

Supplementary Information

Catalytic Atroposelective Synthesis of Axially Chiral Benzonitriles via Chirality Control during Bond Dissociation and CN Group Formation

Ya Lv,¹ Guoyong Luo,² Qian Liu,¹ Zhichao Jin,^{1*} Xinglong Zhang^{4*} and Yonggui Robin Chi^{1,3*}

¹State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China.

²School of Pharmacy, Guizhou University of Traditional Chinese Medicine, Huaxi District, Guiyang 550025, China.

³Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

⁴Institute of High Performance Computing, A*STAR (Agency for Science, Technology and Research), Singapore 138632, Singapore.

*Corresponding authors e-mails:

zcjin@gzu.edu.cn

Zhang_Xinglong@ihpc.a-star.edu.sg

robinchi@ntu.edu.sg.

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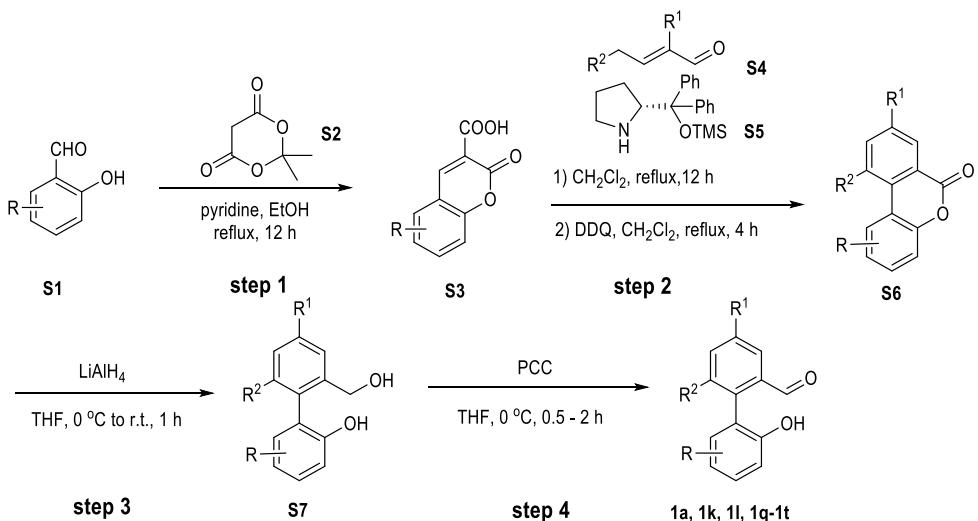
Supplementary Methods

General information

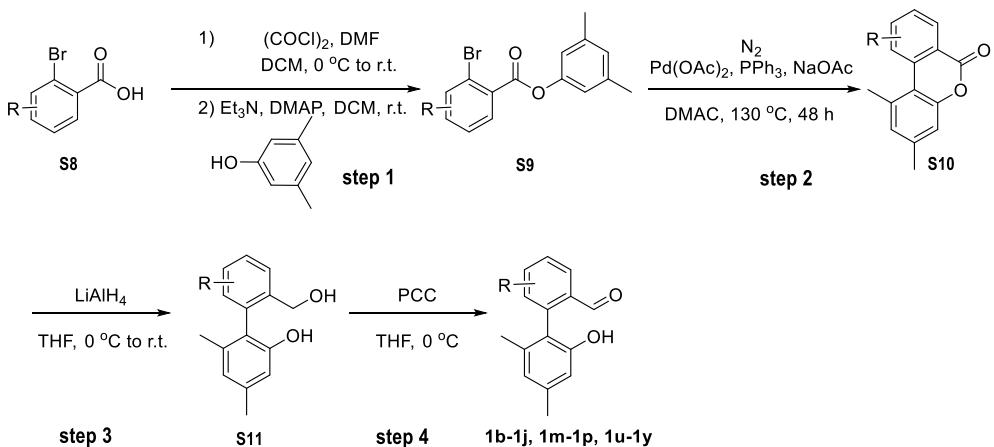
Commercially available materials purchased from Energy Chemical were used as received. Unless otherwise specified, all reactions were prepared using 4.0 mL vial under N₂ atmosphere in glove-box from UNILAB SP. NMR spectra were recorded on a Brüker ASCEND 400 (400 MHz) spectrometer (¹H: 400 MHz, ¹³C: 101 MHz, ¹⁹F: 377 MHz, ³¹P: 162 MHz). Chemical shifts (δ) for ¹H and ¹³C NMR spectra are given in ppm relative to TMS. The residual solvent signals were used as references for ¹H and ¹³C NMR spectra and the chemical shifts converted to the TMS scale (CDCl₃: δ H = 7.26 ppm, δ C = 77.16 ppm; Acetone-*d*₆: δ H = 2.05 ppm, δ C = 206.26, 29.84 ppm; DMSO-*d*₆: δ H = 2.50 ppm, δ C = 39.52 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, and etc. All first-order splitting patterns were assigned on the base of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). High resolution mass spectrometer analysis (HRMS) was performed on Thermo Fisher Q Exactive mass spectrometer. HPLC analyses were measured on Waters systems with Empower 3 system controller, Alliance column heater, and 2998 Diode Array Waters 2489 UV/Vis detector. Chiralcel brand chiral columns from Daicel Chemical Industries were used with models IA, IB, IC, AD-H, AS-H or OD-H in 4.6 x 250 mm size. UPLC analyses were measured on Waters systems with Empower 3 system controller, Waters UPLC H-Class, and Waters ACQUITY UPLC PDA detector. Chiralcel brand chiral columns from Daicel Chemical Industries were used with models IA-U, IB-U, IC-U, or OD-3 in 3.0 x 100 mm size. Optical rotations were measured on a Insmark IP-digi Polarimeter in a 1 dm cuvette. The concentration (*c*) is given in g / 100 mL. Melting point (m.p.): melting points were measured on a Beijing Tech Instrument X-4 digital display micro melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was carried out on pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

Synthesis of substrates¹

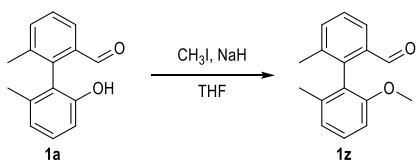
Method A:



Method B:



Method C:



Supplementary Figure 1. Synthetic route of substrates

Method A:

step 1: To a solution of **S1** (5.0 g, 36.7 mmol) in ethanol (50.0 mL), **S2** (36.7 mmol) and a catalytic amount of pyridine (0.1 mL) were in sequence added. The reaction mixture was stirred at 80 °C for 4 h. The mixture was allowed to cool to room temperature before being stirred at 0 °C for another hour. The solid which precipitated

out of solution was filtered off, washed thoroughly with ethanol and dried in vacuo to afford the desired acids **S3**.

step 2: To a solution of **S3** (24.5 mmol) in dichloromethane (50 mL), aldehydes **S4** (36.7 mmol) and catalyst **S5** (1.6 g, 4.9 mmol) were added. The reaction mixture was allowed to reflux for 12 h, followed by addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (11.1 g, 49.0 mmol). After 4 h, the reaction mixture was cooled to room temperature and filtered through celite to remove insoluble solids. The filtrate was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (50:1 petroleum ether / EtOAc) to afford lactones **S6**.

step 3: To a solution of **S6** (3.0 g, 36.7 mmol) in THF (5 mL / mmol **S6**) at 0 °C was added LiAlH₄ (1.2 e.q.) slowly. The solution was warmed to room temperature and stirred for 1h, then the reaction mixture was quenched carefully with 2 M HCl, extracted with ethyl acetate, and dried over Na₂SO₄. The solvent was removed in vacuo and the residue was chromatographed on silica gel (5:1 petroleum ether / EtOAc)) to give the alcohols **S7**.

step 4: 1.5 equivalents of pyridinium chlorochromate and 1.0 g of silica gel were added in portions at 0 °C to a solution of the **alcohols S7** in THF (5.0 mL / mmol **S7**). After stirring at 0 °C for 0.5 to 2.0 h, the reaction mixture was filtered through celite to remove insoluble solids. The filtrate was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (10:1 petroleum ether / EtOAc) to afford the hydroxy aldehydes.

Method B:

step 1: To a suspension of 1.0 equivalent of 2-bromo-3-methylbenzoic acids **S8** in dry dichloromethane (10.0 mL / 0.75 mmol **S8**) and 5 drops of DMF as catalyst, 1.1 equivalents of oxalyl chloride was added at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for another 3 h. This solution was added dropwise to a solution of 1.0 equivalent of phenol and 1.5 equivalents of triethylamine dissolved in dichloromethane (10.0 mL / 0.75 mmol **S8**), to which have been added 0.05 equivalents

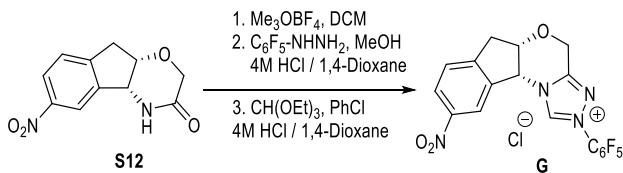
of *N*, *N*-dimethylpyridin-4-amine as catalyst. Then the mixture is stirred at room temperature for 3 h. After evaporation of the solvent under reduced pressure, the residue is chromatographed to yield the esters **S9**.

step 2: A mixture of the esters **S9** (1.0 equiv.), Pd(OAc)₂ (0.1 equiv.), PPh₃ (0.2 equiv.), and NaOAc (2.0 equiv.) were added to *N,N*-dimethylacetamide (DMAC ,7.5 mL / mmol), and the reaction mixture was heated to 130 °C under N₂ atmosphere. After 24 h, the reaction mixture was cooled to room temperature and filtered through celite to remove insoluble solids. The filtrate was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (50:1 petroleum ether / EtOAc) to afford lactones **S10**. The **step 3** and **step 4** were shown in Method A.

Method C:

To a solution of **1a** (1.33 mmol, 300.0 mg) in THF (20.0 mL) at 0 °C, NaH (1.59 mmol, 60% dispersion in mineral oil, 63.6 mg) was added slowly, then CH₃I (1.46 mmol, 207.0 mg) was added. The mixture was warmed to room temperature and stirred for 1 h, then quenched carefully with 1 M HCl, extracted with ethyl acetate, and dried over Na₂SO₄. The solvent was removed in vacuo and the residue was chromatographed on silica gel (20:1 petroleum ether / EtOAc)) to give **1z** (95% yield, 303.0 mg).

Synthesis of NHC-**G**



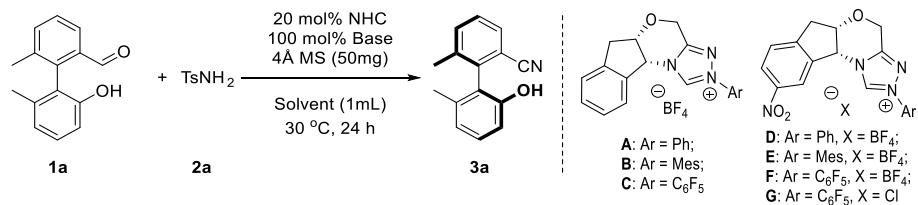
Supplementary Figure 2. Synthetic route of NHC-**G**

To a solution of **S12** (8.5 mmol, 2.0 g) in DCM (50.0 mL) was added Me_3OBF_4 (1.4g, 9.5 mmol), and the mixture was stirred at room temperature for 12 h. Then, the residue was washed with saturated NaHCO₃ (3 × 50.0 mL), separation, $\text{C}_6\text{F}_5\text{-NHNH}_2$

(8.5 mmol, 1.69 g) and 4 M HCl / Dioxane (0.2 mL) was added, and the mixture was stirred at 60 °C for 1 h. The mixture was concentrated in vacuo, and the residue was dissolved in PhCl (20.0 mL) followed by the addition of (EtO)₃CH (68.5 mmol, 11.5 mL) and 4M HCl / Dioxane (5.0 mL). The mixture was heated at 130 °C for 4 h. The solvent was removed on a rotary evaporator, the crude product was purified by column chromatography (50:1 DCM / MeOH) to give **G** in an overall 20.3% yield (800.0 mg).

Condition optimization

Supplementary Table 1. Condition optimization for the synthesis of **3a**^a

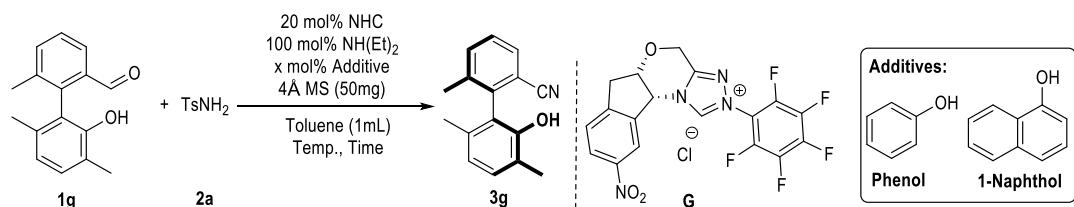


Entry	NHC	Base	Solvent	Yield (%) ^b	er (%) ^c
1	A	Cs ₂ CO ₃	Toluene	95	80:20
2	B	Cs ₂ CO ₃	Toluene	92	60:40
3	C	Cs ₂ CO ₃	Toluene	94	61:39
4	D	Cs ₂ CO ₃	Toluene	24	89:11
5	E	Cs ₂ CO ₃	Toluene	65	60:40
6	F	Cs ₂ CO ₃	Toluene	89	90:10
7	G	Cs ₂ CO ₃	Toluene	97	90:10
8	G	NaOH	Toluene	41	96:4
9	G	CsOAc	Toluene	28	92:8
10	G	K ₂ CO ₃	Toluene	46	96:4
11	G	Na ₂ CO ₃	Toluene	18	96:4
12	G	TEA	Toluene	57	97:3
13	G	DIEA	Toluene	36	97:3
14	G	DABCO	Toluene	49	97:3
15	G	NH(Et) ₂	Toluene	96	98:2
16	G	DBU	Toluene	82	79:21
17	G	NH(i-Pr) ₂	Toluene	84	97:3
18	G	NH(Et) ₂	PhCF ₃	89	95:5
19	G	NH(Et) ₂	PhCl	88	96:4
20	G	NH(Et) ₂	Mesitylene	92	97:3
21	G	NH(Et) ₂	PhOMe	94	96:4
22	G	NH(Et) ₂	EA	75	94:6
23	G	NH(Et) ₂	THF	62	91:9

24	G	NH(Et) ₂	CHCl ₃	91	97:3
25	G	NH(Et) ₂	CH ₂ Cl ₂	93	94:6
26	G	NH(Et) ₂	MeCN	70	75:25
27	G	NH(Et) ₂	MTBE	90	93:7
28 ^d	G	NH(Et) ₂	Toluene	87	98:2
29 ^e	G	NH(Et) ₂	Toluene	78	98:2

^a General conditions (unless otherwise specified): **1a** (0.10 mmol), **2a** (0.11 mmol), NHC-**G** (0.02 mmol), base (0.10 mmol), 4Å MS (50 mg) and solvent (1.0 mL) at 30 °C for 24 h. ^b Yields of isolated products after column chromatography. ^c The er values of **3a** were determined by HPLC using a chiral stationary phase. ^d NHC-**G** (0.01mmol). ^e without 4Å MS.

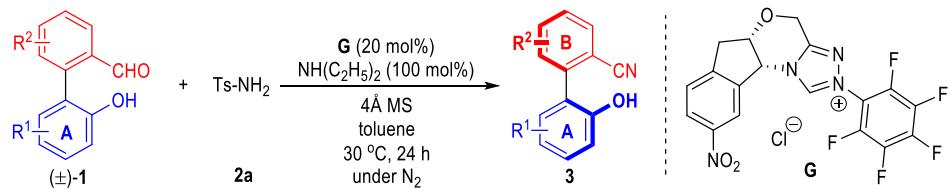
Supplementary Table 2. Condition optimization for the synthesis of **3g**^a



Entry	Additive (mmol%)	Temp.	Time	Yield (%) ^b	er (%) ^c
1	--	30 °C	12 h	92	89:11
2	Phenol (0.2)	30 °C	12 h	97	88:12
3	1-Naphthol (0.2)	30 °C	24 h	96	93:7
4	1-Naphthol (0.4)	30 °C	24 h	96	93:7
5	1-Naphthol (0.5)	30 °C	24 h	95	93:7
6	1-Naphthol (1.0)	30 °C	24 h	98	93:7
7	1-Naphthol (0.2)	0 °C	24 h	82	95:5
8	1-Naphthol (0.2)	0 °C	36 h	97	95:5

^a General conditions (unless otherwise specified): **1g** (0.10 mmol), **2a** (0.11 mmol), NHC (0.02 mmol), base (0.10 mmol), additive (0.20-1.00 mmol) 4Å MS (50 mg) and solvent (1.0 mL) at 30 °C for 24 h. ^b Yields of isolated products after column chromatography. ^c The er values of **3g** were determined by HPLC using a chiral stationary phase.

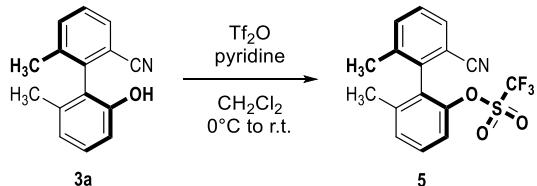
General procedure for the catalytic reactions



To a 4.0 mL oven-dried vial equipped with a magnetic stir bar was added chiral NHC pre-catalyst **G** (0.02 mmol, 9.2 mg), 4 Å molecular sieves (50 mg), substrates **1** (0.10 mmol) and **2a** (0.11 mmol). Then dried toluene (1.0 mL) and $\text{NH}(\text{C}_2\text{H}_5)_2$ (0.10 mmol, 10.3 μL) was added via syringe in a glove box under N_2 atmosphere. Then the reaction mixture was stirred for 24 hours at 30 °C and then subjected to column chromatography on silica gel (10:1 petroleum ether / EtOAc) directly to give the desired pure products **3** in 62% to 99% isolated yields.

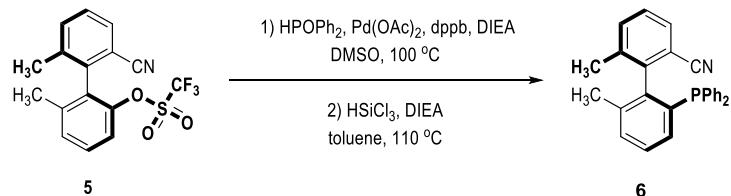
Synthetic transformations of axially chiral products and their applications

General procedure for the enantioselective synthesis of (**5**)



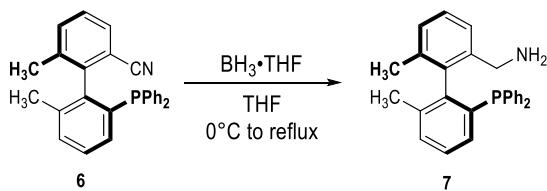
To a Schlenk tube was added **3a** (0.67 mmol, 150.0 mg) and the tube was closed with a septum. The reaction tube was evacuated and backfilled with N_2 for 3 times and then anhydrous dichloromethane (5.0 mL) and pyridine (0.81 mmol, 63.8 mg) were added via syringe. The resulting solution was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.81 mmol 227.5 mg) was slowly added. After that the reaction mixture was raised to room temperature and stirred for 2 h. Then the reaction mixture was directly subjected to column chromatography eluting with CH_2Cl_2 to give the pure product **5** in 90% yield (213.6 mg, 97:3 er).

General procedure for the enantioselective synthesis of (6)



A mixture of the triflate **5** (0.60 mmol, 213.6 mg), HP(O)Ph₂ (1.30 mmol, 263.8 mg), Pd(OAc)₂ (0.05 mmol, 6.8 mg), dppb (0.05 mmol, 12.8 mg) and DIEA (3.08 mmol, 510.0 µL) in DMSO (2.0 mL) was heated to 100 °C and stirred for 3 h under N₂. Then the reaction mixture was cooled to room temperature and concentrated in vacuum. Ethyl acetate (30.0 mL) was added and the solution was washed with H₂O (3 × 10.0 mL), dried over Na₂SO₄ and the solvent was removed in vacuum. The residue containing phosphine oxide was used directly subjected to a flame-dried Schlenk tube and was evacuated and backfilled with N₂ for 3 times. Anhydrous toluene (2.0 mL) and DIEA (15.73 mmol, 2.6 mL) were then added via syringe and the mixture was treated with HSiCl₃ (5.24 mmol, 530.0 µL,) at room temperature. Then the reaction was heated to reflux with stirring for 2 h. After cooling to room temperature, saturated NaHCO₃ aqueous solution was added to quench the reaction and the resulting precipitate was removed by filtration over celite and washed with diethyl ether (3 × 10.0 mL). The combined organic layer was separated and dried over MgSO₄. After concentration under vacuum, the residue was purified via SiO₂ flash chromatography (20:1 petroleum ether / EtOAc) to afford the pure product **6** in 73% yield (170.7 mg, 97:3 er). The product **6** was recrystallized from CH₂Cl₂ / petroleum ether to further improve its optical purity (> 99:1 er value) before subjecting to the following steps.

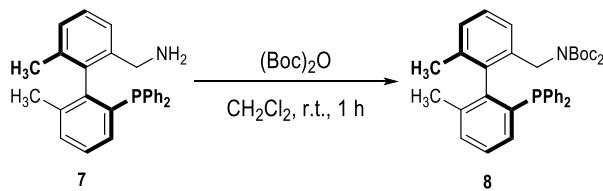
General procedure for the enantioselective synthesis of 7 (11, 18)



To a cooled solution of **6** (0.26 mmol, 100.0 mg) in dry THF (15.0 mL) at 0 °C was added borane-tetrahydrofuran (0.91 mmol, 1 M in THF, 3.6 mL) dropwisely. The

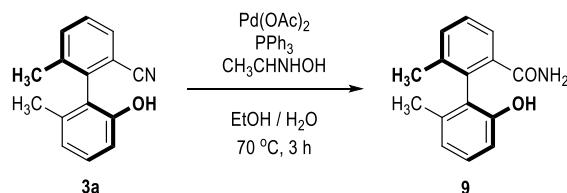
solution was then raised to room temperature and stirred for 1h. After that the reaction was gradually heated to 70 °C over 30 min and stirred under reflux for 30 min. Then the mixture was cooled to 0 °C and MeOH (5.0 mL) was slowly added to quench the reaction. The resulting solution was stirred at room temperature for 20 min and concentrated under reduced pressure. The residue was dissolved in THF (20.0 mL) and 1 M HCl (5.0 mL) was added. The mixture was stirred for 5 min at room temperature and then heated to reflux with stirring for 2 min. The solution was then cooled to room temperature and poured into saturated aqueous NaHCO₃ (20.0 mL). After removing the organic solvent in vacuo, the aqueous mixture was extracted with CH₂Cl₂ (3 × 20.0 mL) and dried over Na₂SO₄. After concentration, the residue was purified by column chromatography eluting with Et₃N / MeOH / CH₂Cl₂ (1:10:100) to give the product **7** in 80% yield (81.0 mg).

General procedure for the enantioselective synthesis of (8)



A mixture of **7** (0.05 mmol, 20.0 mg), (Boc)₂O (0.10 mmol, 22.1 mg), *N,N*-dimethylpyridin-4-amine (0.001 mmol, 1.3 mg) was stirred in CH₂Cl₂ (1.0 mL) at room temperature for 1 h. Then the mixture was concentrated in vacuo and the resulting residue was purified via column chromatography on silica gel (20:1 petroleum ether / EtOAc) to give **8** in 94% yield (28.4 mg, >99:1 er).

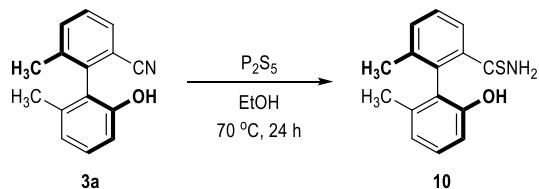
General procedure for the enantioselective synthesis of (9)



A mixture of **3a** (0.20 mmol, 44.7 mg), acetaldehyde oxime (1.60 mmol, 94.4 mg), Pd(OAc)₂ (0.02 mmol, 0.9 mg), and PPh₃ (0.02 mmol, 1.0 mg) was dissolved in EtOH /

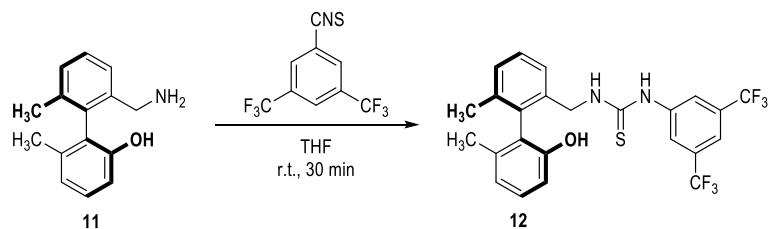
H_2O (0.8 mL / 0.2 mL) and stirred at 70 °C for 3 h. Then the mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was purified via column chromatography on silica gel (3:1 petroleum ether / EtOAc) to give **9** in 93% yield (47.8 mg, 96:4 er).

General procedure for the enantioselective synthesis of (**10**)



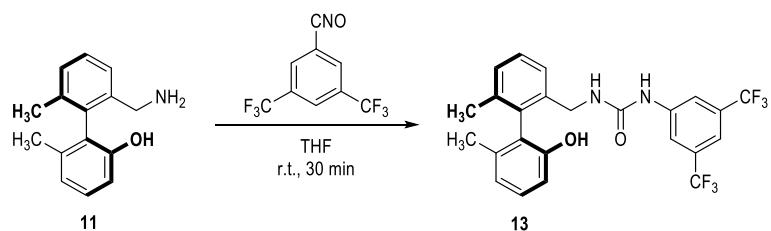
A solution of P_2S_5 (0.60 mmol, 133.4 mg) in ethanol (2.0 mL) was stirred at room temperature for 1 h. Then **3a** (0.20 mmol, 44.7 mg) was added and the reaction mixture was stirred at 70 °C for 24 h. After removing the solvent, the residue was purified via column chromatography (5:1 petroleum ether / EtOAc) to give **10** in 83% yield (42.8 mg, 98:2 er).

General procedure for the enantioselective synthesis of (**12**)



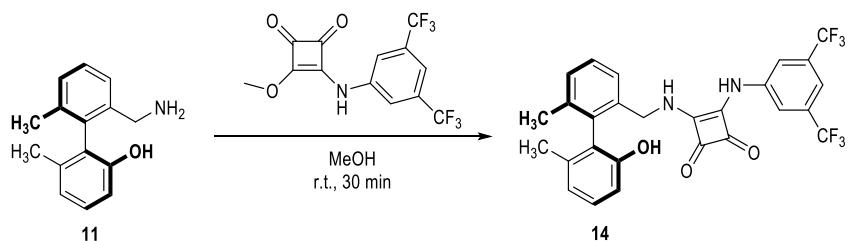
To a solution of **9** (0.18 mmol, 40.0 mg) in THF (2.0 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.18 mmol, 47.7 mg). The reaction was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was subjected to column chromatography on silica gel (6:1 petroleum ether / EtOAc) to give the product **11** in 90% yield (79.0 mg, 98:2 er).

General procedure for the enantioselective synthesis of (13)



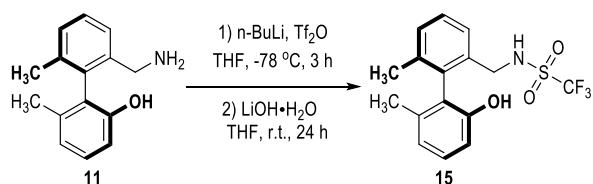
To a solution of **11** (0.18 mmol, 40.0 mg) in THF (2.0 mL) was added 3,5-bis(trifluoromethyl)phenyl isocyanate (0.18 mmol, 45.0 mg). The reaction was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was subjected to column chromatography on silica gel (6:1 petroleum ether / EtOAc) to give the product **13** in 66% yield (56.0 mg, 98:2 er).

General procedure for the enantioselective synthesis of (14)



To a solution of **11** (0.10 mmol, 22.7 mg) in MeOH (1.0 mL) was added 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (0.10 mmol, 33.9 mg). The reaction was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was subjected to column chromatography on silica gel (3:1 petroleum ether / EtOAc) to give the product **14** in 95% yield (51.0 mg, 96:4 er).

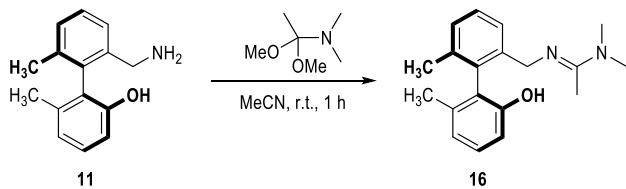
General procedure for the enantioselective synthesis of (15)



To a solution of amine **11** (0.43 mmol, 130.0 mg) in THF (8.0 mL) at -78 °C was added *n*-BuLi (0.87 mmol, 1.6 M in hexane, 540.0 µL). After stirring for 30 min at -78 °C,

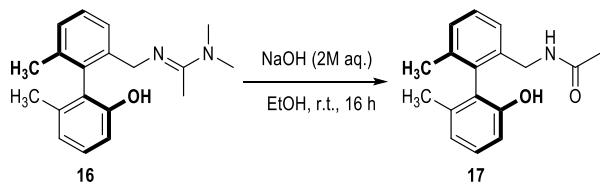
trifluoromethanesulfonic anhydride (0.87 mmol) was slowly added into the mixture and the reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for an additional 2 h. Then the reaction mixture was warmed to room temperature and quenched with 1 M HCl (10.0 mL). The resulting mixture was extracted with ethyl acetate (30.0 mL \times 2), washed with brine (30.0 mL), dried over Na_2SO_4 , and concentrated. The residue was dissolved in THF (10.0 mL) and a solution of LiOH H_2O (5.21 mmol, 219.0 mg) in H_2O (3.0 mL) was added. The mixture was stirred at room temperature for 24 h and then quenched with 1 M HCl (10.0 mL). The mixture was extracted with ethyl acetate (30.0 mL \times 3), washed with brine (30.0 mL \times 2), dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified via column chromatography on silica gel (6:1 petroleum ether / EtOAc) to give the product **15** in an overall 33.0% yield (67.8 mg, 97:3 er).

General procedure for the enantioselective synthesis of **16** (**19**)



To a solution of **11** (0.10 mmol, 22.7 mg) in MeCN (1.0 mL) was added 1,1-dimethoxy-*N,N*-dimethylethan-1-amine (0.11 mmol, 33.9 mg). After being stirred at room temperature for 1 h, the mixture was concentrated in vacuo. The crude residue was purified by column chromatography eluting with $\text{Et}_3\text{N} / \text{MeOH} / \text{CH}_2\text{Cl}_2$ (1:10:100) to give the product **16** in 64% yield (19.0 mg).

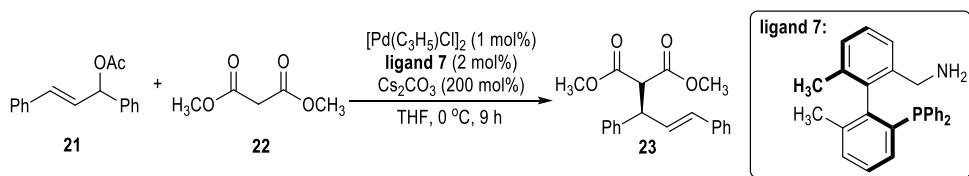
General procedure for the enantioselective synthesis of **17** (**20**)



To a stirred solution of **16** (0.10 mmol, 29.6 mg) in EtOH (0.5 mL) was added 2 M aqueous solution of NaOH (0.5 mL). After 16 h the volatiles were removed and the aqueous mixture was extracted with CH_2Cl_2 (3 \times 10.0 mL), dried over Na_2SO_4 , and

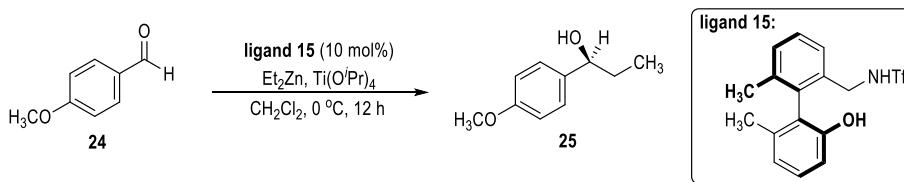
concentrated. The residue was purified by column chromatography on silica gel (5:1 to 3:1 petroleum ether / EtOAc) to give the product **17** in 92% yield (25.9 mg, 98:2 er).

General procedure for the enantioselective synthesis of (23)



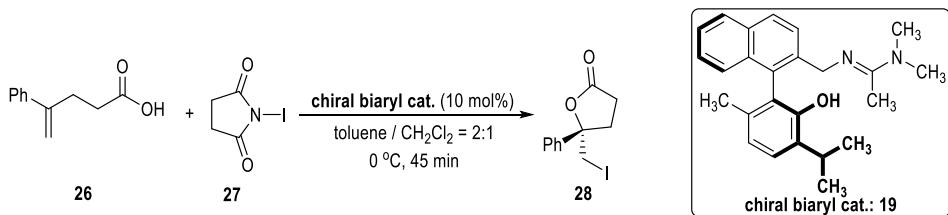
To a 4.0 mL oven-dried vial equipped with a magnetic stir bar was added chiral ligand **7** (0.002 mmol, 0.8 mg), $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ (0.001 mmol, 0.4 mg) and Cs_2CO_3 (65.2 mg, 0.2 mmol) in a glove box under N_2 atmosphere. The solution of the substrates **21** (0.15 mmol, 37.9 mg) and **22** (0.10 mmol, 13.2 mg) in dried THF (2.0 mL) was added via syringe. Then the reaction mixture was stirred at 0 °C for 9 h and then subjected to column chromatography on silica gel (20:1 petroleum ether / EtOAc) to give the product **23** in 85% yield (27.6 mg, 83:17 er).

General procedure for the enantioselective synthesis of (25)



To a solution of ligand **15** (0.015 mmol, 5.4 mg) in dichloromethane (2.0 mL) was added $\text{Ti}(\text{O}'\text{Pr})_4$ (0.60 mmol, 178.0 μL) at room temperature. After stirring for 15 min, aldehyde **24** (0.50 mmol, 60.7 μL) was added and the reaction mixture was cooled to 0 °C. Diethylzinc (0.90 mmol, 1.0 M in hexane, 0.9 mL) was slowly added into the solution and the reaction mixture was stirred for 12 h at 0 °C. Then the reaction was quenched with 1 M HCl solution (10.0 mL) and the resulting mixture was extracted with ethyl acetate (30.0 mL \times 2), washed with brine (30.0 mL \times 2), dried over MgSO_4 , and concentrated in vacuo. The residue was purified via column chromatography on silica gel (5:1 petroleum ether / EtOAc) to give the product **25** in 95% yield (78.9 mg, 76:24 er).

General procedure for the enantioselective synthesis of (**28**)



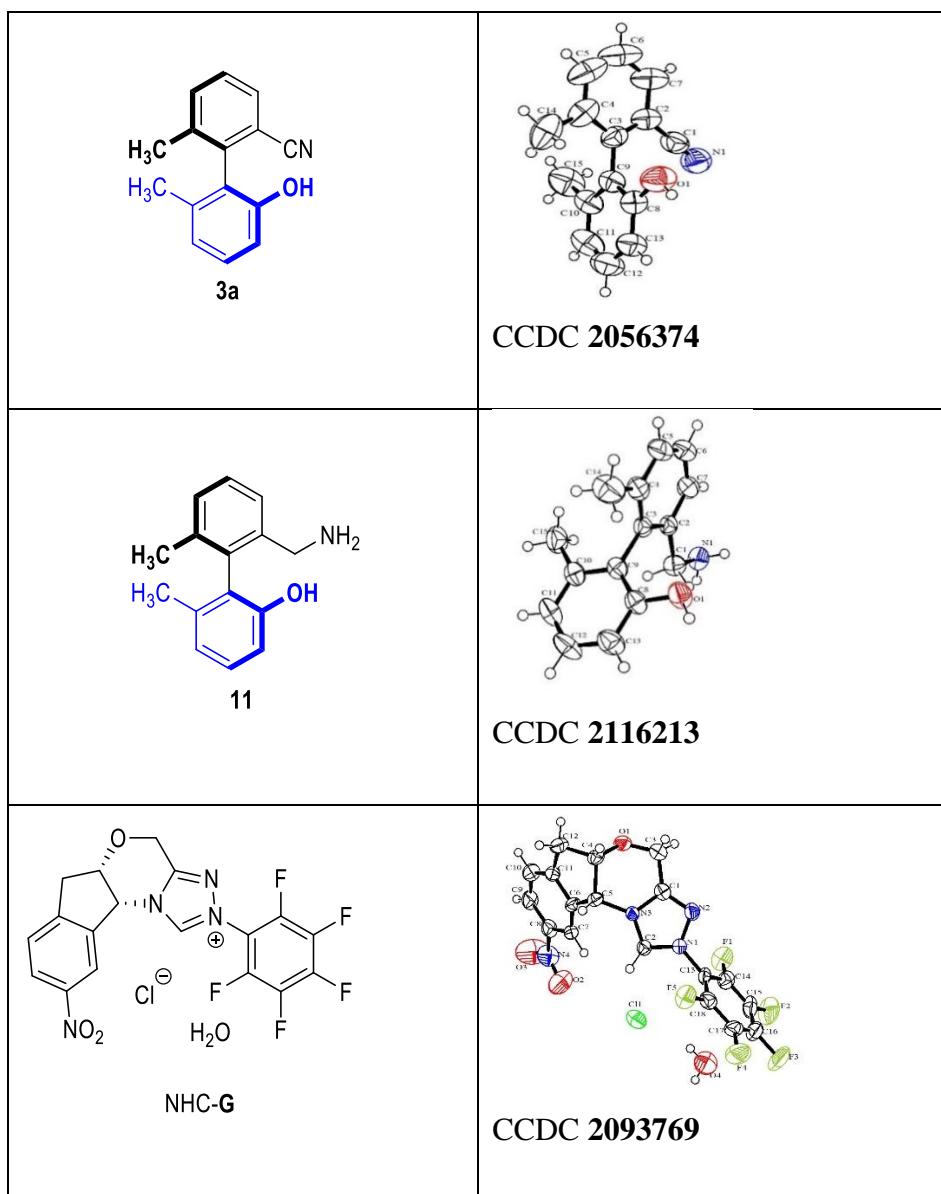
To a solution of **19** (0.10 mmol, 22.7 mg) in toluene / CH_2Cl_2 (1.0 mL / 0.5 mL) was added the carboxylic acid **26** (17.6 mg, 0.10 mmol) at 0°C . After stirring for 10 min, NIS **27** (27.0 mg, 0.12 mmol) was added and the reaction was stirred for an additional 45 min at 0°C . After concentration, the resulting residue was purified via column chromatography on silica gel (5:1 petroleum ether / EtOAc) to give the product **28** in 92% yield (27.8 mg, 74:26 er).

X-ray crystallography of compounds **3a**, **11** and **NHC-G**

Good quality crystal of **3a** (white block crystal) was obtained by vaporization of a CH_2Cl_2 / petroleum ether solution of compound **3a**. A colorless block crystal of compound **11** was obtained by vaporization of a CH_2Cl_2 / petroleum ether solution. A colorless block crystal of **NHC-G** was obtained by vaporization of dichloromethane / MeOH solution.

CCDC: **2056374**, **2116213** and **2093769** contain the supplementary X-ray crystallographic data of **3a**, **11** and **NHC-G** respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Table 3. X-ray crystallography of compounds 3a, 11 and NHC-G



Density functional theory (DFT) calculations

Computational methods

Density functional theory (DFT) calculations were performed with *Gaussian 16* rev. B.01². Geometry optimizations were performed using the M06-2X³ functional with the Karlsruhe-family basis set of double- ζ valence def2-SVP^{4,5} for all atoms. Minima and transition structures on the potential energy surface (PES) were confirmed using harmonic frequency analysis at the same level of theory, showing respectively zero and one imaginary frequency. Gibbs energies were evaluated at the reaction temperature of 30 °C, using a quasi-RRHO treatment of vibrational entropies⁶, using the Good Vibes code⁷. Vibrational entropies of frequencies below 100 cm⁻¹ were obtained according to a free rotor description, using a smooth damping function to interpolate between the two limiting descriptions. The free energies were further corrected using standard concentration of 1 mol/L, which were used in solvation calculations.

Single point (SP) corrections were performed using the domain-based local pair natural orbital – coupled cluster with perturbative triple excitations (DLPNO-CCSD(T)) calculations^{8,9} using ORCA version 5.0.1¹⁰⁻¹². T₀ approximation which neglects the couplings between different triples by the off-diagonal Fock matrix elements, instead of the recently published iterative T₁ algorithm¹³, was employed. The NormalPNO settings with T_{CutPairs} = 10⁻⁴, T_{CutDO} = 10⁻², T_{CutPNO} = 3.33 × 10⁻⁷ and T_{CutMKN} = 10⁻³ was used throughout. The TightSCF convergence with KDIIS algorithm¹⁴ for SCF iterations were used. The complete basis set (CBS) extrapolation scheme of Helgaker et al¹⁵⁻¹⁷, was performed using either the correlation-consistent double-/triple- ζ cc-pV(DT)Z basis set¹⁸⁻²⁰ or the aug-cc-pV(DT)Z²¹⁻²² basis sets, which are augmented with diffuse functions. The auxiliary basis sets required for the integral evaluations in the DLPNO-CCSD(T) correlation energy calculations were generated automatically using the “AutoAux” command from the automated auxiliary basis set construction module²³ of ORCA. DEFGRID2 grid for integration was employed throughout.

For the basis sets augmented with diffuse functions, the aug-cc-pV(DT)Z basis set produces linear dependency errors due to the addition of diffuse functions using the

“AutoAux” command, in this case, DLPNO-CCSD(T) was run separately with aug-cc-pVDZ or aug-cc-pVTZ basis set with corresponding auxiliary basis sets aug-cc-pVD(T)Z/C^{21,24} and the obtained values are extrapolated manually according to the following formulae:

$$E_{\text{SCF}}^{(X)} = E_{\text{SCF}}^{(\infty)} + A \exp(-\alpha \sqrt{X}) \quad \text{Eq (1)}$$

$$E_{\text{corr}}^{(\infty)} = \frac{X^\beta E_{\text{corr}}^{(X)} - Y^\beta E_{\text{corr}}^{(Y)}}{X^\beta - Y^\beta} \quad \text{Eq (2)}$$

for the extrapolation of HF energy (Eq (1)) and of correlation energy (Eq (2)) to the basis set limit, respectively. $E_{\text{SCF/corr}}^{(X)}$ is the SCF/correlation energy calculated with basis set of cardinal number X , and $E_{\text{SCF/corr}}^{(\infty)}$ is the basis set limit SCF/correlation energy and A , α , and β are constants. For correlation energy, X and Y are the cardinal numbers of the basis sets used for extrapolation ($X=2$, $Y=3$ herein). For Extrapolate(2/3, cc), $\alpha=4.42$, and $\beta=2.46$ and for Extrapolate(2/3, aug-cc), $\alpha=4.3$, and $\beta=2.51$.

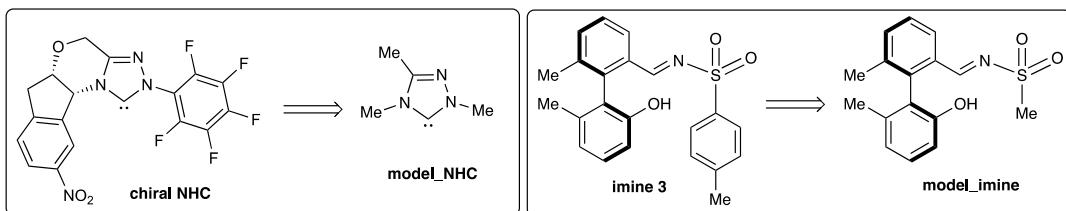
The integral equation formalism variant of the polarizable continuum model (IEF-PCM) with the SMD implicit continuum solvation model²⁵ was included to account for the solvent effect of toluene. Unless otherwise stated, the final SMD (toluene)-DLPNO-CCSD(T)/ cc-pV(DT)Z//M06-2X/def2-SVP Gibbs energies are used for discussion throughout. *All Gibbs energy values in the text and figures are quoted in kcal mol⁻¹*. All molecular structures and molecular orbitals were visualized using *PyMOL* software²⁶.

Geometries of all optimized structures (in .xyz format with their associated energy in Hartrees) are included in a separate folder named *optimised_xyz_structures* with an associated README file. All these data have been deposited and uploaded to zenodo.org (DOI: 10.5281/zenodo.5573970) under open access.

Model system calculation

To initially explore the potential energy surface of this reaction and to increase computational efficiency, we carried out a model calculation in which a model NHC and a model imine is used (Supplementary Figure 3). Note that for the model NHC used,

the reaction centre is similar as the chiral NHC catalyst used in the reaction. For the imine simplification, we note that the methanesulfinate group has similar reactivity as *p*-toluenesulfinate group. We use this model reaction to determine the key steps for the overall transformation, from which we applied the full model to the key step to determine the stereoselectivity.

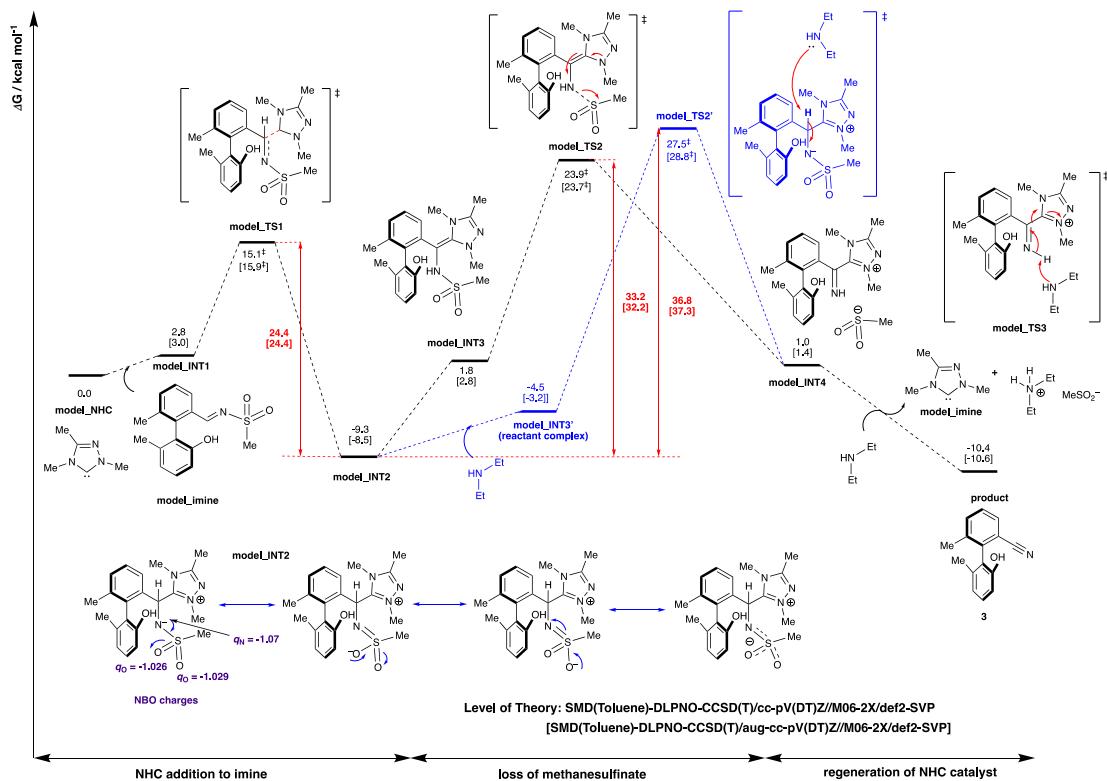


Supplementary Figure 3. Model NHC and model imine used for the calculation of Gibbs energy profile.

The full Gibbs energy profile for this model reaction is shown in Supplementary Figure 4. The Gibbs energies were calculated at SMD(Toluene)-DLPNO-CCSD(T)/CBS//M06-2X/def2-SVP, using complete basis set (CBS) extrapolation at (2/3,cc) or (2/3,aug-cc) (in square brackets) procedure as outlined in the computational methods section. The reaction proceeds with firstly the addition of NHC catalyst to the imine C=N bond, giving a highly exergonic adduct **model_INT2**, at -9.3 [-8.5] kcal mol⁻¹. This is followed by the loss of methanesulfinate anion, via transition state, **model_TS2**, at 23.9 [23.7] kcal mol⁻¹. The final deprotonation of imine intermediate via **model_TS3**, regenerates the NHC catalyst and yields the nitrile product. We note that the use of basis set augmented with diffuse functions (aug-cc-pVD(T)Z) gives similar energies (within 1 kcal mol⁻¹) as the basis set not augmented with diffuse functions (cc-pVD(T)Z), thus, for full system calculations, we use Extrapolate(2/3,cc) without diffuse functions for increased computational efficiency.

We herein focus on the steps of NHC addition and the loss of methanesulfinate since these steps are likely stereo-determining in the overall transformation of the full system as the regeneration of NHC catalyst via **model_TS3** through deprotonation is likely facile and simply carries the stereochemical information from previous steps forward. From the Gibbs energy profile in Supplementary Figure 4, we can see that the

NHC adduct, **model_INT2**, is the resting state of the catalytic cycle. The rate-limiting step is the loss of methanesulfinate, **model_TS2**, with an energetic span of 33.2 [32.2] kcal mol⁻¹ (from **model_INT2** to **model_TS2**). Moreover, the addition of NHC, **model_TS1**, is reversible, as the subsequent loss of methanesulfinate has a barrier of 33.2 [32.2] kcal mol⁻¹, which is higher than the barrier for the reversible process of adduct dissociation (going from **model_INT2** to **model_INT1**) with a barrier of 24.4 [24.4] kcal mol⁻¹. We note that this rate-limiting barrier is very high and is not consistent with the good reactivity at ambient temperature used for the reaction. We further carried out investigation of the full system to determine the energetic span for the actual system used in the reaction (*vide infra*).

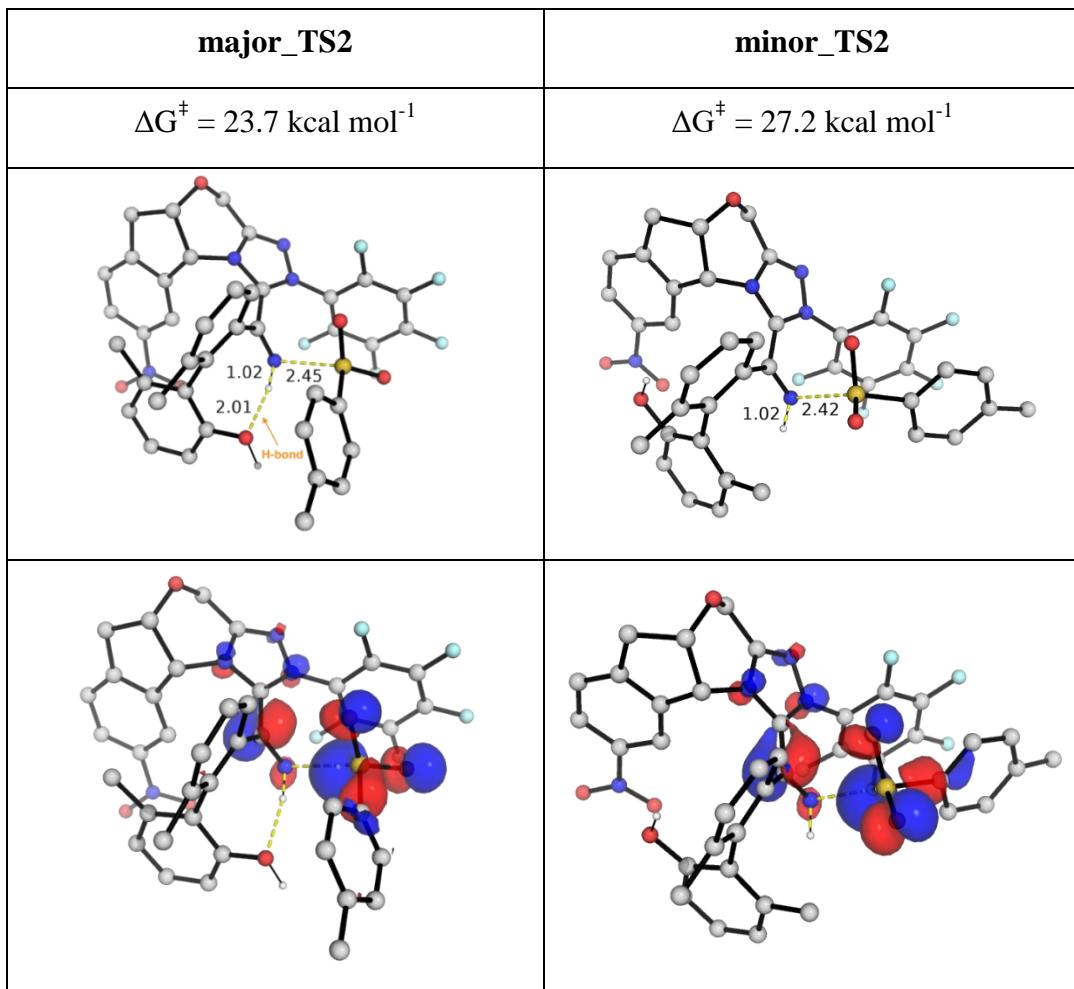


Supplementary Figure 5. Gibbs energy profile for the model reaction calculated at SMD(Toluene)-DLPNO-CCSD(T)/CBS//M06-2X/def2-SVP, using complete basis set (CBS) extrapolation at (2/3,cc) or (2/3,aug-cc) (in square brackets) procedure.

We also checked the alternative mechanism, in which the base-assisted deprotonation of the NHC-imine adduct via **model_TS2'** occurs to give the imine intermediate **model_INT4** directly, as proposed in a previous study of NHC-catalysed desulfonylation of tosylated aldimines²⁷. However, this TS (**model_TS2'** at 27.5 [28.8]

kcal mol^{-1}) has an energetic span that is 3.6 [5.1] kcal mol^{-1} higher than the loss of methanesulfinate from the aza-Breslow intermediate (**model_TS2**). With these results, we focus on the step of loss of anion in the full system as both the rate-limiting and stereo-determining step.

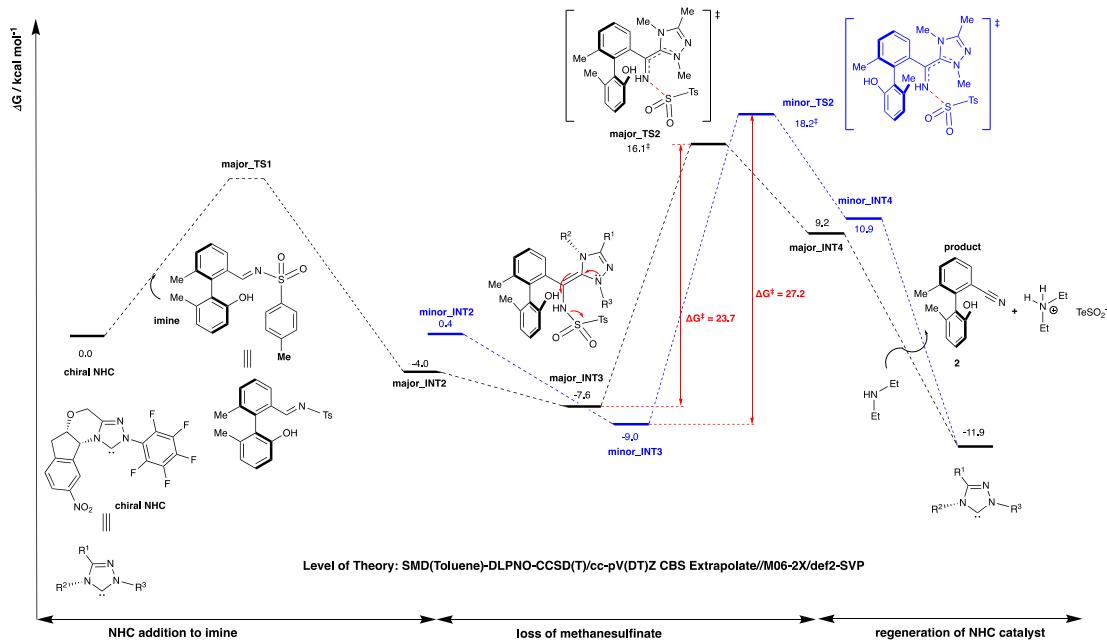
Key steps and key transition state structures for the full reaction



Supplementary Figure 6. DFT optimized transition state structures and their HOMO plots for the rate-determining step of loss of *p*-toluenesulfinate in the full reaction.

For the full reaction, we focus on the step of loss of toluenesulfinate from the Breslow intermediate as reflected by **model_TS2** in Supplementary Figure 5. Conformational sampling was carried out at the GFN2-xTB²⁸ level of theory using the *crest* program²⁹⁻³¹ from Grimme and co-workers. Note that since no TS structure could be located on the GFN2-xTB potential energy surface, we performed conformational

sampling on the aza-Breslow intermediate. A total of 104 conformers were located by the crest program, and these are sorted into 19 clusters of distinct conformers using the clustering_traj.py³² with an RMSD cutoff of 1.0 Å (excluding H atoms). The 4 lowest energy structures were reoptimised at M06-2X/def2-SVP level of theory to yield the relevant TS structures for the rate-determining step of loss of toluenesulfinate. The lowest Gibbs energy structures for the TSs leading to both major and minor products, **major_TS2** and **minor_TS2**, are shown in Figure 6.



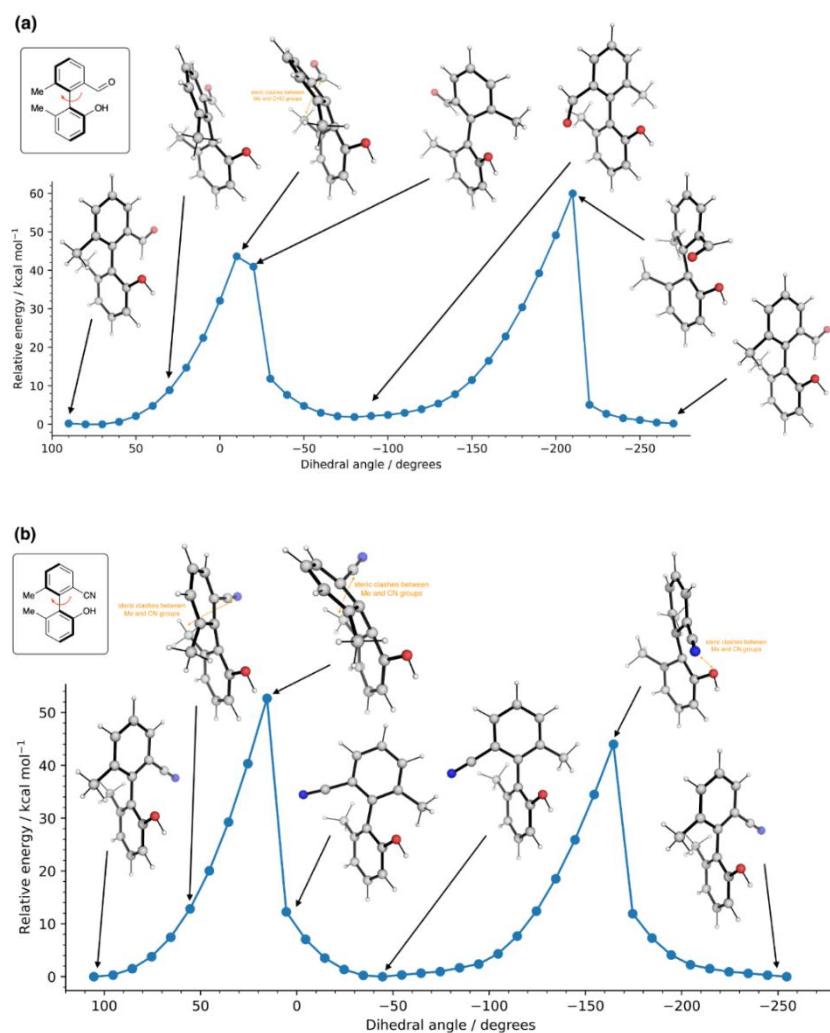
Supplementary Figure 6. Gibbs energy profile for the key steps of the full reaction calculated at SMD(Toluene)-DLPNO-CCSD(T)/cc-pV(DT)Z CBS Extrapolation//M06-2X/def2-SVP.

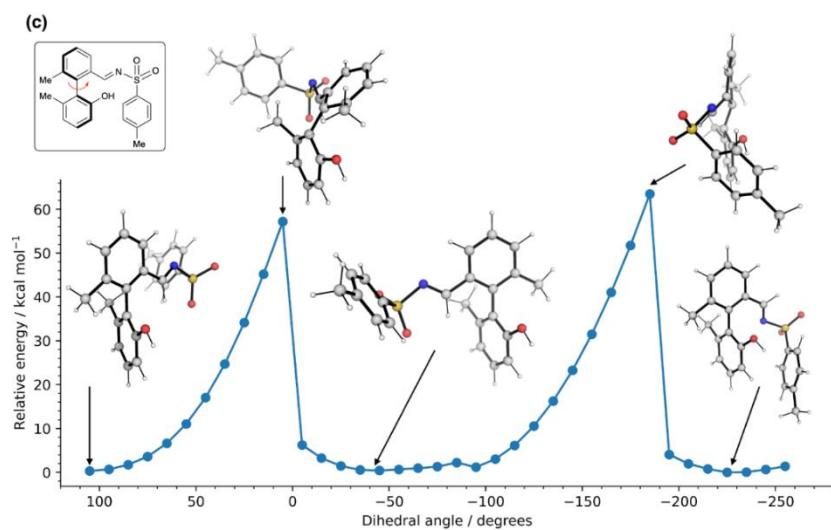
The Gibbs energy profile for the key step of the full system is shown in Supplementary Figure 6. The energetic span for the rate-determining TS leading to the major product is 23.7 kcal mol⁻¹ and to the minor product is 27.2 kcal mol⁻¹. This barrier difference of 3.5 kcal mol⁻¹ translates to an enantiomeric excess of 99%, at experimental temperature of 30°C, which is in good agreement with experimental observations. In addition, the energetic span of 23.7 kcal mol⁻¹ is consistent with excellent reactivity at experimental temperature of 30°C. Their HOMO structures are

similar, and **major_TS2** is likely more favoured due to the hydrogen bonding formed between the OH group on the substrate and the amine group of the Breslow intermediate.

Rotational barriers for atropisomers

Supplementary Figure 7 shows the relaxed PES scan about the dihedral angles for the barriers of isomerisation of atropisomers of (a) **1a**, (b) **3a**, and (c) condensed imine. The barriers for isomerisation are all well over 50 kcal mol⁻¹, indicating that these atropisomers will not racemise easily at the reaction temperature of 30 °C.





Supplementary Figure 7. Relaxed PES scan about the dihedral angles for the barriers of isomerisation of (a) substrate **1a**, (b) product **3a**, and (c) condensed imine

Optimised structures and absolute energies, zero-point energies

Geometries of all optimized structures (in .xyz format with their associated energy in Hartrees) have been deposited and uploaded to zenodo.org (DOI: 10.5281/zenodo.5573970) under open access.

Absolute values (in Hartrees) for SCF energy, zero-point vibrational energy (ZPE), enthalpy and quasi-harmonic Gibbs free energy (at 30 °C/303.15 K) for optimised structures are given below. Single point corrections in SMD toluene using DLPNO-CCSD(T)/cc-pV(DT)Z CBS Extrapolate level of theory are also included (Supplementary Table 4). The individual energy values for (aug-)cc-pV(DT)Z basis sets and for extrapolated energies are included in Supplementary Table 5 and Supplementary Table 6.

Supplementary Table 4. Optimised structures and absolute energies, zero-point energies

Structure	E/au	ZPE/au	H/au	T.S/au	qh-G/au	SP SMD (toluene) DLPNO-CCSD(T) /cc-pV(DT)Z CBS Extrapolate
model_system						
Et₂NH₂Ms	-802.26423	0.209038	-802.04122	0.050974	-802.09067	-802.106771761
model_imine	-1297.3011	0.303744	-1296.9757	0.069216	-1297.0413	-1297.057584649
model_NHC	-359.72744	0.144296	-359.57359	0.039996	-359.61336	-359.734096841
model_INT1	-1657.0724	0.449095	-1656.592	0.089979	-1656.6768	-1656.808959381
model_TS1	-1657.0516	0.44998	-1656.5711	0.086668	-1656.6537	-1656.791717706
model_INT2	-1657.0875	0.452629	-1656.6046	0.086001	-1656.6865	-1656.833728768
model_INT3	-1657.0826	0.451871	-1656.6004	0.085618	-1656.682	-1656.815595236
model_TS2	-1657.0514	0.450388	-1656.5709	0.084953	-1656.6522	-1656.778899839
model_INT4	-1657.078	0.449421	-1656.5976	0.087806	-1656.681	-1656.813275761
model_INT3'	-1870.6262	0.604494	-1869.9829	0.106287	-1870.0821	-1870.382825950
model_TS2'	-1870.5768	0.600681	-1869.9385	0.101509	-1870.0344	-1870.330222484
Full system						
NHC	-1633.1919	0.262908	-1632.9043	0.07842	-1632.9774	-1633.365826
substrate_1	-729.63651	0.252446	-729.36729	0.056997	-729.4226	-729.5741718
substrate_1-c2	-729.63341	0.252251	-729.36439	0.0568	-729.41954	-729.5719554
TsNH₂	-874.78436	0.155925	-874.61621	0.048451	-874.66261	-874.5913381
Et₂N	-213.51354	0.150026	-213.35549	0.035622	-213.39093	-213.5363377
product	-708.58387	0.241686	-708.32566	0.056235	-708.38037	-708.4984566
major_TS2	-3161.3151	0.649318	-3160.6149	0.132663	-3160.737	-3161.1548
major_TS2-c2	-3161.3219	0.649753	-3160.6214	0.133526	-3160.7436	-3161.153644
major_TS2-c3	-3161.3099	0.649559	-3160.6099	0.132688	-3160.7315	-3161.15015
major_TS2-c4	-3161.3099	0.650099	-3160.609	0.134329	-3160.7313	-3161.144974
minor_TS2	-3161.3158	0.649746	-3160.6153	0.133319	-3160.7375	-3161.151609
major_INT2	-3161.3385	0.651677	-3160.6368	0.130192	-3160.756959	-3161.190316
major_INT3	-3161.3527	0.651003	-3160.6507	0.133176	-3160.772938	-3161.194197

major_INT4	-3161.3198	0.650182	-3160.618	0.135629	-3160.741952	-3161.165459	
minor_INT2	-3161.3296	0.652316	-3160.6271	0.132009	-3160.748028	-3161.183229	
minor_INT3	-3161.3596	0.651797	-3160.6571	0.132231	-3160.77859	-3161.197593	
minor_INT4	-3161.3377	0.651058	-3160.6356	0.133459	-3160.758143	-3161.169332	

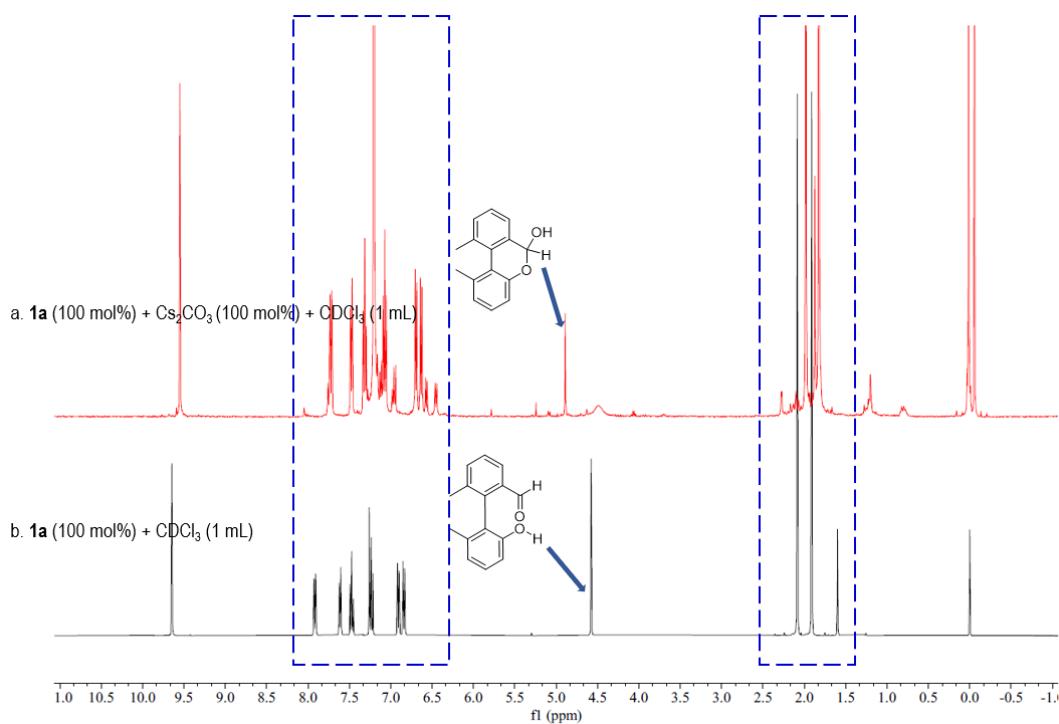
Supplementary Table 5. Raw energy values obtained at SMD(toluene)-DLPNO-CCSD(T)/cc-pV(DT)Z basis sets and the complete basis set (CBS) extrapolation. Final single-point (SP) energy = Extrapolated SCF energy + Extrapolated correlation energy. $\alpha = 4.42$ and $\beta = 2.46$ in the extrapolation of SCF and correlation energies. All values have the units of a.u.

Structure	SCF with SMD correction			Correlation			Final SP Energy
	cc-pVDZ	cc-pVTZ	Extrapolated	cc-pVDZ	cc-pVTZ	Extrapolated	
model_system							
Et₂NH₂M_s	-799.73979 9018	-799.90538 2516	-799.95923 2958	-1.5670959 81	-1.9334593 69	-2.1475388 03	-802.106771 761
model_imine	-1292.3507 13901	-1292.6519 32034	-1292.7498 93061	-3.1969679 18	-3.8980335 04	-4.3076915 88	-1297.05758 4649
model_NHC	-357.92299 4234	-358.01620 8822	-358.04652 3720	-1.2686224 29	-1.5330553 57	-1.6875731 21	-359.734096 841
model_INT1	-1650.2703 96404	-1650.6567 38374	-1650.7823 83055	-4.4908202 35	-5.4601574 09	-6.0265763 26	-1656.80895 9381
model_TS1	-1650.2399 43402	-1650.6276 14341	-1650.7536 91224	-4.4998302 86	-5.4707076 03	-6.0380264 82	-1656.79171 7706
model_INT2	-1650.2673 54080	-1650.6560 00373	-1650.7823 94457	-4.5051044 72	-5.4810524 57	-6.0513343 11	-1656.83372 8768
model_INT3	-1650.2448 98291	-1650.6334 66029	-1650.7598 34565	-4.5112049 10	-5.4860962 52	-6.0557606 71	-1656.81559 5236
model_TS2	-1650.2058 46635	-1650.5806 14833	-1650.7024 95535	-4.5301626 27	-5.5061180 84	-6.0764043 04	-1656.77889 9839
model_INT4	-1650.2685 56189	-1650.6365 95358	-1650.7562 87670	-4.5111221 75	-5.4868404 59	-6.0569880 91	-1656.81327 5761
model_INT3'	-1862.5997 99293	-1863.0424 77792	-1863.1864 44026	-5.3737941 66	-6.5241734 99	-7.1963819 24	-1870.38282 5950
model_TS2'	-1862.5208	-1862.9616	-1863.1049	-5.3995017	-6.5518600	-7.2252248	-1870.33022

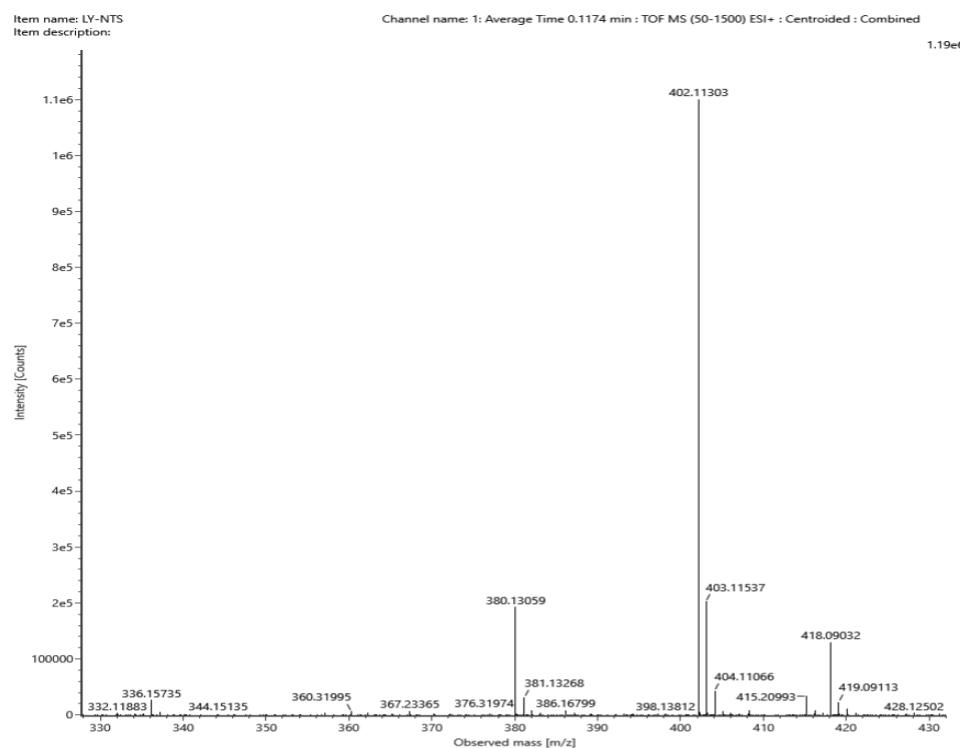
	92530	54638	97631	67	53	54	2484
Full System							
NHC	-1626.3356 19693	-1626.7924 85702	-1626.9410 65945	-4.6535972 80	-5.7715182 37	-6.4247600 54	-1633.36582 6
substrate_1	-725.98059 2246	-726.16257 0798	-726.22175 3178	-2.5209008 97	-3.0457374 93	-3.3524185 78	-729.574171 8
substrate_1-c2	-725.97583 5382	-726.15816 5793	-726.21746 2602	-2.5220147 61	-3.0474575 20	-3.3544928 09	-729.571955 4
TsNH₂	-871.98152 3630	-872.18099 0155	-872.24585 9907	-1.7156636 31	-2.1131894 08	-2.3454781 58	-874.591338 1
Et₂N	-212.33781 2151	-212.39895 8746	-212.41884 4611	-0.8451856 87	-1.0170604 24	-1.1174930 75	-213.536337 7
product	-704.98396 5067	-705.15704 7882	-705.21333 7223	-2.4818445 77	-2.9888548 42	-3.2851193 55	-708.498456 6
major_TS2	-3148.1747 27490	-3148.9604 91447	-3149.2160 34643	-8.7749315 48	-10.771877 556	-11.938765 637	
major_TS2-c2	-3148.189 755503	-3148.972 161576	-3149.226 612733	-8.765 892068	-10.761 137393	-11.927 031704	-3161.15364 4
major_TS2-c3	-3148.1800 46923	-3148.9657 69449	-3149.2212 99171	-8.7675206 97	-10.762886 435	-11.928851 106	
major_TS2-c4	-3148.1680 54423	-3148.9516 63987	-3149.2065 06538	-8.7754407 68	-10.771877 222	-11.938467 552	-3161.14497 4
minor_TS2	-3148.2095 00774	-3148.9909 16285	-3149.2450 45294	-8.7557086 96	-10.751434 603	-11.917609 735	-3161.15160 9
major_INT2	-3148.2046 04326	-3149.0010 66214	-3149.2600 88550	-8.7680327 99	-10.763943 939	-11.930227 310	-3161.19031 6
major_INT3	-3148.2147 08086	-3149.0137 55581	-3149.2736 18799	-8.7577242 18	-10.754051 614	-11.920578 217	-3161.19419 7
major_INT4	-3148.2067 34153	-3148.9894 08987	-3149.2439 47549	-8.7585929 67	-10.754960 817	-11.921511 059	-3161.16545 9
minor_INT2	-3148.2039 46802	-3149.0015 62434	-3149.2609 59986	-8.7596152 65	-10.755816 345	-11.922269 138	-3161.18322 9
minor_INT3	-3148.2247 43854	-3149.0229 32938	-3149.2825 16986	-8.7538879 27	-10.749163 877	-11.915076 083	-3161.19759 3
minor_INT4	-3148.2251 26187	-3149.0023 81899	-3149.2551 58075	-8.7519768 39	-10.747889 320	-11.914173 473	-3161.16933 2

Supplementary Table 6. Raw energy values obtained at SMD(toluene)-DLPNO-CCSD(T)/aug-cc-pV(DT)Z basis sets and the complete basis set (CBS) extrapolation. Final single-point (SP) energy = Extrapolated SCF energy + Extrapolated correlation energy. $\alpha = 4.3$ and $\beta = 2.51$ in the extrapolation of SCF and correlation energies. All values have the units of a.u.

Structure	SCF with SMD correction			Correlation			Final SP Energy
	aug-cc-pV DZ	aug-cc-pV TZ	Extrapolat ed	aug-cc-pV DZ	aug-cc-pV TZ	Extrapolat ed	
model_system							
Et₂NH₂Ms	-799.77587 16	-799.91099 26	-799.95722 91	-1.6591811 62	-1.9715942 74	-2.1484113 39	-802.105640 5
model_imine	-1292.4081 35117	-1292.6620 54645	-1292.7489 4238804	-3.3539009 19	-3.9653053 14	-4.3113430 64947602	-1297.06028 5
model_NHC	-357.93927 5380	-358.01993 6405	-358.04753 7489756	-1.3232415 90	-1.5571654 10	-1.6895597 356342993	-359.737097 2
model_INT1	-1650.3382 29680	-1650.6686 20860	-1650.7816 7614242	-4.7120677 30	-5.5553905 70	-6.0326876 60539143	-1656.81436 4
model_TS1	-1650.3109 12401	-1650.6400 11619	-1650.7526 2480993	-4.7273263 43	-5.5678497 86	-6.0435624 96299464	-1656.79618 7
model_INT2	-1650.3410 98744	-1650.6689 68362	-1650.7811 6080085	-4.7371878 38	-5.5799684 53	-6.0569586 59386785	-1656.83811 9
model_INT3	-1650.3154 61981	-1650.6458 49460	-1650.7589 0347599	-4.7407596 89	-5.5837297 68	-6.0608272 057004315	-1656.81973 1
model_TS2	-1650.2806 08887	-1650.5947 54261	-1650.7022 5045378	-4.7639103 98	-5.6060862 80	-6.0827342 24458418	-1656.78498 5
model_INT4	-1650.3392 00377	-1650.6499 82339	-1650.7563 2761881	-4.7442165 51	-5.5857496 61	-6.0620338 14522222	-1656.81836 1
model_INT3'	-1862.6794 57	-1863.0557 77	-1863.1845 48	-5.6512951 49	-6.6420739 05	-7.2028269 11	-1870.38737 5
model_TS2'	-1862.6018 45	-1862.9754 86	-1863.1033 41	-5.6804256 41	-6.6707761 73	-7.2312868 16275702	-1870.33462 8
diethylamine	-212.34902 3014	-212.40134 4425	-212.41924 8086645	-0.8807877 70	-1.0322439 22	-1.1179638 589743786	-213.537211 9
product	-705.00996 8746	-705.16311 1799	-705.21551 5229103	-2.5837032 04	-3.0334080 46	-3.2879283 821122827	-708.503443 6



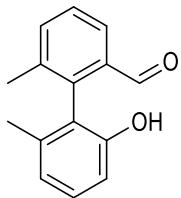
Supplementary Figure 8. Evidence of bridged hemiacetal **1a'** via ¹H NMR analysis



Supplementary Figure 9. Evidence of imine intermediate **4a**.

Characterization of substrates and products

2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (**1a**)



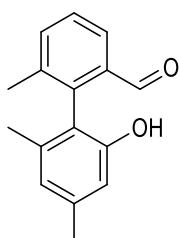
White solid, 17% yield over 4 steps, 1.4 g; m.p. 97-98 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.63 (d, *J* = 0.8 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.75 (s, 1H), 2.08 (s, 3H), 1.91 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.9, 153.0, 139.4, 138.9, 137.9, 136.5, 134.8, 129.6, 128.8, 125.6, 122.6, 122.5, 113.2, 20.2, 19.2.

HRMS (ESI, m/z) calcd. for C₁₅H₁₄O₂H⁺ [M+H]⁺: 227.1067, found: 227.1073.

2'-hydroxy-4',6,6'-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (**1b**)



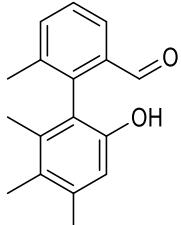
White solid, 22% yield over 4 steps, 720 mg; m.p. 75-76 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.7 (d, *J* = 0.7 Hz, 1H), 7.9 (d, *J* = 7.2 Hz, 1H), 7.6 (d, *J* = 7.5 Hz, 1H), 7.5 (t, *J* = 7.7 Hz, 1H), 6.7 (s, 1H), 6.7 (s, 1H), 4.5 (s, 1H), 2.3 (s, 3H), 2.1 (s, 3H), 1.9 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.2, 152.9, 139.7, 139.6, 139.2, 137.5, 136.4, 135.0, 128.6, 125.5, 123.4, 119.6, 113.8, 21.4, 20.2, 19.3.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₂H⁺ [M+H]⁺: 241.1223, found: 241.1234.

6'-hydroxy-2',3',4',6-tetramethyl-[1,1'-biphenyl]-2-carbaldehyde (**1c**)



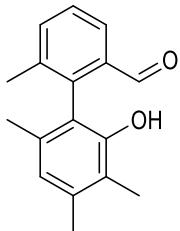
White solid, 6% yield over 4 steps, 220 mg; m.p. 124-125 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.64 (d, *J* = 0.9 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 6.69 (s, 1H), 4.33 (s, 1H), 2.32 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H), 1.84 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.8, 150.1, 140.1, 139.1, 137.9, 136.1, 135.5, 135.1, 128.5, 127.6, 125.3, 120.0, 114.4, 20.9, 19.3, 17.3, 15.3.

HRMS (ESI, m/z) calcd. for C₁₇H₁₈O₂H⁺ [M+H]⁺: 255.1380, found: 255.1382.

2'-hydroxy-3',4',6,6'-tetramethyl-[1,1'-biphenyl]-2-carbaldehyde (1d)



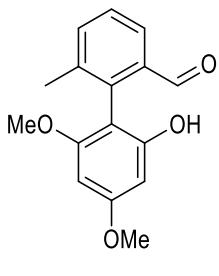
White solid, 11% yield over 4 steps, 390 mg; m.p. 110-111 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.62 (d, *J* = 0.8 Hz, 1H), 7.90 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.60 (dd, *J* = 7.5, 0.6 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 6.73 (s, 1H), 4.38 (s, 1H), 2.30 (s, 3H), 2.17 (s, 3H), 2.08 (s, 3H), 1.83 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.8, 150.1, 140.1, 139.1, 137.9, 136.1, 135.5, 135.1, 128.5, 127.6, 125.3, 120.0, 114.4, 20.9, 19.3, 17.3, 15.3.

HRMS (ESI, m/z) calcd. for C₁₇H₁₈O₂H⁺ [M+H]⁺: 255.1380, found: 255.1387.

2'-hydroxy-4',6'-dimethoxy-6-methyl-[1,1'-biphenyl]-2-carbaldehyde (1e)



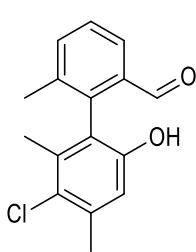
White solid, 14 % yield over 4 steps, 540 mg; m.p. 178-179 °C.

¹H NMR (400 MHz, Acetone-d₆) δ 8.36 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 6.27 (s, 2H), 6.25 (d, *J* = 1.4 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 2.13 (s, 3H).

¹³C NMR (101 MHz, Acetone-d₆) δ 192.5, 161.7, 158.8, 156.0, 139.5, 138.8, 135.2, 134.9, 127.2, 123.5, 104.4, 93.7, 90.2, 55.1, 54.7, 18.7.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₄H⁺ [M+H]⁺: 273.1121, found: 273.1131.

3'-chloro-6'-hydroxy-2',4',6-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (1f)



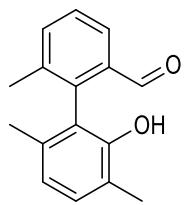
White solid, 8% yield over 4 steps, 320 mg; m.p. 125-126 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 6.76 (s, 1H), 5.18 (s, 1H), 2.39 (s, 3H), 2.06 (s, 3H), 1.96 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.7, 151.0, 139.1, 138.9, 137.6, 136.4, 135.4, 134.7, 128.8, 126.9, 125.6, 121.5, 115.5, 21.0, 19.2, 18.1.

HRMS (ESI, m/z) calcd. for C₁₆H₁₅ClO₂H⁺ [M+H]⁺: 275.0833, found: 275.0835.

2'-hydroxy-3',6,6'-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (1g)

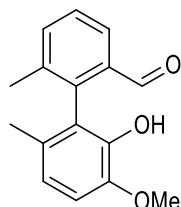


White solid, 15% yield over 4 steps, 490 mg; m.p. 109-110 °C.
¹H NMR (400 MHz, CDCl₃) δ 9.61 (d, *J* = 0.6 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.45 (s, 1H), 2.26 (s, 3H), 2.07 (s, 3H), 1.86 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.5, 150.8, 139.0, 139.0, 136.3, 135.0, 134.8, 130.7, 128.8, 125.5, 121.8, 121.8, 121.5, 19.9, 19.1, 15.8.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₂H⁺ [M+H]⁺: 241.1223, found: 241.1230.

2'-hydroxy-3'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (1h)

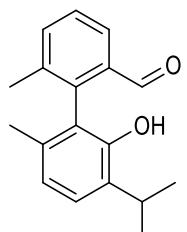


White solid, 11% yield over 4 steps, 396 mg; m.p. 69-70 °C.
¹H NMR (400 MHz, CDCl₃) δ 9.65 (d, *J* = 0.9 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.86 – 6.77 (m, 2H), 5.76 (s, 1H), 3.88 (s, 3H), 2.07 (s, 3H), 1.85 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.9, 144.6, 142.8, 140.6, 137.9, 135.6, 133.9, 129.3, 127.8, 124.6, 122.4, 120.6, 110.1, 55.9, 19.3, 19.0.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₃H⁺ [M+H]⁺: 257.1172, found: 257.1174.

2'-hydroxy-3'-isopropyl-[1,1'-biphenyl]-2-carbaldehyde (1i)

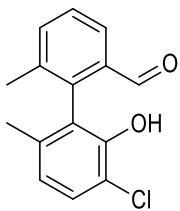


White solid, 9% yield over 4 steps, 340 mg; m.p. 86-87 °C.
¹H NMR (400 MHz, CDCl₃) δ 9.63 (d, *J* = 0.5 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 4.36 (s, 1H), 3.18 – 3.28 (m, 1H), 2.08 (s, 3H), 1.86 (s, 3H), 1.27 (d, *J* = 2.1 Hz, 3H), 1.25 (d, *J* = 2.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 149.9, 139.3, 139.1, 136.5, 135.2, 134.5, 132.4, 129.1, 126.3, 125.7, 122.2, 121.9, 27.2, 22.8, 22.7, 20.0, 19.2.

HRMS (ESI, m/z) calcd. for C₁₈H₂₀O₂H⁺ [M+H]⁺: 269.1536, found: 269.1544.

3'-chloro-2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (1j)



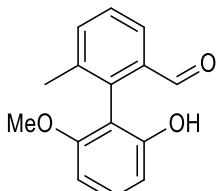
White solid, 9% yield over 4 steps, 320 mg; m.p. 77-78 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.63 (d, *J* = 0.8 Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.52 (s, 1H), 2.06 (s, 3H), 1.89 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.3, 148.5, 139.5, 137.9, 137.2, 136.0, 134.0, 128.5, 128.4, 125.4, 124.2, 122.7, 117.6, 19.8, 19.1.

HRMS (ESI, m/z) calcd. for C₁₅H₁₃ClO₂H⁺ [M+H]⁺: 261.0677, found: 261.0683.

2'-hydroxy-6'-methoxy-6-methyl-[1,1'-biphenyl]-2-carbaldehyde (1k)



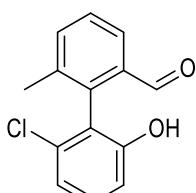
White solid, 9% yield over 4 steps, 420 mg; m.p. 155-156 °C.

¹H NMR (400 MHz, Acetone-*d*₆) δ 9.70 (s, 1H), 8.35 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 8.3 Hz, 1H), 6.68 (t, *J* = 8.1 Hz, 2H), 3.68 (s, 3H), 2.10 (s, 3H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 192.3, 158.2, 155.5, 138.9, 138.9, 135.0, 134.7, 129.9, 127.3, 123.6, 111.8, 108.5, 102.4, 55.2, 18.6.

HRMS (ESI, m/z) calcd. for C₁₅H₁₄O₃H⁺ [M+H]⁺: 243.1016, found: 243.1018.

2'-chloro-6'-hydroxy-6-methyl-[1,1'-biphenyl]-2-carbaldehyde (1l)



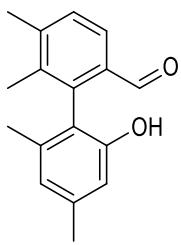
White solid, 20% yield over 4 steps, 1.6 g; m.p. 105-106 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.66 (d, *J* = 0.8 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H), 7.13 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.26 (s, 1H), 2.14 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.1, 154.2, 139.1, 136.7, 136.3, 134.6, 134.3, 130.4, 129.3, 125.9, 122.3, 121.7, 114.2, 19.1.

HRMS (ESI, m/z) calcd. for C₁₄H₁₁ClO₂H⁺ [M+H]⁺: 247.0520, found: 247.0526.

2'-hydroxy-4',5,6,6'-tetramethyl-[1,1'-biphenyl]-2-carbaldehyde (1m)



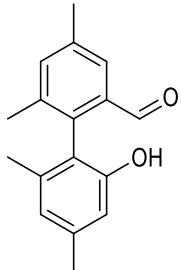
White solid, 10% yield over 4 steps, 340 mg; m.p. 137-138 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.55 (d, *J* = 0.8 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 6.72 (s, 1H), 6.66 (s, 1H), 4.68 (s, 1H), 2.41 (s, 3H), 2.33 (s, 3H), 1.98 (s, 3H), 1.85 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.7, 152.8, 144.8, 139.4, 138.9, 137.5, 137.3, 133.1, 130.4, 125.3, 123.2, 119.9, 113.5, 21.3, 21.3, 20.1, 15.5.

HRMS (ESI, m/z) calcd. for C₁₇H₁₈O₂H⁺ [M+H]⁺: 255.1379, found: 255.1381.

2'-hydroxy-4,4',6,6'-tetramethyl-[1,1'-biphenyl]-2-carbaldehyde (1n)



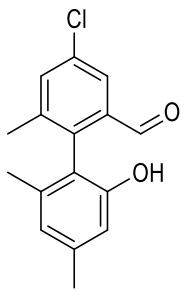
White solid, 10% yield over 4 steps, 367 mg; m.p. 134-135 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.62 (s, 1H), 7.71 (s, 1H), 7.42 (s, 1H), 6.72 (s, 1H), 6.66 (s, 1H), 4.59 (s, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 2.05 (s, 3H), 1.87 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.1, 152.9, 139.6, 139.0, 138.7, 137.7, 137.4, 136.3, 135.0, 125.9, 123.4, 119.5, 113.6, 21.4, 21.2, 20.2, 19.2.

HRMS (ESI, m/z) calcd. for C₁₇H₁₈O₂H⁺ [M+H]⁺: 255.1380, found: 255.1385.

4-chloro-2'-hydroxy-4',6,6'-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (1o)



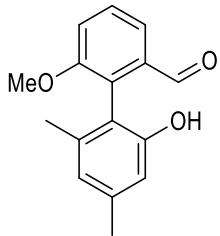
White solid, 10% yield over 4 steps, 318 mg; m.p. 46-47 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.51 (s, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 6.70 (s, 1H), 6.58 (s, 1H), 5.94 (s, 1H), 2.29 (s, 3H), 2.05 (s, 3H), 1.84 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 153.0, 141.2, 139.8, 139.3, 137.5, 135.8, 135.6, 134.4, 124.9, 123.3, 118.6, 113.9, 21.3, 20.0, 19.1.

HRMS (ESI, m/z) calcd. for C₁₆H₁₅ClO₂H⁺ [M+H]⁺: 275.0833, found: 275.0823.

2'-hydroxy-6-methoxy-4',6'-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (1p)



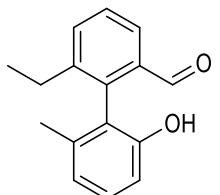
White solid, 17% yield over 4 steps, 580 mg; m.p. 130-131 °C.

¹H NMR (400 MHz, Acetone-*d*₆) δ 9.66 (d, *J* = 0.7 Hz, 1H), 7.98 (s, 1H), 7.55 – 7.46 (m, 2H), 7.36 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.66 (d, *J* = 6.2 Hz, 2H), 3.78 (s, 3H), 2.27 (s, 3H), 1.92 (s, 3H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 191.9, 157.8, 154.8, 138.5, 138.4, 135.4, 130.8, 128.7, 122.0, 118.0, 117.4, 116.3, 113.3, 55.3, 20.4, 19.3.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₃H⁺ [M+H]⁺: 257.1172, found 257.1174.

6-ethyl-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-2-carbaldehyde (1q)



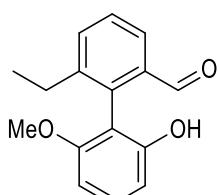
Colourless oil, 8% yield over 4 steps, 720 mg.

¹H NMR (400 MHz, CDCl₃) δ 9.57 (d, *J* = 0.6 Hz, 1H), 7.88 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.21 (s, 1H), 2.39 (q, *J* = 7.6 Hz, 2H), 1.90 (s, 3H), 1.07 (t, *J* = 7.6 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.4, 153.7, 145.0, 139.2, 138.4, 135.2, 135.0, 129.9, 129.3, 125.9, 122.7, 122.7, 113.5, 26.0, 20.7, 15.1.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₂H⁺ [M+H]⁺: 241.1223, found: 241.1232.

6-ethyl-2'-hydroxy-6'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (1r)



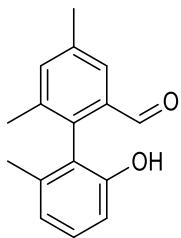
White solid, 12% yield over 4 steps, 970 mg; m.p. 111-113 °C.

¹H NMR (400 MHz, Acetone-*d*₆) δ 9.68 (d, *J* = 0.7 Hz, 1H), 8.34 (s, 1H), 7.76 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.61 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 8.3 Hz, 1H), 6.68 (dd, *J* = 8.6, 4.7 Hz, 2H), 3.68 (s, 3H), 2.45 (q, *J* = 7.6 Hz, 2H), 1.04 (t, *J* = 7.6 Hz, 3H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 192.3, 158.4, 155.7, 144.8, 138.3, 134.8, 133.7, 129.9, 127.6, 123.7, 111.6, 108.4, 102.3, 55.1, 25.7, 14.2.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₃H⁺ [M+H]⁺: 257.1172, found: 257.1174.

2'-hydroxy-4,6,6'-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (1s)



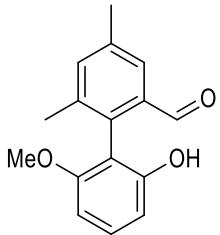
White solid, 14% yield over 4 steps, 1.2 g; m.p. 120-121 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H), 7.70 (s, 1H), 7.42 (s, 1H), 7.20 (t, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 5.09 (s, 1H), 2.41 (s, 3H), 2.04 (s, 3H), 1.90 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.0, 153.1, 138.6, 138.6, 137.9, 137.4, 136.4, 134.5, 129.3, 125.8, 122.5, 122.2, 112.9, 21.1, 20.1, 19.0.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₂H⁺ [M+H]⁺: 241.1223, found: 241.1231.

2'-hydroxy-6'-methoxy-4,6-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (1t)



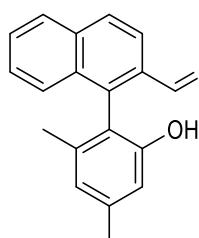
White solid, 10% yield over 4 steps, 850 mg; m.p. 181-183 °C.

¹H NMR (400 MHz, Acetone-*d*₆) δ 9.67 (s, 1H), 8.29 (s, 1H), 7.56 (s, 1H), 7.38 (s, 1H), 7.26 (t, *J* = 8.3 Hz, 1H), 6.67 (dd, *J* = 12.9, 4.6 Hz, 2H), 3.68 (s, 3H), 2.38 (s, 3H), 2.06 (s, 3H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 192.3, 158.3, 155.6, 138.8, 136.9, 136.0, 136.0, 134.6, 129.7, 123.9, 111.9, 108.5, 102.4, 55.1, 20.1, 18.5.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₃H⁺ [M+H]⁺: 257.1172, found: 257.1174.

1-(2-hydroxy-4,6-dimethylphenyl)-2-naphthaldehyde (1u)



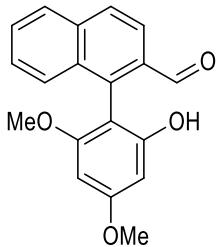
White solid, 23% yield over 4 steps, 750 mg; m.p. 142-143 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.87 (d, *J* = 0.7 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.98 (dd, *J* = 11.1, 8.5 Hz, 2H), 7.70 – 7.59 (m, 2H), 7.47 – 7.52(m, 1H), 6.83 (s, 1H), 6.75 (s, 1H), 4.70 (s, 1H), 2.42 (s, 3H), 1.86 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.8, 153.6, 140.9, 140.1, 138.6, 136.6, 132.2, 132.2, 129.3, 129.1, 128.6, 127.5, 126.5, 123.4, 122.4, 118.0, 113.8, 21.4, 20.1.

HRMS (ESI, m/z) calcd. for C₁₉H₁₆O₂H⁺ [M+H]⁺: 277.1223, found: 277.1231.

1-(2-hydroxy-4,6-dimethoxyphenyl)-2-naphthaldehyde (1v**)**



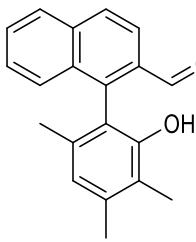
White solid, 18% yield over 4 steps, 660 mg; m.p. 172-173 °C.

¹H NMR (400 MHz, Acetone-*d*₆) δ 9.96 (s, 1H), 8.34 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 3H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.48 (m, 1H), 6.38 – 6.34 (m, 2H), 3.87 (s, 3H), 3.61 (s, 3H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 192.4, 162.2, 159.6, 156.9, 140.4, 136.5, 133.3, 132.3, 128.5, 128.2, 127.9, 127.1, 126.5, 121.7, 102.8, 93.8, 90.3, 55.2, 54.8.

HRMS (ESI, m/z) calcd. for C₁₉H₁₆O₄H⁺ [M+H]⁺: 309.1121, found: 309.1125.

1-(2-hydroxy-3,4,6-trimethylphenyl)-2-naphthaldehyde (1w**)**



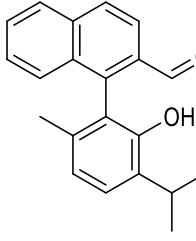
White solid, 13% yield over 4 steps, 440 mg; m.p. 167-168 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.86 (d, *J* = 0.6 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.99 (dd, *J* = 15.5, 8.4 Hz, 2H), 7.65 – 7.69 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.52 (m, 1H), 6.83 (s, 1H), 4.40 (s, 1H), 2.39 (s, 3H), 2.23 (s, 3H), 1.82 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 151.5, 140.8, 138.5, 136.7, 134.8, 132.4, 132.3, 129.4, 129.3, 128.6, 127.6, 126.5, 123.7, 122.5, 120.2, 117.9, 20.1, 19.8, 11.7.

HRMS (ESI, m/z) calcd. for C₂₀H₁₈O₂H⁺ [M+H]⁺: 291.1380, found: 291.1392.

1-(2-hydroxy-3-isopropyl-6-methylphenyl)-2-naphthaldehyde (1x**)**



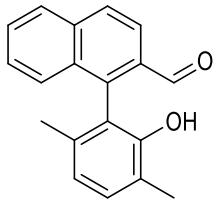
White solid, 25% yield over 4 steps, 920 mg; m.p. 178-179 °C.

¹H NMR (400 MHz, CDCl₃) δ 9.82 (d, *J* = 0.6 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 4.39 (s, 1H), 3.20 – 3.30 (m, 1H), 1.82 (s, 3H), 1.32 – 1.26 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 150.9, 140.7, 136.8, 135.8, 132.5, 132.5, 132.3, 129.6, 129.5, 128.8, 127.9, 126.7, 126.6, 122.7, 122.2, 120.6, 27.2, 22.9, 22.8, 20.1.

HRMS (ESI, m/z) calcd. for C₂₁H₂₀O₂H⁺ [M+H]⁺: 305.1536, found: 305.1543.

1-(2-hydroxy-3,6-dimethylphenyl)-2-naphthaldehyde (1y)

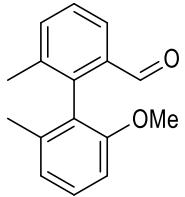


White solid, 11% yield over 4 steps, 350 mg; m.p. 162-163 °C.
¹H NMR (400 MHz, CDCl₃) δ 9.82 (d, *J* = 0.7 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.97 (dd, *J* = 16.2, 8.4 Hz, 2H), 7.63 – 7.67 (m, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.50 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 4.40 (s, 1H), 2.29 (s, 3H), 1.83 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.6, 151.9, 140.7, 136.8, 136.2, 132.4, 132.2, 131.3, 129.6, 129.5, 128.8, 127.8, 126.6, 122.7, 122.0, 121.8, 120.6, 20.1, 16.0.

HRMS (ESI, m/z) calcd. for C₁₉H₁₆O₂H⁺ [M+H]⁺: 277.1223, found: 277.1231.

2'-methoxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (1z)

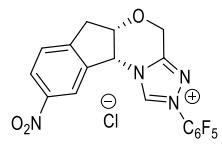


White solid, 97% yield, 310 mg; m.p. 40-41 °C.
¹H NMR (400 MHz, CDCl₃) δ 9.6 (d, *J* = 0.9 Hz, 1H), 7.9 (d, *J* = 6.9 Hz, 1H), 7.5 (d, *J* = 7.1 Hz, 1H), 7.4 (t, *J* = 7.6 Hz, 1H), 7.3 (t, *J* = 8.0 Hz, 1H), 6.9 (d, *J* = 7.7 Hz, 1H), 6.8 (d, *J* = 8.3 Hz, 1H), 3.7 (s, 3H), 2.0 (s, 3H), 1.9 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.2, 156.9, 141.7, 138.0, 137.8, 135.6, 134.1, 129.0, 127.6, 124.8, 124.6, 122.5, 108.1, 55.6, 20.0, 19.2.

HRMS (ESI, m/z) calcd. for C₁₆H₁₆O₂H⁺ [M+H]⁺: 241.1223, found: 241.1218.

(5a*R*,10b*S*)-2-(2,3,4,5,6-pentafluorophenyl)-9-nitro-5a,10b-dihydro-4H,6H-inden o[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-i um chloride (NHC-G)



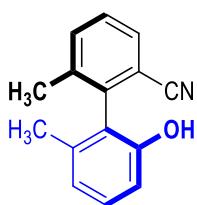
White solid, 20% yield, 800 mg; m.p. 200-201 °C.
¹H NMR (400 MHz, DMSO-*d*₆) δ 12.17 (s, 1H), 8.52 (s, 1H), 8.29 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 4.1 Hz, 1H), 5.38 (d, *J* = 16.3 Hz, 1H), 5.13 (d, *J* = 16.3 Hz, 1H), 5.07 (t, *J* = 4.5 Hz, 1H), 3.64 (dd, *J* = 18.0, 4.9 Hz, 1H), 3.30 (d, *J* = 17.9 Hz, 1H).

¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.2, 149.5, 147.7, 147.6, δ 144.1 – 143.4 (m), 141.7 – 140.7 (m), 140.0 – 139.2 (m), 137.8, 137.3 – 136.7 (m), 127.1, 125.4, 121.1, 77.6, 61.7, 60.2, 37.6.

¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -145.2 – -145.5 (m, 2F), -148.2 (t, 1F, *J* = 23.2 Hz), -159.7 – -160.1 (m, 2F).

HRMS (ESI, m/z) calcd. for C₁₈H₁₀ClF₅N₄O₃H⁺ [M+H]⁺: 460.0362, found: 460.0352;

(S)-2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (3a)



White solid, 96% yield, 21.6 mg; m.p. 170-171 °C.

[*a*]_D²⁵ = +33.0 (*c* = 0.5 in MeOH);

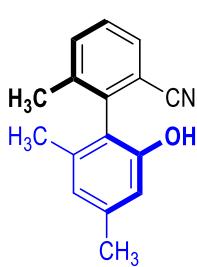
¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 4.84 (s, 1H), 2.11 (s, 3H), 1.98 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 192.9, 153.0, 139.4, 138.9, 137.9, 136.5, 134.8, 129.6, 128.8, 125.6, 122.6, 122.5, 113.2, 20.2, 19.2.

HRMS (ESI, m/z) calcd. for C₁₅H₁₃NOH⁺ [M+H]⁺: 224.1070, found: 224.1073;

HPLC analysis: 98:2 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, *λ* = 254 nm), Rt (major) = 32.9 min, Rt (minor) = 40.9 min.

(S)-2'-hydroxy-4',6,6'-trimethyl-[1,1'-biphenyl]-2-carbonitrile (3b)



White solid, 97% yield, 23.0 mg; m.p. 82-83 °C.

[*a*]_D²⁵ = +17.4 (*c* = 1.0 in CHCl₃).

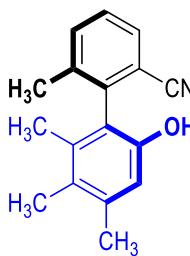
¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 6.74 (s, 1H), 6.62 (s, 1H), 4.54 (s, 1H), 2.32 (s, 3H), 2.11 (s, 3H), 1.95 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 152.1, 140.0, 139.8, 139.5, 136.9, 134.6, 130.9, 128.4, 123.7, 121.0, 118.0, 114.6, 113.9, 21.3, 19.7, 19.5.

HRMS (ESI, m/z) calcd. for C₁₆H₁₅NOH⁺ [M+H]⁺: 238.1226, found: 238.1228.

HPLC analysis: 98:2 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, *λ* = 254 nm), Rt (major) = 31.4 min, Rt (minor) = 40.0 min.

(S)-6'-hydroxy-2',3',4',6-tetramethyl-[1,1'-biphenyl]-2-carbonitrile (3c)



White solid, 99% yield, 24.9 mg; m.p. 223-224 °C.

$[\alpha]^{25}_D = +23.4$ ($c = 0.5$ in MeOH).

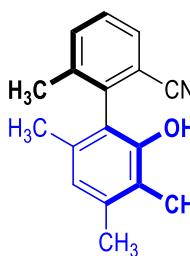
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.62 (d, $J = 7.7$ Hz, 1H), 7.54 (d, $J = 7.7$ Hz, 1H), 7.38 (t, $J = 7.7$ Hz, 1H), 6.64 (s, 1H), 4.33 (s, 1H), 2.29 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.89 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 149.6, 140.9, 139.5, 138.2, 135.1, 134.5, 130.8, 128.2, 127.8, 121.6, 118.1, 114.7, 114.7, 20.9, 19.8, 16.9, 15.3.

HRMS (ESI, m/z) calcd. for $\text{C}_{17}\text{H}_{17}\text{NOH}^+ [\text{M}+\text{H}]^+$: 252.1383, found: 252.1387.

HPLC analysis: 92:8 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 31.9 min, Rt (minor) = 38.6 min.

(S)-2'-hydroxy-3',4',6,6'-tetramethyl-[1,1'-biphenyl]-2-carbonitrile (3d)



White solid, 96% yield, 24.1 mg; m.p. 116-117 °C.

$[\alpha]^{25}_D = +33.3$ ($c = 0.5$ in MeOH).

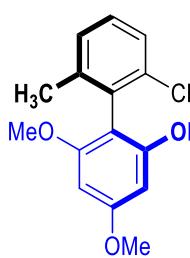
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 7.7$ Hz, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.40 (t, $J = 7.7$ Hz, 1H), 6.74 (s, 1H), 4.28 (s, 1H), 2.29 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H), 1.91 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 149.9, 139.8, 139.6, 138.1, 134.6, 133.0, 131.0, 128.4, 123.9, 120.8, 119.8, 117.7, 114.7, 20.0, 19.6, 19.1, 11.5.

HRMS (ESI, m/z) calcd. for $\text{C}_{17}\text{H}_{17}\text{NOH}^+ [\text{M}+\text{H}]^+$: 252.1383, found: 252.1386.

UPLC analysis: 96:4 er (IB-U column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.3 mL / min, $\lambda = 254$ nm), Rt (major) = 9.4 min, Rt (minor) = 5.3 min.

(R)-2'-hydroxy-4',6'-dimethoxy-6-methyl-[1,1'-biphenyl]-2-carbonitrile (3e)



White solid, 78% yield, 20.1 mg; m.p. 90-91 °C.

$[\alpha]^{25}_D = +22.8$ ($c = 0.5$ in MeOH).

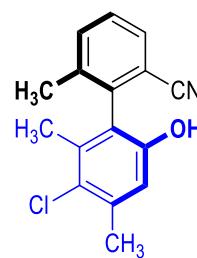
$^1\text{H NMR}$ (400 MHz, Acetone- d_6) δ 8.36 (s, 1H), 7.57 (d, $J = 7.7$ Hz, 1H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.36 (t, $J = 7.7$ Hz, 1H), 6.25 (d, $J = 1.4$ Hz, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 2.13 (s, 3H).

¹³C NMR (101 MHz, Acetone-*d*₆) δ 161.8, 158.6, 155.8, 139.9, 138.9, 133.6, 129.8, 127.4, 118.5, 115.4, 106.4, 93.9, 90.3, 55.1, 54.6, 19.1.

HRMS (ESI, m/z) calcd. for C₁₆H₁₅NO₃H⁺ [M+H]⁺: 270.1125, found: 270.1127.

HPLC analysis: 95:5 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, λ = 254 nm), Rt (major) = 30.2 min, Rt (minor) = 28.3 min.

(S)-3'-chloro-6'-hydroxy-2',4',6-trimethyl-[1,1'-biphenyl]-2-carbonitrile (3f)



White solid, 98% yield, 26.8 mg; m.p. 160-161 °C.

[*a*]_D²⁵ = +18.0 (*c* = 0.4 in MeOH).

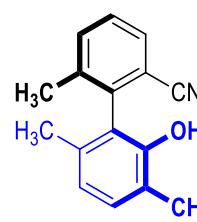
¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 6.74 (s, 1H), 4.57 (s, 1H), 2.39 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 150.4, 139.4, 139.4, 138.0, 135.1, 134.8, 131.0, 128.7, 127.1, 122.8, 117.7, 115.7, 114.5, 21.1, 19.7, 17.7.

HRMS (ESI, m/z) calcd. for C₁₆H₁₄ClNOH⁺ [M+H]⁺: 272.0837, found: 272.0845.

UPLC analysis: 86:14 er (IB-U column, 25 °C, *n*-hexane / *i*-PrOH = 97 / 3, 0.4 mL / min, λ = 254 nm), Rt (major) = 8.5 min, Rt (minor) = 6.5 min.

(S)-2'-hydroxy-3',6,6'-trimethyl-[1,1'-biphenyl]-2-carbonitrile (3g)



White solid, 97% yield, 23.0 mg; m.p. 110-111 °C.

[*a*]_D²⁵ = +28.6 (*c* = 0.5 in MeOH).

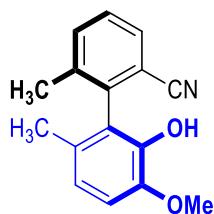
¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 4.39 (s, 1H), 2.25 (s, 3H), 2.09 (s, 3H), 1.94 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 150.4, 139.9, 139.5, 134.7, 134.4, 131.1, 128.6, 123.4, 122.2, 121.3, 117.8, 114.5, 19.6, 19.4, 15.8.

HRMS (ESI, m/z) calcd. for C₁₆H₁₅NOH⁺ [M+H]⁺: 238.1226, found: 238.1227.

UPLC analysis: 95:5 er (IB-U column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.5 mL / min, λ = 254 nm), Rt (major) = 9.2 min, Rt (minor) = 4.2 min.

(S)-2'-hydroxy-3'-methoxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (3h)



White solid, 85% yield, 21.6 mg; m.p. 83-84 °C.

$[\alpha]^{25}_D = +38.4$ ($c = 0.5$ in MeOH).

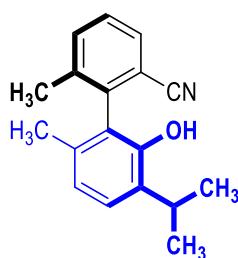
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.60 (d, $J = 7.6$ Hz, 1H), 7.52 (d, $J = 7.7$ Hz, 1H), 7.36 (t, $J = 7.7$ Hz, 1H), 6.83 (q, $J = 8.3$ Hz, 2H), 5.62 (s, 1H), 3.91 (s, 3H), 2.10 (s, 3H), 1.94 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 144.8, 142.8, 140.9, 138.8, 134.4, 130.6, 129.0, 128.1, 123.7, 121.2, 118.4, 113.9, 110.7, 56.2, 19.8, 19.1.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{H}^+ [\text{M}+\text{H}]^+$: 254.1176, found: 254.1177;

HPLC analysis: 90:10 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 40.5 min, Rt (minor) = 49.9 min.

(S)-2'-hydroxy-3'-isopropyl-6,6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (3i)



White solid, 94% yield, 25.0 mg; m.p. 74-75 °C.

$[\alpha]^{25}_D = +49.0$ ($c = 0.5$ in MeOH).

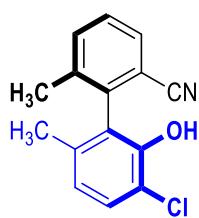
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.68 (d, $J = 7.7$ Hz, 1H), 7.60 (d, $J = 7.7$ Hz, 1H), 7.44 (t, $J = 7.7$ Hz, 1H), 7.20 (d, $J = 7.9$ Hz, 1H), 6.91 (d, $J = 7.9$ Hz, 1H), 4.34 (s, 1H), 3.17 – 3.27 (m, 1H), 2.12 (s, 3H), 1.96 (s, 3H), 1.31 – 1.26 (m, 6H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 149.3, 139.7, 139.7, 134.8, 133.9, 132.1, 131.2, 128.7, 126.4, 123.4, 122.4, 117.6, 114.8, 27.1, 22.7, 22.5, 19.6, 19.3.

HRMS (ESI, m/z) calcd. for $\text{C}_{18}\text{H}_{19}\text{NOH}^+ [\text{M}+\text{H}]^+$: 266.1540, found: 266.1541.

UPLC analysis: 96:4 er (IB-U column, 25 °C, *n*-hexane / *i*-PrOH = 97 / 3, 0.3 mL / min, $\lambda = 254$ nm), Rt (major) = 6.8 min, Rt (minor) = 4.4 min.

(S)-3'-chloro-2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (3j)



White solid, 77% yield, 19.9 mg; m.p. 223-224 °C.

$[\alpha]^{25}_D = +54.1$ ($c = 0.5$ in MeOH).

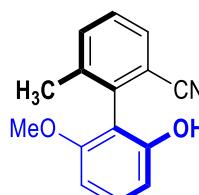
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.61 (d, $J = 7.7$ Hz, 1H), 7.54 (d, $J = 7.7$ Hz, 1H), 7.39 (t, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 1H), 6.87 (d, $J = 8.3$ Hz, 1H), 5.51 (s, 1H), 2.09 (s, 3H), 1.97 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 148.3, 140.0, 138.6, 136.8, 134.5, 130.6, 128.9, 128.3, 125.1, 123.0, 118.0, 117.7, 113.6, 19.7, 19.3.

HRMS (ESI, m/z) calcd. for $\text{C}_{15}\text{H}_{12}\text{ClNOH}^+$ [$\text{M}+\text{H}$] $^+$: 258.0680, found: 258.0681.

HPLC analysis: 86:14 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 40.2 min, Rt (minor) = 27.9 min.

(R)-2'-hydroxy-6'-methoxy-6-methyl-[1,1'-biphenyl]-2-carbonitrile (3k)



White solid, 83% yield, 19.9 mg; m.p. 223-224 °C.

$[\alpha]^{25}_D = +64.3$ ($c = 0.5$ in MeOH).

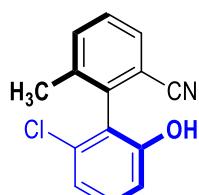
$^1\text{H NMR}$ (400 MHz, Acetone- d_6) δ 8.41 (s, 1H), 7.60 (dd, $J = 7.7$, 0.6 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.38 (t, $J = 7.7$ Hz, 1H), 7.25 (t, $J = 8.3$ Hz, 1H), 6.69 – 6.62 (m, 2H), 3.71 (s, 3H), 2.12 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, Acetone- d_6) δ 157.9, 155.2, 139.4, 138.9, 133.7, 130.1, 129.9, 127.6, 118.4, 114.8, 113.6, 108.7, 102.6, 55.2, 19.1.

HRMS (ESI, m/z) calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_2\text{H}^+$ [$\text{M}+\text{H}$] $^+$: 240.1020, found: 240.1020.

UPLC analysis: 93:7 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.5 mL / min, $\lambda = 254$ nm), Rt (major) = 4.7 min, Rt (minor) = 10.8 min.

(R)-2'-chloro-6'-hydroxy-6-methyl-[1,1'-biphenyl]-2-carbonitrile (3l)



White solid, 89% yield, 21.6 mg; m.p. 175-176 °C.

$[\alpha]^{25}_D = +38.5$ ($c = 0.5$ in MeOH).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (d, $J = 7.7$ Hz, 1H), 7.57 (d, $J = 7.6$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.25 (dd, $J = 10.7$, 5.6 Hz, 1H),

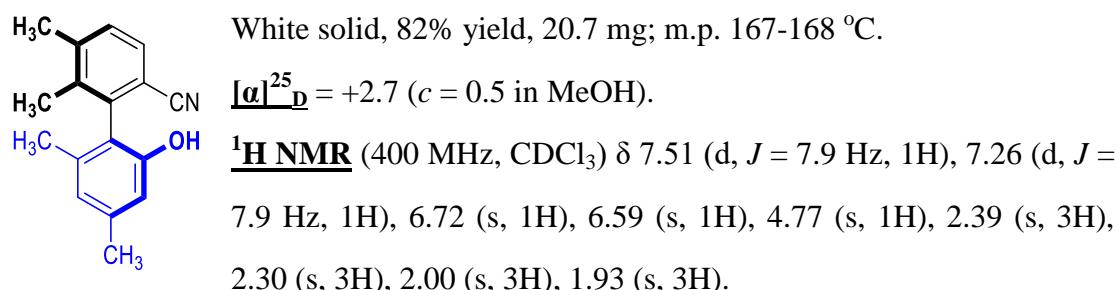
7.13 (d, $J = 0.9$ Hz, 1H), 6.84 (dd, $J = 8.2, 0.9$ Hz, 1H), 5.12 (s, 1H), 2.15 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 154.0, 139.5, 138.0, 134.7, 134.0, 130.7, 130.7, 128.9, 123.5, 121.8, 117.8, 114.5, 114.1, 19.6.

HRMS (ESI, m/z) calcd. for $\text{C}_{14}\text{H}_{10}\text{ClNOH}^+$ $[\text{M}+\text{H}]^+$: 244.0524, found: 244.0524.

UPLC analysis: 95:5 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.5 mL / min, λ = 254 nm), Rt (major) = 3.4 min, Rt (minor) = 4.7 min.

(S)-2'-hydroxy-4',5,6,6'-tetramethyl-[1,1'-biphenyl]-2-carbonitrile (3m)

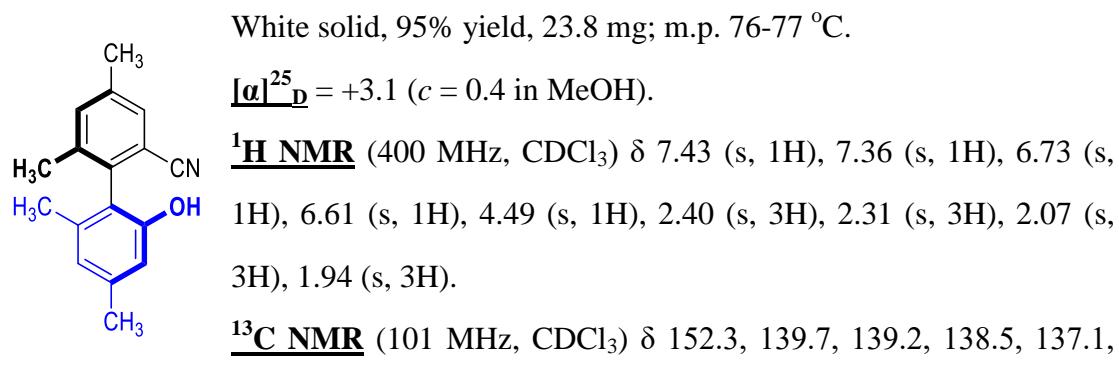


$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 152.4, 143.1, 139.7, 139.6, 138.0, 137.0, 130.5, 129.9, 123.5, 121.6, 118.4, 113.9, 111.9, 21.3, 21.2, 19.6, 16.2.

HRMS (ESI, m/z) calcd. for $\text{C}_{17}\text{H}_{17}\text{NOH}^+$ $[\text{M}+\text{H}]^+$: 252.1382, found: 252.1388.

HPLC analysis: 97:3 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.4 mL / min, λ = 254 nm), Rt (major) = 37.3 min, Rt (minor) = 27.9 min.

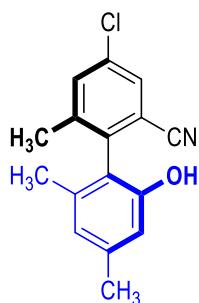
(S)-2'-hydroxy-4,4',6,6'-tetramethyl-[1,1'-biphenyl]-2-carbonitrile (3n)



HRMS (ESI, m/z) calcd. for $\text{C}_{17}\text{H}_{17}\text{NOH}^+$ $[\text{M}+\text{H}]^+$: 252.1382, found: 252.1387.

HPLC analysis: 97:3 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, λ = 254 nm), Rt (major) = 27.6 min, Rt (minor) = 46.2 min.

(S)-4-chloro-2'-hydroxy-4',6,6'-trimethyl-[1,1'-biphenyl]-2-carbonitrile (3o)



White solid, 62% yield, 16.6 mg; m.p. 70-71 °C.

$[\alpha]^{25}_D = +10.3$ ($c = 0.4$ in MeOH).

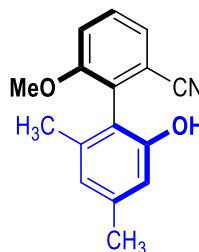
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.59 (d, $J = 1.9$ Hz, 1H), 7.53 (d, $J = 1.6$ Hz, 1H), 6.74 (s, 1H), 6.59 (s, 1H), 4.53 (s, 1H), 2.32 (s, 3H), 2.10 (s, 3H), 1.95 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 152.1, 141.3, 140.1, 139.0, 137.1, 134.5, 133.9, 130.2, 123.8, 120.0, 116.8, 115.8, 114.0, 21.3, 19.7, 19.4.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{14}\text{ClNOH}^+$ [$\text{M}+\text{H}$] $^+$: 272.0837, found: 272.0840.

HPLC analysis: 94:6 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 21.1 min, Rt (minor) = 23.0 min.

(R)-2'-hydroxy-6-methoxy-4',6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (3p)



White solid, 97% yield, 24.7 mg; m.p. 138-139 °C.

$[\alpha]^{25}_D = +33.4$ ($c = 0.5$ in CHCl_3).

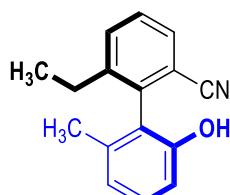
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42 (t, $J = 8.0$ Hz, 1H), 7.35 (dd, $J = 7.7, 0.9$ Hz, 1H), 7.20 (d, $J = 8.3$ Hz, 1H), 6.72 (s, 1H), 6.55 (s, 1H), 4.96 (s, 1H), 3.76 (s, 3H), 2.28 (s, 3H), 1.99 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 157.7, 152.8, 139.8, 137.9, 129.8, 129.6, 125.0, 123.5, 118.3, 117.8, 115.6, 115.6, 114.1, 56.1, 21.4, 19.6.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{H}^+$ [$\text{M}+\text{H}$] $^+$: 254.1175, found: 254.1174.

UPLC analysis: 98:2 er (IB-U column, 25 °C, *n*-hexane / *i*-PrOH = 70 / 30, 0.8 mL / min, $\lambda = 254$ nm), Rt (major) = 8.9 min, Rt (minor) = 6.7 min.

(S)-6-ethyl-2'-hydroxy-6'-methyl-[1,1'-biphenyl]-2-carbonitrile (3q)



White solid, 82% yield, 19.4 mg; m.p. 82-83 °C.

$[\alpha]^{25}_D = -14.7$ ($c = 0.5$ in MeOH).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.64 (dd, $J = 13.2, 7.7$ Hz, 2H), 7.47 (t, $J = 7.8$ Hz, 1H), 7.24 (t, $J = 7.9$ Hz, 1H), 6.94 (d, $J = 7.6$

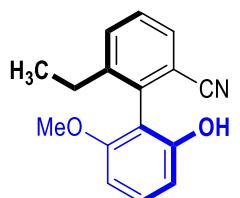
Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 4.83 (s, 1H), 2.44 (q, J = 7.6 Hz, 2H), 2.01 (s, 3H), 1.10 (t, J = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 152.6, 145.1, 139.3, 137.5, 133.1, 130.9, 129.7, 128.7, 123.7, 122.6, 117.9, 114.4, 113.3, 26.2, 19.7, 14.4.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{15}\text{NOH}^+$ $[\text{M}+\text{H}]^+$: 238.1226, found: 238.1227.

HPLC analysis: 93:7 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, λ = 254 nm), Rt (major) = 27.3 min, Rt (minor) = 34.0 min.

(*R*)-6-ethyl-2'-hydroxy-6'-methoxy-[1,1'-biphenyl]-2-carbonitrile (3r)



White solid, 91% yield, 22.9 mg; m.p. 124-125 °C.

$[\alpha]^{25}_{\text{D}} = +3.9$ ($c = 0.5$ in MeOH).

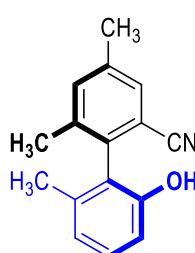
^1H NMR (400 MHz, Acetone- d_6) δ 8.39 (s, 1H), 7.63 – 7.57 (m, 2H), 7.42 (t, J = 7.7 Hz, 1H), 7.25 (t, J = 8.3 Hz, 1H), 6.68 – 6.62 (m, 2H), 3.71 (s, 3H), 2.46 (q, J = 7.6 Hz, 2H), 1.03 (t, J = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, Acetone- d_6) δ 158.1, 155.4, 145.2, 138.4, 132.3, 130.1, 129.9, 127.9, 118.3, 114.9, 113.5, 108.6, 102.5, 55.2, 26.3, 14.0.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{H}^+$ $[\text{M}+\text{H}]^+$: 254.1175, found: 254.1174.

HPLC analysis: 93:7 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.4 mL / min, λ = 254 nm), Rt (major) = 36.9 min, Rt (minor) = 38.8 min.

(*S*)-2'-hydroxy-4,6,6'-trimethyl-[1,1'-biphenyl]-2-carbonitrile (3s)



White solid, 99% yield, 22.1 mg; m.p. 130-131 °C.

$[\alpha]^{25}_{\text{D}} = -2.3$ ($c = 0.5$ in MeOH).

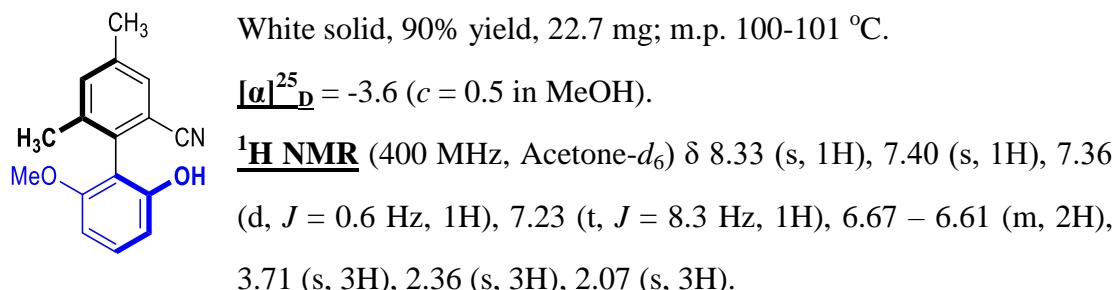
^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.38 (s, 1H), 7.21 (t, J = 7.9 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 4.56 (s, 1H), 2.41 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 152.5, 139.0, 138.7, 137.5, 136.5, 135.7, 131.4, 129.6, 123.7, 122.6, 117.9, 114.1, 113.1, 20.9, 19.6, 19.6.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{15}\text{NOH}^+$ $[\text{M}+\text{H}]^+$: 238.1226, found: 238.1228.

HPLC analysis: 97:3 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.4 mL / min, λ = 254 nm), Rt (major) = 56.2 min, Rt (minor) = 60.9 min.

(R)-2'-hydroxy-6'-methoxy-4,6-dimethyl-[1,1'-biphenyl]-2-carbonitrile (3t)

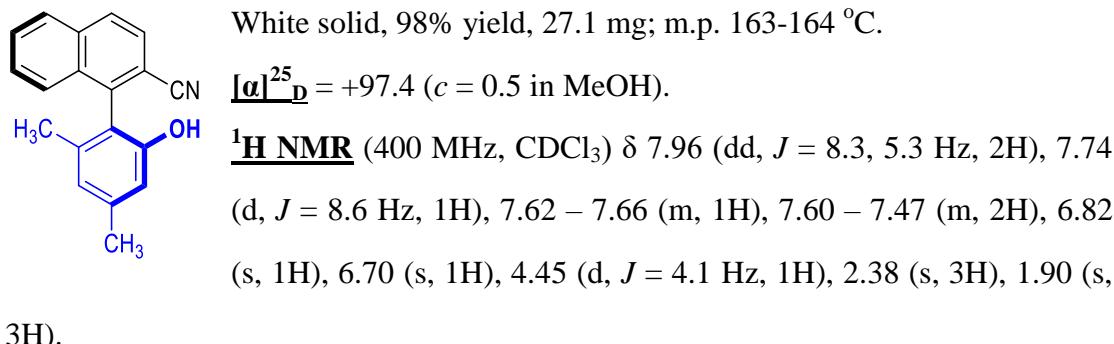


$^{13}\text{C NMR}$ (101 MHz, Acetone- d_6) δ 158.1, 155.4, 139.1, 137.5, 135.9, 134.6, 130.1, 129.9, 118.5, 114.6, 113.5, 108.6, 102.5, 55.2, 19.8, 19.0.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{H}^+ [\text{M}+\text{H}]^+$: 254.1175, found: 254.1178.

HPLC analysis: 93:7 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.4 mL / min, λ = 254 nm), Rt (major) = 39.4 min, Rt (minor) = 42.8 min.

(S)-1-(2-hydroxy-4,6-dimethylphenyl)-2-naphthonitrile (3u)

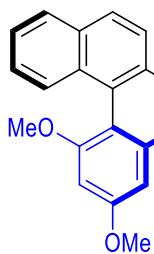


$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 151.3, 141.5, 135.7, 135.2, 131.9, 131.7, 129.4, 129.3, 128.7, 128.4, 127.2, 126.7, 122.4, 122.3, 121.7, 118.3, 111.8, 19.7, 16.0.

HRMS (ESI, m/z) calcd. for $\text{C}_{19}\text{H}_{15}\text{NOH}^+ [\text{M}+\text{H}]^+$: 274.1226, found: 274.1233.

UPLC analysis: 93:7 er (IB-U column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, λ = 254 nm), Rt (major) = 13.4 min, Rt (minor) = 10.3 min.

(R)-1-(2-hydroxy-4,6-dimethoxyphenyl)-2-naphthonitrile (3v)



White solid, 97% yield, 30.0 mg; m.p. 166-167 °C.

$[\alpha]^{25}_D = +18.5$ ($c = 0.5$ in MeOH).

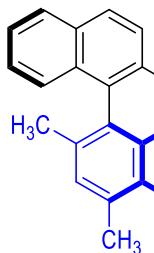
$^1\text{H NMR}$ (400 MHz, Acetone- d_6) δ 8.39 (s, 1H), 8.01 (dd, $J = 8.7, 1.8$ Hz, 2H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.66 – 7.61 (m, 2H), 7.56 – 7.50 (m, 1H), 6.34 (dd, $J = 5.2, 2.2$ Hz, 2H), 3.85 (s, 3H), 3.65 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, Acetone- d_6) δ 162.3, 159.3, 156.5, 140.4, 135.0, 132.7, 128.3, 128.2, 128.2, 127.1, 127.1, 126.7, 118.7, 112.3, 105.0, 94.0, 90.5, 55.2, 54.7.

HRMS (ESI, m/z) calcd. for $\text{C}_{19}\text{H}_{15}\text{NO}_3\text{H}^+ [\text{M}+\text{H}]^+$: 306.1125, found: 306.1127.

HPLC analysis: 95:5 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 90 / 10, 0.5 mL / min, $\lambda = 254$ nm), Rt (major) = 42.4 min, Rt (minor) = 40.1 min.

(S)-1-(2-hydroxy-3,4,6-trimethylphenyl)-2-naphthonitrile (3w)



White solid, 98% yield, 28.0 mg; m.p. 177-178 °C.

$[\alpha]^{25}_D = -21.6$ ($c = 0.5$ in MeOH).

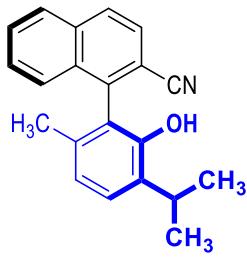
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.96 (t, $J = 7.9$ Hz, 2H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.63 – 7.67 (m, 1H), 7.49 – 7.57 (m, 2H), 6.82 (s, 1H), 4.24 (s, 1H), 2.34 (s, 3H), 2.19 (s, 3H), 1.87 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 150.8, 141.5, 138.8, 135.1, 134.2, 131.9, 129.2, 129.2, 128.6, 128.2, 127.1, 126.6, 124.2, 120.1, 119.8, 118.2, 111.9, 20.3, 19.4, 11.7.

HRMS (ESI, m/z) calcd. for $\text{C}_{20}\text{H}_{17}\text{NOH}^+ [\text{M}+\text{H}]^+$: 288.1383, found: 288.1382.

HPLC analysis: 96:4 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 62.0 min, Rt (minor) = 57.0 min.

(S)-1-(2-hydroxy-3-isopropyl-6-methylphenyl)-2-naphthonitrile (3x)



White solid, 94% yield, 28.5 mg; m.p. 138-139 °C.

$[\alpha]^{25}_D = +17.3$ ($c = 0.4$ in MeOH).

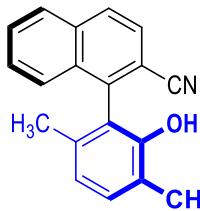
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.01 (t, $J = 8.9$ Hz, 2H), 7.79 (d, $J = 8.5$ Hz, 1H), 7.67 – 7.71 (m, 1H), 7.56 (dd, $J = 4.6, 1.8$ Hz, 2H), 7.31 (d, $J = 7.9$ Hz, 1H), 6.99 (d, $J = 7.9$ Hz, 1H), 4.34 (s, 1H), 3.19 – 3.30 (m, 1H), 1.92 (s, 3H), 1.34 (d, $J = 1.3$ Hz, 3H), 1.32 (d, $J = 1.3$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 150.1, 141.2, 135.1, 135.0, 132.3, 131.7, 129.3, 129.2, 128.6, 128.3, 127.1, 126.8, 126.5, 122.5, 122.2, 118.0, 111.9, 27.1, 22.7, 22.7, 19.5.

HRMS (ESI, m/z) calcd. for $\text{C}_{21}\text{H}_{19}\text{NOH}^+ [\text{M}+\text{H}]^+$: 302.1540, found: 302.1538.

HPLC analysis: 90:10 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 34.6 min, Rt (minor) = 53.3 min.

(S)-1-(2-hydroxy-3,6-dimethylphenyl)-2-naphthonitrile (3y)



White solid, 98% yield, 26.8 mg; m.p. 134-135 °C.

$[\alpha]^{25}_D = +24.7$ ($c = 0.5$ in MeOH).

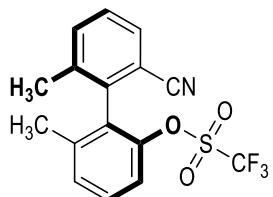
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.97 (t, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 8.6$ Hz, 1H), 7.63 – 7.67 (m, 1H), 7.52 (dd, $J = 4.8, 1.8$ Hz, 2H), 7.19 (d, $J = 7.7$ Hz, 1H), 6.90 (d, $J = 7.7$ Hz, 1H), 4.34 (d, $J = 2.4$ Hz, 1H), 2.29 (s, 3H), 1.89 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 151.3, 141.5, 135.7, 135.2, 131.9, 131.7, 129.4, 129.3, 128.7, 128.4, 127.2, 126.7, 122.4, 122.3, 121.7, 118.3, 111.8, 19.7, 16.0.

HRMS (ESI, m/z) calcd. for $\text{C}_{19}\text{H}_{15}\text{NOH}^+ [\text{M}+\text{H}]^+$: 274.1226, found: 274.1232.

HPLC analysis: 86:14 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 96 / 4, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 31.6 min, Rt (minor) = 28.0 min.

(S)-2'-cyano-6,6'-dimethyl-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (5)



Colourless oil, 90% yield, 213.6 mg.

$[\alpha]^{25}_D = +12.8$ ($c = 0.5$ in CHCl_3).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.63 (d, $J = 7.7$ Hz, 1H), 7.56 (d, $J = 7.4$ Hz, 1H), 7.44 (td, $J = 7.8, 3.4$ Hz, 2H), 7.39 (d, $J = 7.2$ Hz, 1H), 7.29 (d, $J = 8.1$ Hz, 1H), 2.11 (d, $J = 4.2$ Hz, 6H).

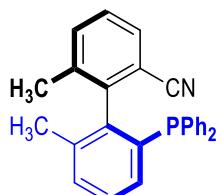
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 146.9, 139.7, 138.8, 137.4, 134.7, 130.8, 130.7, 130.4, 130.3, 129.1, 119.1, 118.3 (q, $J = 321.2$ Hz), 117.5, 114.0, 19.7, 19.6.

$^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ -74.6.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{12}\text{F}_3\text{NO}_3\text{SNa}^+ [\text{M}+\text{Na}]^+$: 378.0382, found 378.0385.

HPLC analysis: 97:3 er (IE column, 25 °C, *n*-hexane / *i*-PrOH = 98 / 2, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 25.4 min, Rt (minor) = 24.1 min.

(S)-2'-(diphenylphosphanyl)-6,6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (6)



White solid, 73% yield, 170.7 mg; m.p. 129-130 °C.

$[\alpha]^{25}_D = +21.6$ ($c = 0.5$ in CHCl_3).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.47 (d, $J = 7.6$ Hz, 1H), 7.41 (d, $J = 7.6$ Hz, 1H), 7.35 – 7.26 (m, 9H), 7.18 – 7.22 (m, 4H), 7.03 – 7.06 (m, 1H), 1.97 (s, 3H), 1.81 (s, 3H).

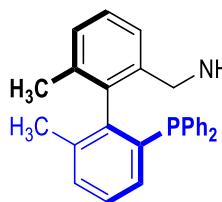
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 143.8 (d, $J = 7.3$ Hz), 142.9 (d, $J = 31.4$ Hz), 138.4 (d, $J = 2.2$ Hz), 137.4 (d, $J = 11.3$ Hz), 136.4 (dd, $J = 11.2, 7.8$ Hz), 136.2 (d, $J = 5.9$ Hz), 134.3 – 133.5 (m), 134.2, 132.0, 131.2, 130.3, (d, $J = 12.0$ Hz), 128.7 (d, $J = 12.0$ Hz), 128.5 (d, $J = 9.4$ Hz), 128.5 – 128.3 (m), 127.9, 118.1, 114.2 (d, $J = 3.0$ Hz), 19.9 (d, $J = 2.7$ Hz), 19.8 (d, $J = 3.7$ Hz).

$^{31}\text{P NMR}$ (162 MHz, CDCl_3) δ -13.94.

HRMS (ESI, m/z) calcd. for $\text{C}_{27}\text{H}_{22}\text{NPH}^+ [\text{M}+\text{H}]^+$: 392.1563, found 392.1562.

HPLC analysis: 97:3 er (ID column, 25 °C, *n*-hexane / *i*-PrOH = 90 / 10, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 14.0 min, Rt (minor) = 18.5 min.

(S)-(2'-(diphenylphosphanyl)-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methanamine (7)



White solid, 80% yield, 81.0 mg; m.p. 96-97 °C.

$[\alpha]^{25}_{D} = +71.9$ ($c = 0.5$ in CHCl_3).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.4 – 7.3 (m, 6H), 7.3 – 7.2 (m, 6H), 7.1 (td, $J = 7.6, 1.7$ Hz, 2H), 7.1 – 7.0 (m, 2H), 3.4 (d, $J = 14.8$ Hz, 1H), 3.2 (d, $J = 14.9$ Hz, 1H), 2.9 (s, 2H), 1.9 (s, 3H), 1.6 (s, 3H).

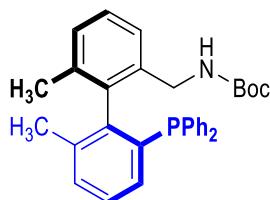
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 144.8 (d, $J = 32.2$ Hz), 138.8 (d, $J = 1.6$ Hz), 138.2 (d, $J = 7.9$ Hz), 137.0 (d, $J = 9.5$ Hz), 136.7, 136.5, 136.5, 134.1 (d, $J = 7.2$ Hz), 133.9 (d, $J = 7.0$ Hz), 131.8, 131.0, 128.7, 128.6 (d, $J = 1.9$ Hz), 128.6 – 128.1 (m), 127.6, 124.4, 43.5 (d, $J = 2.8$ Hz), 20.0 (d, $J = 2.7$ Hz), 20.0 (d, $J = 3.3$ Hz).

$^{31}\text{P NMR}$ (162 MHz, CDCl_3) δ -14.41.

HRMS (ESI, m/z) calcd. for $\text{C}_{27}\text{H}_{26}\text{NPH}^+ [\text{M}+\text{H}]^+$: 396.1876, found 396.18730.

tert-butyl

(S)-((2'-(diphenylphosphanyl)-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methyl)carbamate (8)



White solid, 80% yield, 170.7 mg.

$[\alpha]^{25}_{D} = +93.3$ ($c = 0.2$ in CHCl_3).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36 – 7.25 (m, 8H), 7.21 (td, $J = 7.5, 1.9$ Hz, 3H), 7.18 – 7.09 (m, 4H), 7.07 – 7.00 (m, 1H), 3.96 – 4.03 (m, 1H), 3.33 – 3.23 (m, 1H), 1.90 (s, 3H), 1.71 (s, 3H), 1.41 (s, 9H).

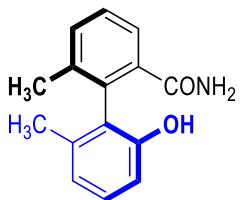
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 156.0, δ 144.6 (d, $J = 32.0$ Hz), 138.4 (d, $J = 7.9$ Hz), 136.9, 136.8, 136.7, 136.6 – 136.3 (m), 134.3 (d, $J = 20.4$ Hz), 133.9 (d, $J = 20.3$ Hz), 131.7, 131.0, 128.8 (d, $J = 6.6$ Hz), 128.5, 128.4 (dd, $J = 18.2, 5.7$ Hz), 79.0, 42.3, 28.5, 20.1 (d, $J = 3.7$ Hz), 19.9 (d, $J = 2.5$ Hz).

$^{31}\text{P NMR}$ (162 MHz, CDCl_3) δ -14.52.

HRMS (ESI, m/z) calcd. for $\text{C}_{32}\text{H}_{34}\text{NO}_2\text{PNa}^+ [\text{M}+\text{Na}]^+$: 518.2219, found 518.2213.

HPLC analysis: 97:3 er (AS-H column, 25 °C, *n*-hexane / *i*-PrOH = 98 / 2, 0.5 mL / min, $\lambda = 254$ nm), Rt (major) = 12.3 min, Rt (minor) = 10.2 min.

(S)-2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carboxamide (9)



White solid, 93% yield, 47.8 mg; m.p. 129-130 °C.

$[\alpha]^{25}_D = +37.3$ ($c = 0.4$ in MeOH).

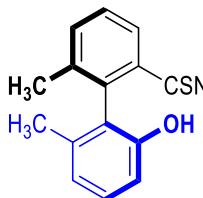
$^1\text{H NMR}$ (400 MHz, Acetone- d_6) δ 8.09 (s, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.31 (t, $J = 7.6$ Hz, 1H), 7.12 (t, $J = 7.8$ Hz, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 6.47 (d, $J = 30.0$ Hz, 2H), 1.95 (s, 3H), 1.86 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, Acetone- d_6) δ 172.2, 155.1, 138.6, 138.6, 138.4, 135.7, 132.2, 129.5, 128.3, 128.1, 126.4, 122.8, 114.8, 20.2, 20.1.

HRMS (ESI, m/z) calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}_2\text{Na}^+$ [$\text{M}+\text{Na}$] $^+$: 264.0995, found: 264.0999.

UPLC analysis: 96:4 er (IC-U column, 25 °C, *n*-hexane / *i*-PrOH = 90 / 10, 0.5 mL / min, $\lambda = 254$ nm), Rt (major) = 8.0 min, Rt (minor) = 7.0 min.

(S)-2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-carbothioamide (10)



A yellow solid, 83% yield, 42.8 mg; m.p. 118-119 °C.

$[\alpha]^{25}_D = -95.6$ ($c = 0.5$ in MeOH).

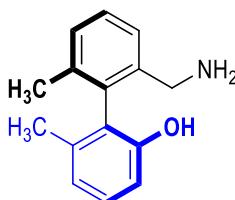
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.61 (dd, $J = 7.1, 2.1$ Hz, 1H), 7.42 (s, 1H), 7.37 – 7.30 (m, 2H), 7.16 (q, $J = 7.8$ Hz, 2H), 6.87 (dt, $J = 7.7, 1.0$ Hz, 1H), 6.76 (d, $J = 8.1$ Hz, 1H), 5.35 (s, 1H), 1.95 (d, $J = 4.6$ Hz, 6H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 205.1, 152.2, 142.6, 138.1, 137.7, 131.8, 130.7, 129.1, 128.3, 126.7, 125.8, 123.3, 113.2, 19.9, 19.8.

HRMS (ESI, m/z) calcd. for $\text{C}_{15}\text{H}_{15}\text{NOSH}^+$ [$\text{M}+\text{H}$] $^+$: 258.0947, found: 258.0939.

UPLC analysis: 99:1 er (IA-U column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 4.9 min, Rt (minor) = 5.8 min.

(S)-2'-(aminomethyl)-6,6'-dimethyl-[1,1'-biphenyl]-2-ol (11)



White solid, 71% yield, 72.1 mg; m.p. 161-162 °C.

$[\alpha]^{25}_D = +107.0$ ($c = 0.5$ in CHCl_3).

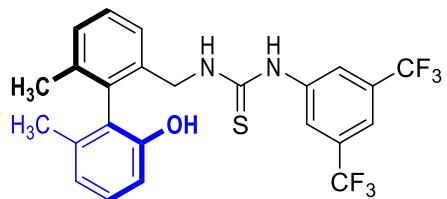
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.24 (dd, $J = 5.0, 2.5$ Hz, 2H),

7.18 – 7.10 (m, 2H), 6.85 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 4.18 (s, 3H), 3.57 (d, J = 12.6 Hz, 1H), 3.41 (d, J = 12.4 Hz, 1H), 1.94 (s, 3H), 1.84 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 154.2, 139.8, 138.0, 137.1, 136.6, 129.7, 128.5, 128.0, 127.9, 126.1, 122.1, 115.8, 45.0, 19.9, 19.8.

HRMS (ESI, m/z) calcd. for $\text{C}_{15}\text{H}_{17}\text{NONa}^+$ $[\text{M}+\text{Na}]^+$: 250.1202, found: 250.1199.

(S)-1-(3,5-bis(trifluoromethyl)phenyl)-3-((2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methyl)thiourea (12)



White solid, 90% yield, 79.0 mg; m.p. 67-68 °C.

$[\alpha]^{25}_{\text{D}} = -142.2$ ($c = 0.5$ in CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.93 (s, 1H), 7.67 (d, J = 15.8 Hz, 3H), 7.43 (d, J = 7.1 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.10 (t, J = 7.9 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.41 (s, 1H), 4.70 (s, 2H), 4.17 (dd, J = 14.6, 4.7 Hz, 1H), 1.96 (s, 3H), 1.86 (s, 3H).

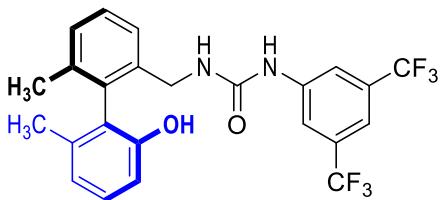
^{13}C NMR (101 MHz, CDCl_3) δ 180.3, 151.7, 138.8, 138.2, 137.3, 135.6, 134.2, 132.7 (q, J = 32.3 Hz), 130.5, 129.2, 128.9, 127.6, 125.2, 124.5, 123.0, 122.8 (q, J = 272.9 Hz), 119.5, 113.0, 47.5, 19.6, 19.6.

^{19}F NMR (377 MHz, CDCl_3) δ -63.01.

HRMS (ESI, m/z) calcd. for $\text{C}_{24}\text{H}_{20}\text{F}_6\text{N}_2\text{OSNa}^+$ $[\text{M}+\text{Na}]^+$: 521.1093, found: 521.1091.

HPLC analysis: 98:2 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 90 / 10, 0.5 mL / min, λ = 254 nm), Rt (major) = 37.2 min, Rt (minor) = 23.5 min.

(S)-1-(3,5-bis(trifluoromethyl)phenyl)-3-((2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methyl)urea (13)



White solid, 66% yield, 56.0 mg; m.p. 178-179 °C.

$[\alpha]^{25}_{\text{D}} = -92.6$ ($c = 0.5$ in CHCl_3);

^1H NMR (400 MHz, CDCl_3) δ 7.62 (s, 2H), 7.38 (s, 1H), 7.32 (s, 1H), 7.30 – 7.22 (m, 3H), 7.11 (t, J =

7.8 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 5.55 (t, J = 5.7 Hz, 1H), 5.44 (s, 1H), 4.08 (dd, J = 15.0, 6.4 Hz, 1H), 3.91 (dd, J = 14.9, 4.9 Hz, 1H), 1.93 (s, 3H), 1.85 (s, 3H).

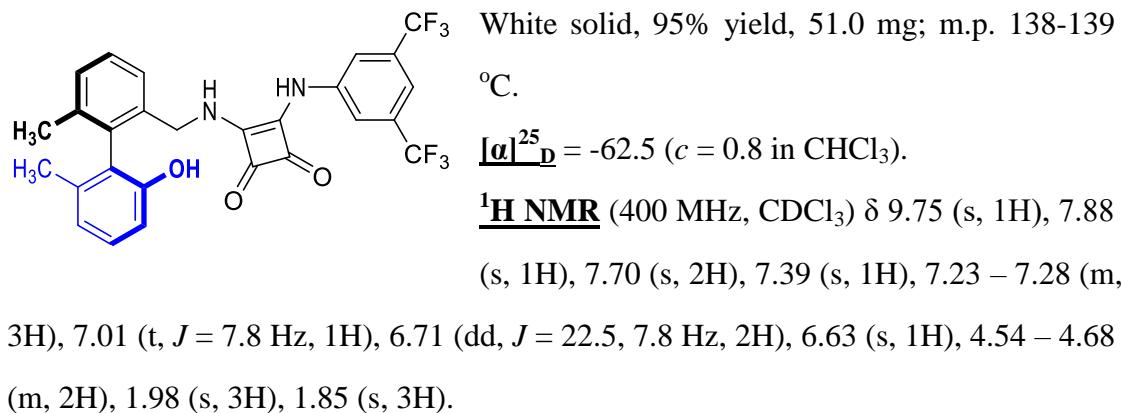
^{13}C NMR (101 MHz, CDCl_3) δ 155.0, 152.0, 140.2, 138.1, 137.3, 137.1, 134.0, 132.0 (q, J = 33.2 Hz), 130.0, 129.0, 128.7, 126.2, 125.5, 123.1 (q, J = 273.0 Hz), 122.9, 118.8, 116.0, 113.2, 42.8, 19.6, 19.5.

^{19}F NMR (377 MHz, CDCl_3) δ -63.32.

HRMS (ESI, m/z) calcd. for $\text{C}_{24}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 505.1321, found: 505.1325.

HPLC analysis: 98:2 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 85 / 15, 0.5 mL / min, λ = 254 nm), Rt (major) = 32.0 min, Rt (minor) = 17.3 min.

(*S*)-3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (14)



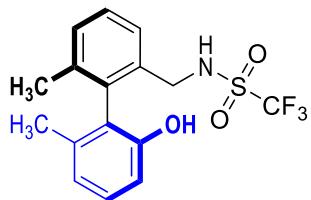
^{13}C NMR (101 MHz, CDCl_3) δ 183.4, 179.9, 169.3, 162.3, 153.1, 139.3, 138.8, 137.4, 135.5, 135.2, 132.6 (q, J = 33.5 Hz), 130.7, 128.8, 128.4, 126.8, 124.9, 124.3 – 121.4 (m), 122.8 (q, J = 272.9 Hz), 122.4, 116.9, 113.3, 48.1, 19.7, 19.5.

^{19}F NMR (377 MHz, CDCl_3) δ -63.34.

HRMS (ESI, m/z) calcd. for $\text{C}_{27}\text{H}_{20}\text{F}_6\text{N}_2\text{O}_3\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 557.1270, found: 557.1273.

HPLC analysis: 96:4 er (IB column, 25 °C, *n*-hexane / *i*-PrOH = 90 / 10, 1.0 mL / min, λ = 254 nm), Rt (major) = 32.1 min, Rt (minor) = 26.4 min.

(S)-1,1,1-trifluoro-N-((2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methyl)methanesulfonamide (15)



Colourless oil, 33% yield, 59.5 mg.

$[\alpha]^{25}_D = -15.7$ ($c = 0.4$ in CHCl_3).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.37 (s, 3H), 7.23 (d, $J = 7.9$ Hz, 1H), 6.95 (d, $J = 6.7$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 5.25 (s, 1H), 4.72 (s, 1H), 4.16 (d, $J = 13.6$ Hz, 1H), 3.96 (d, $J = 13.5$ Hz, 1H), 2.01 (s, 3H), 1.90 (s, 3H).

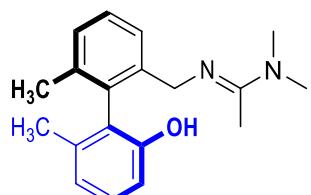
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 151.7, 138.4, 137.3, 134.9, 134.4, 131.1, 129.4, 129.1, 127.6, 124.7, 123.3, 119.6 (q, $J = 321.2$ Hz), 113.4, 47.0, 19.7, 19.6.

$^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ -77.31.

HRMS (ESI, m/z) calcd. for $\text{C}_{16}\text{H}_{16}\text{F}_3\text{NO}_3\text{SNa}^+$ $[\text{M}+\text{Na}]^+$: 382.0695, found: 382.0689.

HPLC analysis: 96:4 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 97 / 3, 0.4 mL / min, $\lambda = 254$ nm), Rt (major) = 27.7 min, Rt (minor) = 38.7 min.

(*S,E*)-*N,N'*-((2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methyl)-*N,N*-dimethylacetimidamide (16)



White solid, 64% yield, 83.5 mg; m.p. 170-171 °C.

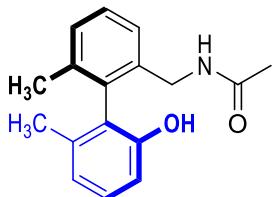
$[\alpha]^{25}_D = -241.6$ ($c = 0.5$ in CHCl_3).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.69 (s, 1H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.22 (dd, $J = 18.5, 7.6$ Hz, 2H), 7.09 (q, $J = 7.5$ Hz, 2H), 6.78 (d, $J = 7.5$ Hz, 1H), 4.32 (d, $J = 9.7$ Hz, 1H), 4.14 (d, $J = 14.3$ Hz, 1H), 3.04 (s, 6H), 1.93 (s, 3H), 1.85 (s, 3H), 1.67 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 162.5, 154.6, 137.8, 137.3, 136.7, 133.5, 130.1, 128.8, 127.8, 127.7, 125.2, 121.5, 113.9, 47.8, 41.5, 40.6, 19.7, 19.6, 14.3.

HRMS (ESI, m/z) calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}^+$ $[\text{M}+\text{H}]^+$: 297.1961, found: 297.1970.

(S)-N-((2'-hydroxy-6,6'-dimethyl-[1,1'-biphenyl]-2-yl)methyl)acetamide (17)



Colourless oil, 92% yield, 24.9 mg.

$[\alpha]^{25}_D = -7.8$ ($c = 0.2$ in CHCl_3).

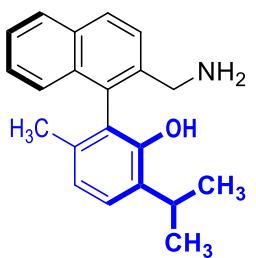
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.25 (d, $J = 2.3$ Hz, 3H), 7.16 (t, $J = 7.8$ Hz, 1H), 6.91 – 6.79 (m, 2H), 6.29 (s, 1H), 6.10 (t, $J = 5.5$ Hz, 1H), 4.19 (dd, $J = 14.4, 6.7$ Hz, 1H), 3.84 (dd, $J = 14.4, 4.4$ Hz, 1H), 1.96 (s, 3H), 1.87 (s, 3H), 1.84 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 170.2, 152.8, 137.9, 137.2, 137.0, 135.0, 129.8, 128.8, 128.4, 126.8, 125.7, 122.3, 113.4, 42.5, 23.0, 19.7, 19.7.

HRMS (ESI, m/z) calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_2\text{Na}^+$ [$\text{M}+\text{Na}$] $^+$: 292.1308, found: 292.1309.

HPLC analysis: 98:2 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 90 / 10, 1.0 mL / min, $\lambda = 254$ nm), Rt (major) = 7.0 min, Rt (minor) = 8.3 min.

(S)-2-(2-(aminomethyl)naphthalen-1-yl)-6-isopropyl-3-methylphenol (18)



White solid, 63% yield, 154.9 mg; m.p. 97-98 °C.

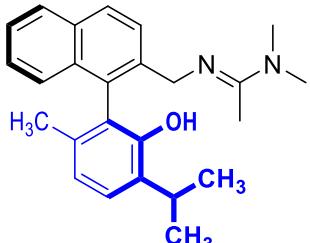
$[\alpha]^{25}_D = +17.2$ ($c = 2.0$ in CHCl_3).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.88 (t, $J = 9.1$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.43 – 7.47 (m, 1H), 7.33 – 7.37 (m, 1H), 7.32 – 7.20 (m, 2H), 6.92 (d, $J = 7.8$ Hz, 1H), 3.85 (d, $J = 12.3$ Hz, 1H), 3.68 (d, $J = 12.3$ Hz, 4H), 3.35 – 3.43 (m, 1H), 1.73 (s, 3H), 1.28 (dd, $J = 6.9, 1.2$ Hz, 6H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 151.8, 137.3, 135.3, 135.1, 134.0, 133.4, 132.9, 128.6, 128.0, 126.8, 126.7, 126.6, 125.9, 125.9, 125.4, 122.1, 45.3, 27.1, 23.1, 22.7, 19.8.

HRMS (ESI, m/z) calcd. for $\text{C}_{21}\text{H}_{23}\text{NONa}^+$ [$\text{M}+\text{Na}$] $^+$: 328.1672, found: 328.1669.

**(*S,E*)-N'-(1-(2-hydroxy-3-isopropyl-6-methylphenyl)naphthalen-2-yl)methyl)-*N*,
N-dimethylacetimidamide (19)**



White solid, 76% yield, 92.0 mg; m.p. 270-271 °C.

$[\alpha]^{25}_D = -43.5$ ($c = 0.3$ in CHCl_3).

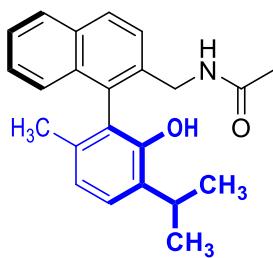
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.94 – 7.78 (m, 3H), 7.44 – 7.48 (m, 1H), 7.38 – 7.28 (m, 3H), 7.22 (d, $J = 7.8$ Hz, 1H),

6.91 (d, $J = 7.8$ Hz, 1H), 4.54 (d, $J = 15.3$ Hz, 1H), 4.40 (d, $J = 15.3$ Hz, 1H), 3.42 – 2.95 (m, 7H), 1.76 (d, $J = 4.3$ Hz, 6H), 1.24 (dd, $J = 6.9, 4.7$ Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 163.3, 150.9, 135.2, 133.4, 133.1, 132.9, 132.5, 132.2, 129.1, 128.3, 127.0, 126.9, 126.5, 126.0, 125.4, 123.4, 122.1, 46.7, 41.5, 26.9, 22.9, 22.9, 22.7, 19.6, 14.6.

HRMS (ESI, m/z) calcd. for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}\text{H}^+ [\text{M}+\text{H}]^+$: 375.2431, found: 375.2432.

(S)-N-((1-(2-hydroxy-3-isopropyl-6-methylphenyl)naphthalen-2-yl)methyl)acetamide (20)



Colourless oil, 97% yield, 33.7 mg.

$[\alpha]^{25}_D = -7.3$ ($c = 0.4$ in CHCl_3).

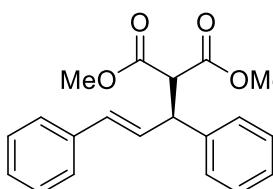
^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, $J = 8.7$ Hz, 2H), 7.53 (dd, $J = 8.5, 3.5$ Hz, 1H), 7.44 – 7.48 (m, 1H), 7.38 – 7.29 (m, 2H), 7.23 (d, $J = 7.9$ Hz, 1H), 6.92 (d, $J = 7.9$ Hz, 1H), 6.16 (t, $J = 5.9$ Hz, 1H), 4.26 – 4.32 (m, 1H), 3.99 – 4.05 (m, 1H), 3.26 – 3.36 (m, 1H), 1.82 (s, 3H), 1.76 (s, 3H), 1.30 – 1.25 (m, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 170.3, 150.4, 135.4, 135.1, 133.3, 133.2, 132.5, 132.0, 129.0, 128.2, 127.0, 126.6, 126.2, 125.9, 125.3, 124.1, 122.2, 42.2, 27.1, 23.0, 22.9, 22.7, 19.6.

HRMS (ESI, m/z) calcd. for $\text{C}_{23}\text{H}_{25}\text{NO}_2\text{Na}^+ [\text{M}+\text{Na}]^+$: 370.1778, found: 370.1769.

HPLC analysis: 96:4 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 80 / 20, 0.5 mL / min, $\lambda = 254$ nm), Rt (major) = 8.3 min, Rt (minor) = 9.1 min.

Dimethyl (S,E)-2-(1,3-diphenylallyl)malonate (23)



Colourless oil, 85% yield, 27.6 mg.

$[\alpha]^{25}_D = -8.8$ ($c = 1.0$ in CHCl_3).

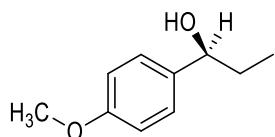
^1H NMR (400 MHz, CDCl_3) δ 7.4 – 7.2 (m, 10H), 6.5 (d, $J = 15.8$ Hz, 1H), 6.3 (dd, $J = 15.7, 8.6$ Hz, 1H), 4.3 (dd, $J = 11.1, 9.1$ Hz, 1H), 4.0 (d, $J = 10.9$ Hz, 1H), 3.7 (s, 3H), 3.5 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.3, 167.8, 140.2, 136.9, 131.9, 129.1, 128.8, 128.5, 127.9, 127.6, 127.2, 126.4, 57.7, 52.7, 52.5, 49.2.

HRMS (ESI, m/z) calcd. for $C_{20}H_{20}O_4Na^+$ [M+Na]⁺: 347.1254, found: 347.1247.

HPLC analysis: 83:17 er (AD-H column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 1.0 mL / min, λ = 254 nm), Rt (major) = 22.0 min, Rt (minor) = 15.9 min.

(S)-1-(4-methoxyphenyl)propan-1-ol (25)



Colourless oil, 95% yield, 78.9 mg.

$[\alpha]^{25}_D = -16.8$ ($c = 1.5$ in CHCl₃).

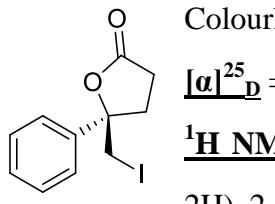
¹H NMR (400 MHz, CDCl₃) δ 7.23 (dd, J = 9.0, 2.5 Hz, 2H), 6.89 – 6.83 (m, 2H), 4.49 (t, J = 6.7 Hz, 1H), 3.78 (s, 3H), 2.13 (s, 1H), 1.86 – 1.64 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 159.0, 136.8, 127.2, 113.8, 75.6, 55.3, 31.8, 10.2.

HRMS (ESI, m/z) calcd. for $C_{10}H_{14}O_2Na^+$ [M+Na]⁺: 189.0886, found: 189.0892.

HPLC analysis: 76:24 er (OD-H column, 25 °C, *n*-hexane / *i*-PrOH = 97 / 3, 1.0 mL / min, λ = 254 nm), Rt (major) = 20.5 min, Rt (minor) = 17.8 min.

(R)-5-(iodomethyl)-5-phenyldihydrofuran-2(3H)-one (28)



Colourless oil, 92% yield, 27.8 mg.

$[\alpha]^{25}_D = +4.5$ ($c = 1.0$ in CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 7.4 – 7.3 (m, 5H), 3.6 (d, J = 1.4 Hz, 2H), 2.8 – 2.6 (m, 3H), 2.6 – 2.5 (m, 1H).

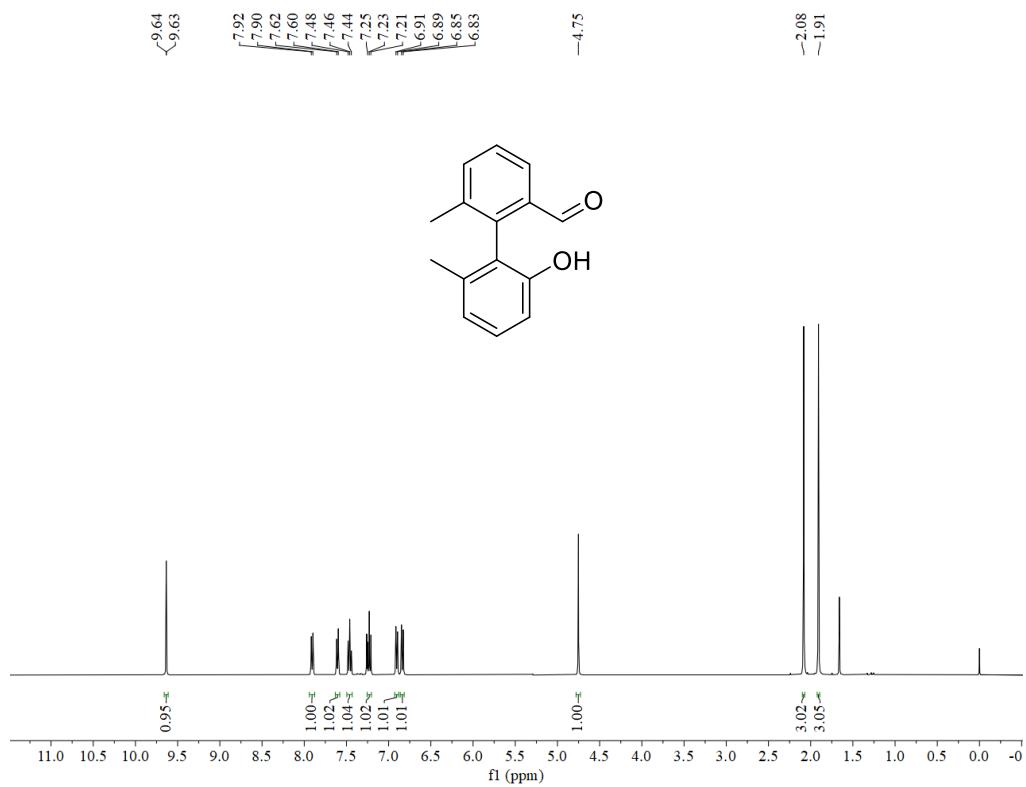
¹³C NMR (101 MHz, CDCl₃) δ 175.4, 140.6, 128.9, 128.6, 124.9, 86.0, 34.0, 29.2, 16.3.

HRMS (ESI, m/z) calcd. for $C_{11}H_{11}IO_2Na^+$ [M+Na]⁺: 324.9696, found: 324.9698.

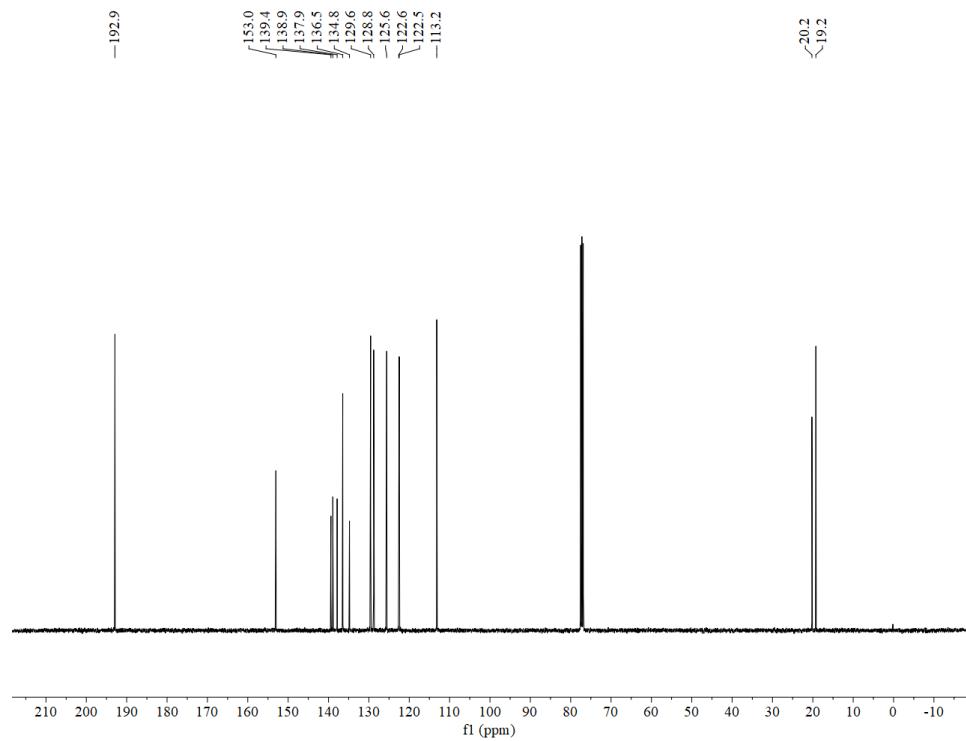
HPLC analysis: 74:26 er (OD-H column, 25 °C, *n*-hexane / *i*-PrOH = 95 / 5, 1.0 mL / min, λ = 254 nm), Rt (major) = 25.5 min, Rt (minor) = 21.4 min.

Supplementary Figures - NMR and HPLC spectra

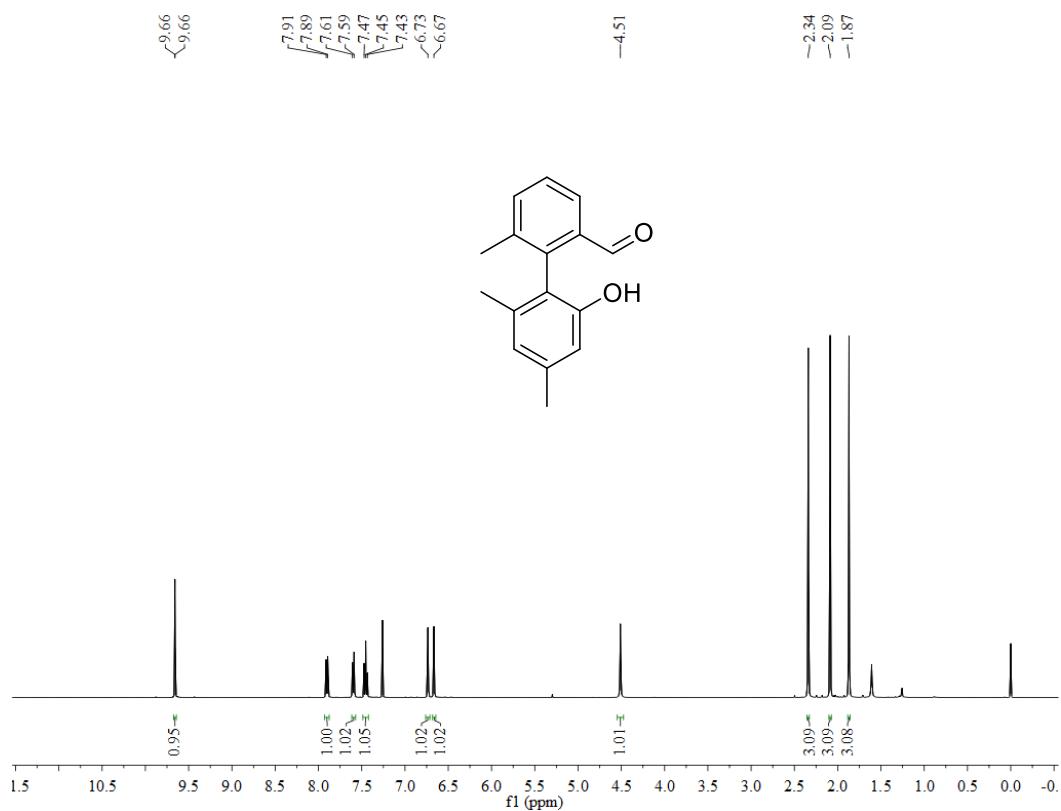
Supplementary Figure 10 ^1H NMR (400 MHz, CDCl_3) of **1a**



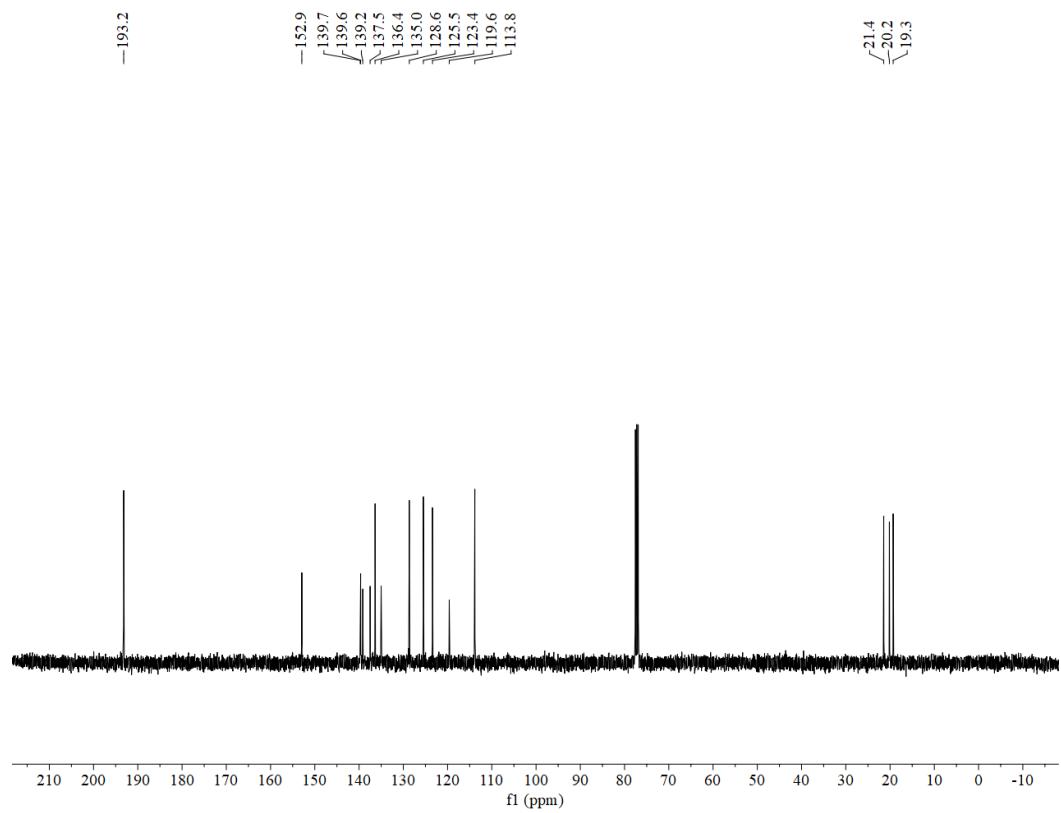
Supplementary Figure 11 ^{13}C NMR (400 MHz, CDCl_3) of **1a**



Supplementary Figure 12 ^1H NMR (400 MHz, CDCl_3) of **1b**



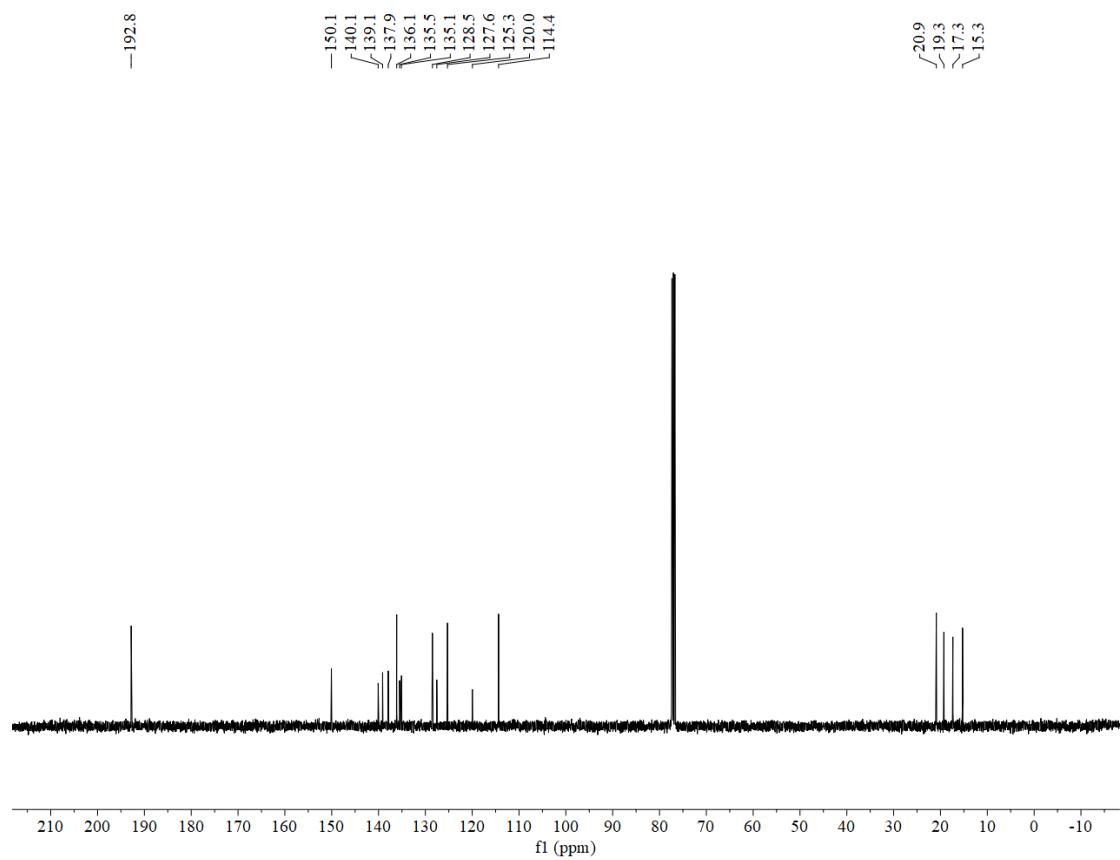
Supplementary Figure 13 ^{13}C NMR (400 MHz, CDCl_3) of **1b**



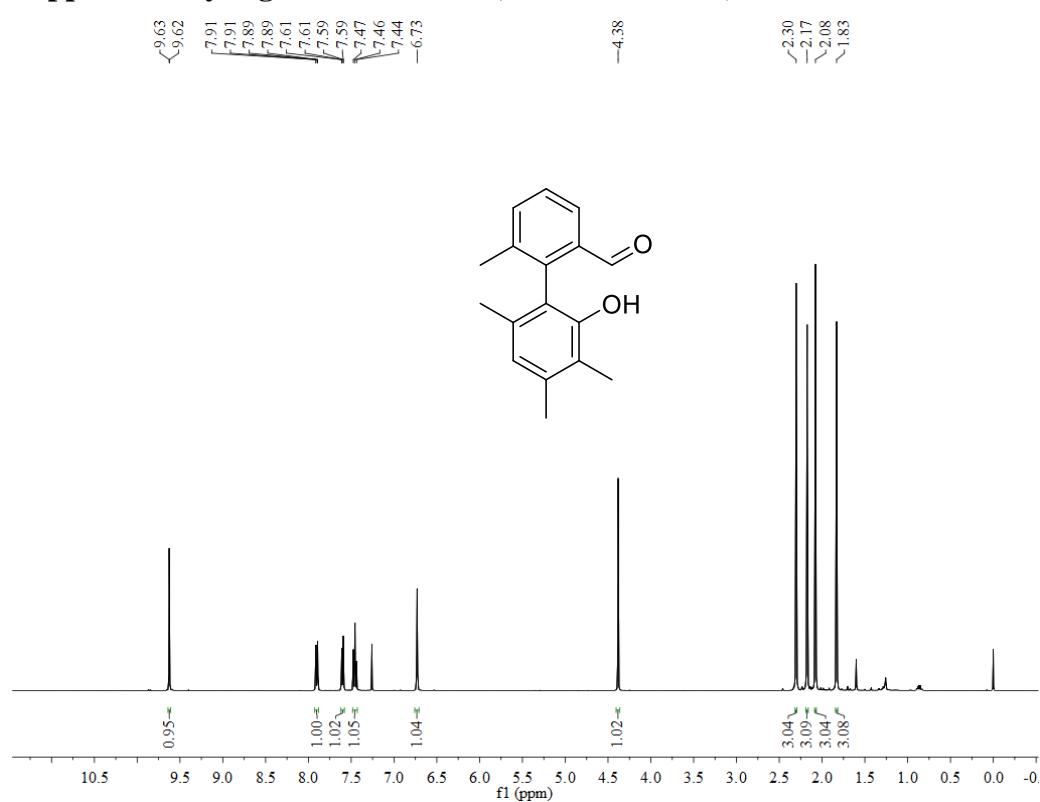
Supplementary Figure 14 ^1H NMR (400 MHz, CDCl_3) of **1c**



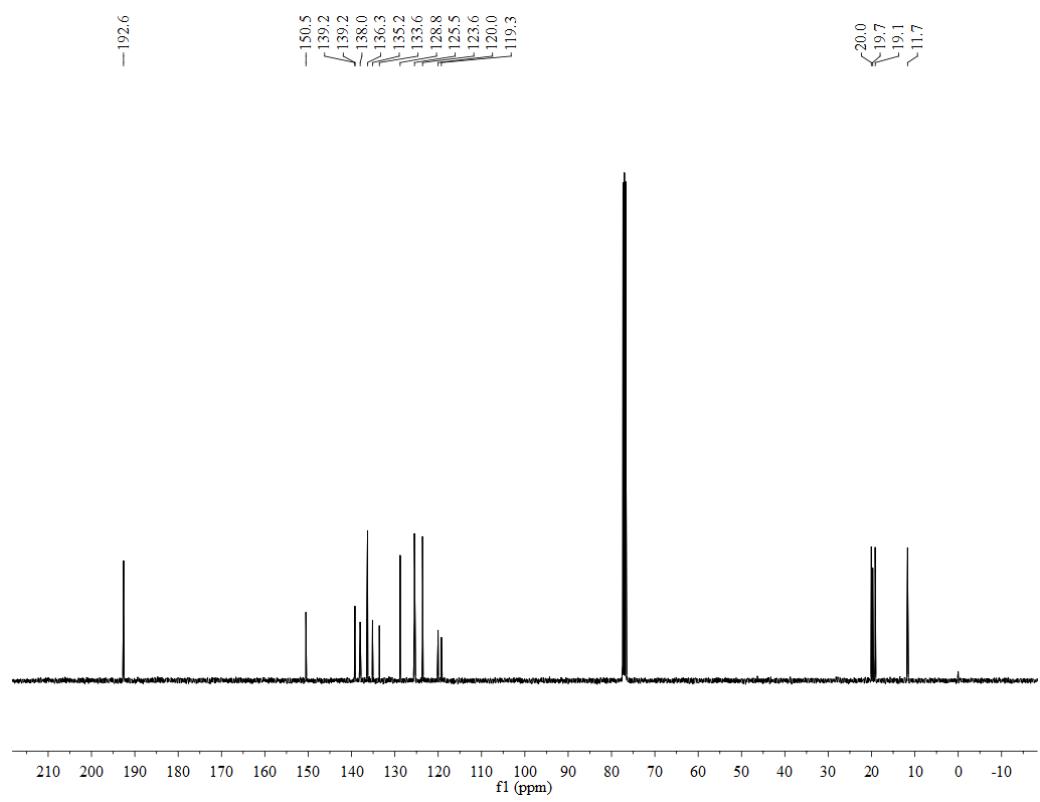
Supplementary Figure 15 ^{13}C NMR (400 MHz, CDCl_3) of **1c**



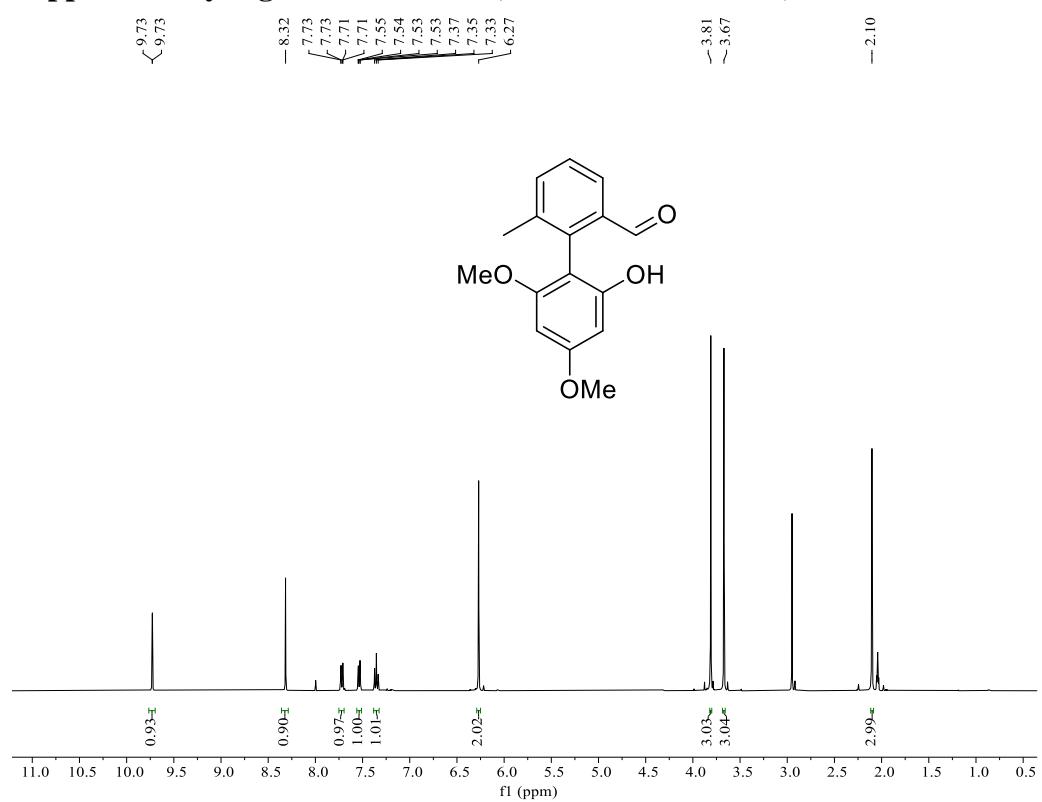
Supplementary Figure 16 ^1H NMR (400 MHz, CDCl_3) of **1d**



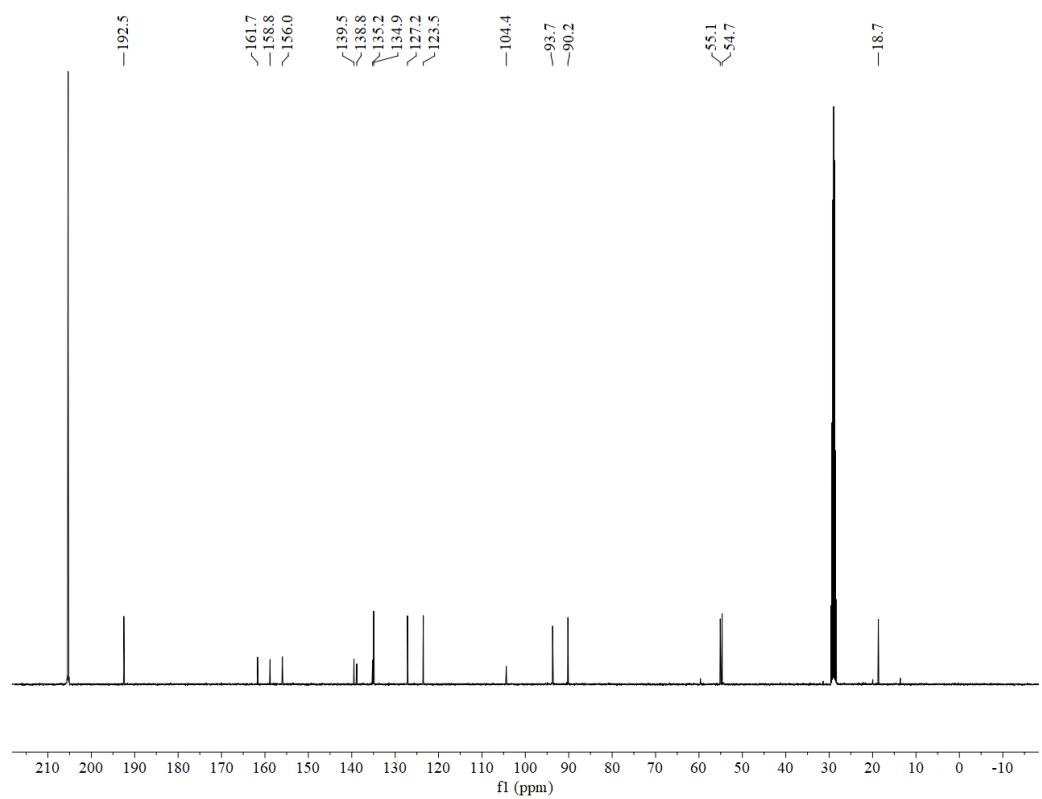
Supplementary Figure 17 ^{13}C NMR (400 MHz, CDCl_3) of **1d**



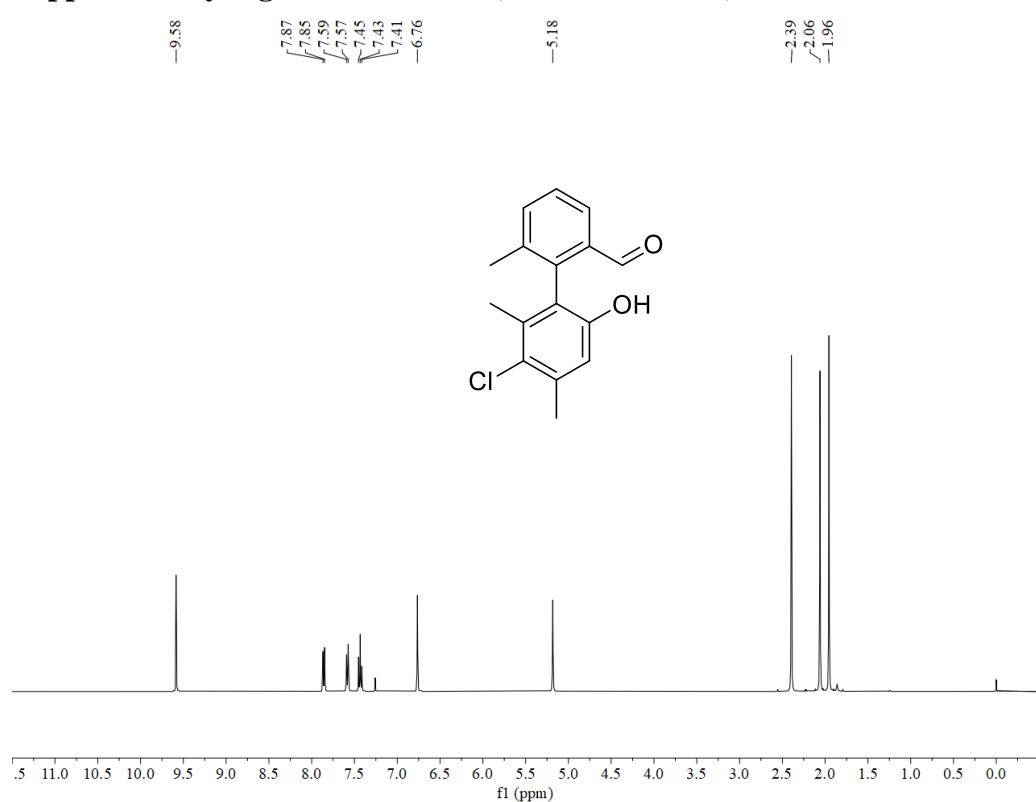
Supplementary Figure 18 ^1H NMR (400 MHz, Acetone- d_6) of **1e**



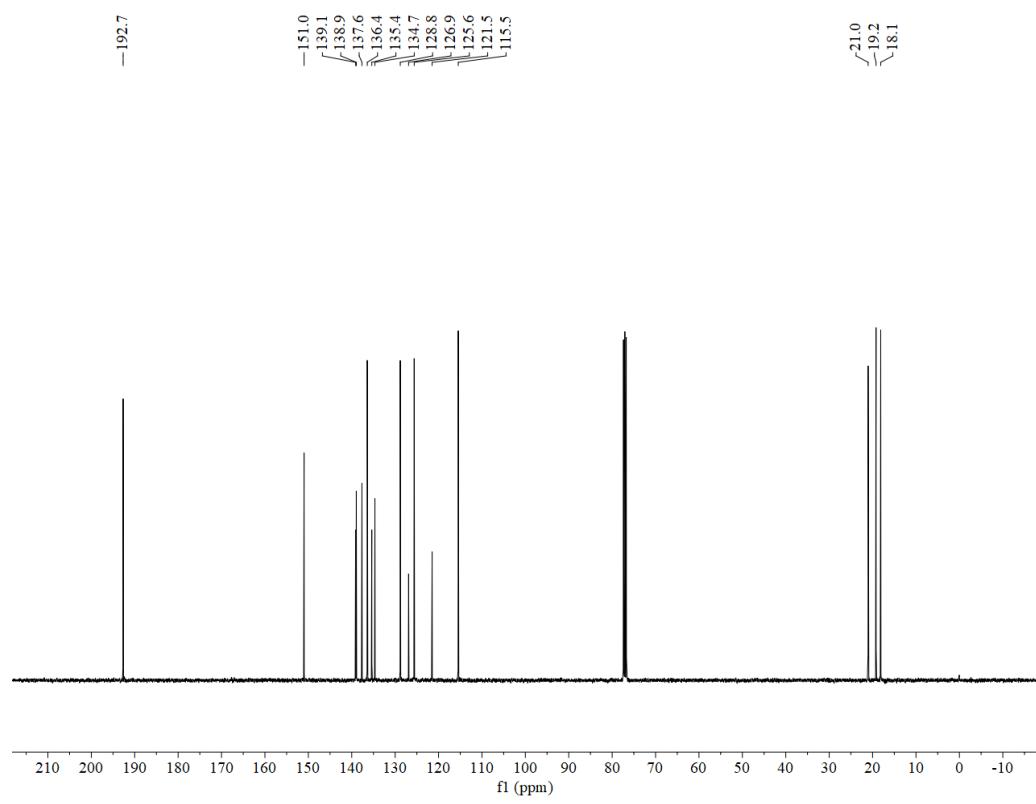
Supplementary Figure 19 ^{13}C NMR (400 MHz, Acetone- d_6) of **1e**



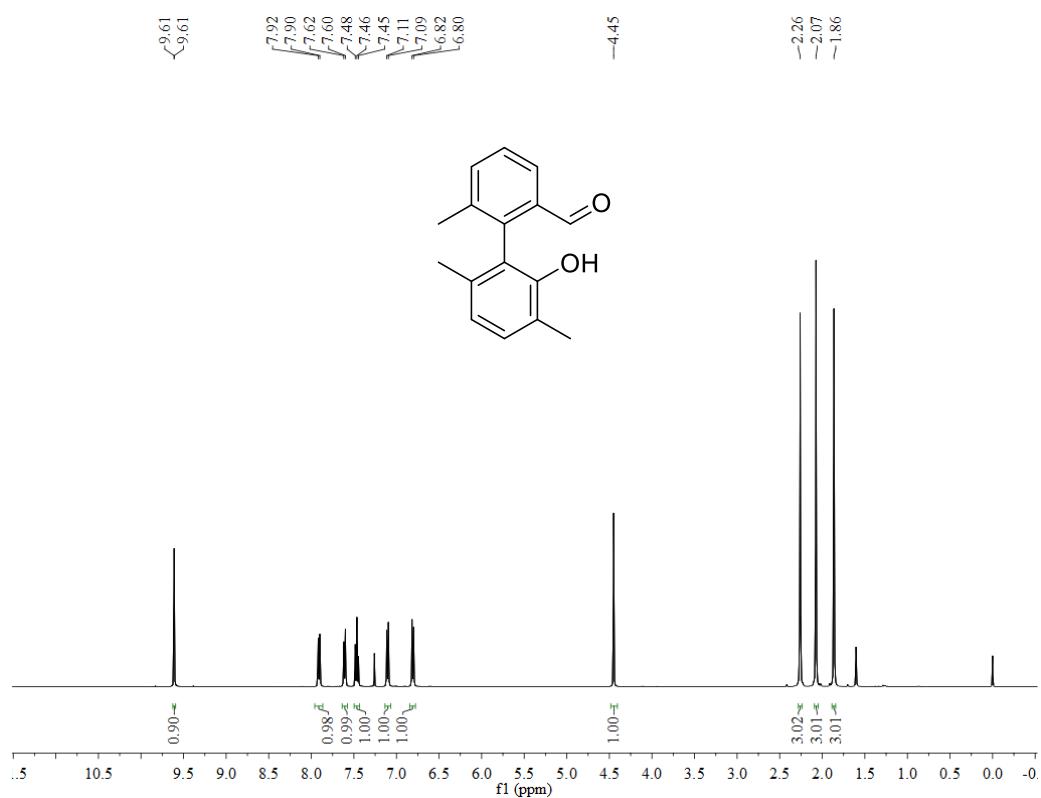
Supplementary Figure 20 ^1H NMR (400 MHz, CDCl_3) of **1f**



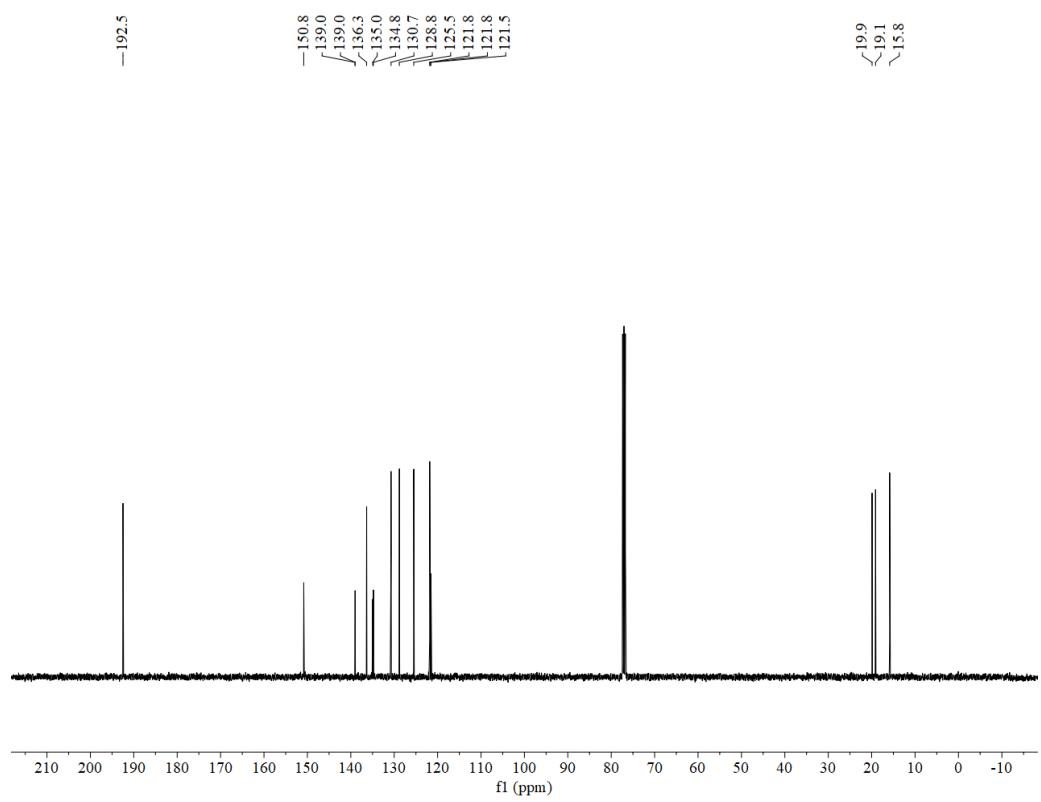
Supplementary Figure 21 ^{13}C NMR (400 MHz, CDCl_3) of **1f**



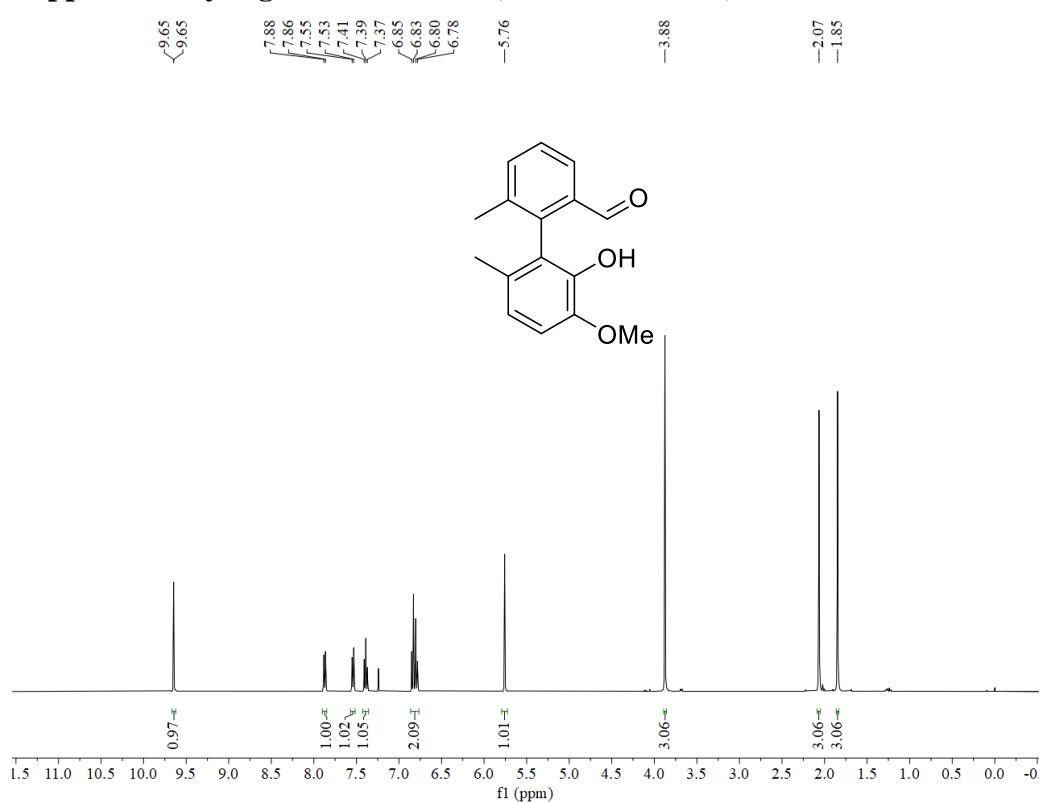
Supplementary Figure 22 ^1H NMR (400 MHz, CDCl_3) of **1g**



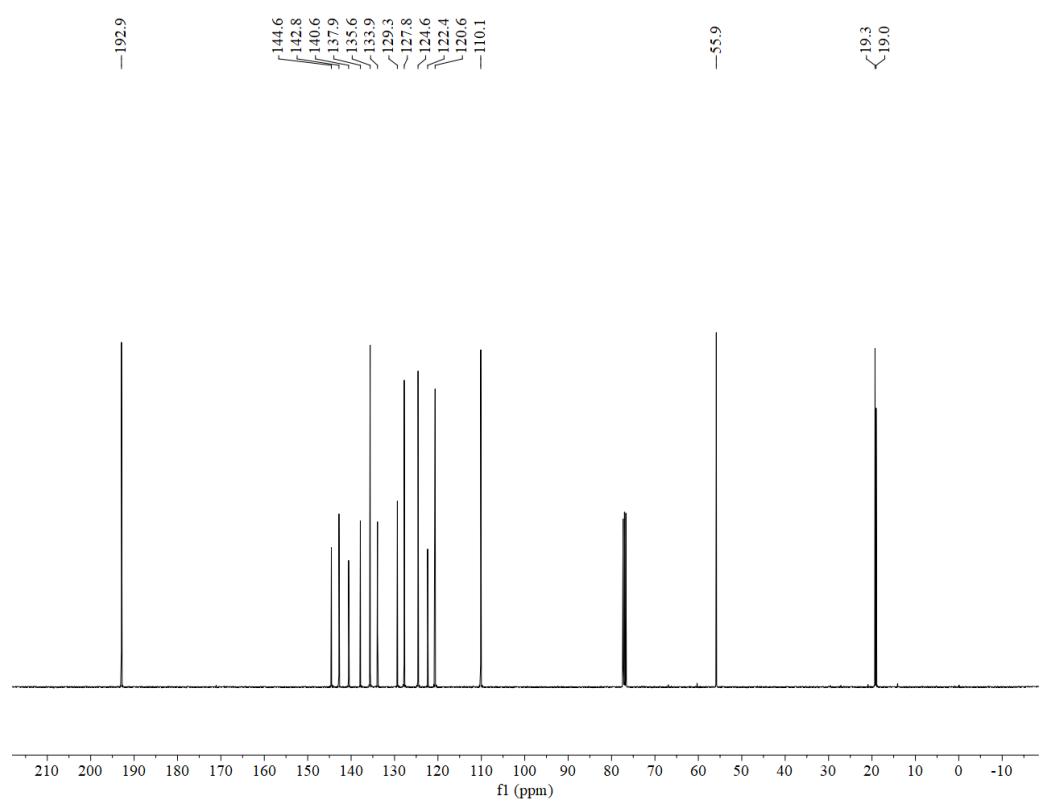
Supplementary Figure 23 ^{13}C NMR (400 MHz, CDCl_3) of **1g**



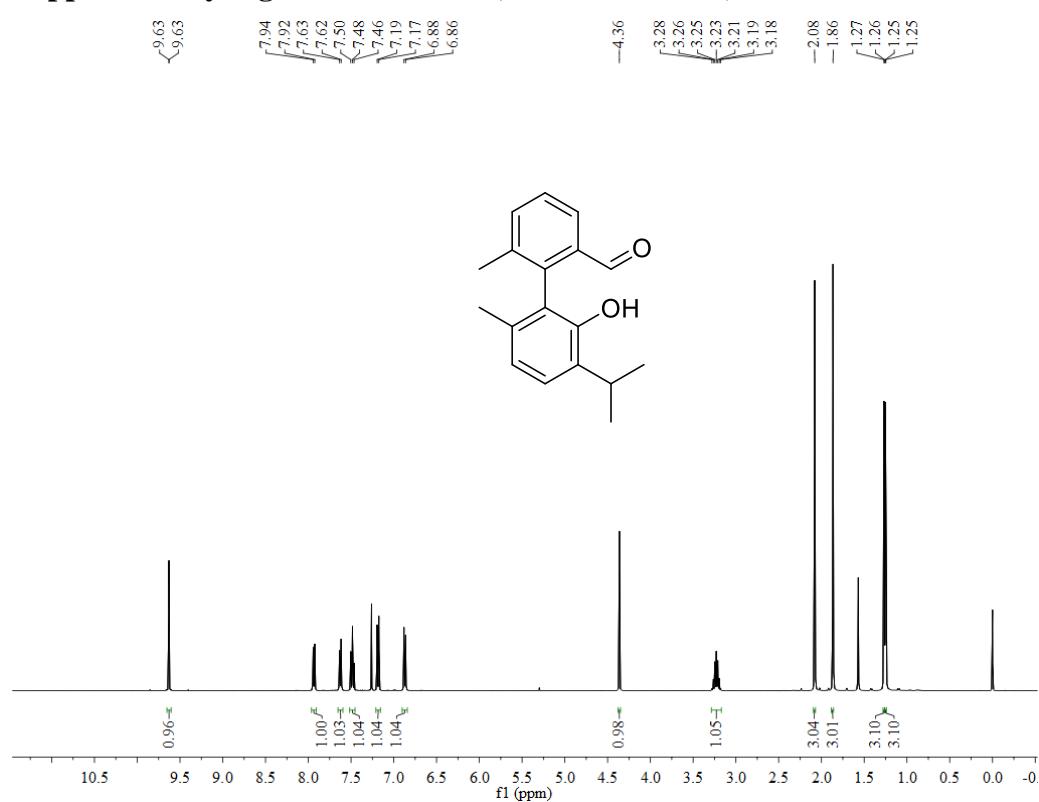
Supplementary Figure 24 ^1H NMR (400 MHz, CDCl_3) of **1h**



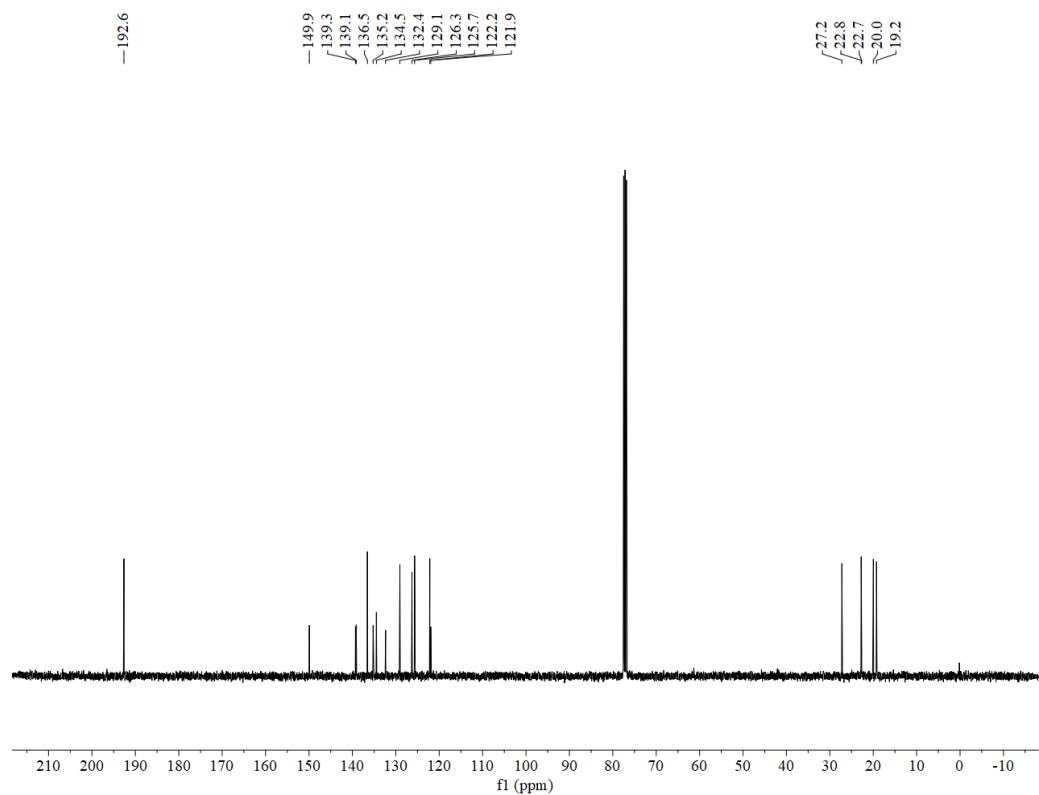
Supplementary Figure 25 ^{13}C NMR (400 MHz, CDCl_3) of **1h**



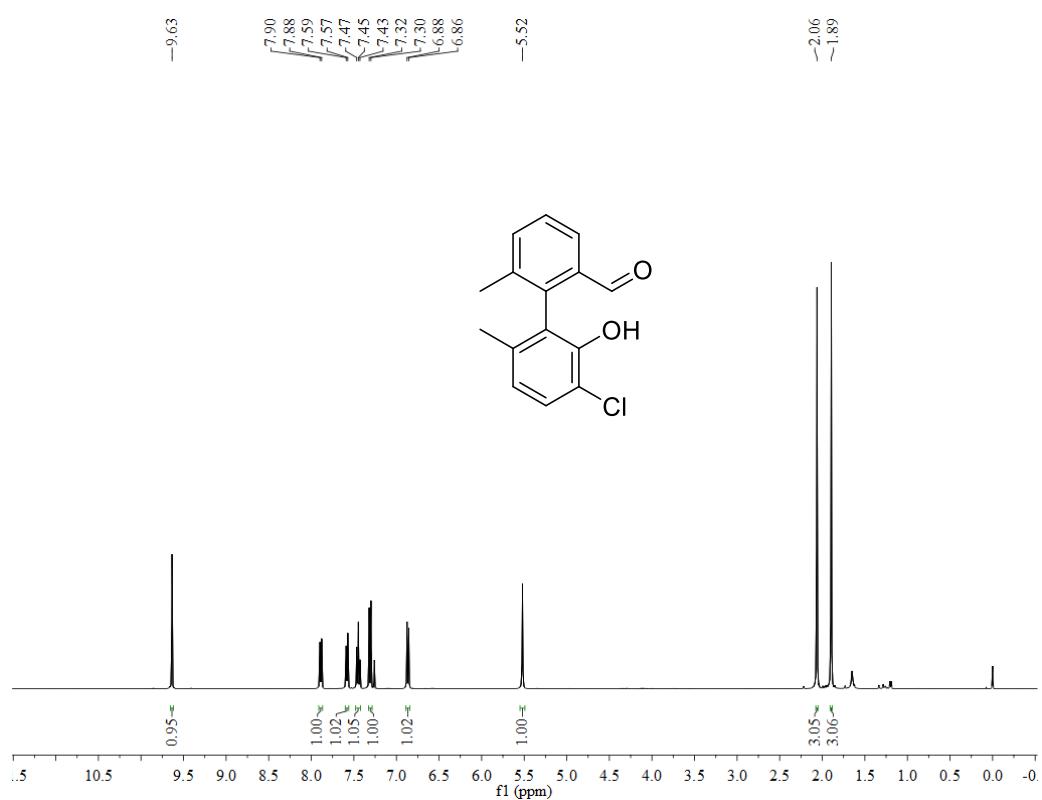
Supplementary Figure 26 ^1H NMR (400 MHz, CDCl_3) of **1i**



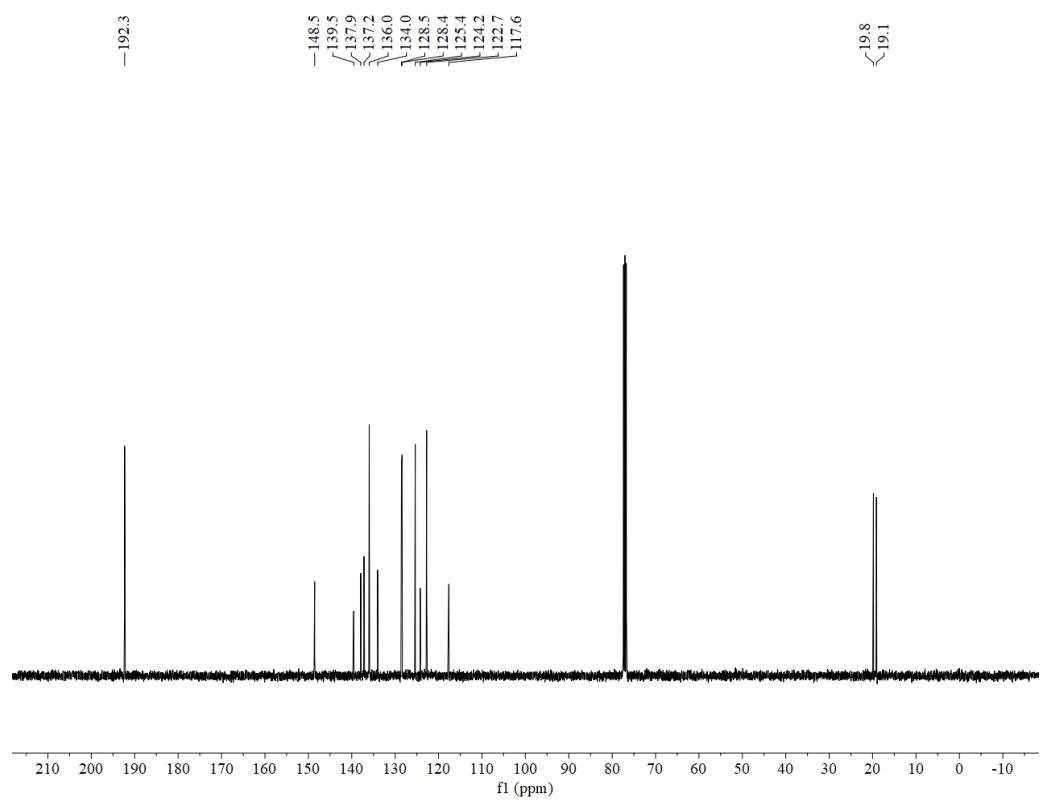
Supplementary Figure 27 ^{13}C NMR (400 MHz, CDCl_3) of **1i**



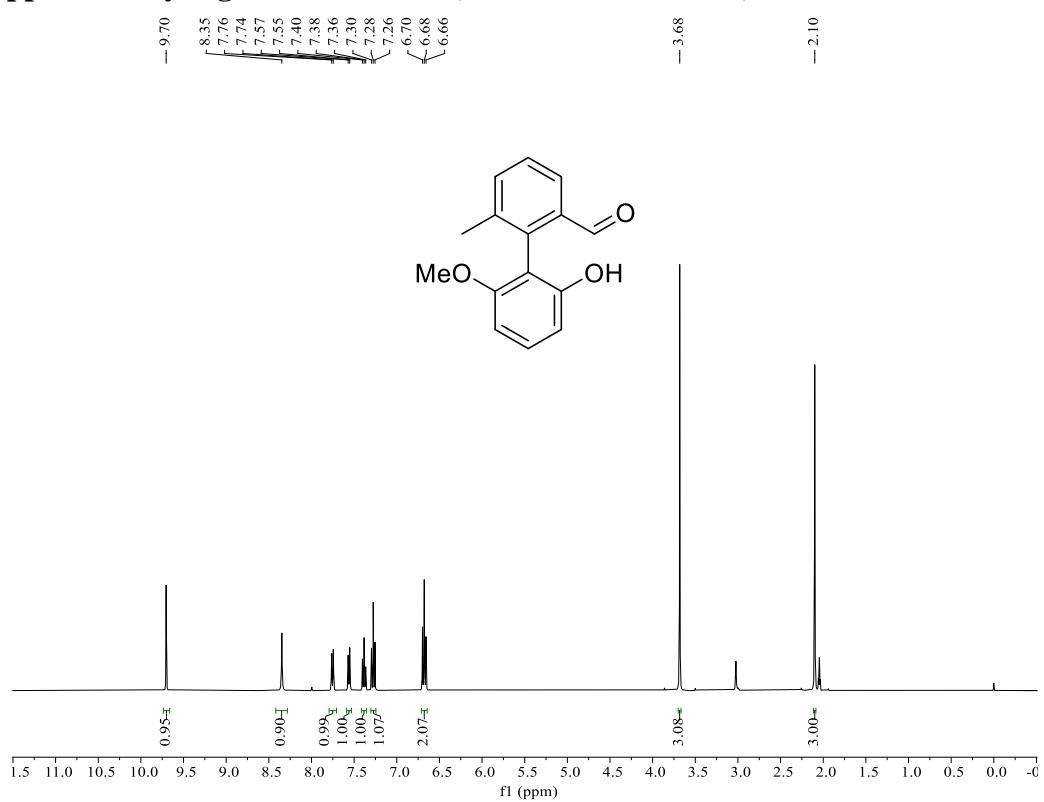
Supplementary Figure 28 ^1H NMR (400 MHz, CDCl_3) of **1j**



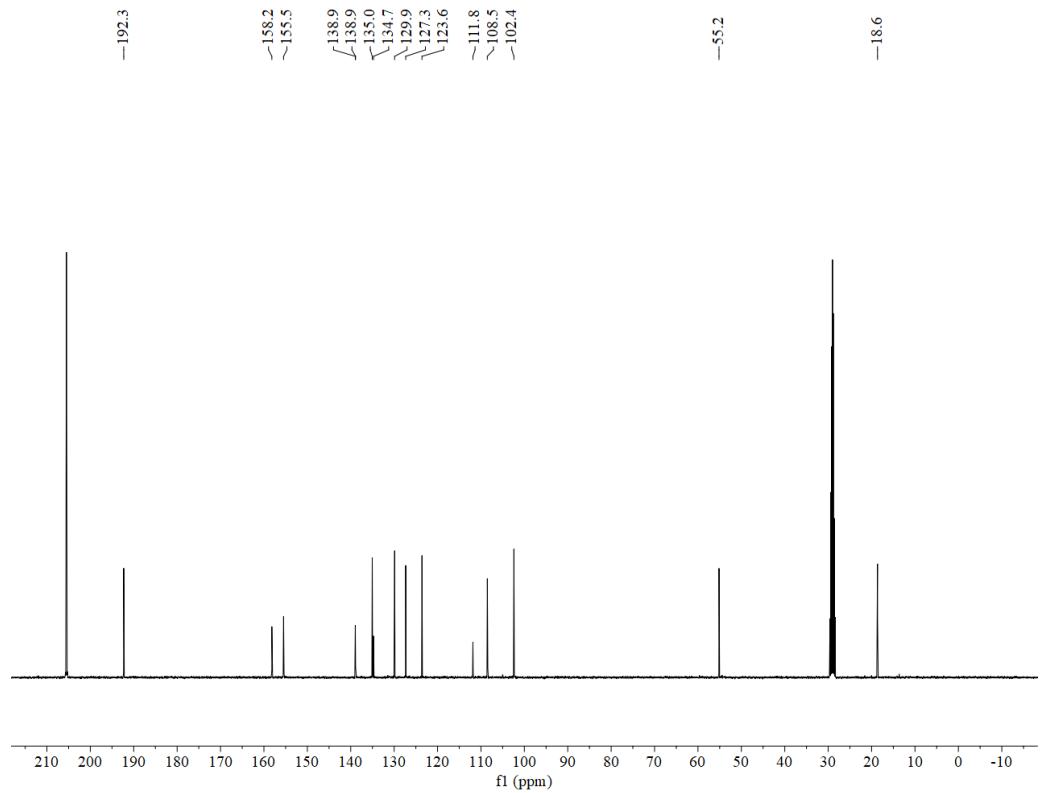
Supplementary Figure 29 ^{13}C NMR (400 MHz, CDCl_3) of **1j**



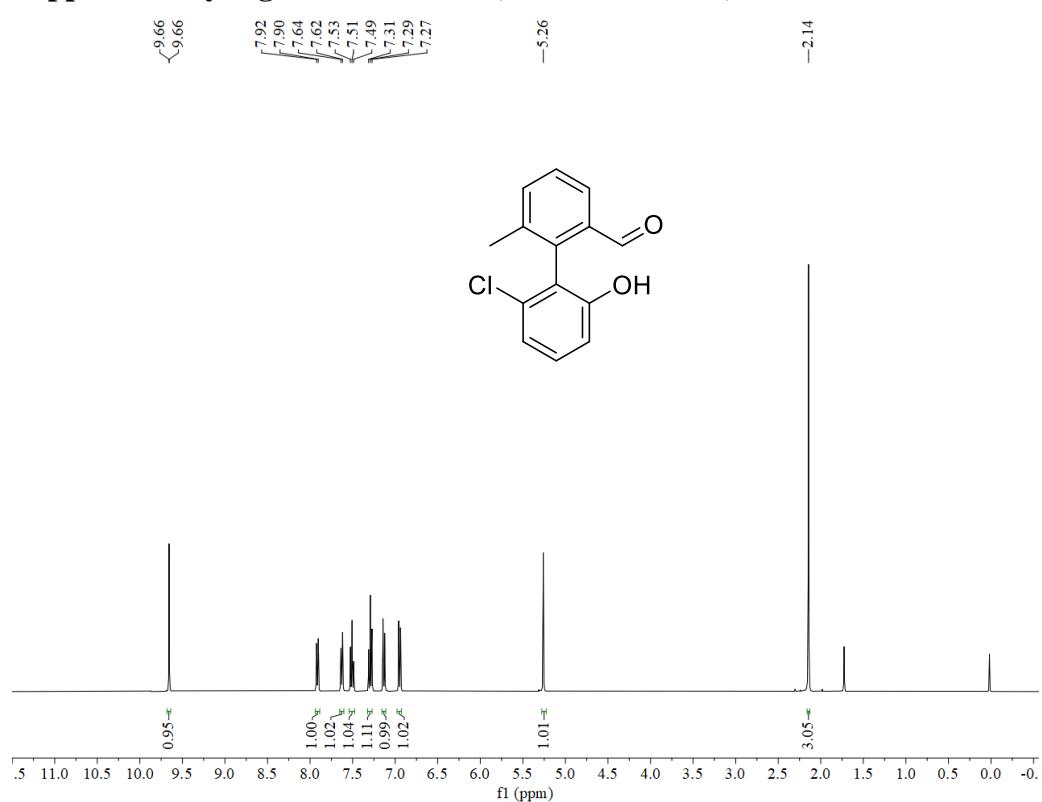
Supplementary Figure 30 ^1H NMR (400 MHz, Acetone- d_6) of **1k**



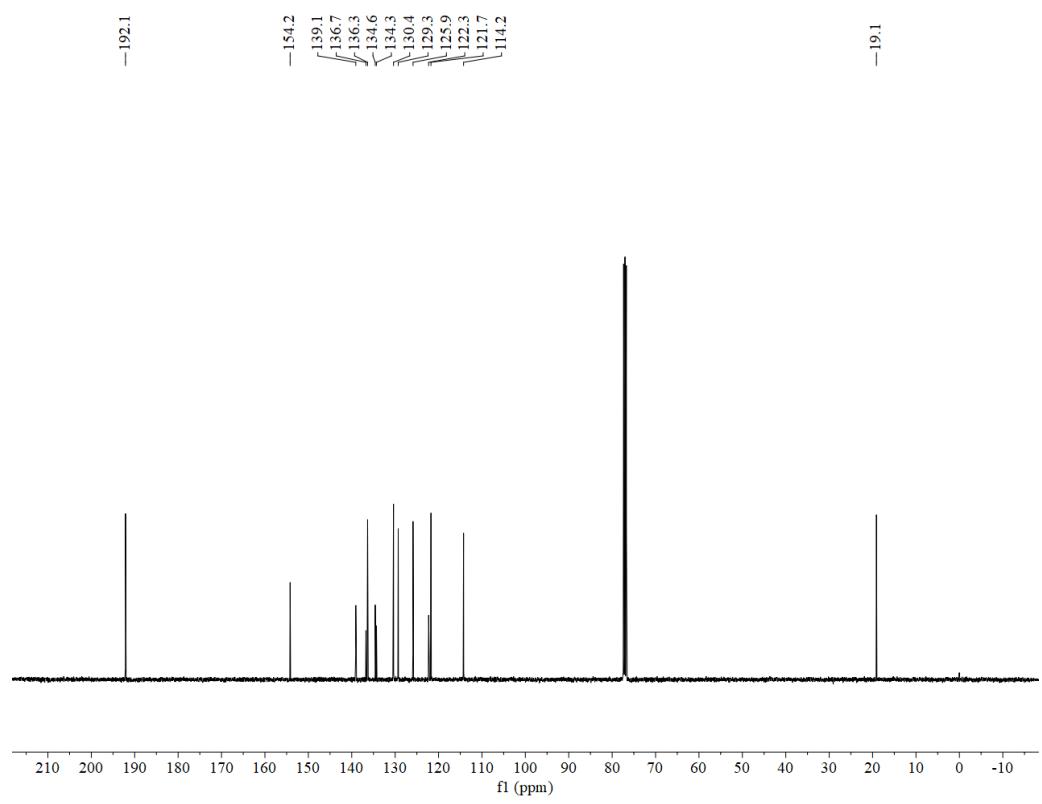
Supplementary Figure 31 ^{13}C NMR (400 MHz, Acetone- d_6) of **1k**



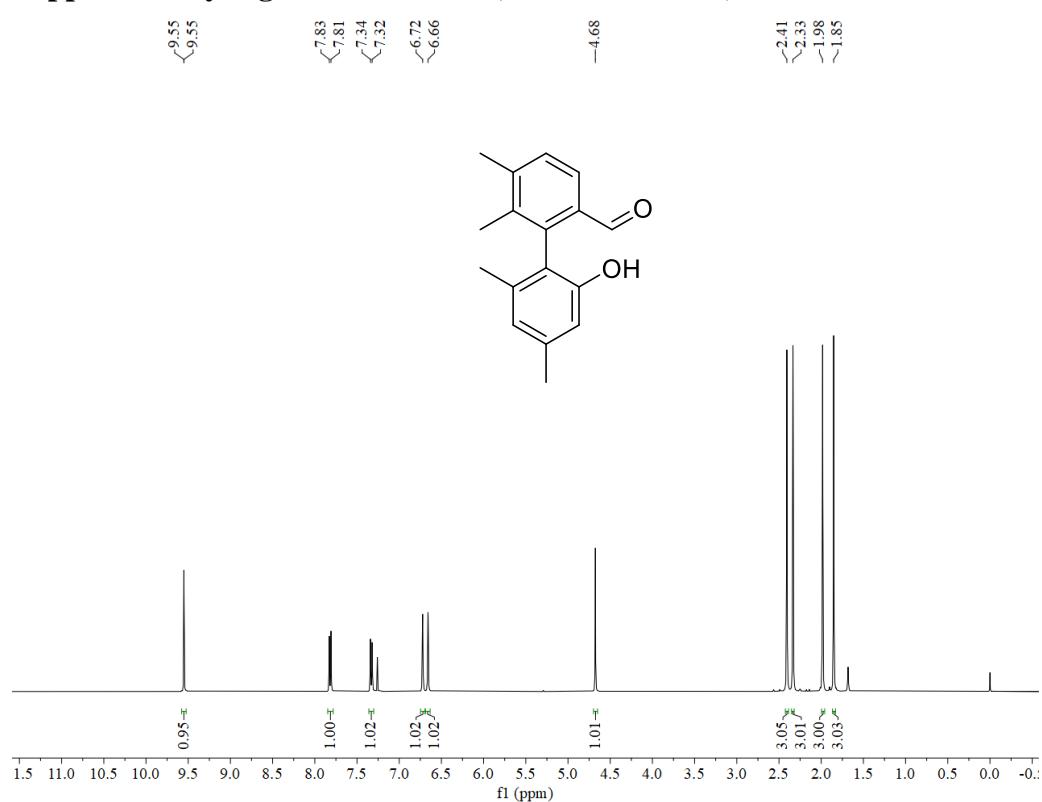
Supplementary Figure 32 ^1H NMR (400 MHz, CDCl_3) of **1l**



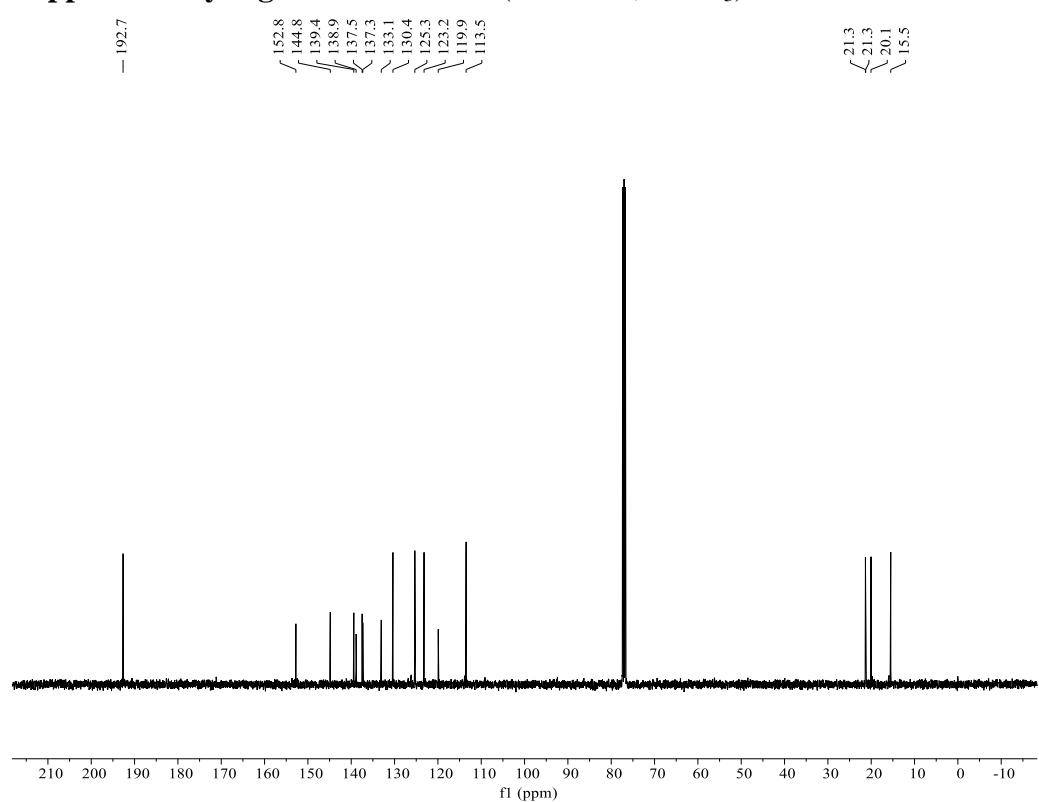
Supplementary Figure 33 ^{13}C NMR (400 MHz, CDCl_3) of **1l**



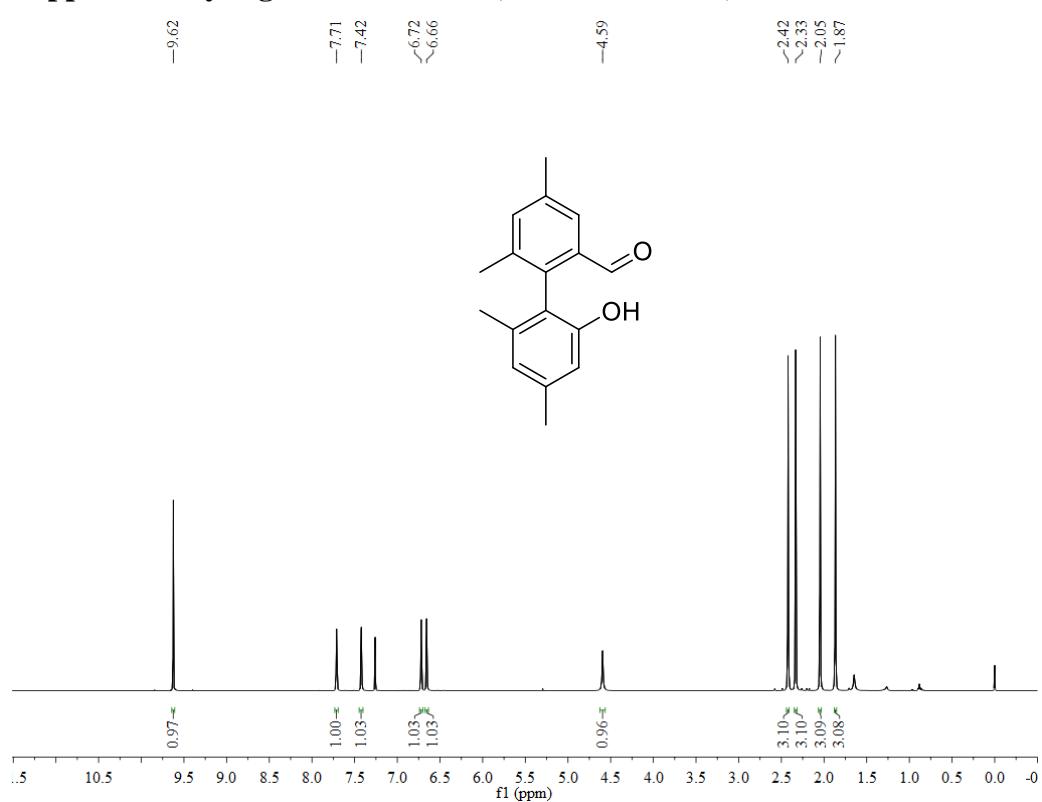
Supplementary Figure 34 ^1H NMR (400 MHz, CDCl_3) of **1m**



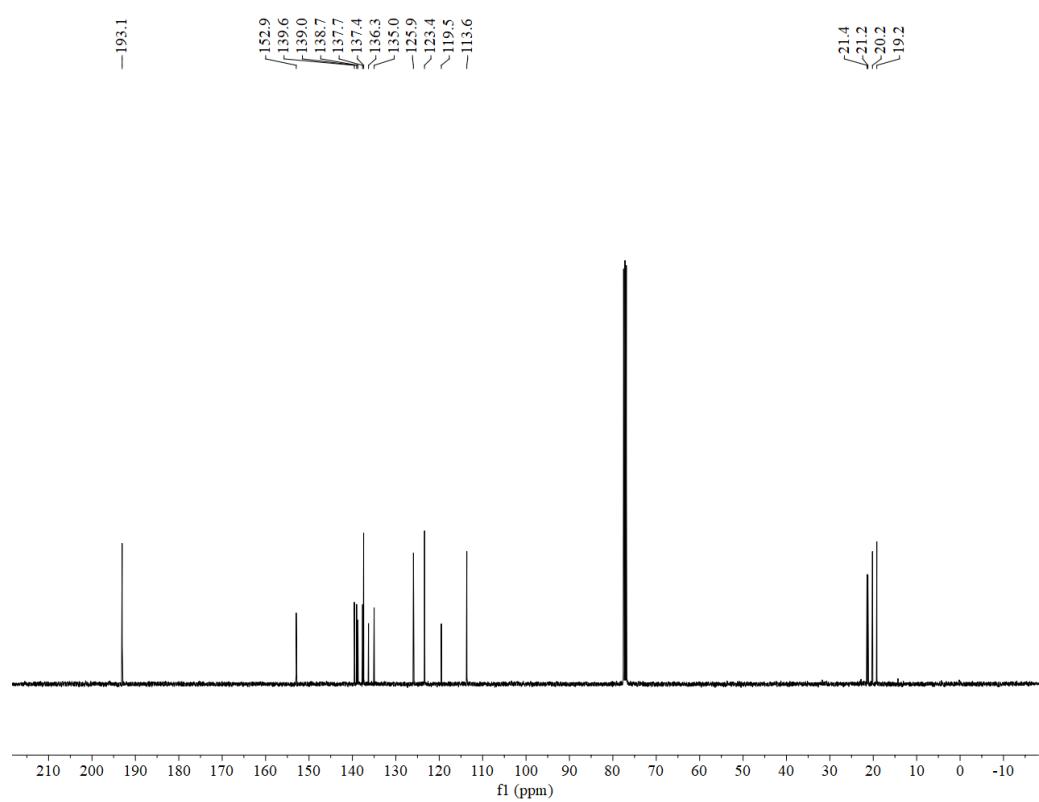
Supplementary Figure 35 ^{13}C NMR (400 MHz, CDCl_3) of **1m**



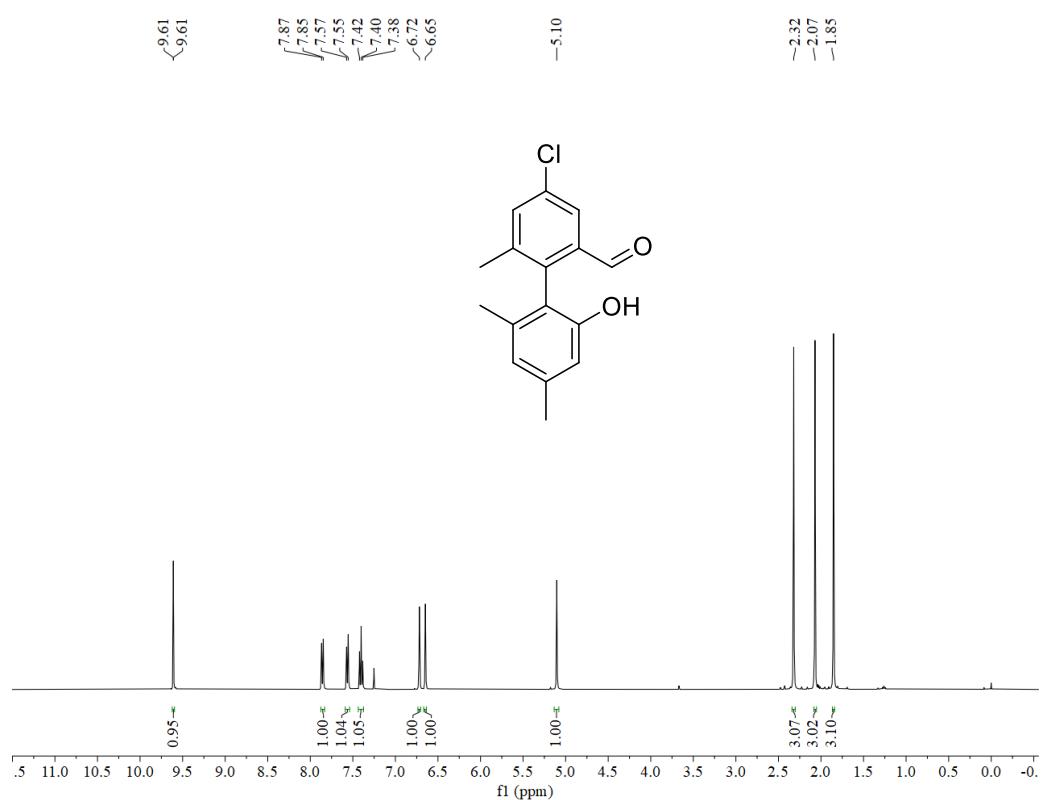
Supplementary Figure 36 ^1H NMR (400 MHz, CDCl_3) of **1n**



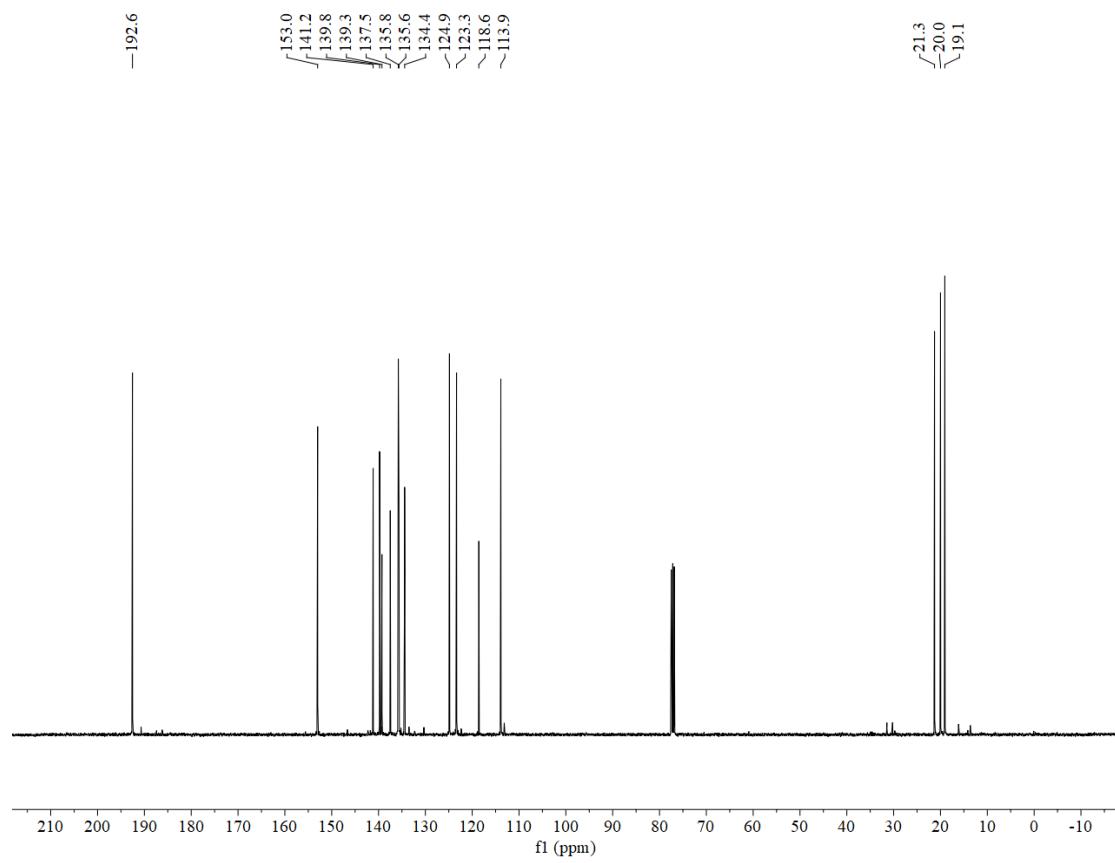
Supplementary Figure 37 ^{13}C NMR (400 MHz, CDCl_3) of **1n**



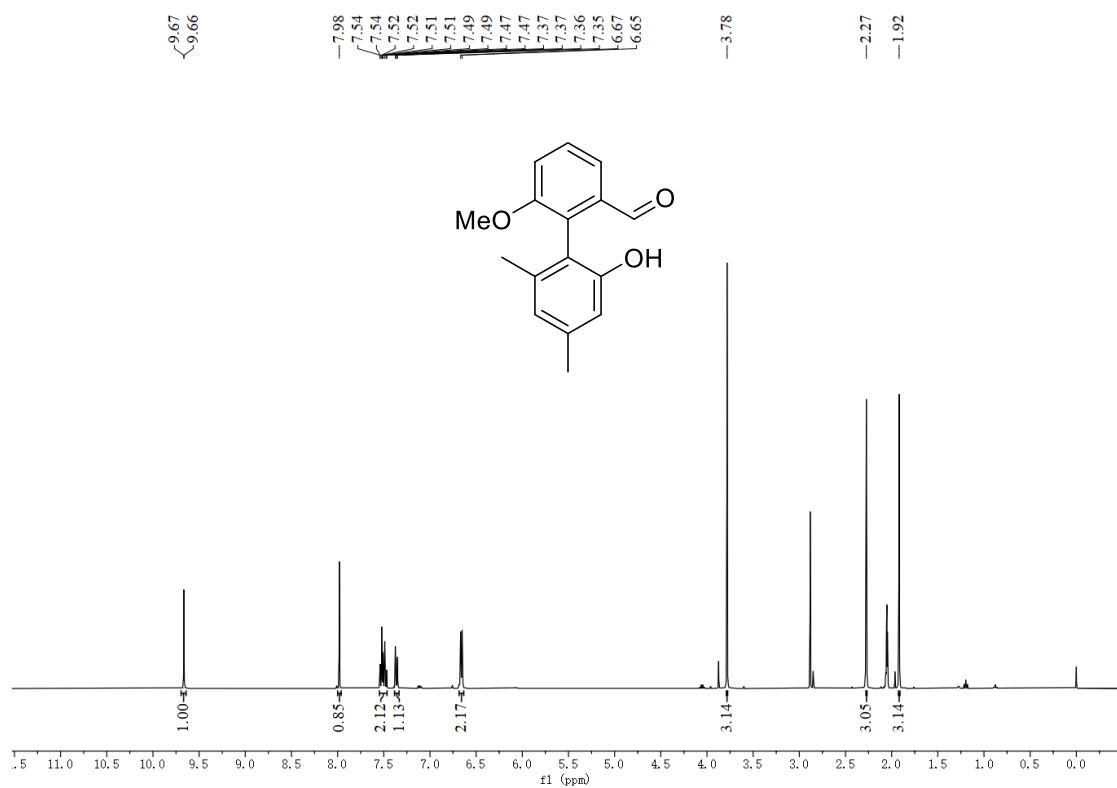
Supplementary Figure 38 ^1H NMR (400 MHz, CDCl_3) of **1o**



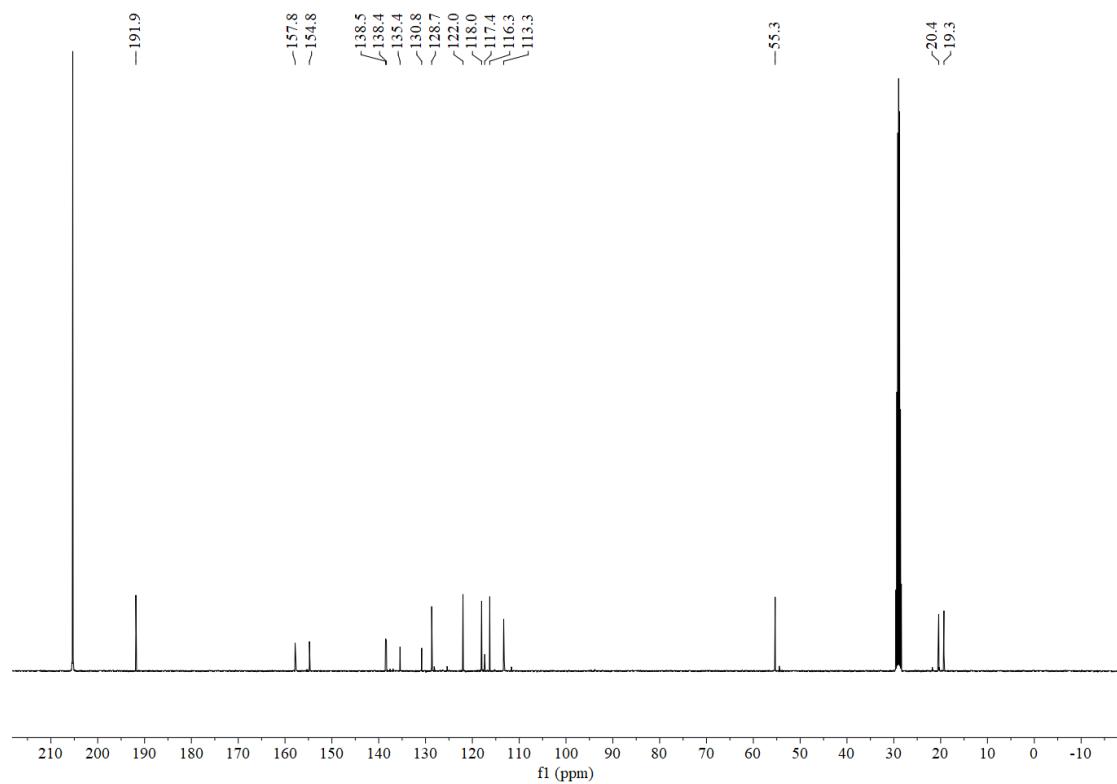
Supplementary Figure 39 ^{13}C NMR (400 MHz, CDCl_3) of **1o**



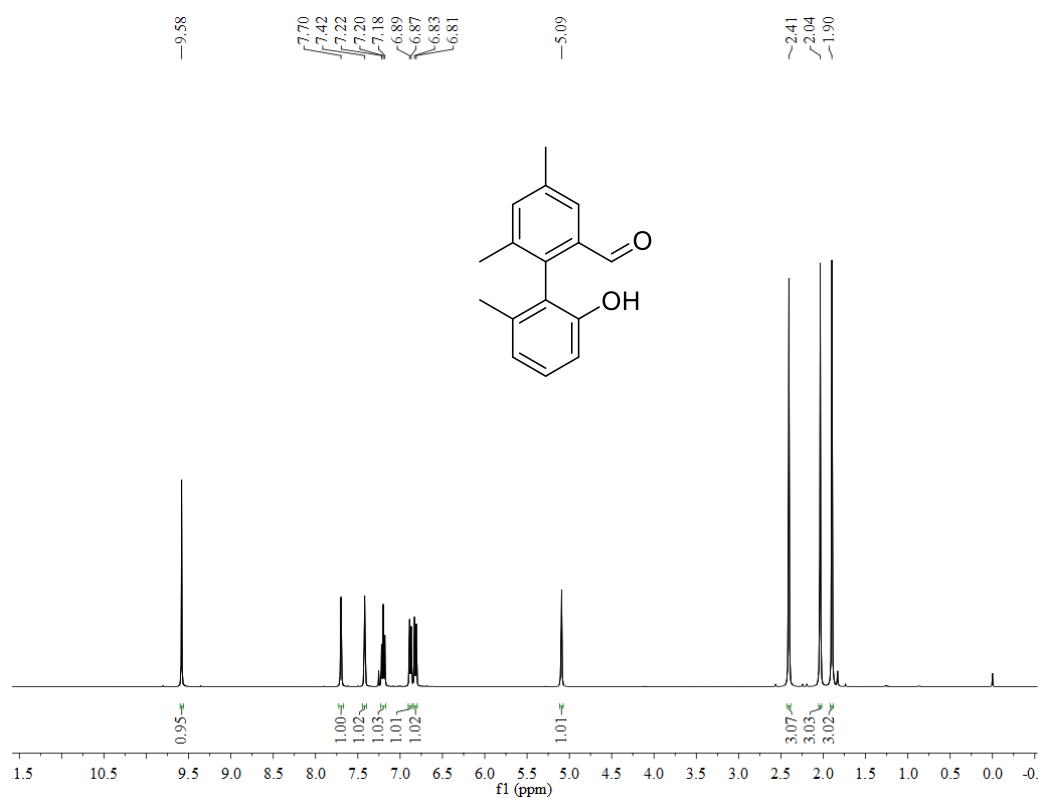
Supplementary Figure 40 ^1H NMR (400 MHz, Acetone- d_6) of **1p**



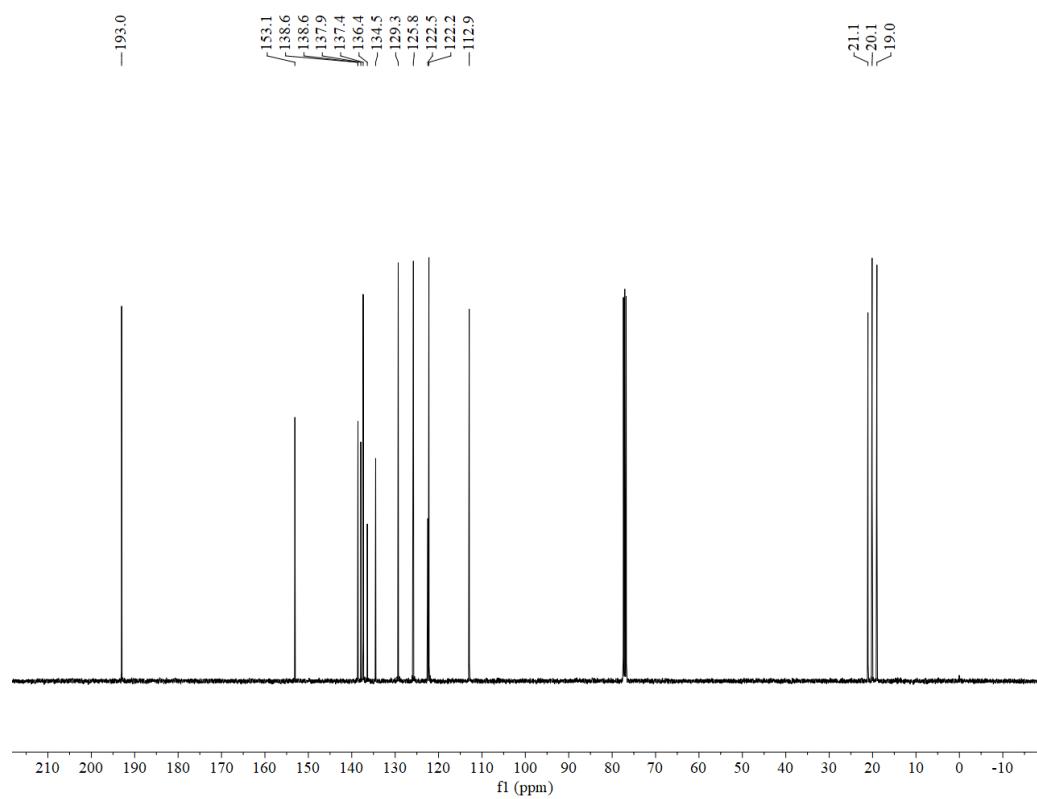
Supplementary Figure 41 ^{13}C NMR (400 MHz, Acetone- d_6) of **1p**



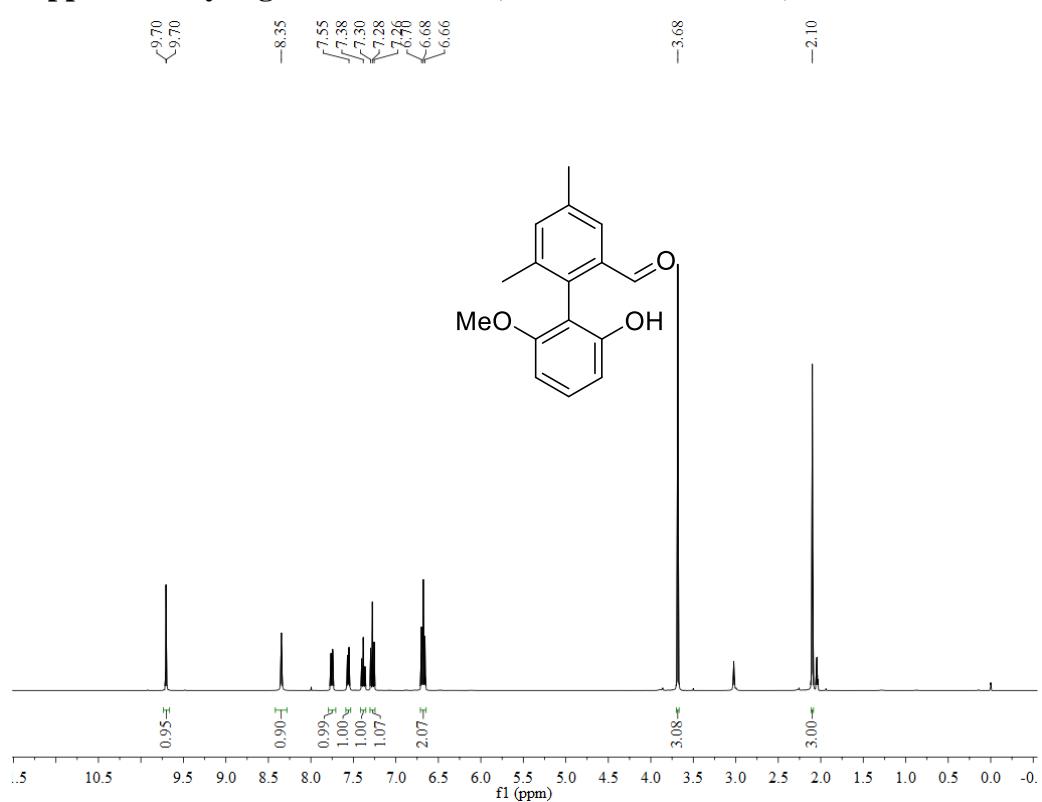
Supplementary Figure 42 ^1H NMR (400 MHz, CDCl_3) of **1q**



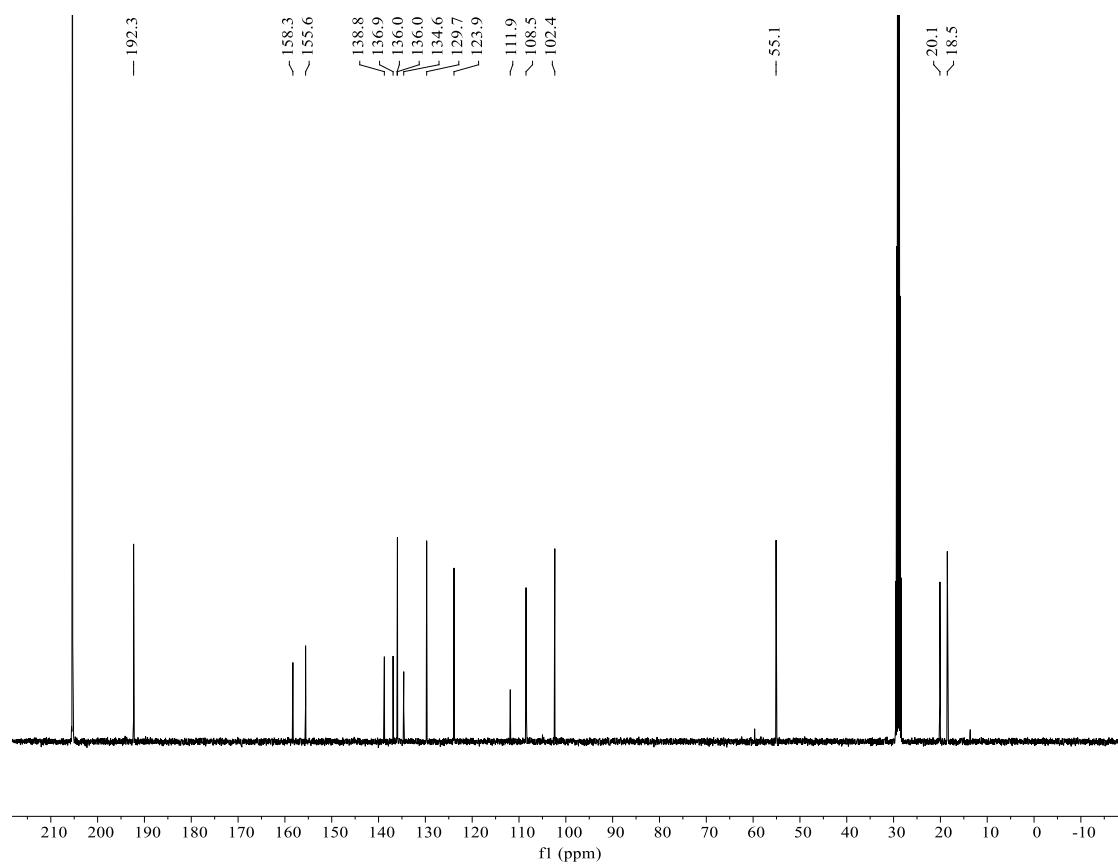
Supplementary Figure 43 ^{13}C NMR (400 MHz, CDCl_3) of **1q**



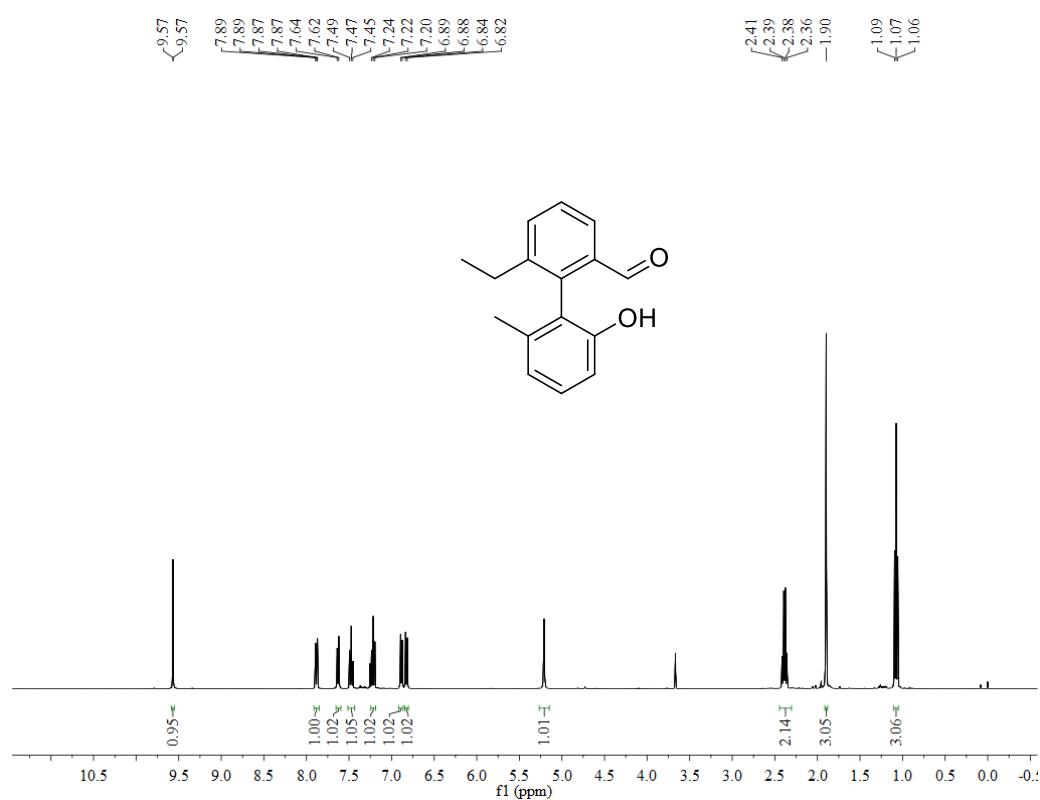
Supplementary Figure 44 ^1H NMR (400 MHz, Acetone- d_6) of **1r**



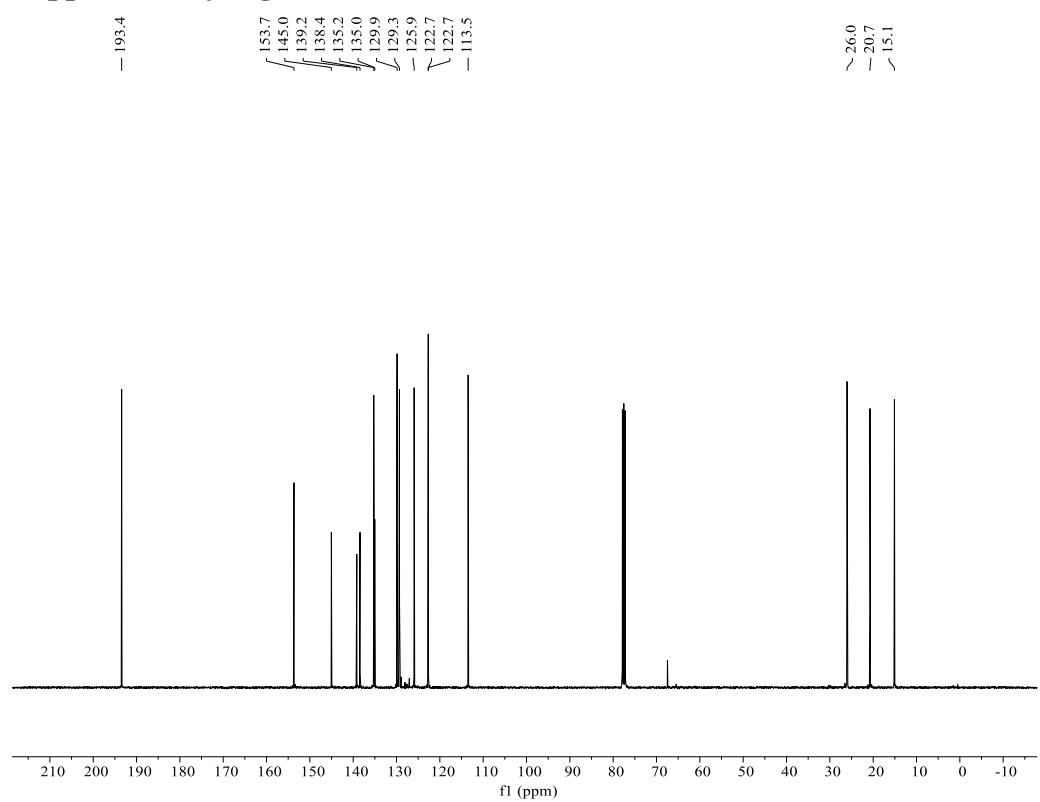
Supplementary Figure 45 ^{13}C NMR (400 MHz, Acetone- d_6) of **1r**



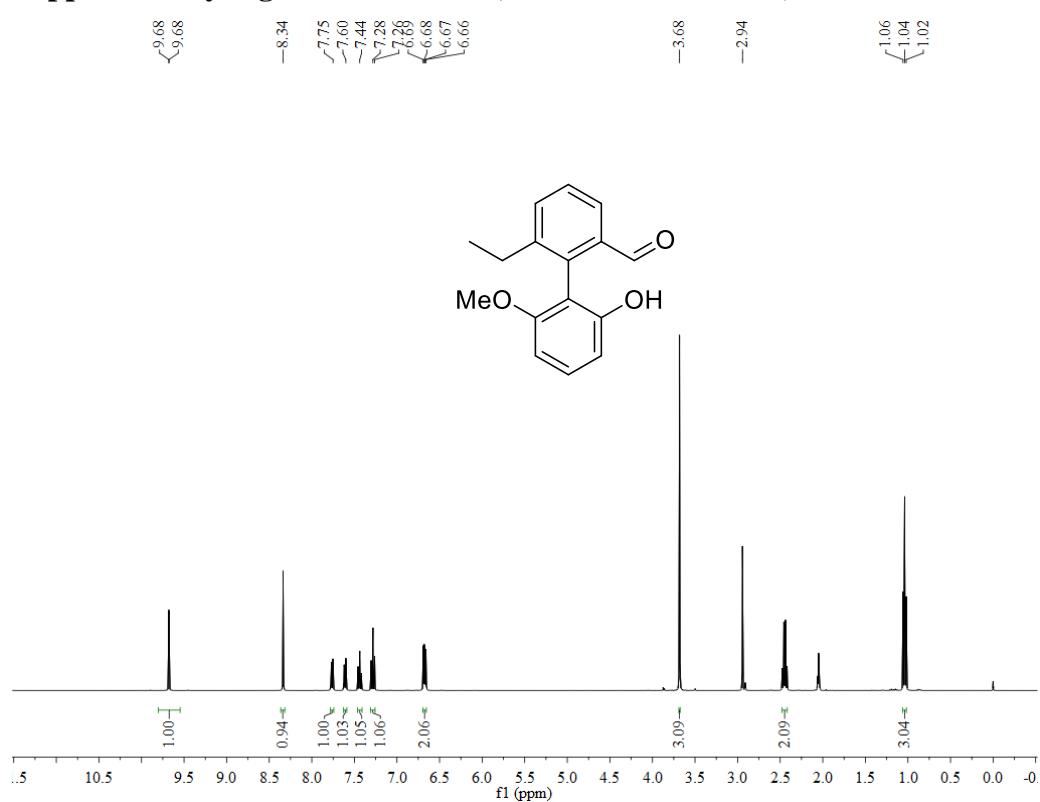
Supplementary Figure 46 ^1H NMR (400 MHz, CDCl_3) of **1s**



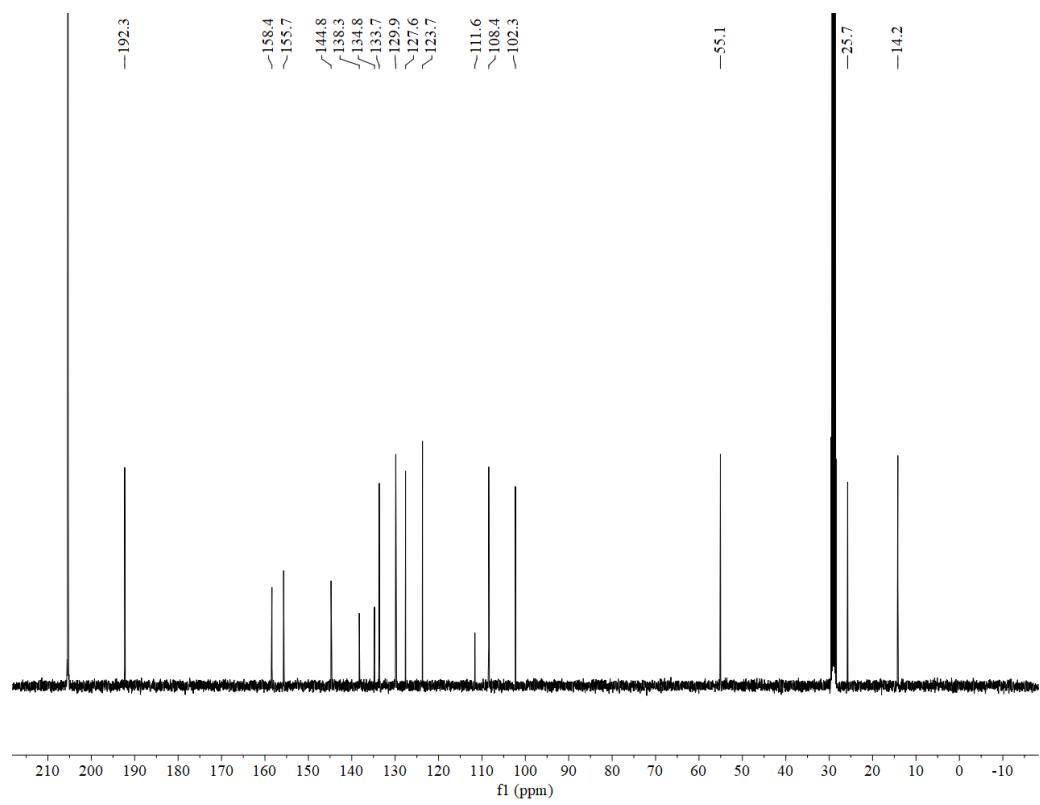
Supplementary Figure 47 ^{13}C NMR (400 MHz, CDCl_3) of **1s**



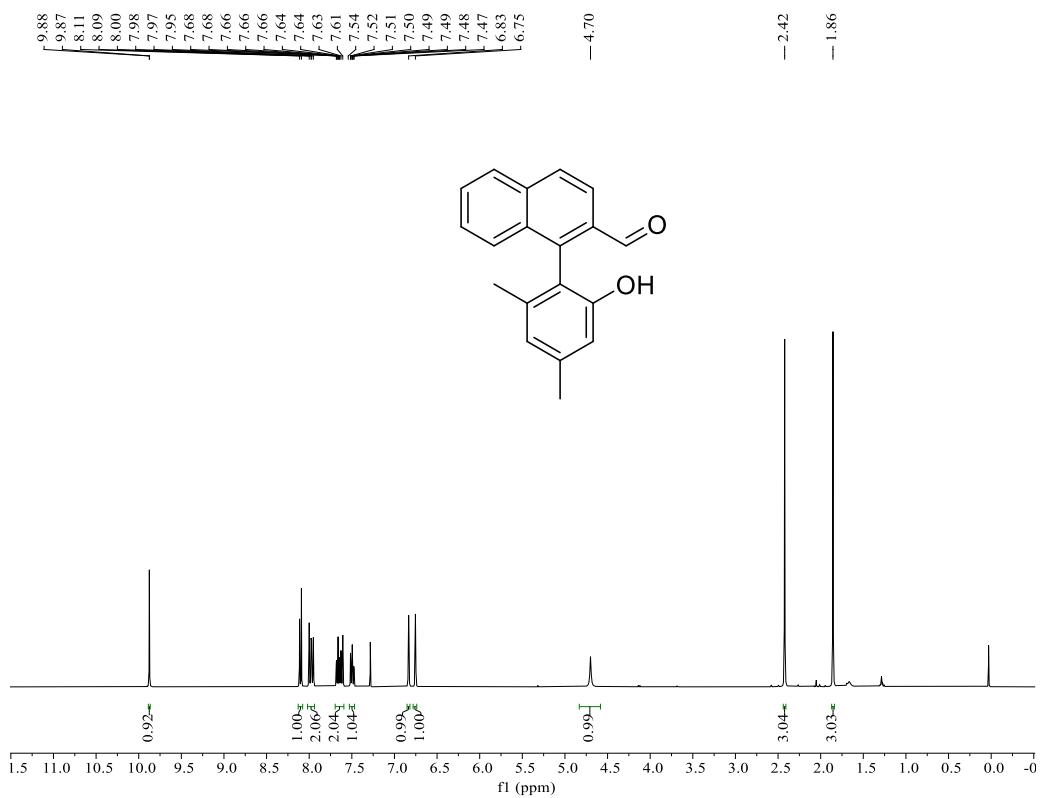
Supplementary Figure 48 ^1H NMR (400 MHz, Acetone- d_6) of **1t**



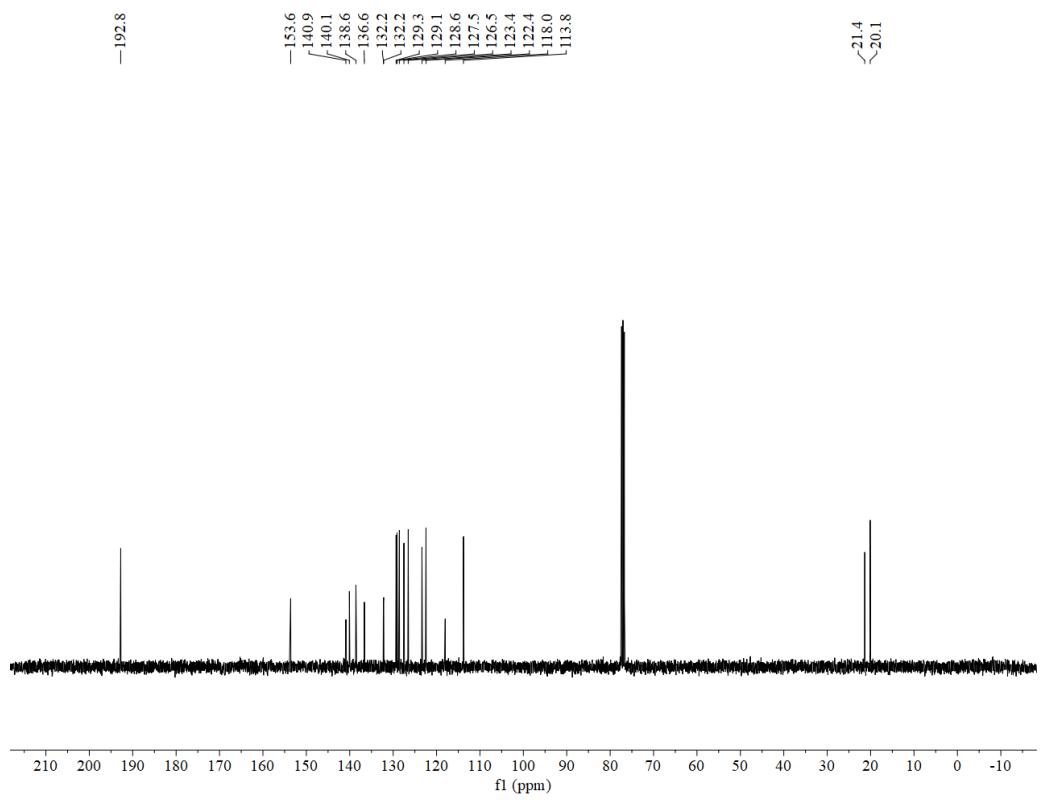
Supplementary Figure 49 ^{13}C NMR (400 MHz, Acetone- d_6) of **1t**



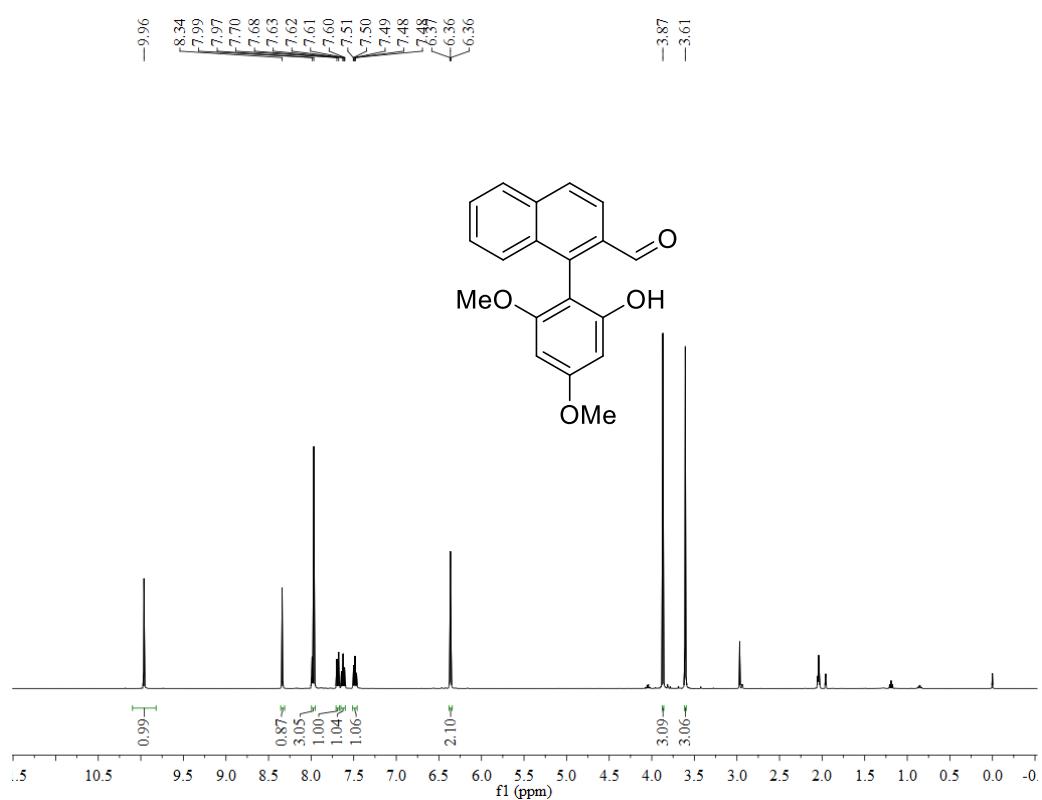
Supplementary Figure 50 ^1H NMR (400 MHz, CDCl_3) of **1u**



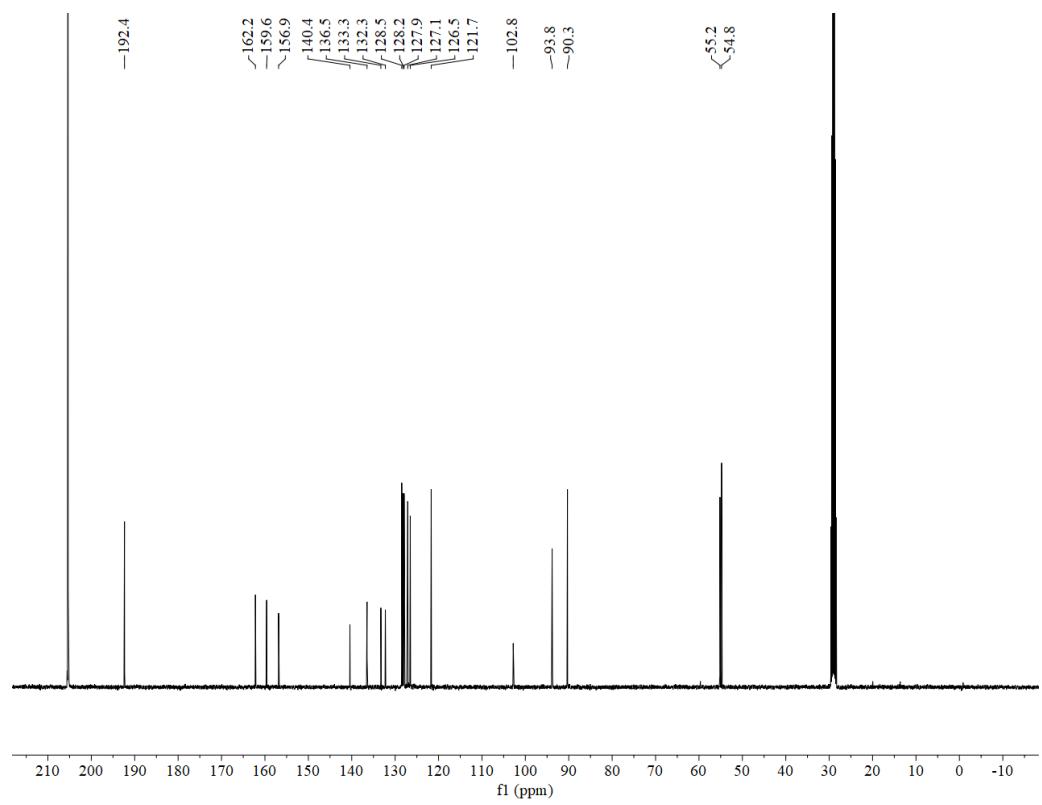
Supplementary Figure 51 ^{13}C NMR (400 MHz, CDCl_3) of **1u**



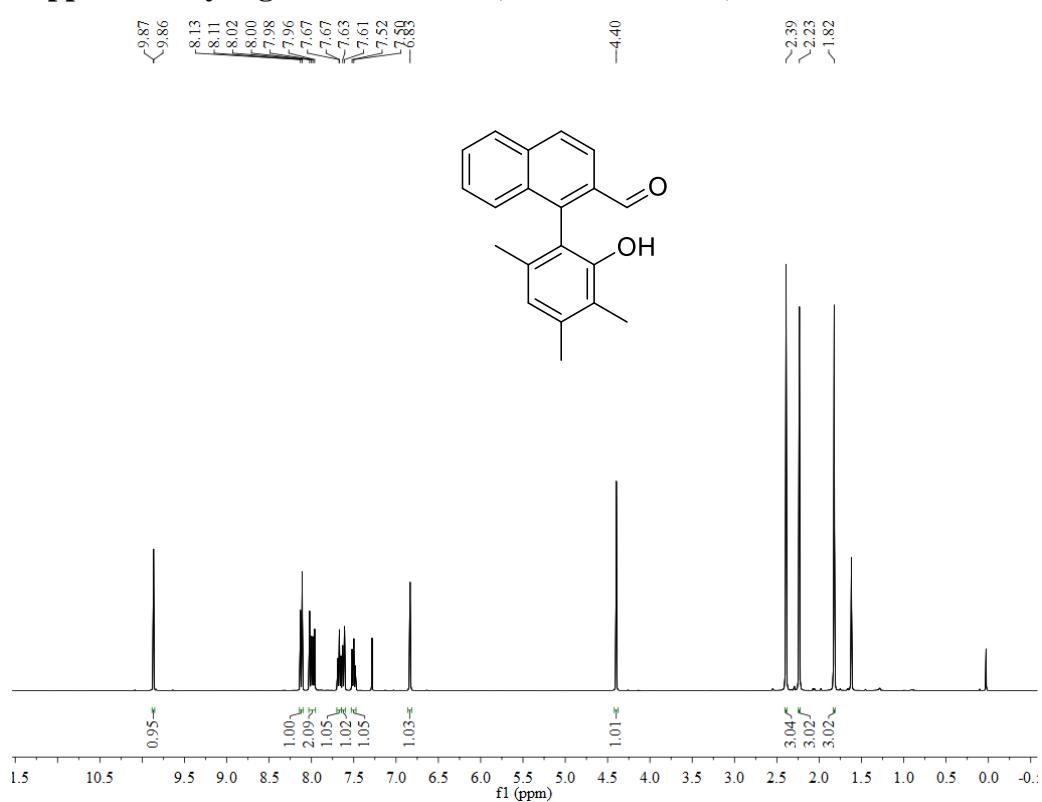
Supplementary Figure 52 ^1H NMR (400 MHz, Acetone- d_6) of **1v**



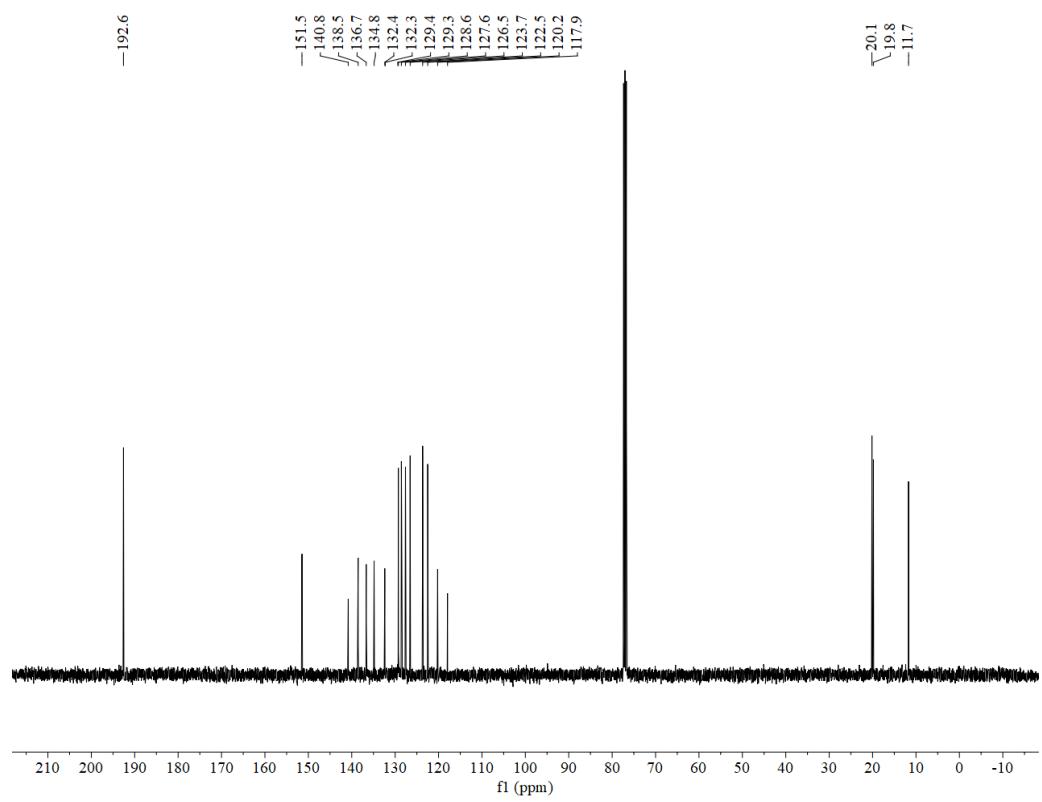
Supplementary Figure 53 ^{13}C NMR (400 MHz, Acetone- d_6) of **1v**



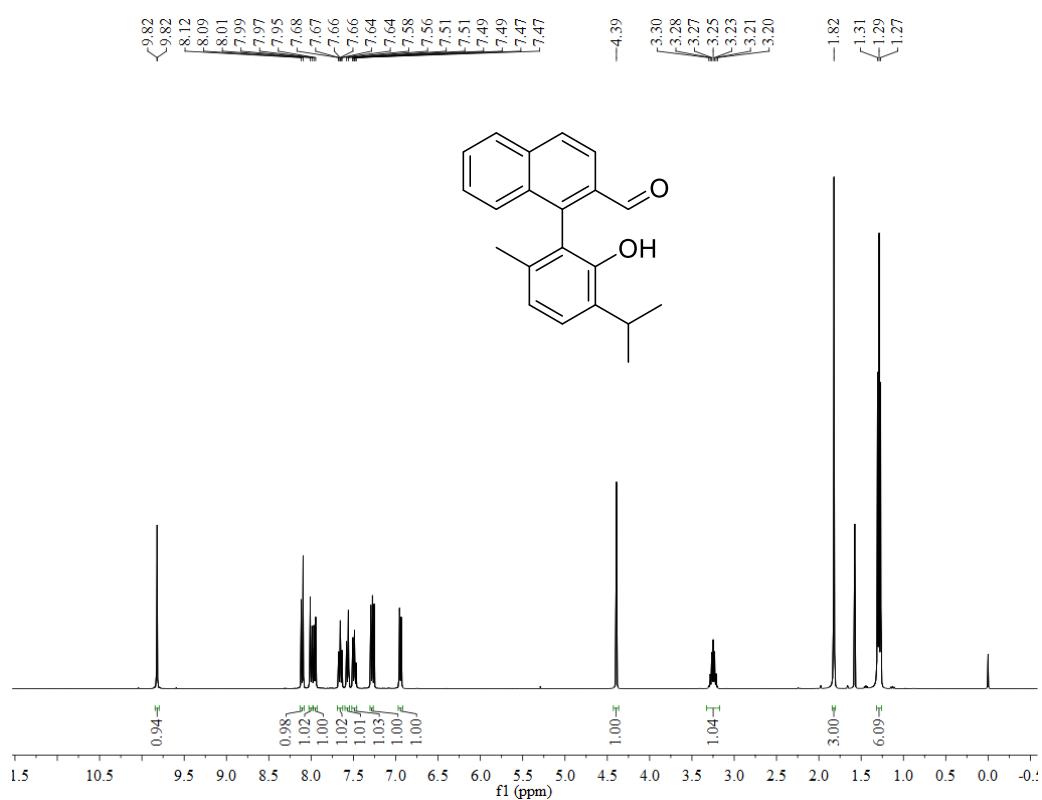
Supplementary Figure 54 ^1H NMR (400 MHz, CDCl_3) of **1w**



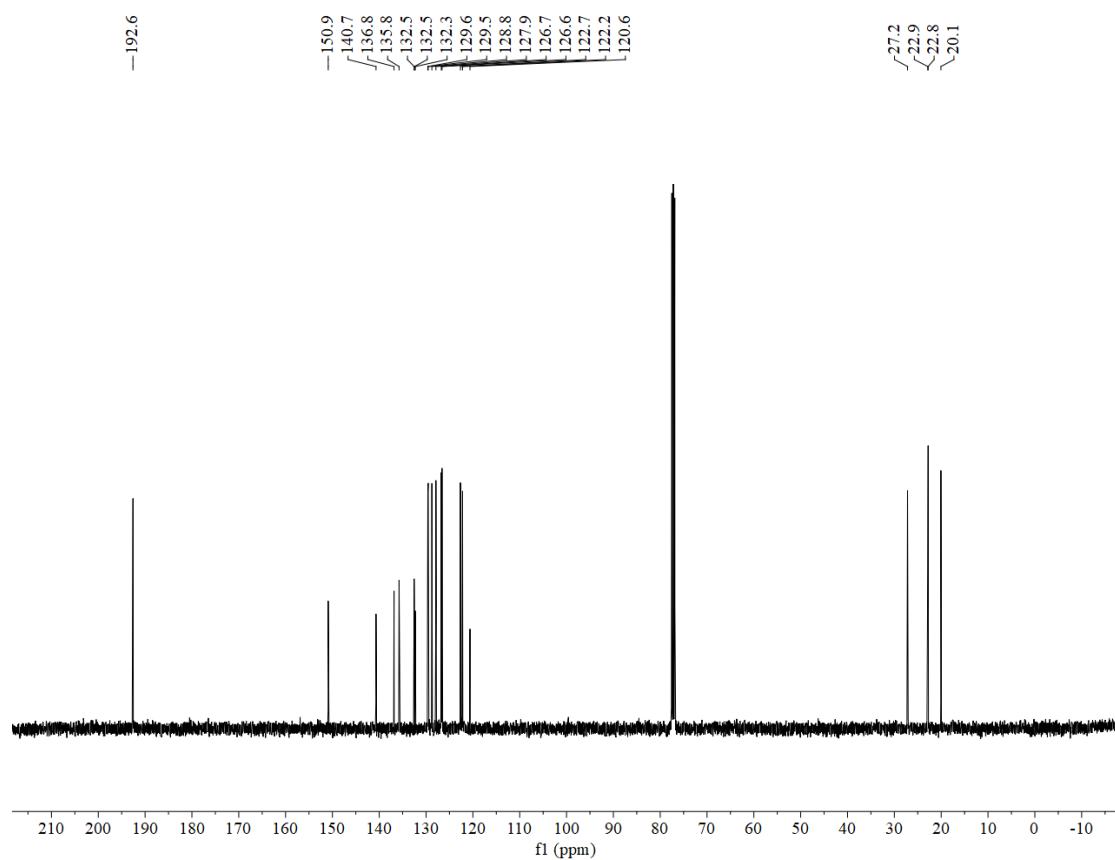
Supplementary Figure 55 ^{13}C NMR (400 MHz, CDCl_3) of **1w**



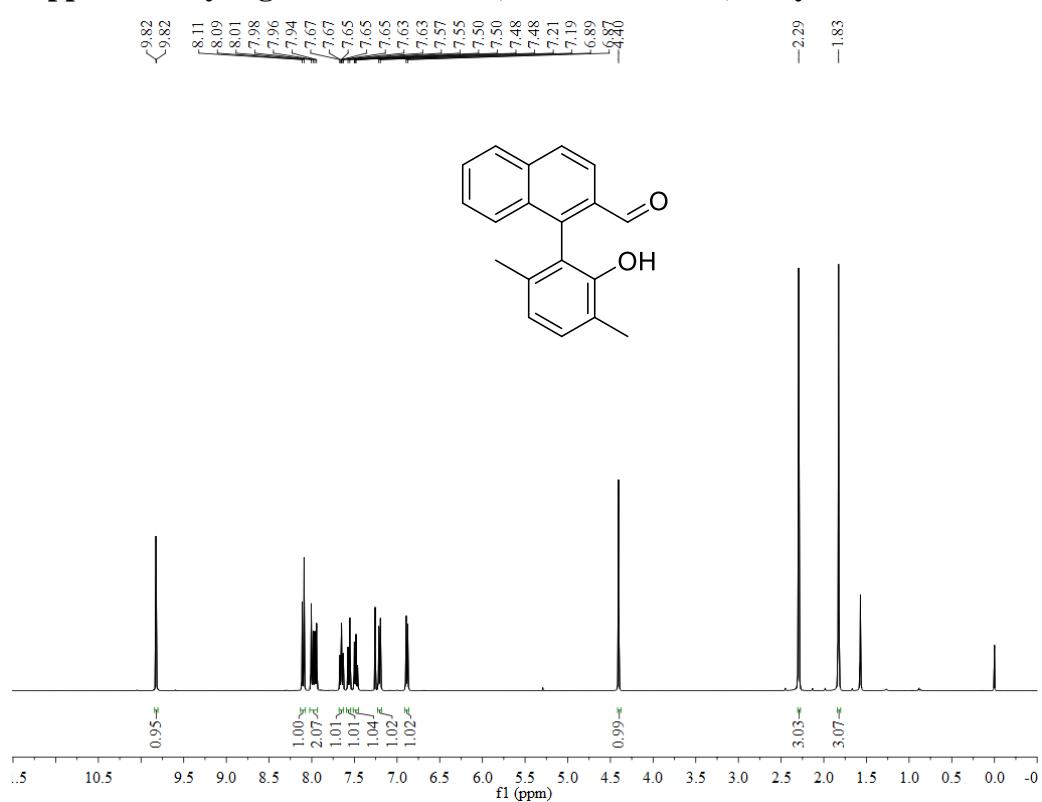
Supplementary Figure 56 ^1H NMR (400 MHz, CDCl_3) of **1x**



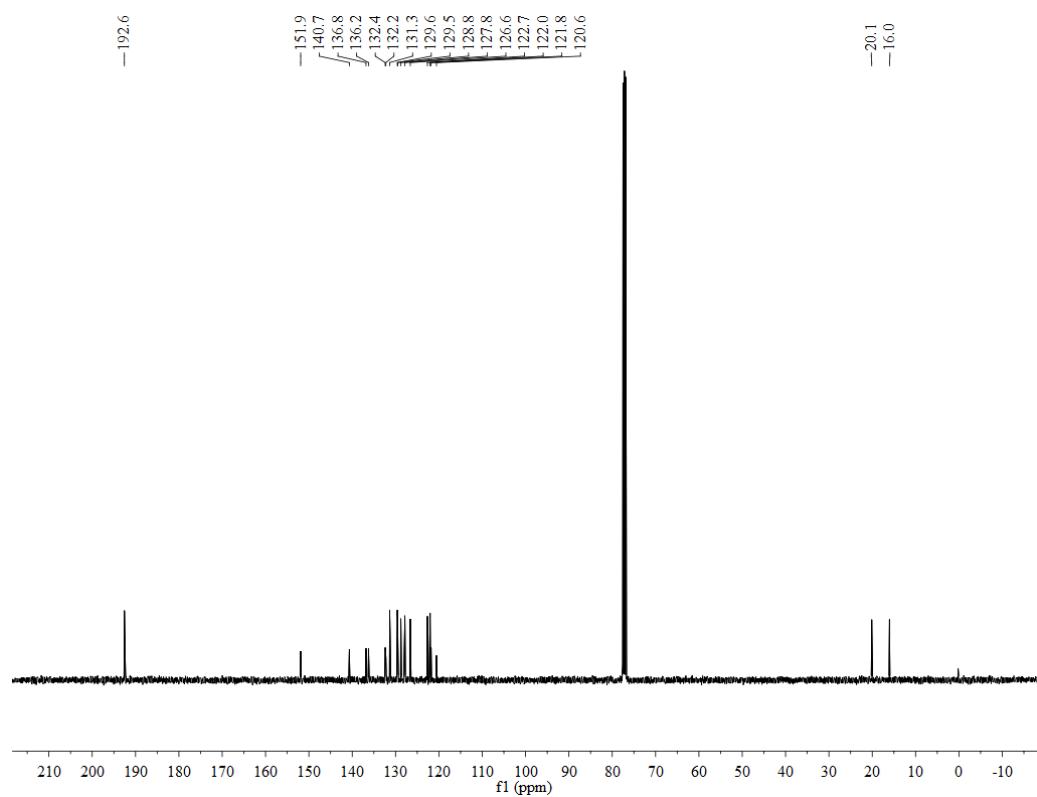
Supplementary Figure 57 ^{13}C NMR (400 MHz, CDCl_3) of **1x**



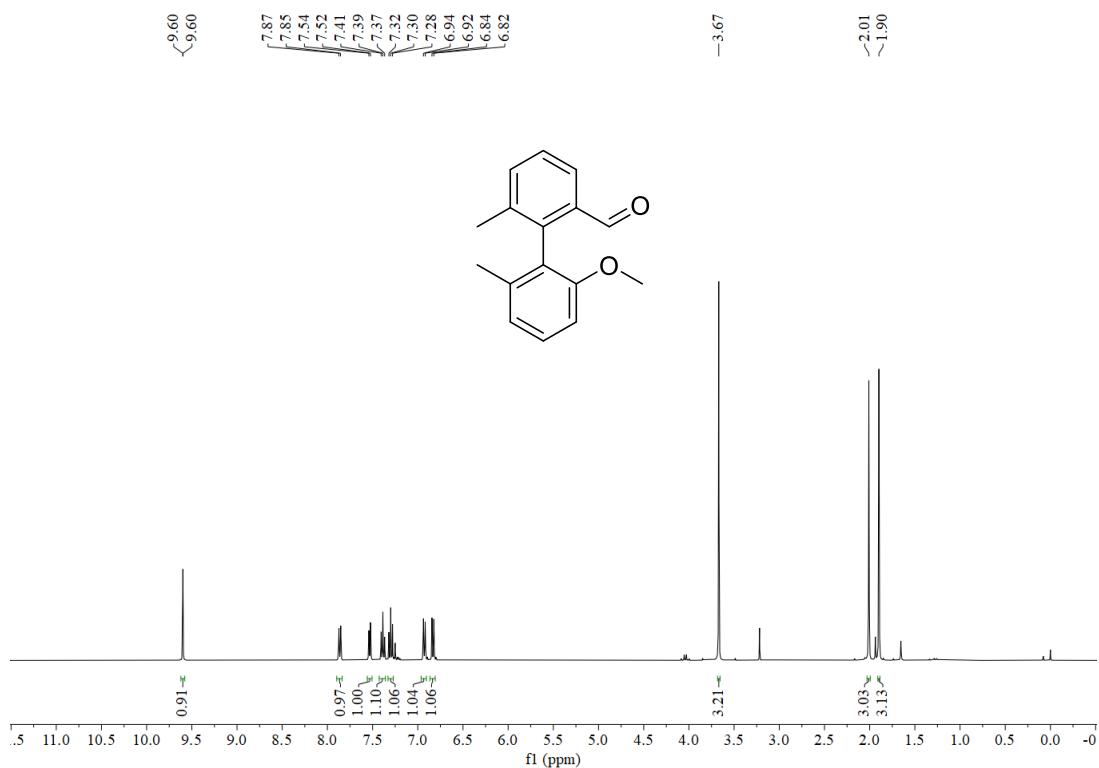
Supplementary Figure 58 ^1H NMR (400 MHz, CDCl_3) of **1y**



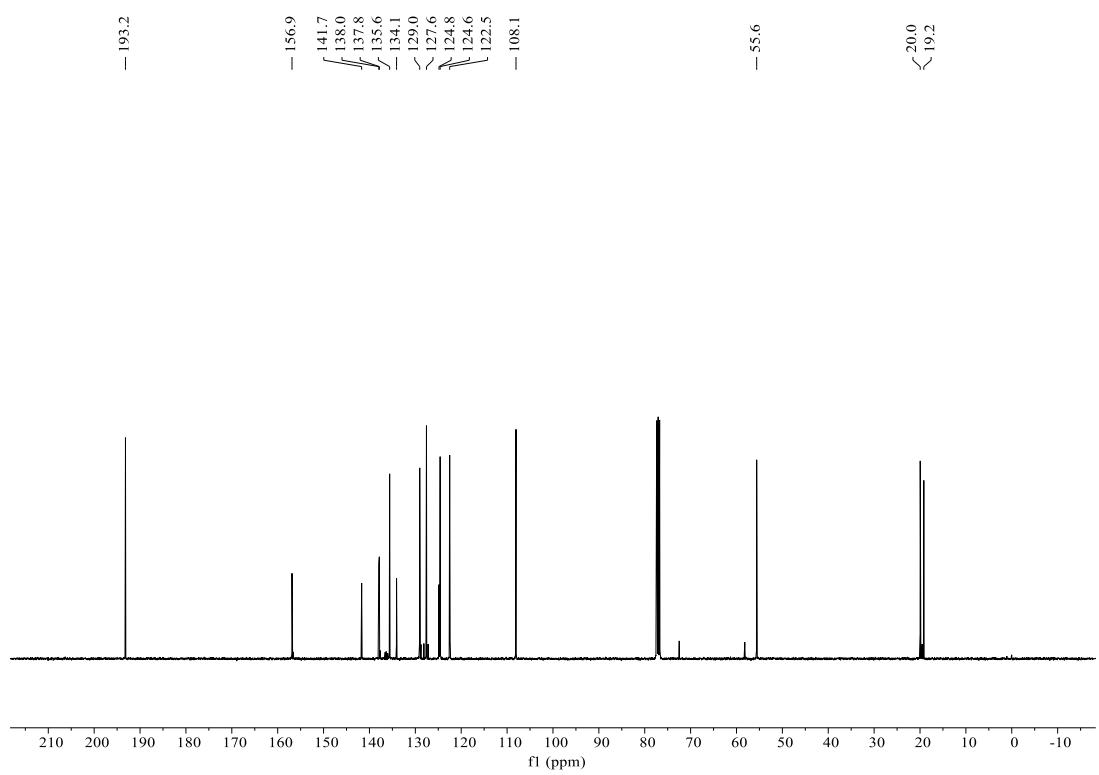
Supplementary Figure 59 ^{13}C NMR (400 MHz, CDCl_3) of **1y**



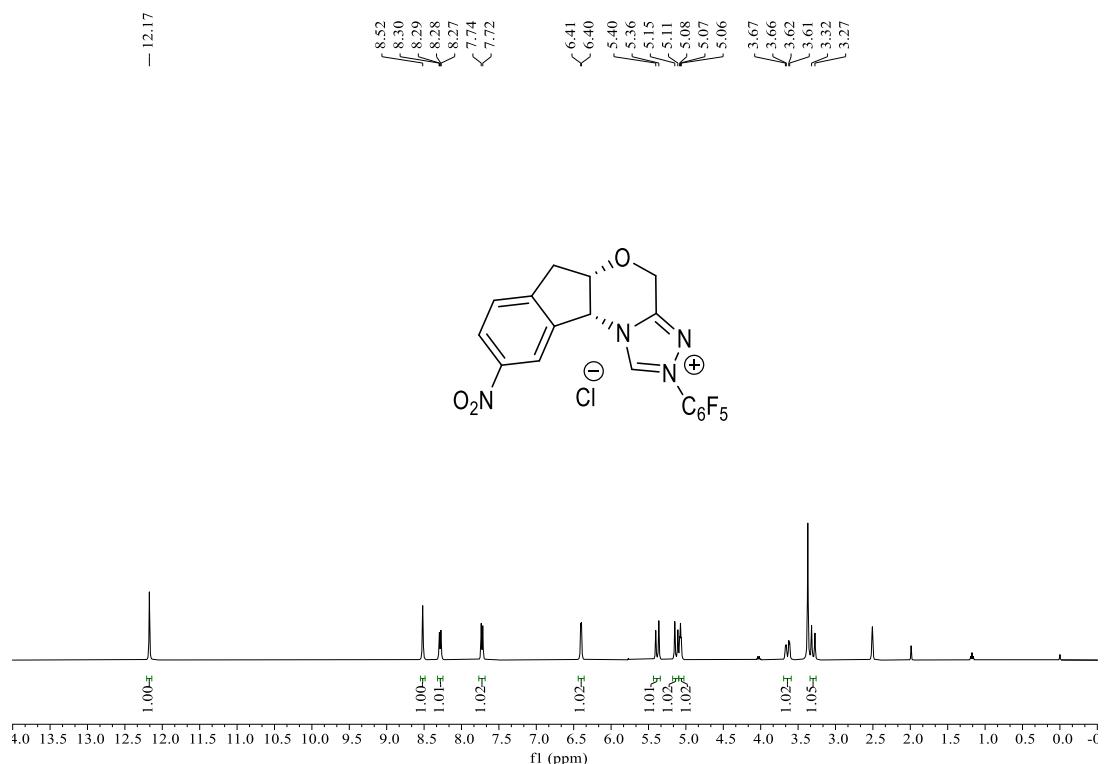
Supplementary Figure 60 ^1H NMR (400 MHz, CDCl_3) of **1z**



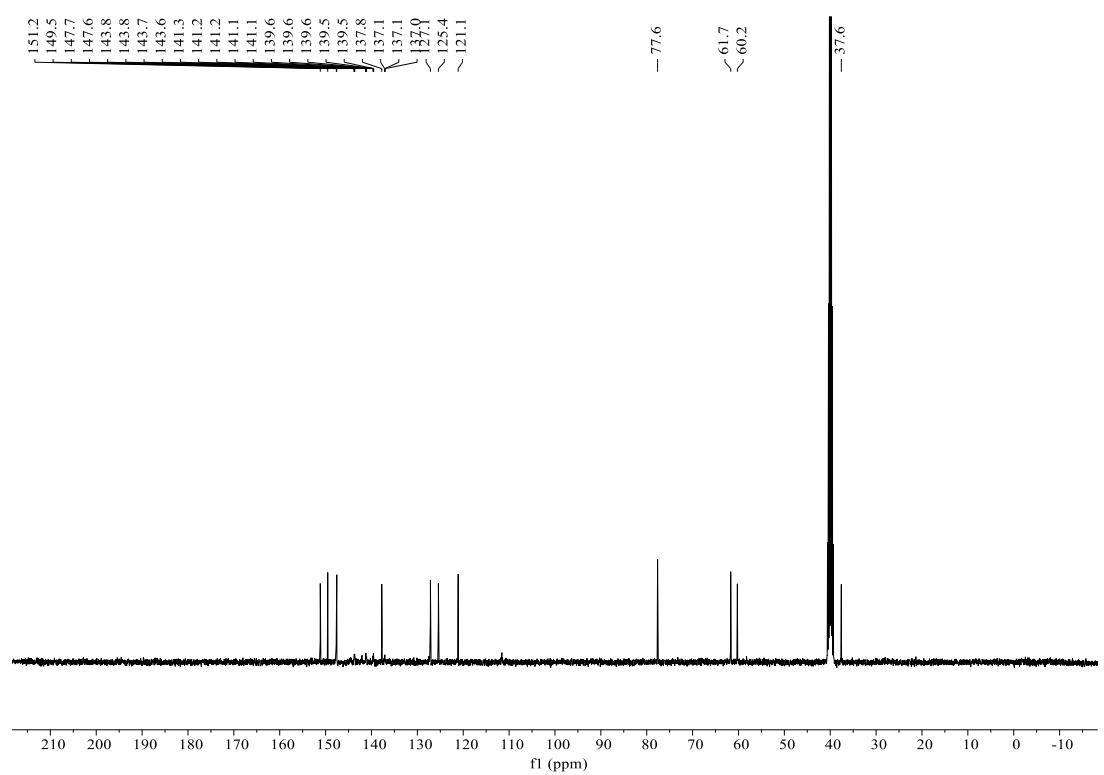
Supplementary Figure 61 ^{13}C NMR (400 MHz, CDCl_3) of **1z**



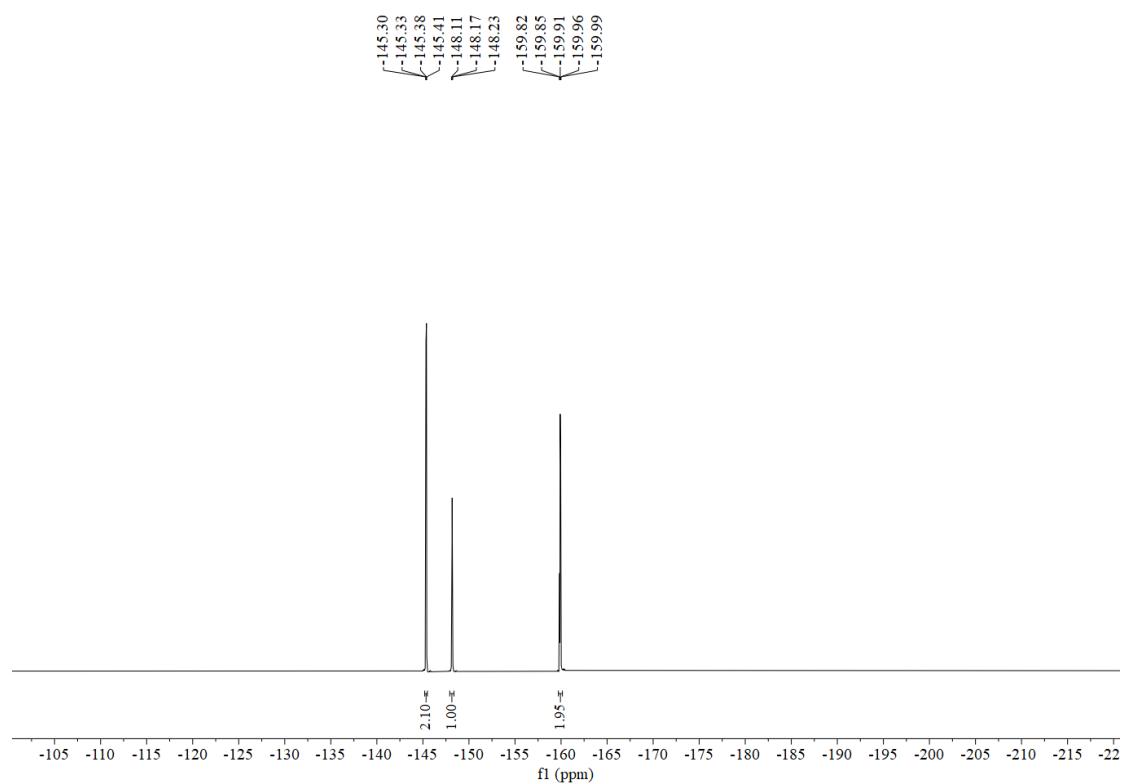
Supplementary Figure 62 ^1H NMR (400 MHz, DMSO- d_6) of NHC-G



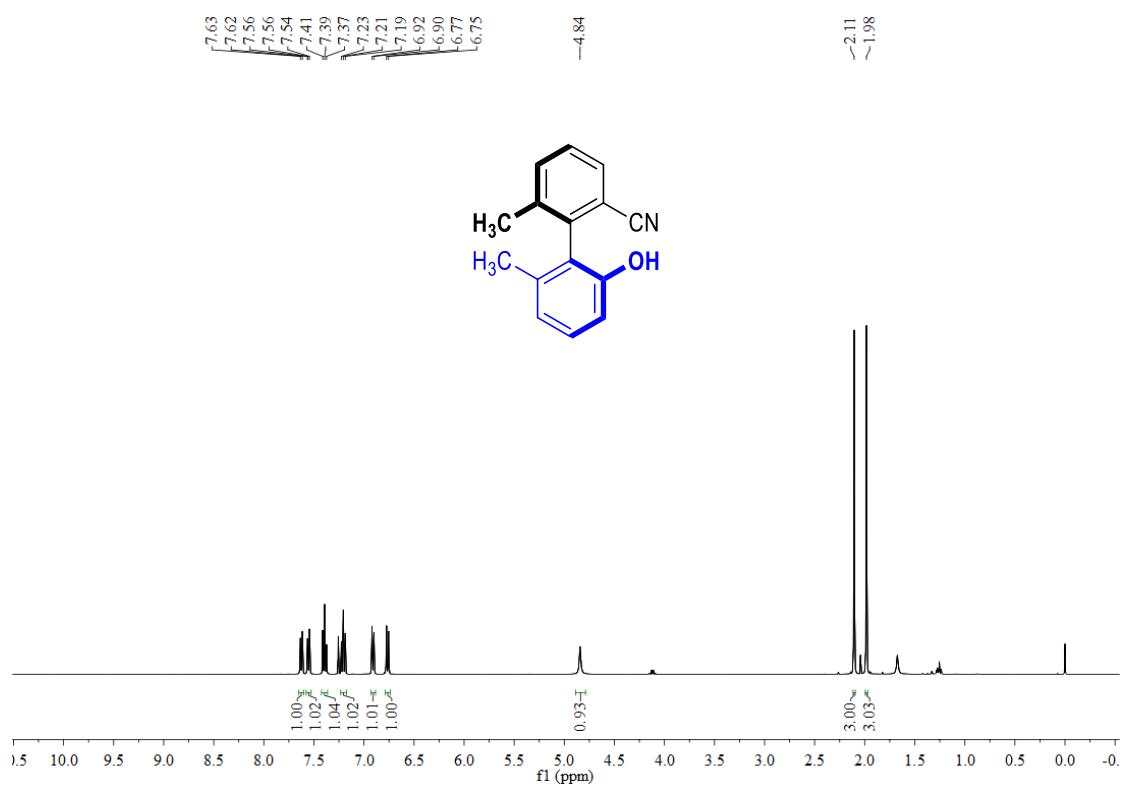
Supplementary Figure 63 ^{13}C NMR (400 MHz, DMSO- d_6) of NHC-G



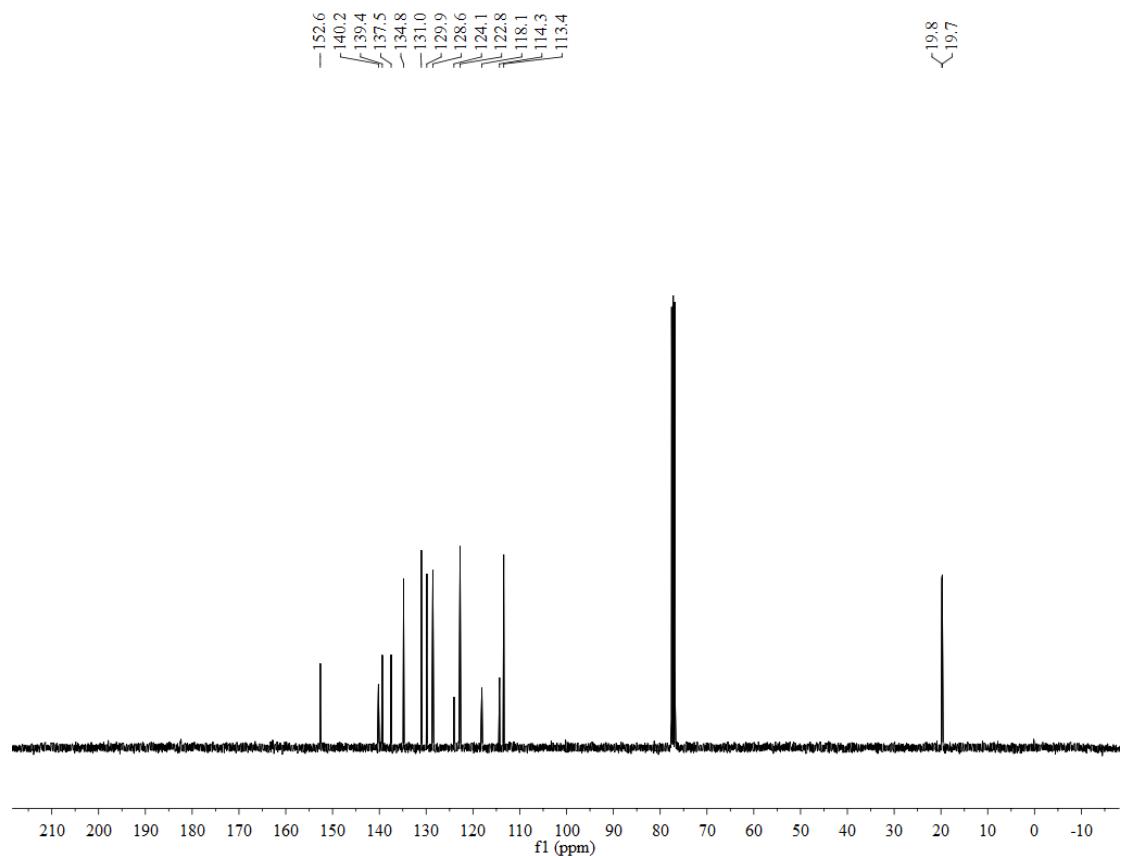
Supplementary Figure 64 ^{19}F NMR (400 MHz, $\text{DMSO}-d_6$) of NHC-G



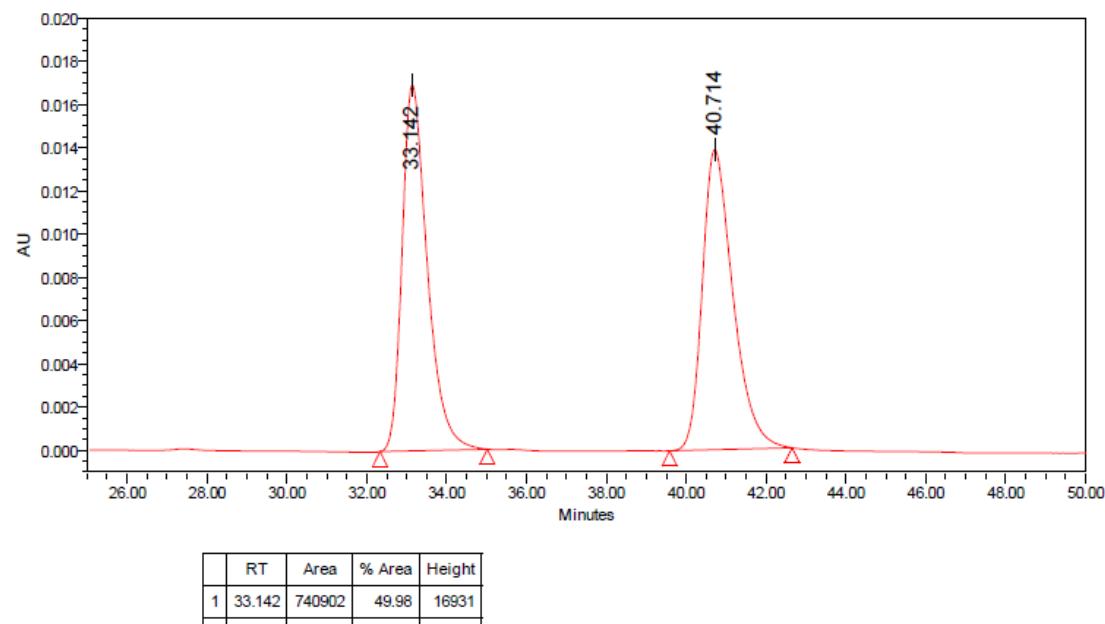
Supplementary Figure 65 ^1H NMR (400 MHz, CDCl_3) of **3a**



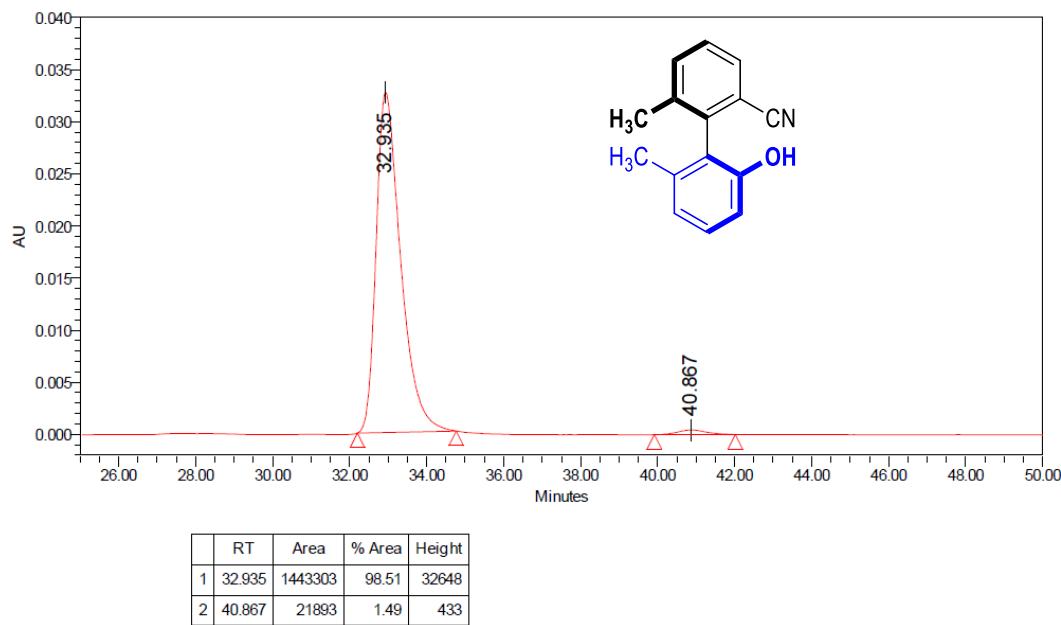
Supplementary Figure 66 ^{13}C NMR (400 MHz, CDCl_3) of **3a**



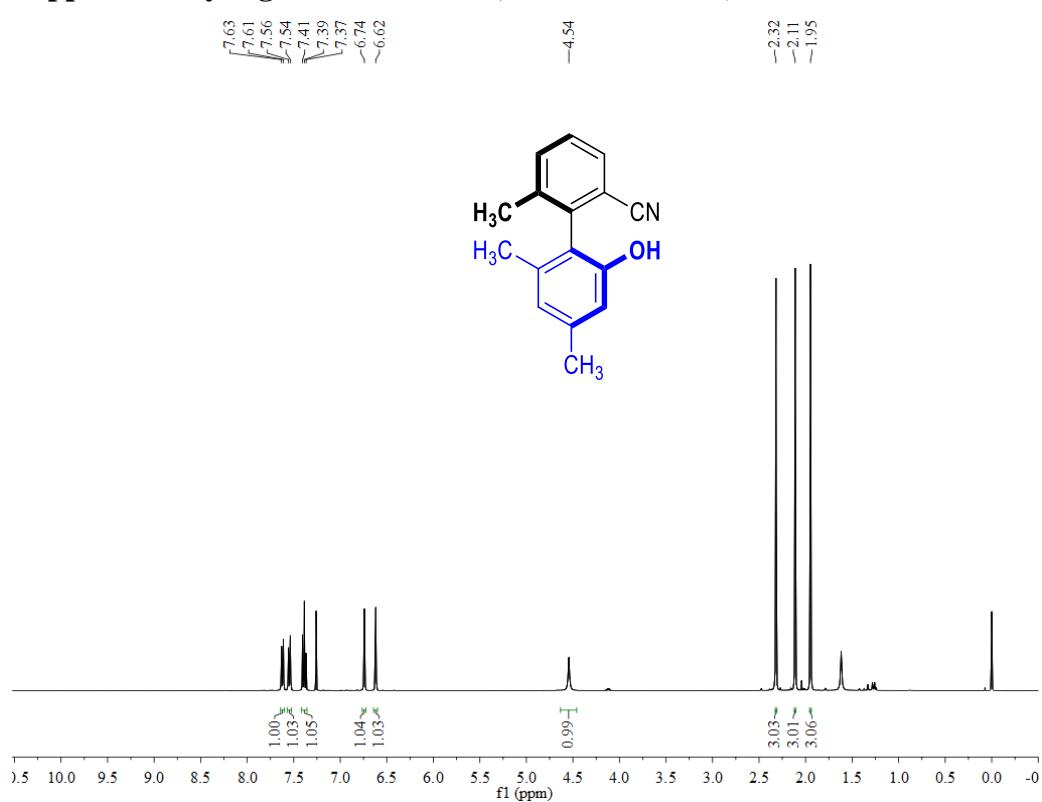
Supplementary Figure 67 HPLC spectra of racemic **3a**



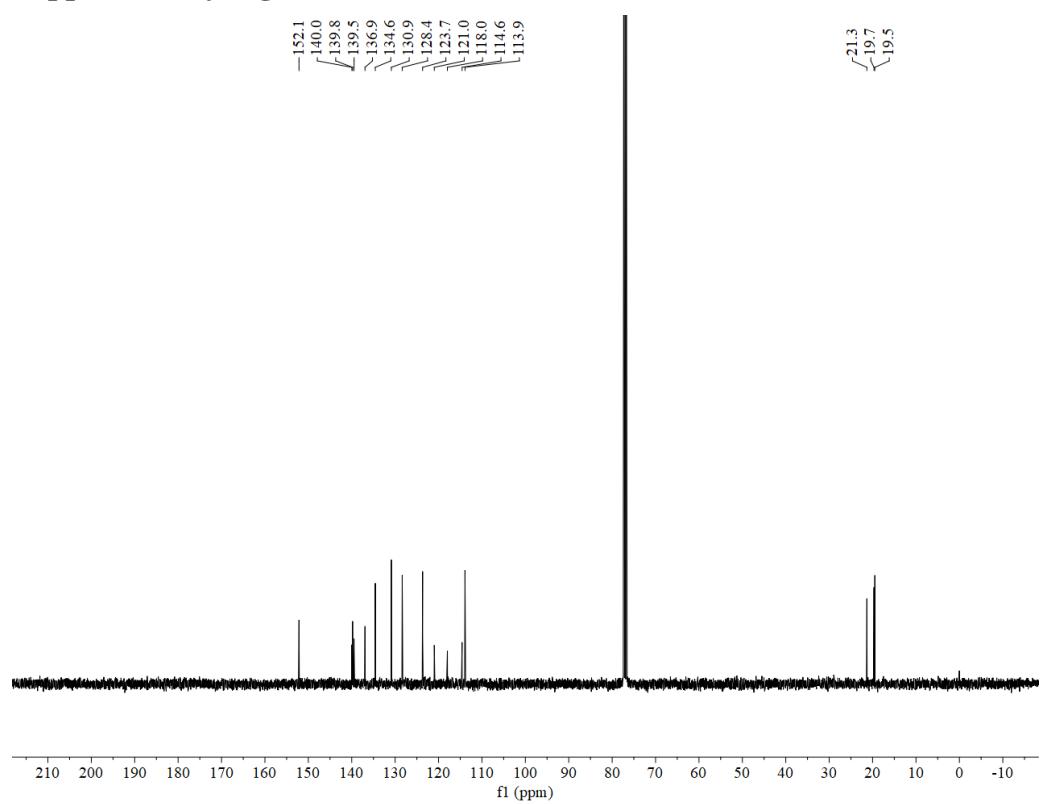
Supplementary Figure 68 HPLC spectra of (*S*)- **3a**



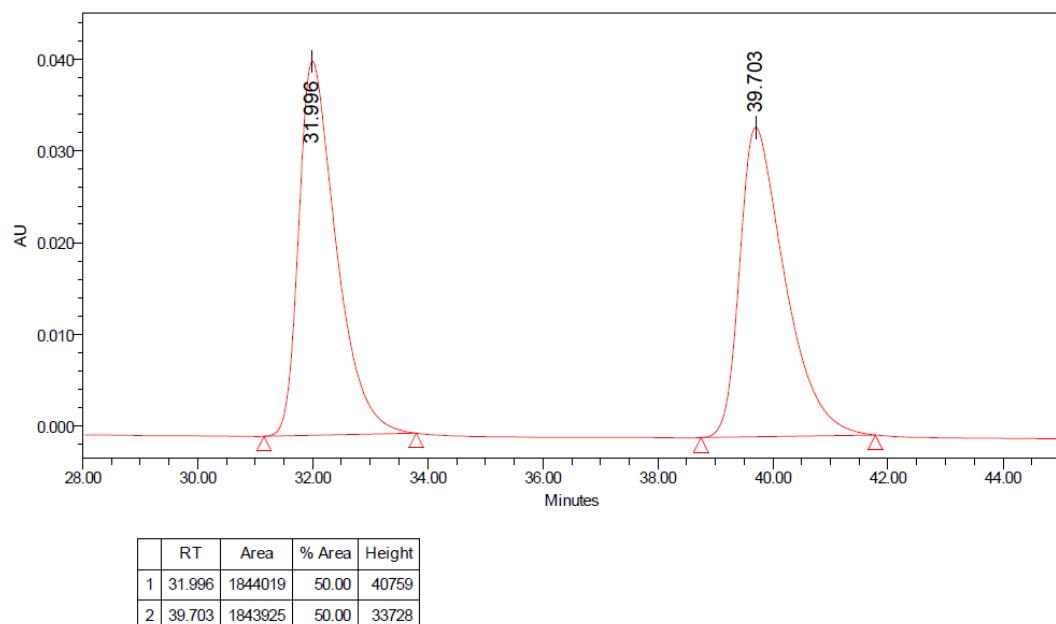
Supplementary Figure 69 ^1H NMR (400 MHz, CDCl_3) of **3b**



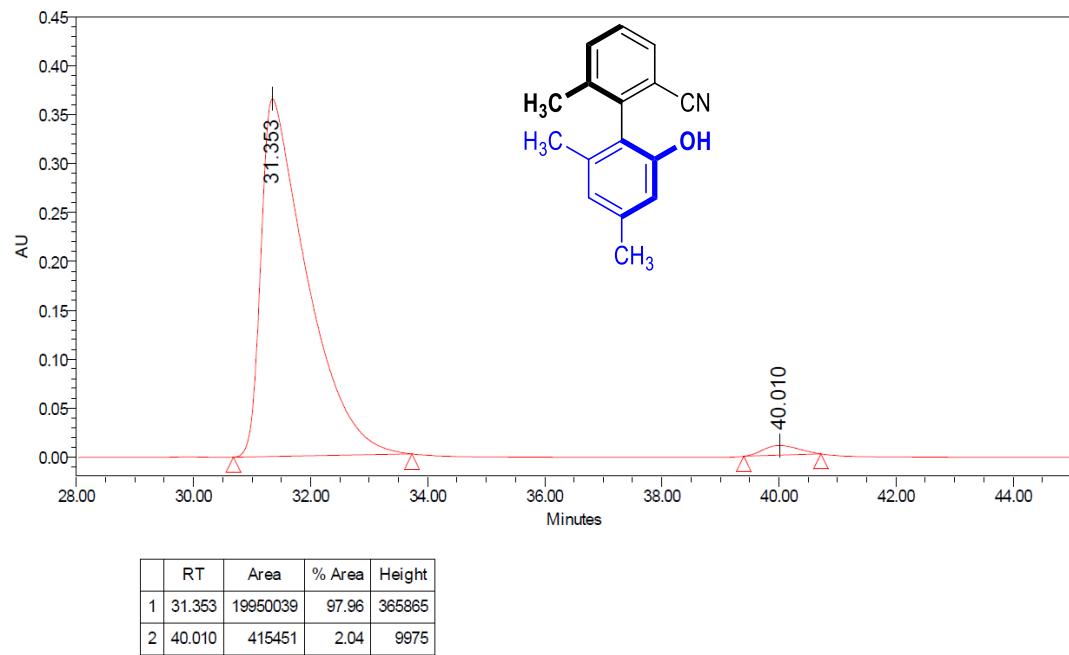
Supplementary Figure 70 ^{13}C NMR (400 MHz, CDCl_3) of **3b**



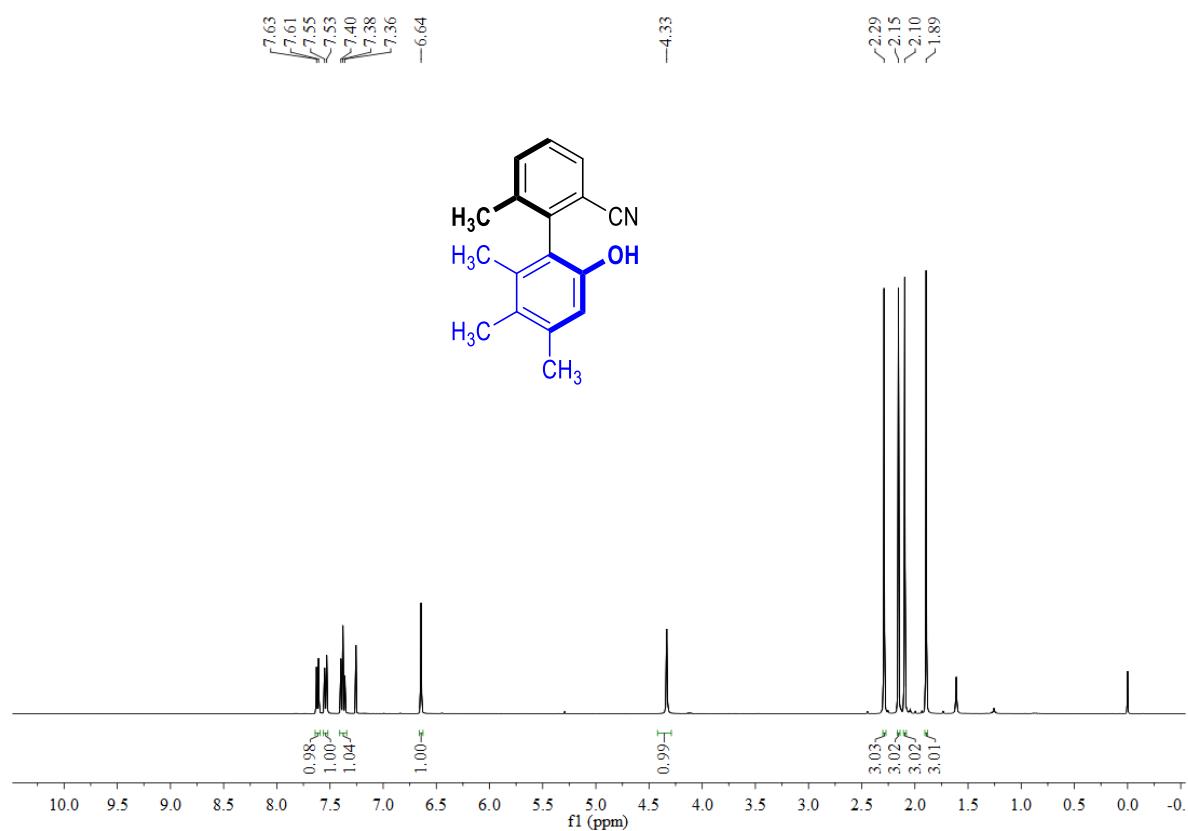
Supplementary Figure 71 HPLC spectra of racemic **3b**



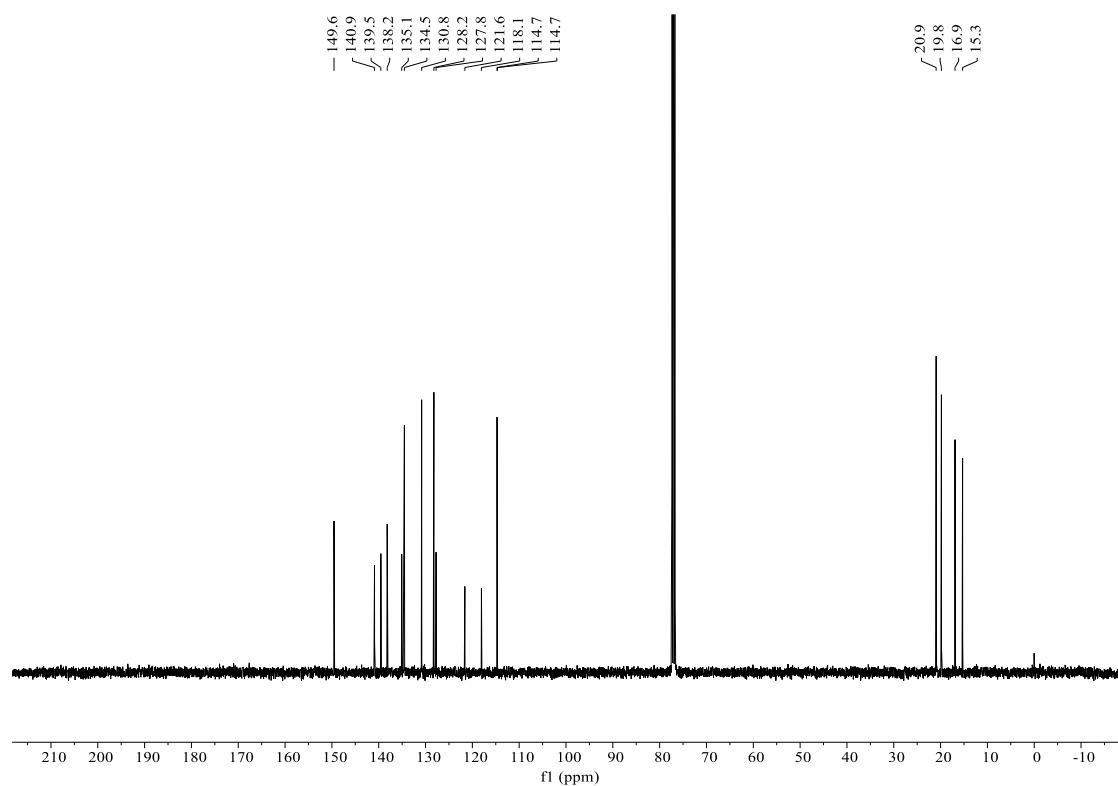
Supplementary Figure 72 HPLC spectra of (*S*)-**3b**



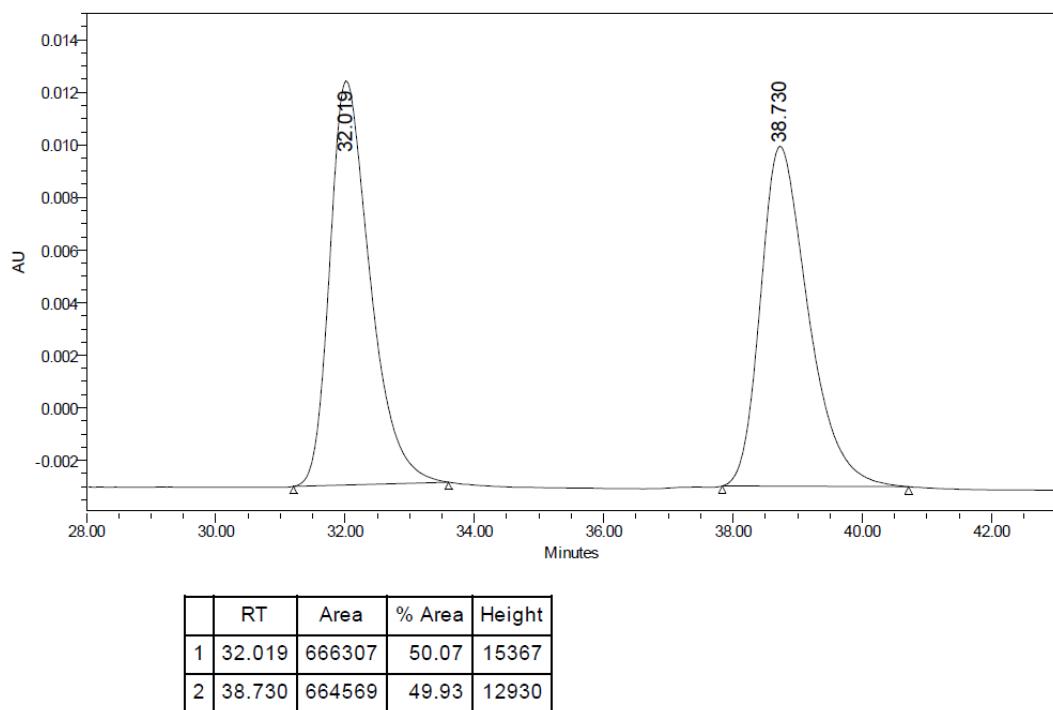
Supplementary Figure 73 ^1H NMR (400 MHz, CDCl_3) of **3c**



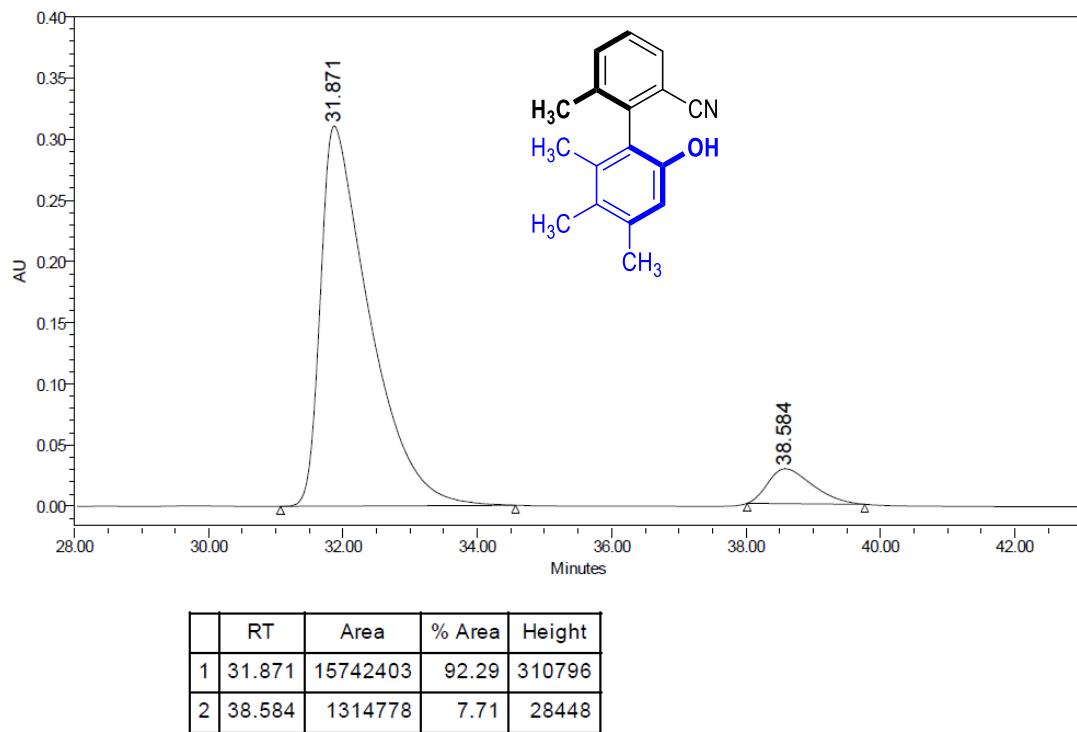
Supplementary Figure 74 ^{13}C NMR (400 MHz, CDCl_3) of **3c**



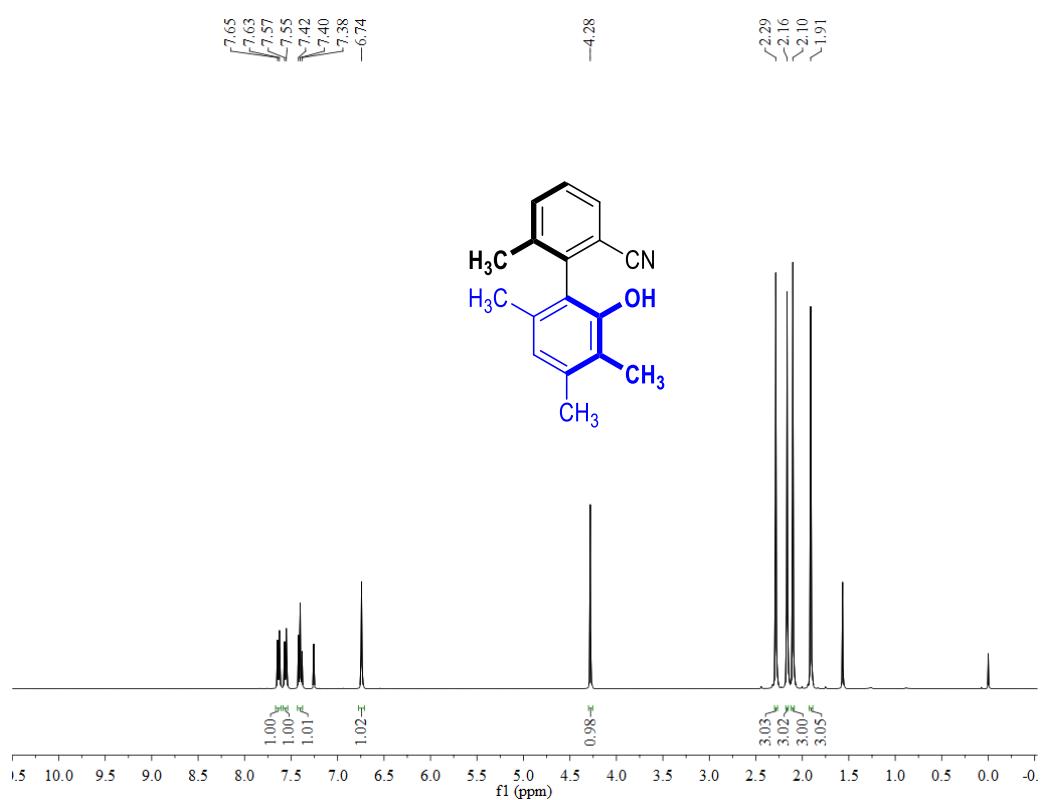
Supplementary Figure 75 HPLC spectra of racemic **3c**



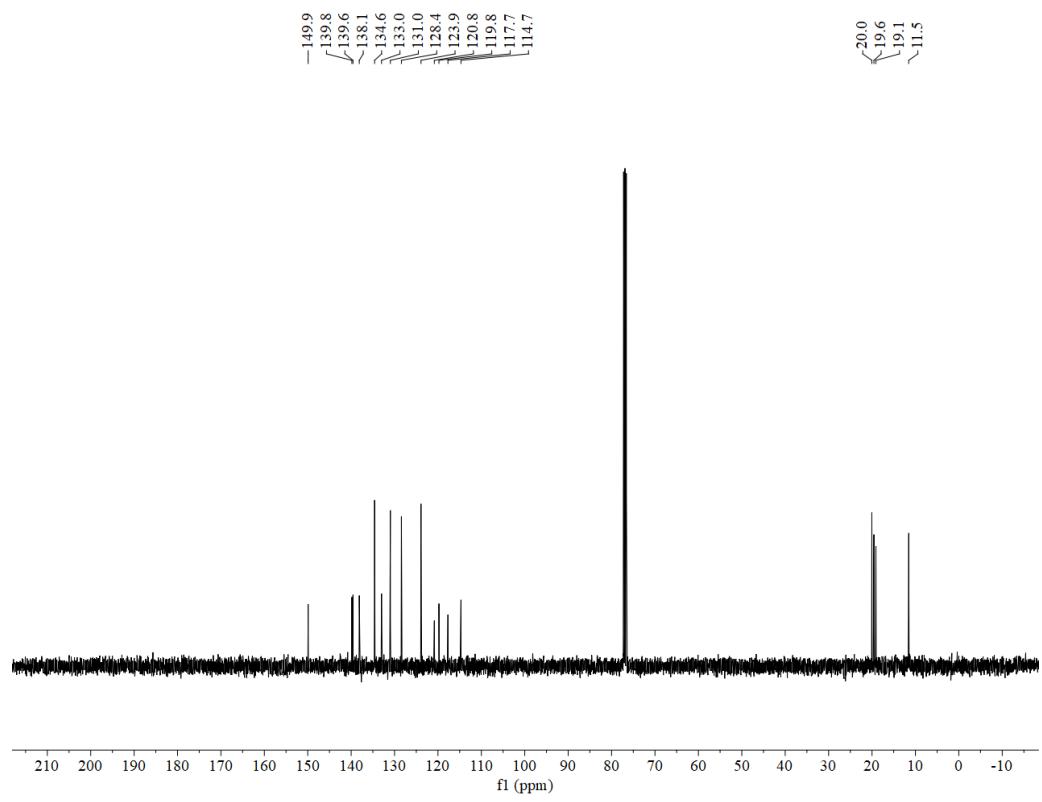
Supplementary Figure 76 HPLC spectra of (*S*)-**3c**



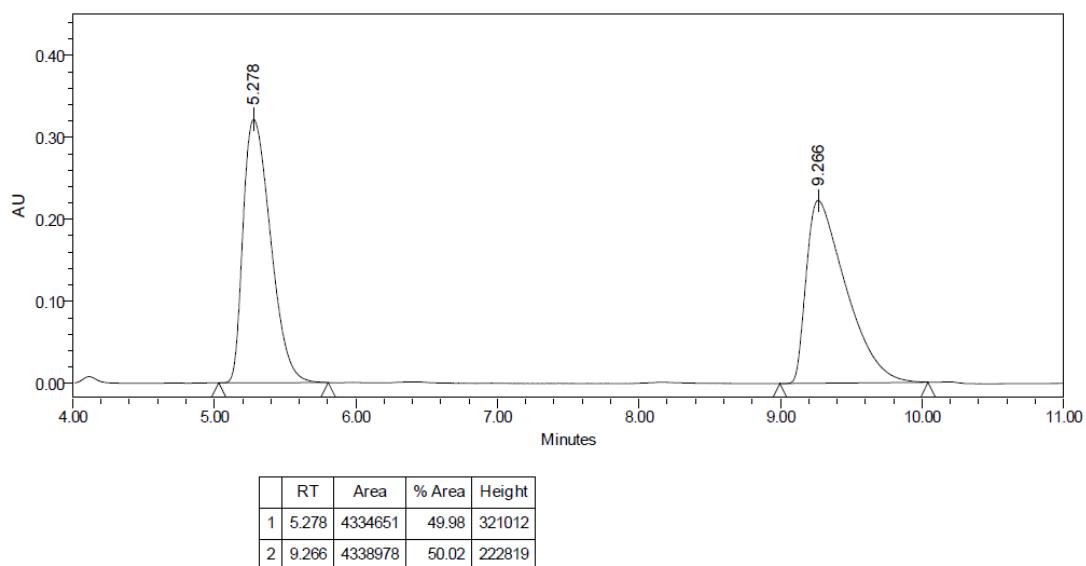
Supplementary Figure 77 ^1H NMR (400 MHz, CDCl_3) of **3d**



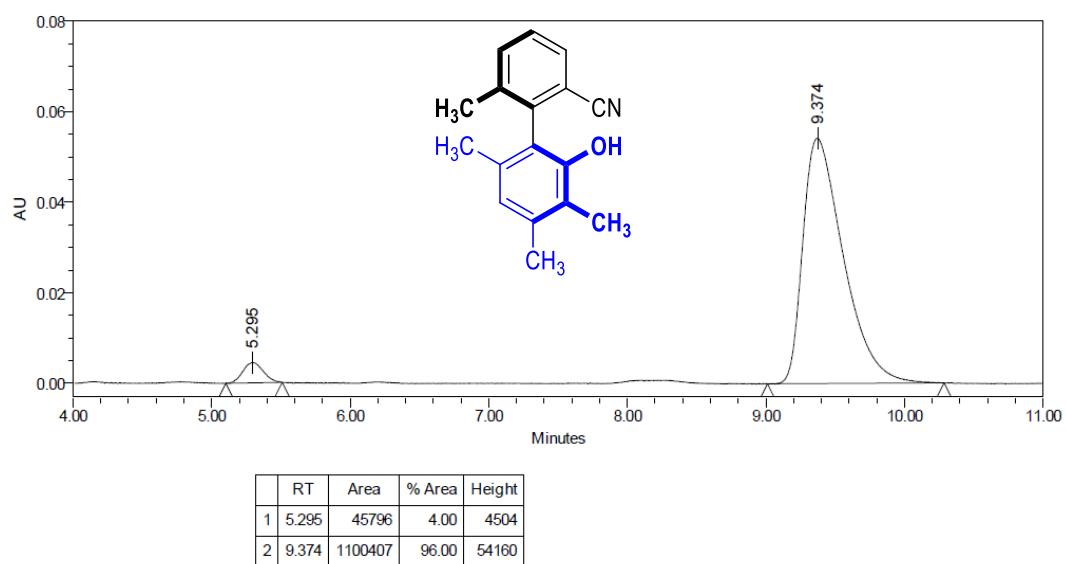
Supplementary Figure 78 ^{13}C NMR (400 MHz, CDCl_3) of **3d**



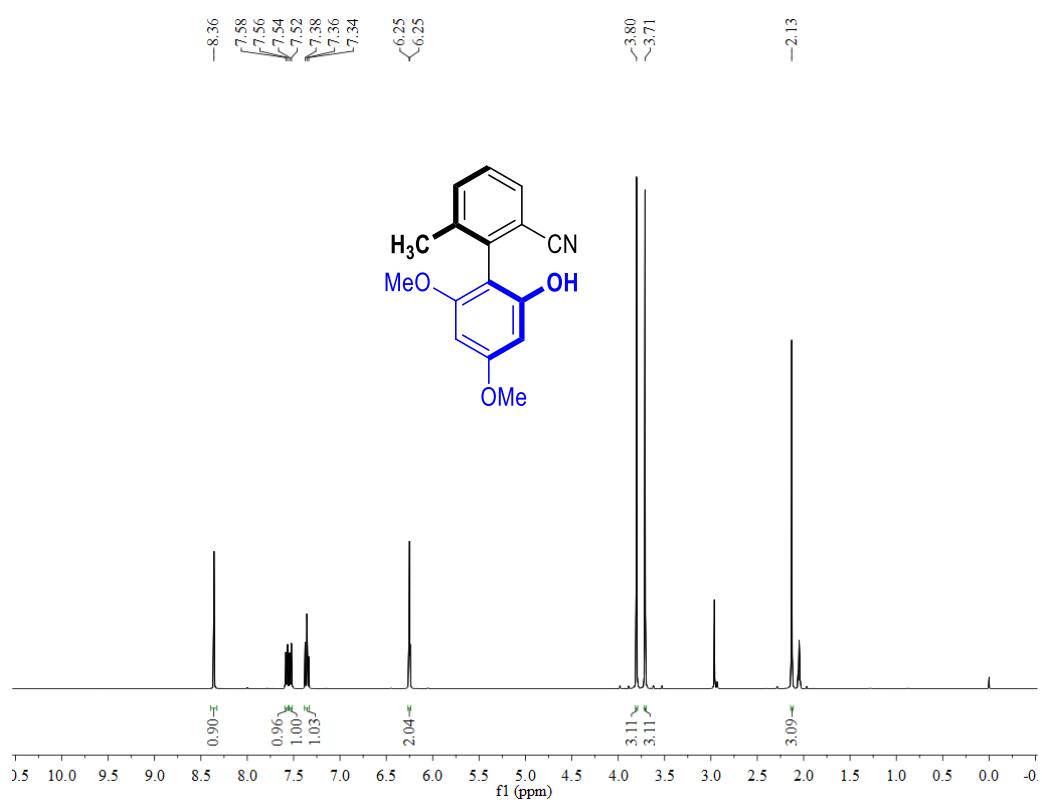
Supplementary Figure 79 HPLC spectra of racemic **3d**



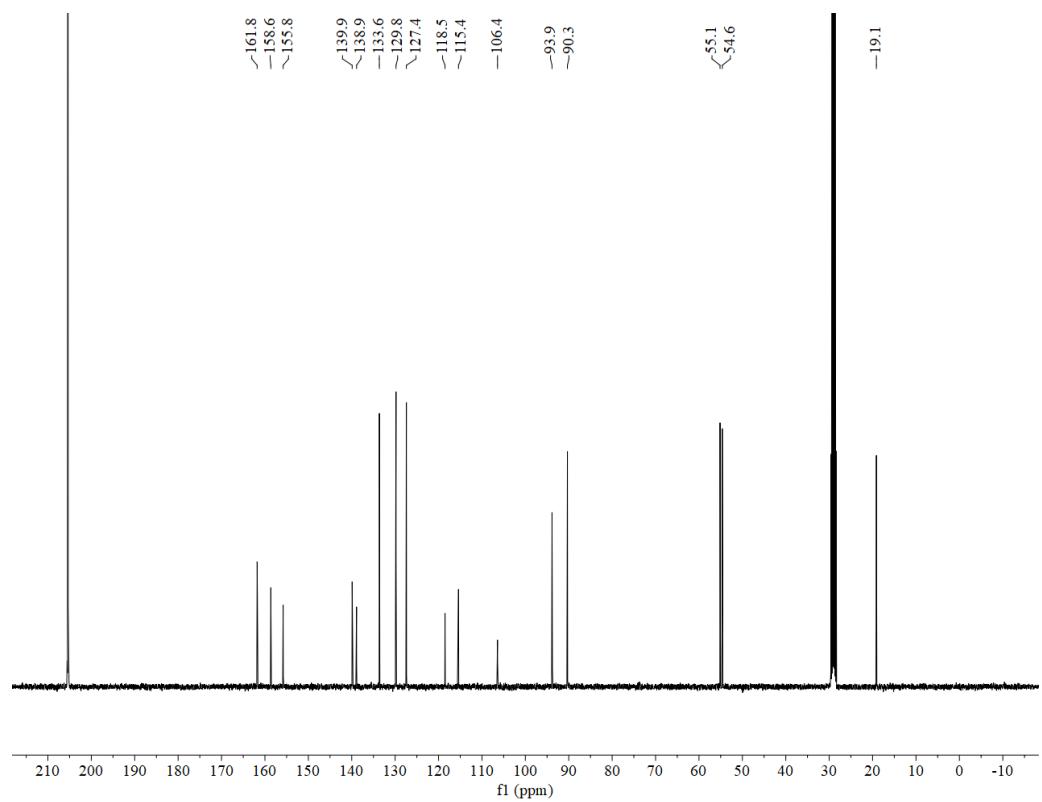
Supplementary Figure 80 HPLC spectra of (*S*)- **3d**



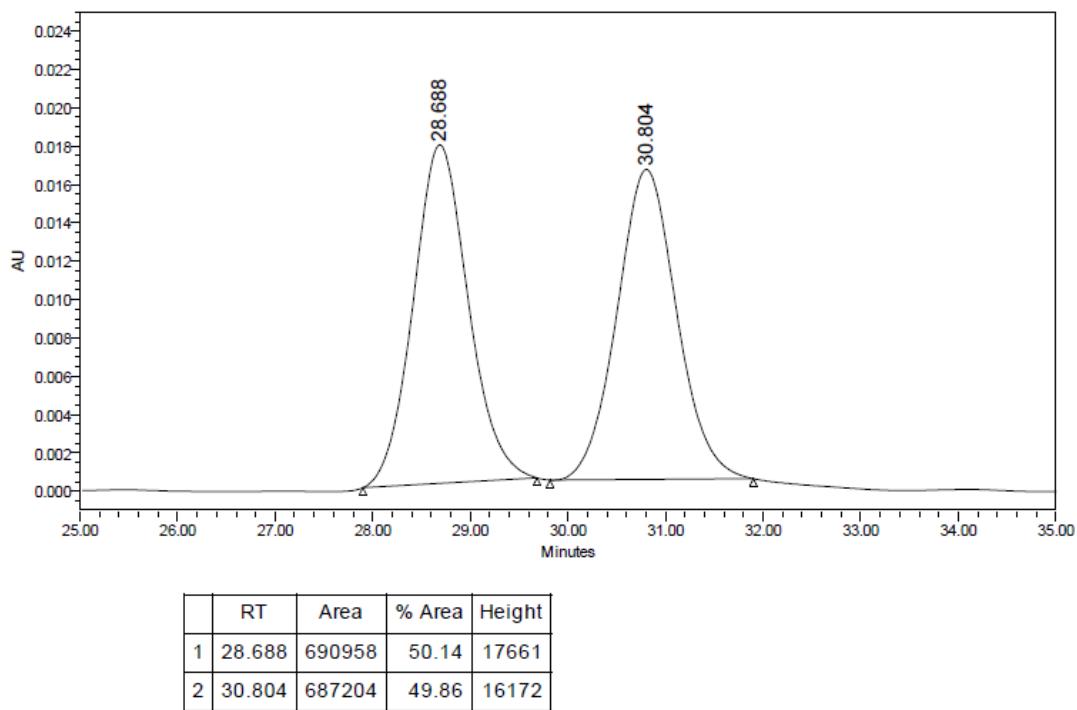
Supplementary Figure 81 ^1H NMR (400 MHz, Acetone- d_6) of **3e**



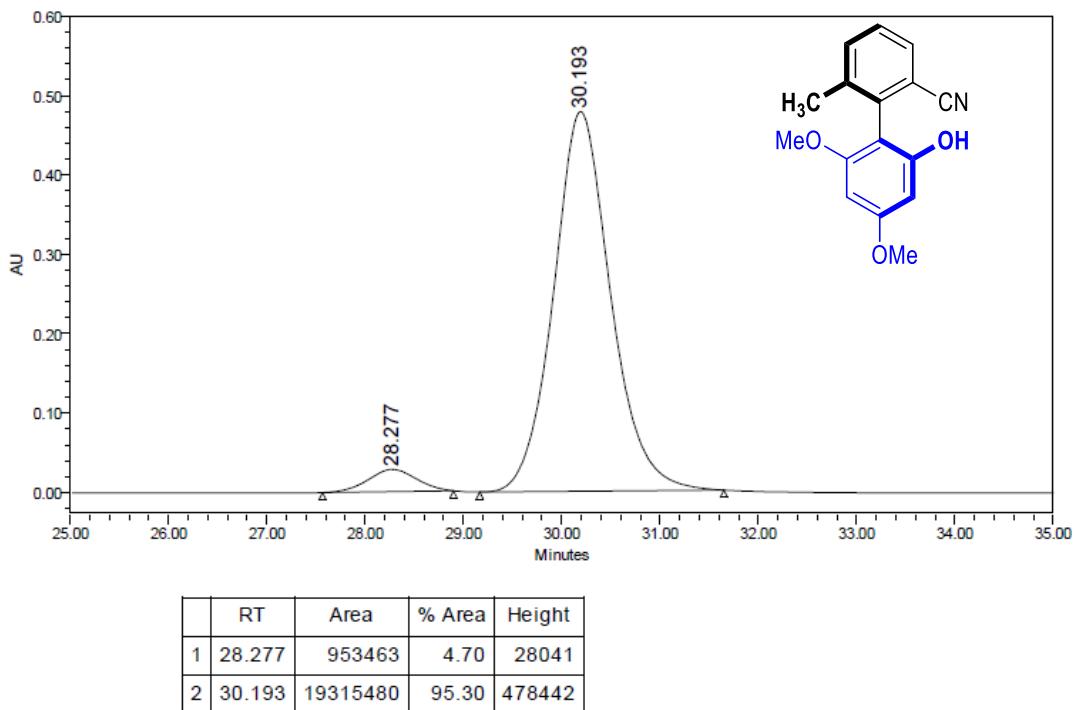
Supplementary Figure 82 ^{13}C NMR (400 MHz, Acetone- d_6) of **3e**



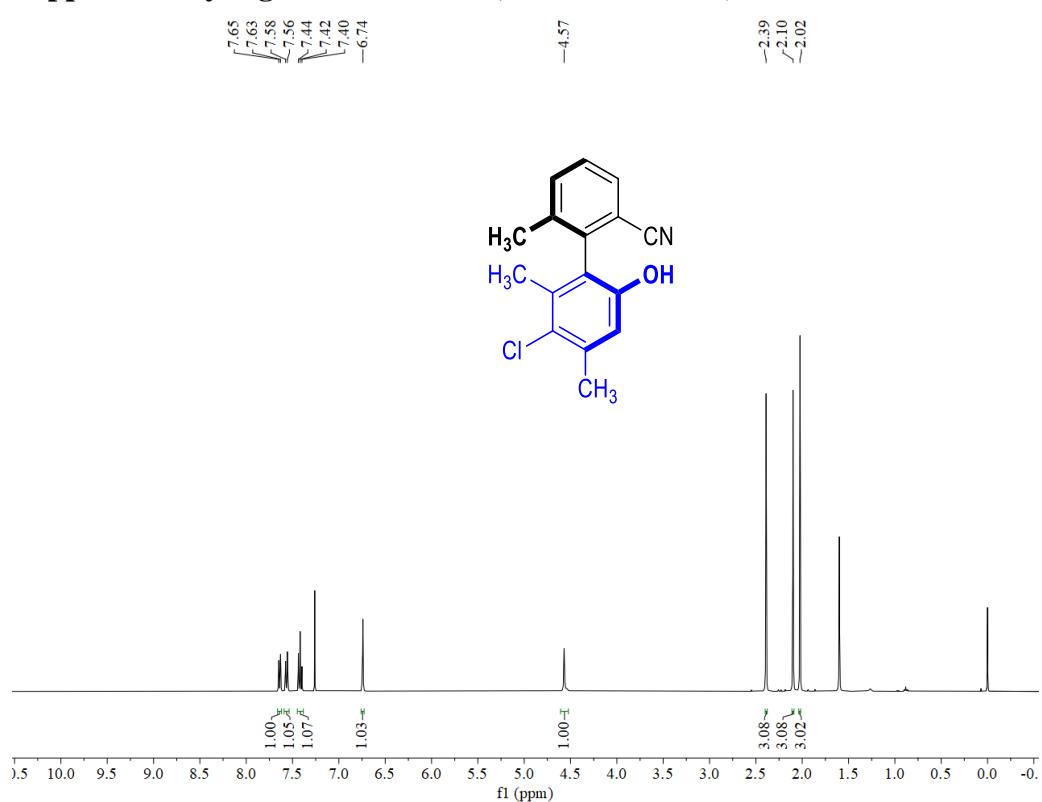
Supplementary Figure 83 HPLC spectra of racemic **3e**



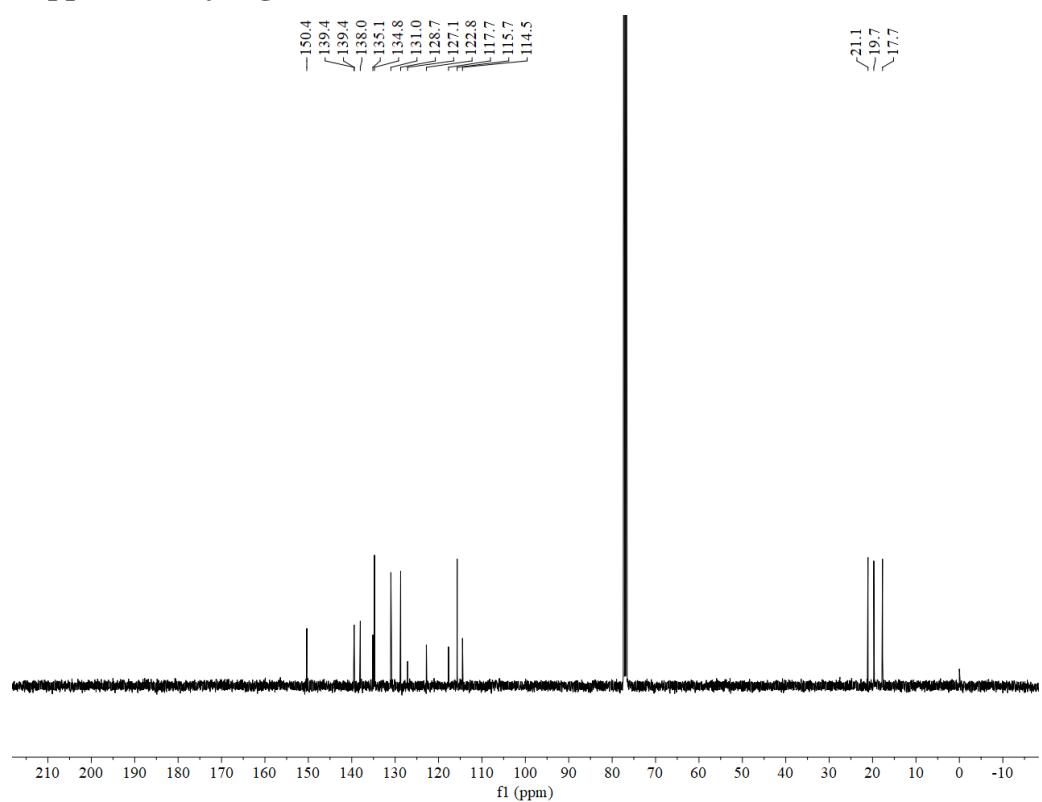
Supplementary Figure 84 HPLC spectra of (*R*)- **3e**



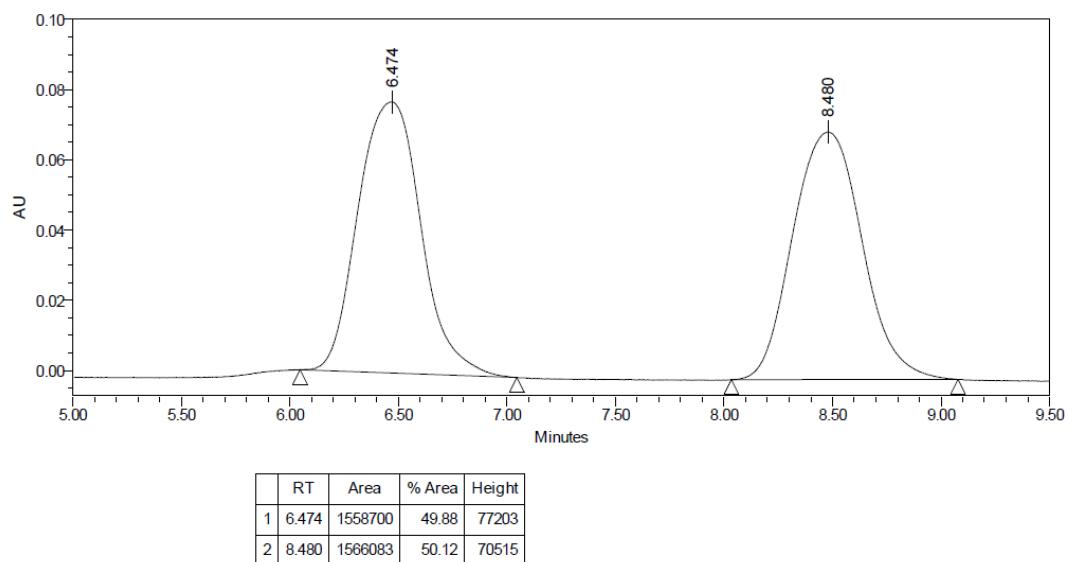
Supplementary Figure 85 ^1H NMR (400 MHz, CDCl_3) of **3f**



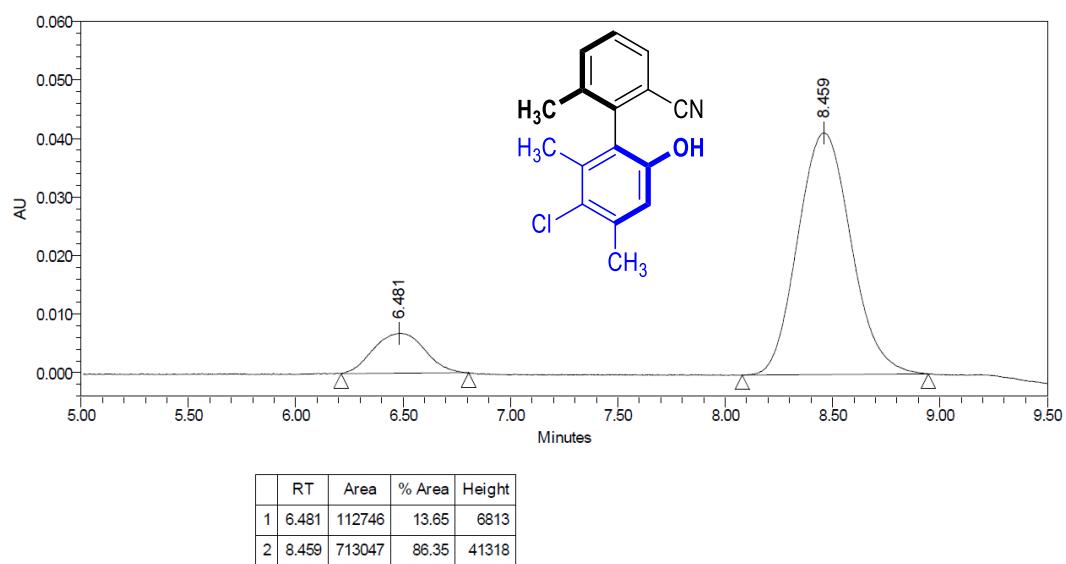
Supplementary Figure 86 ^{13}C NMR (400 MHz, CDCl_3) of **3f**



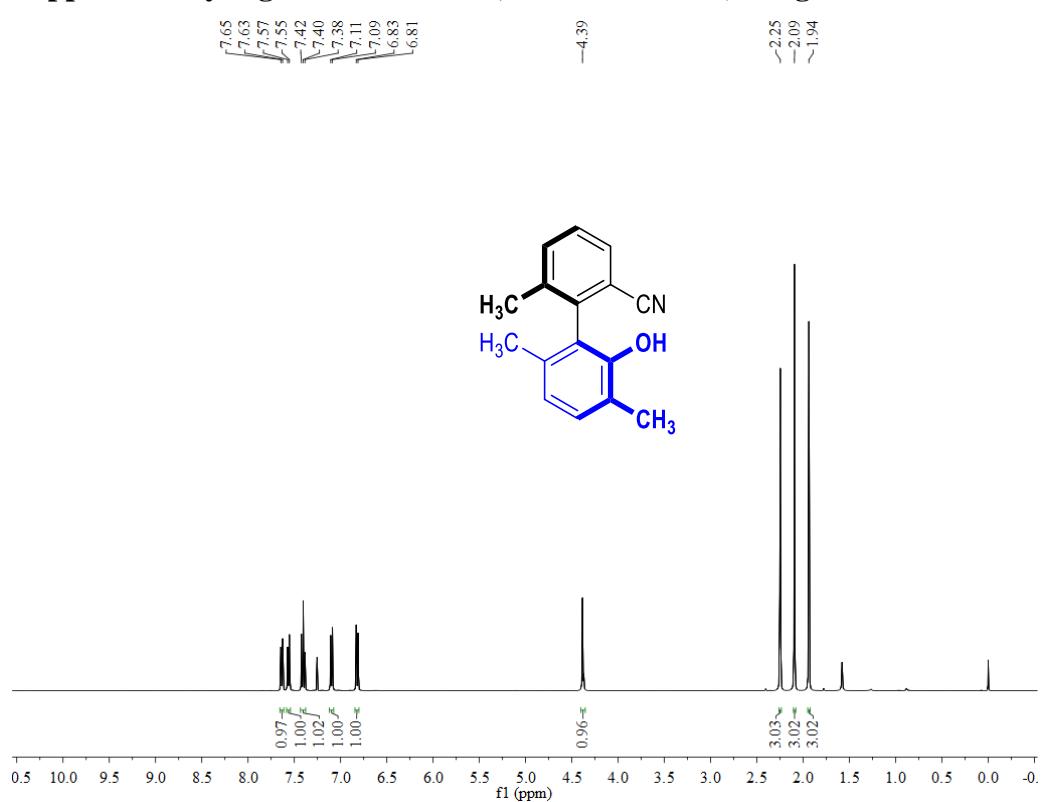
Supplementary Figure 87 HPLC spectra of racemic **3f**



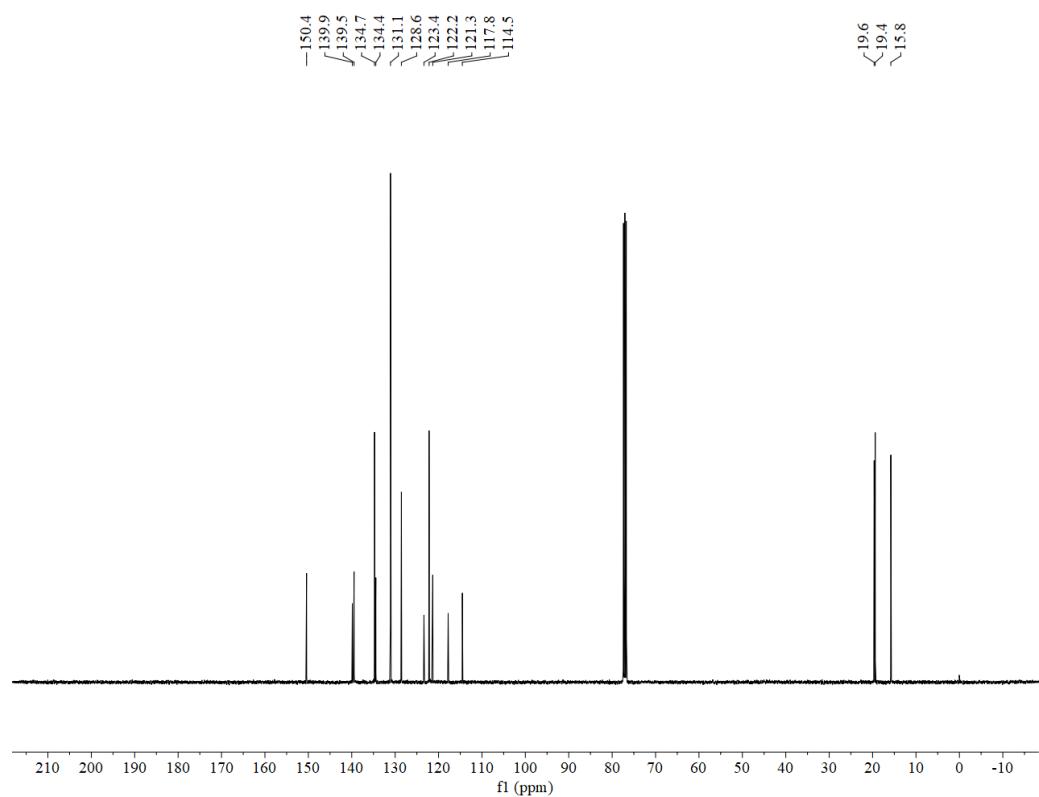
Supplementary Figure 88 HPLC spectra of (*S*)- **3f**



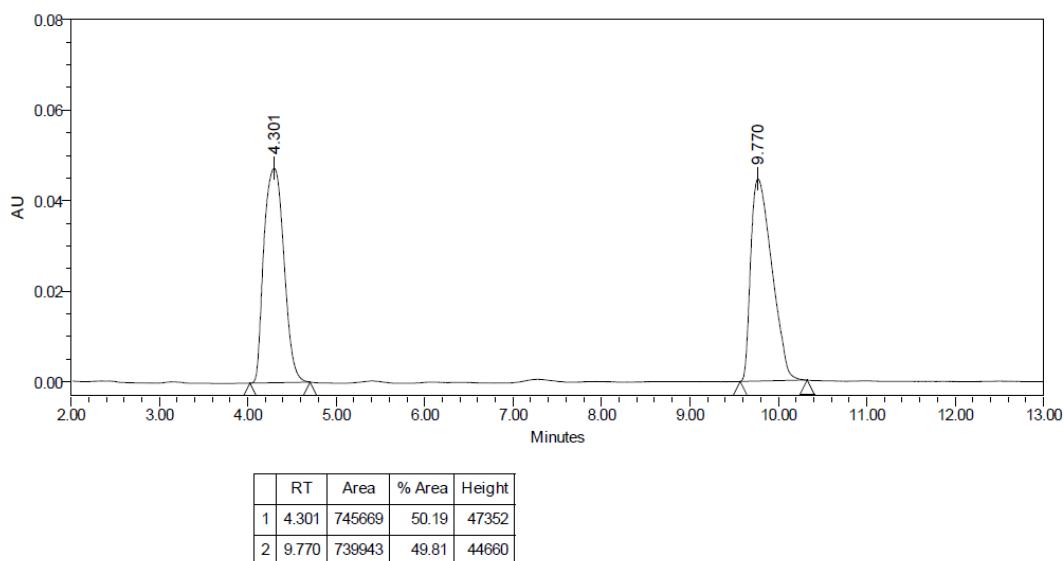
Supplementary Figure 89 ^1H NMR (400 MHz, CDCl_3) of **3g**



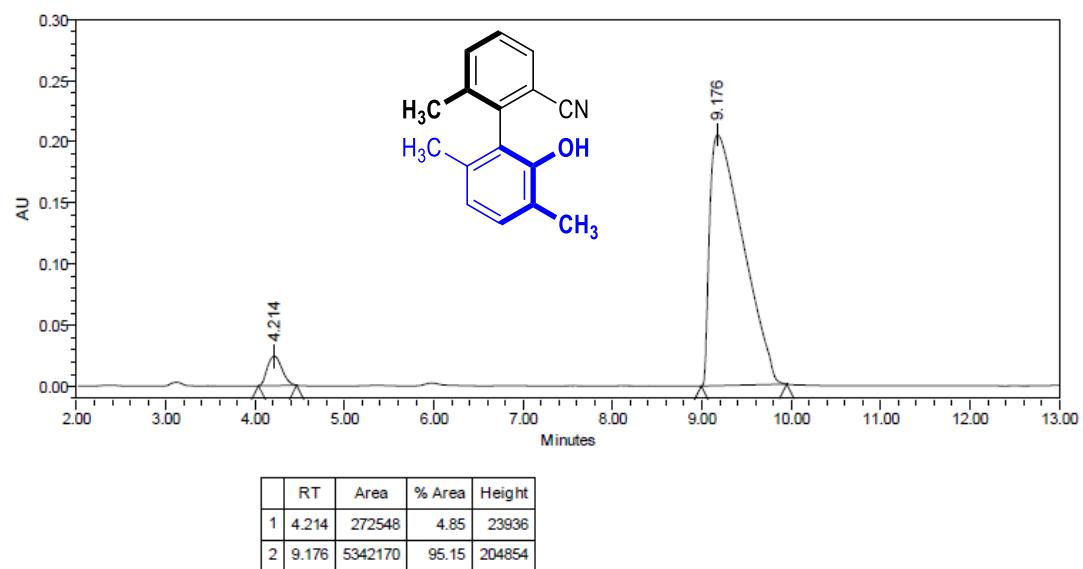
Supplementary Figure 90 ^{13}C NMR (400 MHz, CDCl_3) of **3g**



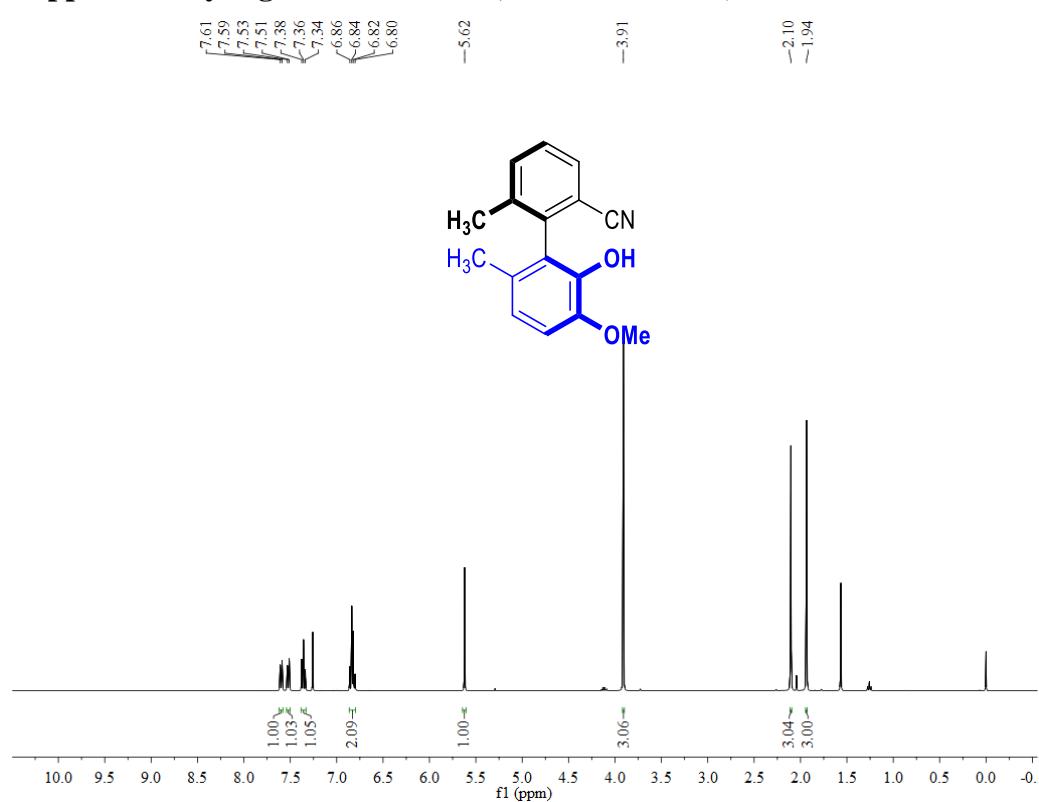
Supplementary Figure 91 HPLC spectra of racemic **3g**



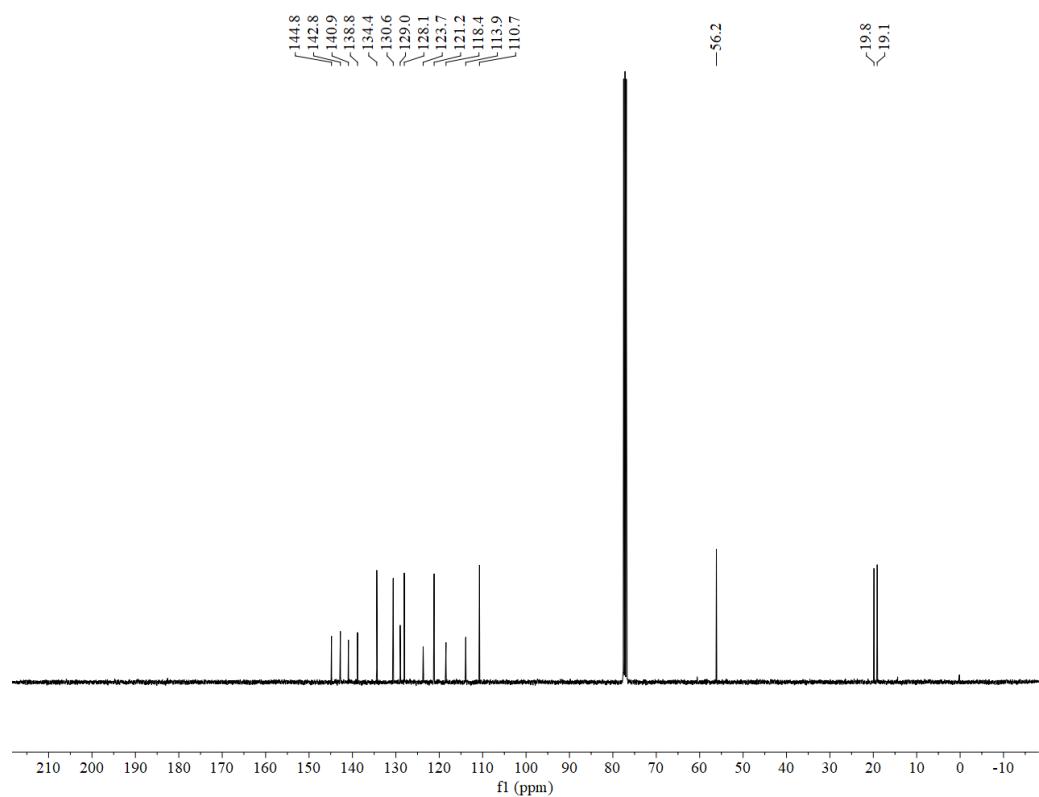
Supplementary Figure 92 HPLC spectra of (*S*)- **3g**



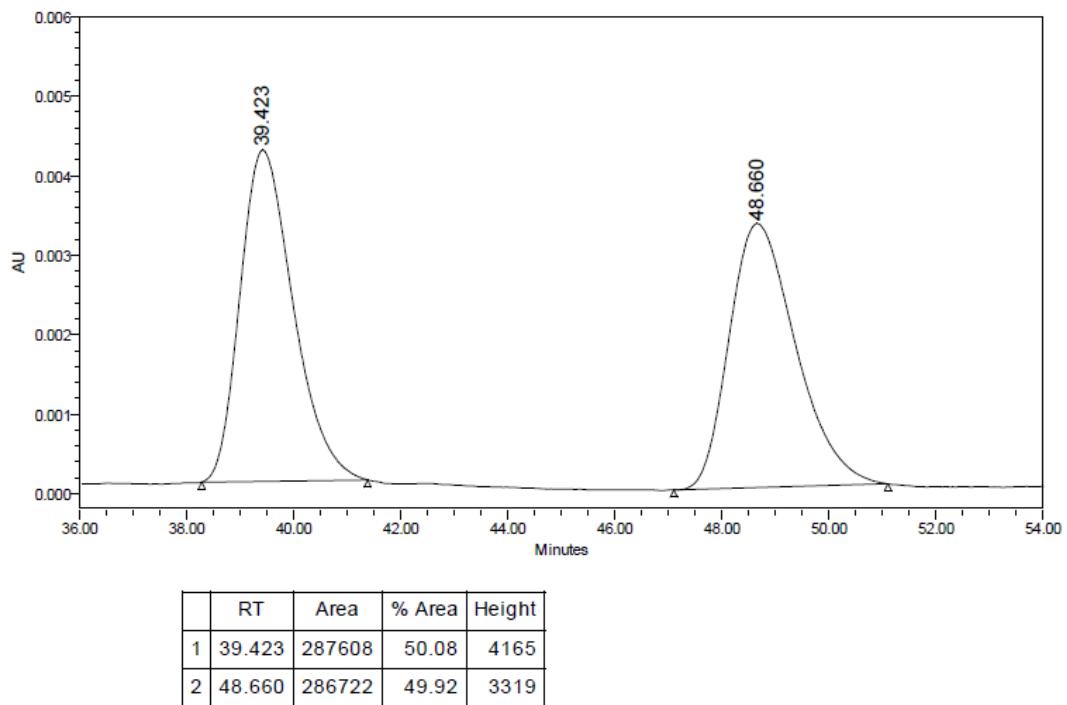
Supplementary Figure 93 ^1H NMR (400 MHz, CDCl_3) of **3h**



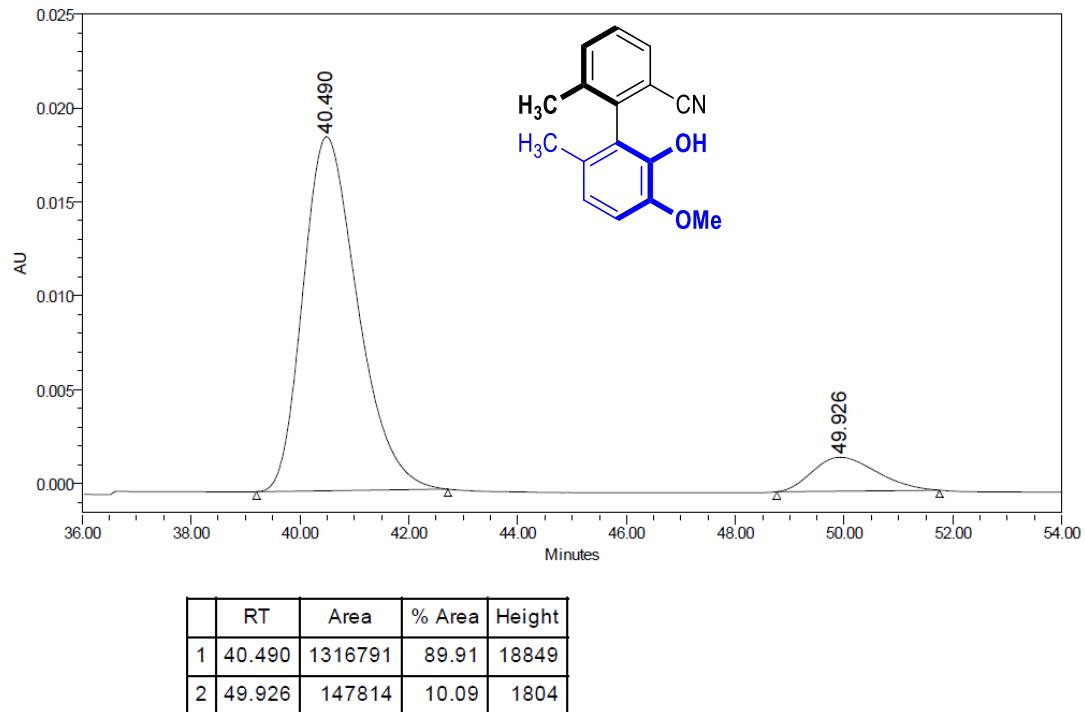
Supplementary Figure 94 ^{13}C NMR (400 MHz, CDCl_3) of **3h**



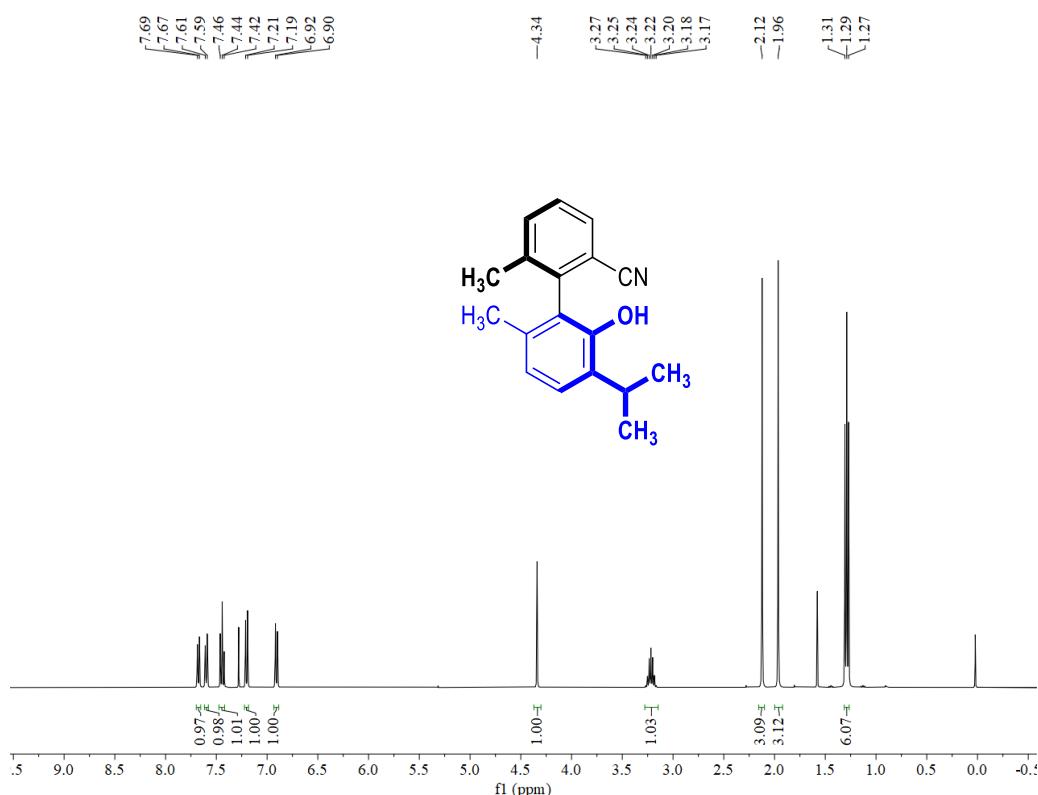
Supplementary Figure 95 HPLC spectra of racemic **3h**



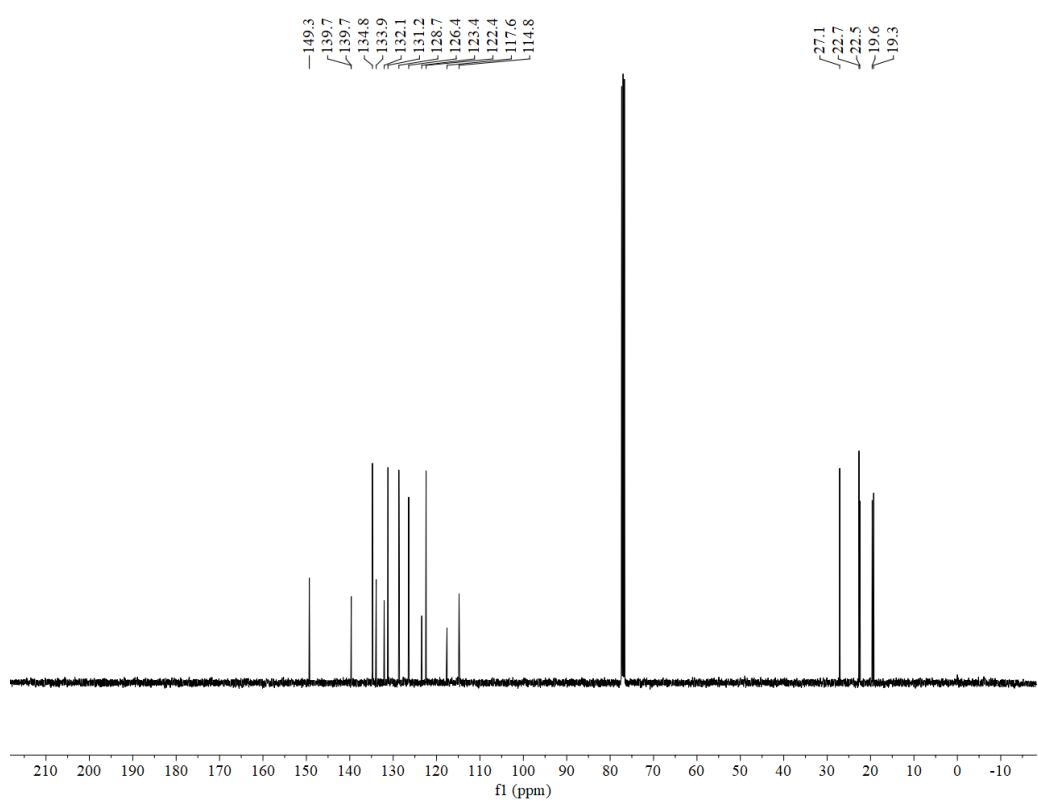
Supplementary Figure 96 HPLC spectra of (*S*)-**3h**



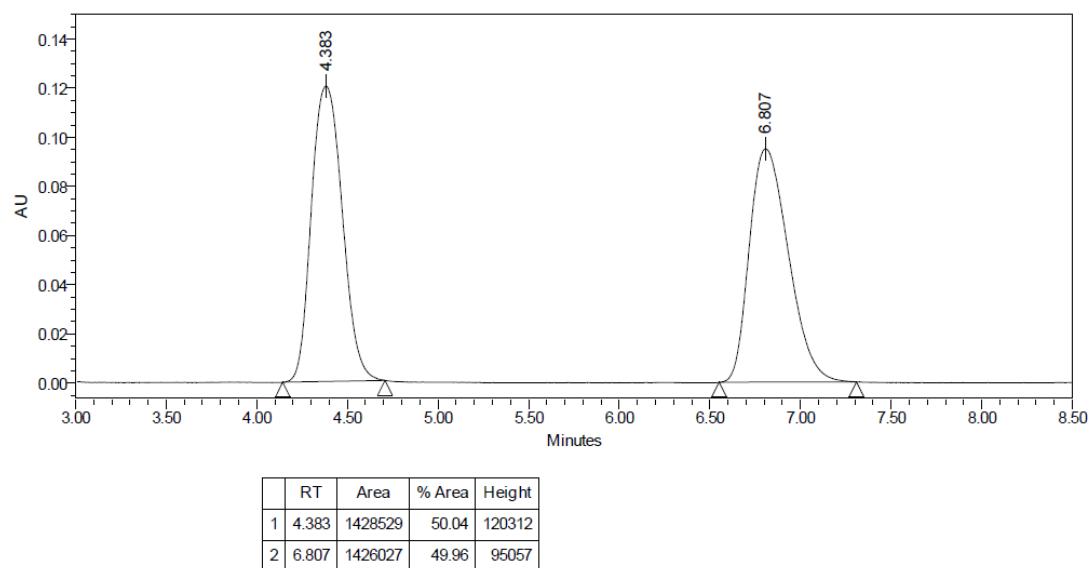
Supplementary Figure 97 ^1H NMR (400 MHz, CDCl_3) of **3i**



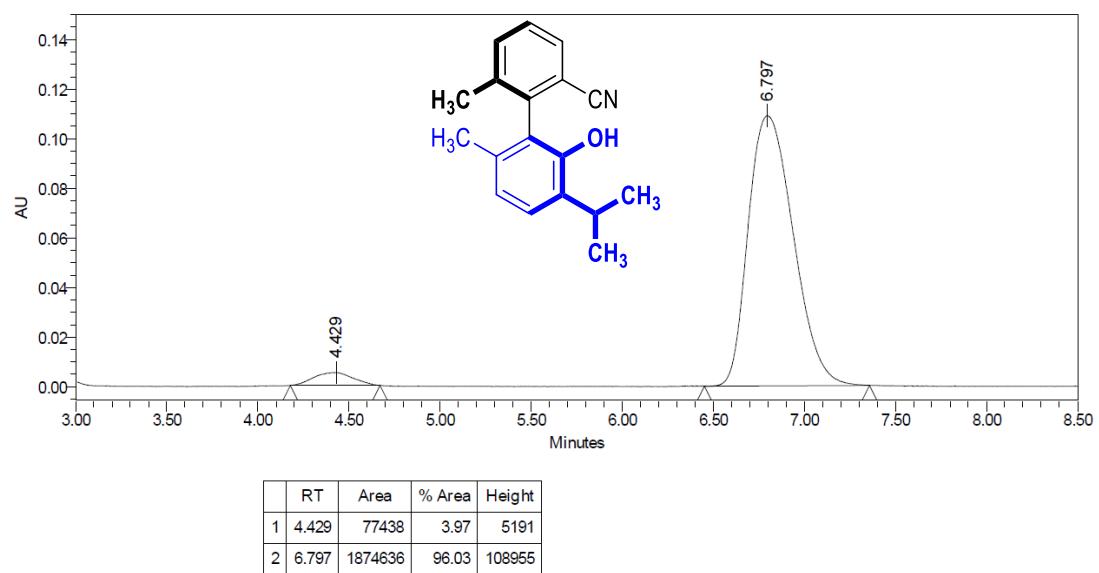
Supplementary Figure 98 ^{13}C NMR (400 MHz, CDCl_3) of 3i



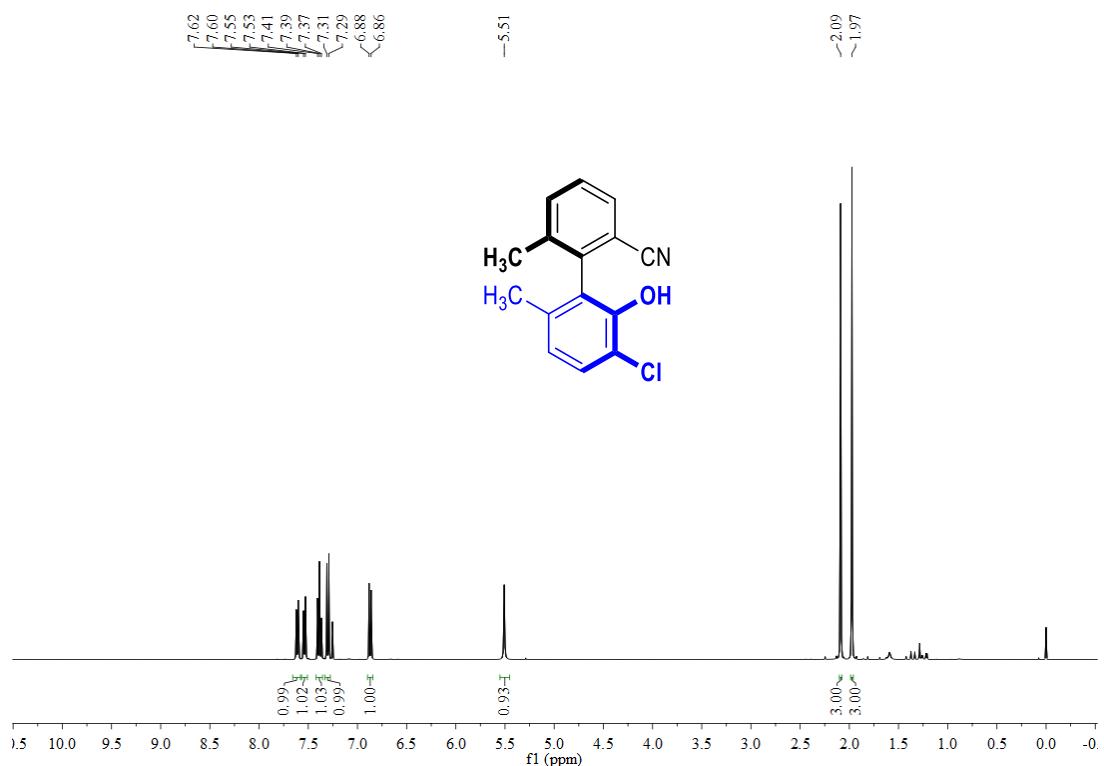
Supplementary Figure 99 HPLC spectra of racemic **3i**



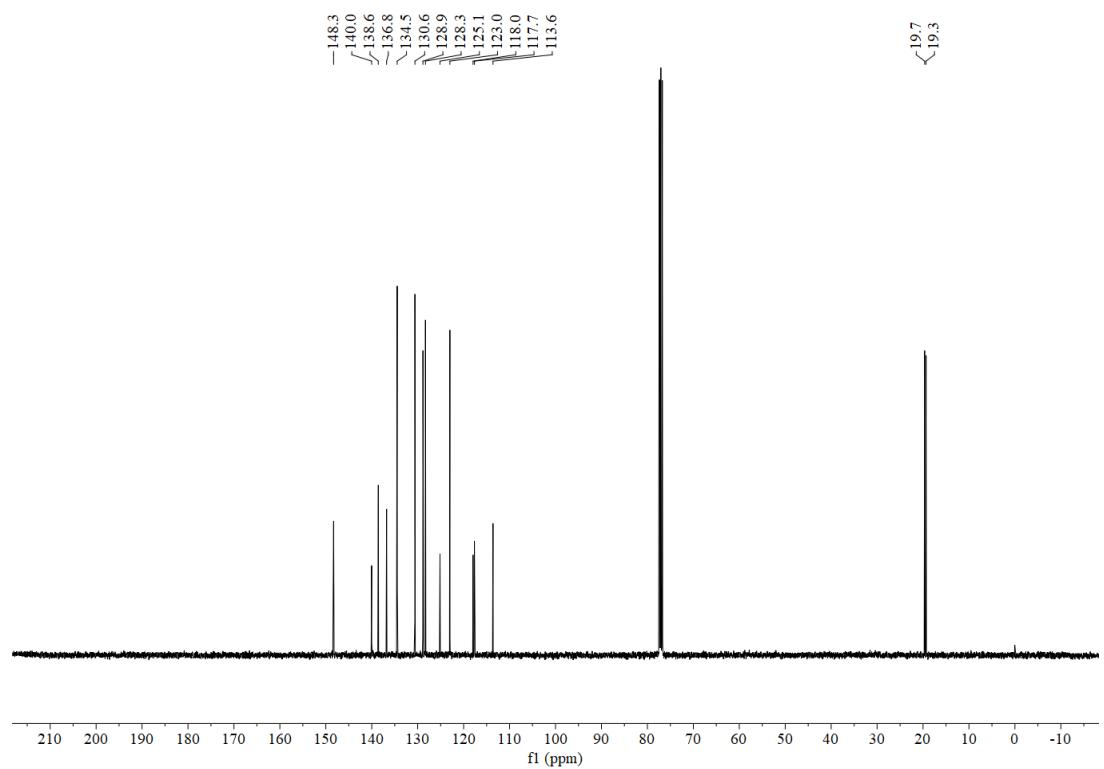
Supplementary Figure 100 HPLC spectra of (*S*)- **3i**



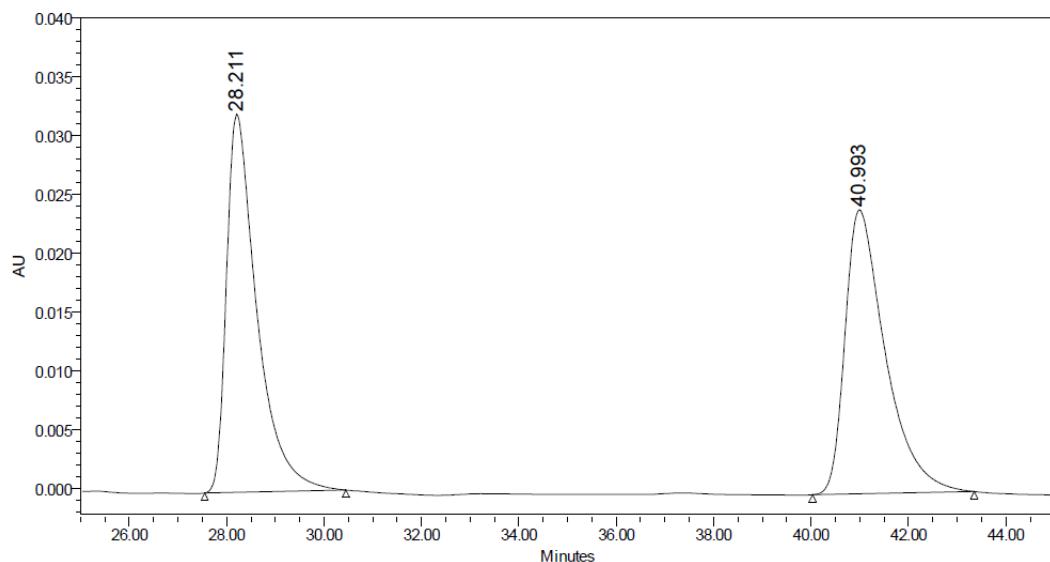
Supplementary Figure 101 ^1H NMR (400 MHz, CDCl_3) of **3j**



Supplementary Figure 102 ^{13}C NMR (400 MHz, CDCl_3) of **3j**

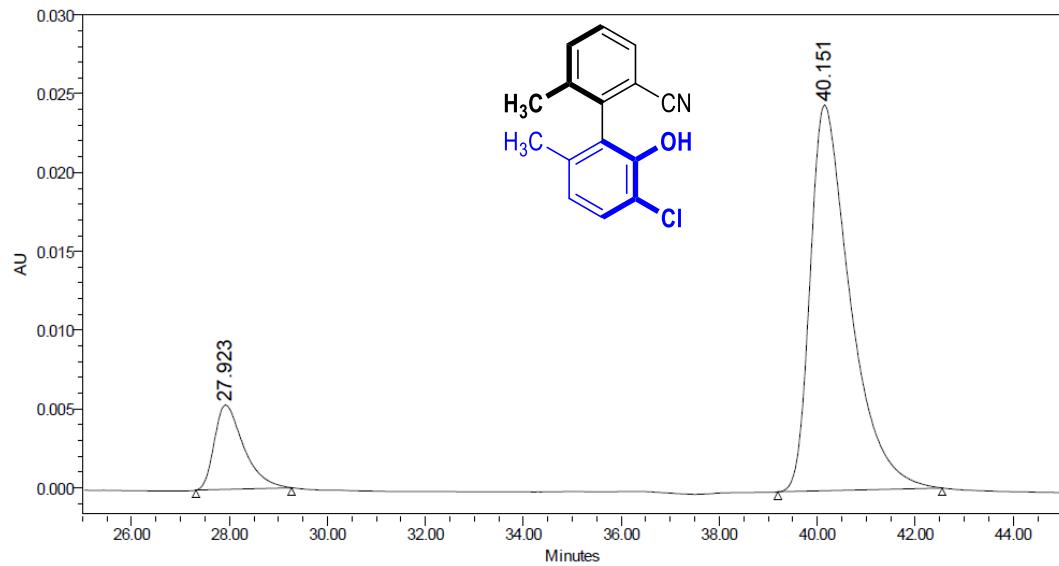


Supplementary Figure 103 HPLC spectra of racemic **3j**



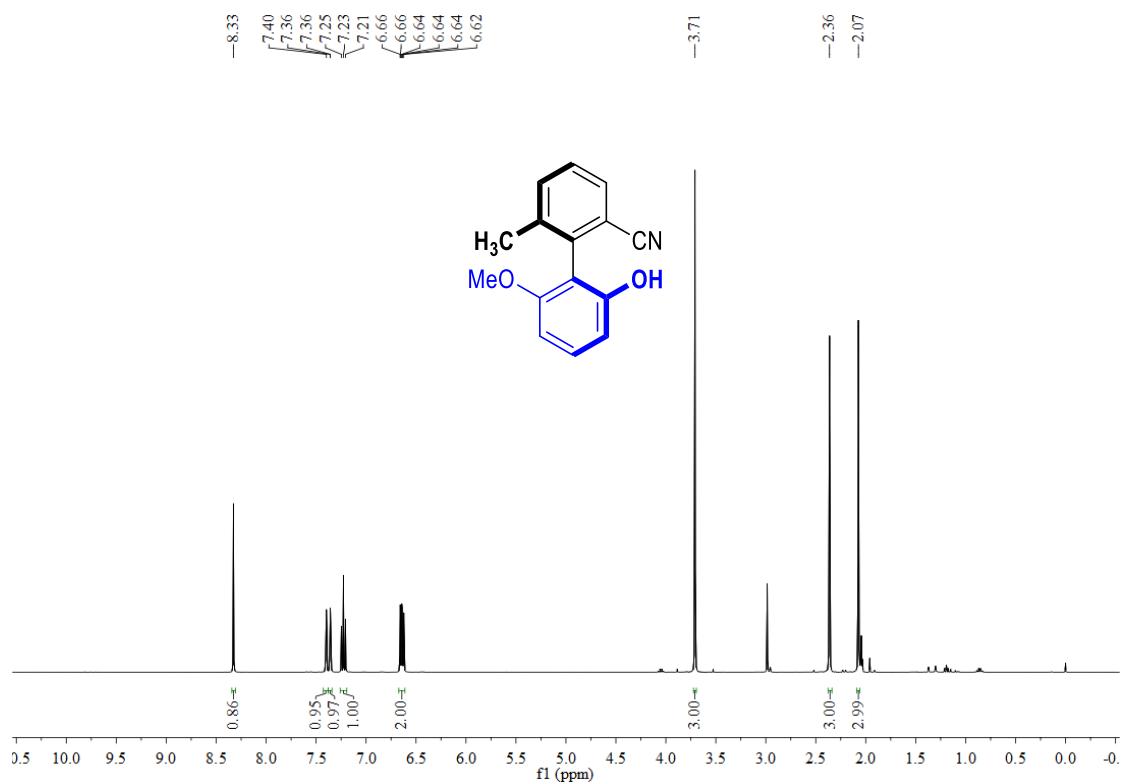
	RT	Area	% Area	Height
1	28.211	1395850	50.17	32097
2	40.993	1386423	49.83	24127

Supplementary Figure 104 HPLC spectra of (*S*)- **3j**

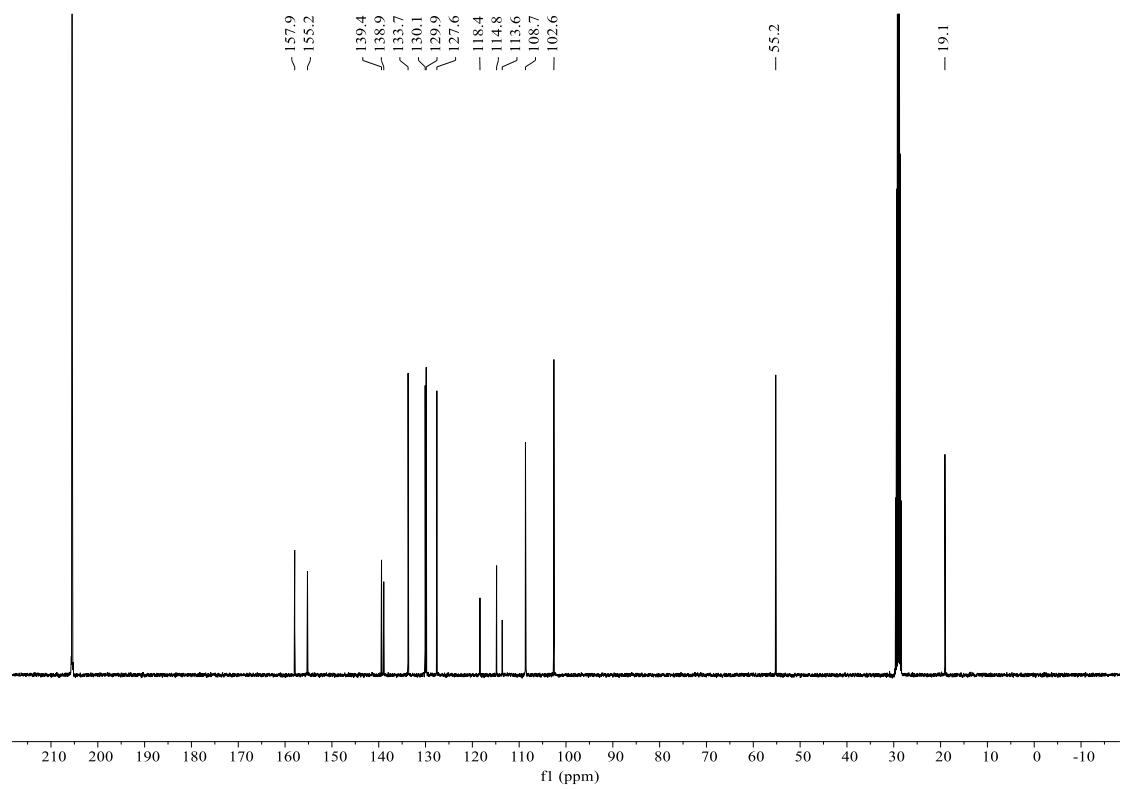


	RT	Area	% Area	Height
1	27.923	222644	13.80	5349
2	40.151	1390247	86.20	24456

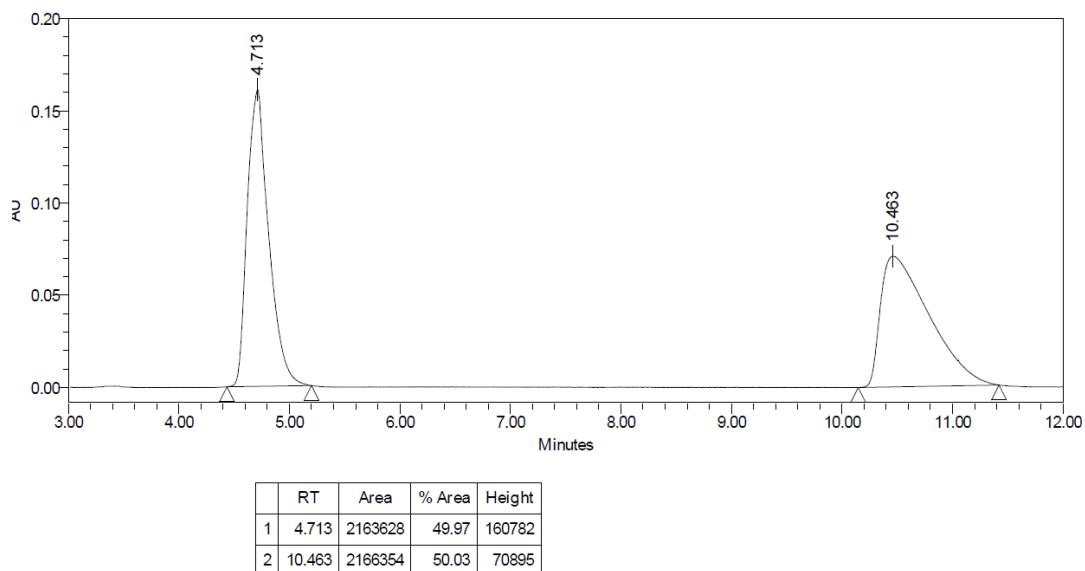
Supplementary Figure 105 ^1H NMR (400 MHz, Acetone- d_6) of **3k**



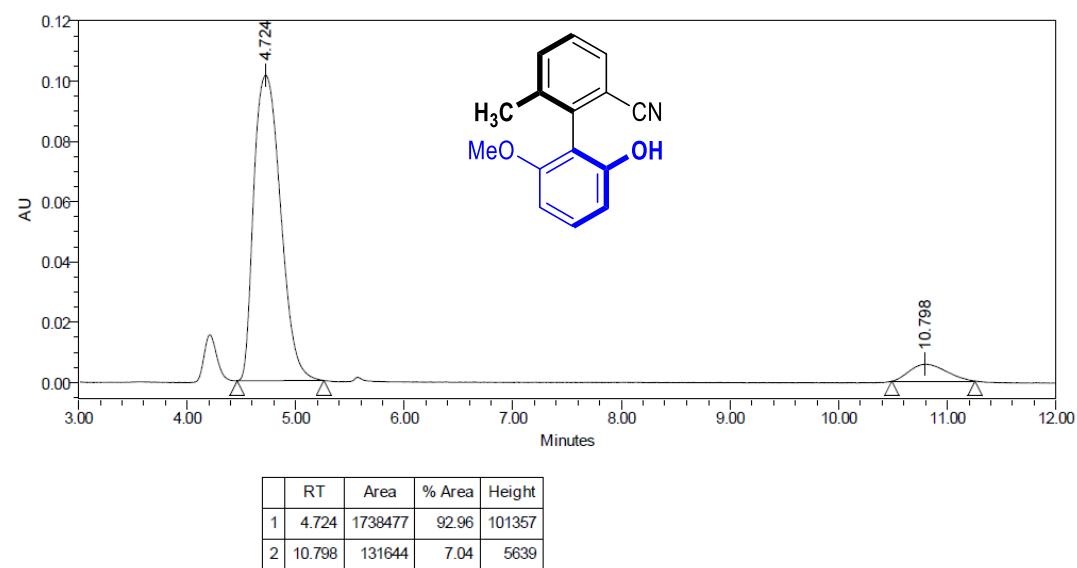
Supplementary Figure 106 ^{13}C NMR (400 MHz, Acetone- d_6) of **3k**



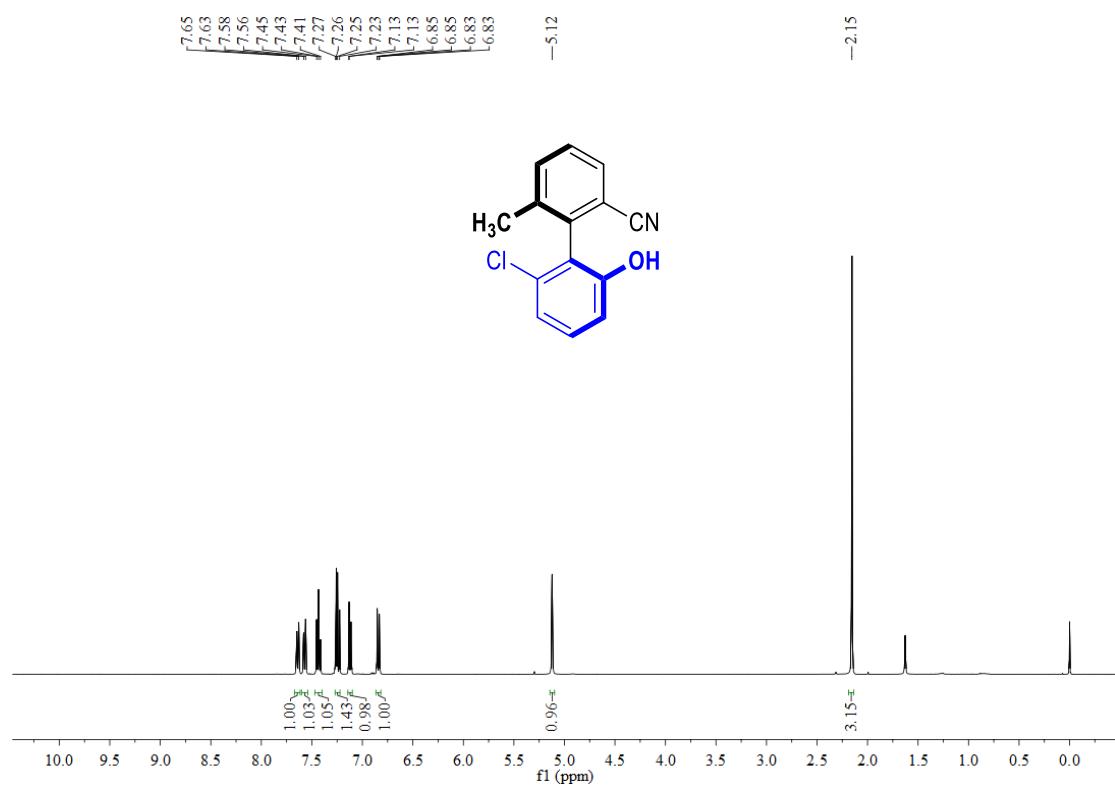
Supplementary Figure 107 HPLC spectra of racemic **3k**



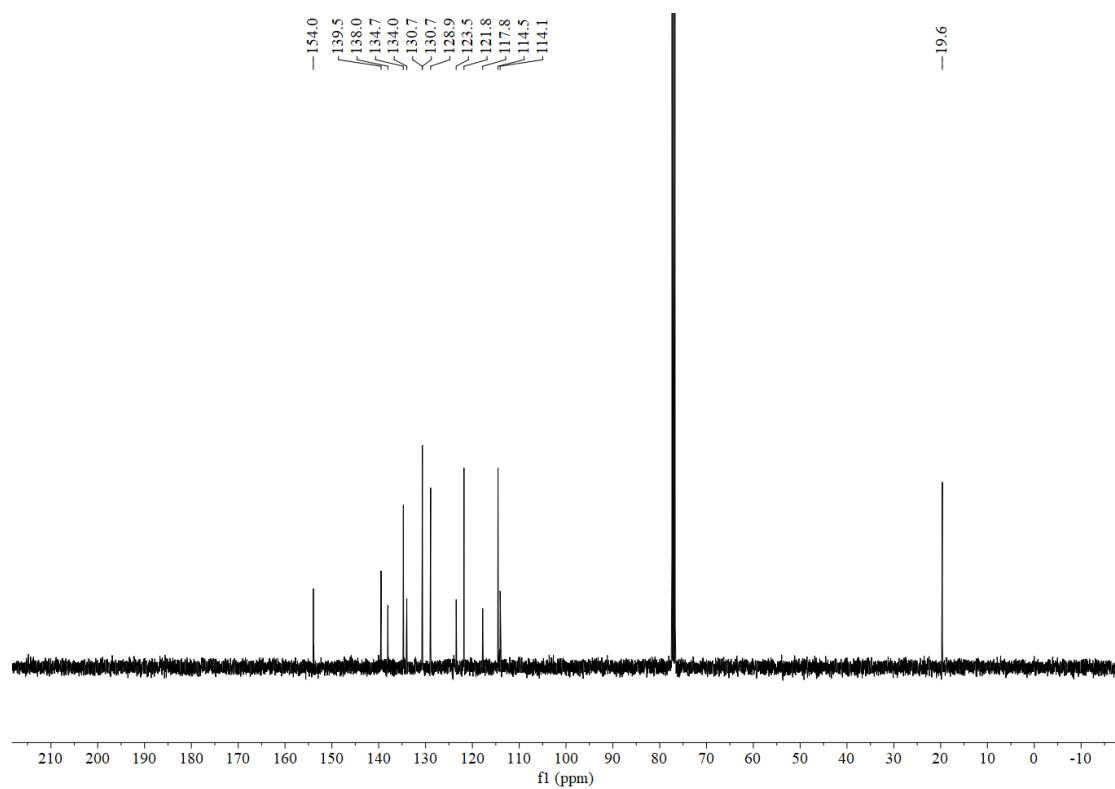
Supplementary Figure 108 HPLC spectra of (*R*)- **3k**



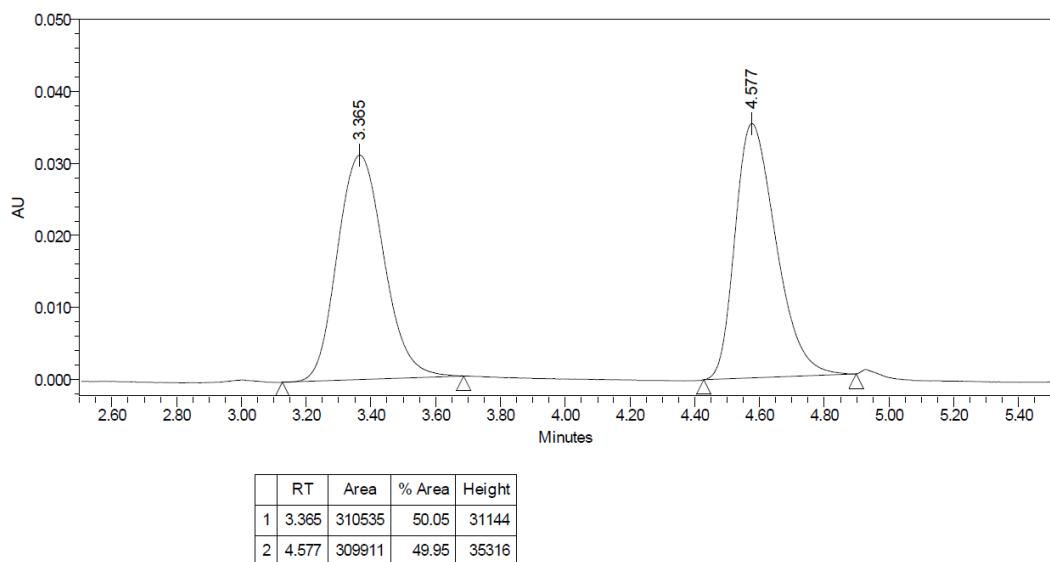
Supplementary Figure 109 ^1H NMR (400 MHz, CDCl_3) of **3l**



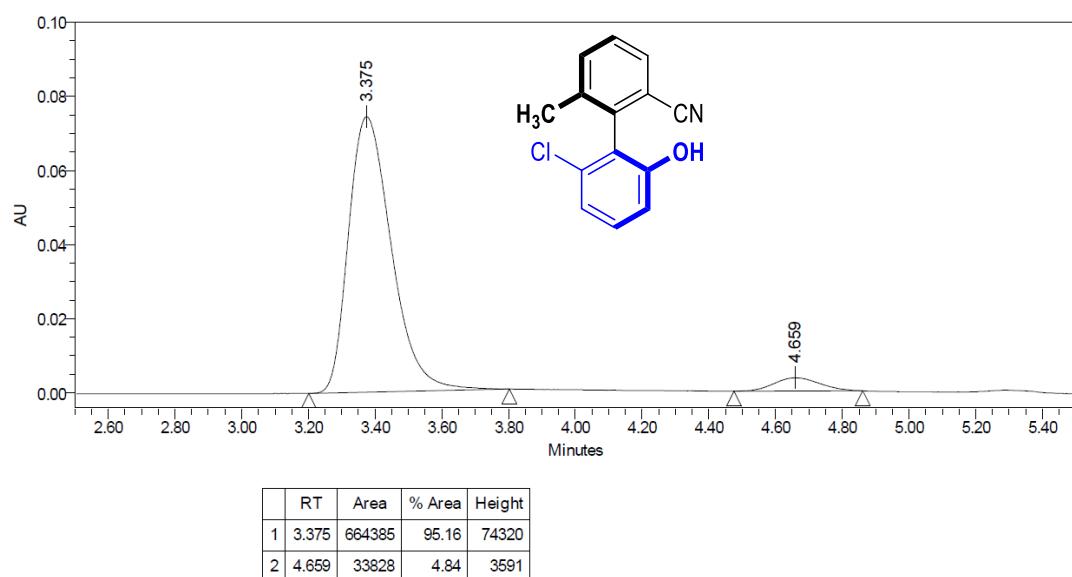
Supplementary Figure 110 ^{13}C NMR (400 MHz, CDCl_3) of **3l**



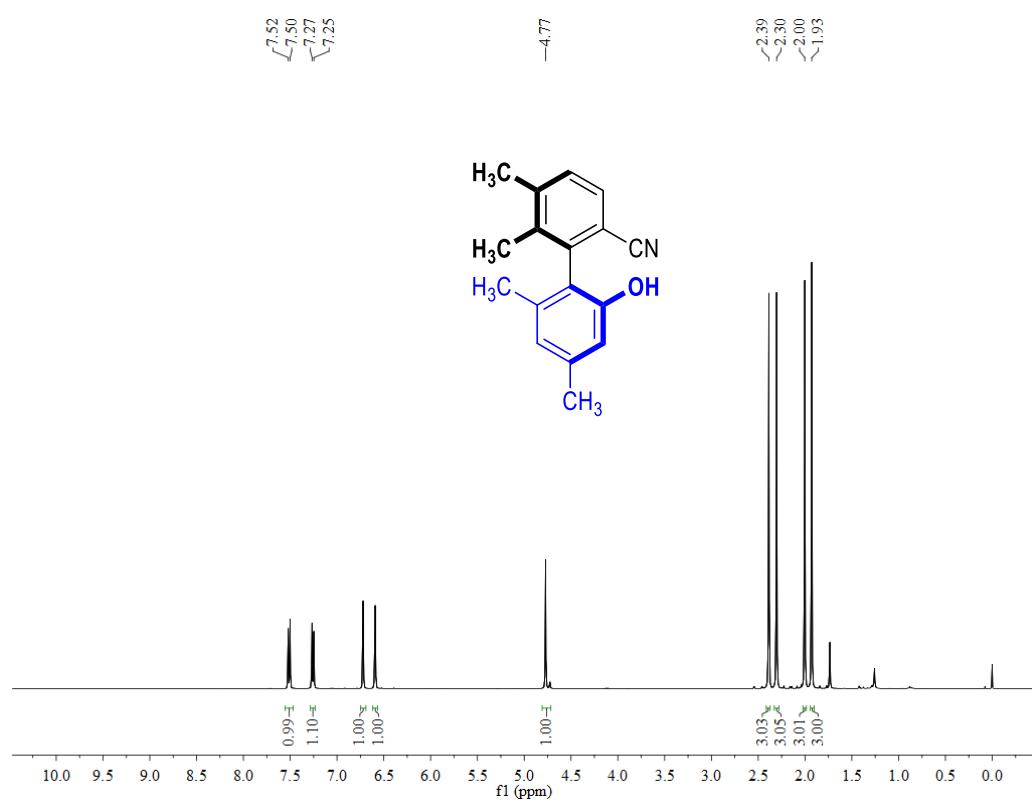
Supplementary Figure 111 HPLC spectra of racemic **3l**



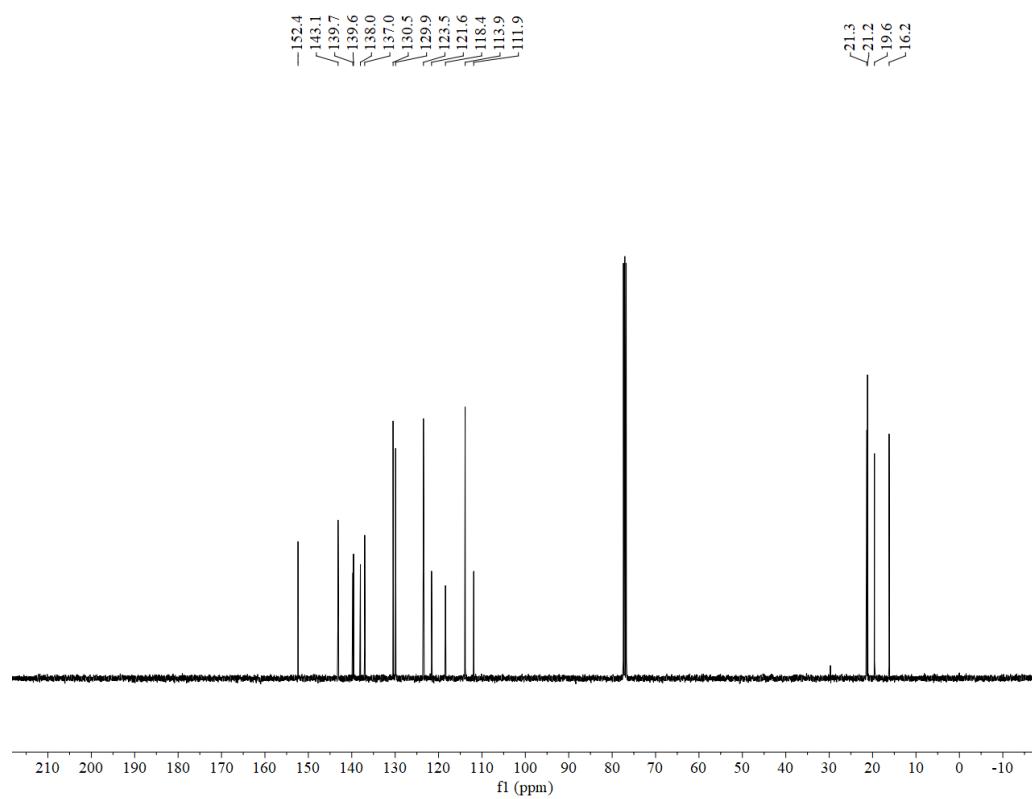
Supplementary Figure 112 HPLC spectra of (*R*)- **3l**



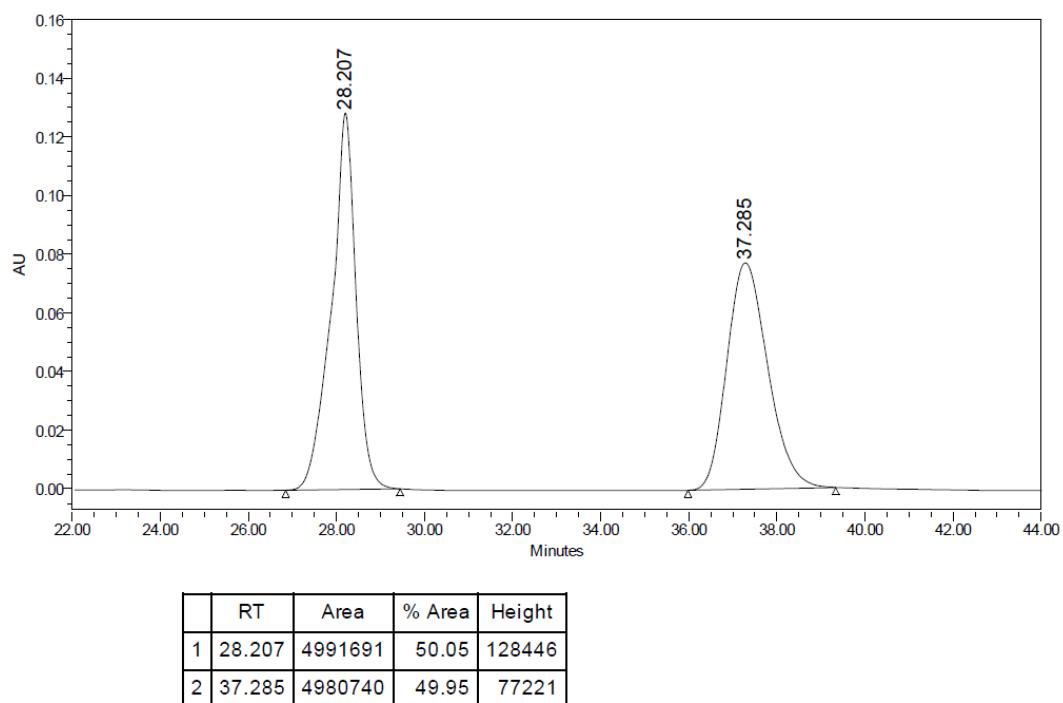
Supplementary Figure 113 ^1H NMR (400 MHz, CDCl_3) of **3m**



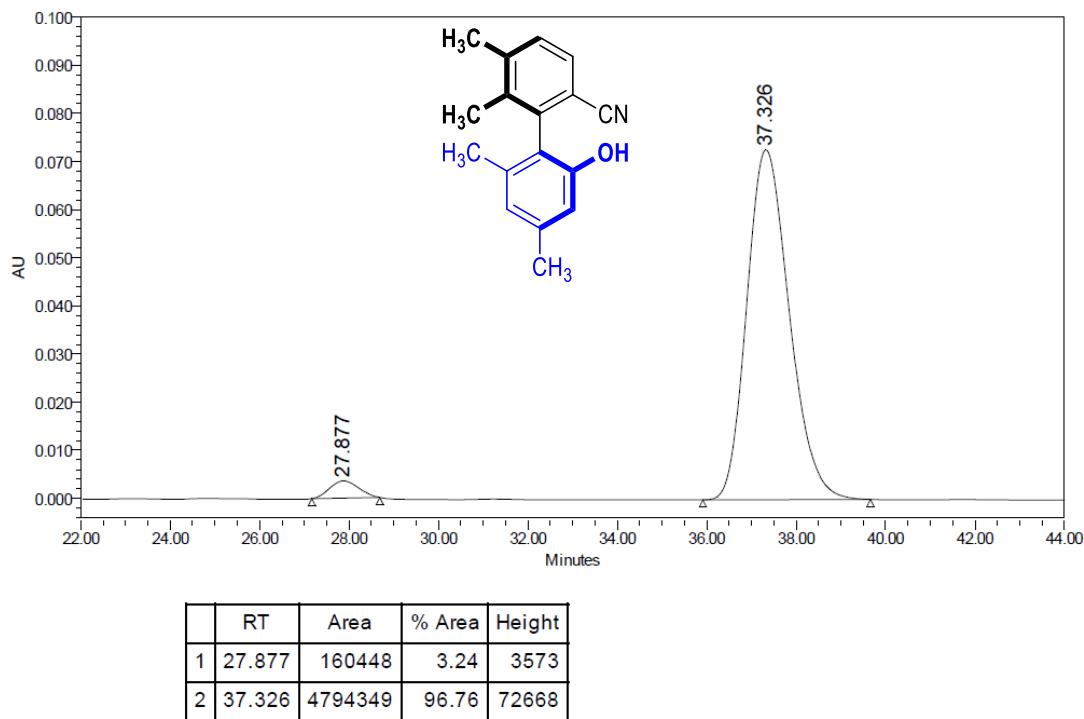
Supplementary Figure 114 ^{13}C NMR (400 MHz, CDCl_3) of **3m**



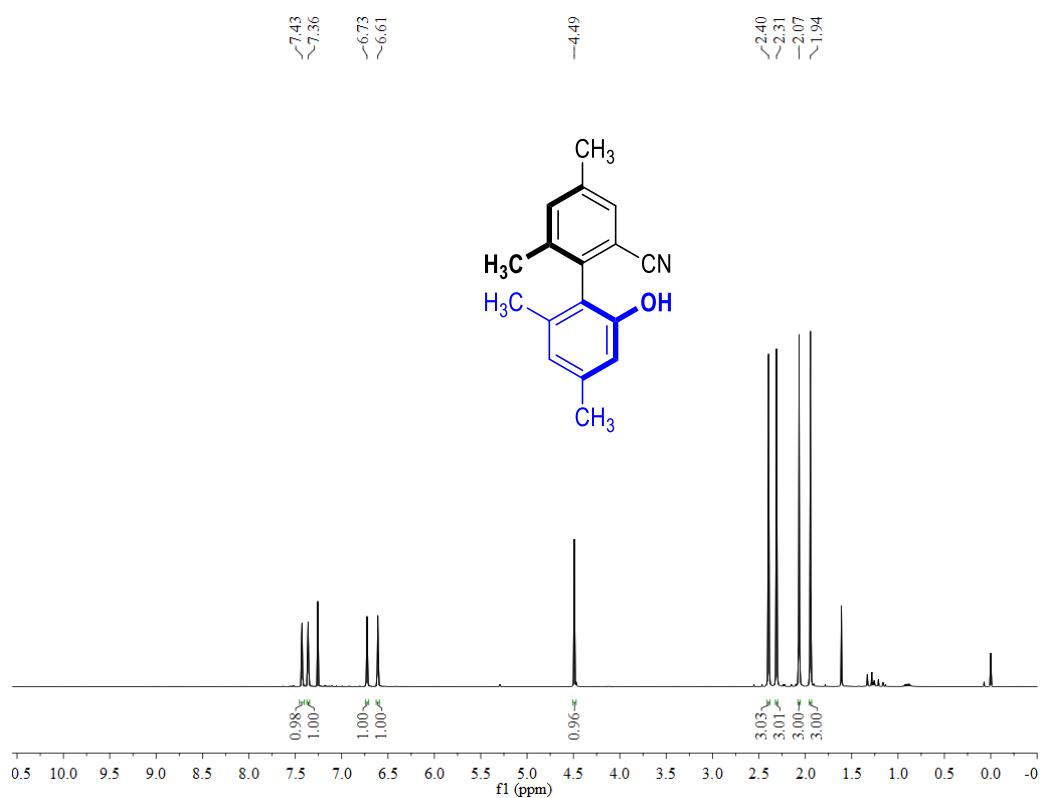
Supplementary Figure 115 HPLC spectra of racemic **3m**



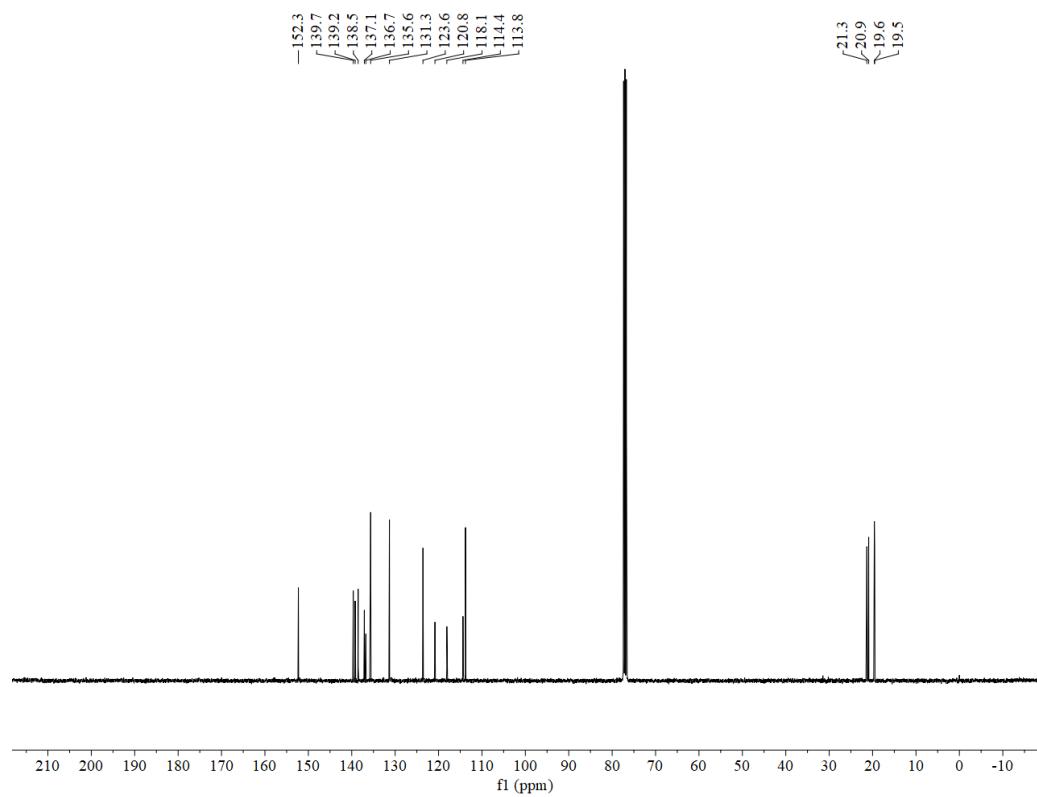
Supplementary Figure 116 HPLC spectra of (*S*)- **3m**



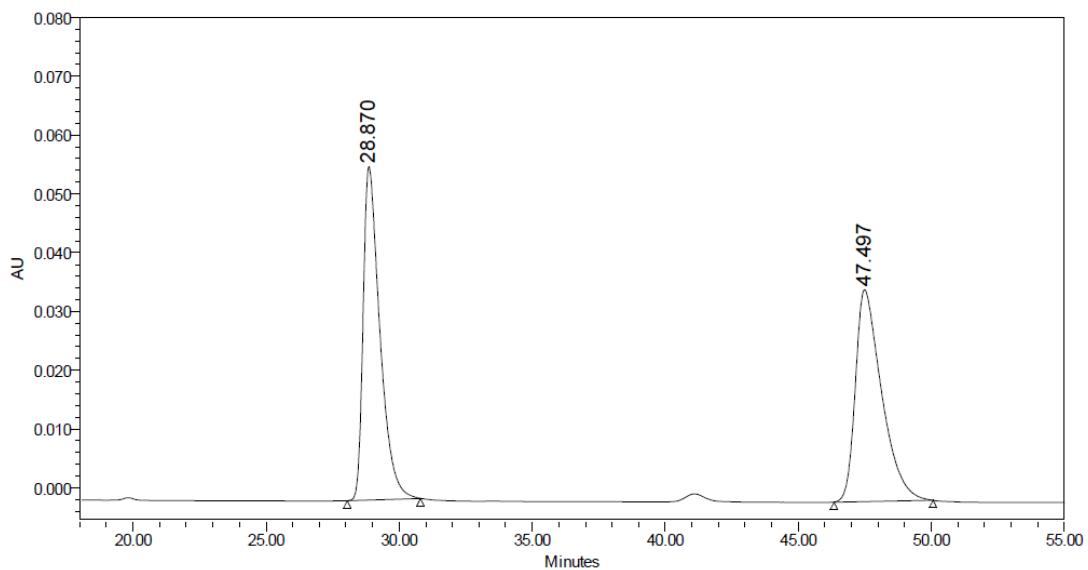
Supplementary Figure 117 ^1H NMR (400 MHz, CDCl_3) of **3n**



Supplementary Figure 118 ^{13}C NMR (400 MHz, CDCl_3) of **3n**

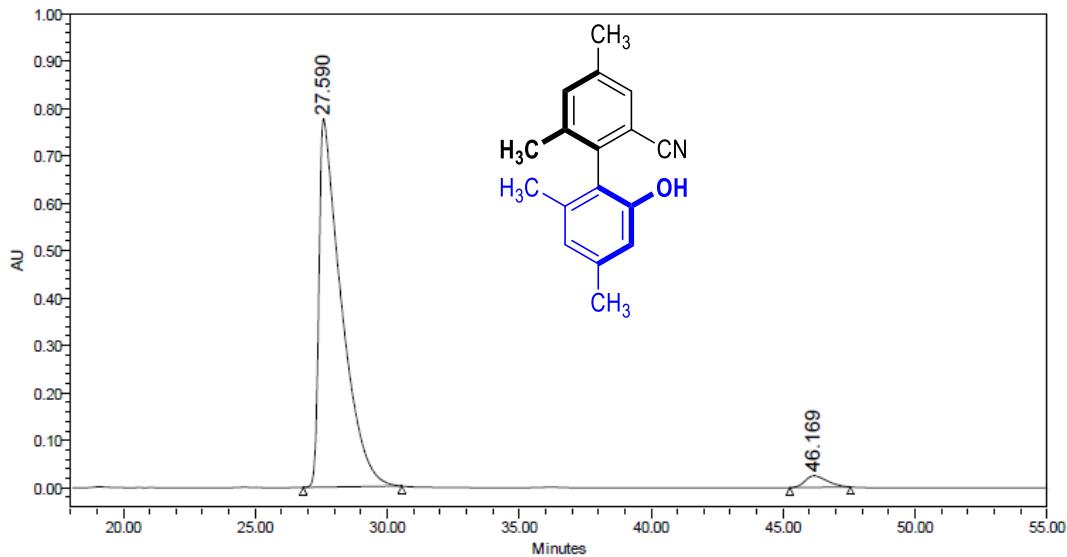


Supplementary Figure 119 HPLC spectra of racemic **3n**



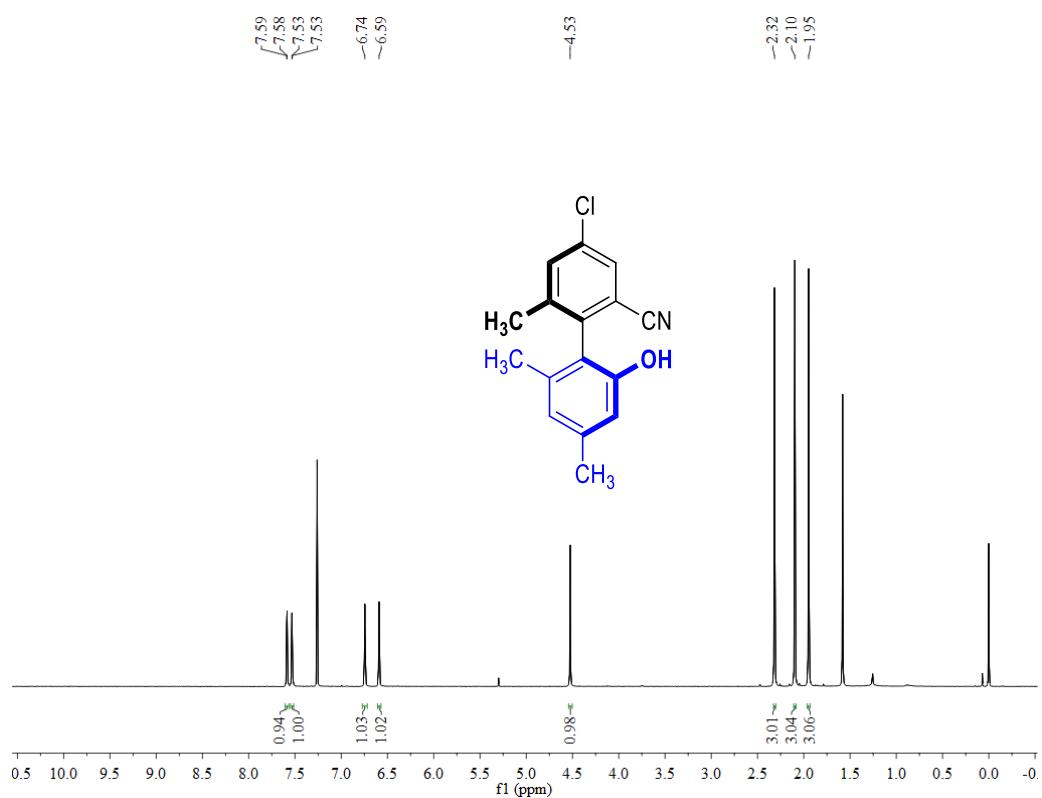
	RT	Area	% Area	Height
1	28.870	2476254	50.02	56712
2	47.497	2473977	49.98	36049

Supplementary Figure 120 HPLC spectra of (*S*)- **3n**

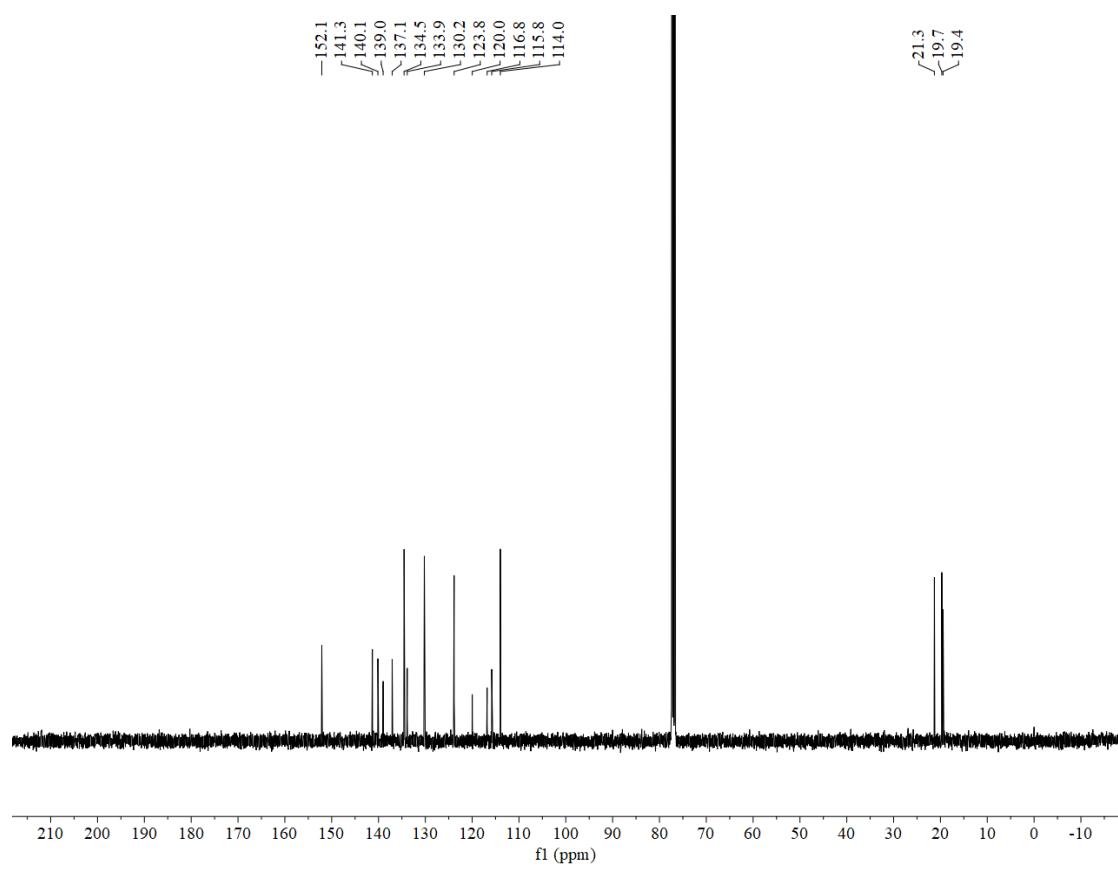


	RT	Area	% Area	Height
1	27.590	45611598	96.98	776306
2	46.169	1422760	3.02	24417

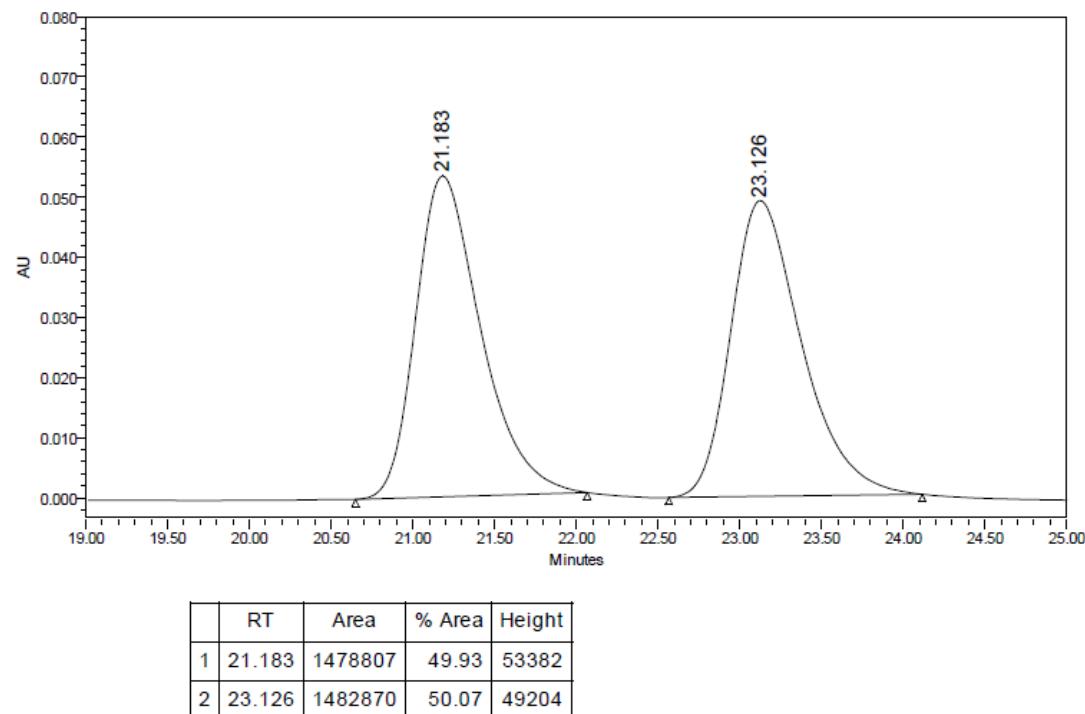
Supplementary Figure 121 ^1H NMR (400 MHz, CDCl_3) of **3o**



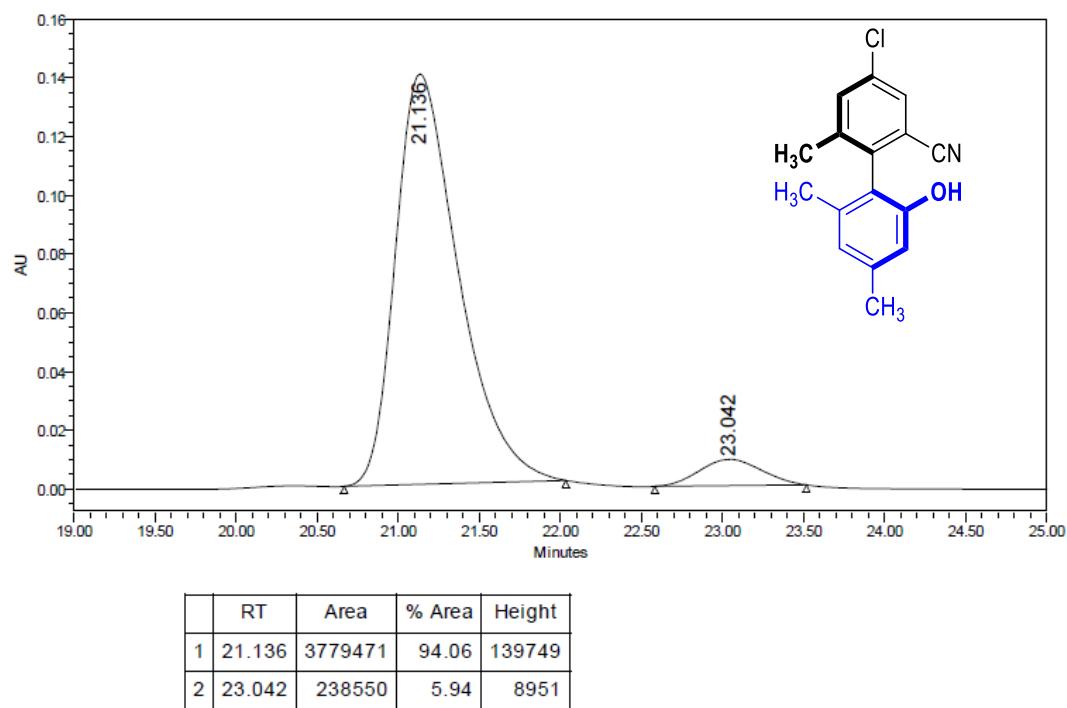
Supplementary Figure 122 ^{13}C NMR (400 MHz, CDCl_3) of **3o**



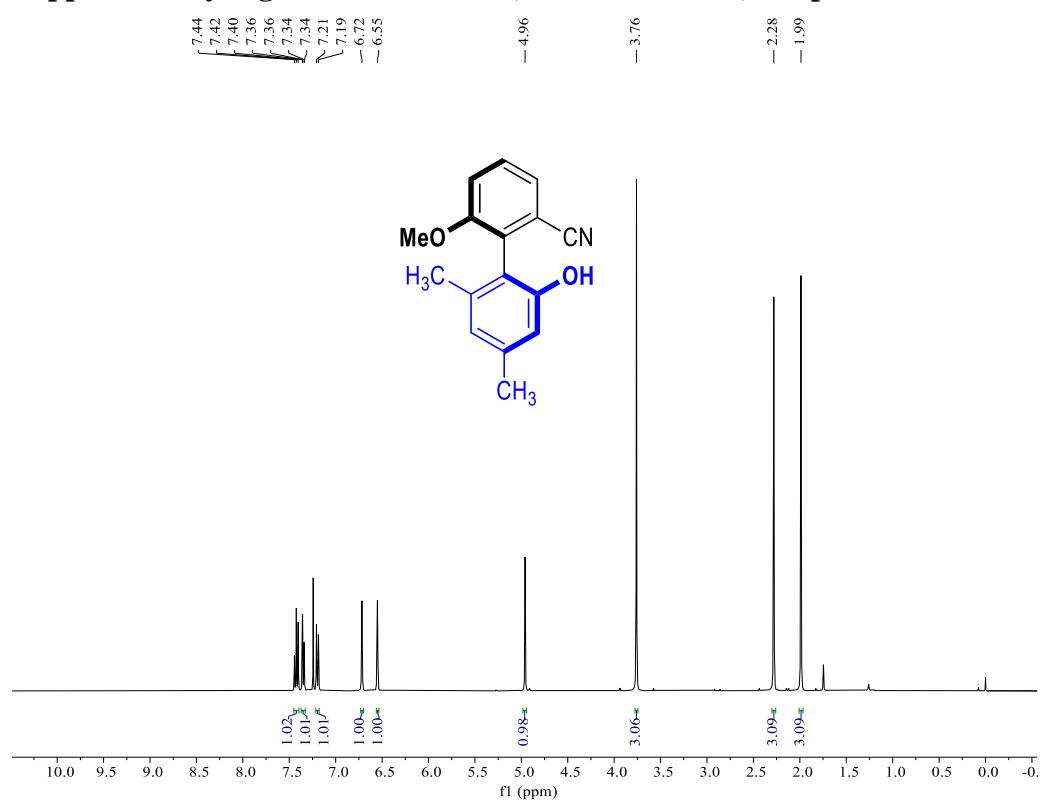
Supplementary Figure 123 HPLC spectra of racemic **3o**



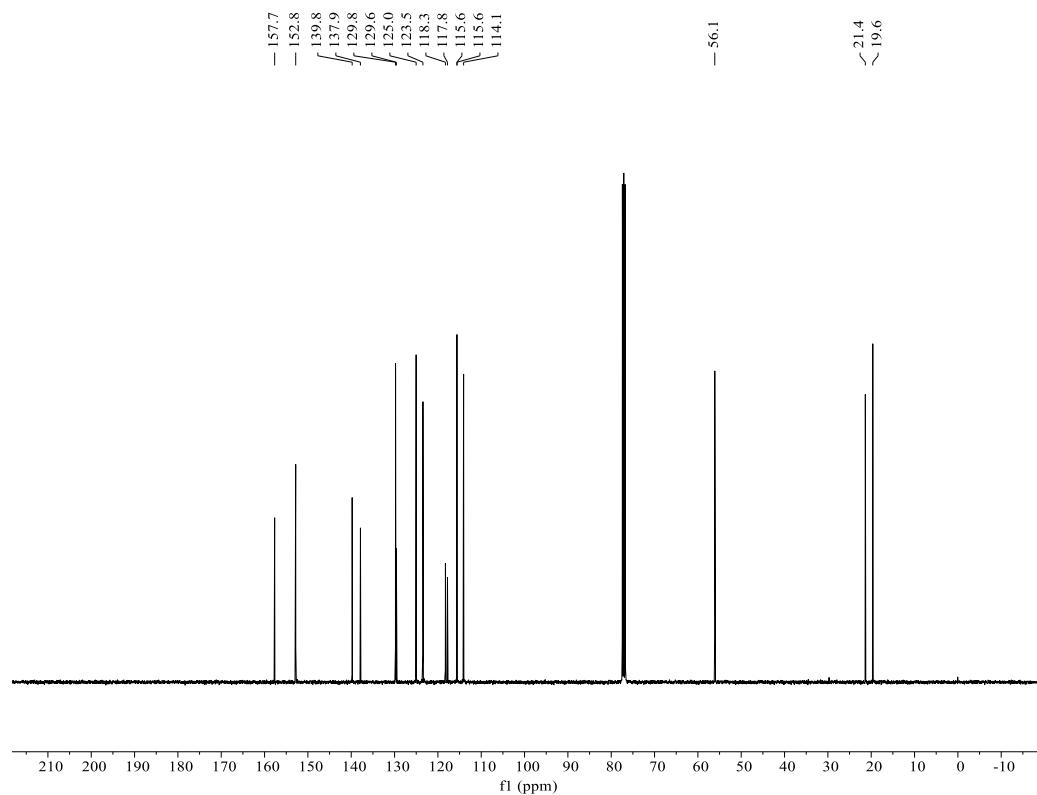
Supplementary Figure 124 HPLC spectra of (*S*)- **3o**



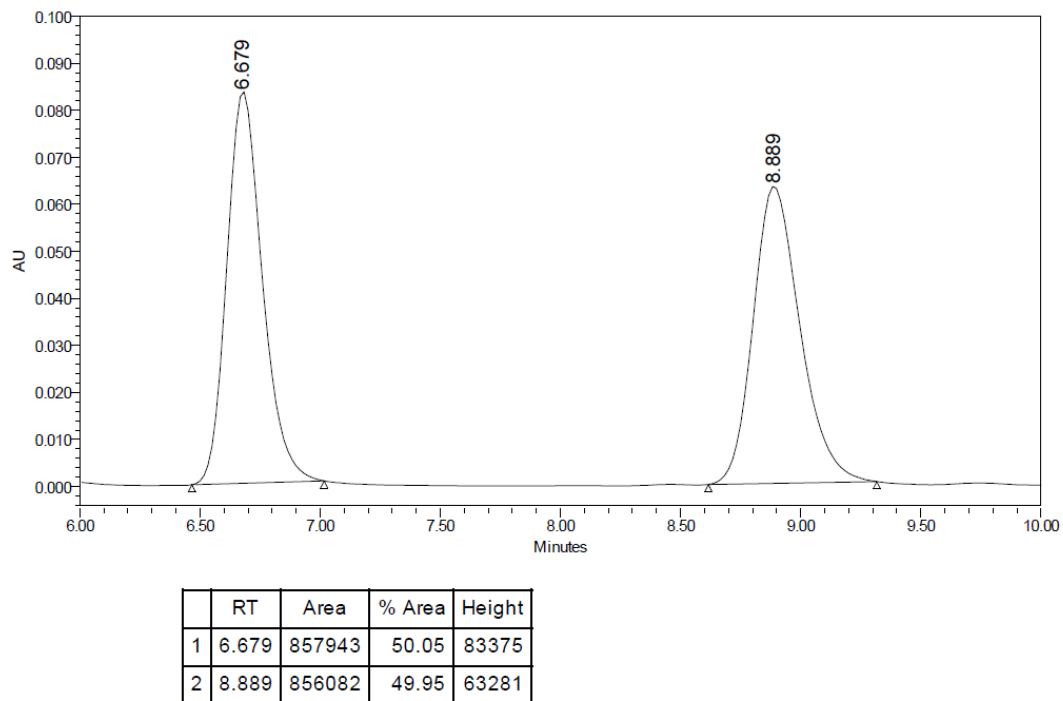
Supplementary Figure 125 ^1H NMR (400 MHz, CDCl_3) of **3p**



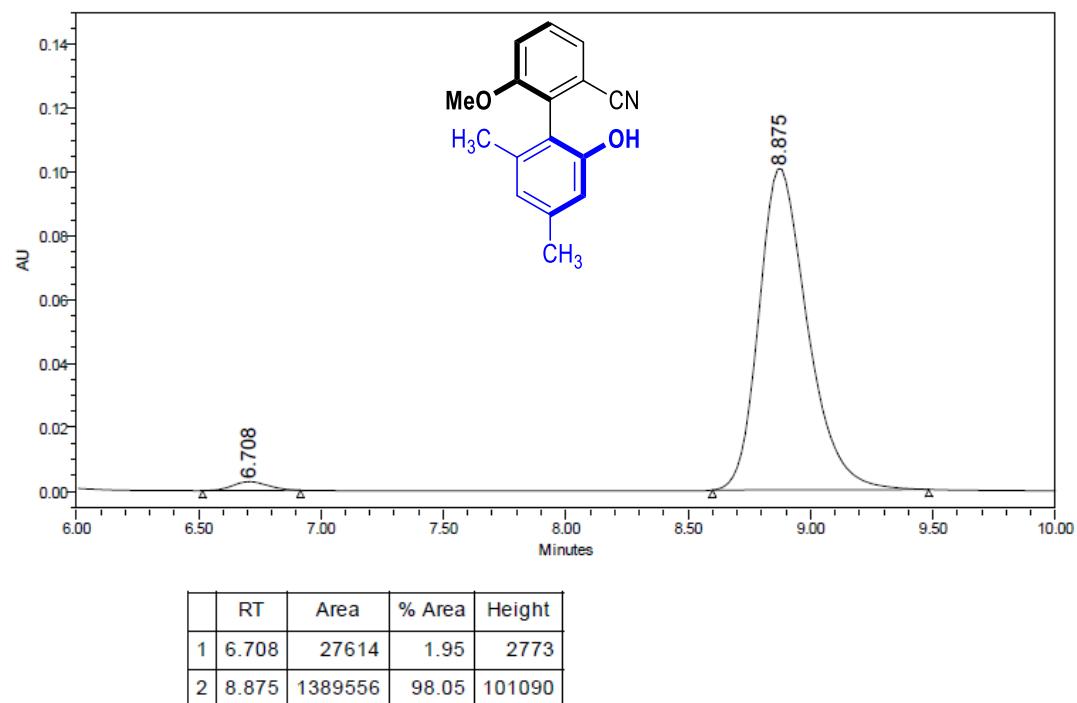
Supplementary Figure 126 ^{13}C NMR (400 MHz, CDCl_3) of **3p**



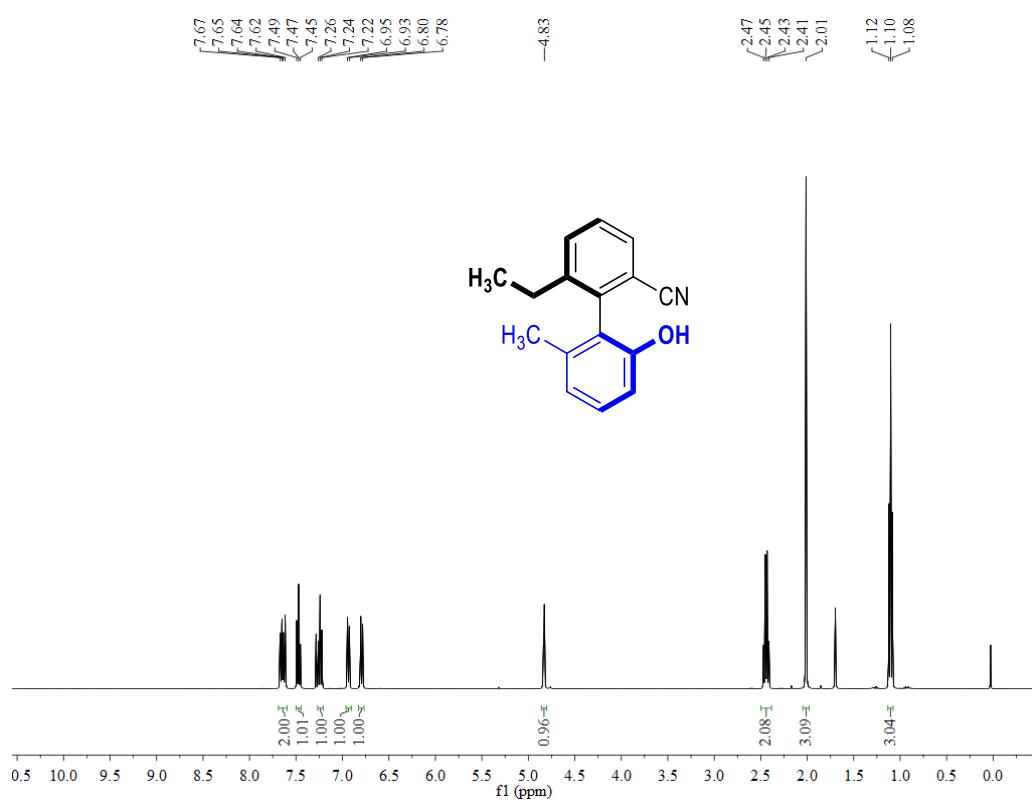
Supplementary Figure 127 HPLC spectra of racemic **3p**



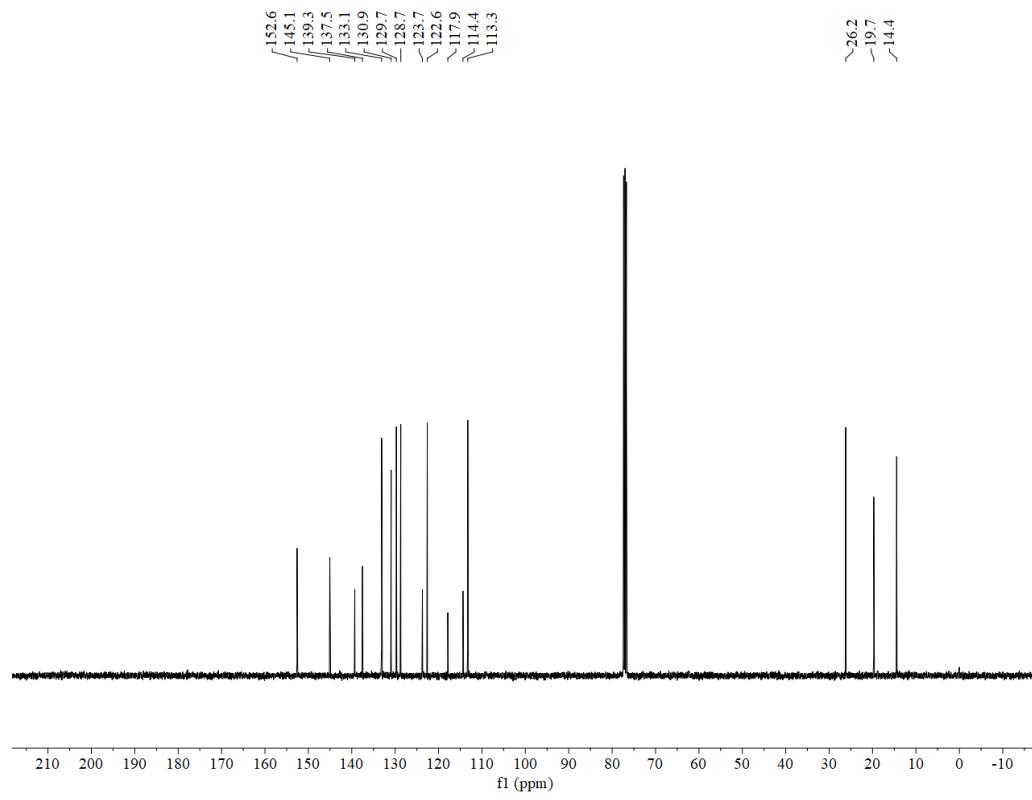
Supplementary Figure 128 HPLC spectra of (*R*)- **3p**



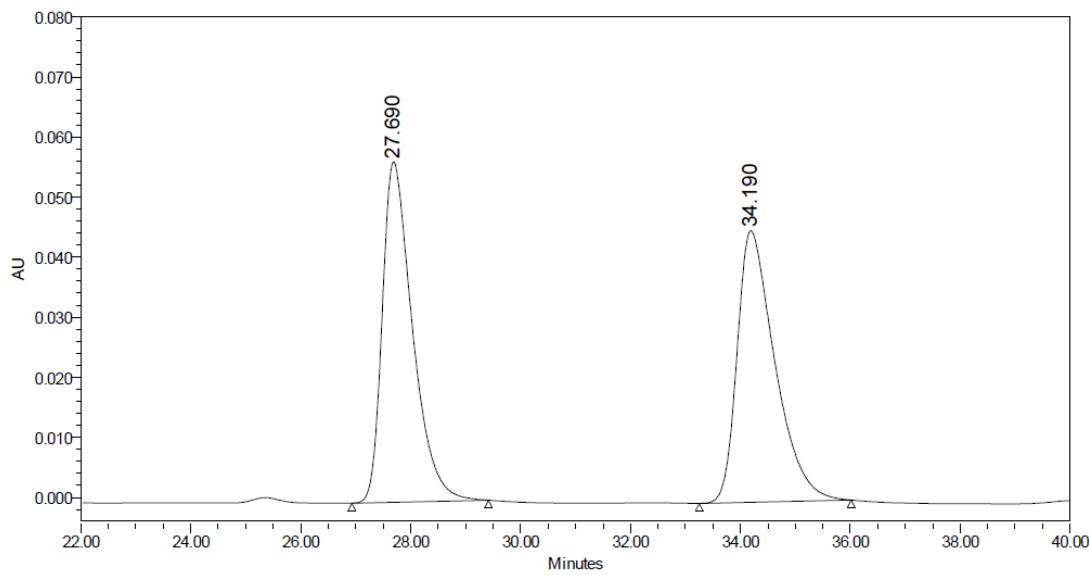
Supplementary Figure 129 ^1H NMR (400 MHz, CDCl_3) of **3q**



Supplementary Figure 130 ^{13}C NMR (400 MHz, CDCl_3) of **3q**

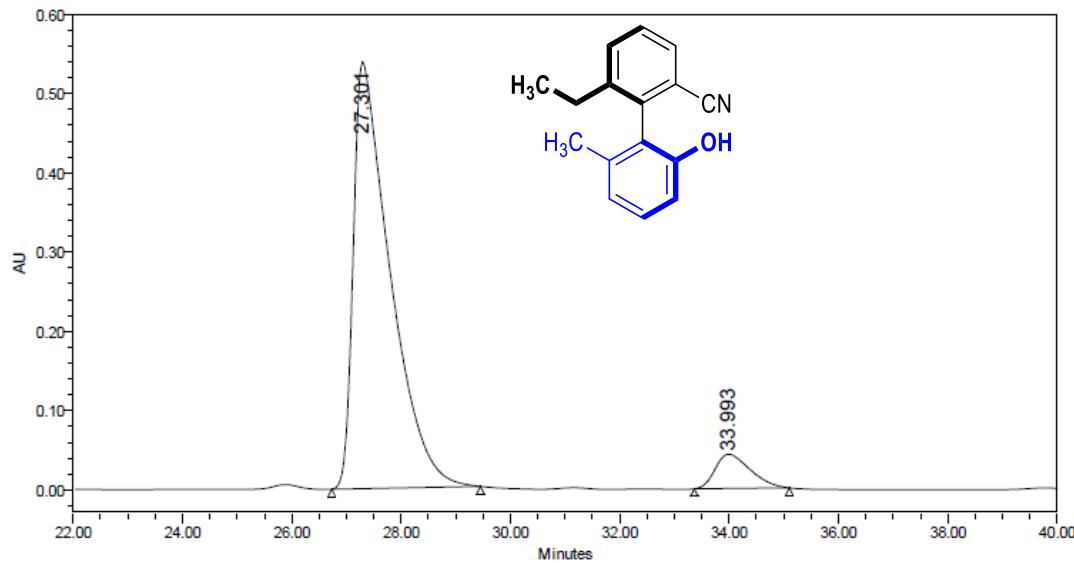


Supplementary Figure 131 HPLC spectra of racemic **3q**



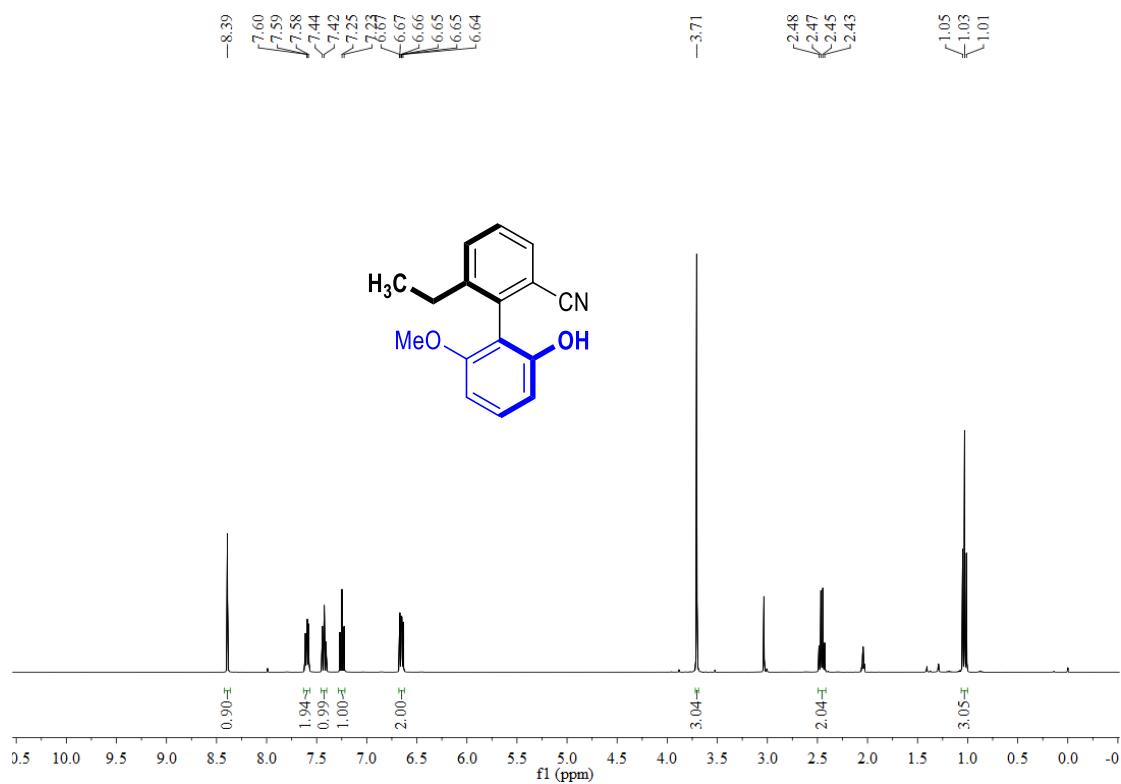
	RT	Area	% Area	Height
1	27.690	2167712	50.11	56685
2	34.190	2158506	49.89	45229

Supplementary Figure 132 HPLC spectra of (*S*)- **3q**

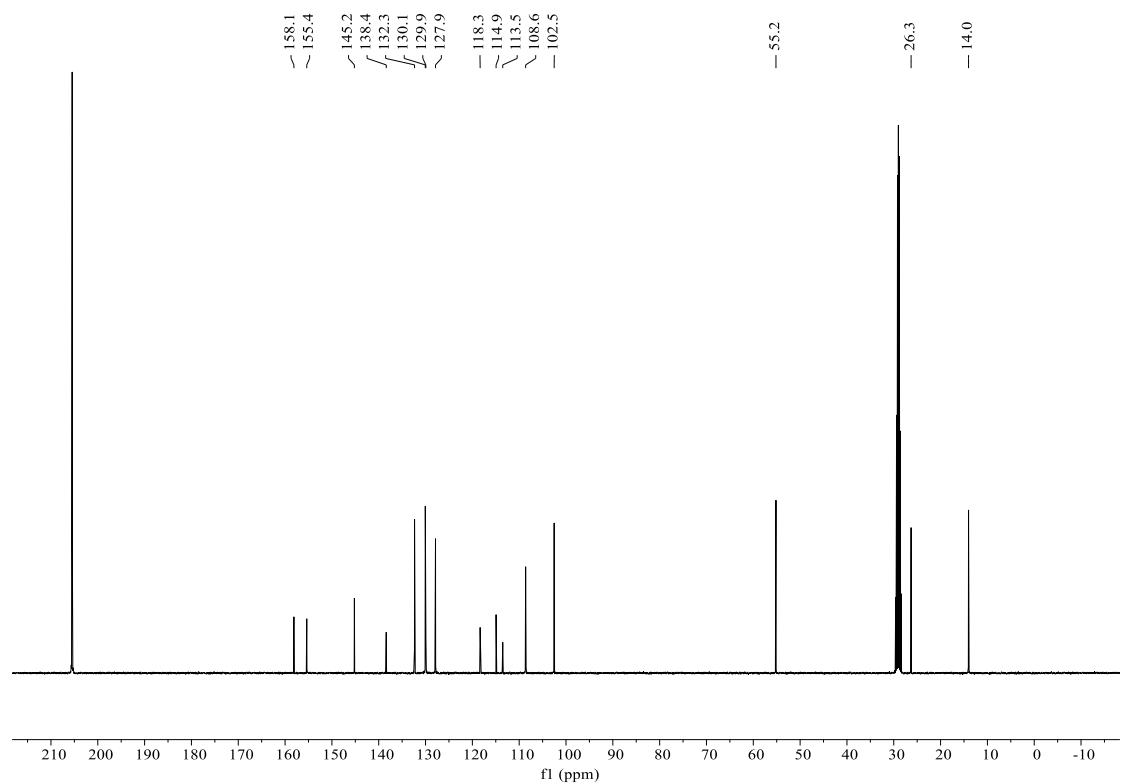


	RT	Area	% Area	Height
1	27.301	25077801	92.90	537973
2	33.993	1915630	7.10	43194

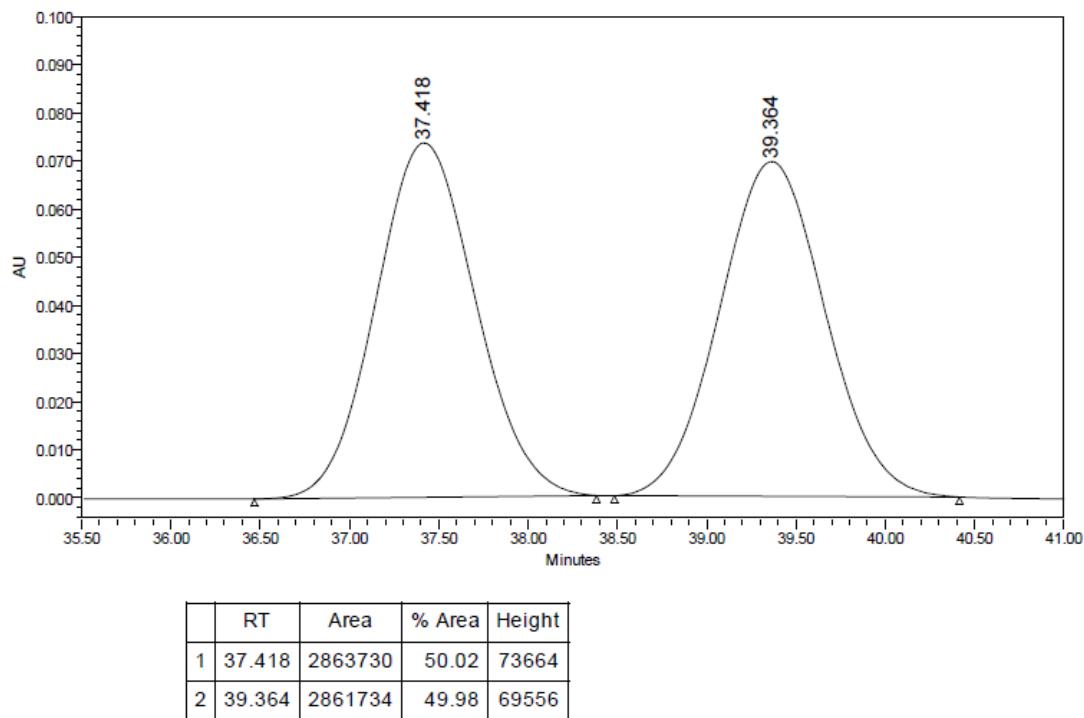
Supplementary Figure 133 ^1H NMR (400 MHz, Acetone- d_6) of **3r**



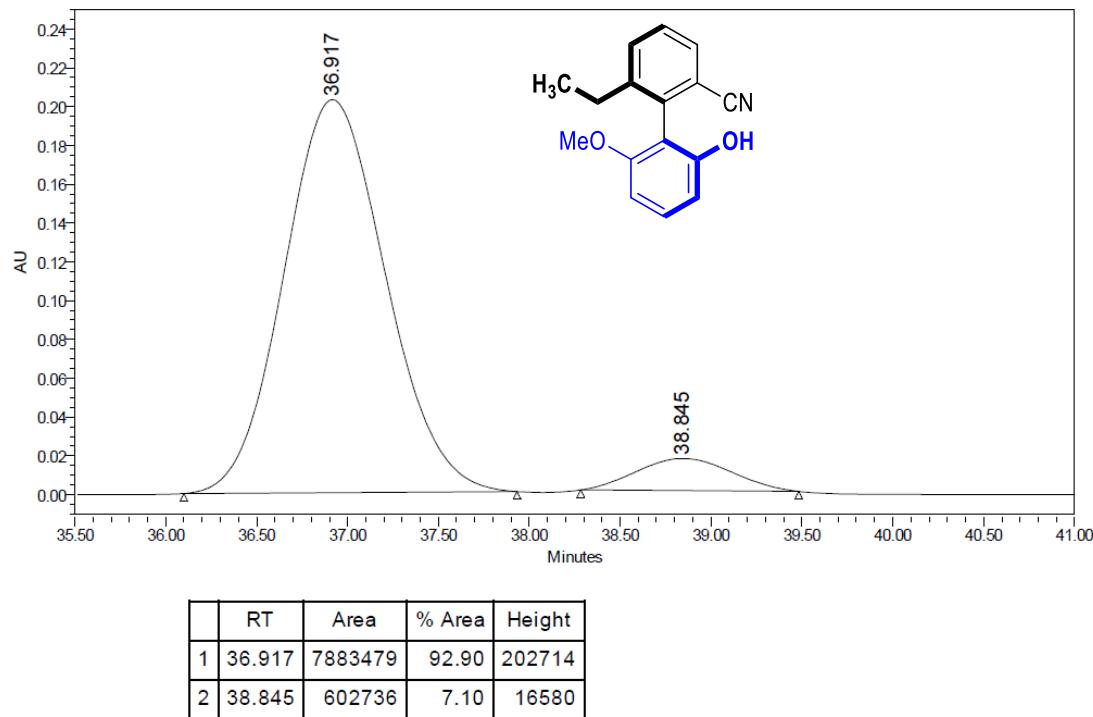
Supplementary Figure 134 ^{13}C NMR (400 MHz, Acetone- d_6) of **3r**



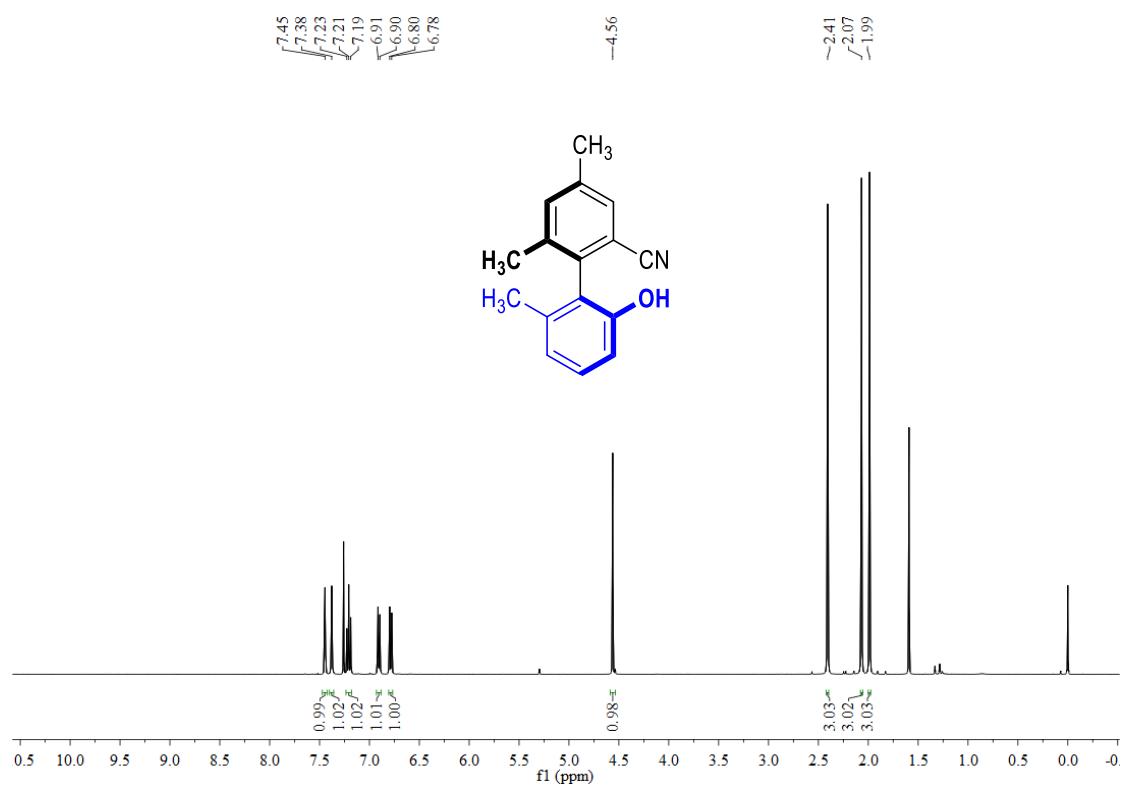
Supplementary Figure 135 HPLC spectra of racemic **3r**



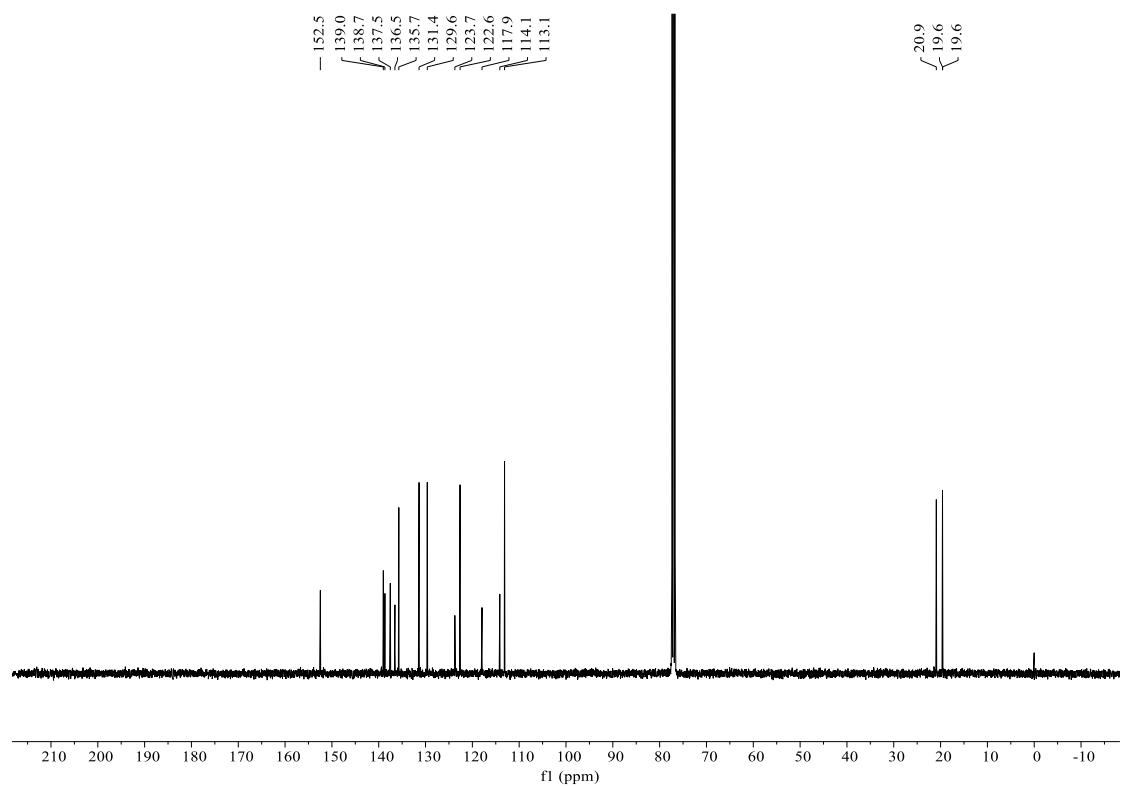
Supplementary Figure 136 HPLC spectra of (*R*)- **3r**



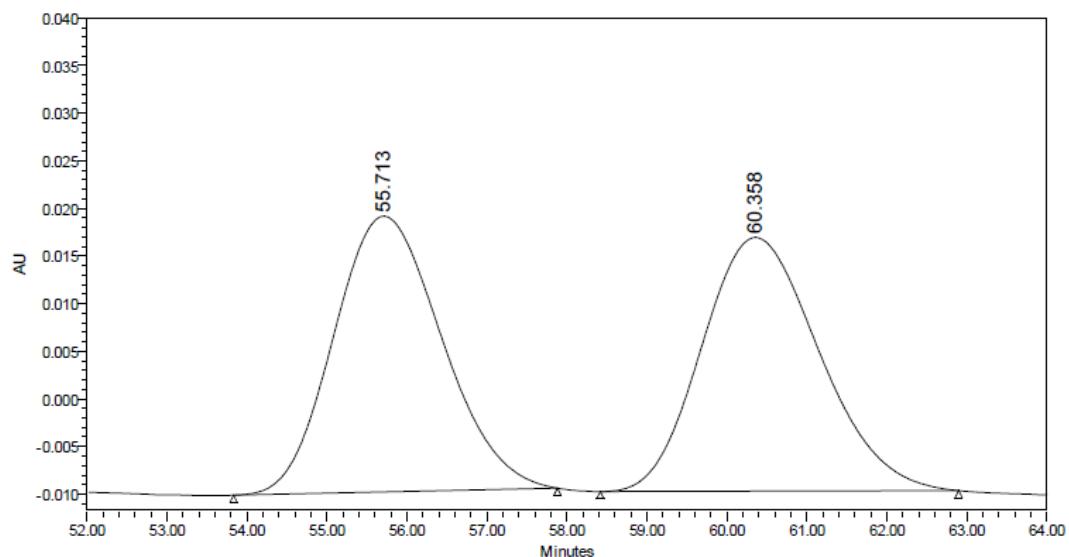
Supplementary Figure 137 ^1H NMR (400 MHz, CDCl_3) of **3s**



Supplementary Figure 138 ^{13}C NMR (400 MHz, CDCl_3) of **3s**

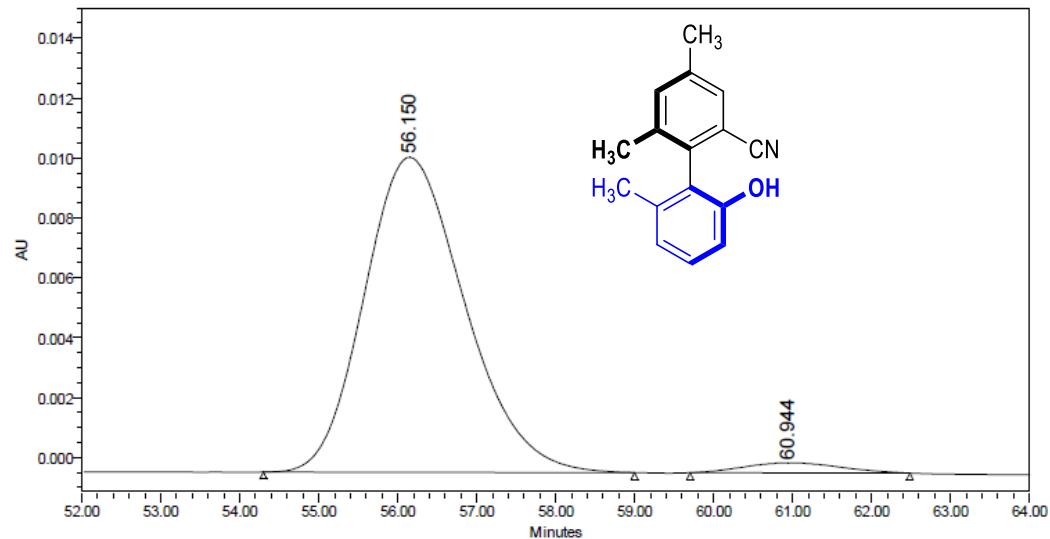


Supplementary Figure 139 HPLC spectra of racemic **3s**



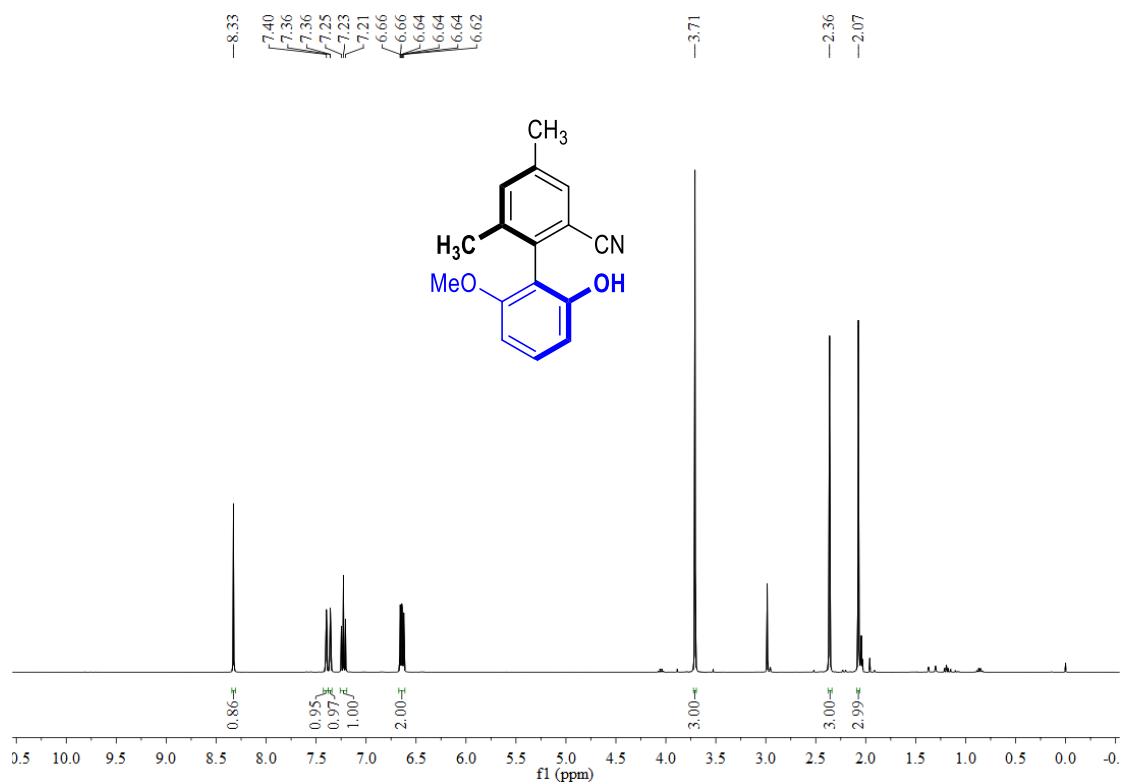
	RT	Area	% Area	Height
1	55.713	2715042	50.02	28953
2	60.358	2712808	49.98	26634

Supplementary Figure 140 HPLC spectra of (*S*)- **3s**

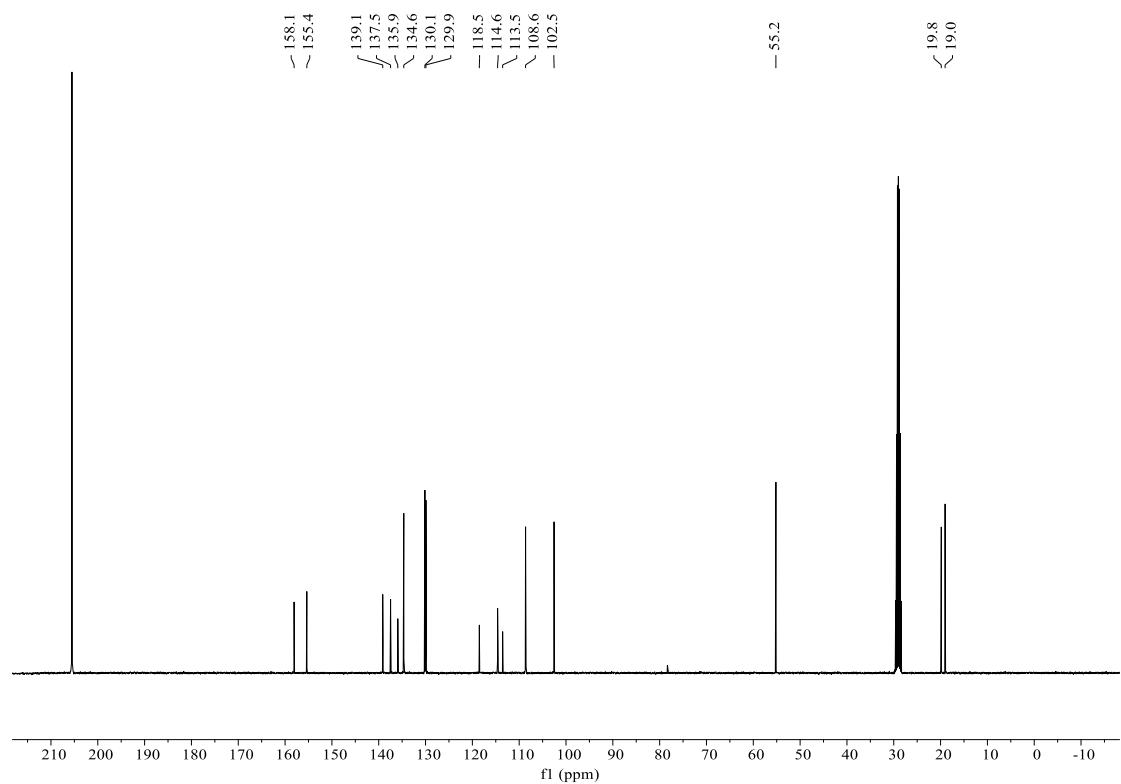


	RT	Area	% Area	Height
1	56.150	929282	97.03	10515
2	60.944	28462	2.97	337

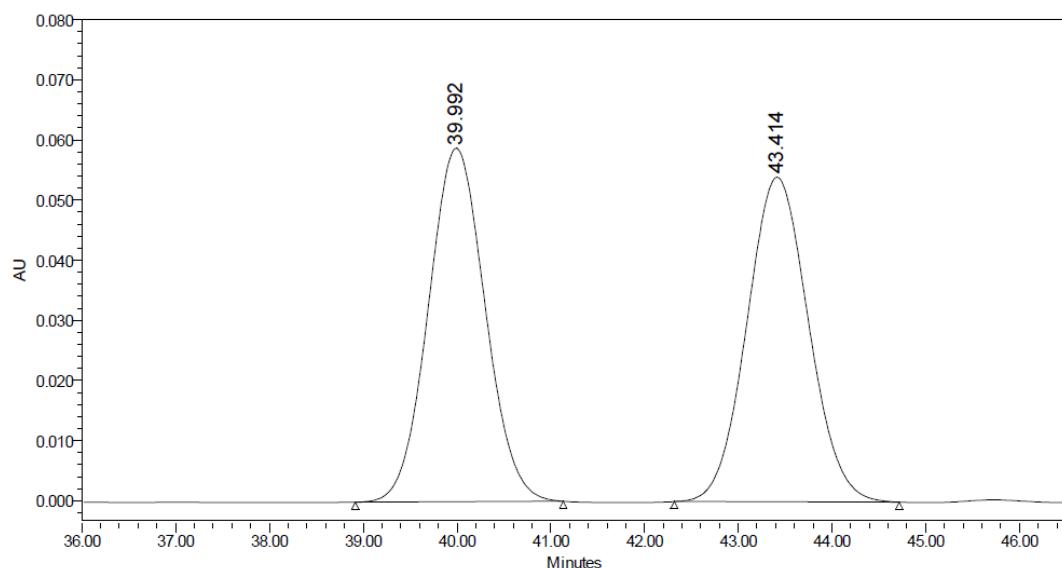
Supplementary Figure 141 ^1H NMR (400 MHz, Acetone- d_6) of **3t**



Supplementary Figure 142 ^{13}C NMR (400 MHz, Acetone- d_6) of **3t**

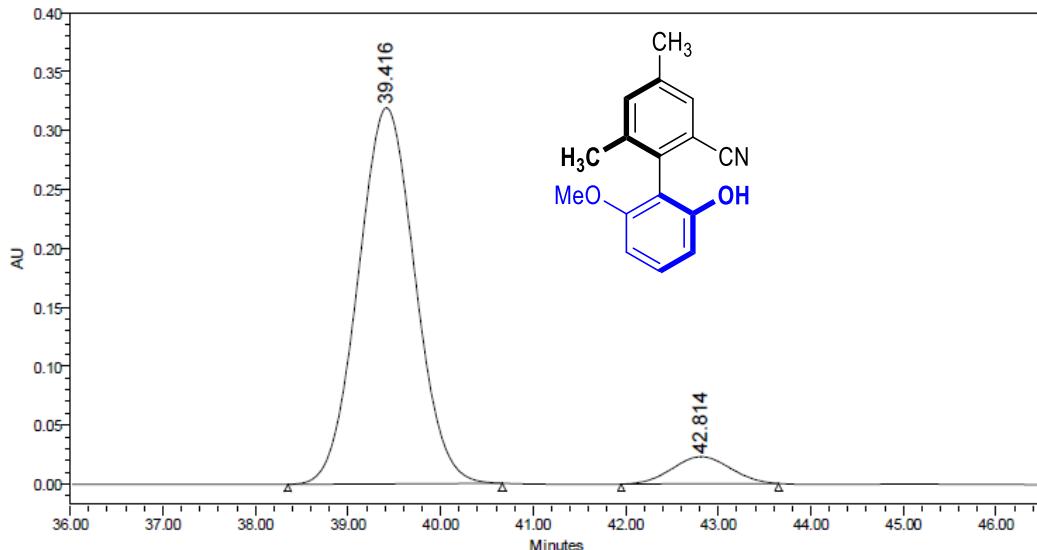


Supplementary Figure 143 HPLC spectra of racemic **3t**



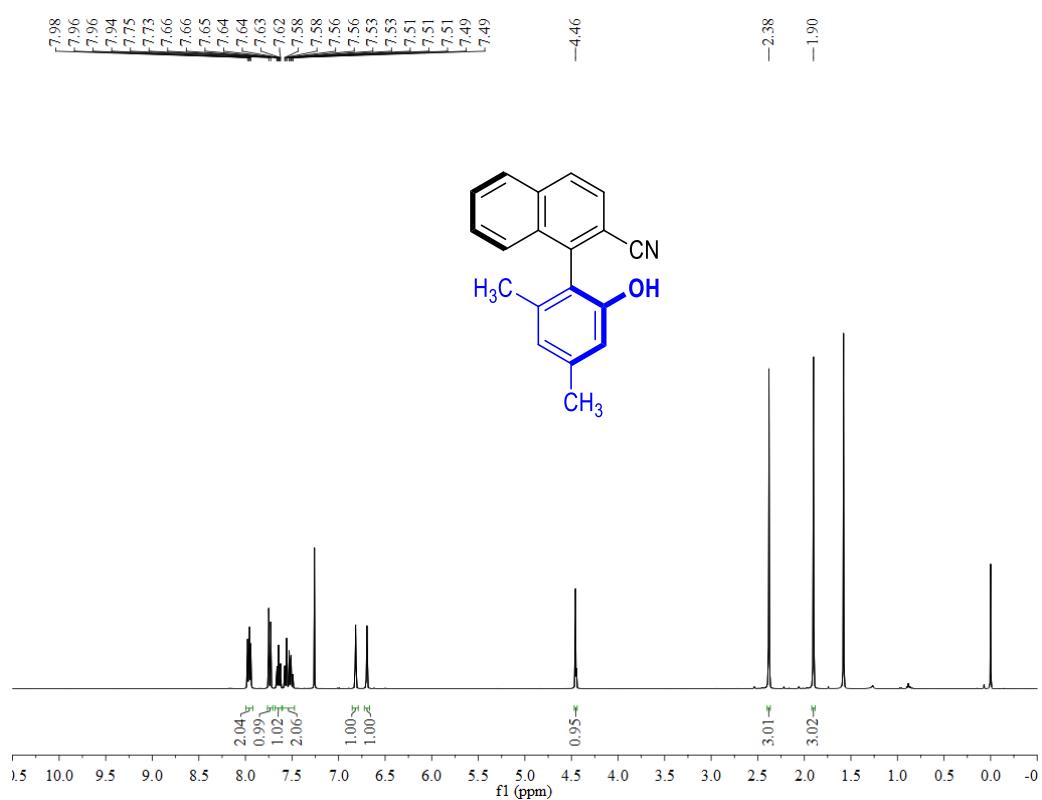
	RT	Area	% Area	Height
1	39.992	2474786	50.07	58774
2	43.414	2467431	49.93	53957

Supplementary Figure 144 HPLC spectra of (*R*)- **3t**

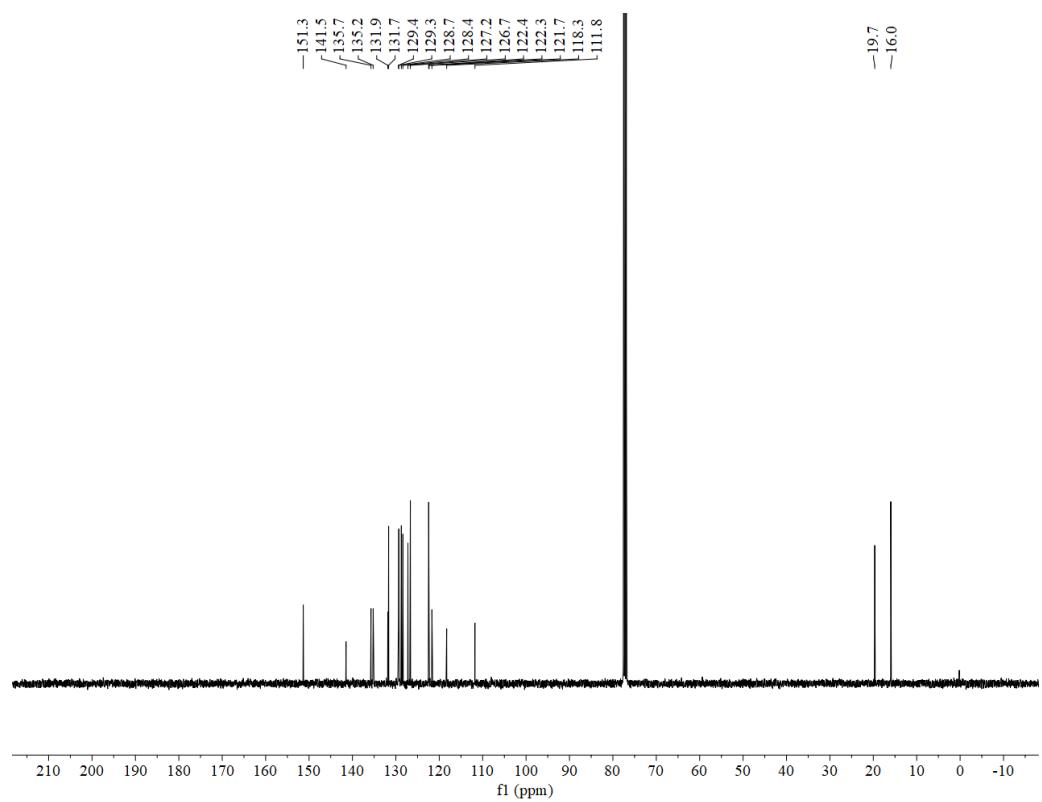


	RT	Area	% Area	Height
1	39.416	13618706	93.11	319263
2	42.814	1007548	6.89	22937

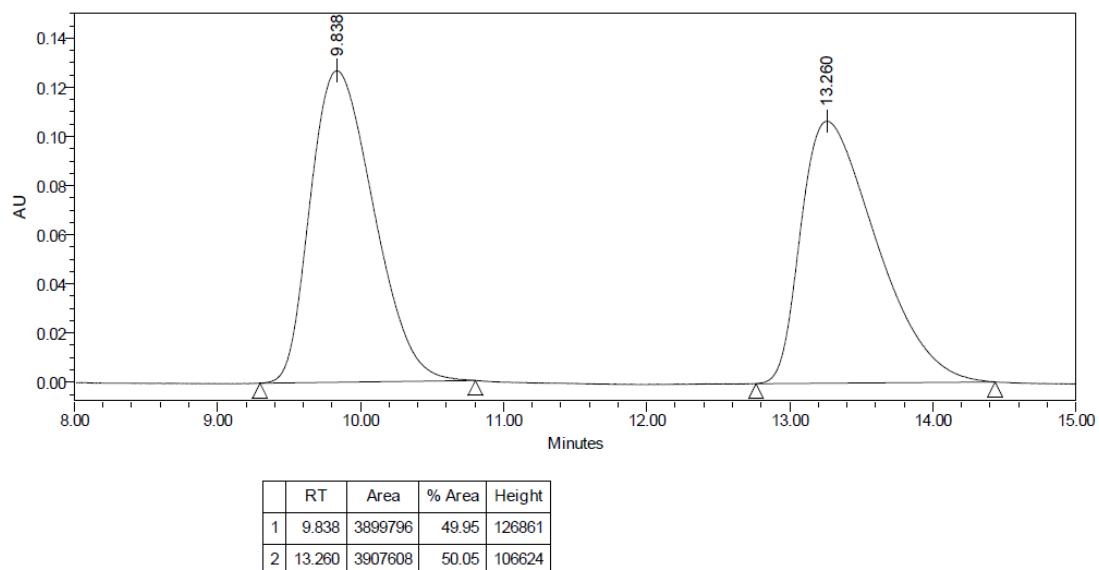
Supplementary Figure 145 ^1H NMR (400 MHz, CDCl_3) of **3u**



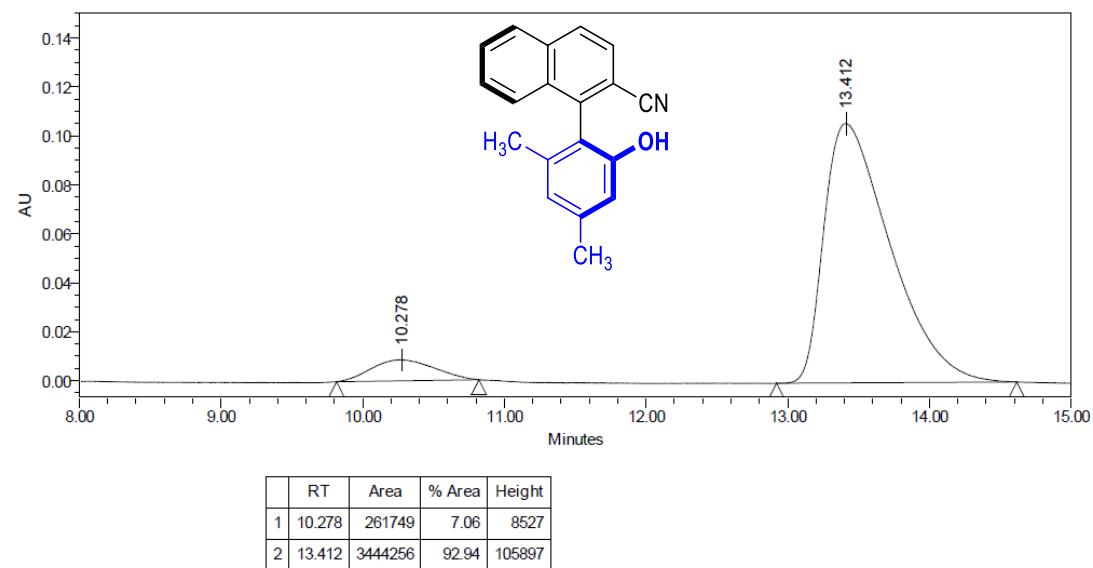
Supplementary Figure 146 ^{13}C NMR (400 MHz, CDCl_3) of **3u**



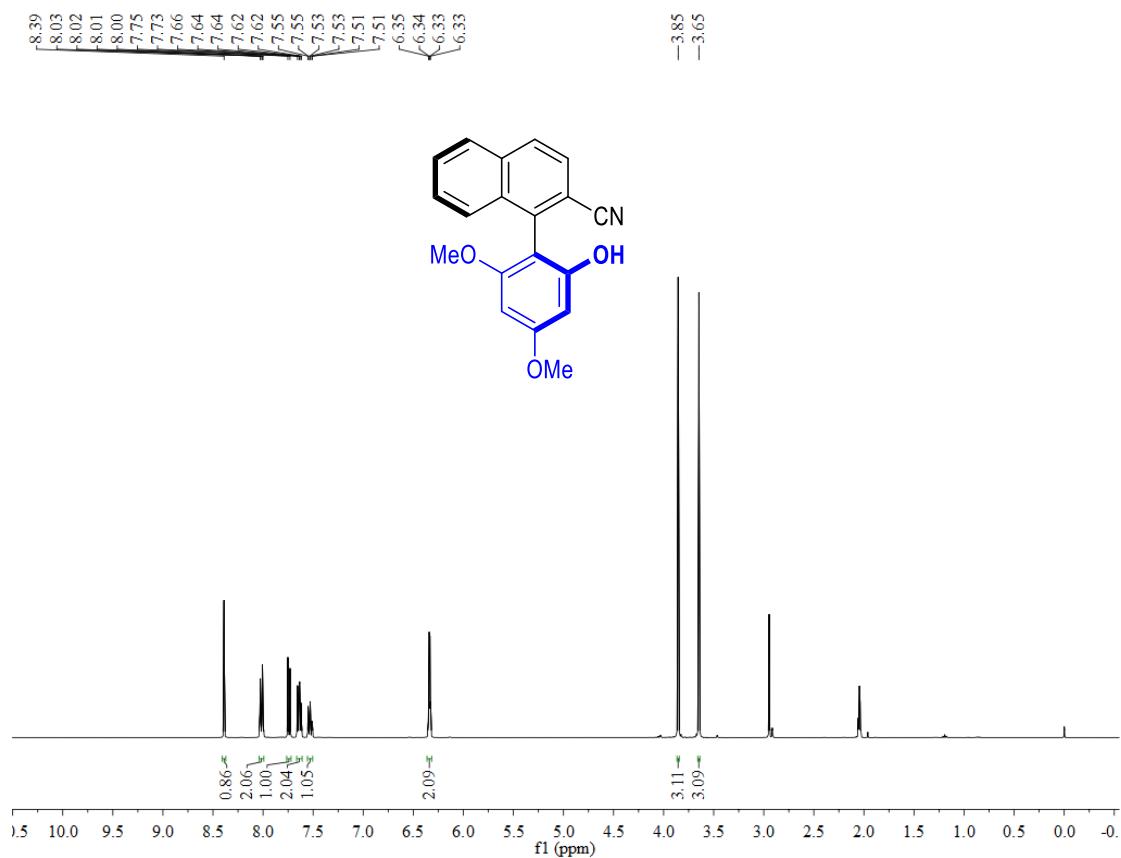
Supplementary Figure 147 HPLC spectra of racemic **3u**



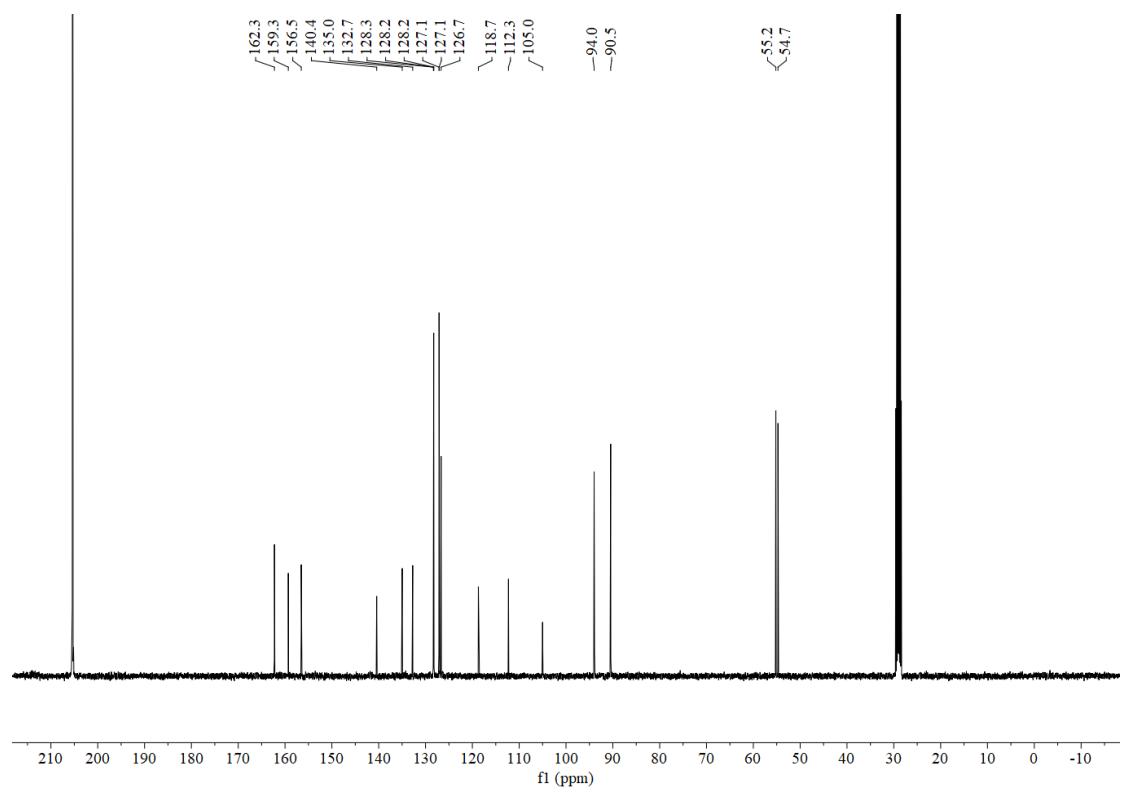
Supplementary Figure 148 HPLC spectra of (*S*)-**3u**



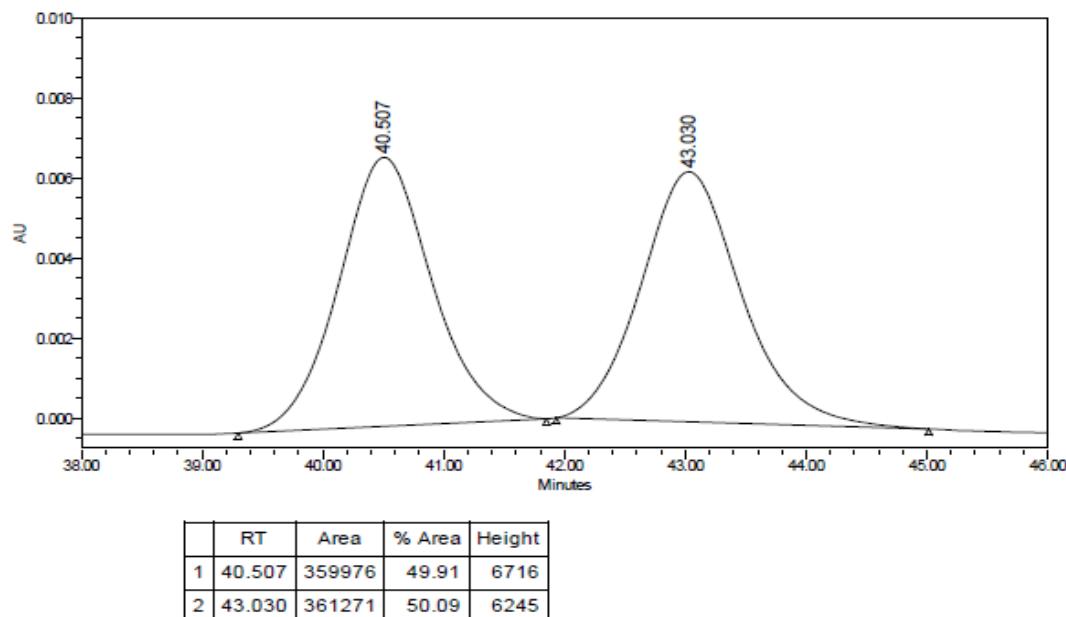
Supplementary Figure 149 ^1H NMR (400 MHz, Acetone- d_6) of **3v**



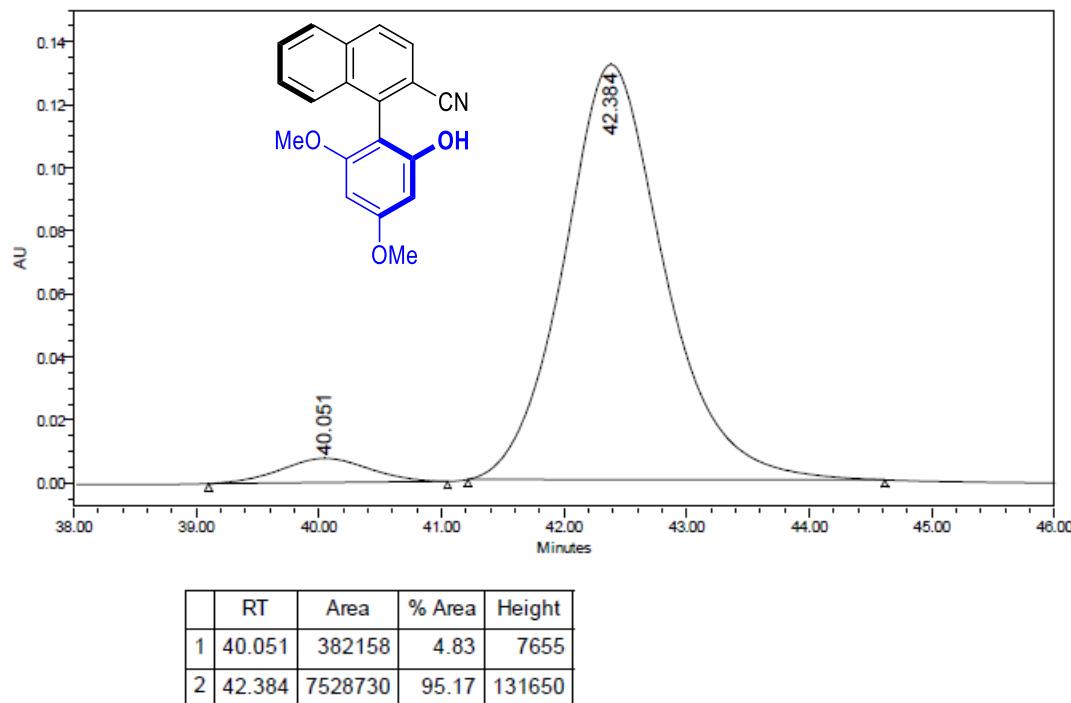
Supplementary Figure 150 ^{13}C NMR (400 MHz, Acetone- d_6) of **3v**



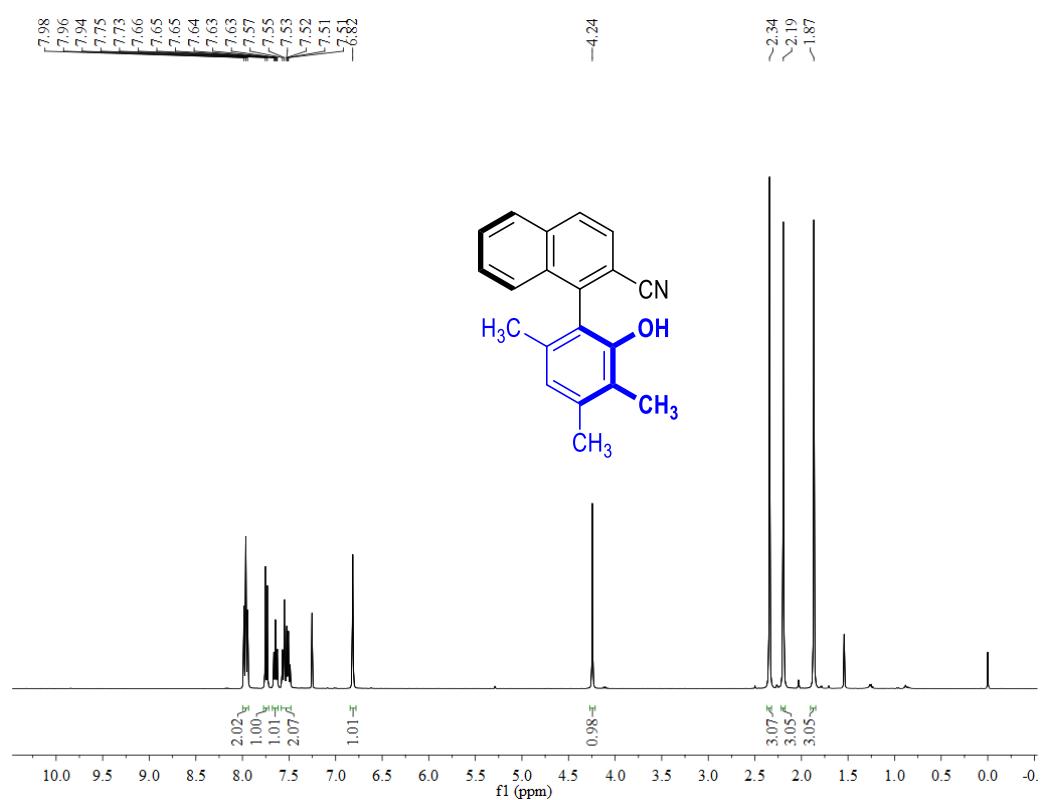
Supplementary Figure 151 HPLC spectra of racemic **3v**



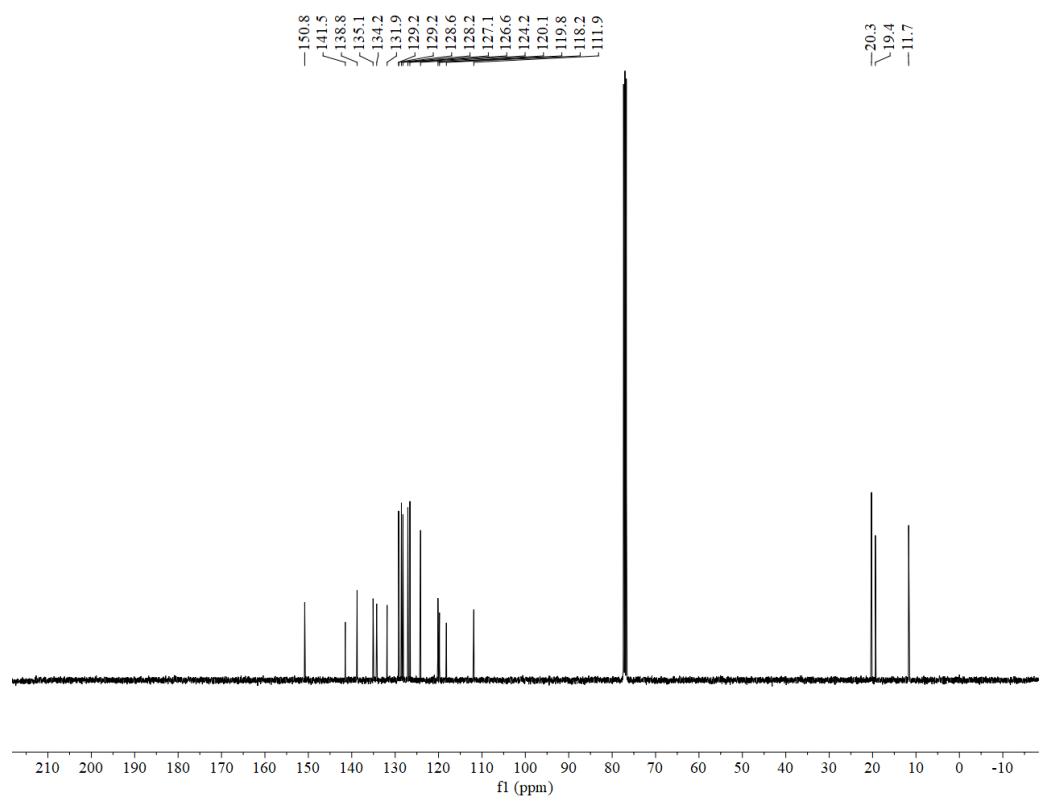
Supplementary Figure 152 HPLC spectra of (*R*)-**3v**



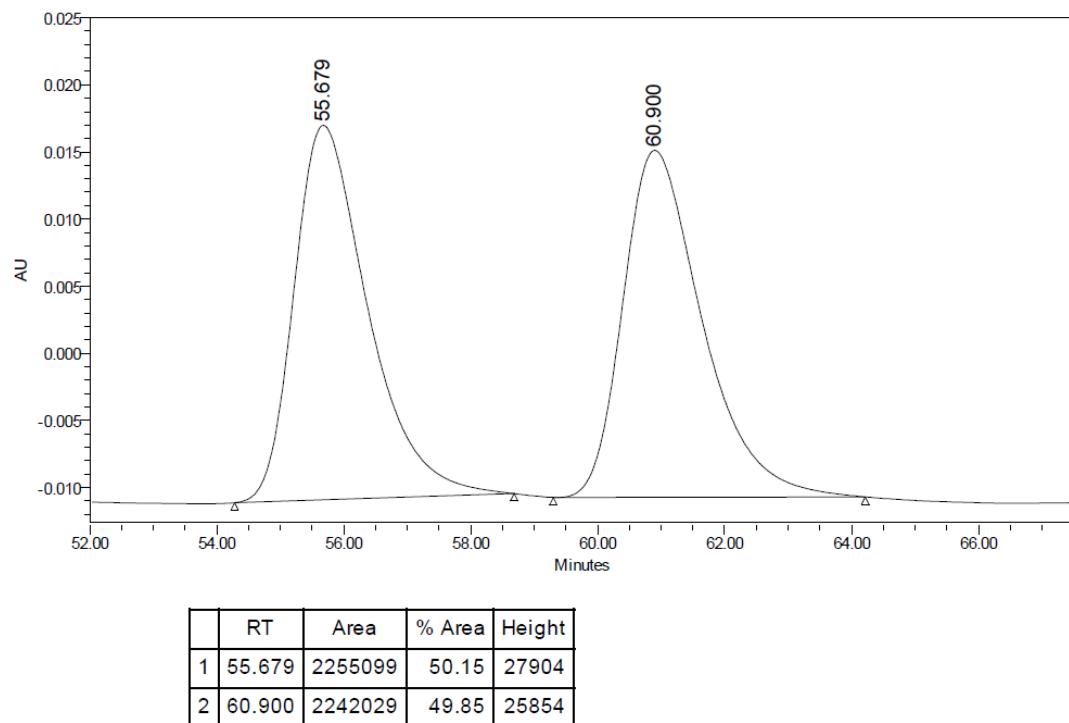
Supplementary Figure 153 ^1H NMR (400 MHz, CDCl_3) of **3w**



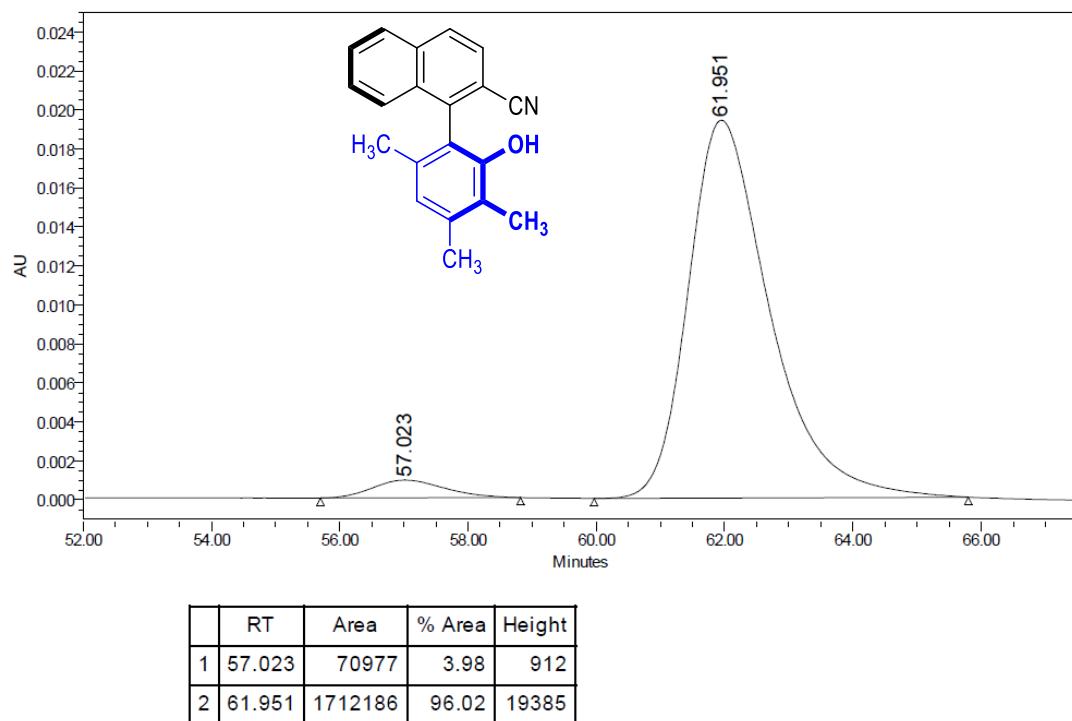
Supplementary Figure 154 ^{13}C NMR (400 MHz, CDCl_3) of **3w**



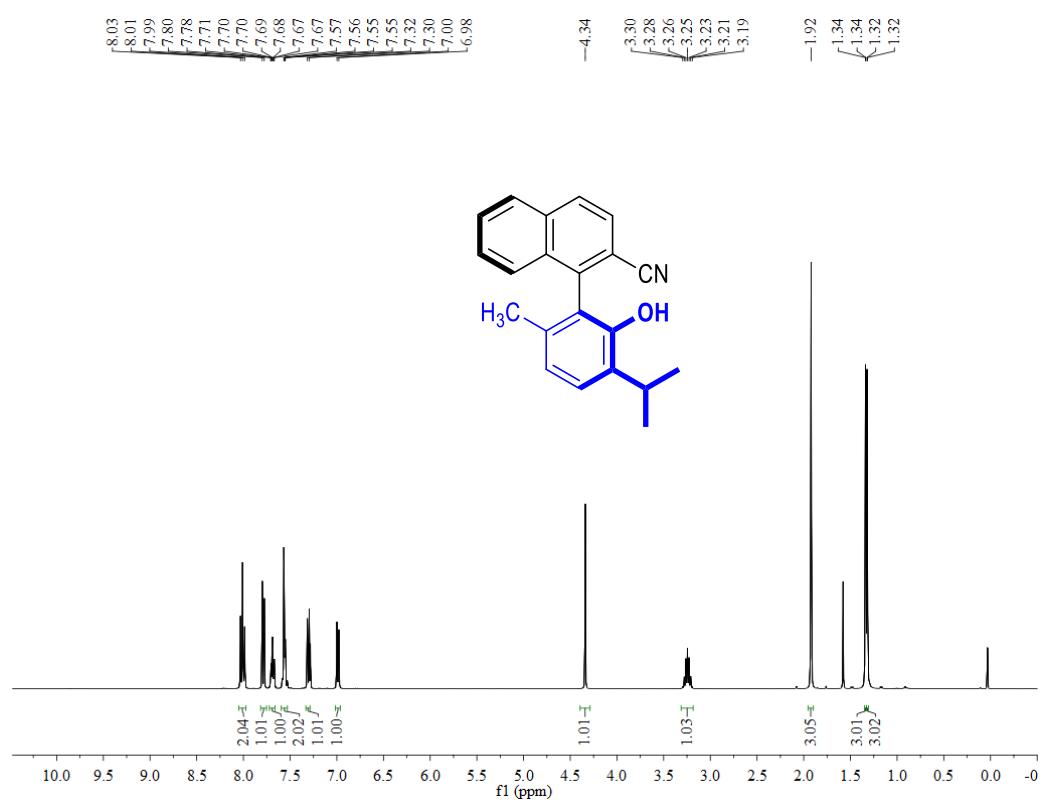
Supplementary Figure 155 HPLC spectra of racemic **3w**



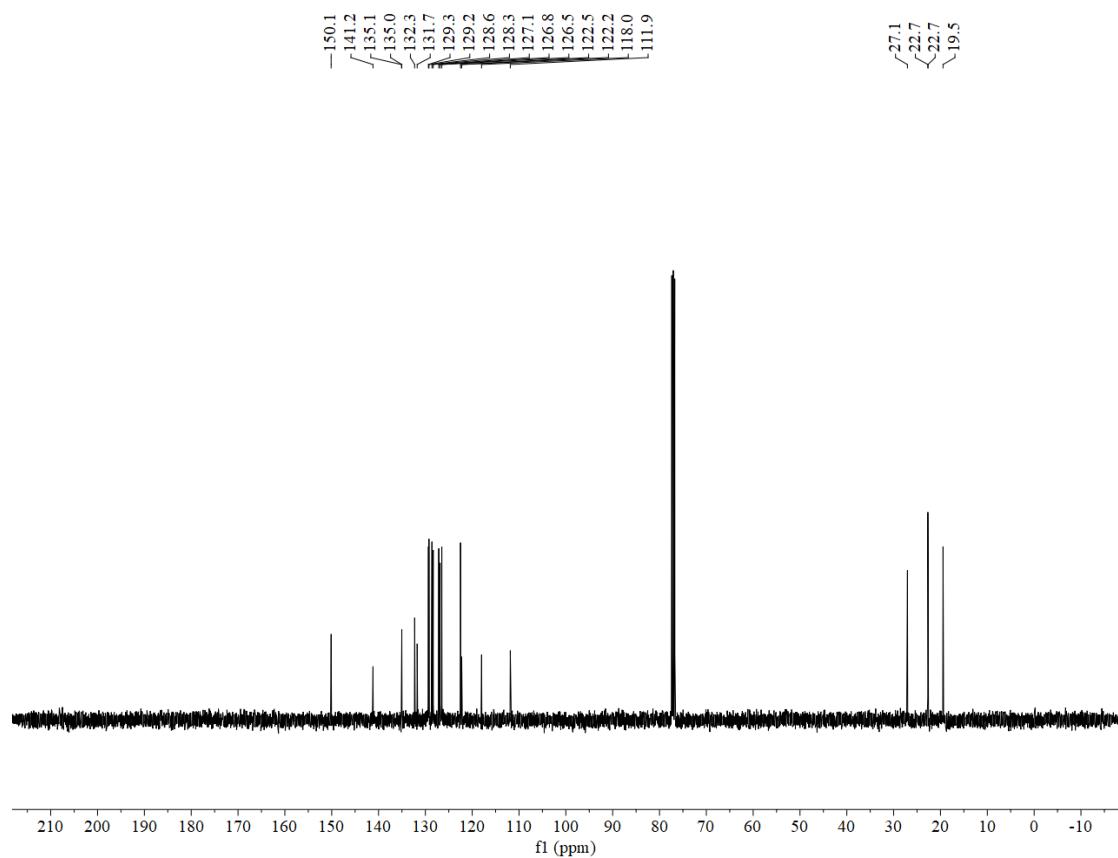
Supplementary Figure 156 HPLC spectra of (*S*)- **3w**



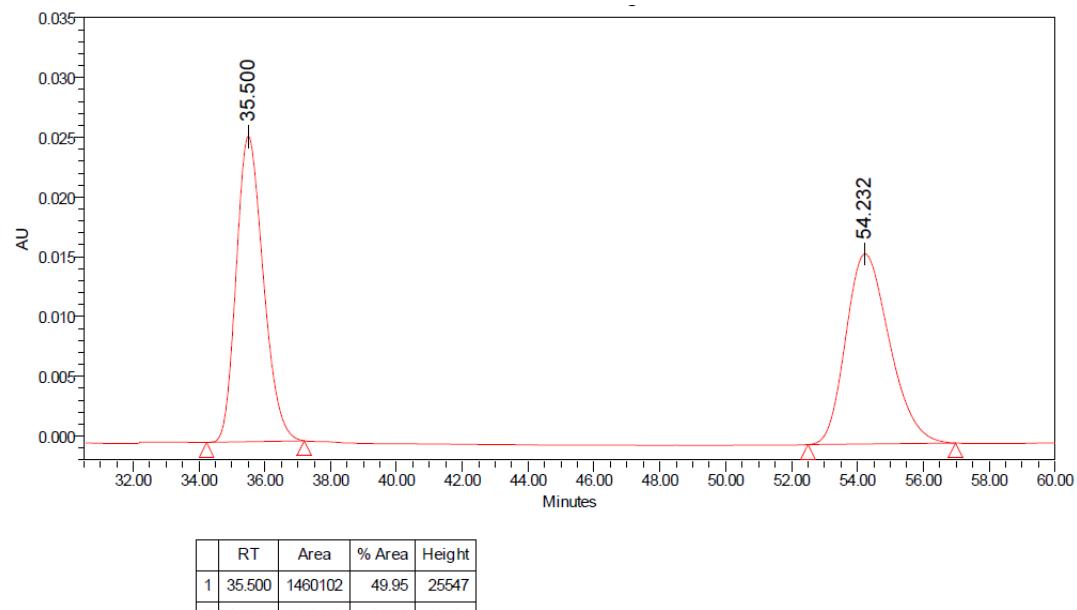
Supplementary Figure 157 ^1H NMR (400 MHz, CDCl_3) of **3x**



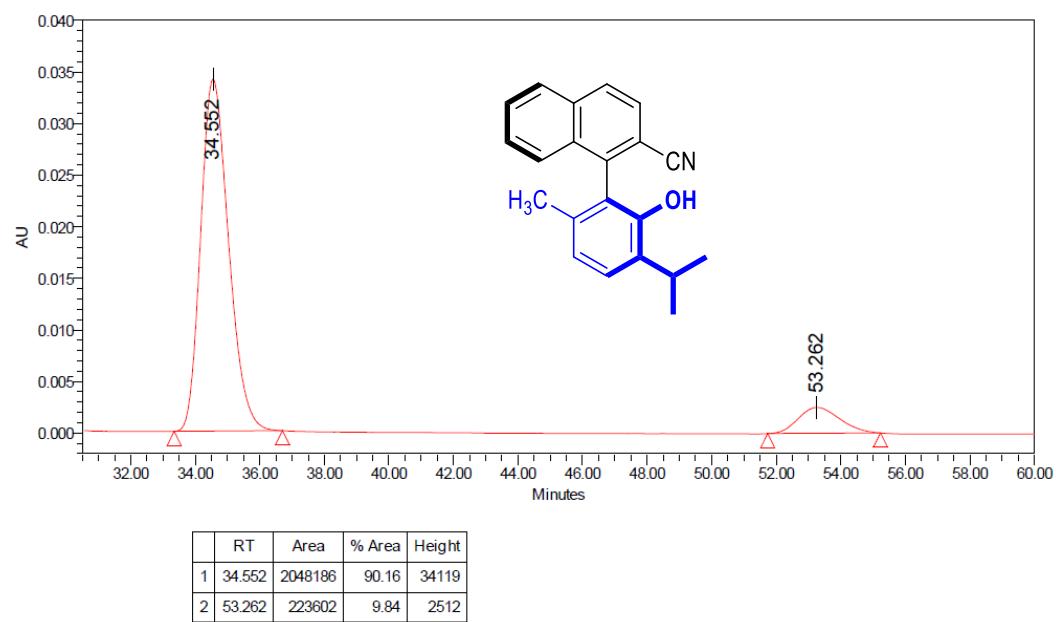
Supplementary Figure 158 ^{13}C NMR (400 MHz, CDCl_3) of **3x**



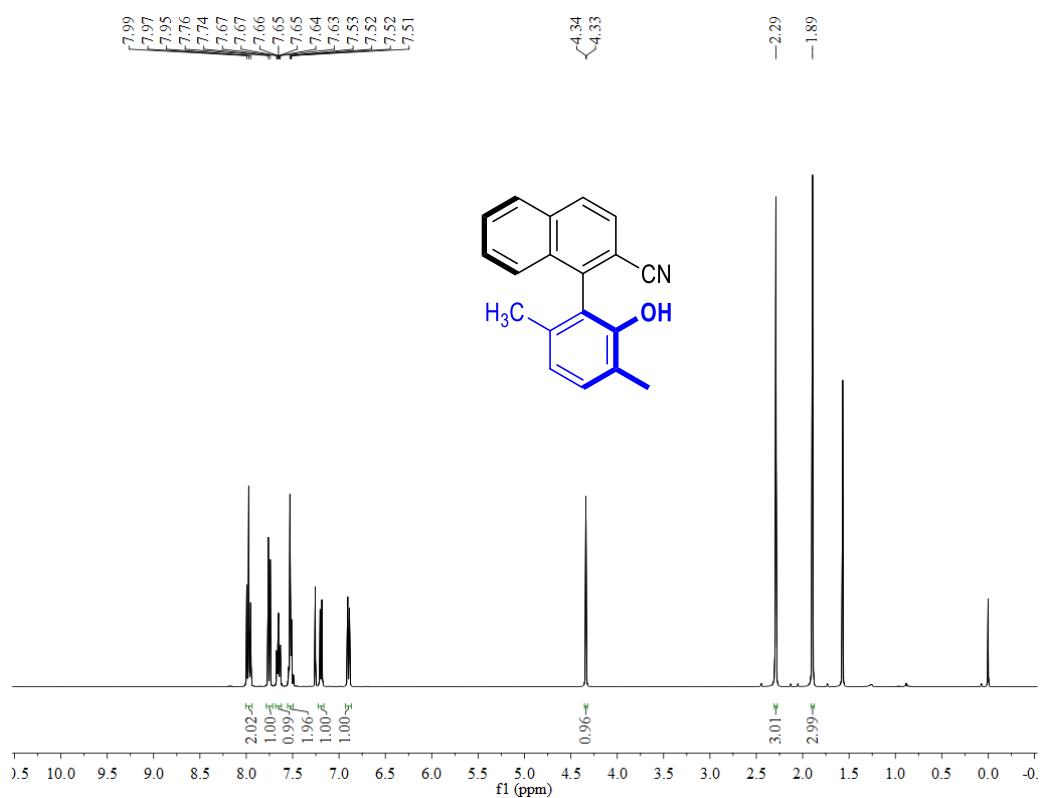
Supplementary Figure 159 HPLC spectra of racemic **3x**



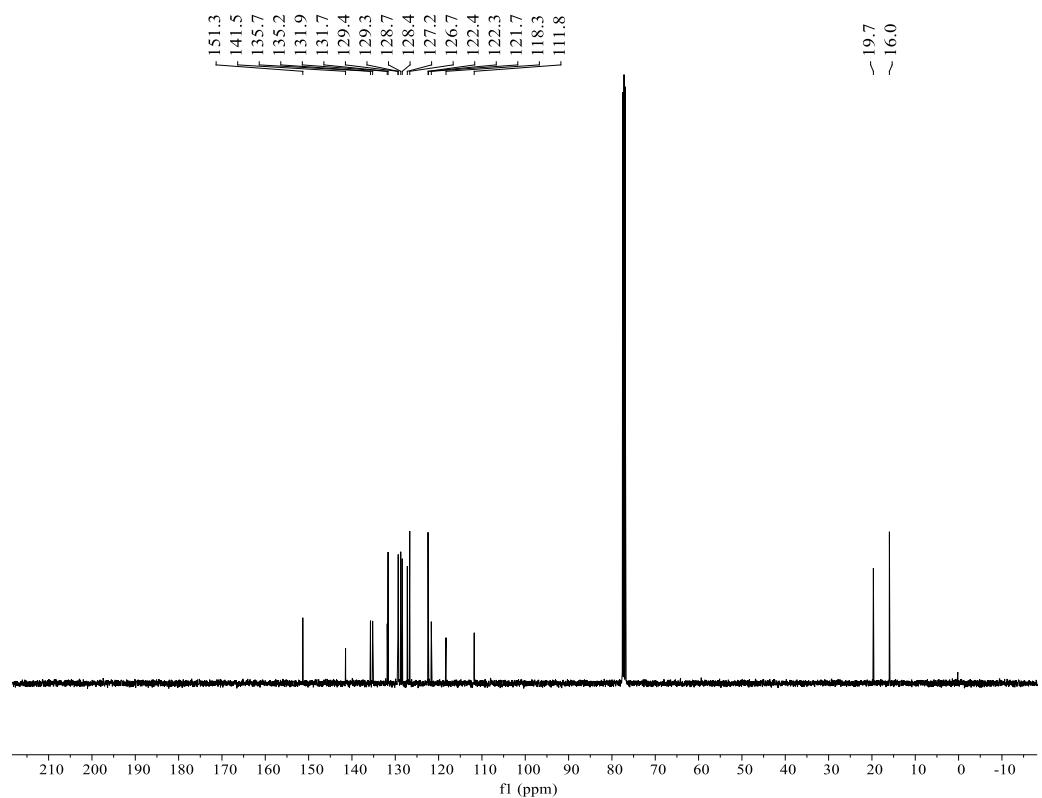
Supplementary Figure 160 HPLC spectra of (*S*)-**3x**



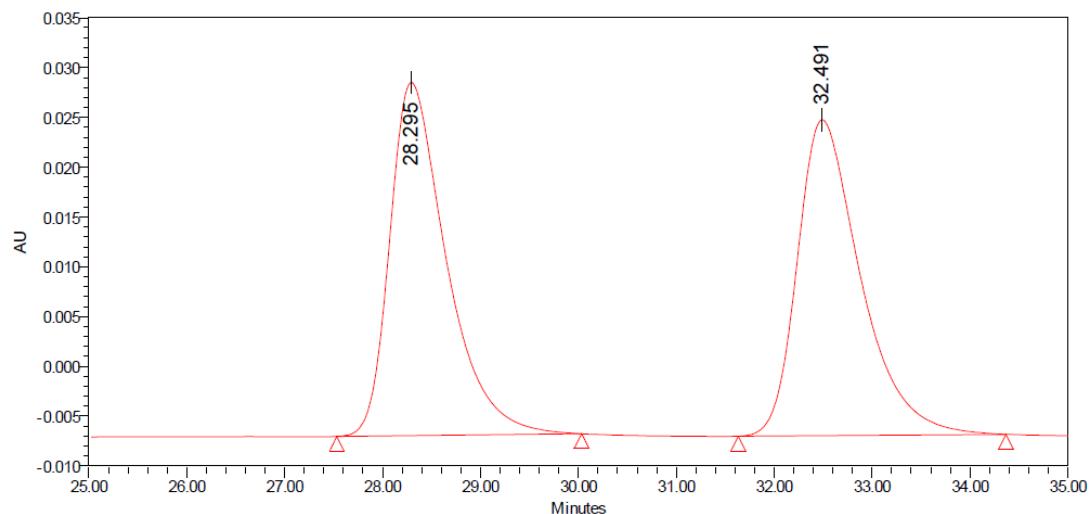
Supplementary Figure 161 ^1H NMR (400 MHz, CDCl_3) of **3y**



Supplementary Figure 162 ^{13}C NMR (400 MHz, CDCl_3) of **3y**

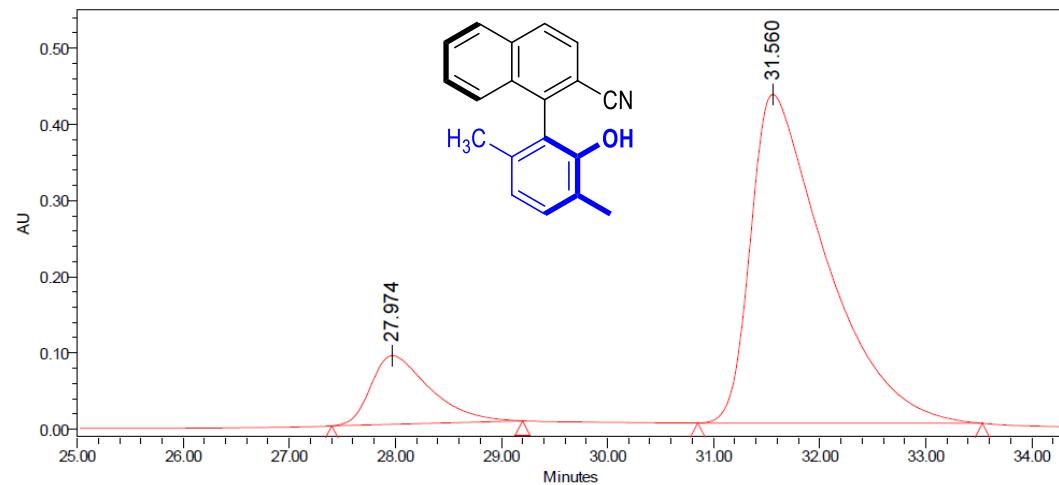


Supplementary Figure 163 HPLC spectra of racemic **3y**



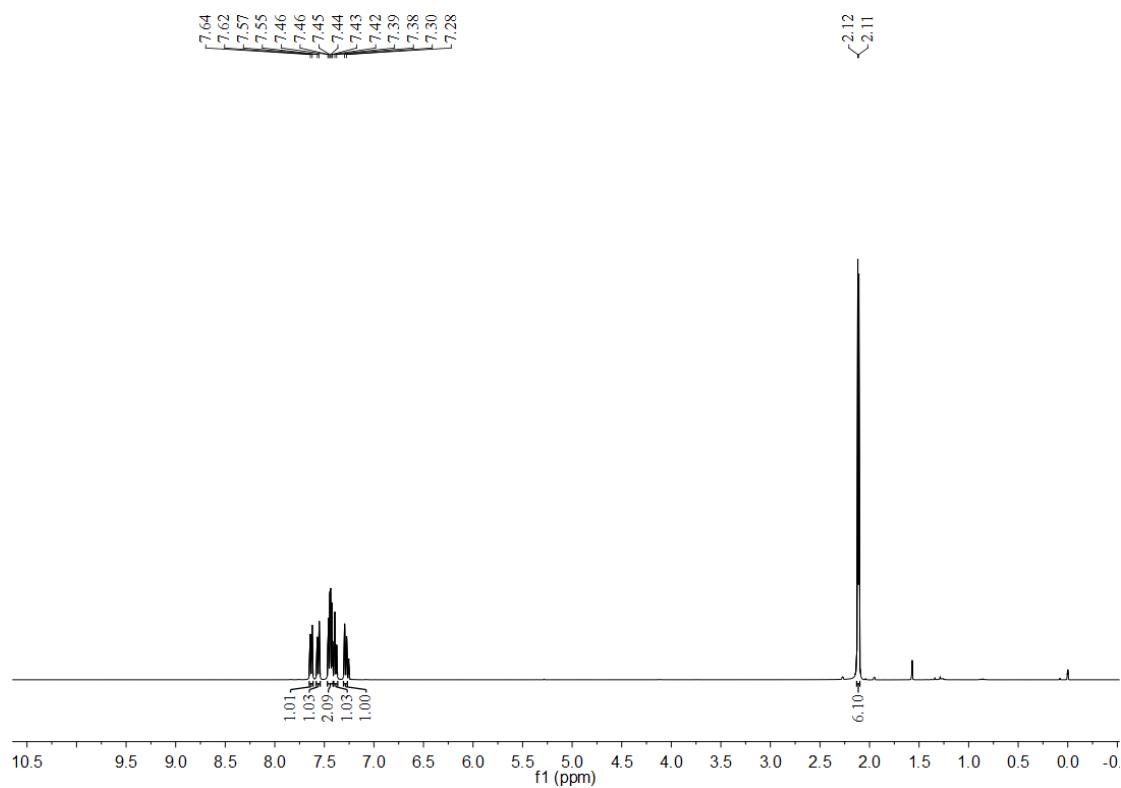
	RT	Area	% Area	Height
1	28.295	1423181	50.00	35461
2	32.491	1423094	50.00	31718

Supplementary Figure 164 HPLC spectra of (*S*)- **3y**

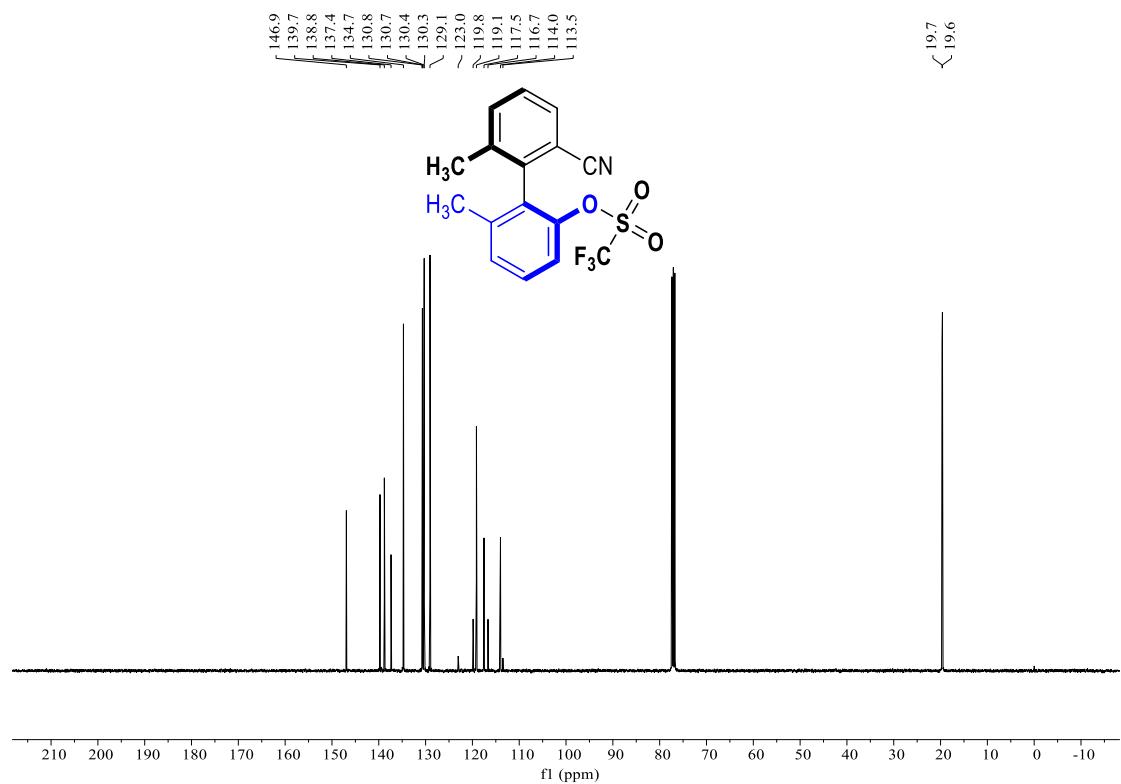


	RT	Area	% Area	Height
1	27.974	3481267	14.05	90106
2	31.560	21299756	85.95	431532

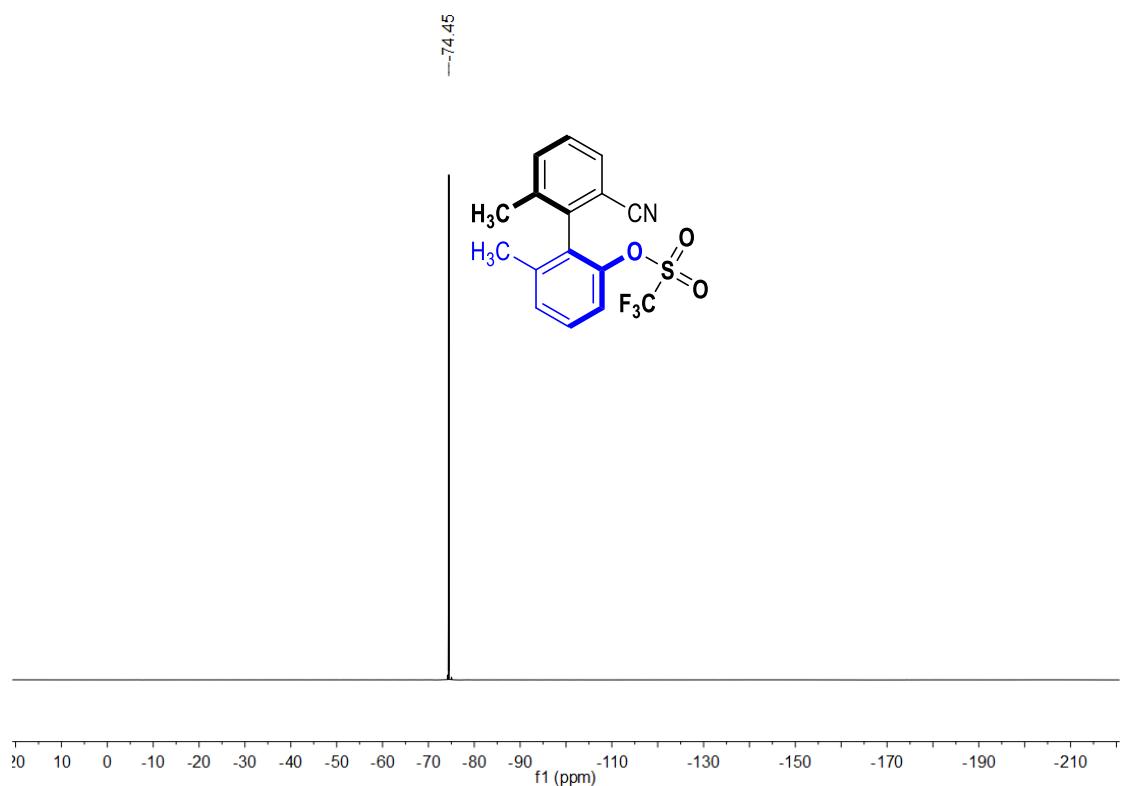
Supplementary Figure 165 ^1H NMR (400 MHz, CDCl_3) of **5**



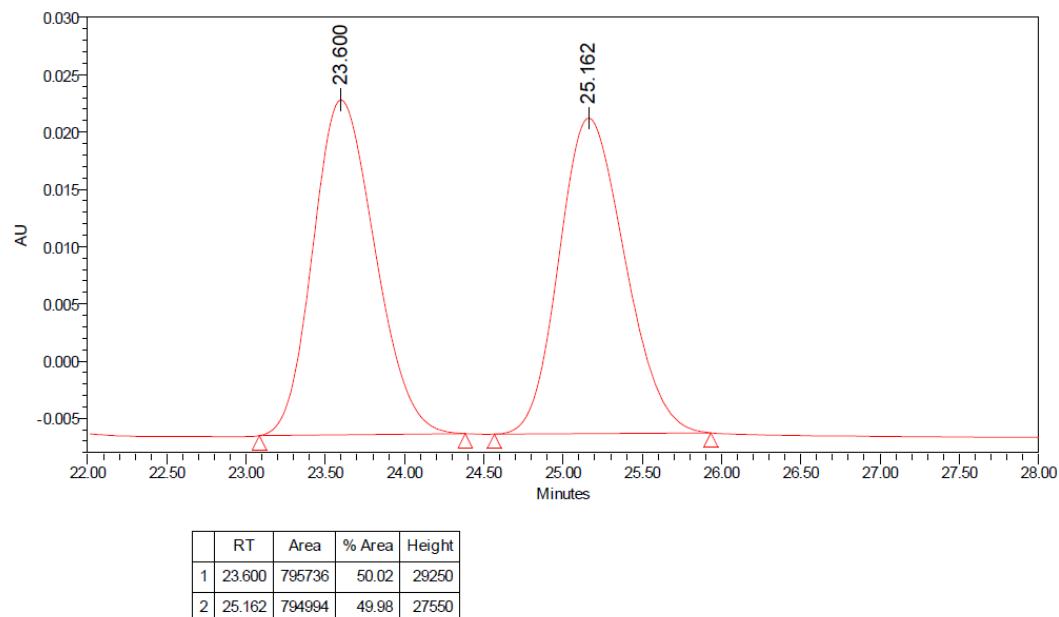
Supplementary Figure 166 ^{13}C NMR (400 MHz, CDCl_3) of **5**



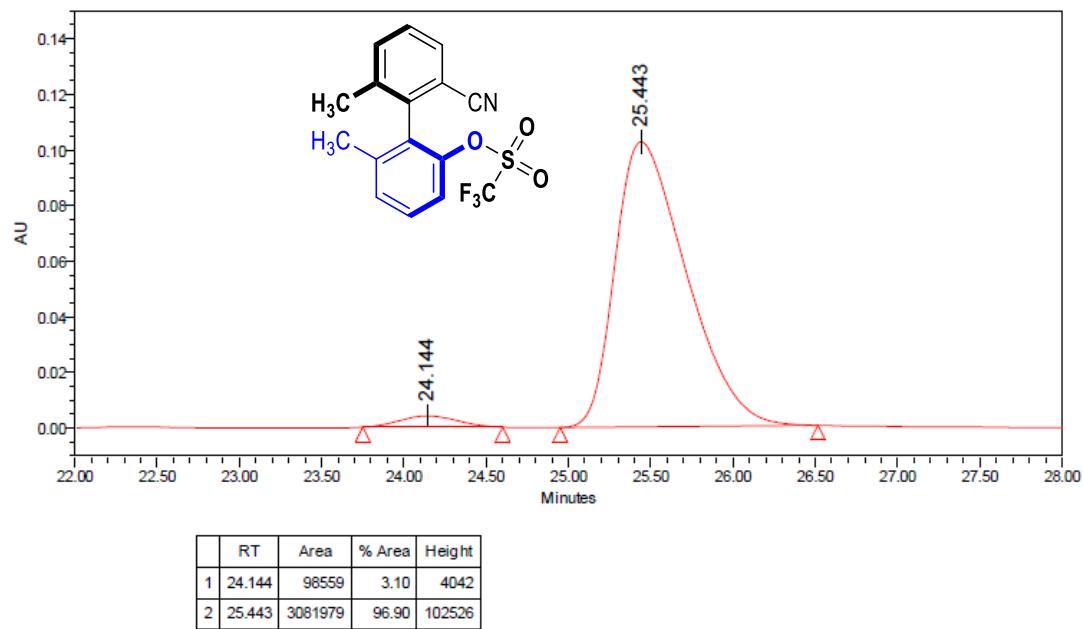
Supplementary Figure 167 ^{19}F NMR (400 MHz, CDCl_3) of **5**



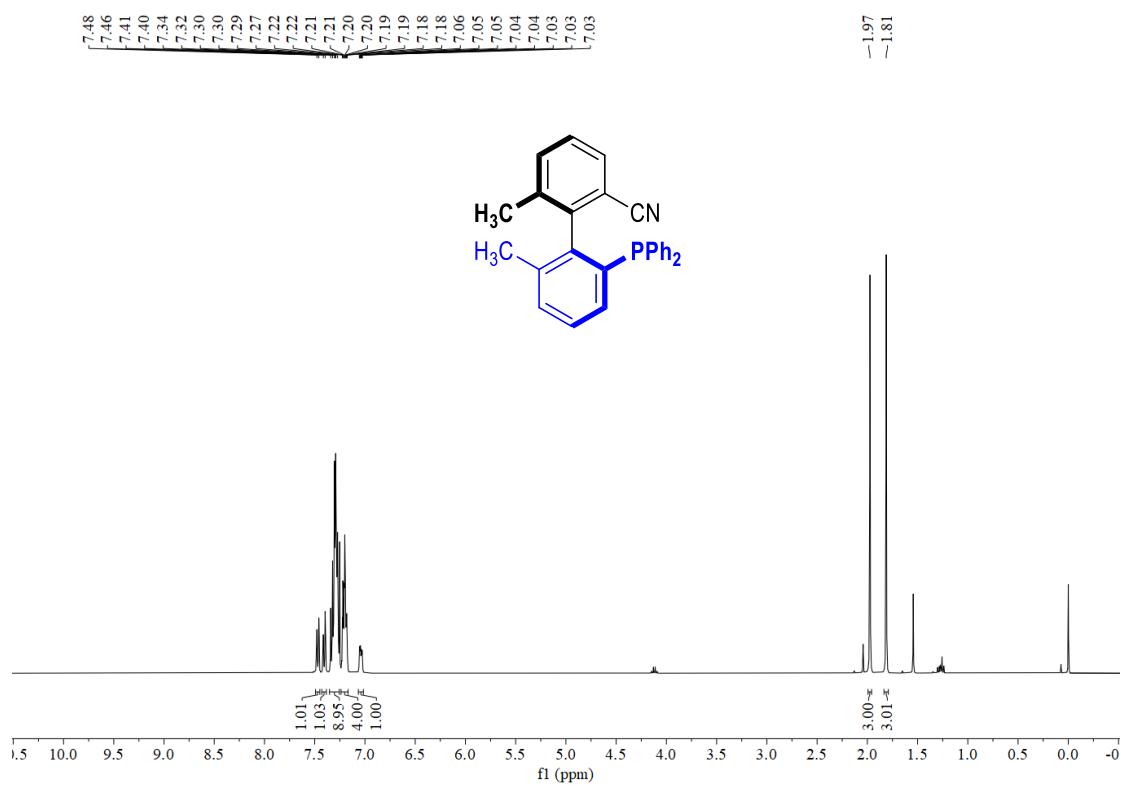
Supplementary Figure 168 HPLC spectra of racemic **5**



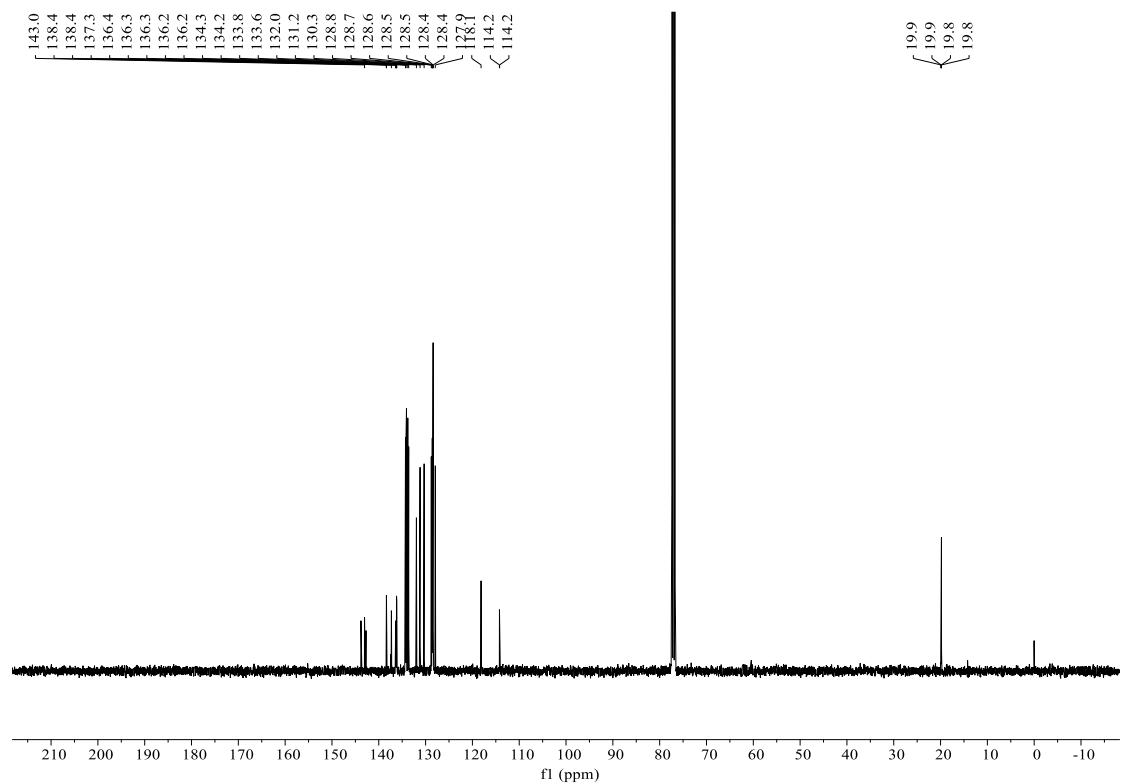
Supplementary Figure 169 HPLC spectra of (*S*)-**5**



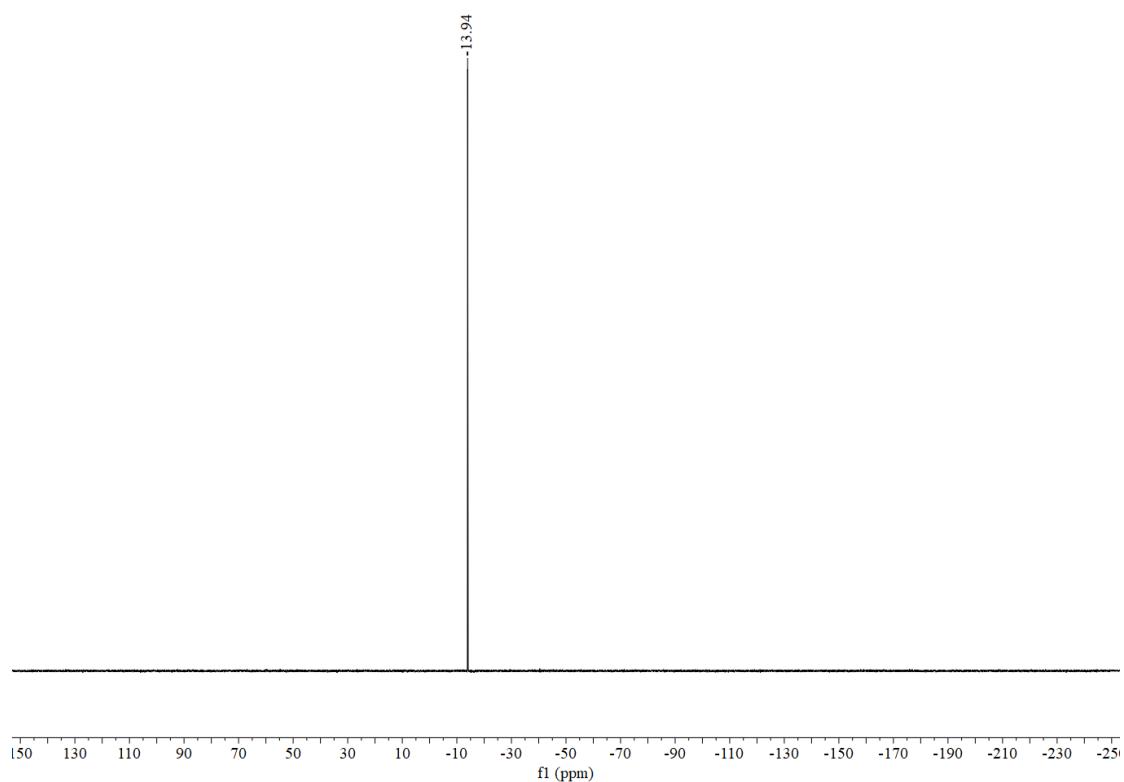
Supplementary Figure 70 ^1H NMR (400 MHz, CDCl_3) of **6**



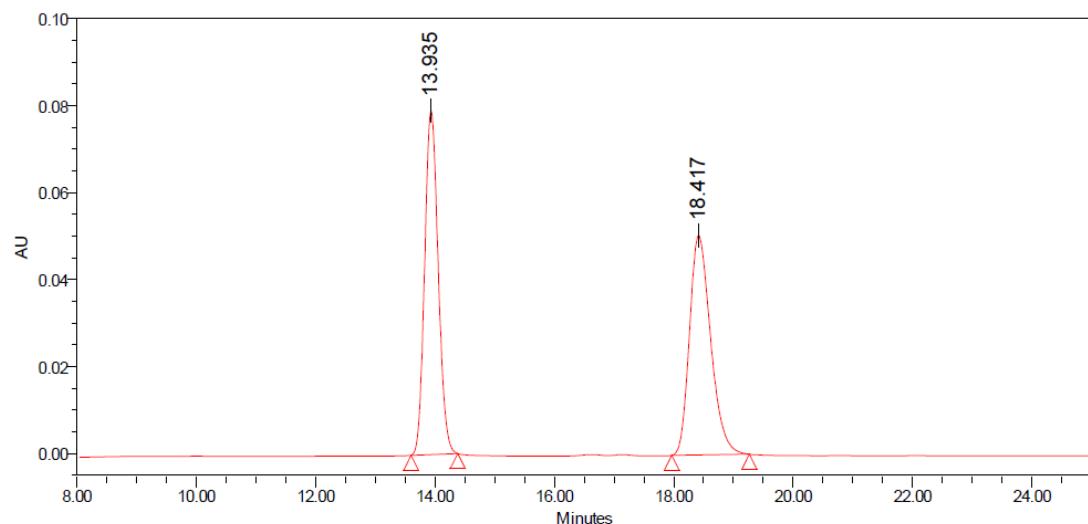
Supplementary Figure 171 ^{13}C NMR (400 MHz, CDCl_3) of **6**



Supplementary Figure 172 ^{31}P NMR (400 MHz, CDCl_3) of **6**

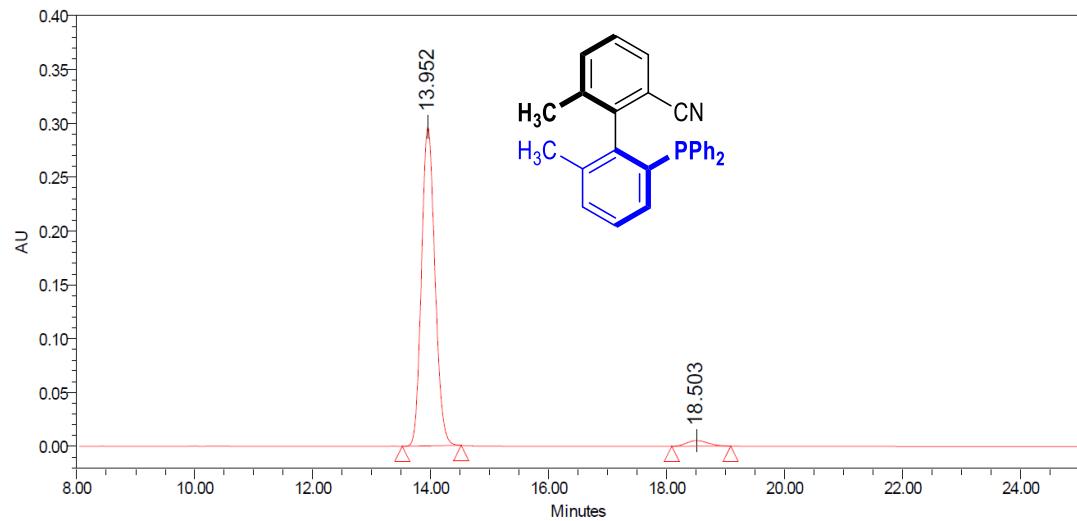


Supplementary Figure 173 HPLC spectra of racemic **6**



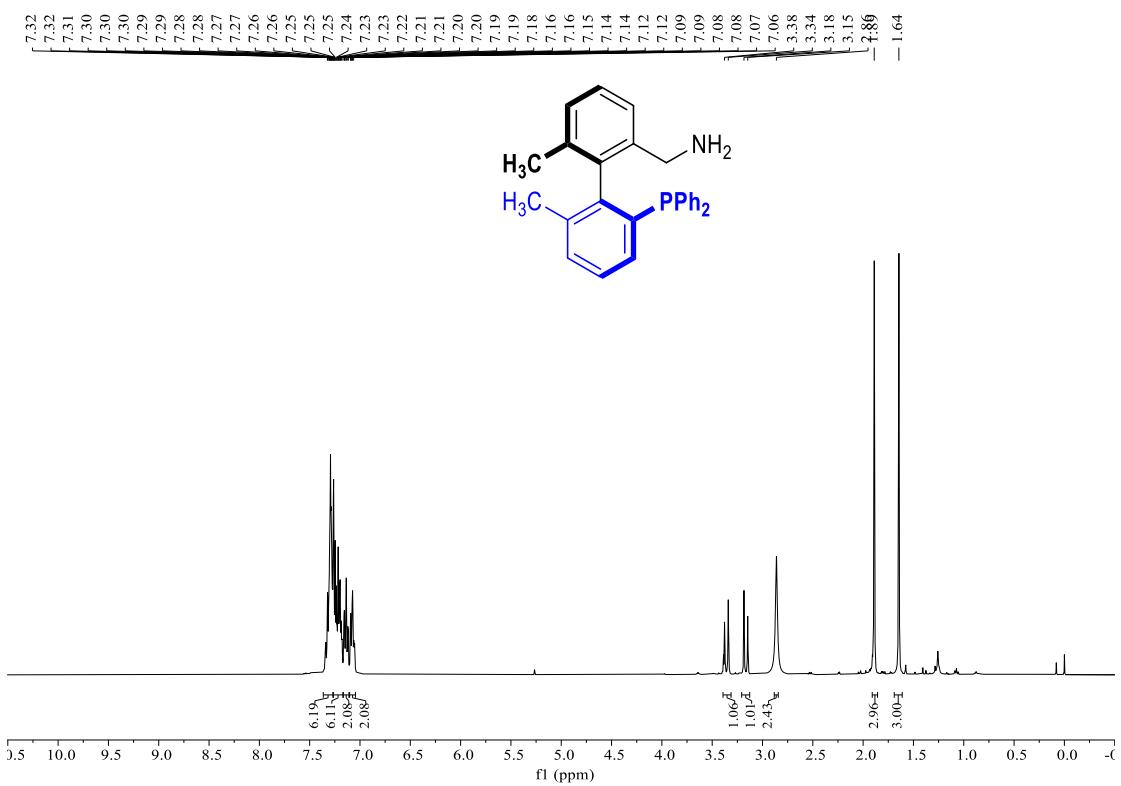
	RT	Area	% Area	Height
1	13.935	1245186	50.07	79122
2	18.417	1241801	49.93	50506

Supplementary Figure 174 HPLC spectra of (*S*)- **6**

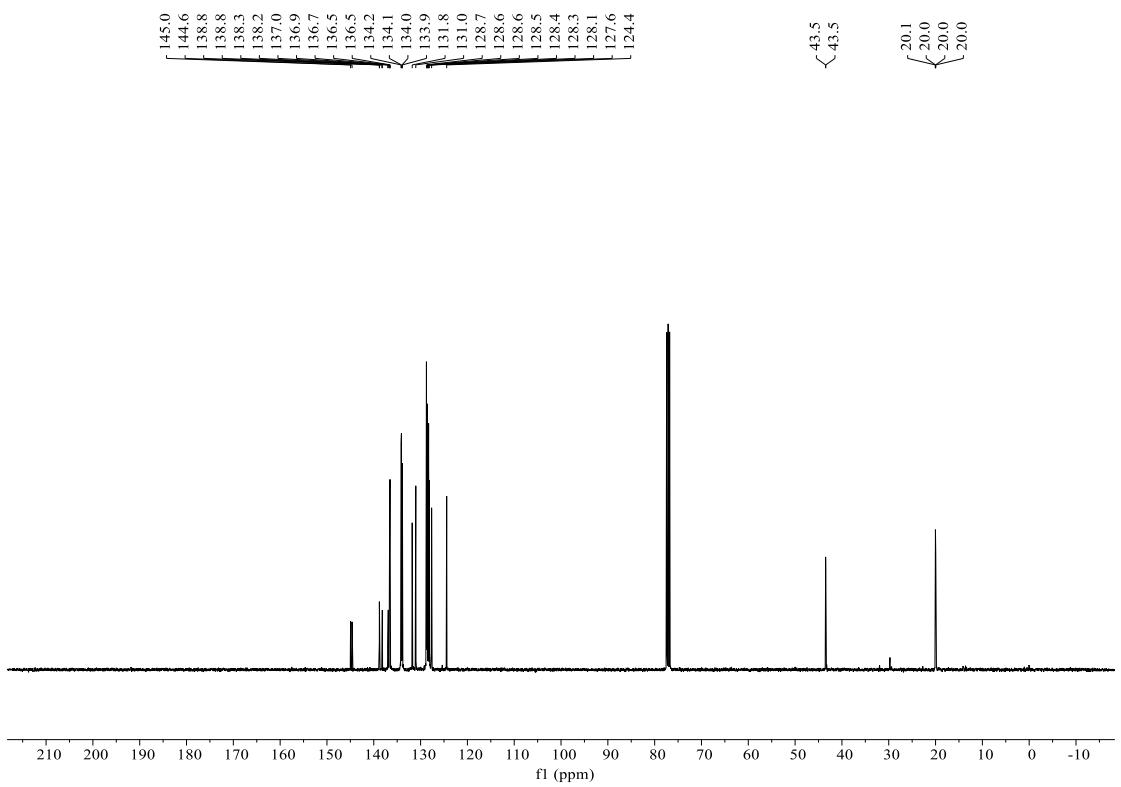


	RT	Area	% Area	Height
1	13.952	4699379	97.28	296779
2	18.503	131636	2.72	5279

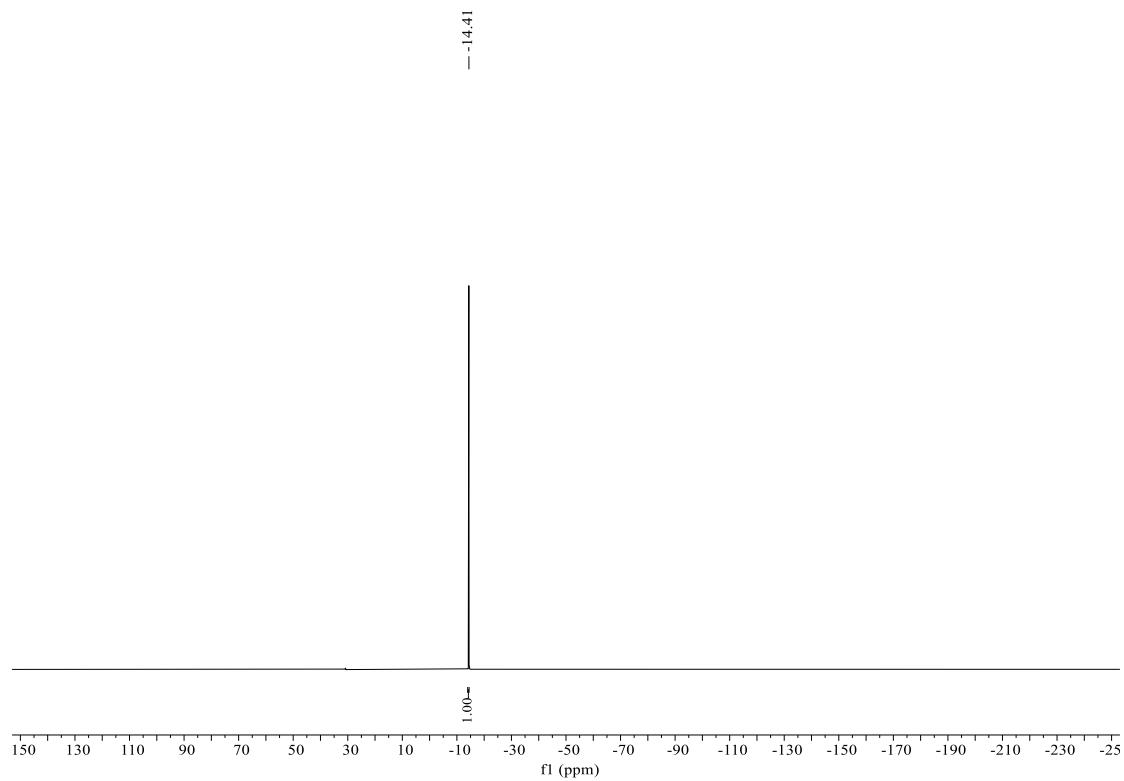
Supplementary Figure 175 ^1H NMR (400 MHz, CDCl_3) of **7**



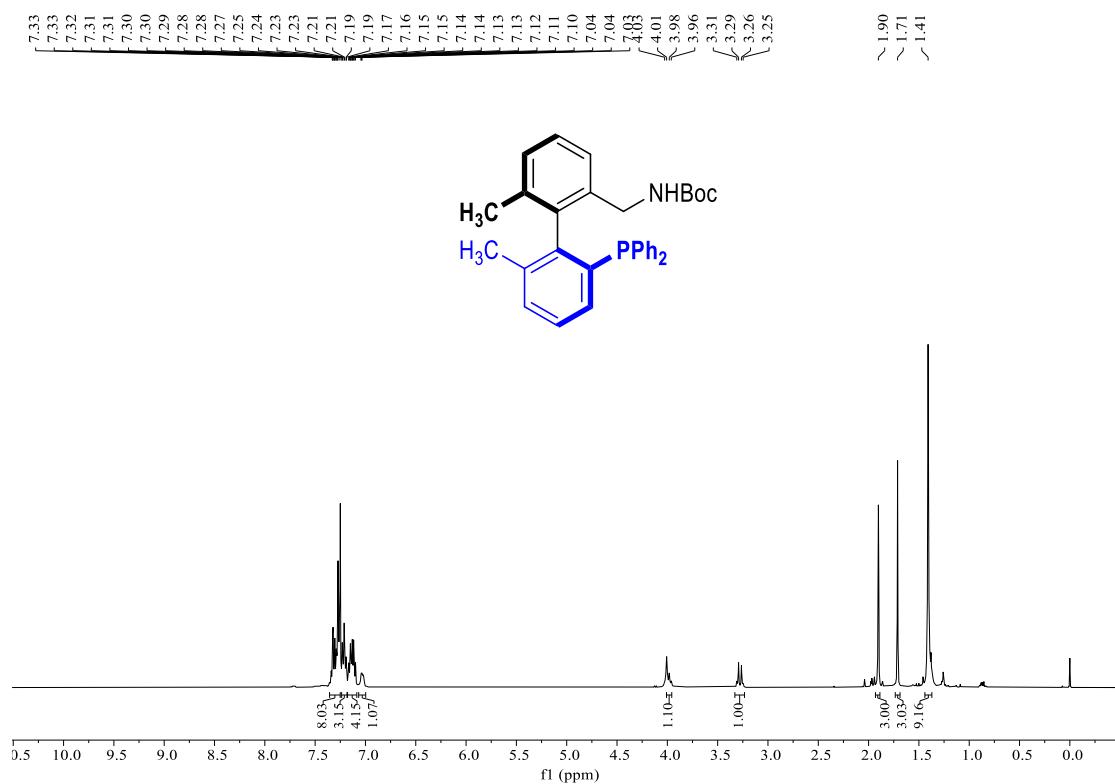
Supplementary Figure 176 ^{13}C NMR (400 MHz, CDCl_3) of 7



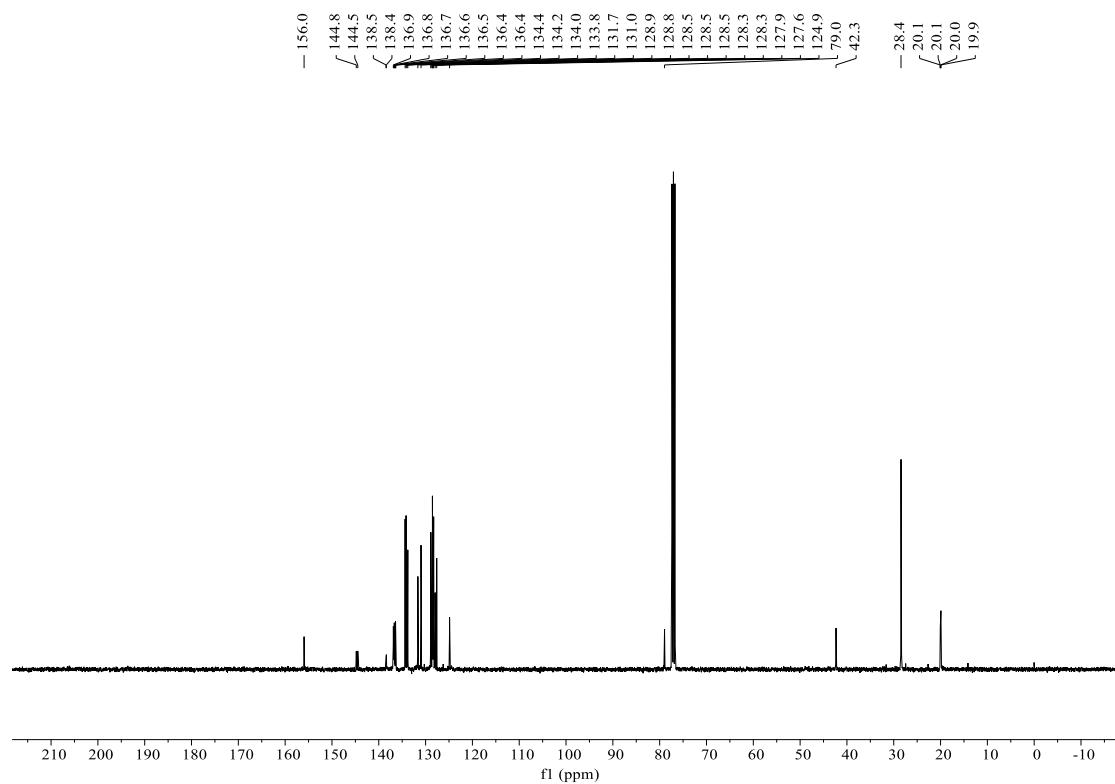
Supplementary Figure 177 ^{31}P NMR (400 MHz, CDCl_3) of **7**



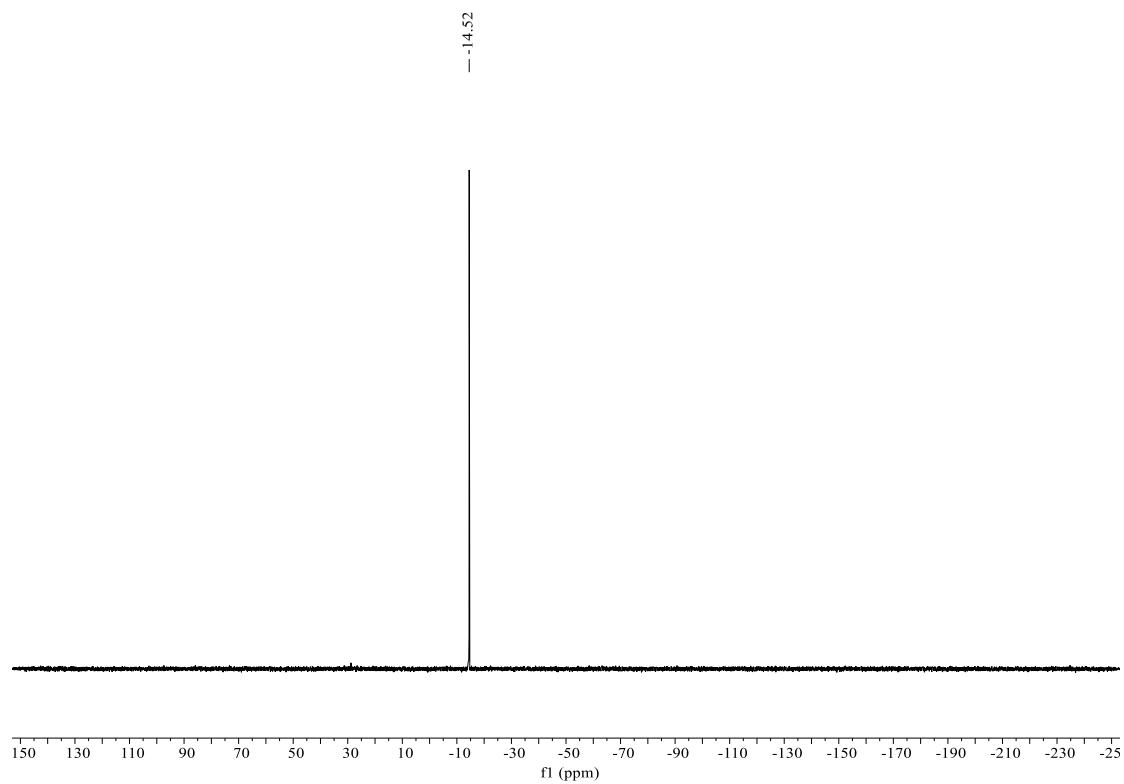
Supplementary Figure 178 ^1H NMR (400 MHz, CDCl_3) of **8**



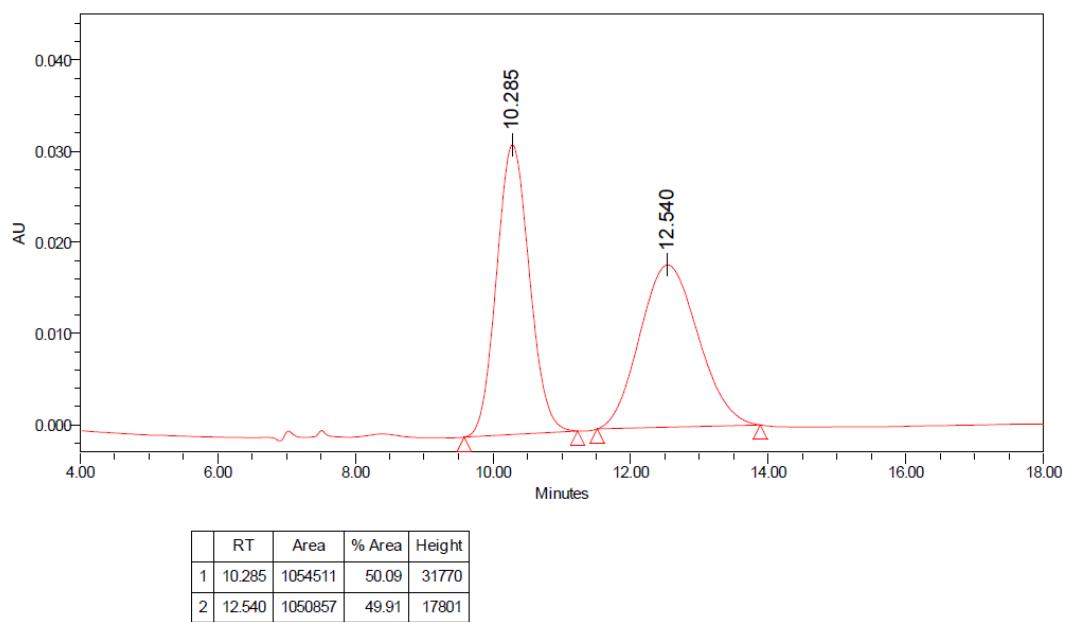
Supplementary Figure 179 ^{13}C NMR (400 MHz, CDCl_3) of **8**



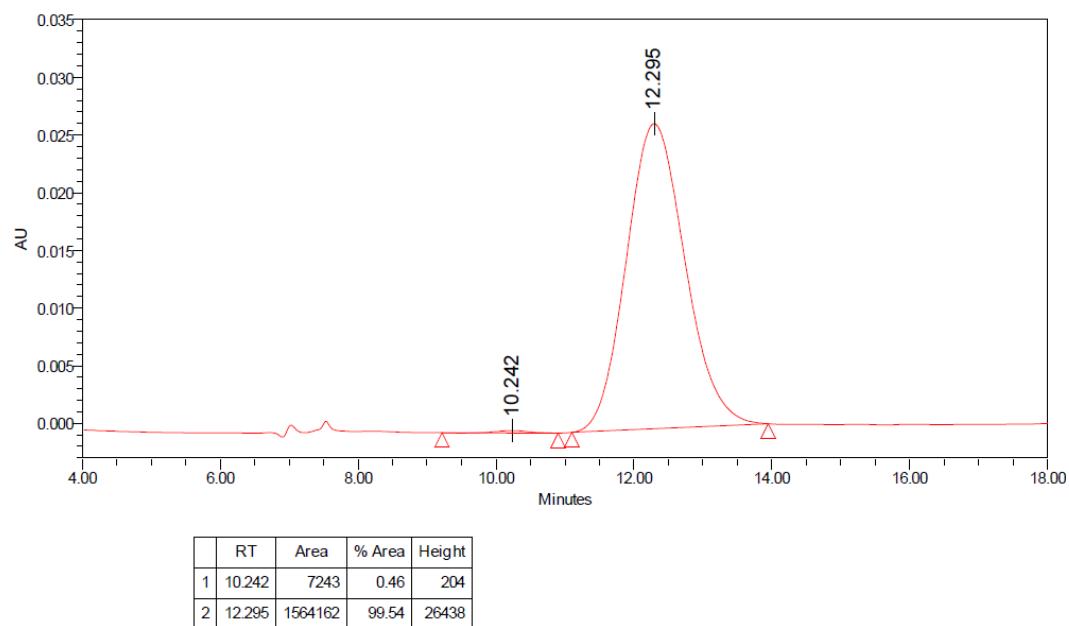
Supplementary Figure 180 ^{31}P NMR (400 MHz, CDCl_3) of **8**



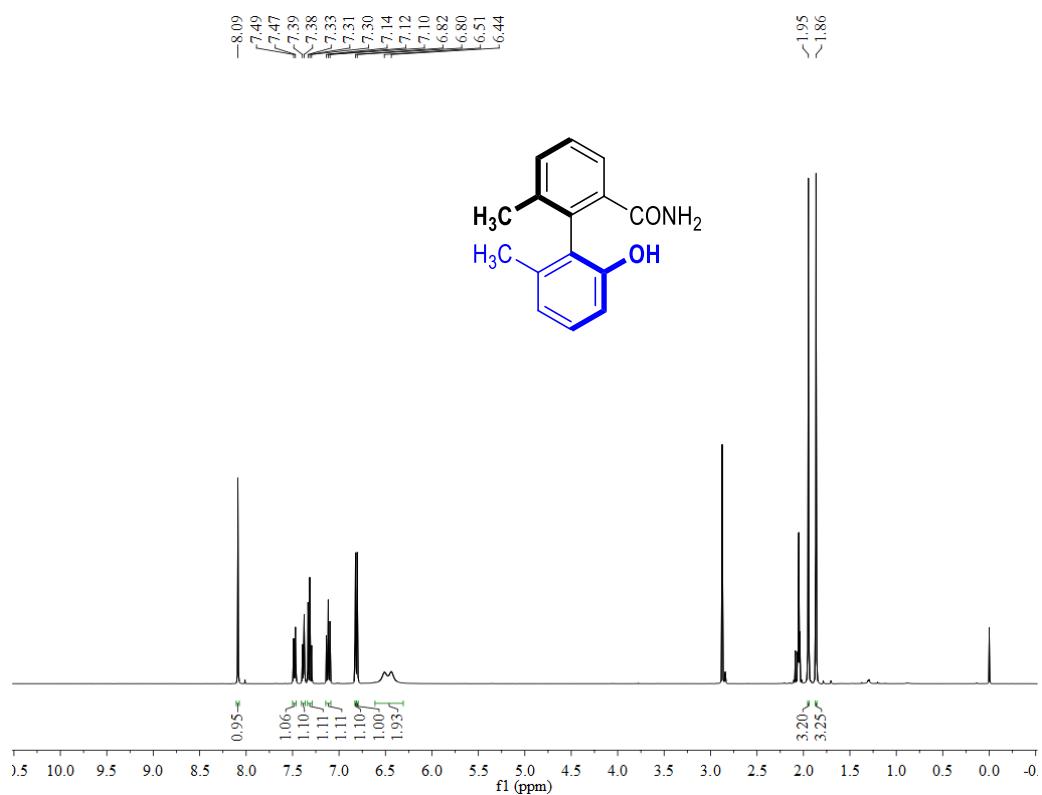
Supplementary Figure 181 HPLC spectra of racemic **8**



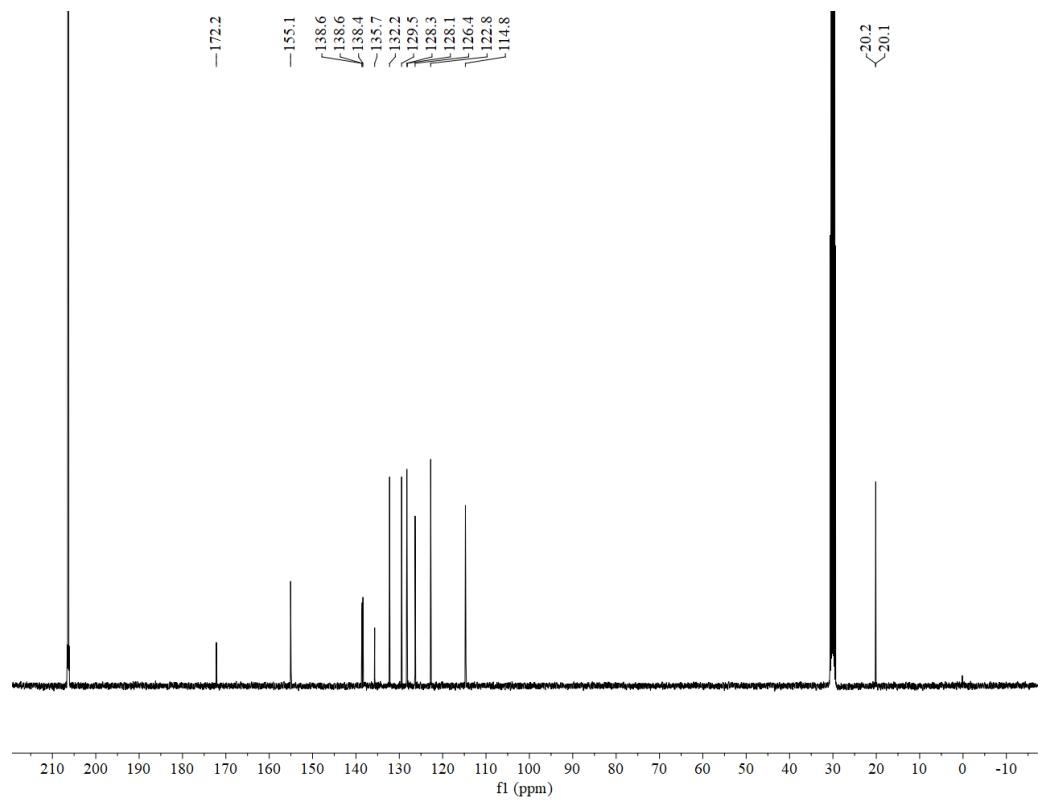
Supplementary Figure 182 HPLC spectra of (*S*)- **8**



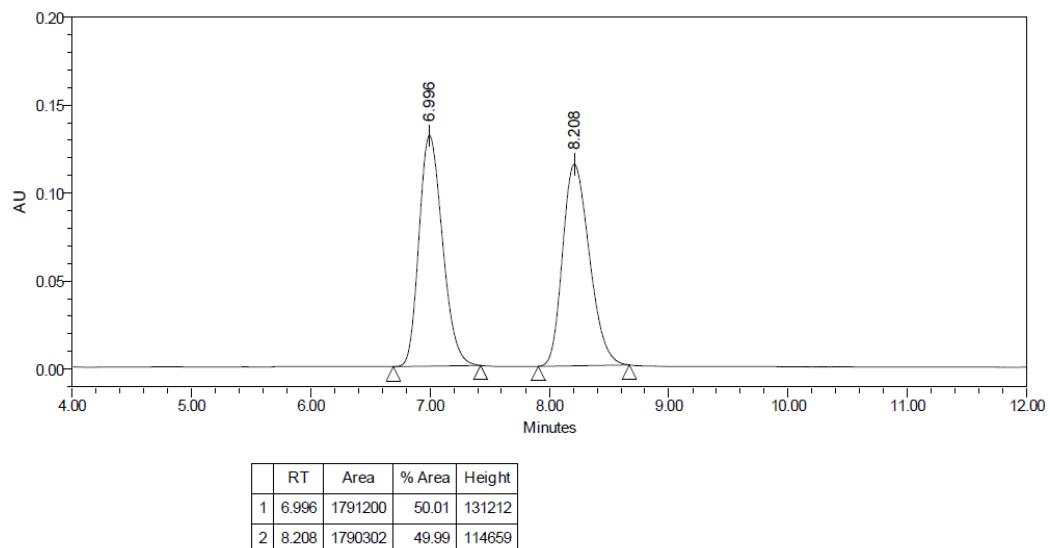
Supplementary Figure 183 ^1H NMR (400 MHz, Acetone- d_6) of **9**



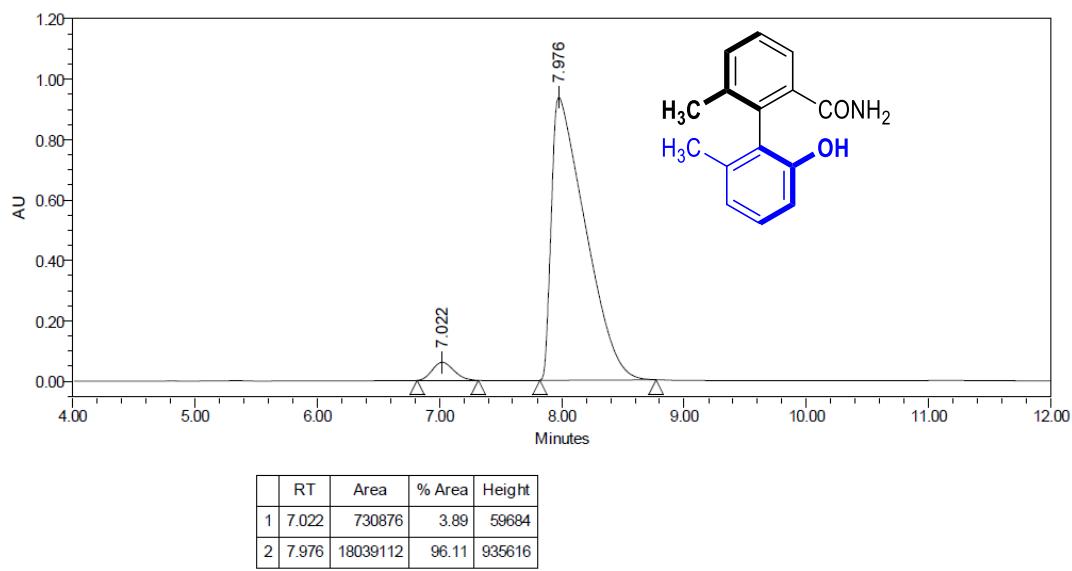
Supplementary Figure 184 ^{13}C NMR (400 MHz, Acetone- d_6) of **9**



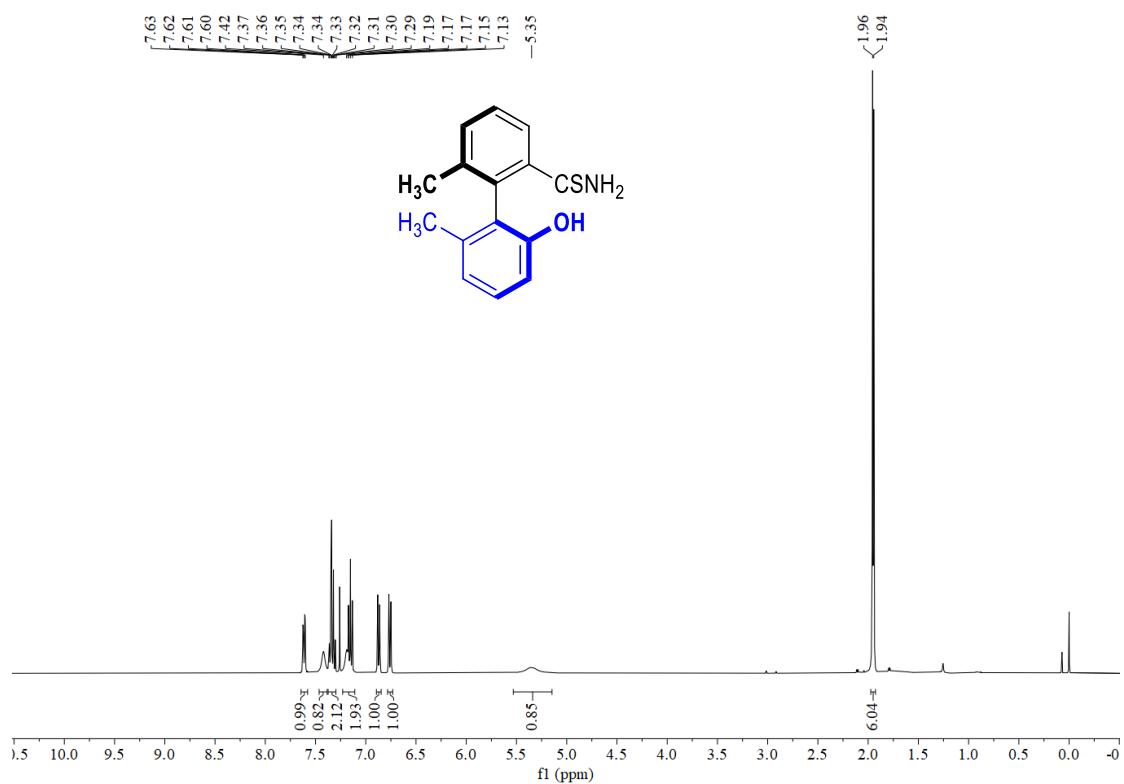
Supplementary Figure 185 HPLC spectra of racemic **9**



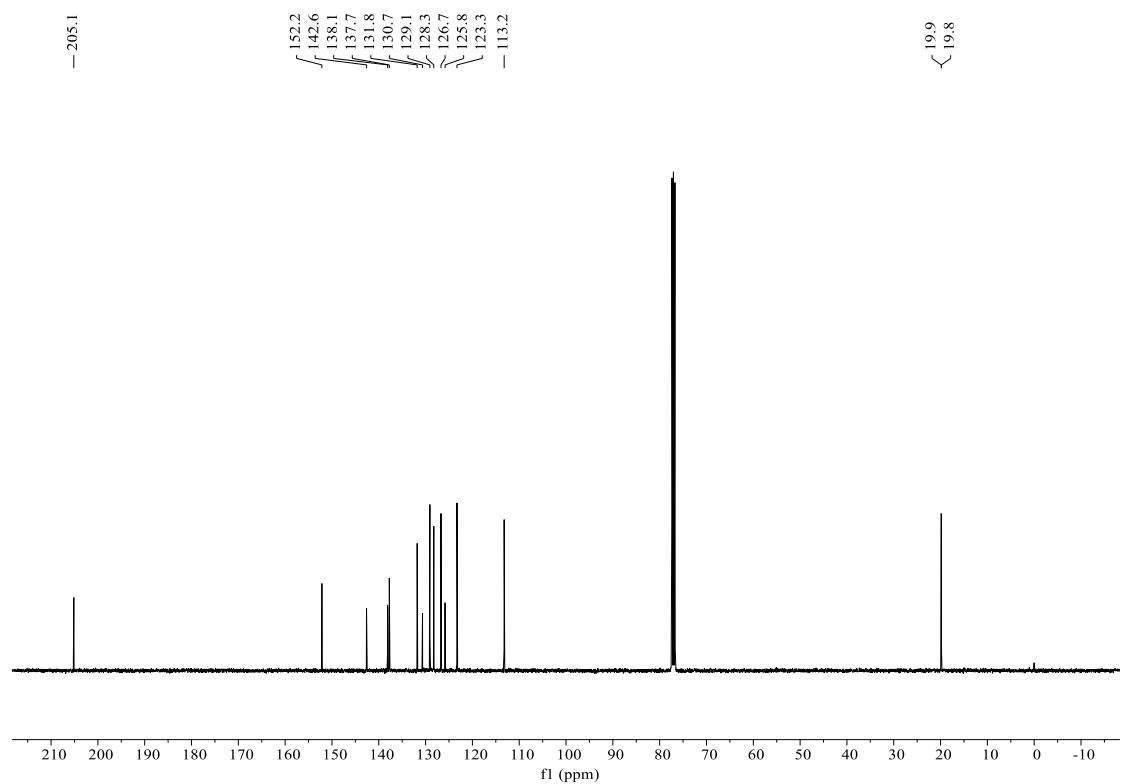
Supplementary Figure 186 HPLC spectra of (*S*)-**9**



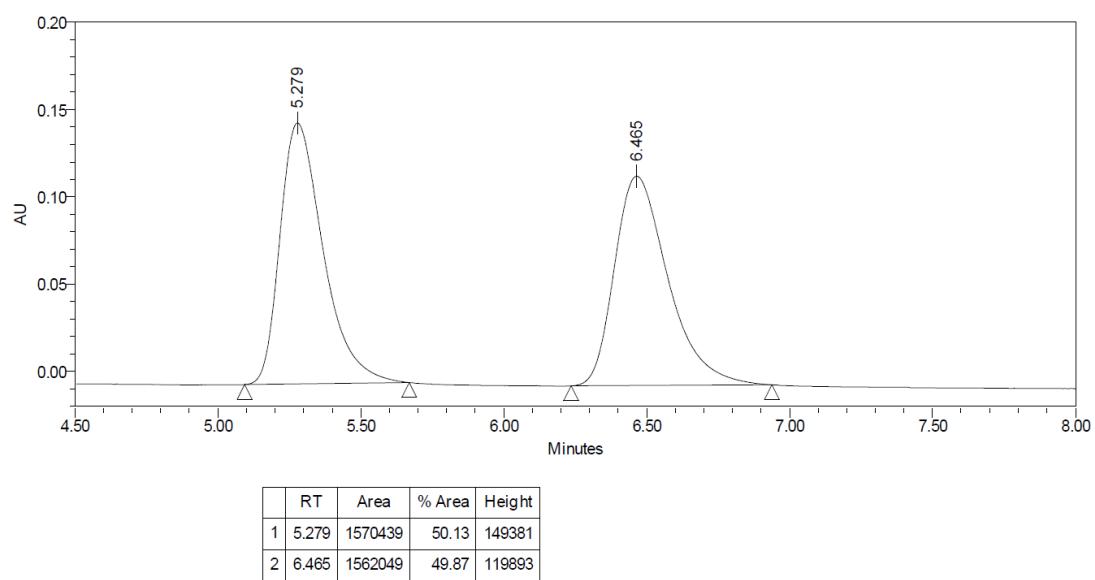
Supplementary Figure 187 ^1H NMR (400 MHz, CDCl_3) of **10**



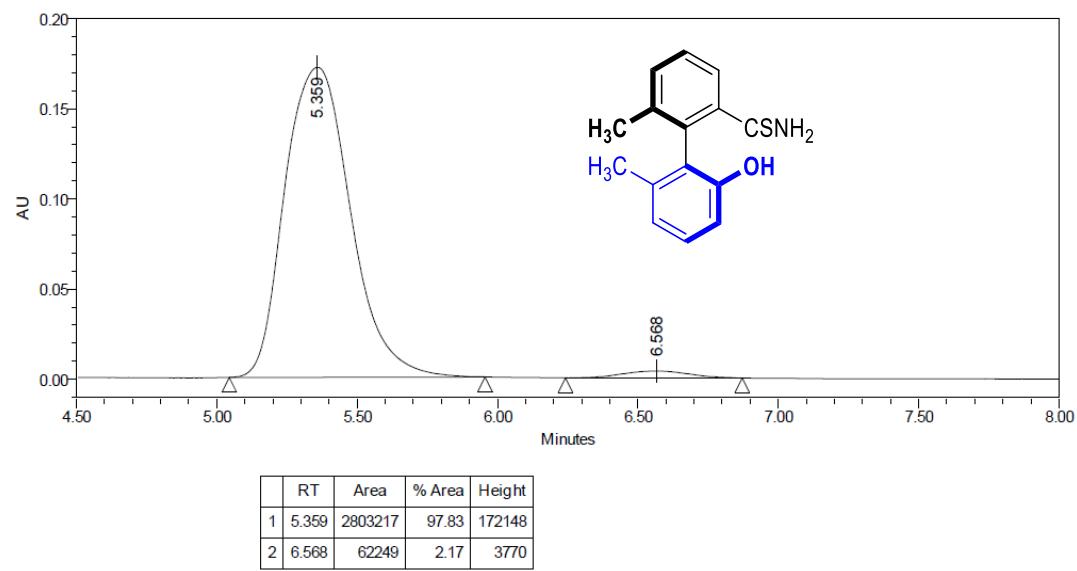
Supplementary Figure 188 ^{13}C NMR (400 MHz, CDCl_3) of **10**



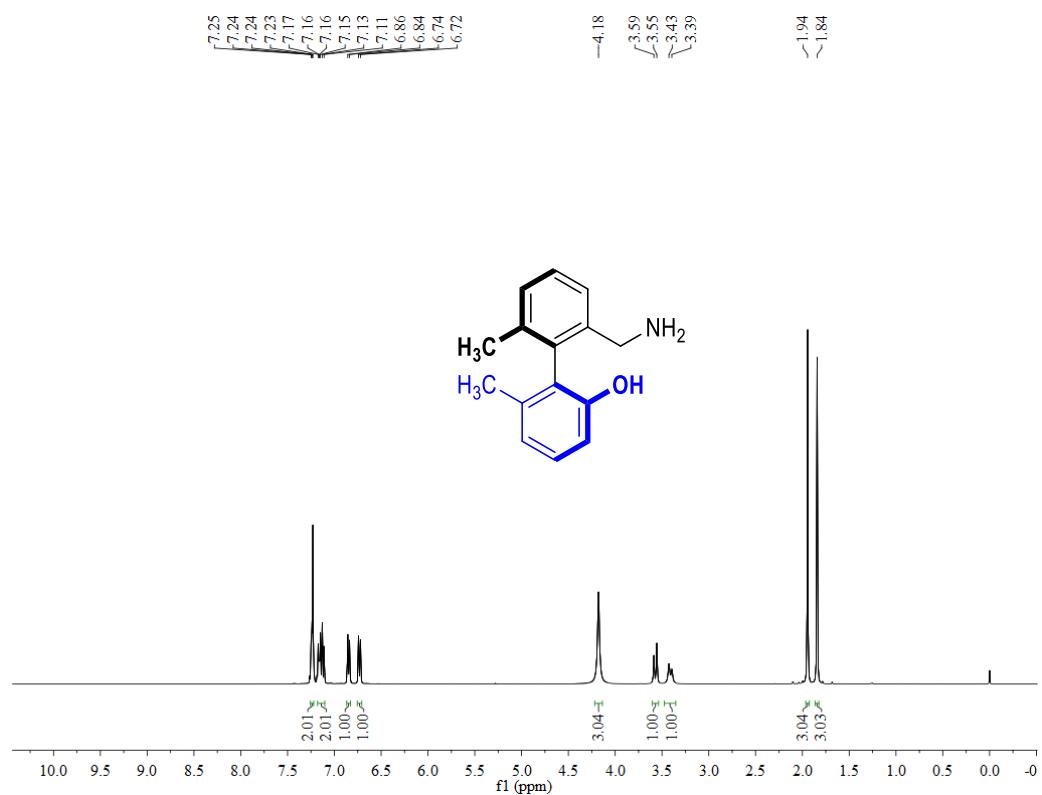
Supplementary Figure 189 HPLC spectra of racemic **10**



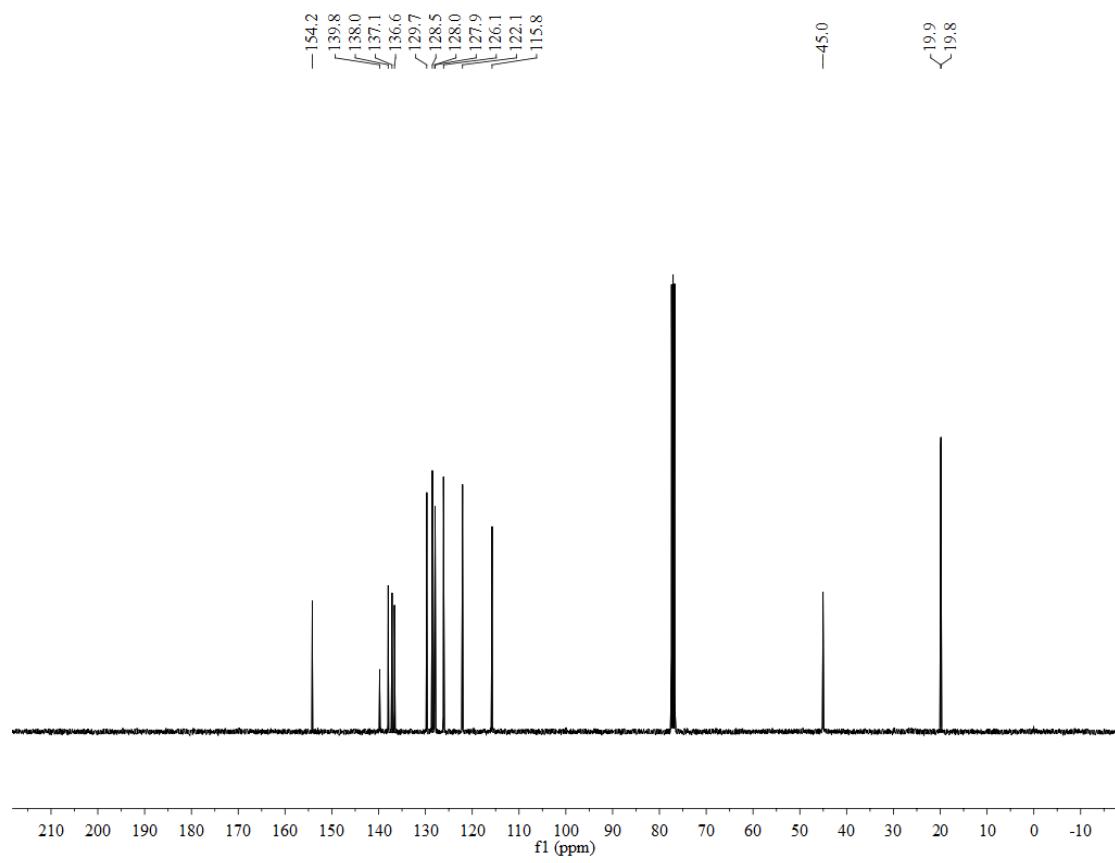
Supplementary Figure 190 HPLC spectra of (*S*)- **10**



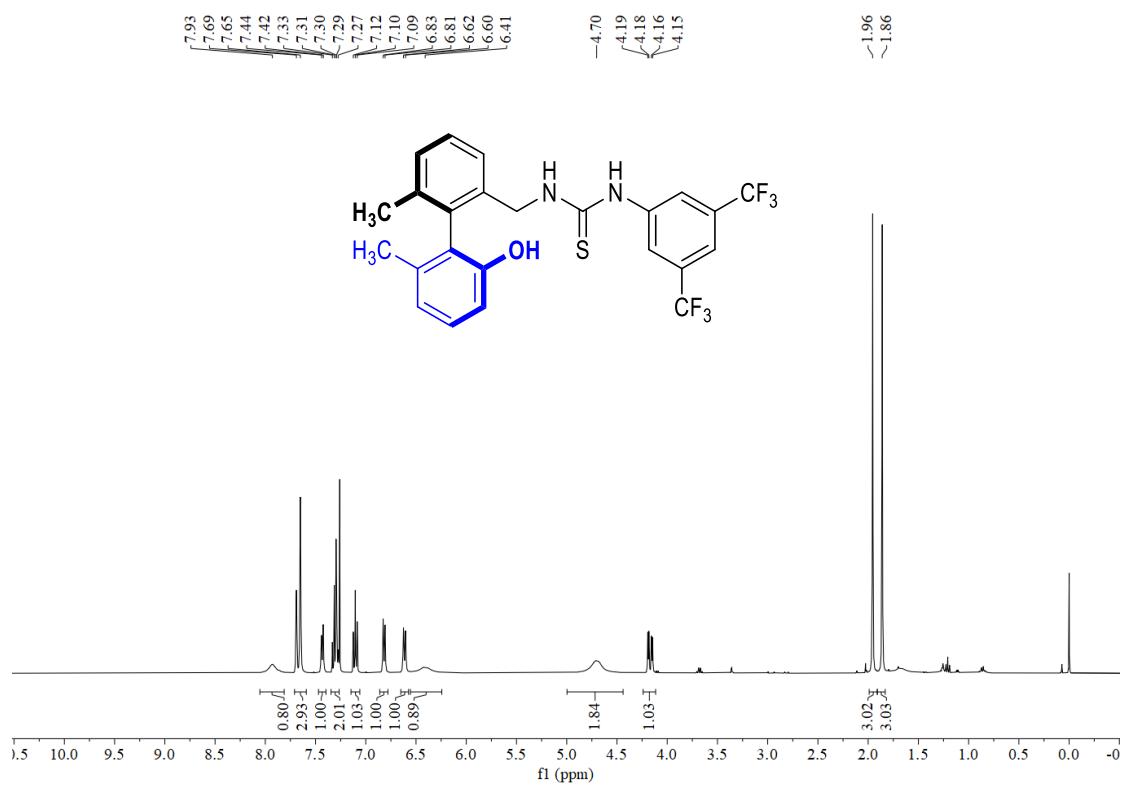
Supplementary Figure 191 ^1H NMR (400 MHz, CDCl_3) of **11**



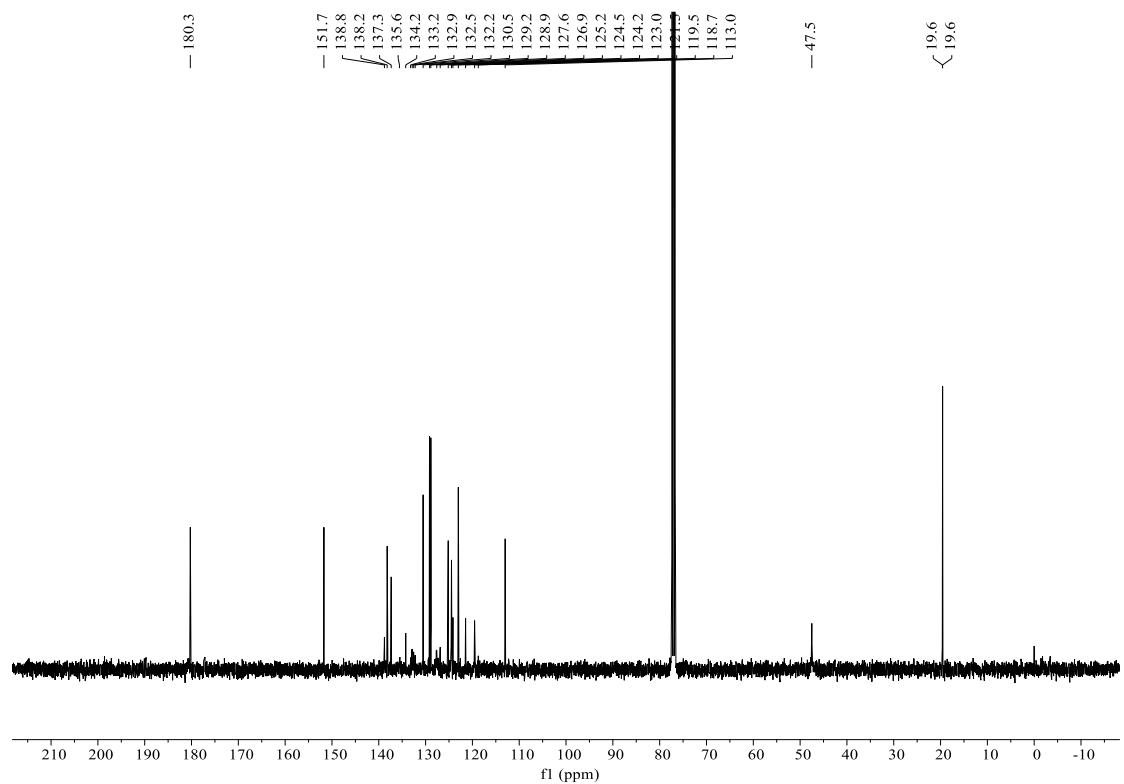
Supplementary Figure 192 ^{13}C NMR (400 MHz, CDCl_3) of **11**



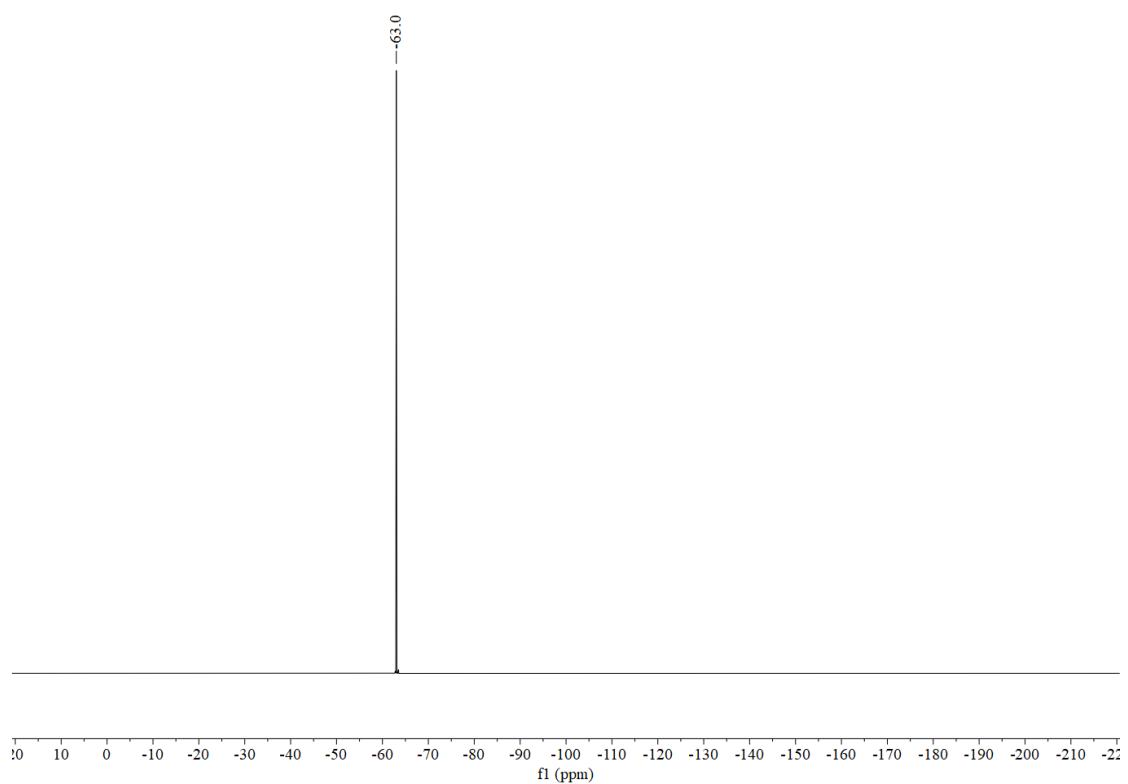
Supplementary Figure 193 ^1H NMR (400 MHz, CDCl_3) of **12**



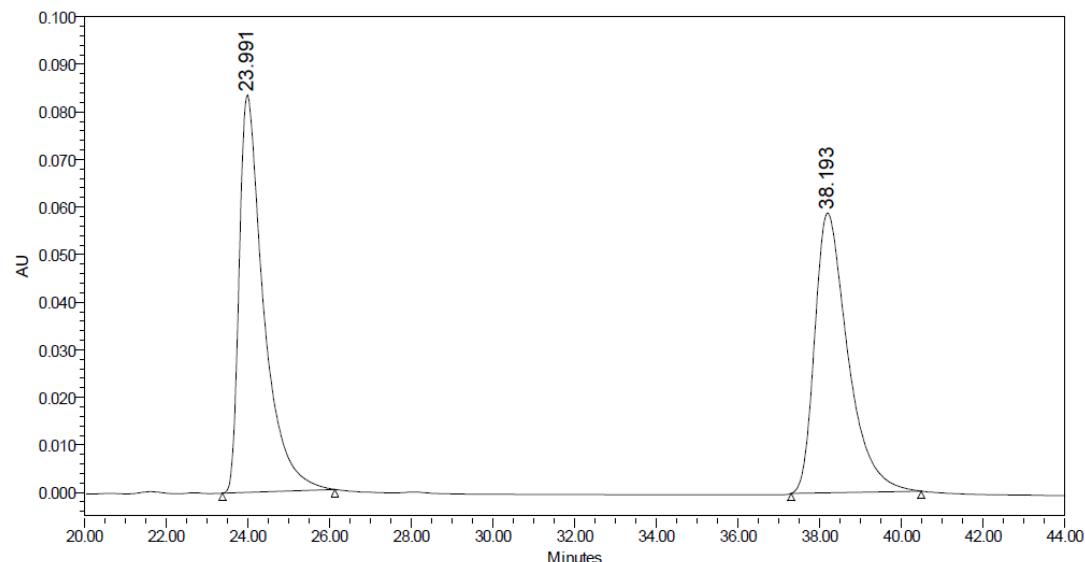
Supplementary Figure 194 ^{13}C NMR (400 MHz, CDCl_3) of **12**



Supplementary Figure 195 ^{19}F NMR (400 MHz, CDCl_3) of **12**

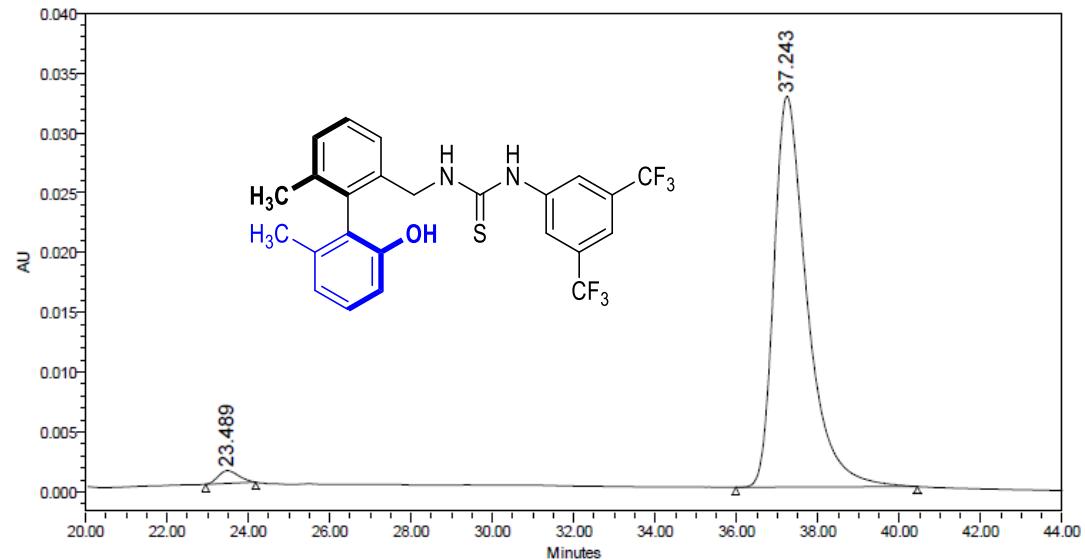


Supplementary Figure 196 HPLC spectra of racemic **12**



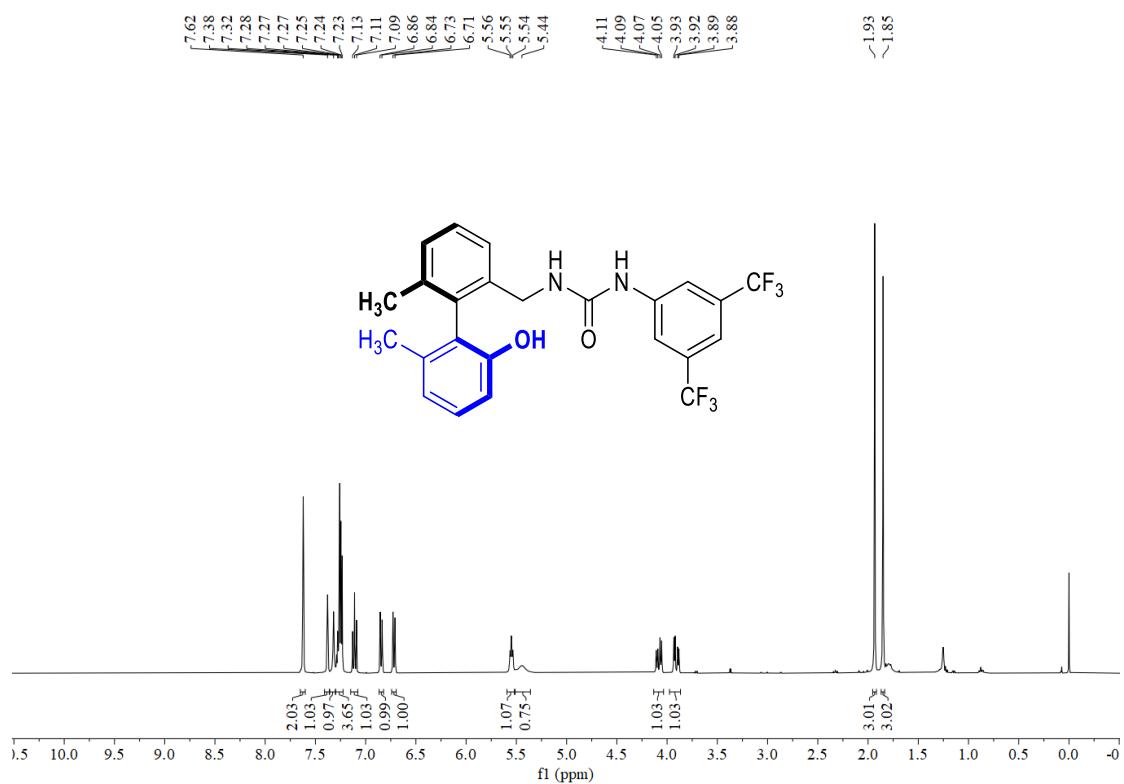
	RT	Area	% Area	Height
1	23.991	3455734	51.08	83473
2	38.193	3309241	48.92	58814

Supplementary Figure 197 HPLC spectra of (*S*)- **12**

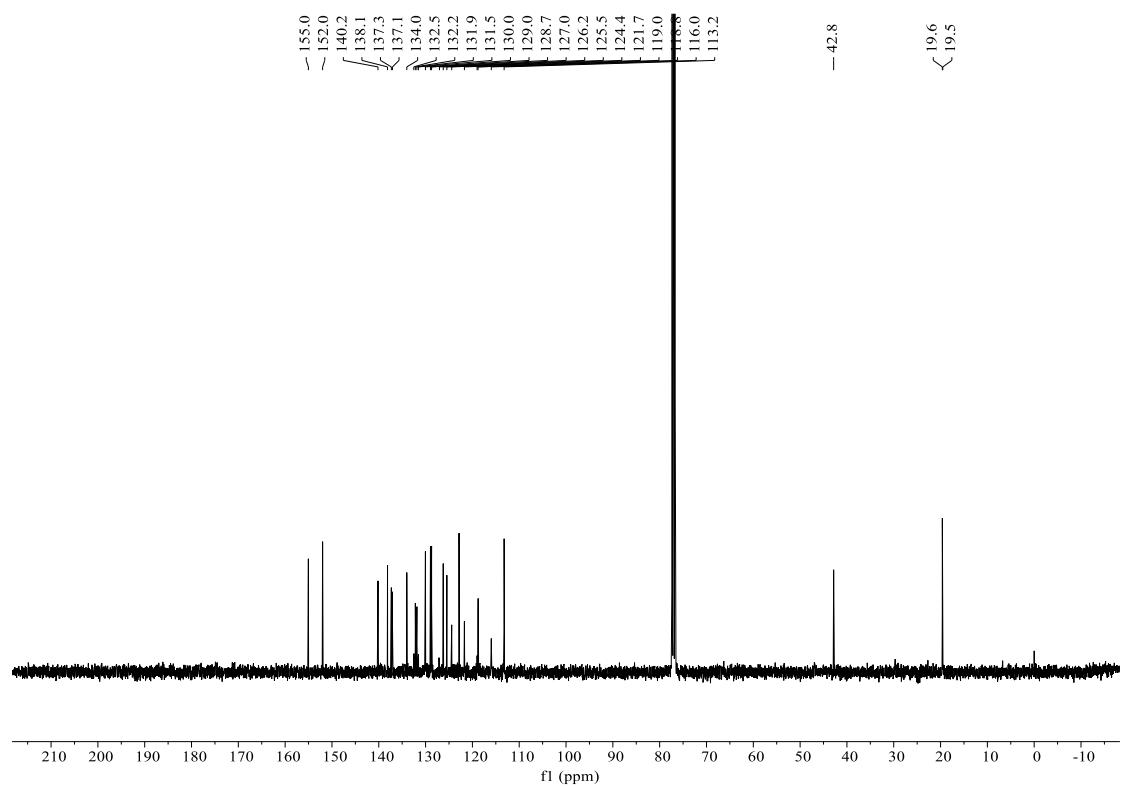


	RT	Area	% Area	Height
1	23.489	37242	1.98	1061
2	37.243	1845287	98.02	32661

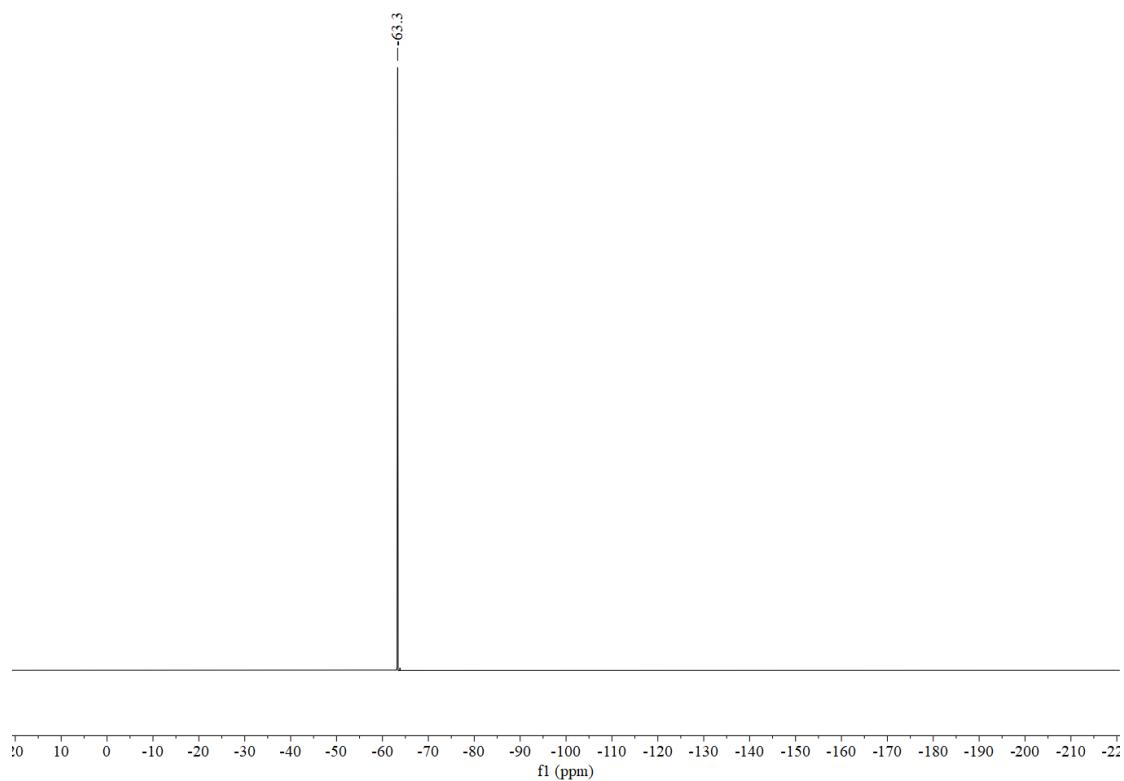
Supplementary Figure 198 ^1H NMR (400 MHz, CDCl_3) of **13**



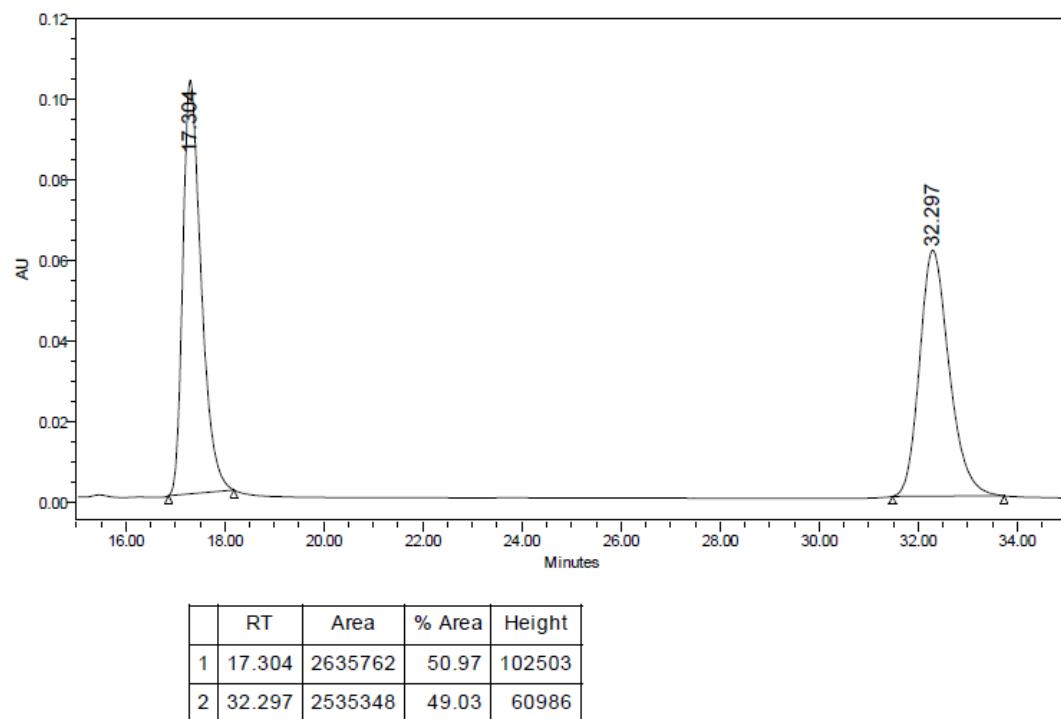
Supplementary Figure 199 ^{13}C NMR (400 MHz, CDCl_3) of **13**



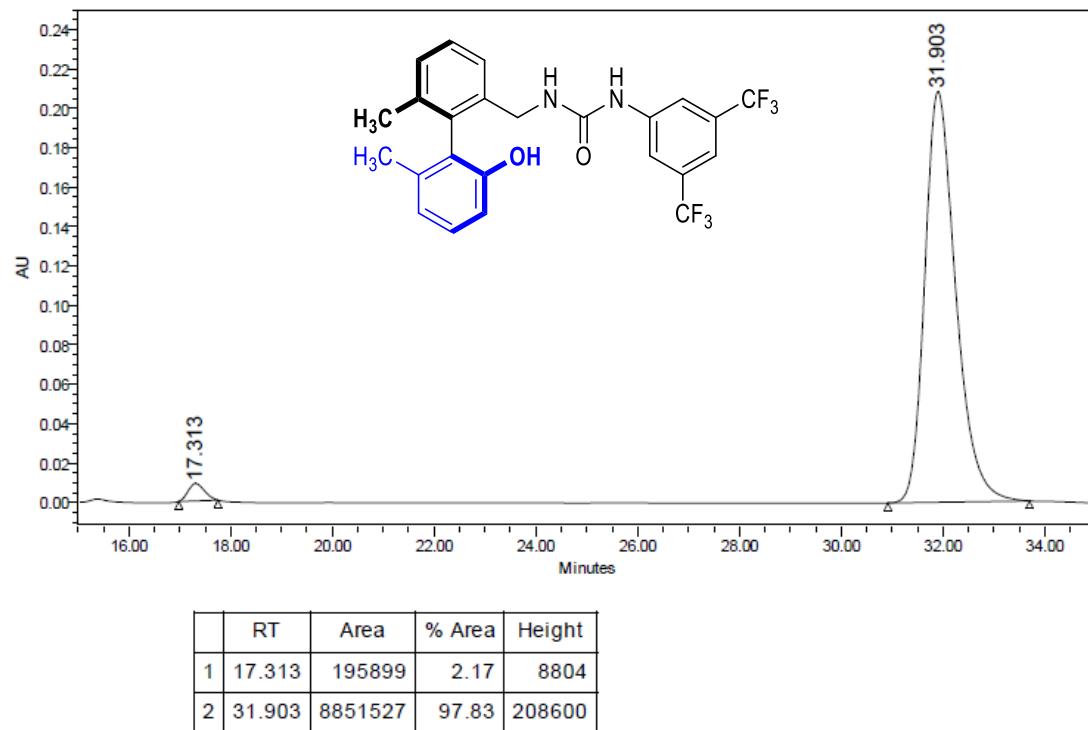
Supplementary Figure 200 ^{19}F NMR (400 MHz, CDCl_3) of **13**



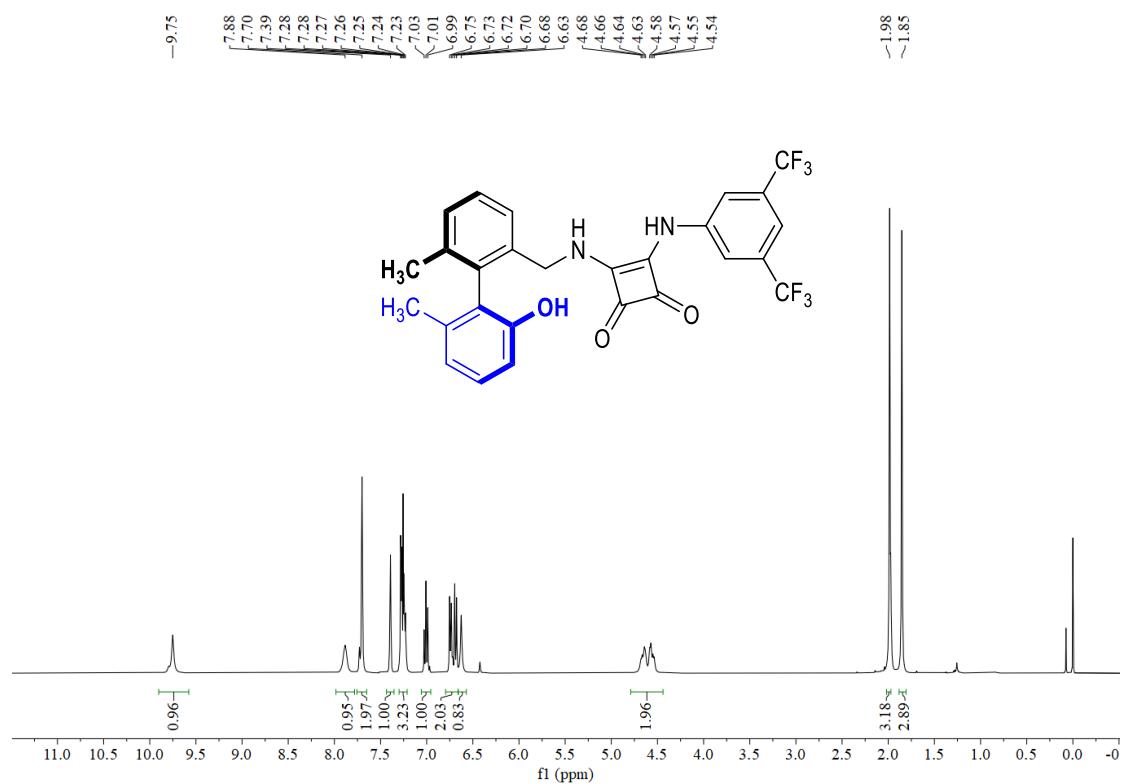
Supplementary Figure 201 HPLC spectra of racemic **13**



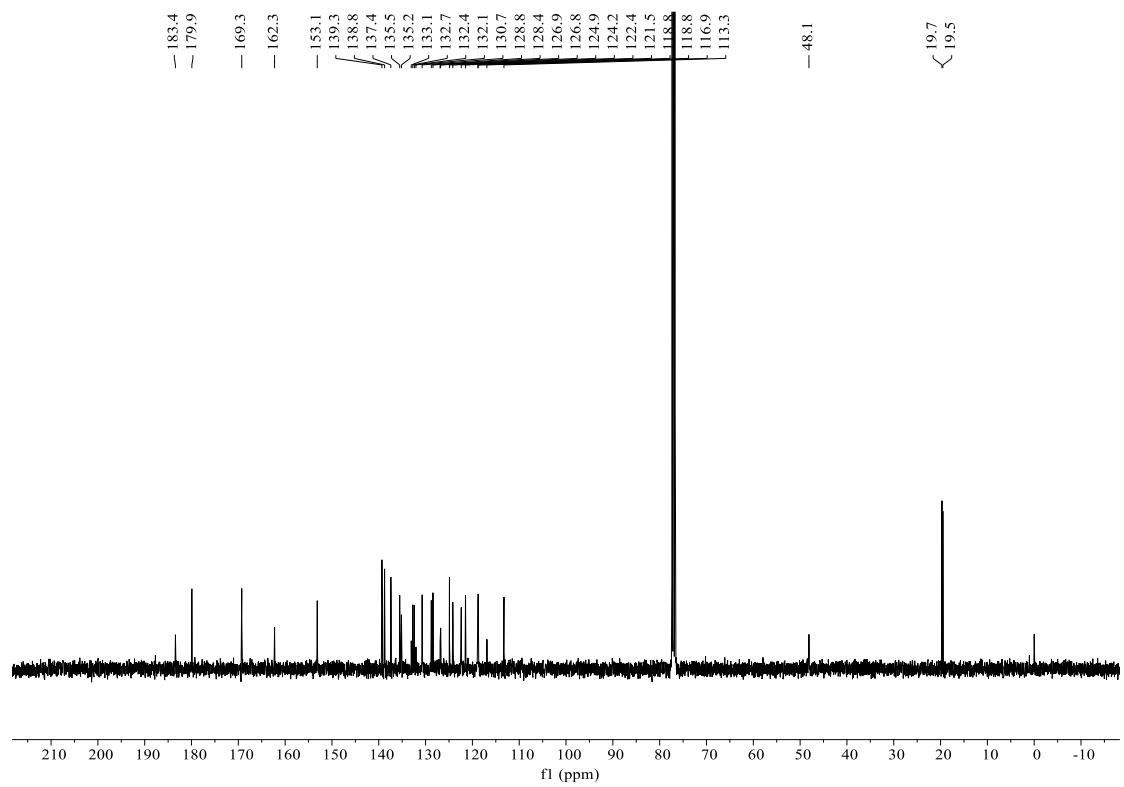
Supplementary Figure 202 HPLC spectra of (*S*)- **13**



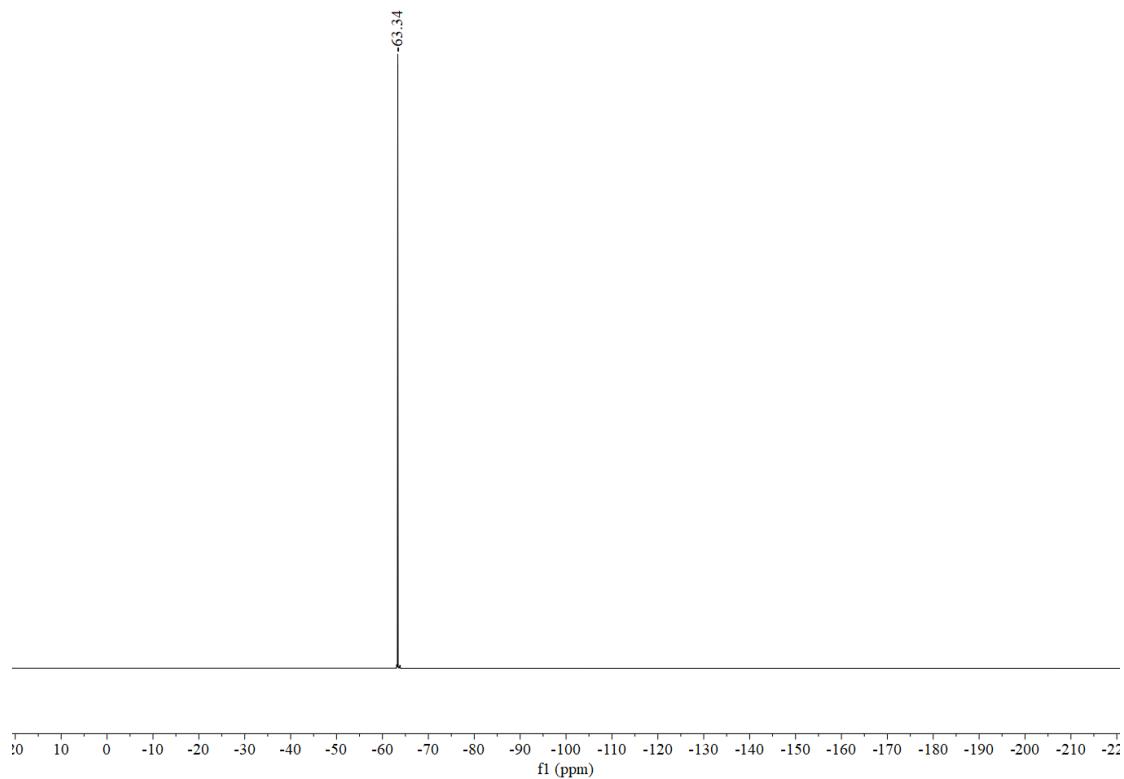
Supplementary Figure 203 ^1H NMR (400 MHz, CDCl_3) of **14**



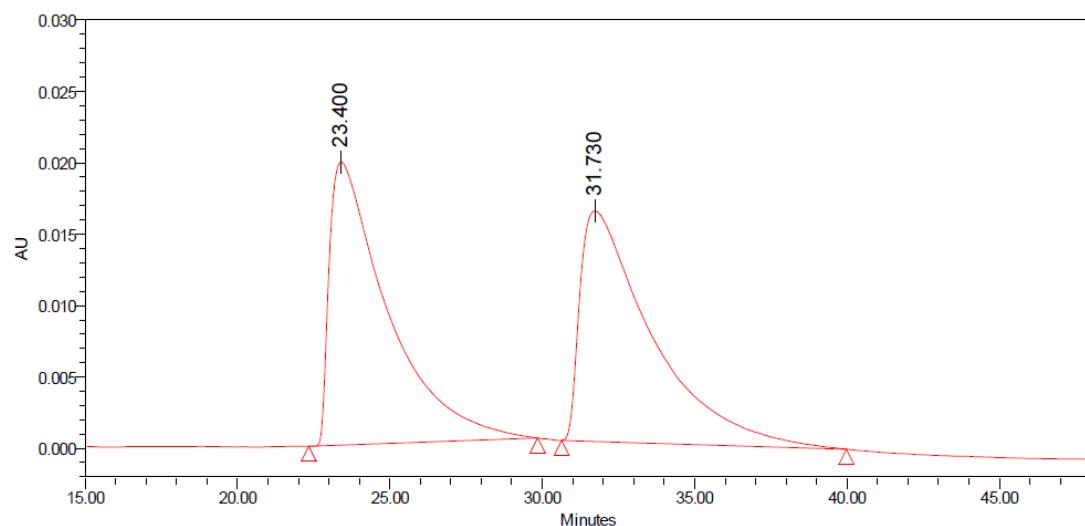
Supplementary Figure 204 ^{13}C NMR (400 MHz, CDCl_3) of **14**



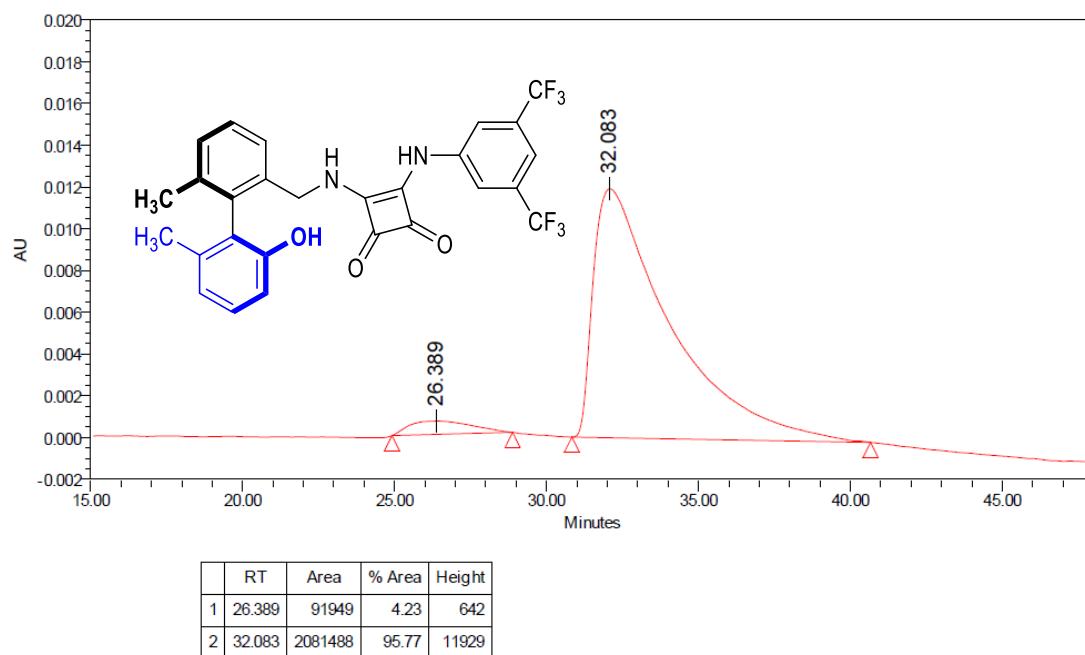
Supplementary Figure 205 ^{19}F NMR (400 MHz, CDCl_3) of **14**



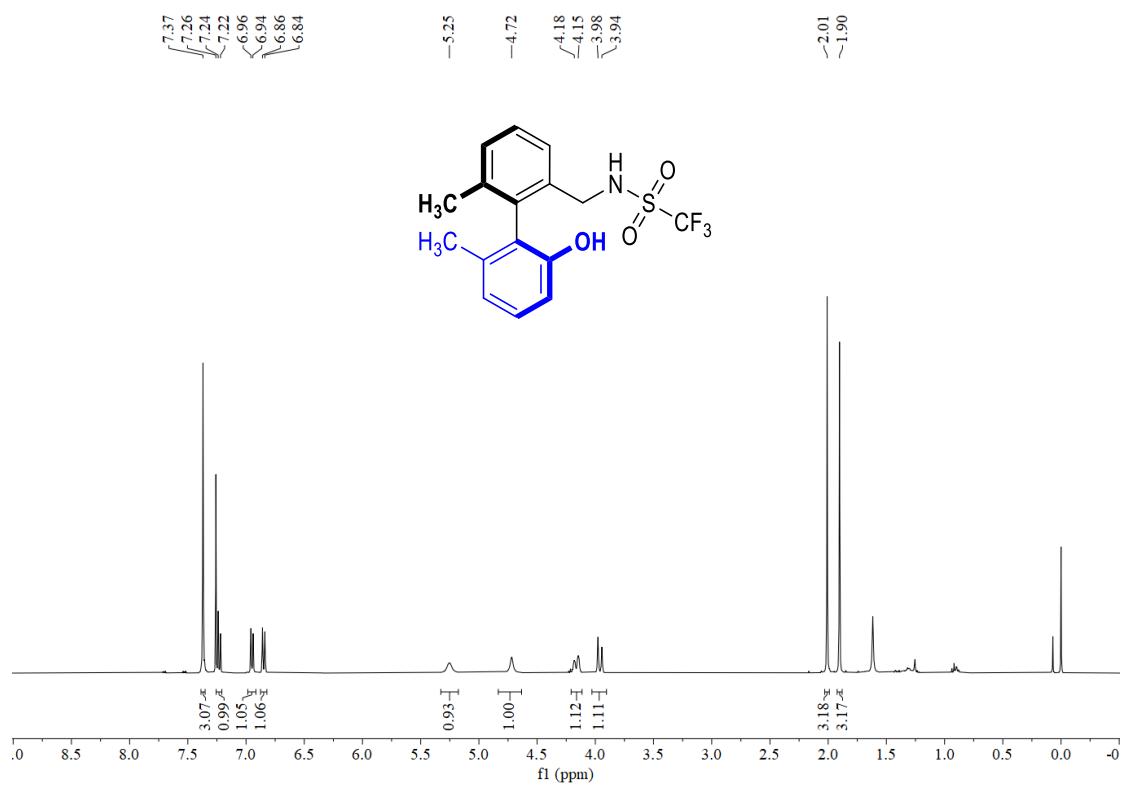
Supplementary Figure 206 HPLC spectra of racemic **14**



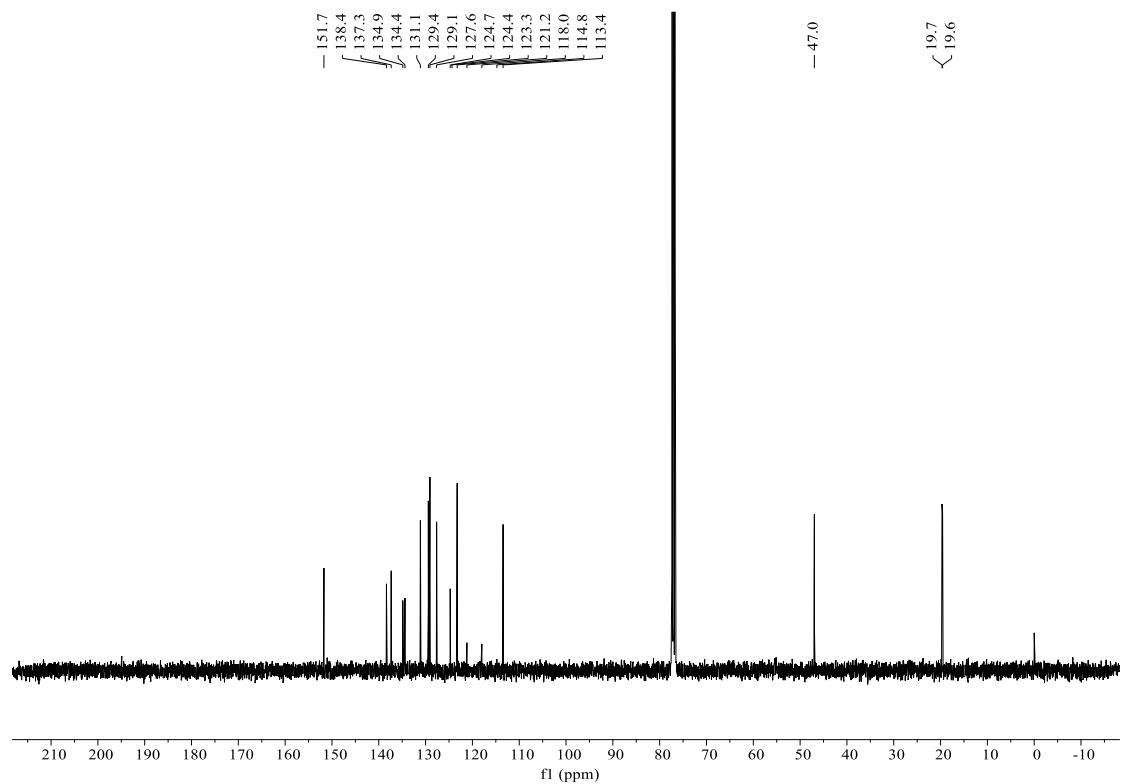
Supplementary Figure 207 HPLC spectra of (*S*)- **14**



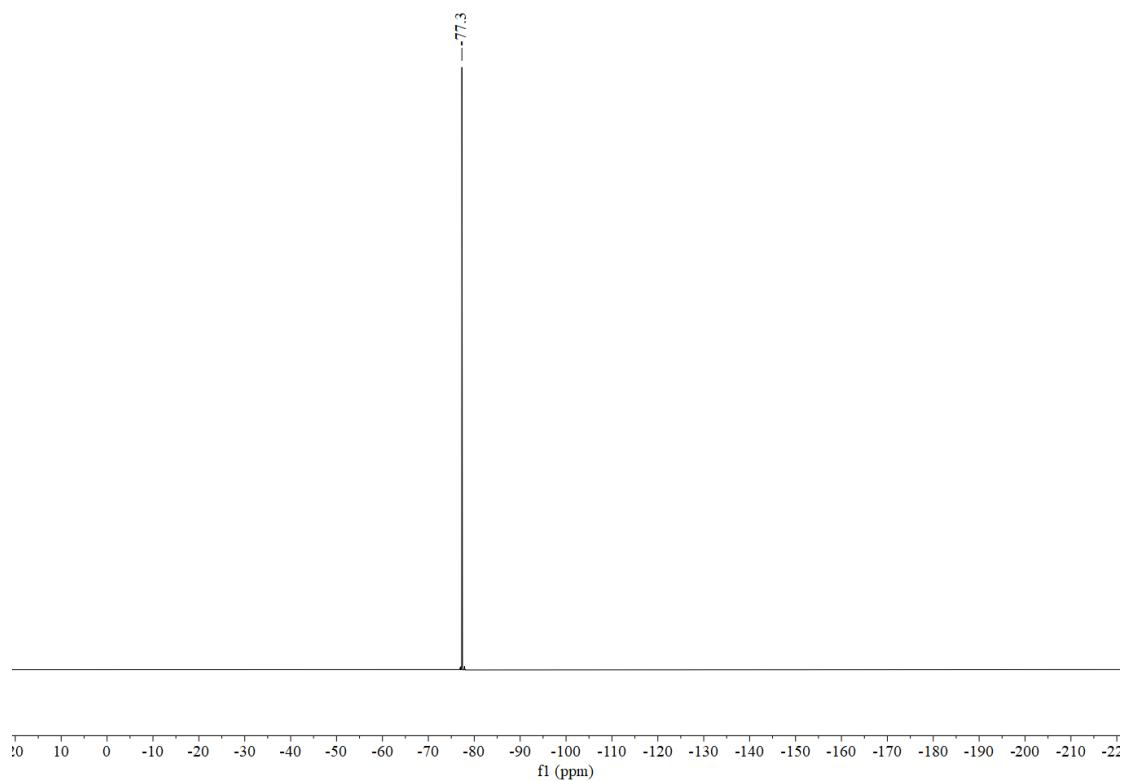
Supplementary Figure 208 ^1H NMR (400 MHz, CDCl_3) of **15**



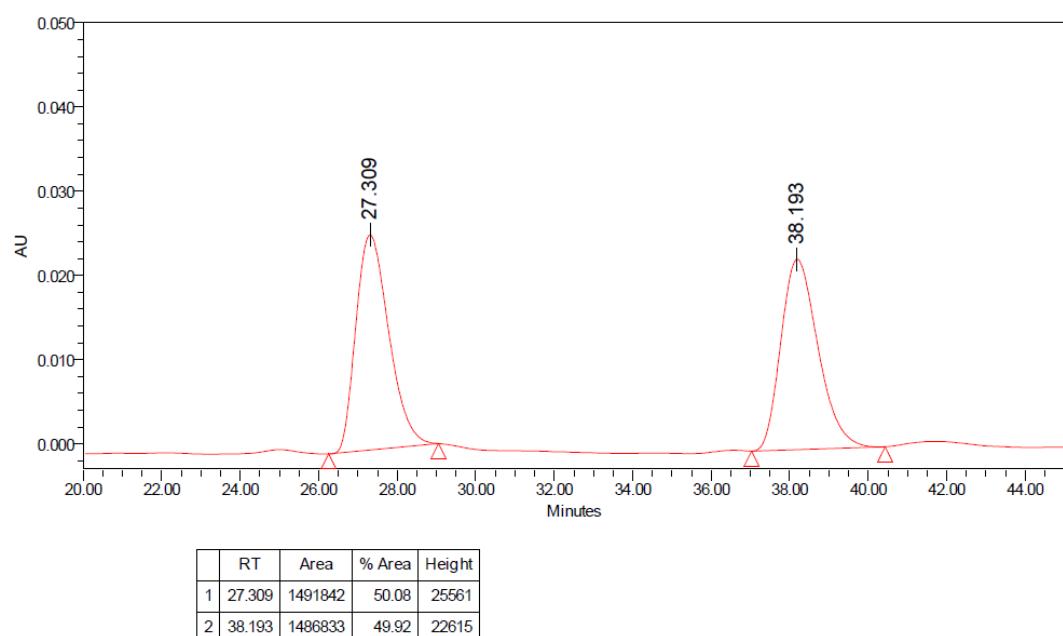
Supplementary Figure 209 ^{13}C NMR (400 MHz, CDCl_3) of **15**



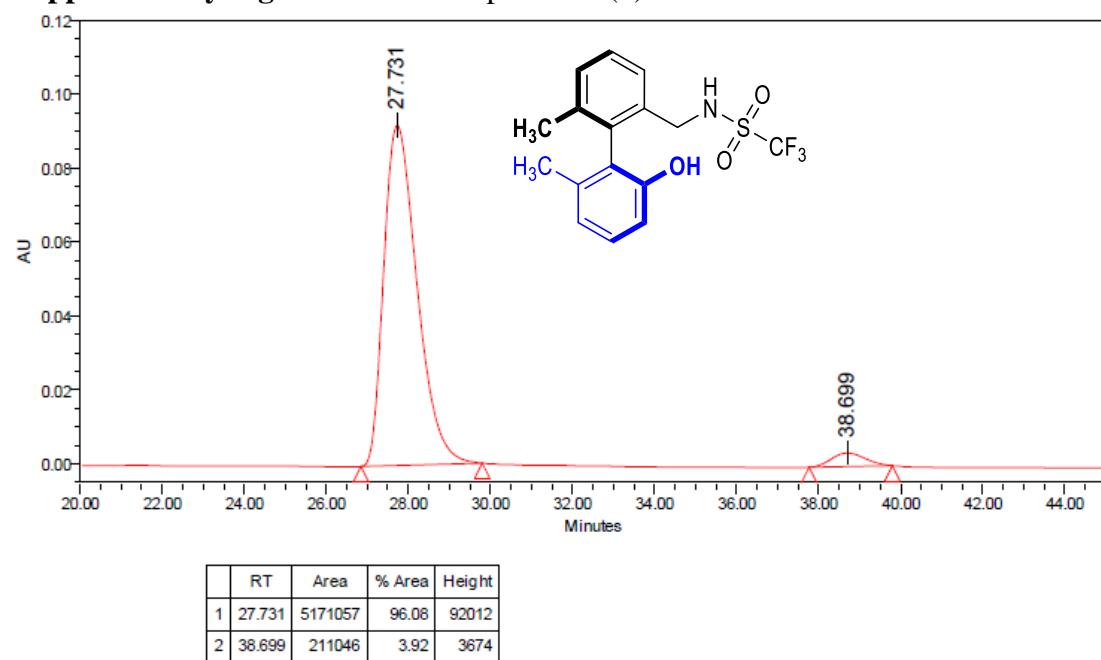
Supplementary Figure 210 ^{19}F NMR (400 MHz, CDCl_3) of **15**



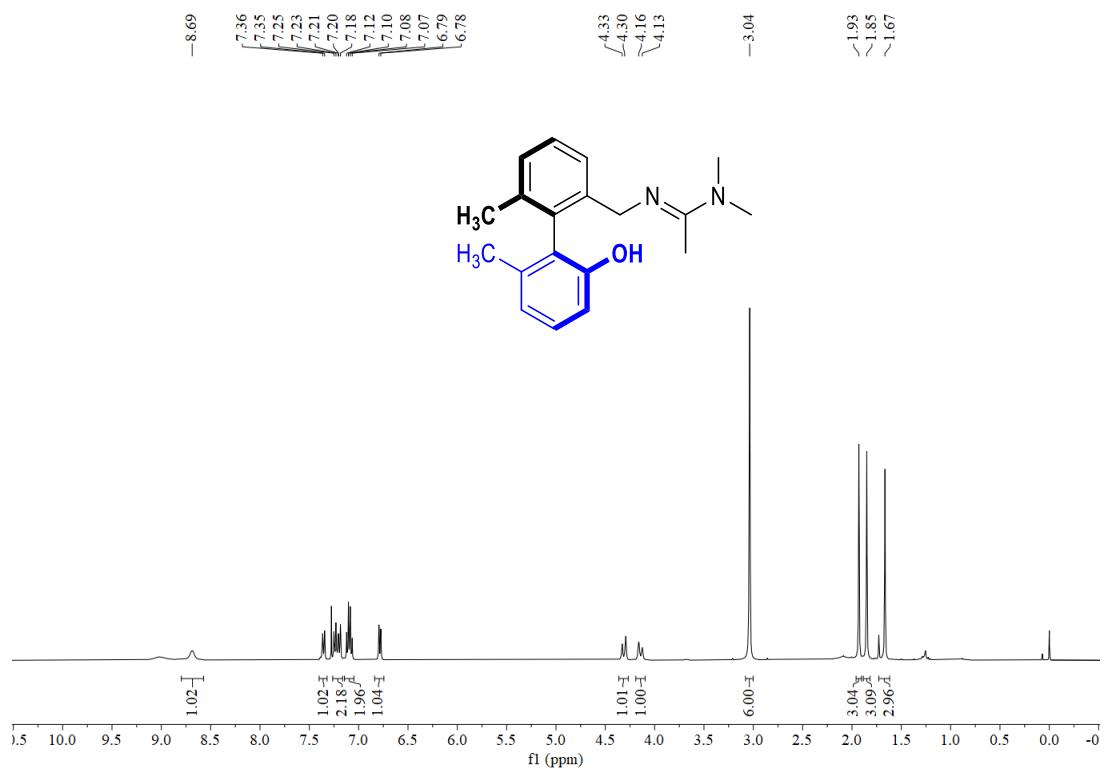
Supplementary Figure 211 HPLC spectra of racemic **15**



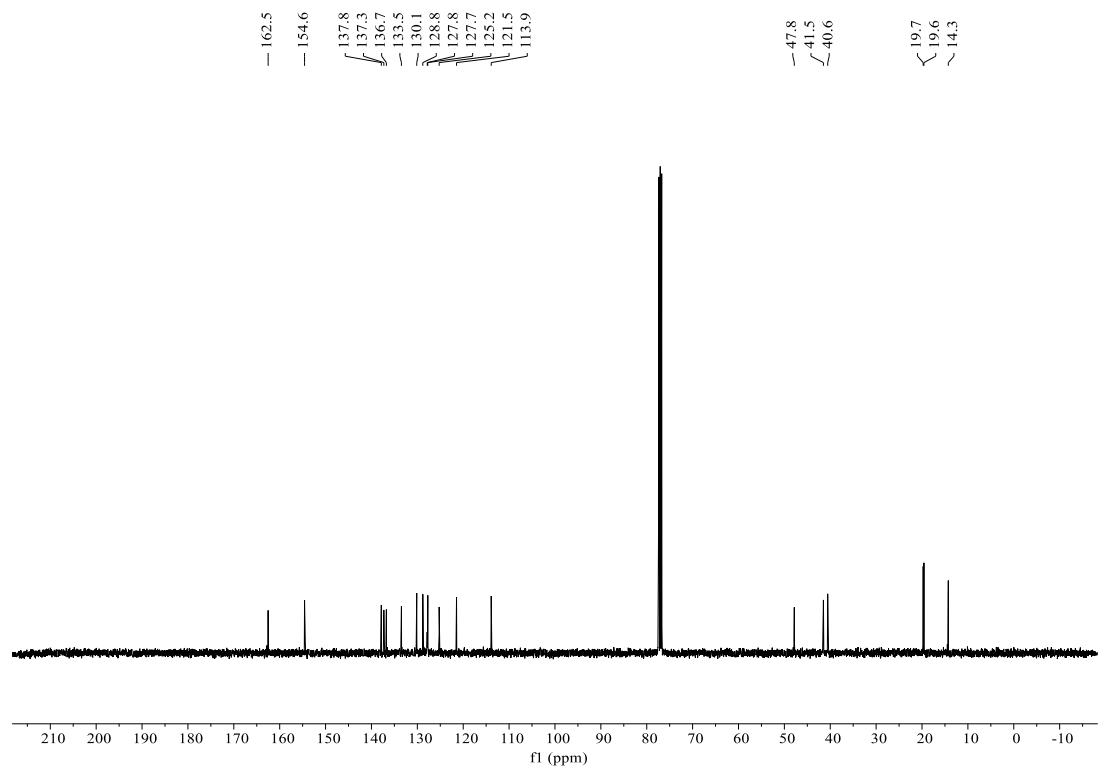
Supplementary Figure 212 HPLC spectra of (*S*)- **15**



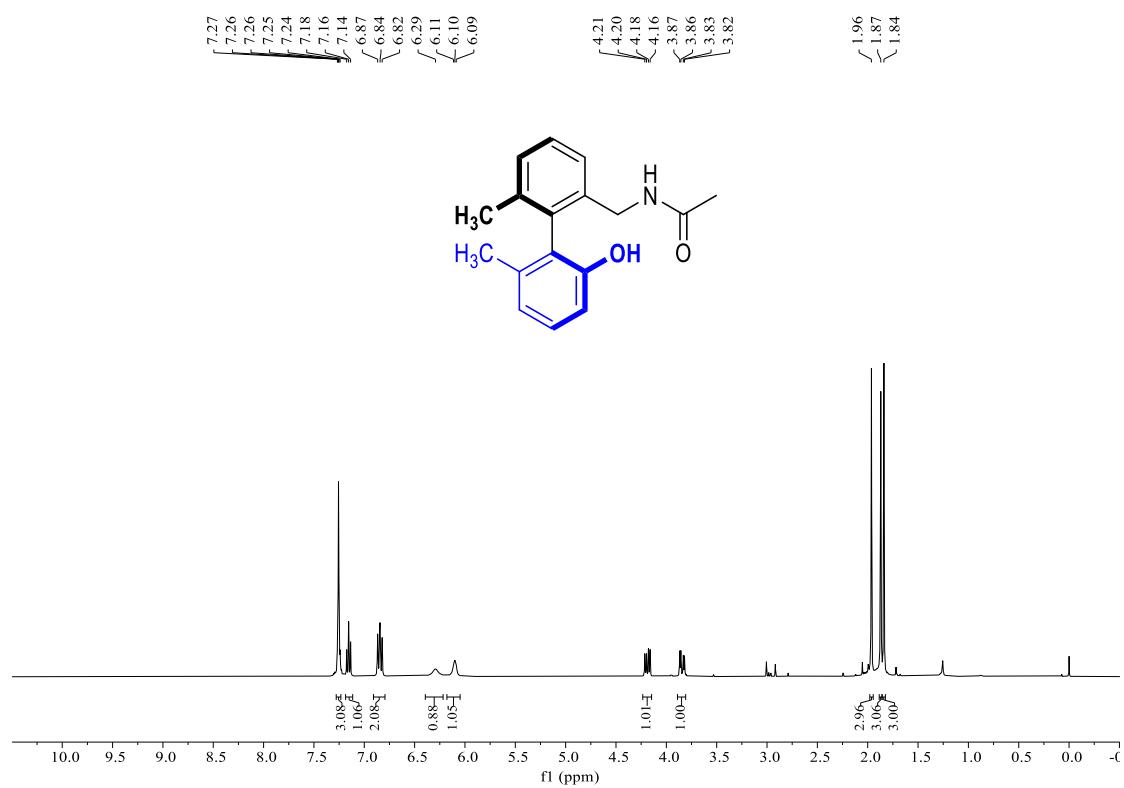
Supplementary Figure 213 ^1H NMR (400 MHz, CDCl_3) of **16**



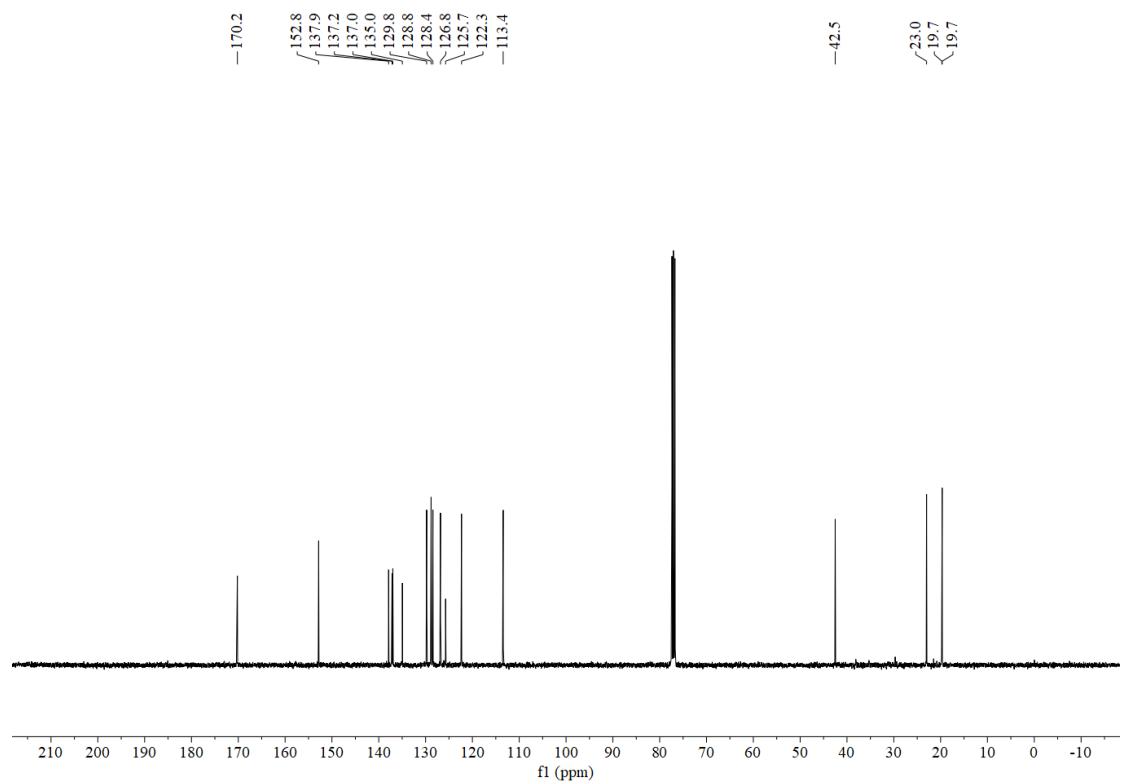
Supplementary Figure 214 ^{13}C NMR (400 MHz, CDCl_3) of **16**



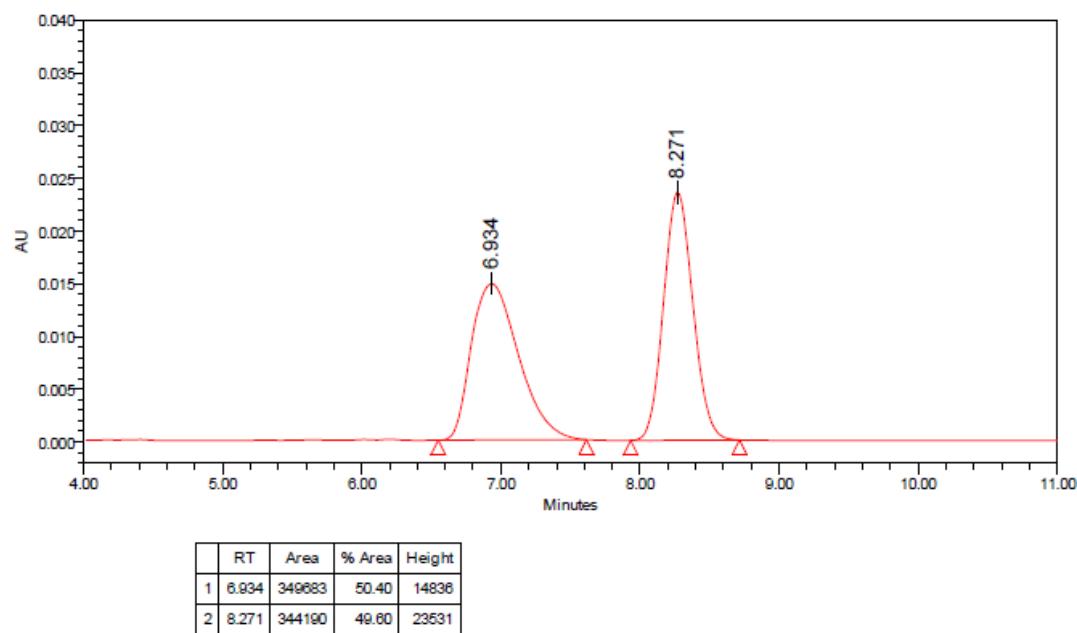
Supplementary Figure 215 ^1H NMR (400 MHz, CDCl_3) of **17**



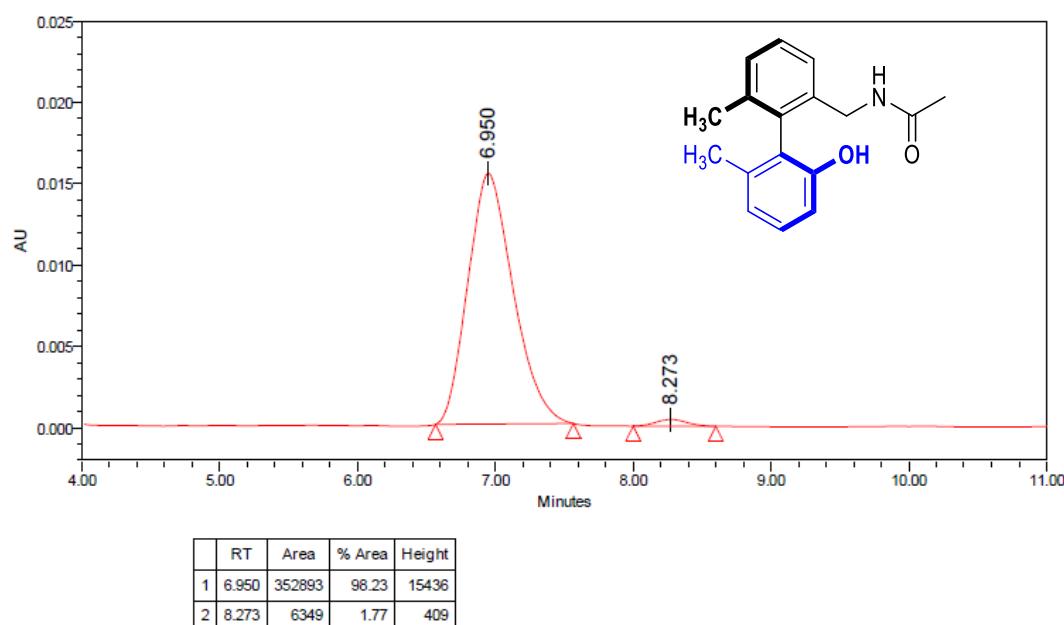
Supplementary Figure 216 ^{13}C NMR (400 MHz, CDCl_3) of **17**



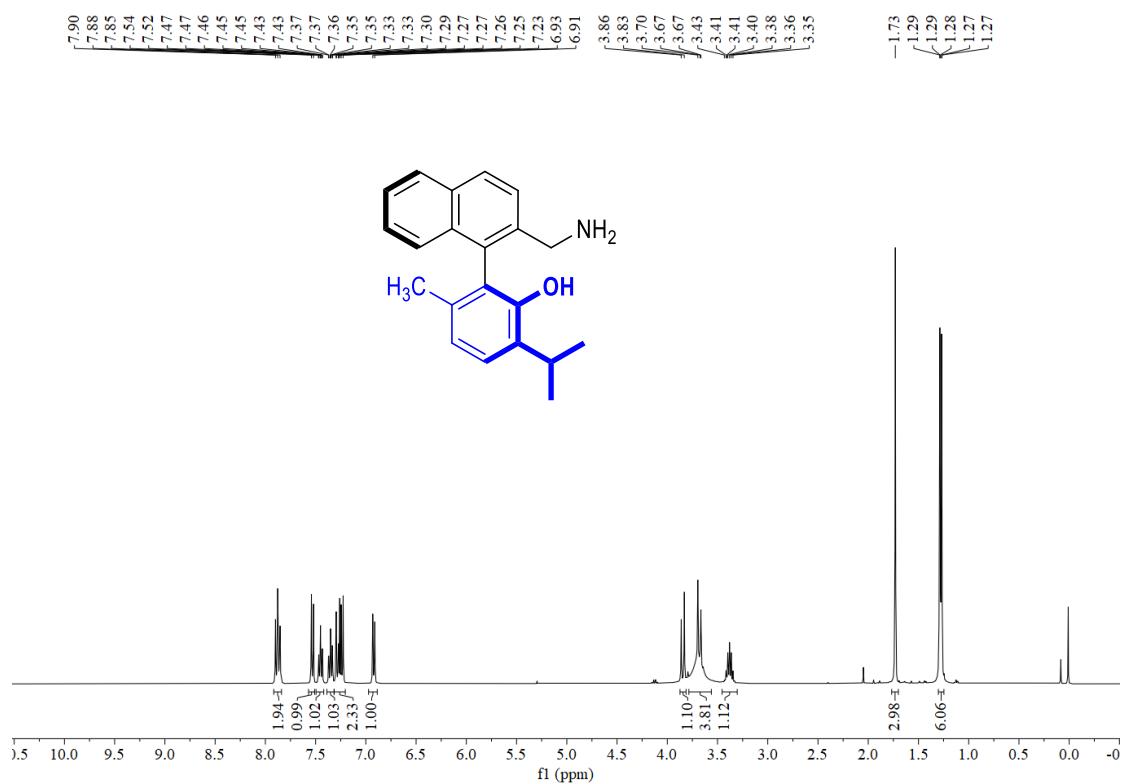
Supplementary Figure 217 HPLC spectra of racemic **17**



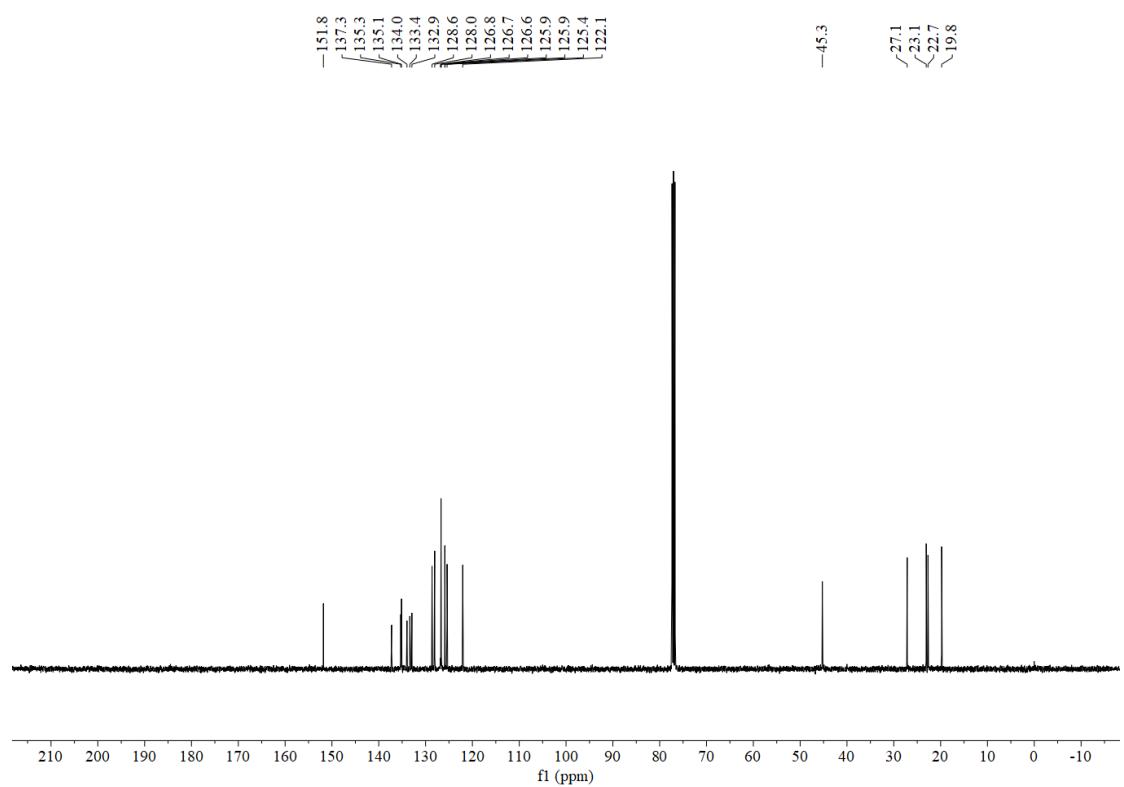
Supplementary Figure 218 HPLC spectra of (*S*)- **17**



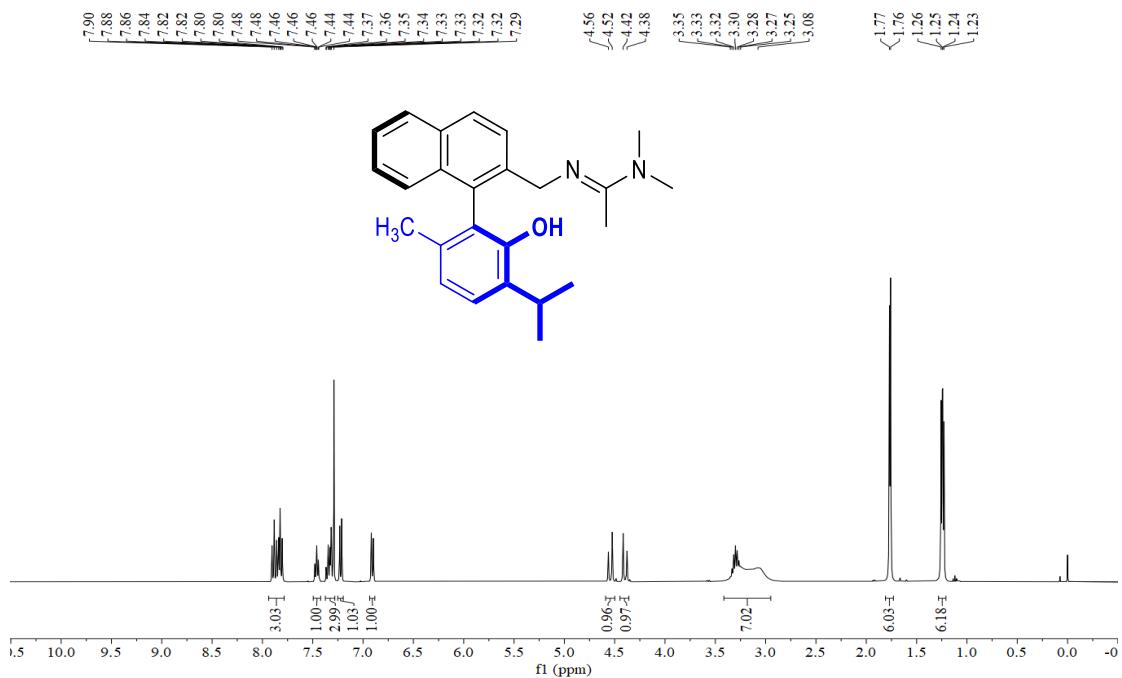
Supplementary Figure 219 ^1H NMR (400 MHz, CDCl_3) of **18**



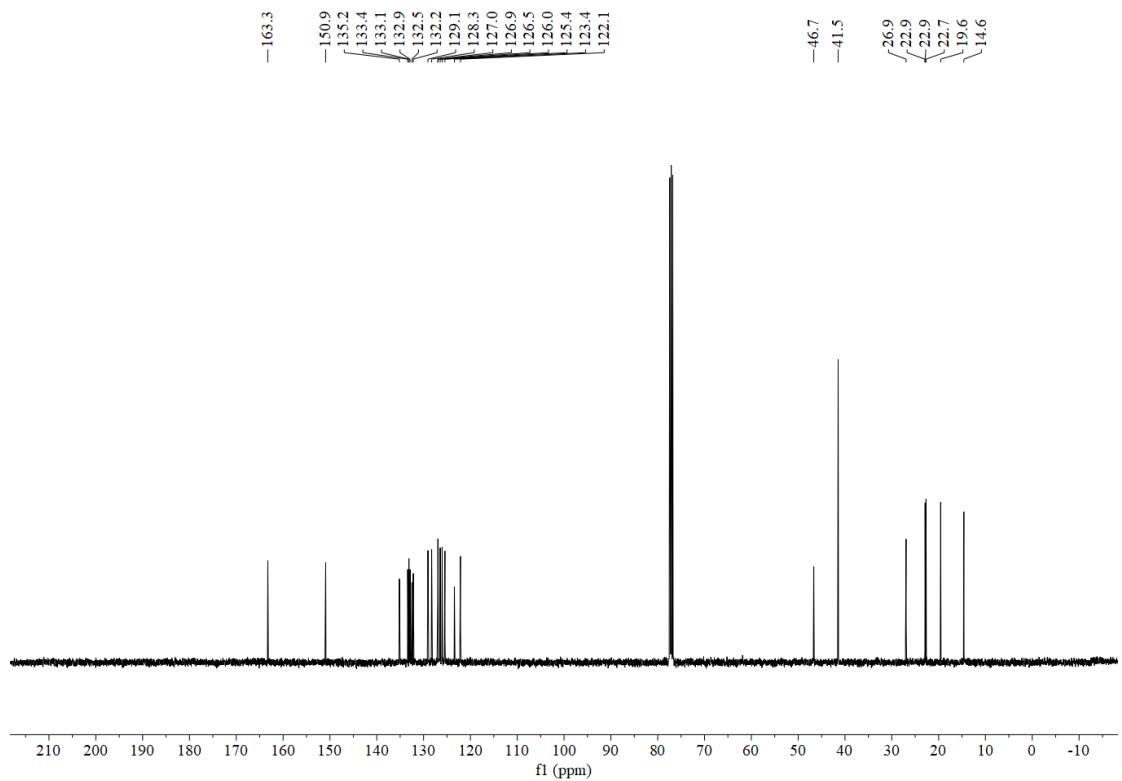
Supplementary Figure 220 ^{13}C NMR (400 MHz, CDCl_3) of **18**



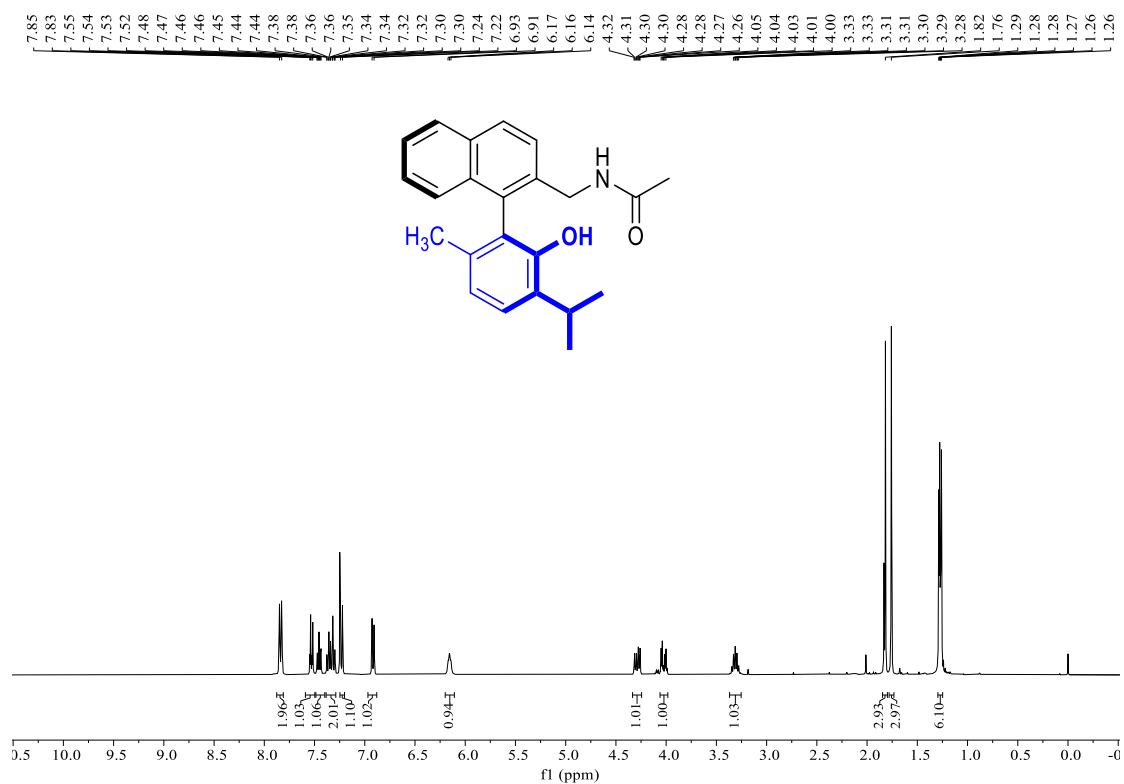
Supplementary Figure 221 ^1H NMR (400 MHz, CDCl_3) of **19**



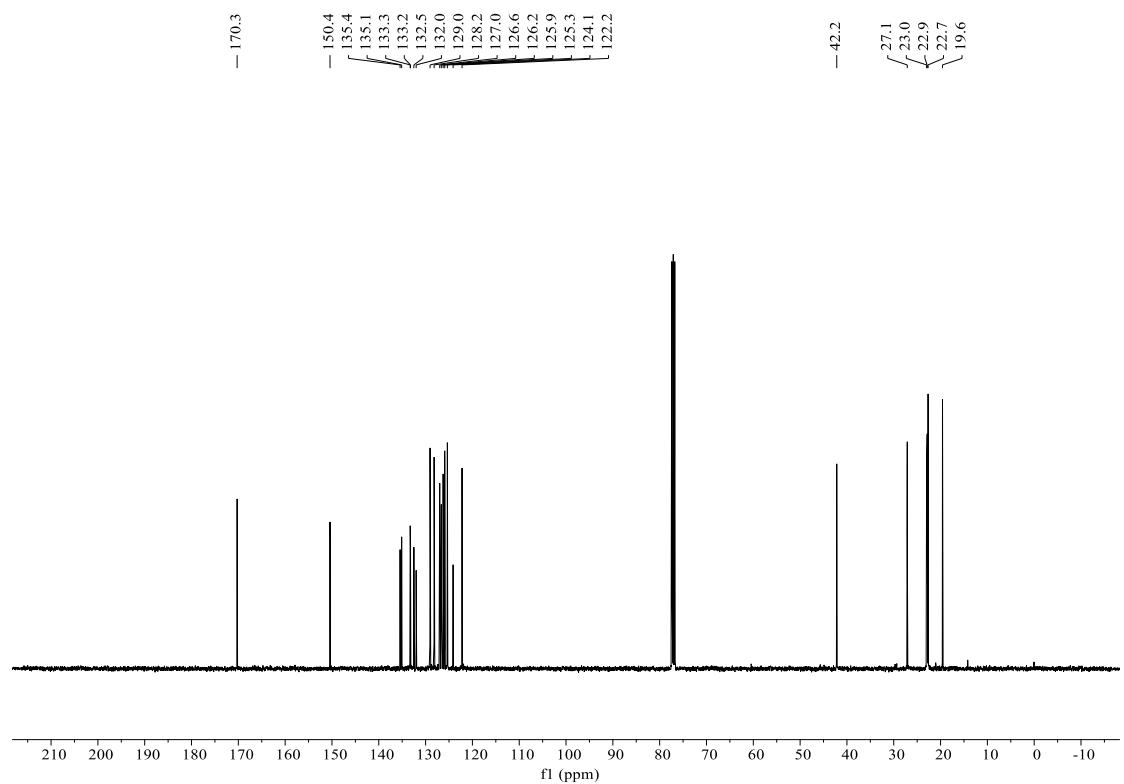
Supplementary Figure 222 ^{13}C NMR (400 MHz, CDCl_3) of **19**



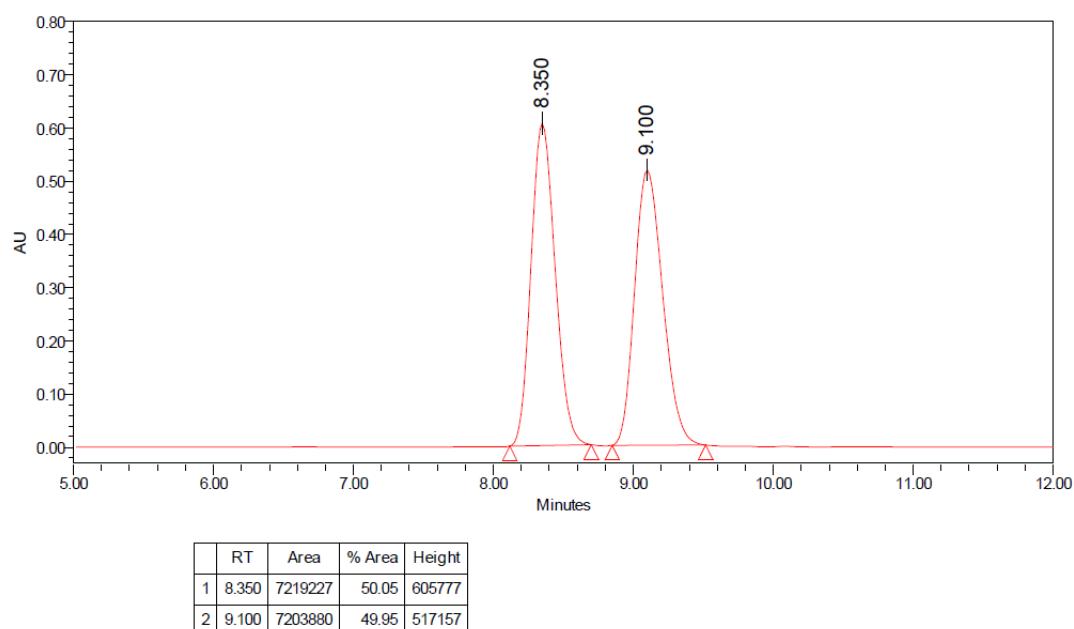
Supplementary Figure 223 ^1H NMR (400 MHz, CDCl_3) of **20**



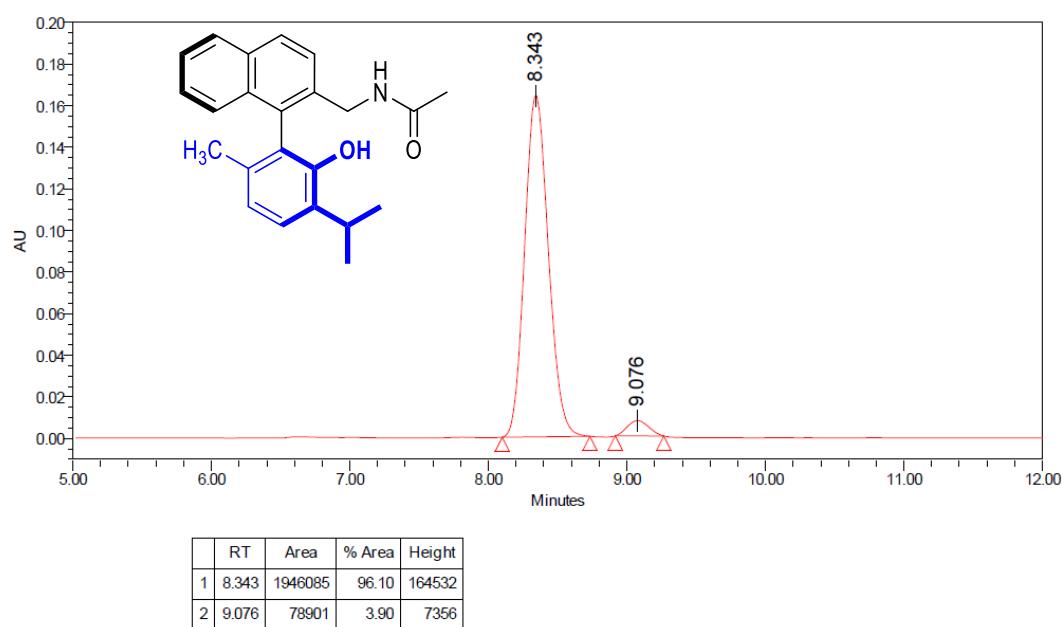
Supplementary Figure 224 ^{13}C NMR (400 MHz, CDCl_3) of **20**



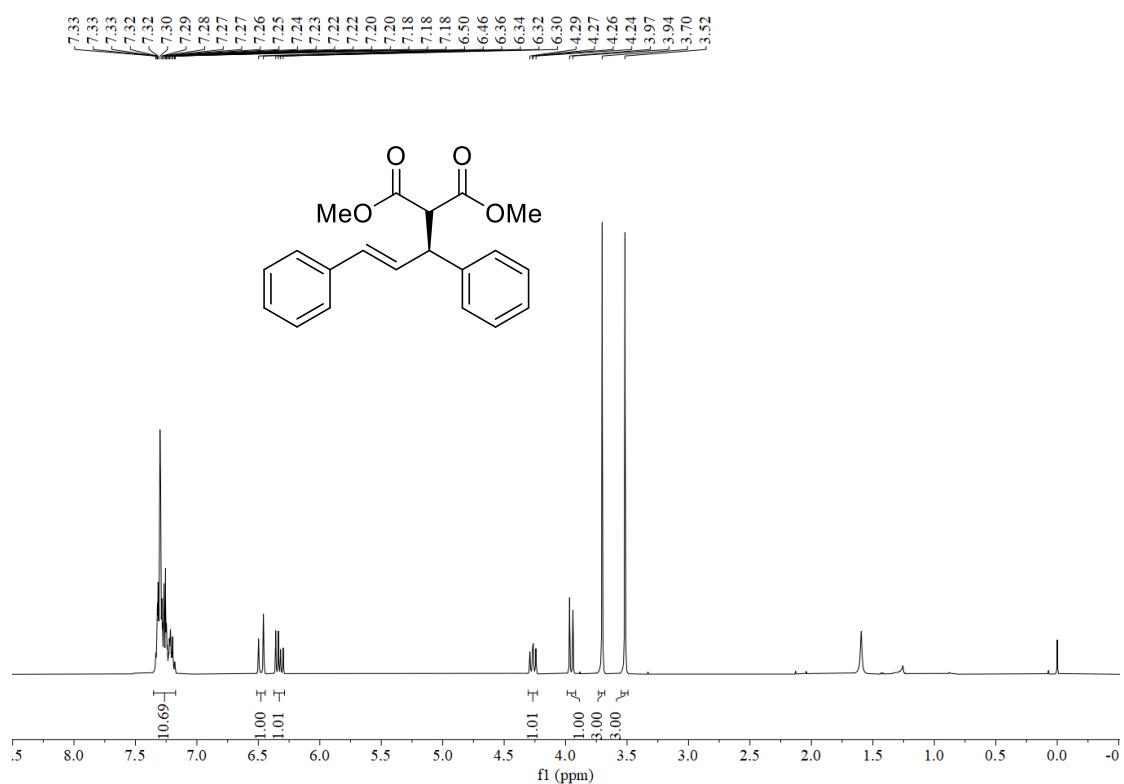
Supplementary Figure 225 HPLC spectra of racemic **20**



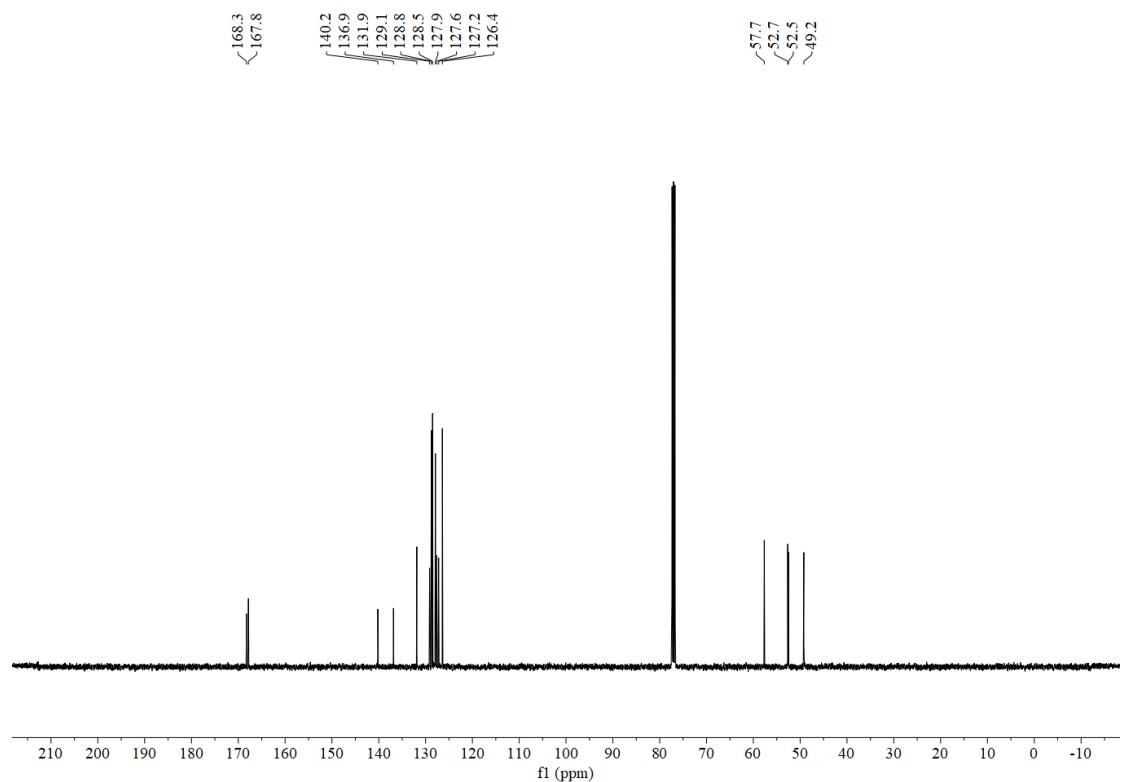
Supplementary Figure 226 HPLC spectra of (*S*)- **20**



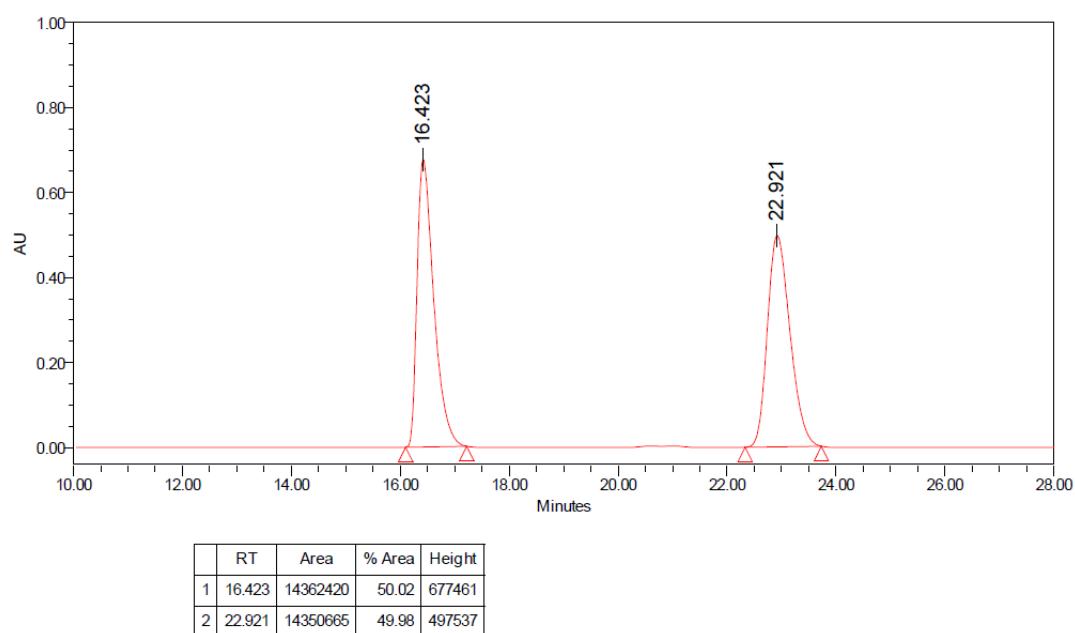
Supplementary Figure 227 ^1H NMR (400 MHz, CDCl_3) of **23**



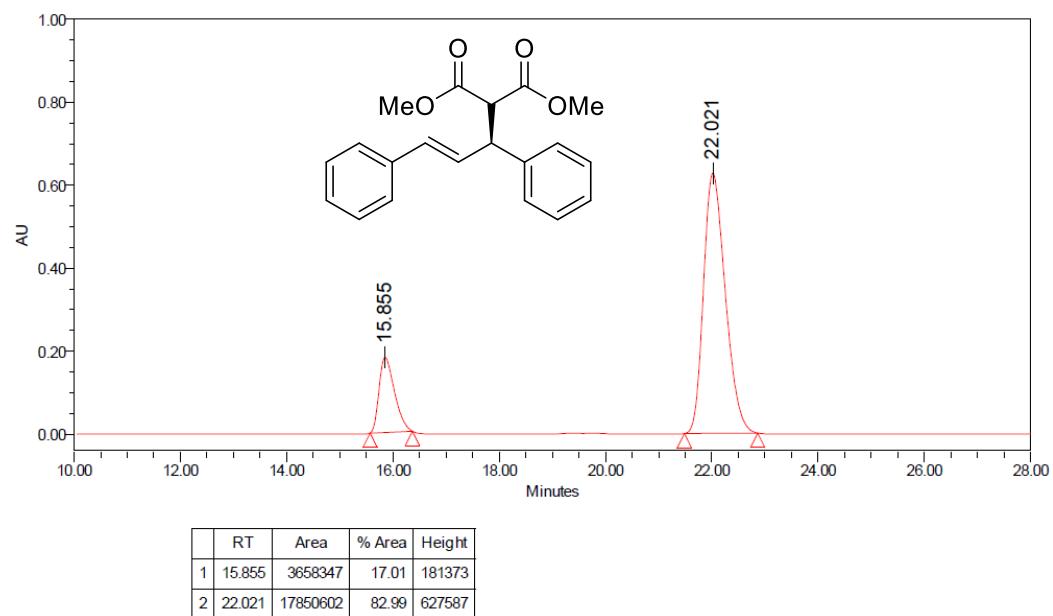
Supplementary Figure 228 ^{13}C NMR (400 MHz, CDCl_3) of **23**



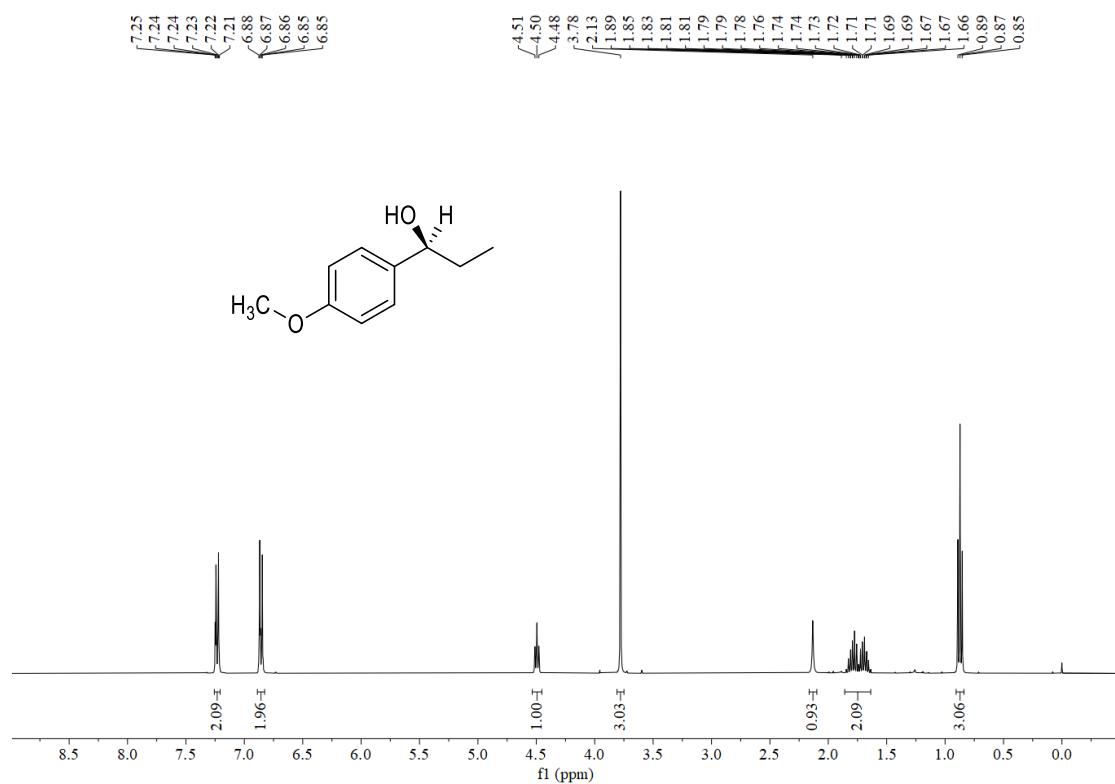
Supplementary Figure 229 HPLC spectra of racemic **23**



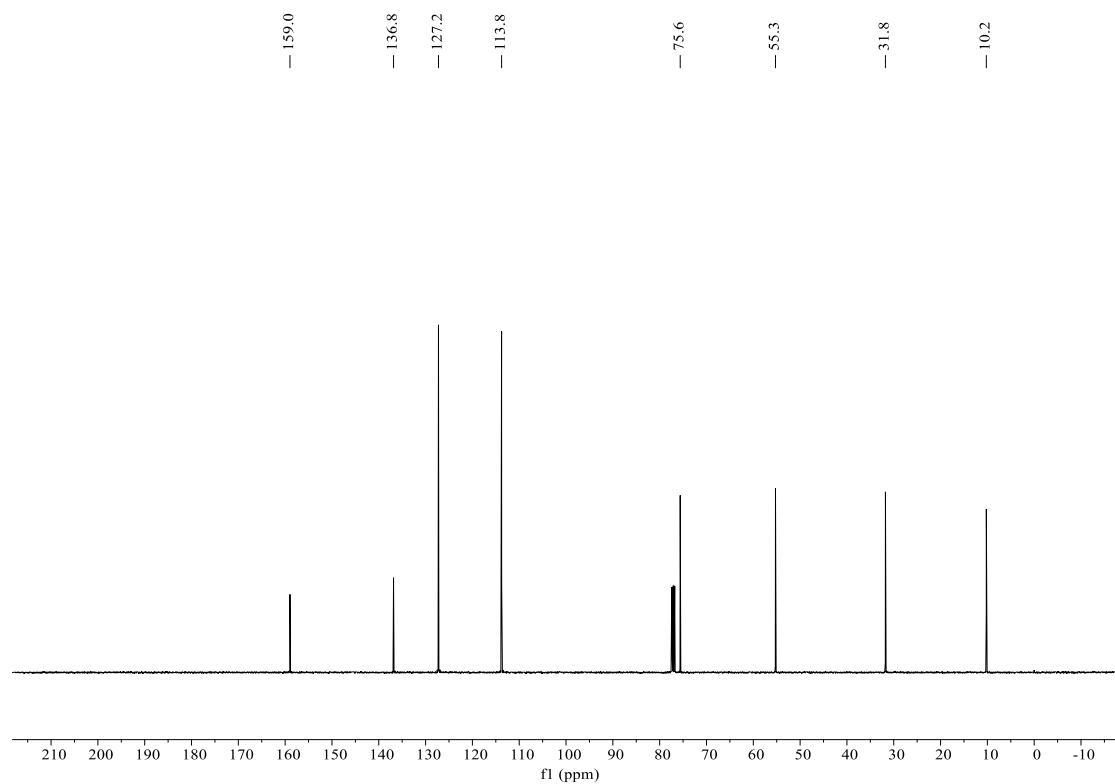
Supplementary Figure 230 HPLC spectra of (*S,E*)-**23**



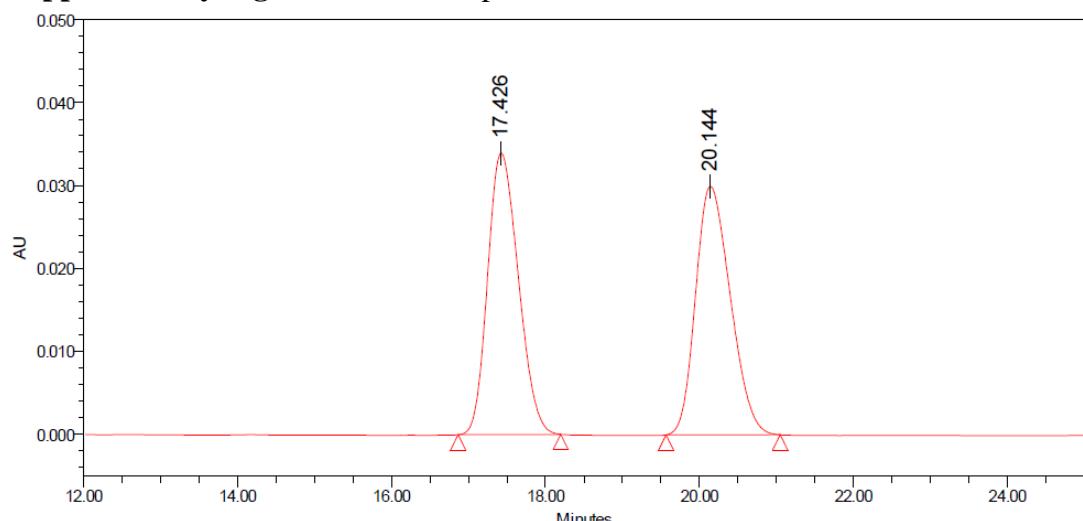
Supplementary Figure 231 ^1H NMR (400 MHz, CDCl_3) of **25**



Supplementary Figure 232 ^{13}C NMR (400 MHz, CDCl_3) of **25**

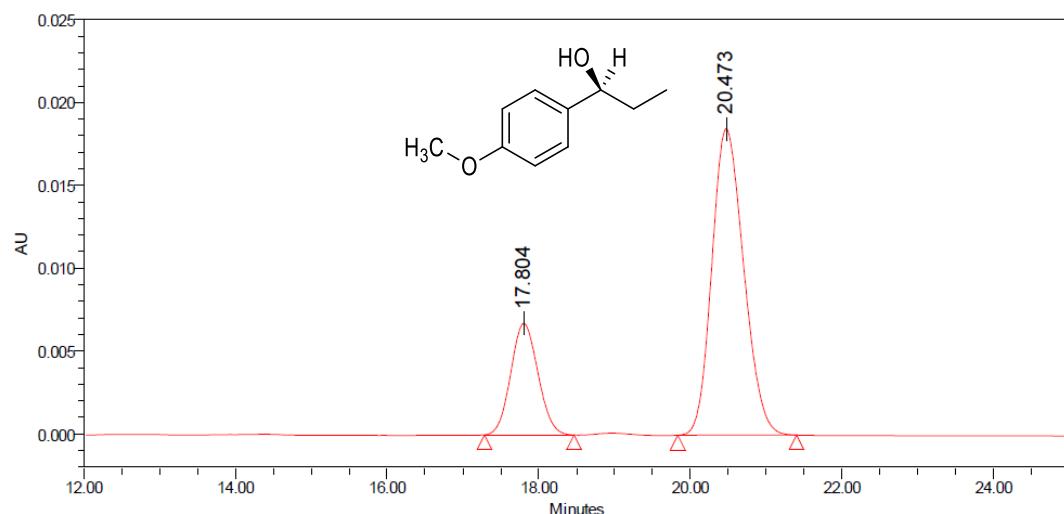


Supplementary Figure 233 HPLC spectra of racemic **25**



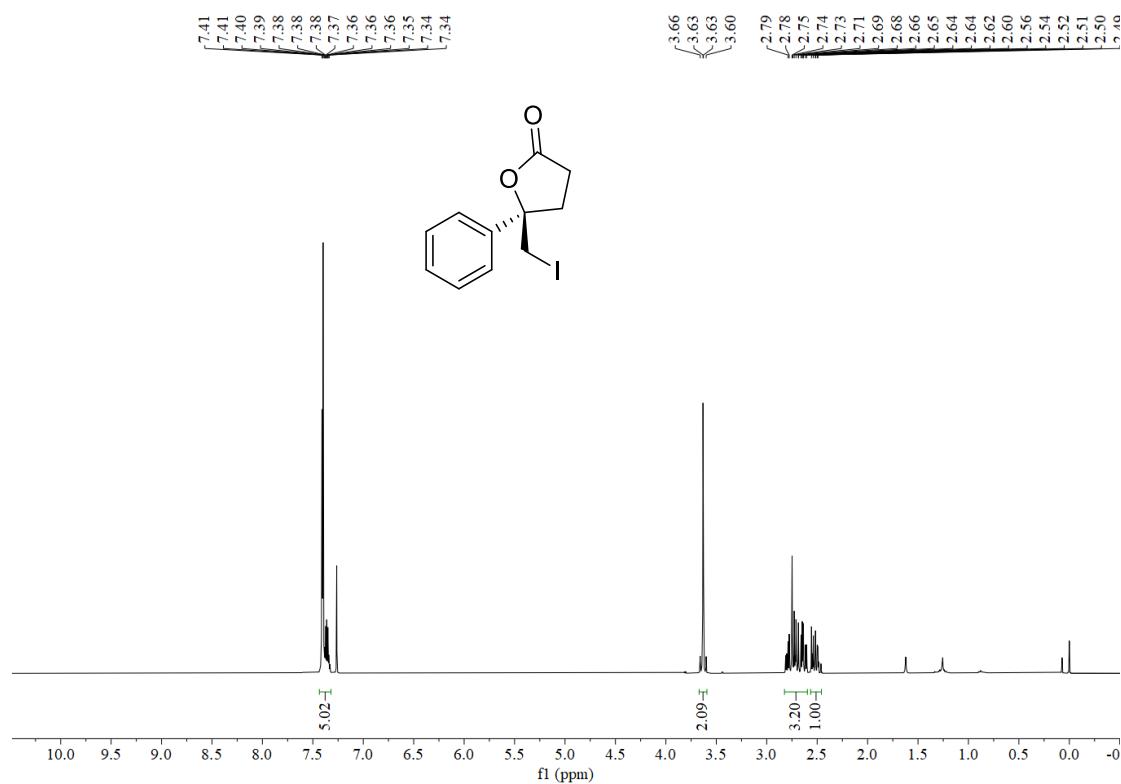
	RT	Area	% Area	Height
1	17.426	943506	50.01	33990
2	20.144	943211	49.99	30003

Supplementary Figure 234 HPLC spectra of (*S*)- **25**

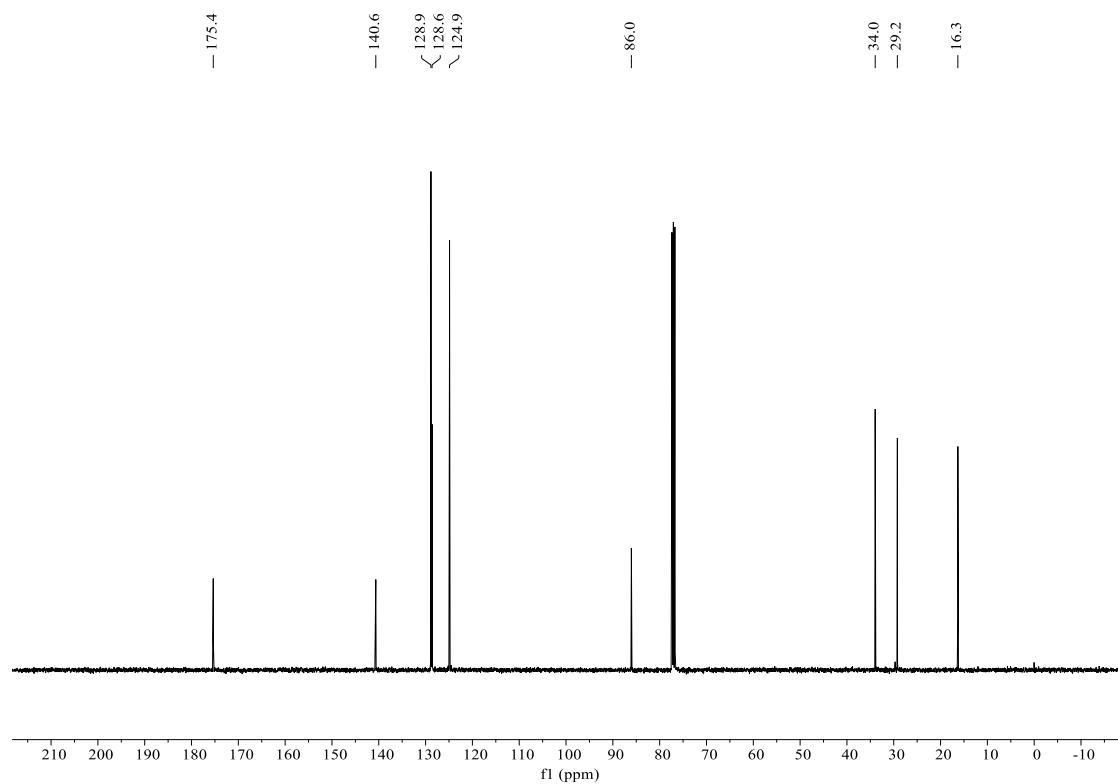


	RT	Area	% Area	Height
1	17.804	167776	23.75	6725
2	20.473	538719	76.25	18498

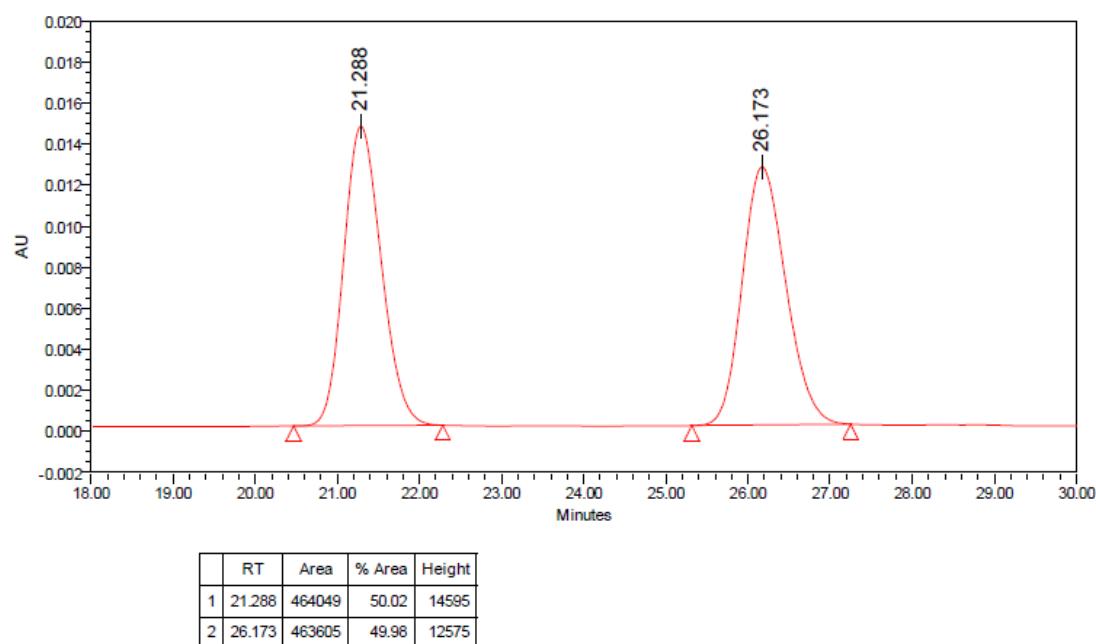
Supplementary Figure 235 ^1H NMR (400 MHz, CDCl_3) of **28**



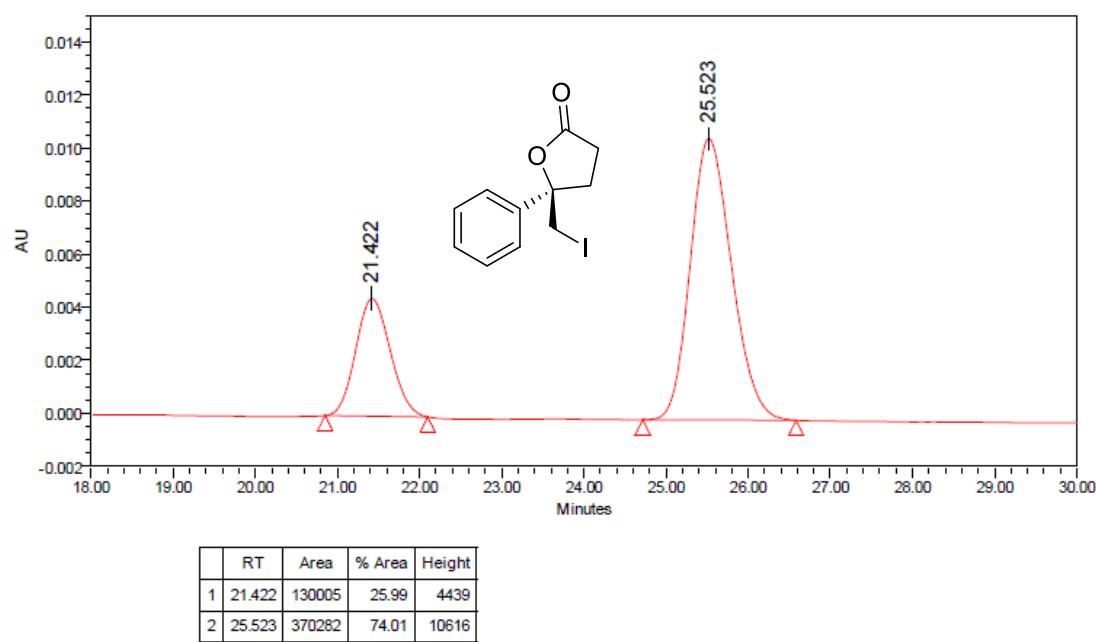
Supplementary Figure 236 ^{13}C NMR (400 MHz, CDCl_3) of **28**



Supplementary Figure 237 HPLC spectra of racemic **28**



Supplementary Figure 238 HPLC spectra of (*R*)- **28**



References:

Full reference for Gaussian software:

Gaussian 16, Revision A.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

1. Guo, D., Zhang, J., Zhang, B. & Wang, J. Ruthenium-catalyzed atropoenantioselective synthesis of axial biaryls via reductive amination and dynamic kinetic resolution. *Org. Lett.* **20**, 6284–6288 (2018).
2. Frisch, M. J. et al. Gaussian 16, Revision B.01. 2016.
3. Zhao, Y. & Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four Mo6-class functionals and 12 other function. *Theor. Chem. Acc.* **120**, 215–241 (2008).
4. Weigend, F. & Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **7**, 3297–3305 (2005).
5. Weigend, F. Accurate coulomb-fitting basis sets for H to Rn. *Phys. Chem. Chem. Phys.* **8**, 1057–1065 (2006).

6. Grimme, S. Supramolecular binding thermodynamics by dispersion-corrected density functional theory. *Chem. Eur. J.* **18**, 9955–9964 (2012).
7. Luchini, G., Alegre-Requena, J. V., Funes-Ardoiz, I. & Paton, R. S. GoodVibes: Automated thermochemistry for heterogeneous computational chemistry data. *F1000Research*, **9**, 291 (2020).
8. Ripplinger, C. & Neese, F. An efficient and near linear scaling pair natural orbital based local coupled cluster method. *J. Chem. Phys.* **138**, 034106 (2013).
9. Ripplinger, C., Sandhoefer, B., Hansen, A. & Neese, F. Natural triple excitations in local coupled cluster calculations with pair natural orbitals. *J. Chem. Phys.* **139**, 134101 (2013).
10. Neese, F. The ORCA program system. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2**, 73–78 (2012).
11. Neese, F. Software Update: The ORCA program system, Version 4.0. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **8**, e1327 (2018).
12. Neese, F., Wennmohs, F., Becker, U. & Ripplinger, C. The ORCA quantum chemistry program package. *J. Chem. Phys.* **152**, 224108 (2020).
13. Guo, Y.; Ripplinger, C.; Becker, U.; Liakos, D. G.; Minenkov, Y.; Cavallo, L.; Neese, F. An Improved Linear Scaling Perturbative Triples Correction for the Domain Based Local Pair-Natural Orbital Based Singles and Doubles Coupled Cluster Method [DLPNO- CCSD(T)]. *J. Chem. Phys.* **148**, 011101 (2018).
14. Kollmar, C. The role of energy denominators in self-consistent field (SCF) calculations for open shell systems", *J. Chem. Phys.* **105**, 8204. (1996)
15. Halkier, A. et al. Basis-set convergence in correlated calculations on Ne, N₂ , and H₂O. *Chem. Phys. Lett.* **286**, 243–252 (1998).
16. Helgaker, T., Klopper, W., Koch, H. & Noga, J. Basis-set convergence of correlated calculations on Water. *J. Chem. Phys.* **106**, 9639–9646 (1997).
17. Halkier, A., Helgaker, T., Jørgensen, P., Klopper, W. & Olsen, J. Basis-set convergence of the energy in molecular hartree-fock calculations. *Chem. Phys. Lett.* **302**, 437–446 (1999).

18. Dunning, T. H. Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen. *J. Chem. Phys.* **90**, 1007–1023 (1989).
19. Woon, D. E. & Dunning, T. H. Gaussian basis sets for use in correlated molecular calculations. III. The atoms aluminum through argon. *J. Chem. Phys.* **98**, 1358–1371 (1993).
20. Woon, D. E. & Dunning, T. H. Gaussian basis sets for use in correlated molecular calculations. V. Core-valence basis sets for boron through neon. *J. Chem. Phys.* **103**, 4572–4585 (1995).
21. Kendall, R. A.; Dunning, Jr., T. H.; Harrison, R. J. Electron affinities of the first-row atoms revisited. Systematic basis sets and wave functions. *J. Chem. Phys.* **96**, 6796 (1992)
22. Woon, D. E. & Dunning, T. H. *J. Gaussian basis sets for use in correlated molecular calculations. III. The atoms aluminum through argon. Chem. Phys.* **98**, 1358 (1993).
23. Stoychev, G. L.; Auer, A. A.; Neese, F. Automatic Generation of Auxiliary Basis Sets. *J. Chem. Theory Comput.* **13**, 554, (2017).
24. Provasi, P. F.; Aucar, G. A.; Sauer, S. P. A. The effect of lone pairs and electronegativity on the indirect nuclear spin–spin coupling constants in CH₂XCH₂X (X=CH₂,(X=CH₂, NH, O, S): *Ab initio* calculations using optimized contracted basis sets. *J. Chem. Phys.* **115**, 1324 (2001).
25. Marenich, A. V., Cramer, C. J. & Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **113**, 6378–6396 (2009).
26. Schrödinger, L. The PyMOL molecular graphics development component, *Version 1.8*, (2015).
27. Sun, F. et al. A Combined experimental and computational study of NHC-promoted desulfonylation of tosylated aldimines. *Org. Chem. Front.* **7**, 578–583 (2020).
28. Bannwarth, C., Ehlert, S. & Grimme, S. GFN2-xTB - An accurate and broadly parametrized self-consistent tight-binding quantum chemical method with multipole

- electrostatics and density-dependent dispersion contributions. *J. Chem. Theory Comput.* **15**, 1652–1671 (2019).
29. Pracht, P. & Grimme, S. Calculation of absolute molecular entropies and heat capacities made simple. *Chem. Sci.* **12**, 6551–6568 (2021).
30. Grimme, S. Exploration of chemical compound, conformer, and reaction space with meta-dynamics simulations based on tight-binding quantum chemical calculations. *J. Chem. Theory Comput.* **15**, 2847–2862 (2019).
31. Pracht, P., Bohle, F. & Grimme, S. Automated exploration of the low-energy chemical space with fast quantum chemical methods. *Phys. Chem. Chem. Phys.* **22**, 7169–7192 (2020).
32. Cezar, H. M. Clustering traj <https://github.com/hmcezar/clustering-traj>. Accessed 07 Aug 2021.