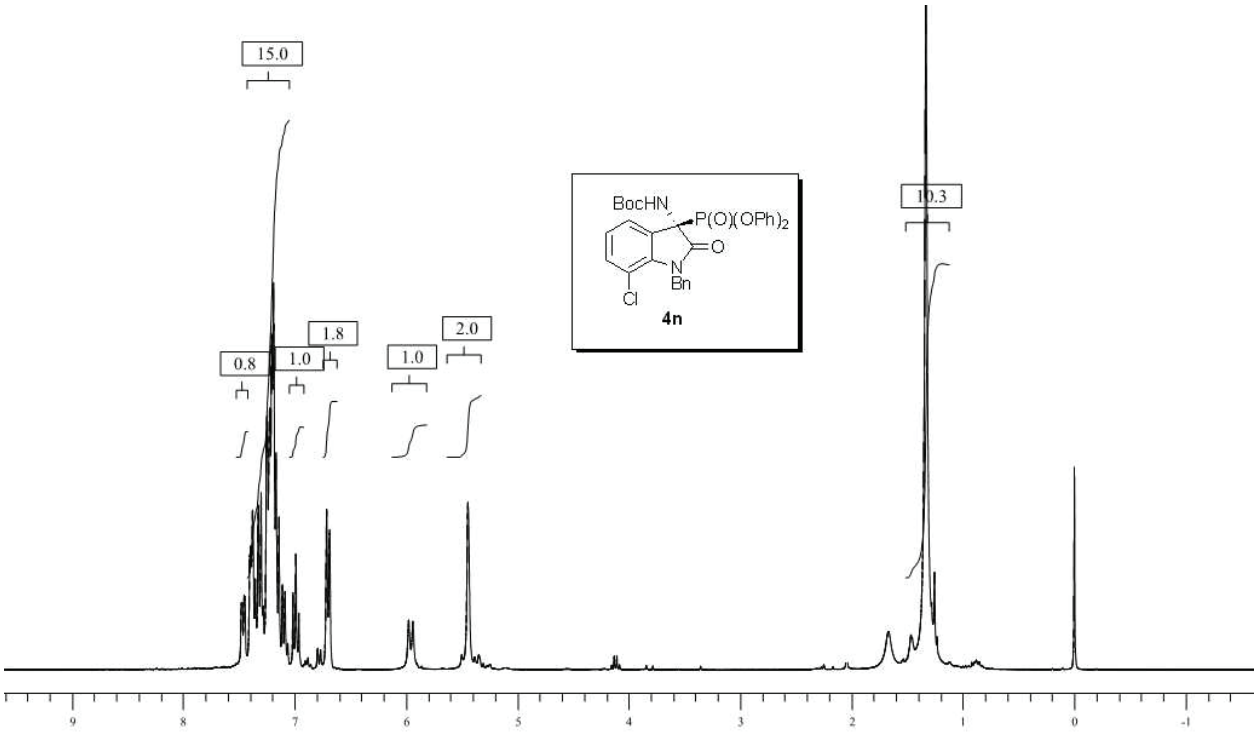
^{13}C NMR of Compound **4l** ($CDCl_3$, 75 MHz)



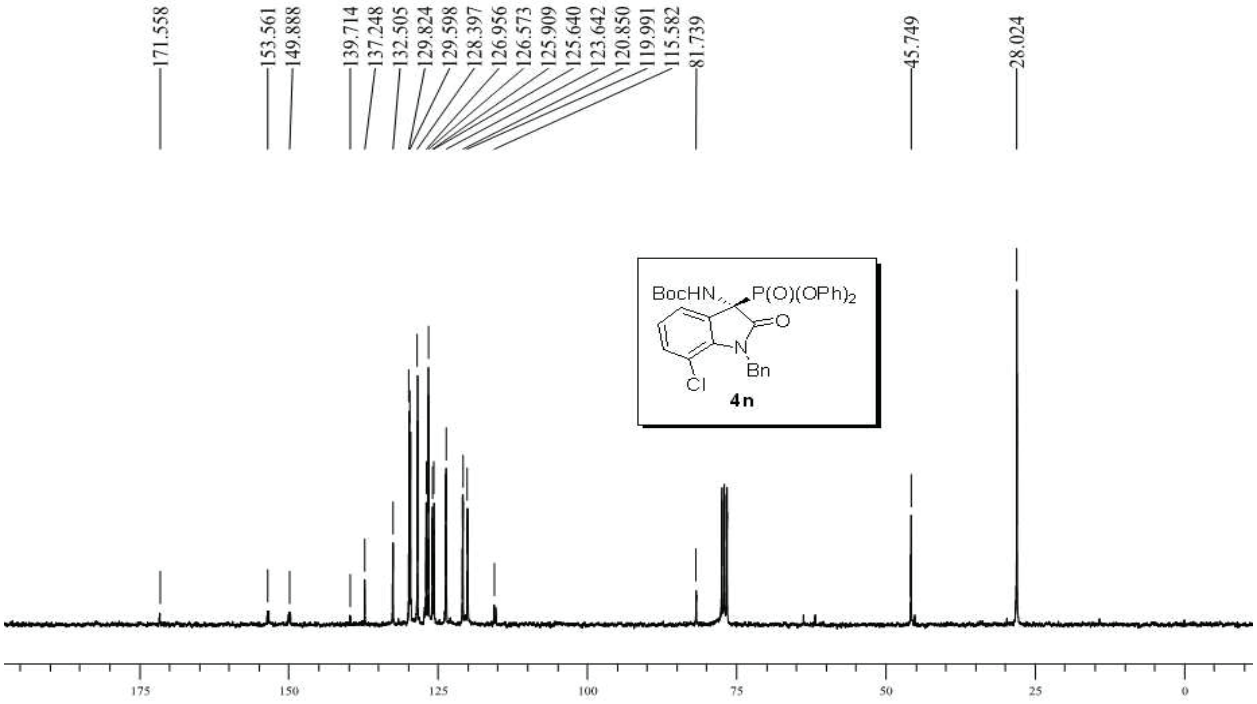
^{1}H NMR of Compound **4m** ($CDCl_3$, 300 MHz)



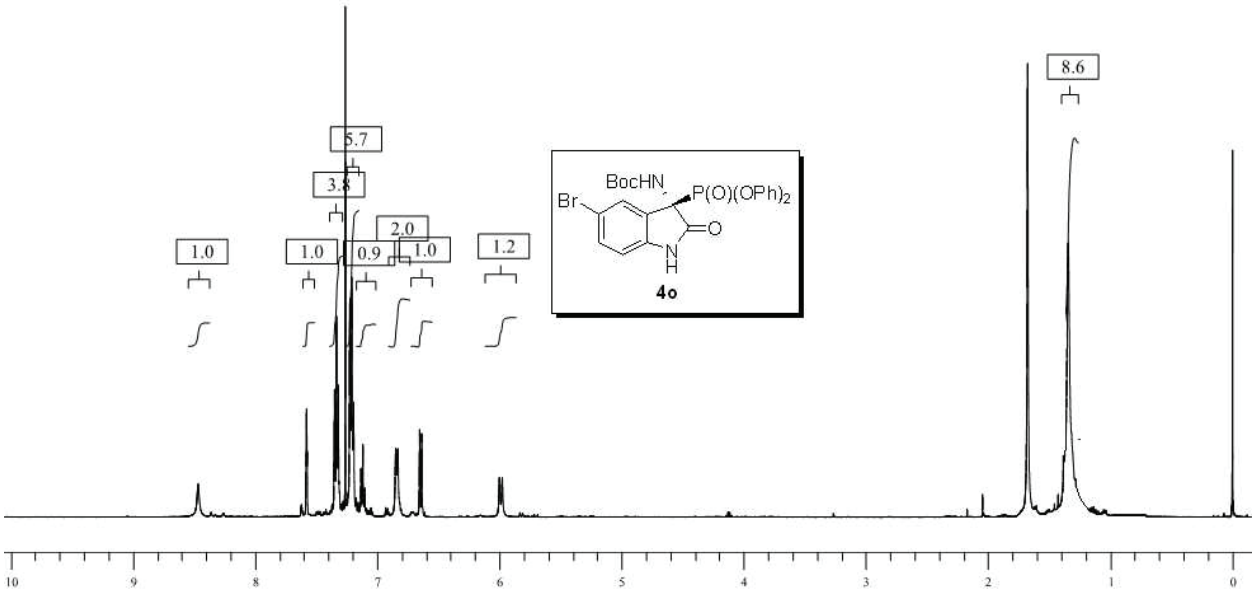
^{13}C NMR of Compound **4m** ($CDCl_3$, 75 MHz)



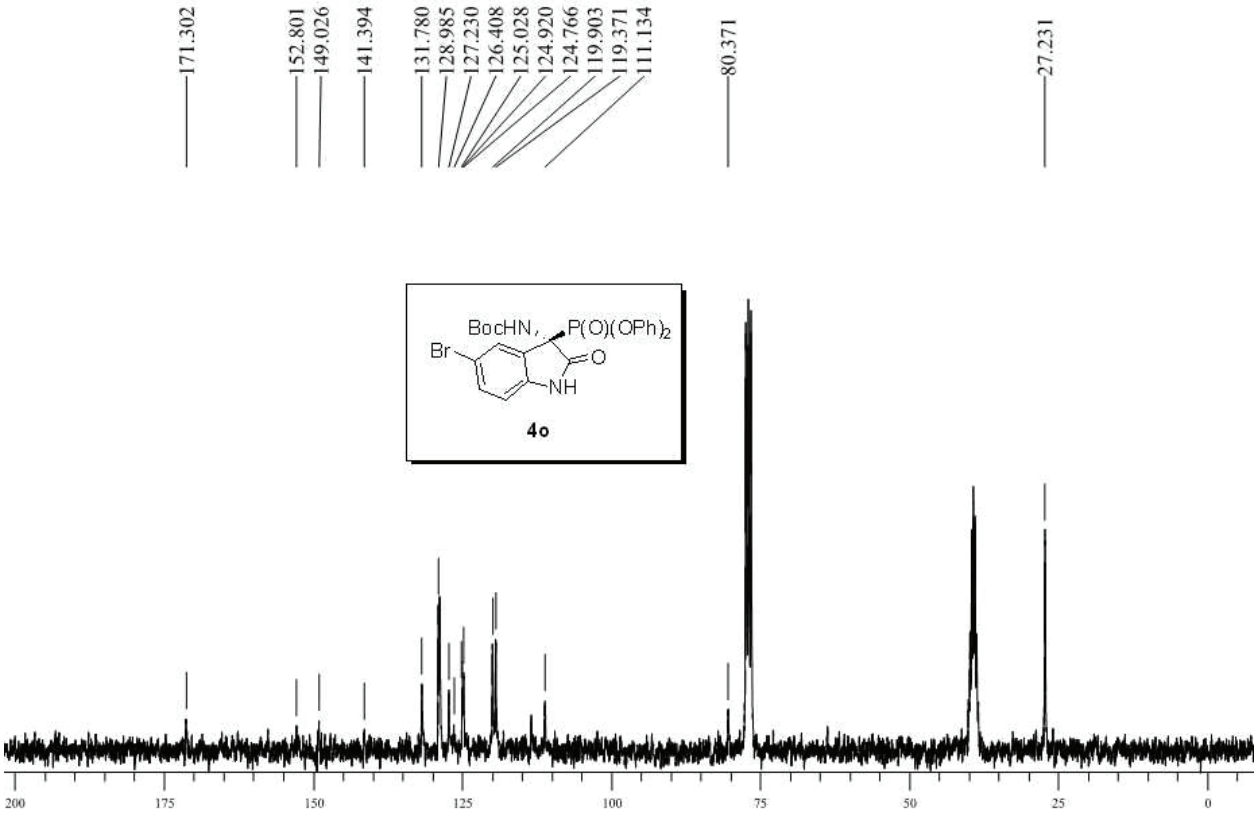
^{1}H NMR of Compound **4n** ($CDCl_3$, 300 MHz)



^{13}C NMR of Compound **4n** ($CDCl_3$, 75 MHz)



^{1}H NMR of Compound **4o** ($CDCl_3$, 300 MHz)



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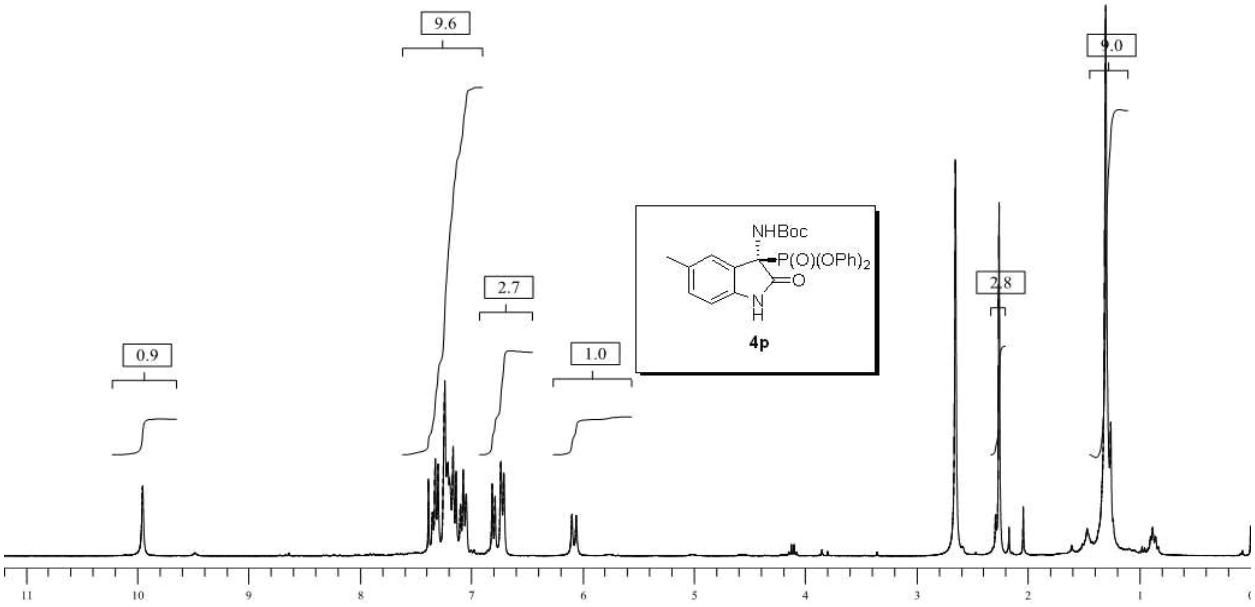
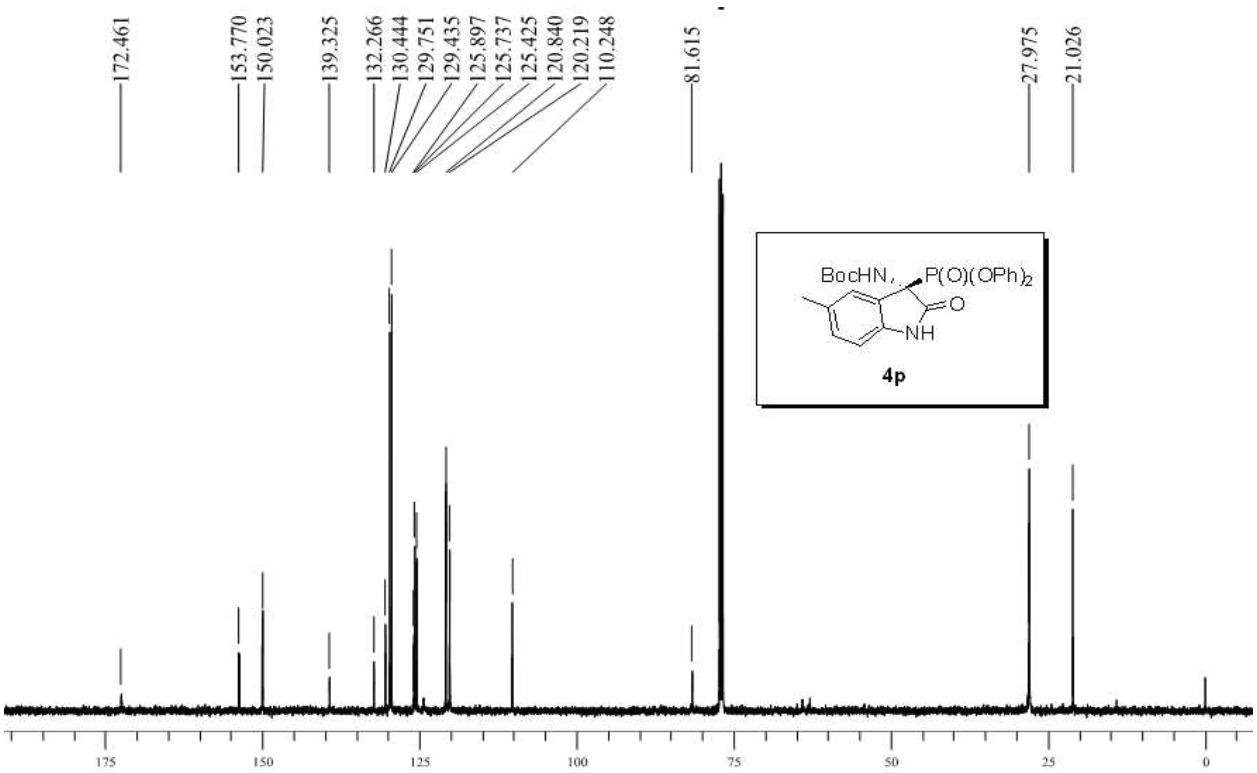
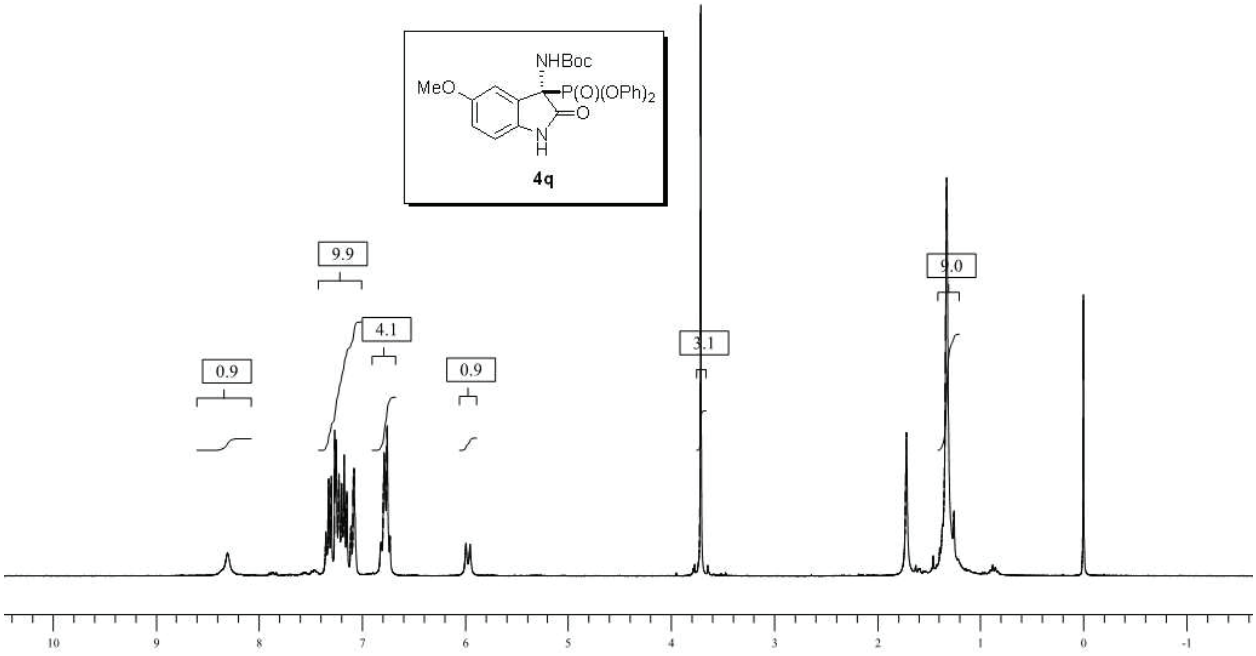


^{1}H NMR of Compound **4p** ($CDCl_3$, 300 MHz)



^{13}C NMR of Compound **4p** ($CDCl_3$, 75 MHz)



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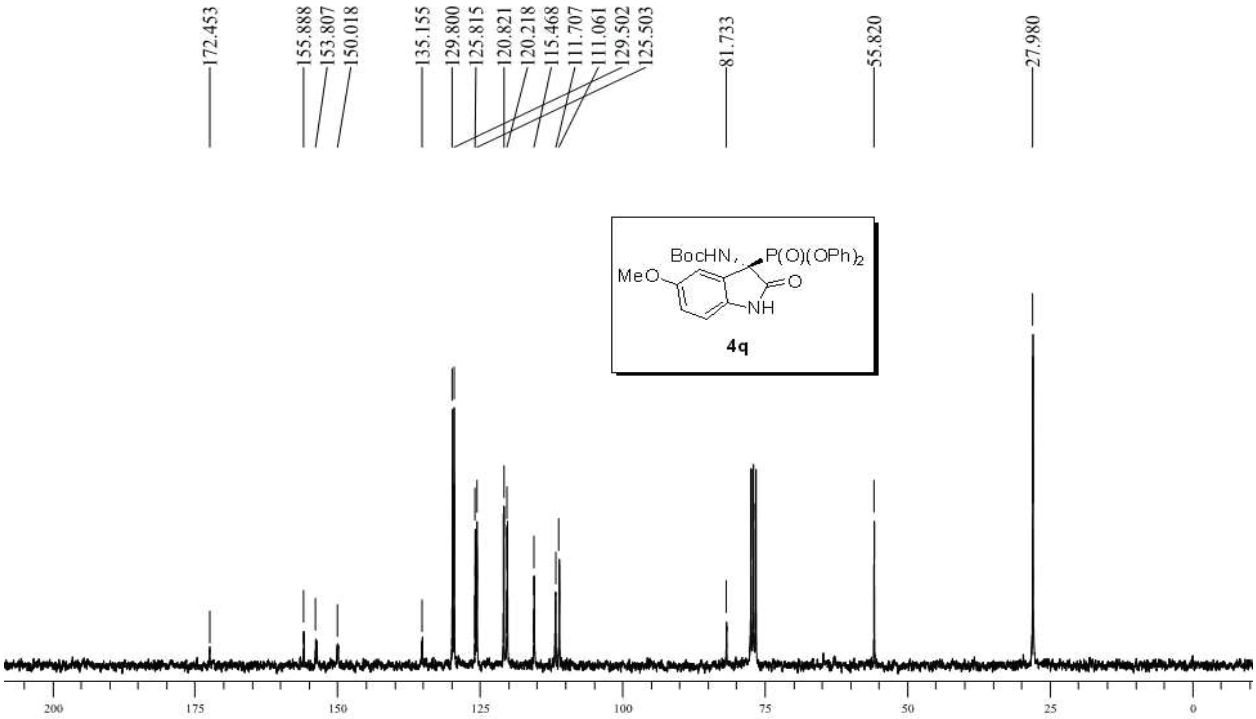
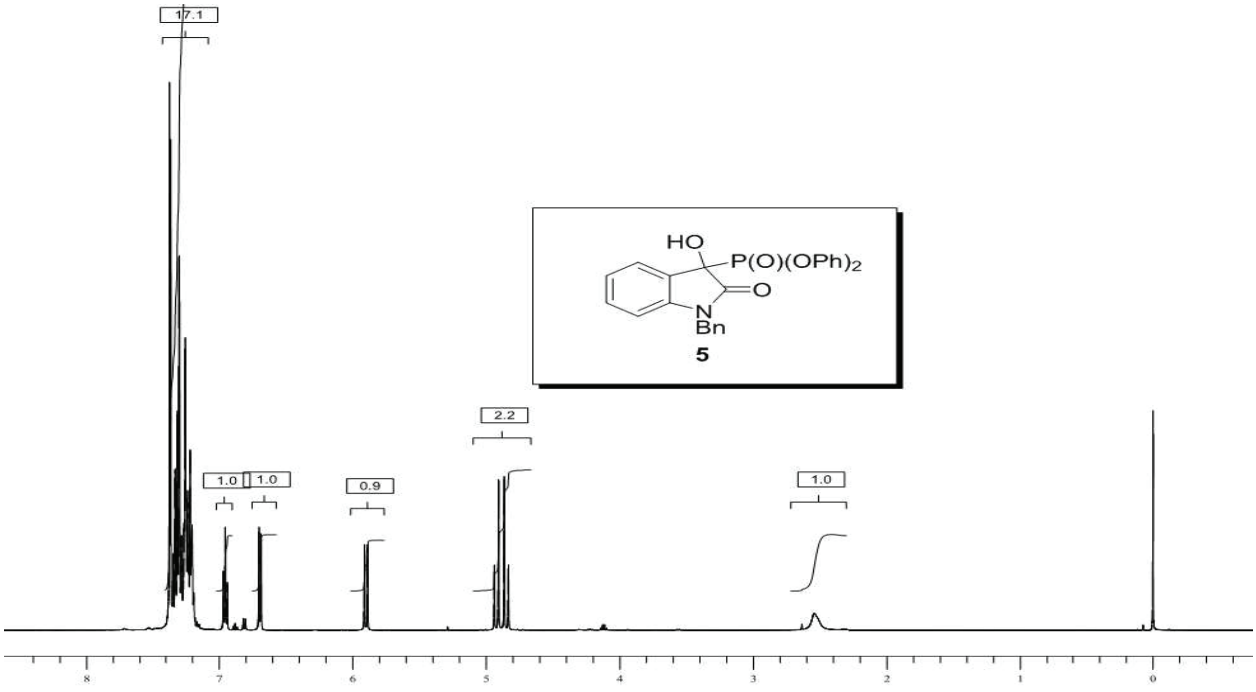
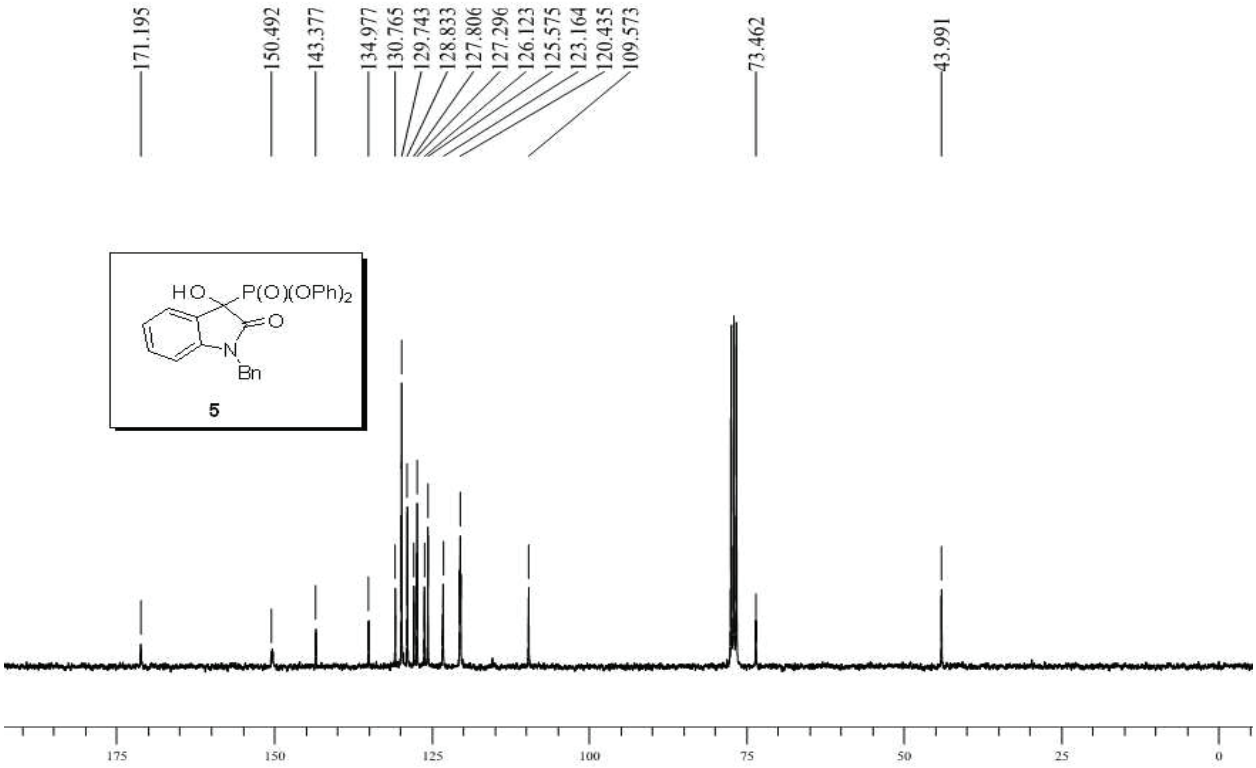


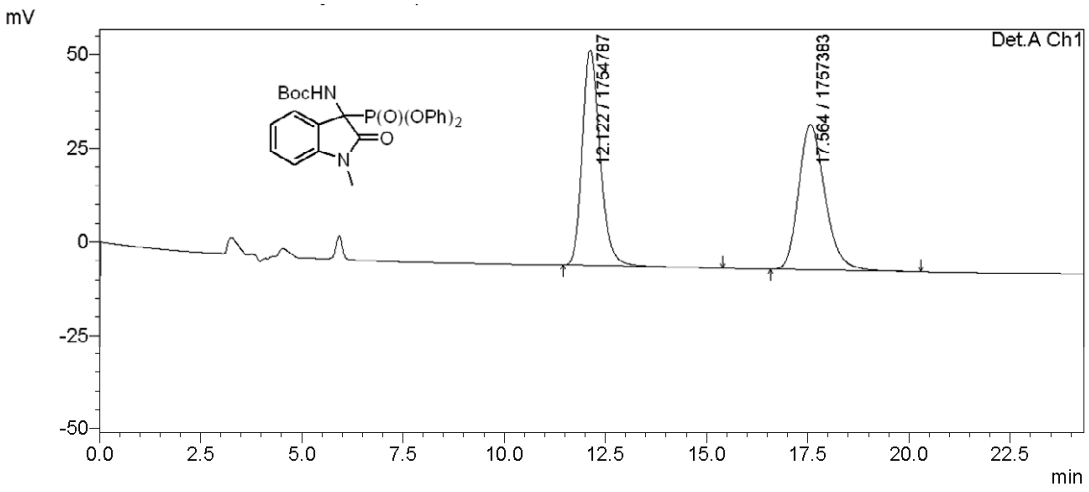
^{13}C NMR of Compound **4q** ($CDCl_3$, 75 MHz)



^{1}H NMR of Compound **5** ($CDCl_3$, 300 MHz)



^{13}C NMR of Compound **5** ($CDCl_3$, 75 MHz)



1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

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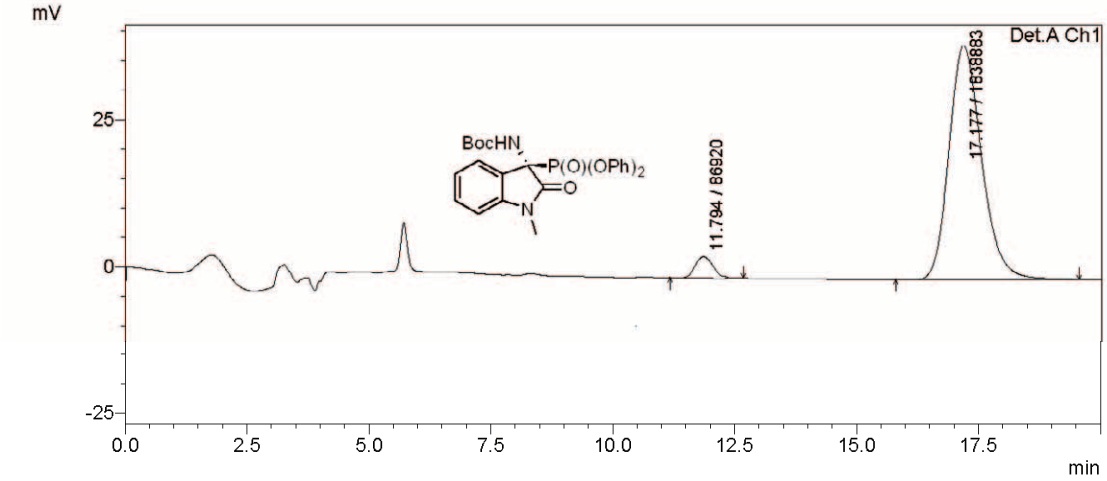
2	17.564	1757383	38699	50.037	40.253
Total		3512171	96140	100.000	100.000

HPLC chromatogram of racemic **4a**



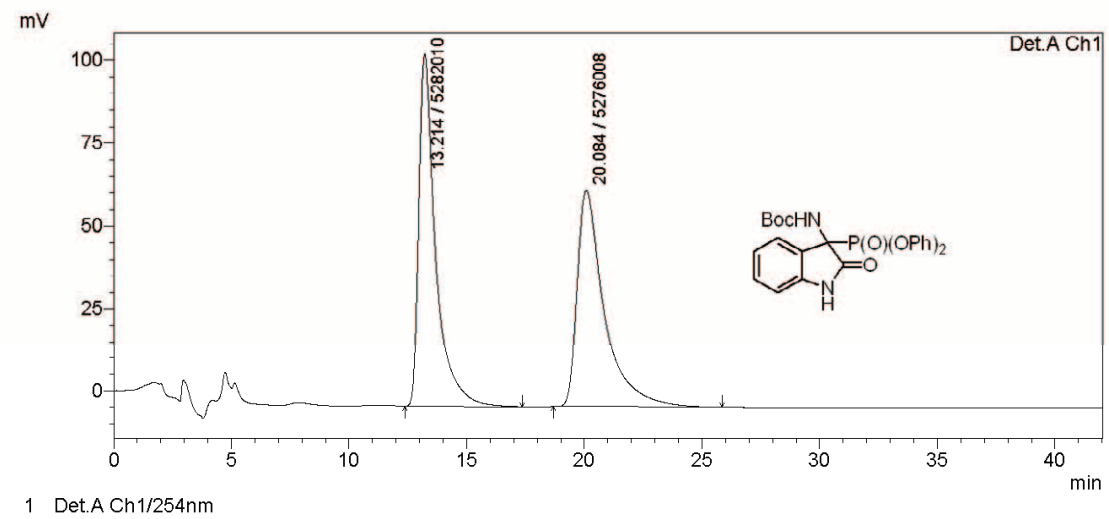
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.794	86920	3624	4.513	8.366
2	17.177	1838883	39699	95.487	91.634
Total		1925802	43323	100.000	100.000

HPLC chromatogram of enantioenriched **4a**

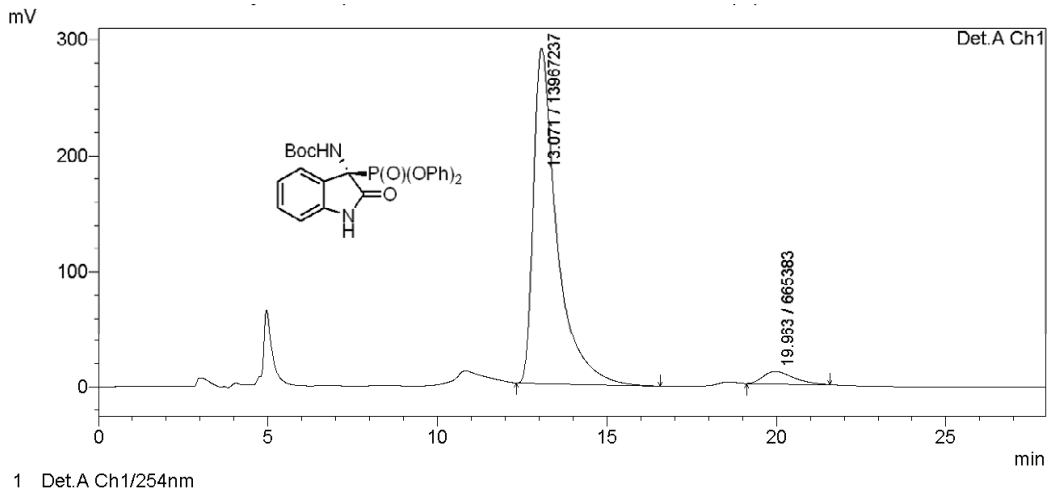


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.214	5282010	106662	50.028	61.900
2	20.084	5276008	65651	49.972	38.100
Total		10558018	172314	100.000	100.000

HPLC chromatogram of racemic **4b**

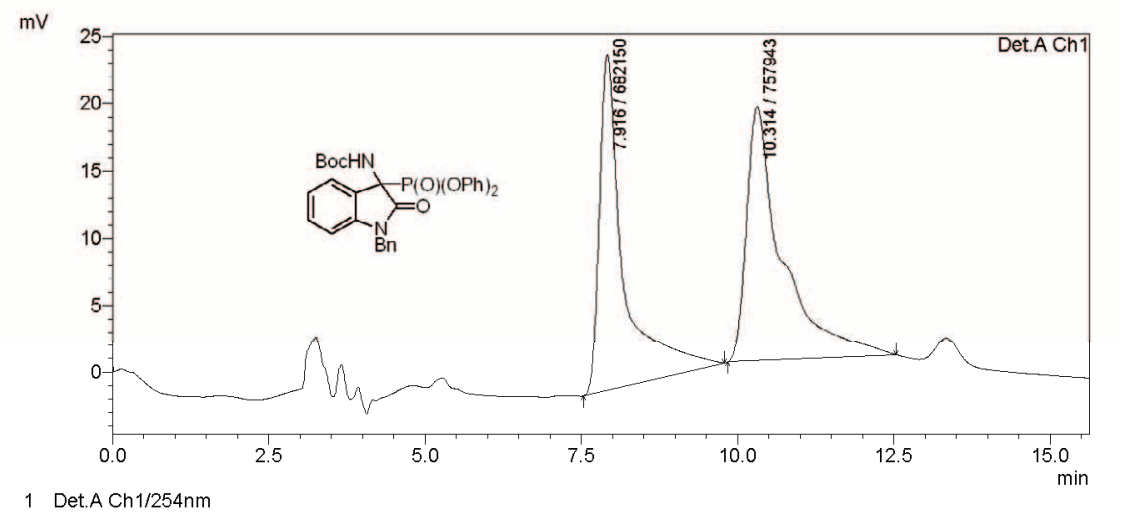


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.071	13967237	290265	95.453	96.430
2	19.963	665383	10746	4.547	3.570
Total		14632620	301011	100.000	100.000

HPLC chromatogram of enantioenriched **4b**

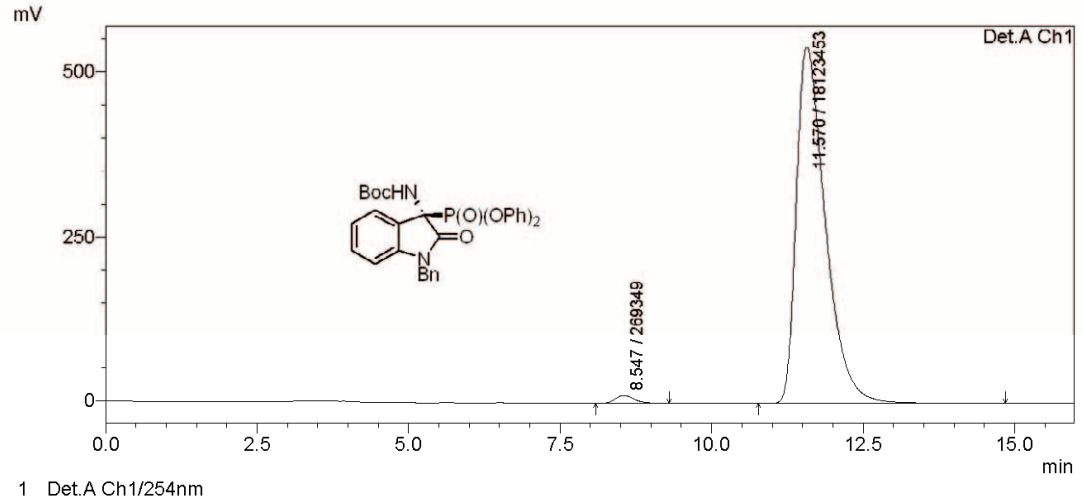


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.916	682150	24997	47.368	56.922
2	10.314	757943	18917	52.632	43.078
Total		1440093	43914	100.000	100.000

HPLC chromatogram of racemic **4c**

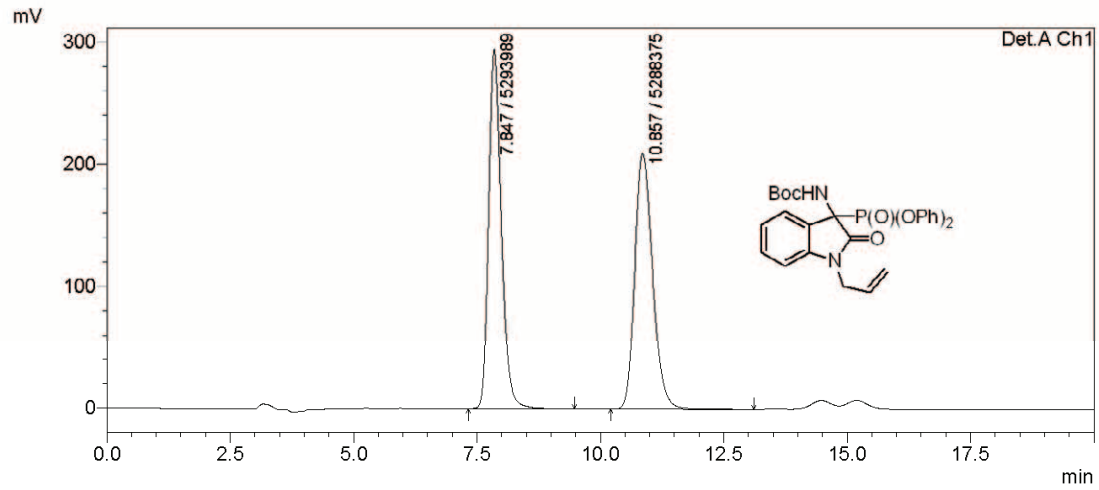


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.547	269349	12107	1.464	2.183
2	11.570	18123453	542370	98.536	97.817
Total		18392802	554477	100.000	100.000

HPLC chromatogram of enantioenriched **4c**



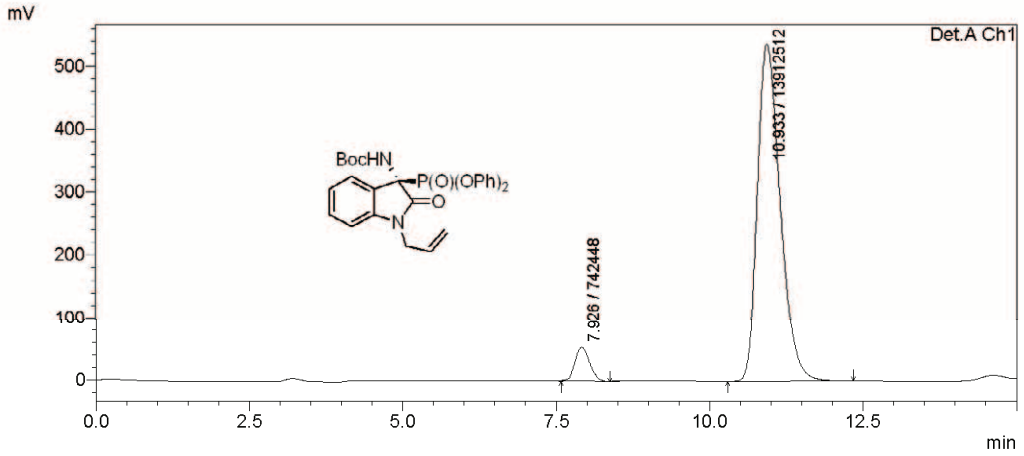
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.847	5293989	294667	50.027	58.421
2	10.857	5288375	209717	49.973	41.579
Total		10582364	504383	100.000	100.000

HPLC chromatogram of racemic **4d**



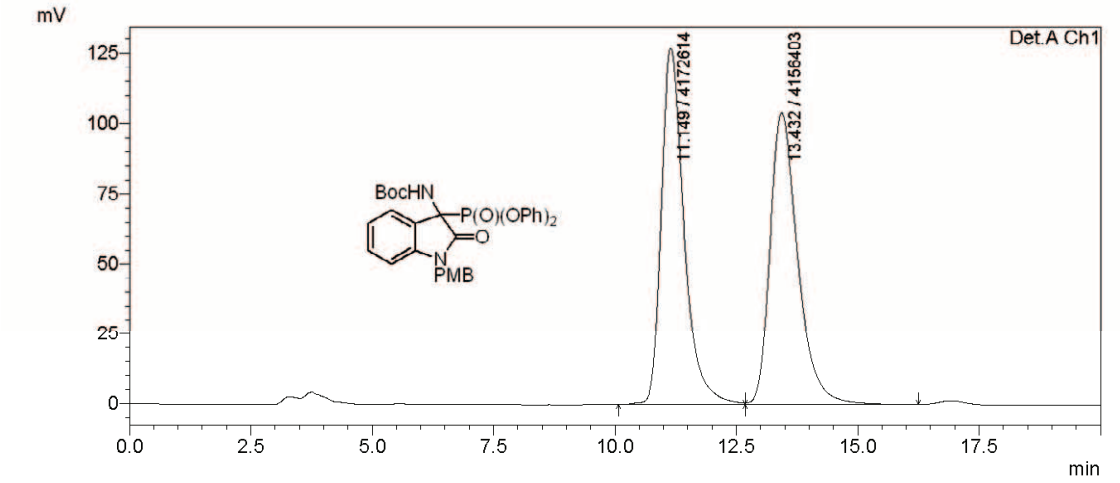
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.926	742448	49442	5.066	8.429
2	10.933	13912512	537111	94.934	91.571
Total		14654960	586553	100.000	100.000

HPLC chromatogram of enantioenriched **4d**

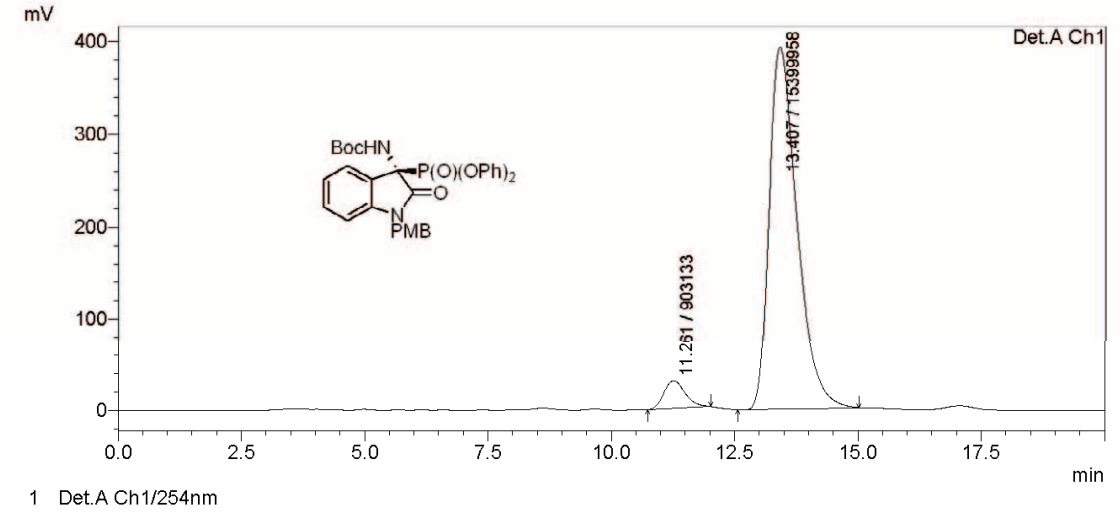


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.149	4172614	127472	50.097	54.988
2	13.432	4156403	104347	49.903	45.012
Total		8329018	231819	100.000	100.000

HPLC chromatogram of racemic **4e**

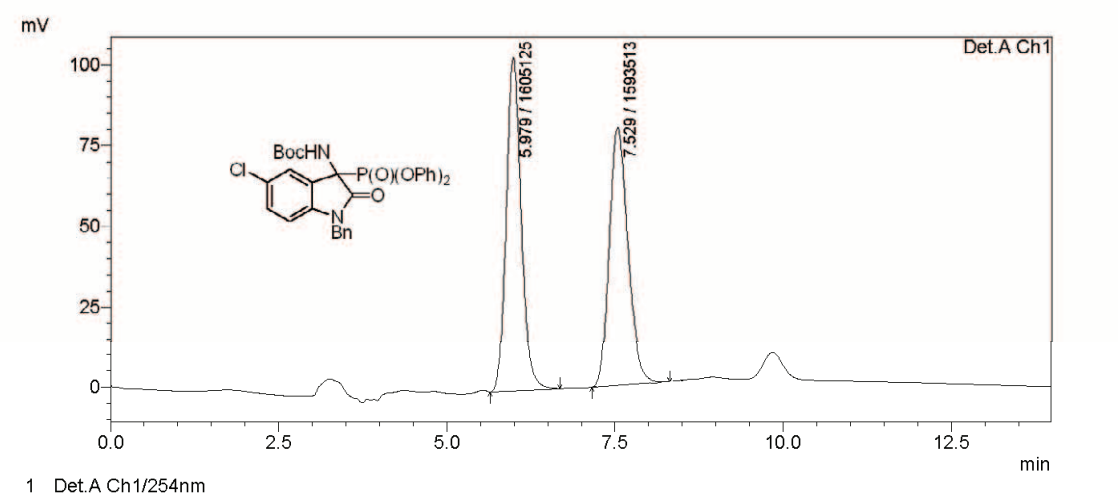


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	11.261	903133	29983	5.540	7.092
2	13.407	15399958	392794	94.460	92.908
Total		16303091	422777	100.000	100.000

HPLC chromatogram of enantioenriched **4e**



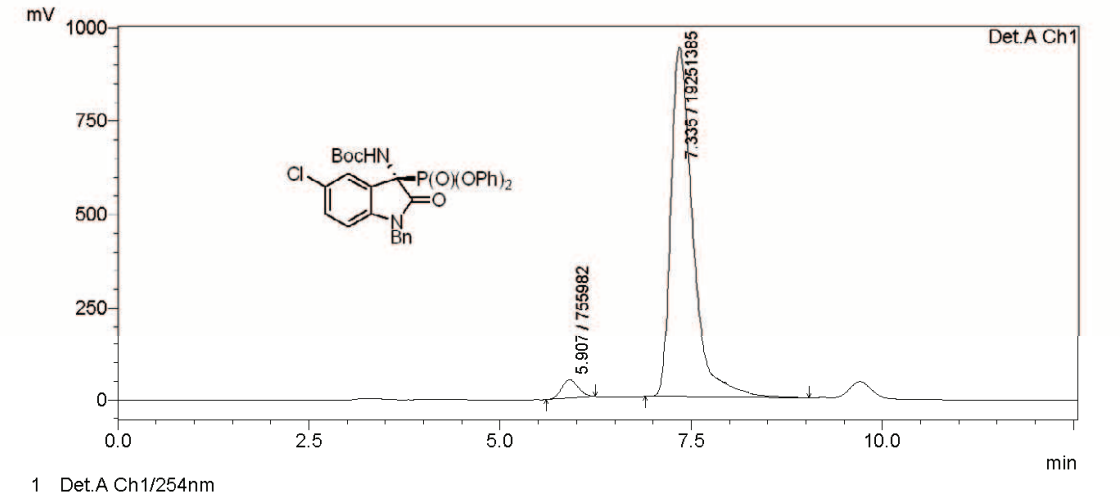
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.979	1605125	103767	50.182	56.907
2	7.529	1593513	78579	49.818	43.093
Total		3198638	182345	100.000	100.000

HPLC chromatogram of racemic **4f**



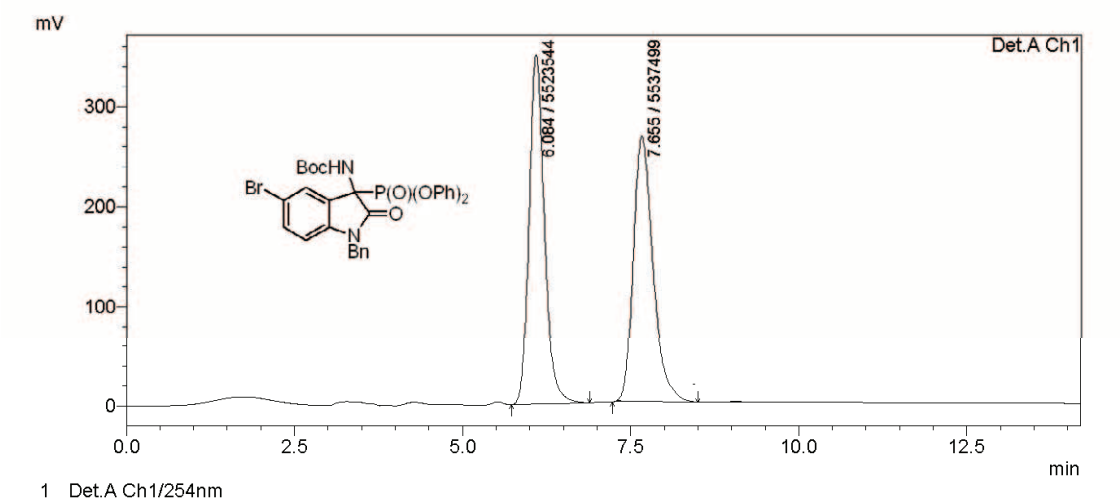
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.907	755982	49505	3.779	4.998
2	7.335	19251385	941025	96.221	95.002
Total		20007367	990530	100.000	100.000

HPLC chromatogram of enantioenriched **4f**



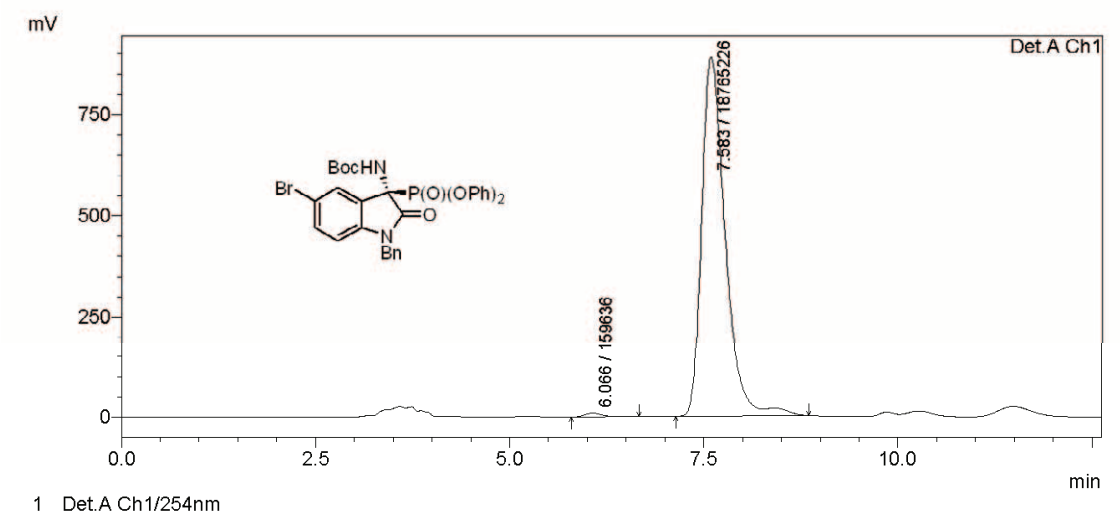
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.084	5523544	349530	49.937	57.287
2	7.655	5537499	260603	50.063	42.713
Total		11061042	610132	100.000	100.000

HPLC chromatogram of racemic **4g**



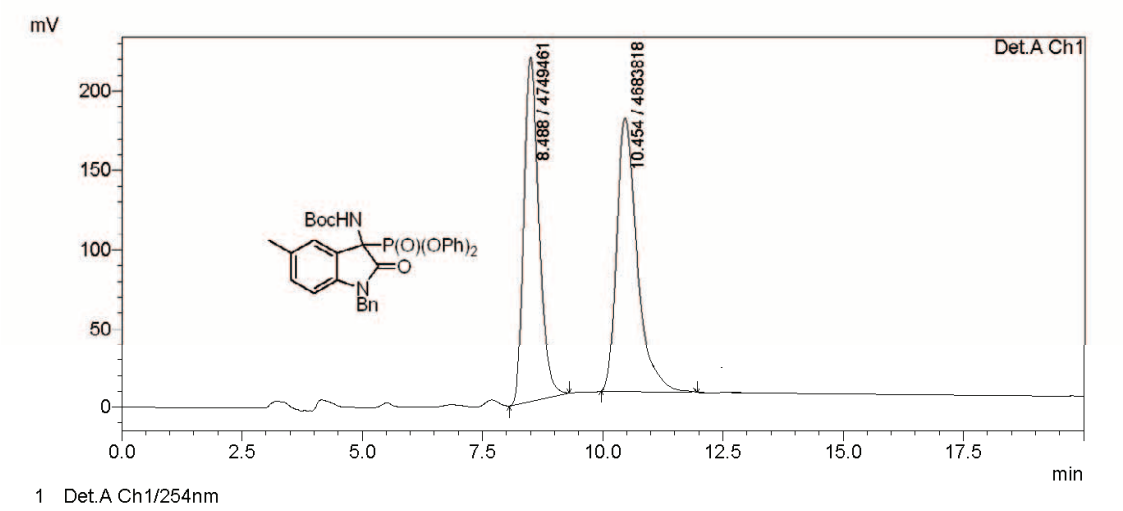
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.066	159636	9739	0.844	1.082
2	7.583	18765226	890351	99.156	98.918
Total		18924862	900090	100.000	100.000

HPLC chromatogram of enantioenriched **4g**



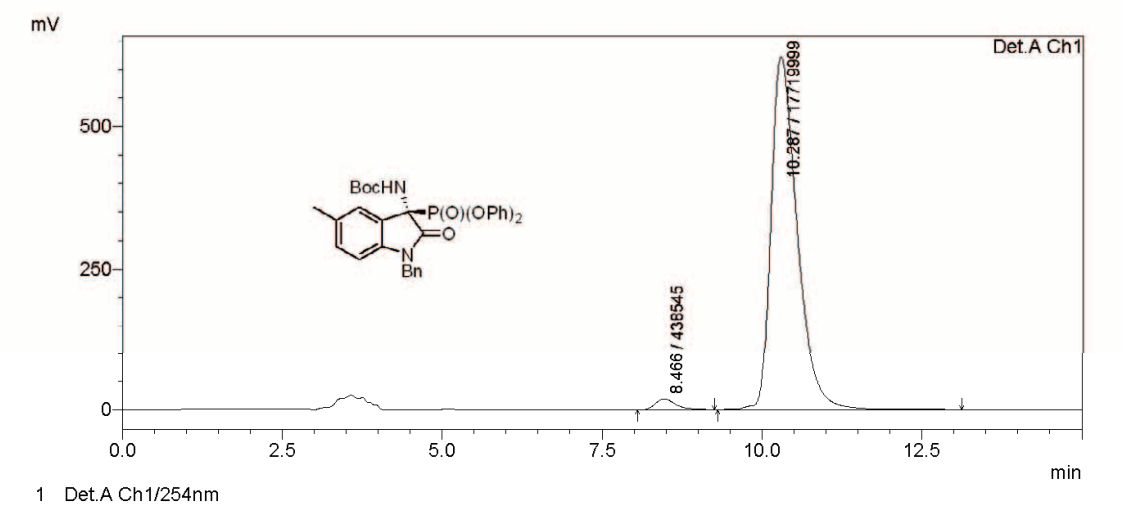
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.488	4749461	217816	50.348	56.478
2	10.454	4683818	167852	49.652	43.522
Total		9433279	385668	100.000	100.000

HPLC chromatogram of racemic **4h**



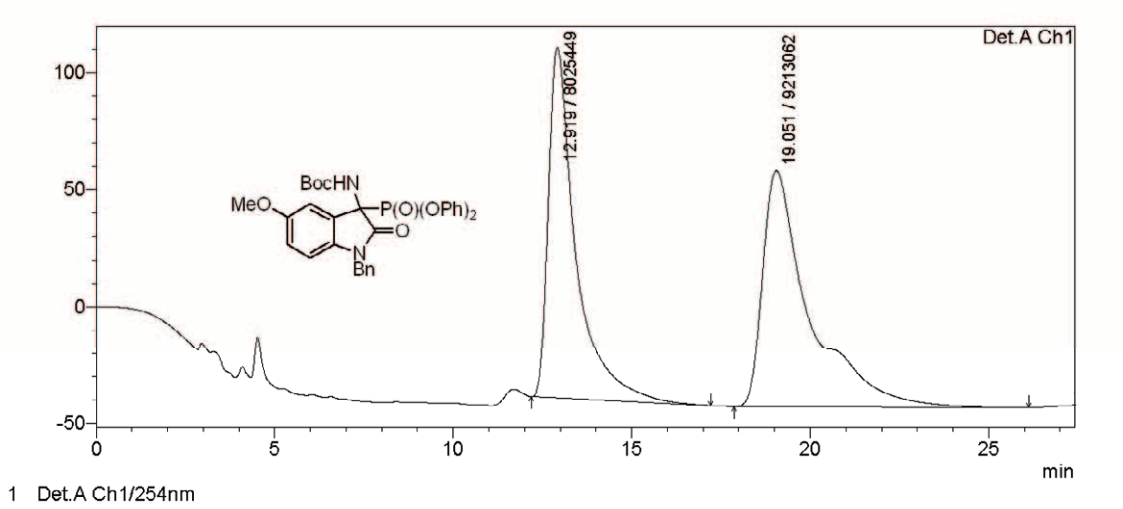
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.466	438545	19497	2.415	3.038
2	10.287	17719999	622327	97.585	96.962
Total		18158544	641824	100.000	100.000

HPLC chromatogram of enantioenriched **4h**



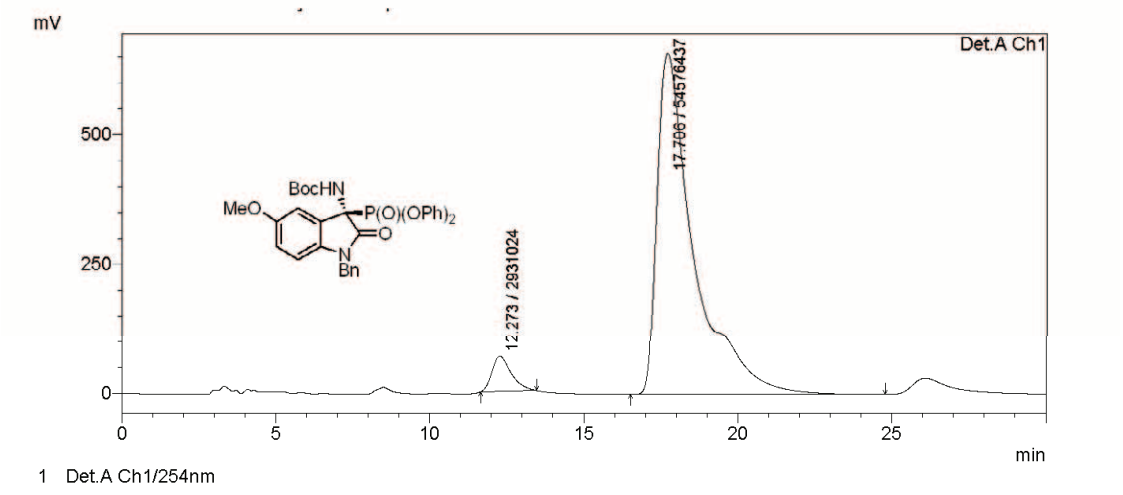
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.919	8025449	150227	46.555	59.771
2	19.051	9213062	101111	53.445	40.229
Total		17238511	251337	100.000	100.000

HPLC chromatogram of racemic **4i**



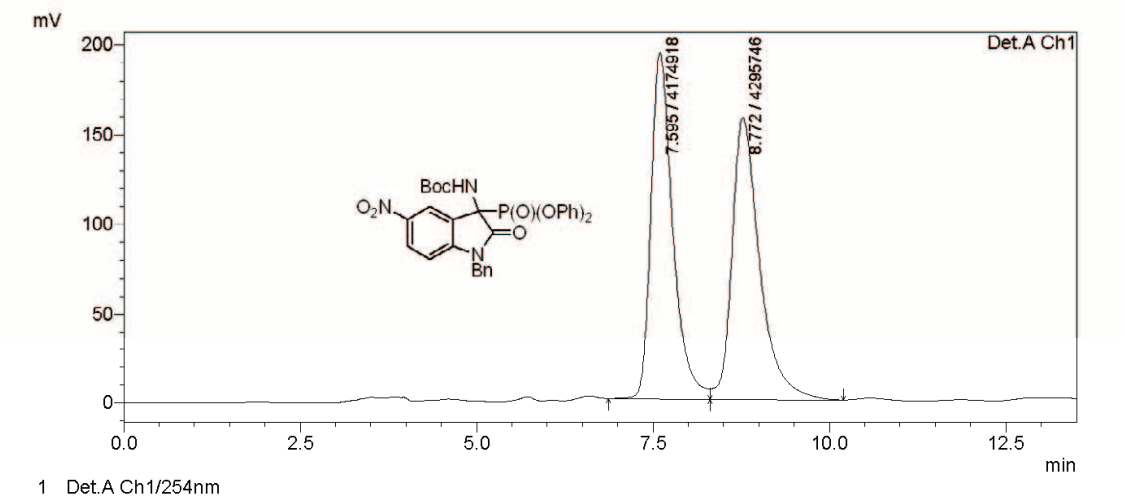
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.273	2931024	67641	5.097	9.310
2	17.706	54576437	658921	94.903	90.690
Total		57507461	726562	100.000	100.000

HPLC chromatogram of enantioenriched **4i**



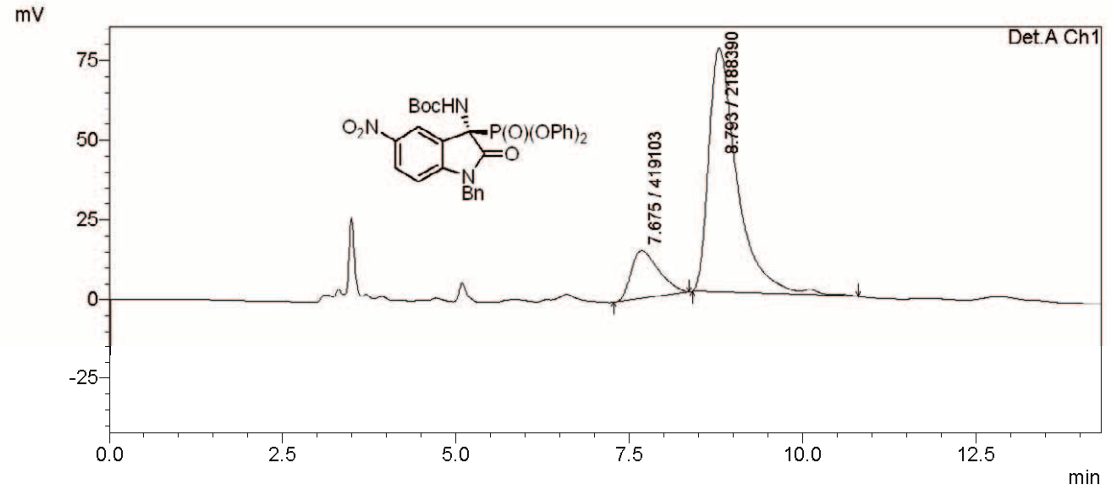
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.595	4174918	193547	49.287	55.123
2	8.772	4295746	157571	50.713	44.877
Total		8470664	351118	100.000	100.000

HPLC chromatogram of racemic **4j**



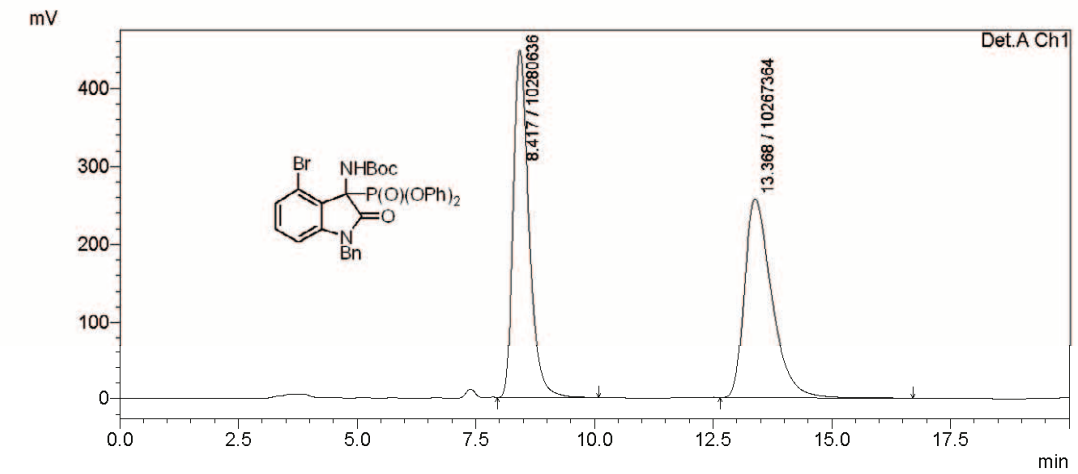
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.675	419103	15065	16.073	16.422
2	8.793	2188390	76672	83.927	83.578
Total		2607493	91736	100.000	100.000

HPLC chromatogram of enantioenriched **4j**

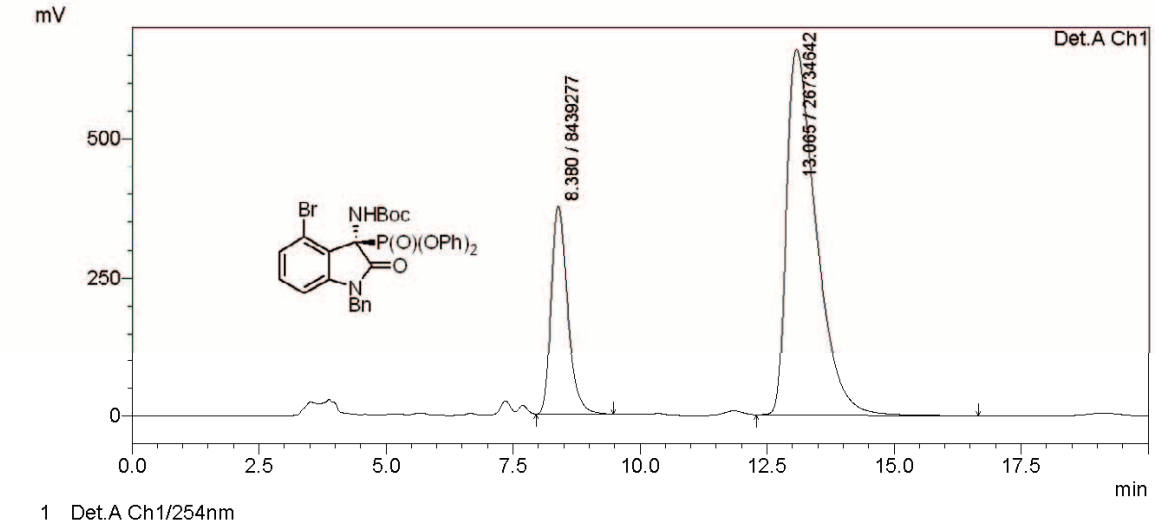


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.417	10280636	447268	50.032	63.502
2	13.368	10267364	257072	49.968	36.498
Total		20548000	704340	100.000	100.000

HPLC chromatogram of racemic **4k**

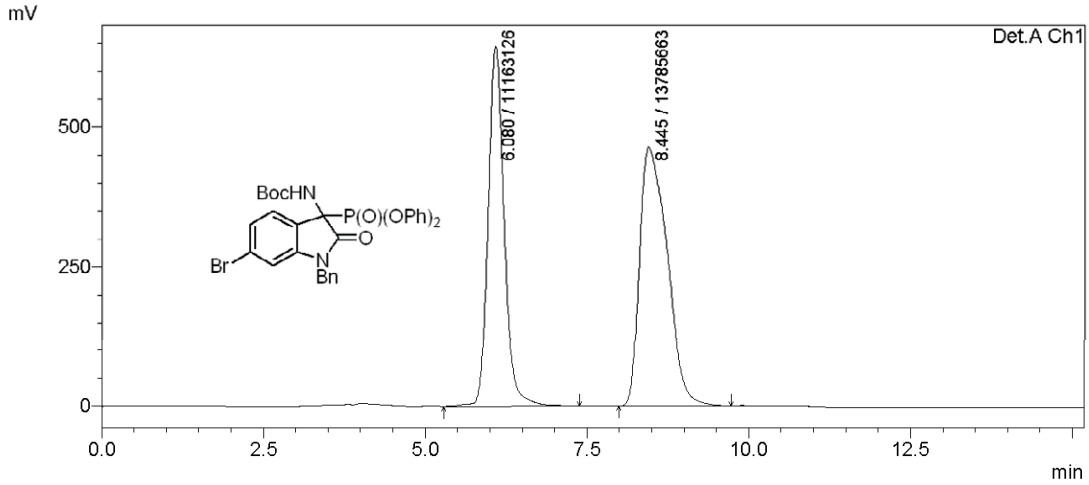


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.380	8439277	376318	23.993	36.291
2	13.065	26734642	660635	76.007	63.709
Total		35173919	1036953	100.000	100.000

HPLC chromatogram of enantioenriched **4k**



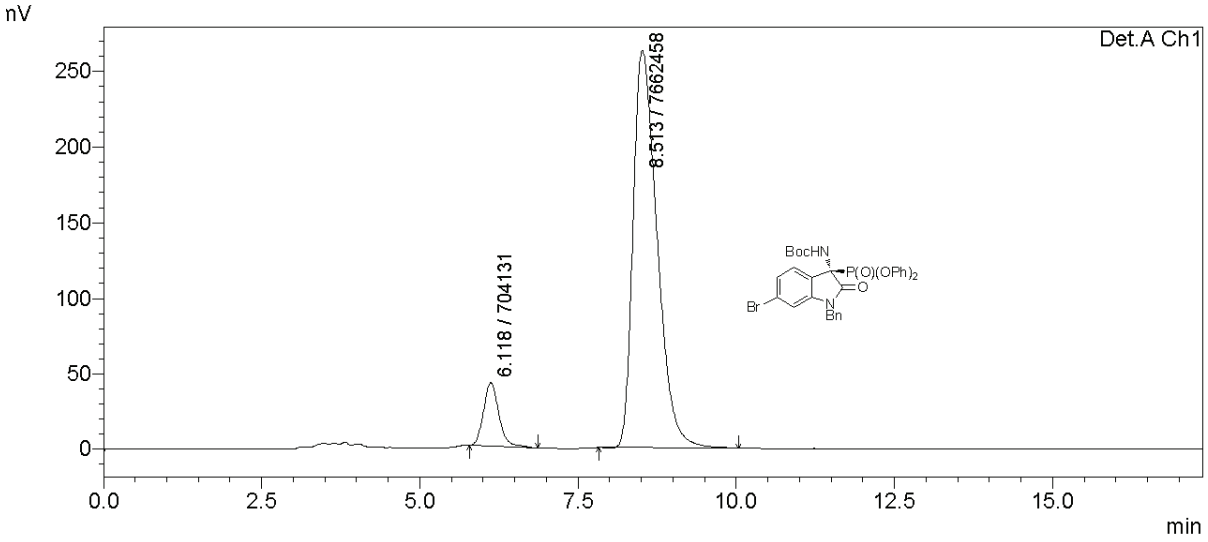
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.080	11163126	645801	44.744	58.169
2	8.445	13785663	464410	55.256	41.831
Total		24948790	1110211	100.000	100.000

HPLC chromatogram of racemic **4l**



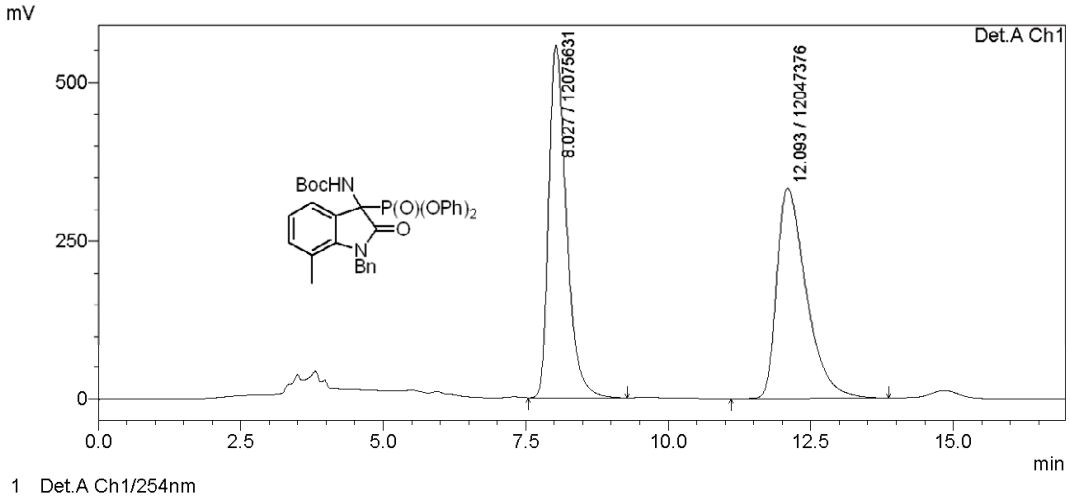
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.118	704131	41833	8.416	13.718
2	8.513	7662458	263121	91.584	86.282
Total		8366589	304954	100.000	100.000

HPLC chromatogram of enantioenriched **4l**

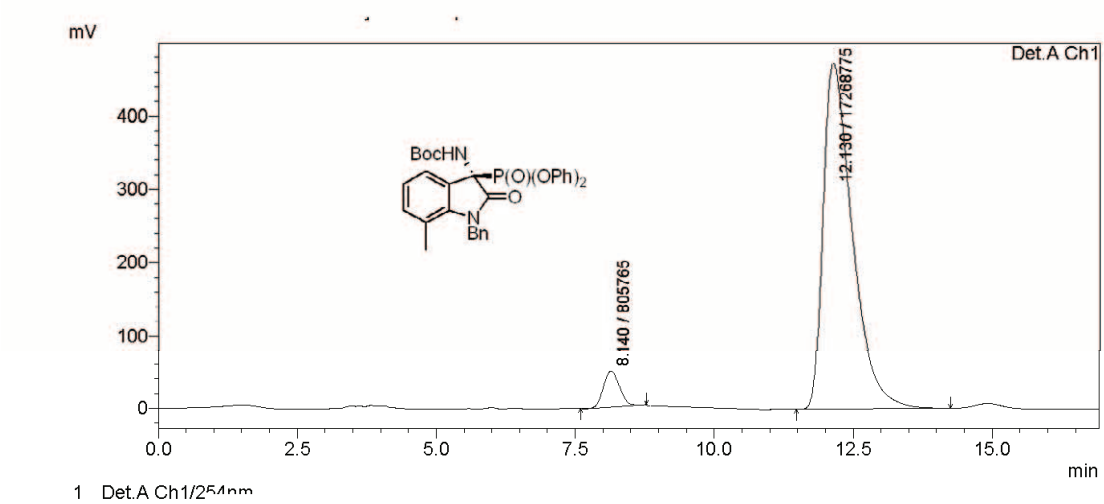


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.027	12075631	557175	50.059	62.540
2	12.093	12047376	333731	49.941	37.460
Total		24123007	890906	100.000	100.000

HPLC chromatogram of racemic **4m**

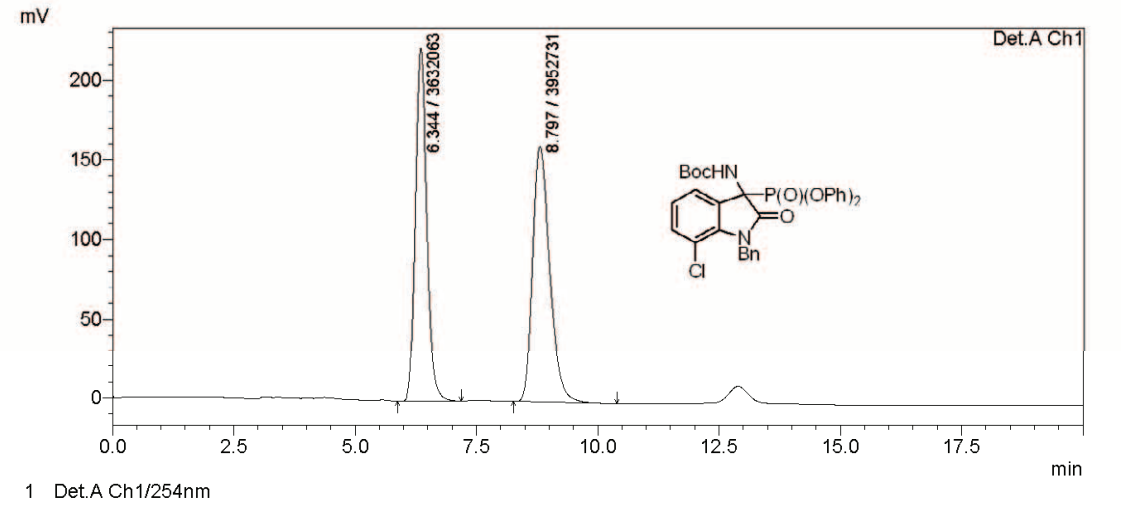


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.140	805765	45116	4.458	8.701
2	12.130	17268775	473428	95.542	91.299
Total		18074540	518545	100.000	100.000

HPLC chromatogram of enantioenriched pound **4m**



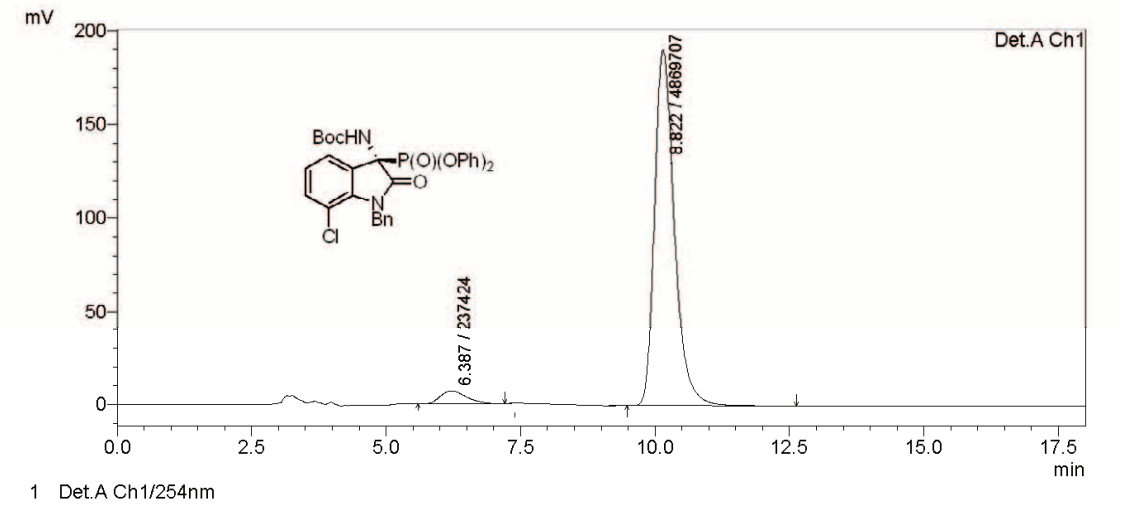
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.344	3632063	222091	47.886	57.940
2	8.797	3952731	161222	52.114	42.060
Total		7584794	383313	100.000	100.000

HPLC chromatogram of racemic **4n**



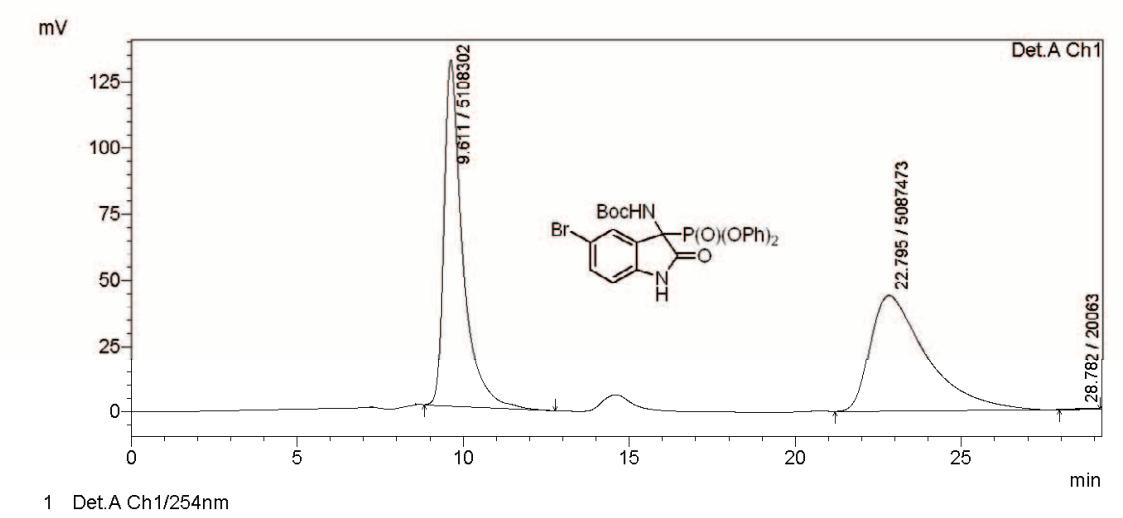
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.387	237424	6937	4.649	3.512
2	8.822	4869707	190562	95.351	96.488
Total		5107131	197499	100.000	100.000

HPLC chromatogram of enantioenriched **4n**

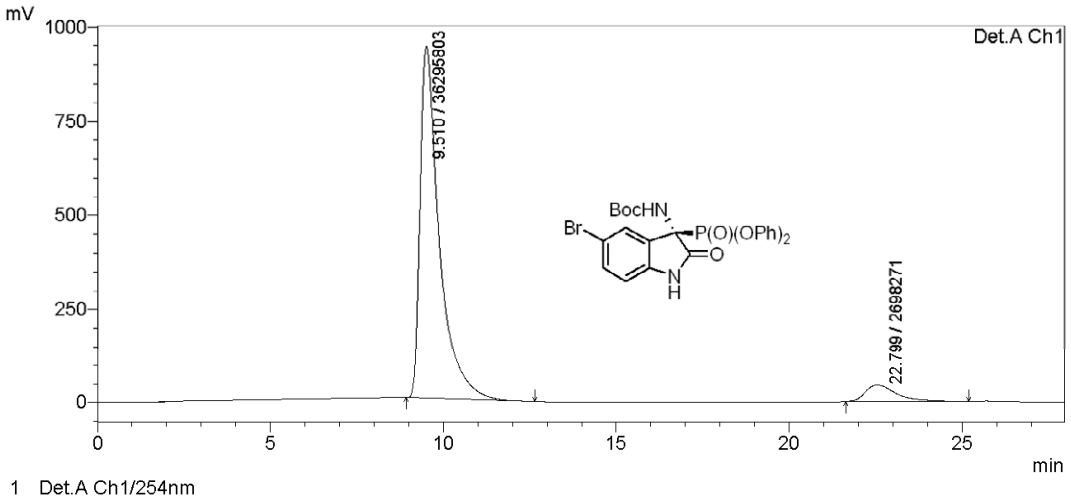


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.611	5108302	130834	50.004	74.700
2	22.795	5087473	43837	49.800	25.029
3	28.782	20063	475	0.196	0.271
Total		10215838	175146	100.000	100.000

HPLC chromatogram of racemic **4o**

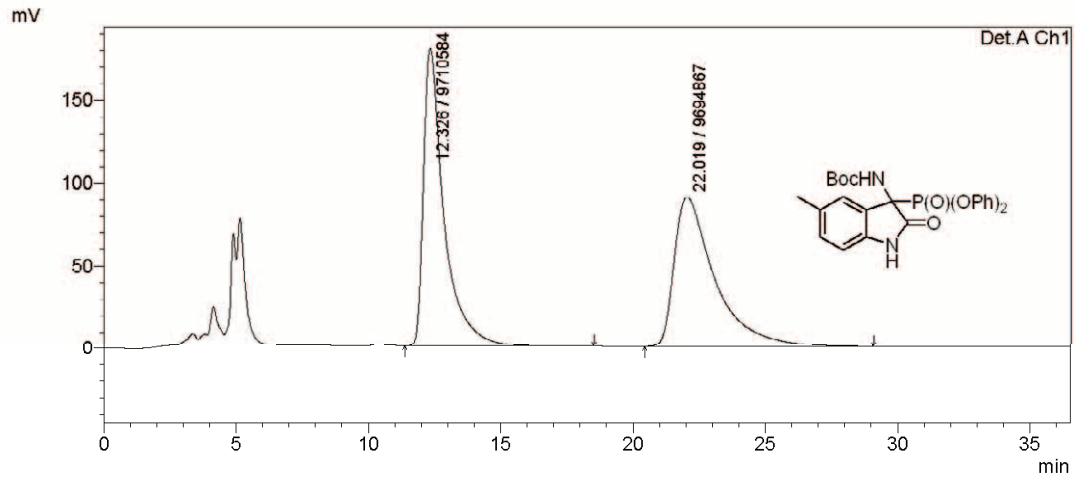


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.510	36295803	937701	93.080	95.591
2	22.799	2698271	43254	6.920	4.409
Total		38994074	980955	100.000	100.000

HPLC chromatogram of enantioenriched **4o**



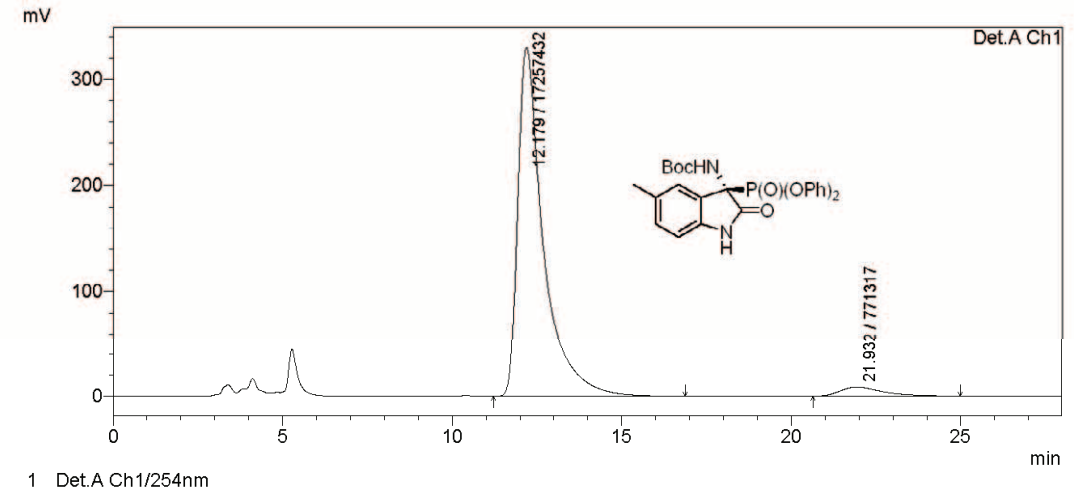
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.326	9710584	180085	50.040	66.565
2	22.019	9694867	90455	49.960	33.435
Total		19405451	270541	100.000	100.000

HPLC chromatogram of racemic **4p**



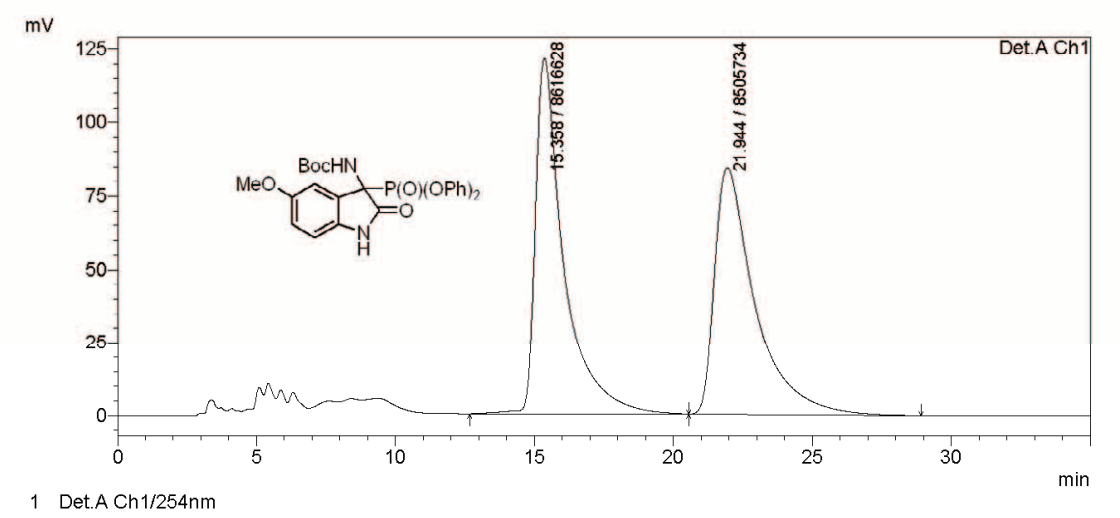
1 Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.179	17257432	330023	95.722	97.446
2	21.932	771317	8648	4.278	2.554
Total		18028748	338671	100.000	100.000

HPLC chromatogram of enantioenriched **4p**

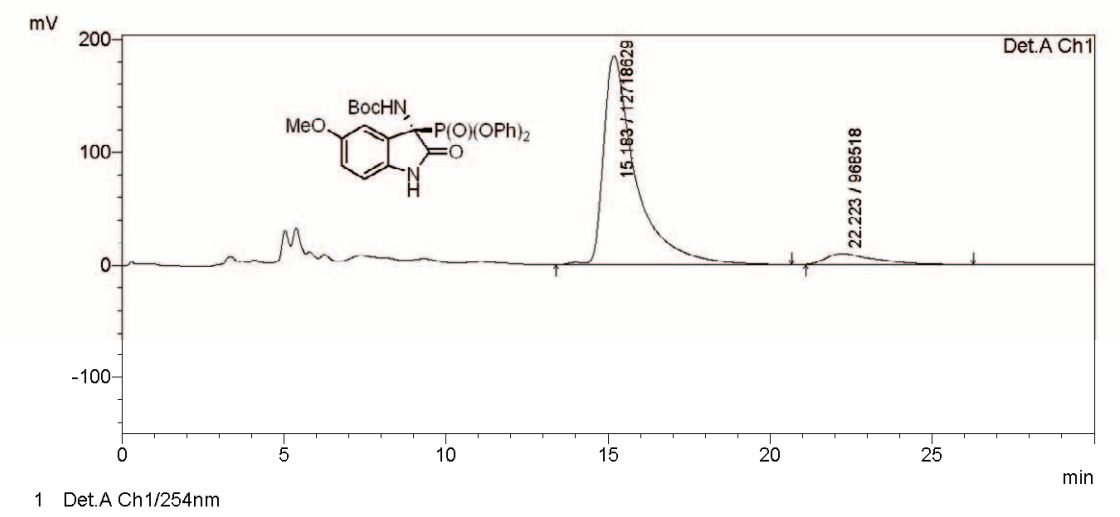


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.358	8616628	121375	50.324	59.028
2	21.944	8505734	84250	49.676	40.972
Total		17122362	205625	100.000	100.000

HPLC chromatogram of racemic **4q**

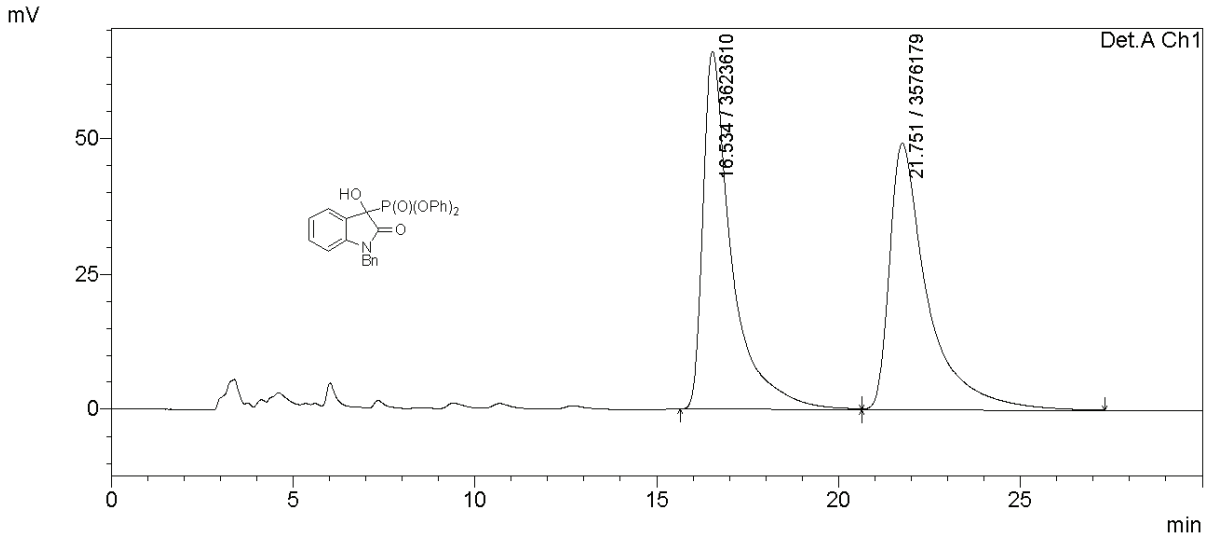


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.183	12718629	184787	92.924	95.181
2	22.223	968518	9355	7.076	4.819
Total		13687147	194142	100.000	100.000

HPLC chromatogram of enantioenriched **4q**



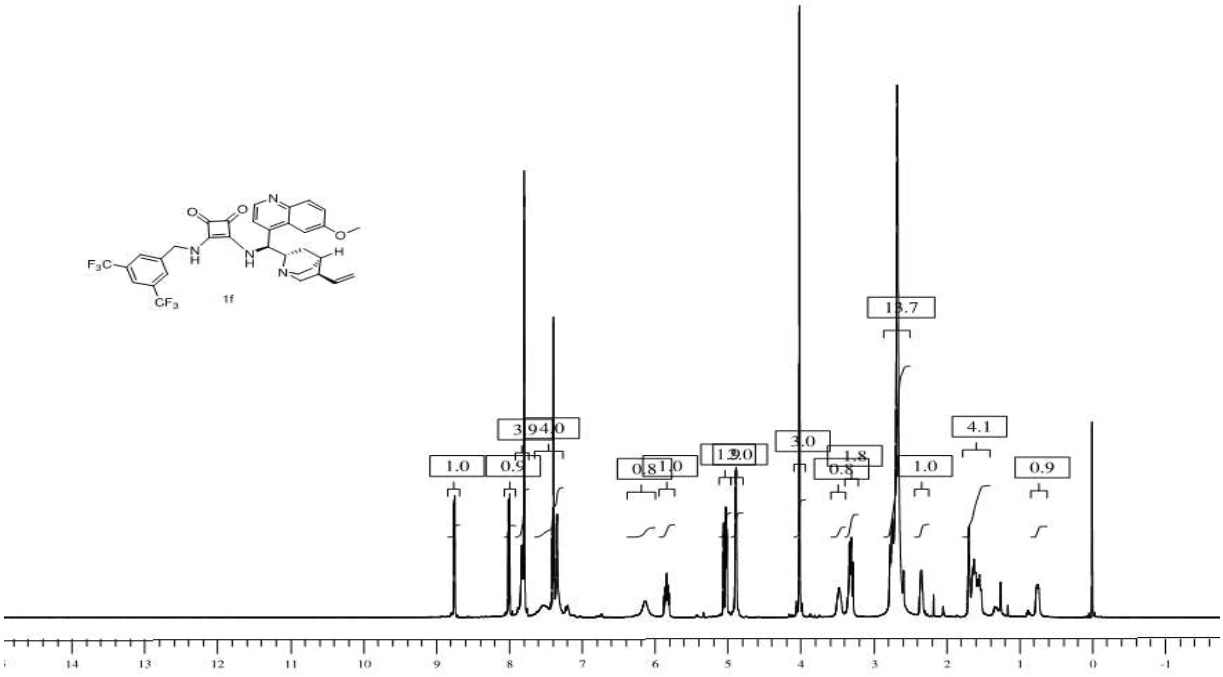
1 Det.A Ch1/254nm

PeakTable

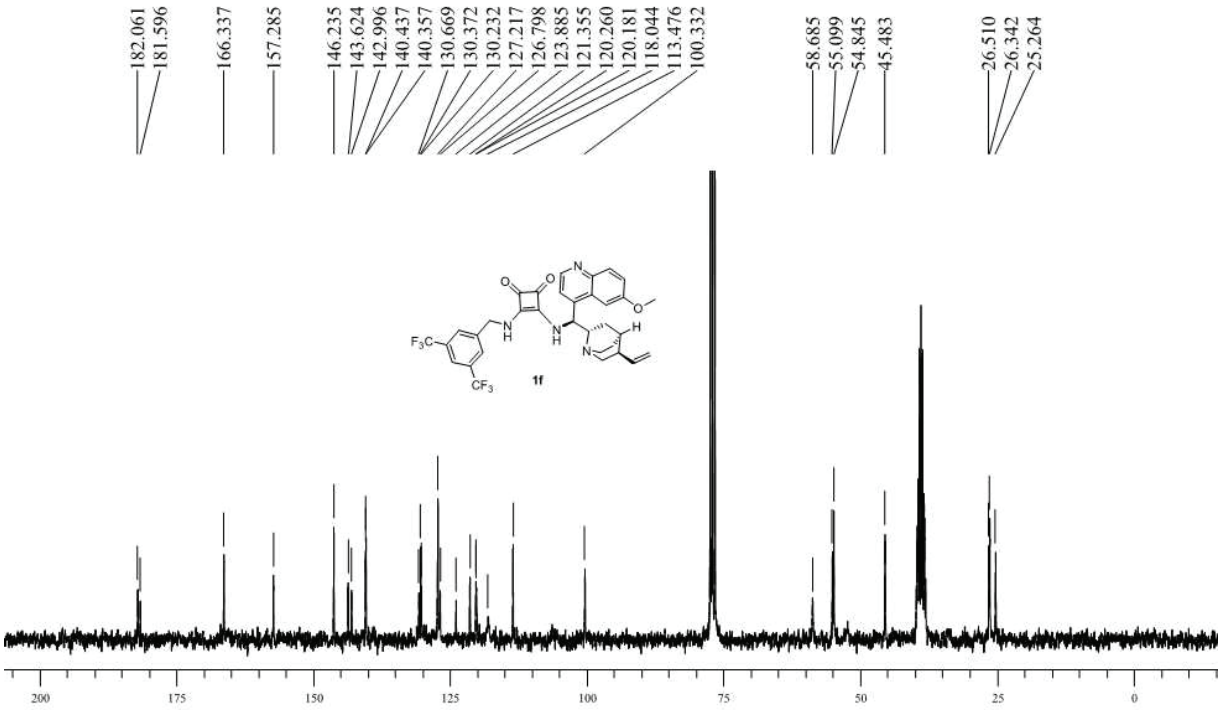
Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.534	3623610	66020	50.329	57.277
2	21.751	3576179	49244	49.671	42.723
Total		7199790	115264	100.000	100.000

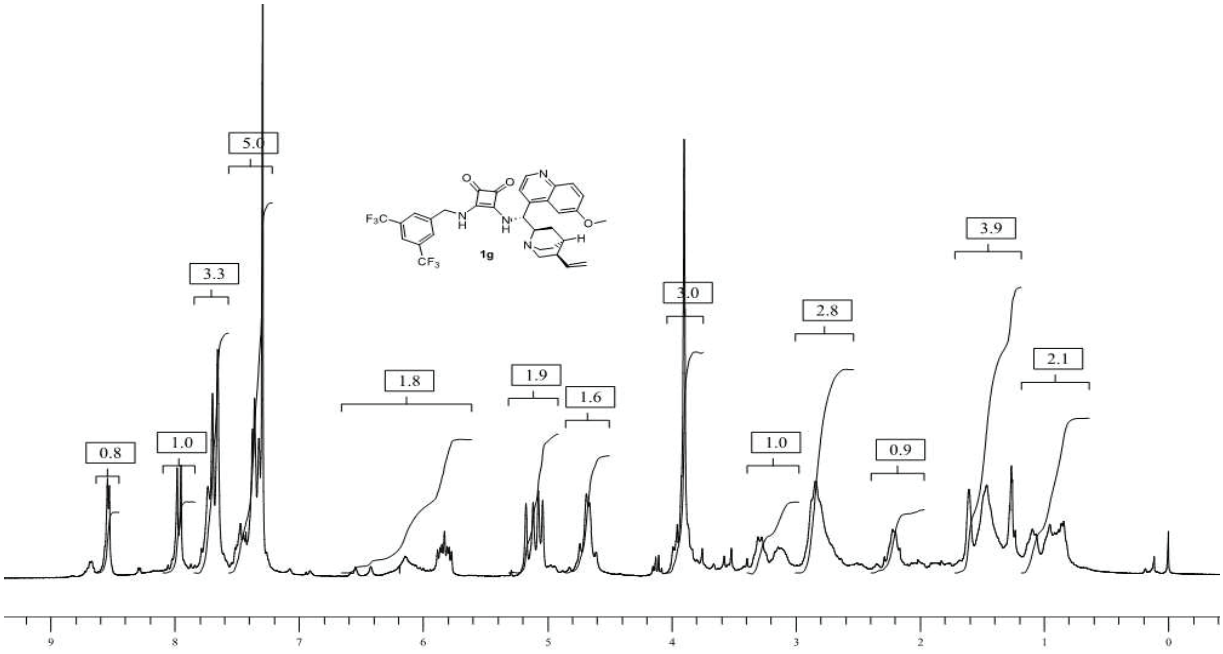
HPLC chromatogram of racemic **5**



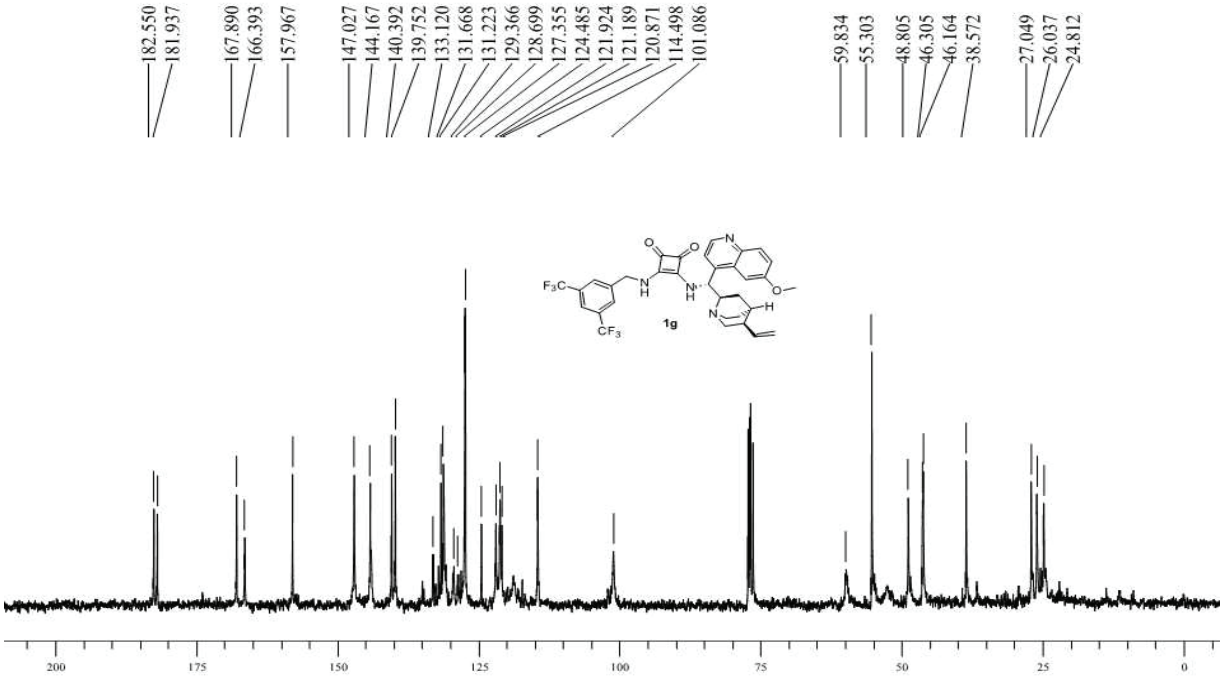
^{1}H NMR of Compound **1f** ($CDCl_3$ + DMSO-d6, 500 MHz)



^{1}H NMR of Compound **1f** ($CDCl_3$ + DMSO-d6, 75MHz)



^{1}H NMR of Compound **1g** ($CDCl_3$, 300 MHz)



^{1}H NMR of Compound **1g** ($CDCl_3$, 75MHz)