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Shengying Wu,[a,c] Jun Tang,[a,c] Jianwei Han,*[b] Dan Mao,[a] Xin Liu,[a] Xing Gao,[a] Jianjun Yu[a] and Limin Wang*[a]

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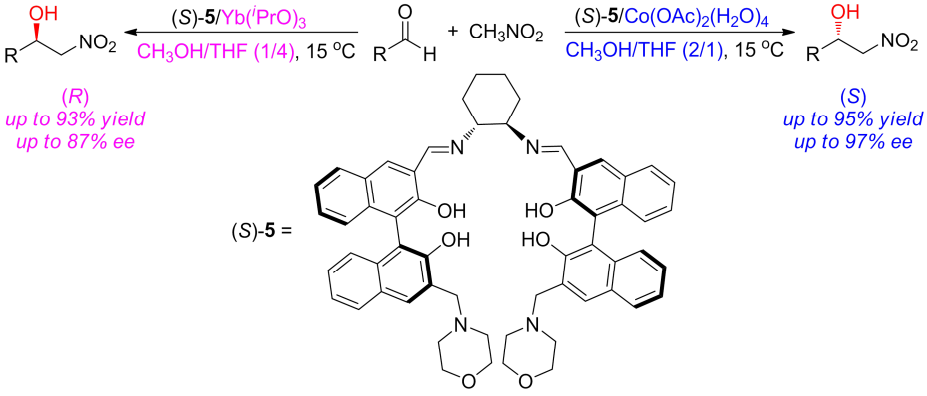

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ABSTRACT

Reversal of enantioselectivity in asymmetric Henry reactions was achieved with novel chiral C_2-symmetric salen ligands bearing morpholine moieties by changing the Lewis acid center from Co(II) to Yb(III). The possible transition state models were supported by mass spectrometry experiments.

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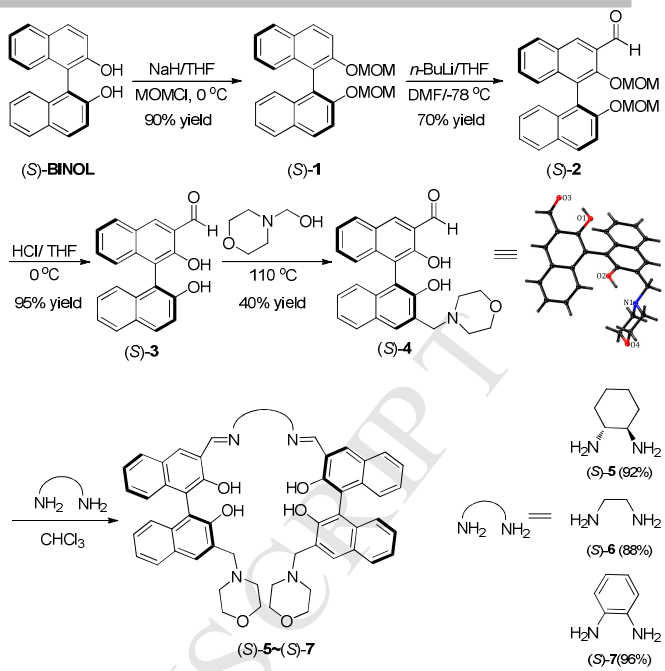
1. Introduction

It is of great importance to use a single chiral source to obtain both enantioenriched products in asymmetric synthesis.[1] So far, various types of chiral metal complexes and organocatalysts have been reported in this regard.[2] Reversal of enantioselectivity by changing metal center of catalytic complexes with the same chiral ligand has received particular attention since the early work reported by Kreuzfeld and co-workers in 1989.[3] Besides the catalytic species, unexpected inversion of enantioselectivity by changing reaction conditions such as solvents, temperature, additives, were also observed in specific reactions. However, from a practical point of view, it is also widely accepted that examination of diverse sets of metal sources is the most potential avenue for effective stereocontrol. Therefore, design of efficient and flexible ligands in conjunction with metals of different ionic radii remained an urgent but challenging research topic.

Henry reaction, a highly versatile carbon–carbon bond forming reaction, was well known. This reaction can be metal-catalyzed such as zinc,[4] copper,[5] cobalt,[6] chromium,[7] magnesium[8] and rare earths[9]. Asymmetric Henry reaction became a good model for the evaluation of chiral metal (M)-ligand (L*) complexes since the pioneering work reported by Shibasaki group in 1992.[9a] Du and Xu had also a tridentate bis(oxazoline) and bis(thiazoline) ligands for L*-M (M = Cu^{II}/Zn^{II}) complexes in the catalytic asymmetric Henry reaction of α-keto esters with nitromethane, in this case, both enantiomers were obtained (up to 85% ee).[10] Recently, Oh group designed a brucine-derived amino alcohol ligand-Cu^{II}/Zn^{II} catalyst system to induce reversal of enantioselectivity in asymmetric Henry reaction.[11] However, Most of these work used organic bases as additives, which could have a great negative effect on the catalytic reactivity and coordination ability. Thus, we envisioned that a ligand which incorporated tertiary amine would be functioned as bases without employing additives.

Meanwhile, chiral salen ligands derived from vicinal diamine and aldehydes were chosen as they could be easily modified and metallosalen complexes had been proven to be very effective in terms of enantioselectivity.[12] Herein, we report the design and synthesis of novel C_2-symmetric salen ligands bearing morpholine functional group based on BINOL framework for obtaining both isomers in asymmetric Henry reactions by changing central metals.

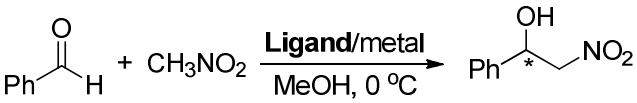


Scheme 1. Synthesis of the chiral ligands (*S*)-**5** ~ (*S*)-**7**.

2. Results and discussion

Inspired by Katsuki's introduction of binaphthyl unit into the salen ligand,[12] as shown in Scheme 1, C_2-symmetric salen ligands bearing morpholine subunit were prepared.[13] Starting with (*S*)-1,1'-binaphthyl-2,2'-diol (BINOL), the mono-aldehyde (*S*)-**3** was prepared according to the known literature.[14] A morpholinomethyl group was introduced *via* a Friedel-Crafts reaction of (*S*)-**3** with morpholinomethanol at high temperature. After a recrystallization with CH_2Cl_2/MeOH (1/2, v/v), the aldehyde (*S*)-**4** was obtained as a yellow crystal in an enantiopure form, whose structure was confirmed by X-ray crystallographic analysis.[15] Condensation of (*S*)-**4** with various 1,2-diamines furnished Schiff bases as the desired salen ligands (*S*)-**5** ~ (*S*)-**7** efficiently in the yield of 88-96%. Additionally, 3-((*E*)-(((*1R,2R*)-2-((*E*)-(((*S*)-2,2'-dihydroxy-[1,1'-binaphthalen]-3-yl)methylene)amino)cyclohexyl)imino)methyl)-[1,1'-binaphthalene]-2,2'-diol ((*S*)-**8**) was also prepared from (*S*)-**3** in the similar manner (Scheme S1).[14]

Table 1. Screening of metal sources in enantioselective Henry reaction[a]



Entry	Ligand	Metal	Yield (%)[b]	ee (%)[c]
1	(*S*)-**5**	$Yb(^iPrO)_3$	78	60 (*R*)
2	(*S*)-**6**	$Yb(^iPrO)_3$	70	35 (*R*)
3	(*S*)-**7**	$Yb(^iPrO)_3$	80	25 (*R*)
4	(*S*)-**8**	$Yb(^iPrO)_3$	trace	/
5[d]	(*S*)-**8**	$Yb(^iPrO)_3$	76	7 (*R*)
6	(*S*)-**5**	/	trace	/
7	(*S*)-**5**	$Sc(^iPrO)_3$	72	37 (*R*)
8	(*S*)-**5**	$La(^iPrO)_3$	67	15 (*R*)
9	(*S*)-**5**	$Co(OAc)_2(H_2O)_4$	90	85 (*S*)
10	(*S*)-**5**	$Ni(OAc)_2$	59	racemic
11	(*S*)-**5**	$Cu(OAc)_2$	37	racemic
12	(*S*)-**5**	$Mn(OAc)_2$	53	11 (*S*)

[a] Reaction conditions: benzaldehyde (0.25 mmol), nitromethane (1.25 mmol), ligand (6 mol%), metal (5 mol%), methanol (1.5 mL), 24 hours of reaction time.

[b] Isolated yields.

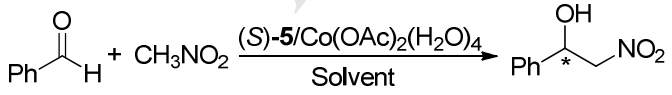
[c] Determined by chiral HPLC.

[d] Triethylamine (0.25 mmol) was added.

In connection with our studies concerning rare earth salts as Lewis acid catalysts,[16] metallosalen complexes were prepared *in situ* by treatment of (*S*)-**3** ~ (*S*)-**7** with ytterbium isopropoxide in MeOH. Then, we evaluated their performances in the benchmark Henry reaction of benzaldehyde with nitromethane (Table 1). To our delight, 5 mol% $Yb(O^iPr)_3$ complexed with 6 mol% (*S*)-**5** at room temperature was found to give a good yield of (*R*)-1-(4-nitrophenyl)-2-nitroethanol in 60% ee, the absolute configuration was confirmed by comparison of the observed specific rotation with literature values.[9] Using salen ligands (*S*)-**6** and (*S*)-**7**, the level of asymmetric induction was poor under the same conditions. With (*S*)-**8** as ligand, the reaction did not occur in methanol without additives, however, when an equivalent triethylamine as base additives was employed, the desired product was obtained in 76% yield and 7% ee. It confirmed the hypothesis that the morpholinomethyl moiety of salen ligand can activate the reactants as a bulky base in additive-free conditions. Hence, the new salen ligand (*S*)-**5** was utilized to screen various metal sources for the inversion of product selectivity in asymmmetric Henry reaction. Other rare earth metal such as La(III) and Sc(III) complexes gave moderate yields and low enantioselectivities (Table 1, entries 7 and 8). We were pleased to find that in the presence of 5 mol% $Co(OAc)_2(H_2O)_4$ and (*S*)-**5** in methanol, the enantioselectivity of the reaction was reversed, and the reaction proceeded smoothly to provide the corresponding (*S*)-1-(phenyl)-2-nitroethanol in 90% yield and 85% ee. However, the metal complexes of (*S*)-**5** with $Ni(OAc)_2$, $Cu(OAc)_2$ and $Mn(OAc)_2$ only gave low enantioselectivities and moderate chemical yields.

Next, an asymmetric Henry reaction of benzaldehyde with nitromethane was carried out in the presence of cobalt-salen catalyst to establish the optimum reaction condition (Table 2). Several polar and non-polar solvents (EtOH, ^{i}PrOH, CH_2Cl_2, THF) were screened. The alcohols gave the desired products in good yields and high enantioselectivities. However, in cases of CH_2Cl_2 and THF, only trace amount of products was observed. Inspired by recent works of enantioselectivity inversion,[17] a co-solvent pair of MeOH/THF (2/1) at the temperature of 0 ^oC resulted in an improvement of product enantioselectivity to the higher of 90%. Finally, the reaction temperature was increased to 15 ^oC, even higher enantioselectivity was attained (Table 2, entry 9). Surprisingly, switching cobalt-salen to ytterbium-salen complexes by using MeOH/THF (2/1) as solvent at 15 ^oC also led to the inversion of product enantioselectivity to larger extent (Table 2, entry 12). Other screenings were also carried out (Tables S1 ~ S2), and MeOH/THF (1/4) gave the best result with 93% yield and 87% ee (Table 2, entry 13).

Table 2. Optimization of enantioselective Henry reaction[a]



Entry	Solvent	Temp(^oC)	Time (h)	Yield (%)[b]	ee (%)[c]
1	MeOH	0	24	90	85 (*S*)
2	EtOH	0	24	76	75 (*S*)
3	i-PrOH	0	24	74	73 (*S*)
4	THF	0	48	trace	/
5	CH_2Cl_2	0	48	trace	/
6	MeOH/THF = 2/1	0	48	73	90 (*S*)
7	MeOH/THF = 2/1	-10	48	23	87 (*S*)
8	MeOH/THF = 2/1	5	48	80	91 (*S*)
9	MeOH/THF = 2/1	15	36	91	92 (*S*)
10	MeOH/THF = 2/1	r.t.	36	95	82 (*S*)
11	MeOH/THF = 2/1	40	36	97	59 (*S*)
12[d]	MeOH/THF = 2/1	15	48	84	68 (*R*)
13[d]	MeOH/THF = 1/4	15	48	93	87 (*R*)

[a] Reaction conditions: benzaldehyde (0.25 mmol), nitromethane (1.25 mmol), ligand (6 mol%), $Co(OAc)_2(H_2O)_4$ (5 mol%), solvent (1.5 mL).

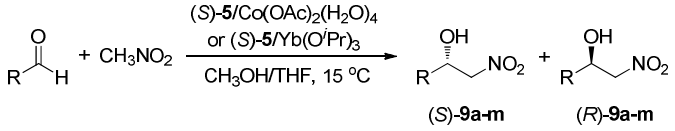
[b] Isolated yields.

[c] Determined by chiral HPLC.

[d] $Yb(O^iPr)_3$ was used.

With the optimal reaction condition in hand, we further studied the generality of asymmetric Henry reaction of various aldehydes with nitromethane in the presence of catalyst (*S*)-5 with $Co(OAc)_2(H_2O)_4$ or $Yb(O^iPr)_3$ as shown in Table 3. The presence of either electron-withdrawing or electron-donating substituents at various positions of the aromatic ring of aryl aldehydes was tolerated with ee value from 80% to 97% when $Co(OAc)_2(H_2O)_4$ were used for the central metal. As expected, electron-rich aldehydes resulted in lower reactivity than electron-deficient aldehydes. Cyclohexanecarbaldehyde gave the product in only moderate yield but excellent enantioselectivity (Table 3, entry 12). Cinnamaldehyde gave the corresponding product in 81% ee, and excellent ee value (>99%) was obtained after recrystallization (Table 3, entry 13). In contrast, $Yb(O^iPr)_3$/(*S*)-5 catalytic system gave (*R*)-configuration of desired product in the range of 10 ~ 87% ee (Table 3, entries 1 to 13).

Table 3. The substrate scope of enantioselective Henry reaction[a]



Entry	R	(*S*)-**5**/$Co(OAc)_2(H_2O)_4$[a]		(*S*)-**5**/$Yb(O^iPr)_3$[b]	
		Yield (%)[c]	ee (%)[d] (*S*)-**9**	Yield (%)[c]	ee(%)[d] (*R*)-**9**
1	Ph	91	92	93	87
2	4-ClC_6H_4	90	88	77	37
3	4-$NO_2C_6H_4$	95	80	96	16
4	4-CNC_6H_4	92	91	98	12
5	4-$CF_3C_6H_4$	90	84	85	10
6	4-FC_6H_4	89	90	84	58
7	2-FC_6H_4	82	94	91	51
8	3-FC_6H_4	72	93	92	65
9	4-MeC_6H_4	82	90	89	66
10	4-$OMeC_6H_4$	81	87	81	62
11	cyclohexyl	65	91	67	52
12	2-furyl	88	97	87	33
13	(*E*)-PhCH=CH	90	81(>99)[e]	84	38

[a] Reaction conditions: aldehyde (0.25 mmol), nitromethane (1.25 mmol), ligand (6 mol%), metal (5 mol%), MeOH/THF (2/1, *v/v*, 1.5 mL), 36 h of reaction time.

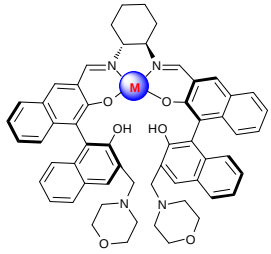
[b] Identical conditions but otherwise for 48 h in MeOH/THF (1/4, *v/v*, 1.5 mL).

[c] Isolated yields.

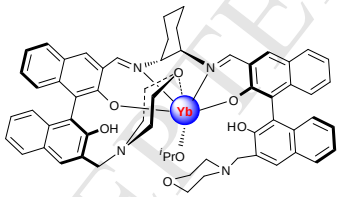
[d] Determined by chiral HPLC.

[e] After recrystallization.

Although the structures of catalytic species awaits further information, the related structures of Co(II)-salen[6,18] and Yb(III)-salen complexes[19] were well documented. Based on the pronounced difference in ionic radii of Co(II) and Yb(III) and the oxophilic and isotropic nature of ytterbium metals, the coordination of metal centers with salen ligand (*S*)-**5** in the formation of metallosalen complexes was proposed in Fig. 1. Both metallosalen complexes were checked by mass spectrometry experiments. The TOF-HRMS/ES$^+$ showed a peak at *m/z* 961.3380, which corresponds to [**10**]$^+$ for cobalt complex, and *m/z* 1076.3403 which corresponds to [**11**]$^+$ for ytterbium complex, respectively. It is worth to note that, in the case of cobalt complex, a peak at *m/z* 1021.3709 may be the [**10**+Co]$^+$ ion, this results suggested dinuclear structure of cobalt complex was formed. In the case of ytterbium complex, a peak at *m/z* 1135.2992 is most likely related to [**11**+O^{i}Pr]$^+$, to take account of the oxophilic and the isotropic nature of ytterbium metals, the model of **12** has been proposed (Fig. 1). On the basis of the above experiments, the stereochemical outcome between different metallosalen complexes can be explained by the following possible transition state models with both complexes (Fig. 2). At this stage, although the insight into the mechanism remained unclear since we failed to obtain the crystallographic information of the catalytic species, from several scenarios we tried, we hypothesized that the (*S*) enantiomer is preferred by a nucleophilic attack of nitromethane on the benzaldehyde from the *re*-face under the chiral environment formed by C2-symmetric chiral ligand and the cobalt atom. In the Yb case, the oxygen atom of the benzaldehyde was approaching to the ytterbium by replacing the oxygen of the morpholine group; Meanwhile, the nitromethane attacks the benzaldehyde from the *si*-face. It appears that the tertiary amine moiety participates in the formation of metallic complexes, and it is essential for the activation of nitromethane.



10, M= Co; 11, M= Yb



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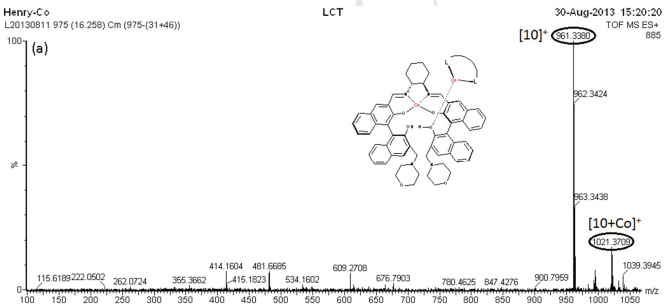

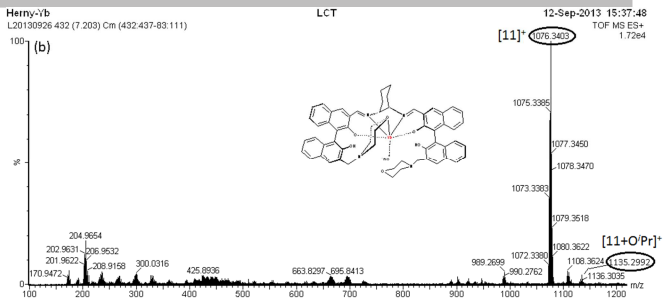

Fig. 1. The TOF-HRMS spectra of (a) Co(II) and (b) Yb(III) complexes.

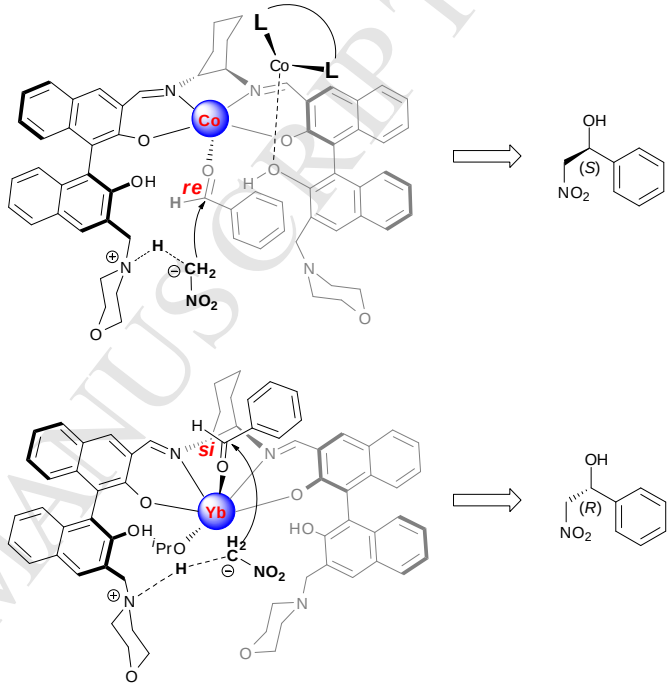

Fig. 2. A possible transition state structure.

3. Conclusion

In summary, we successfully synthesized a class of chiral C_2-symmetric salen ligands bearing morpholine functional moiety. With these ligands in combination with Co(II) or Yb(III), respectively, a controlled selective methodology in asymmetric Henry reaction of a range of aldehydes and nitromethane was developed in obtaining both enantiomeric Henry products.

4. Experimental section

4.1. General procedures

General Methods. Unless otherwise noted, all the reactions were conducted under argon atmosphere. All reagents and solvents were dried and distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively using tetramethylsilane as an internal reference. Chemical shifts (δ) and coupling constants (J) were expressed in parts per million and hertz, respectively. Melting points were uncorrected. High-resolution mass spectrometry (HRMS) was performed with Electron Ionization (EI) resource or on an ESI-TOF spectrometer. The ee was determined by HPLC on AD, or OD column.

4.2. General Procedure for the Synthesis of (S)-4

Morpholinomethanol (10.0 mL) combining with (S)-**3** (1.0 g, 3.18 mmol) was heated at 110 °C for 72 h. After completion of the reaction, the mixture was cooled to room temperature and

diluted with chloroform (100 mL). The solution was washed with saturated $NaHCO_3$ (6×20 mL) and water (3×20 mL). The organic phase was then concentrated under vacuum and the residue was purified by column chromatograph on silica gel eluted with petroleum ether / ethyl acetate (10:1) to give (*S*)-**4** in 40% yield, and the enantiopure form was obtained after a recrystallization with CH_2Cl_2/MeOH.

*4.2.1. (S)-2,2'-dihydroxy-3'-(morpholinomethyl)-[1,1'-binaphthalene]-3-carbaldehyde (**(S)-4**).* Yellow solid, 526.1 mg, 40% yield, m.p 205-206 °C. $[\alpha]_D^{20}$ -152 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (br s, 1H), 10.46 (s, 1H), 10.18 (s, 1H), 8.30 (s, 1H), 7.96-7.98 (m, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.38-7.20 (m, 5H), 7.11 (d, *J* = 8.4 Hz, 1H), 4.02 (d, *J* = 14 Hz, 1H), 3.98 (d, *J* = 14 Hz, 1H), 3.69 (br s, 4H), 2.64 (br s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 153.1, 153.5, 138.0, 137.8, 133.7, 130.4, 130.0, 128.8, 128.3, 127.9, 127.7, 126.5, 125.2, 124.4, 124.3, 123.4, 123.3, 122.2, 118.5, 114.7, 66.6, 62.3, 52.9. FT-IR (cm^{-1}): 1003, 1025, 1031, 1072, 1102, 1117, 1151, 1171, 1185, 1250, 1269, 1293, 1344, 1383, 1423, 1457, 1472, 1503, 1578, 1660, 2845, 2892, 2935, 2959, 3058, 3203, 3436. HRMS (EI) Calcd. for $C_{26}H_{23}NO_4$ 413.1627, found 413.1628.

4.3. General Procedure for the Synthesis of (S)-5 ~ (S)-7

(*S*)-**4** (0.48 mmol) was dissolved completely in $CHCl_3$ (2.0 mL), and diamines NH_2-X-NH_2 (0.24 mmol) was added dropwise. The yellow solution was then allowed to stir at r.t. for 24 h. After removal of the solvent, the crude product was washed by methanol carefully and dried with gentle heating *in vacuo* to provide (*S*)-**5** in 92% yield, (*S*)-**6** in 88% yield, (*S*)-**7** in 96% yield, respectively.

*4.3.1. 3-((E)-(((1R,2R)-2-((E)-(((S)-2,2'-dihydroxy-3'-(morpholinomethyl)-[1,1'-binaphthalen]-3-yl)methylene)amino)cyclohexyl)imino)methyl)-3'-(morpholinomethyl)-[1,1'-binaphthalene]-2,2'-diol (**(S)-5**).* Yellow solid, 201.5 mg, 92% yield, m.p 188-190 °C. $[\alpha]_D^{20}$ -354 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.10 (s, 2H), 10.95 (br s, 2H), 8.51 (s, 2H), 7.81-7.68 (m, 8H), 7.29-7.07 (m, 12H), 4.13 (d, *J* = 13.6 Hz, 2H), 3.92 (d, *J* = 13.6 Hz, 2H), 3.71 (br s, 8H), 3.35-3.32 (m, 2H), 2.66 (br s, 8H), 2.00-1.62 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C=N), 153.6, 152.4, 134.2, 132.9, 132.6, 127.9, 127.4, 127.3, 127.0, 126.7, 126.5, 125.2, 123.8, 123.6, 122.3, 122.1, 121.9, 119.7, 115.9, 115.2, 70.9, 65.6, 61.4, 52.0, 31.7, 22.9. FT-IR (cm^{-1}): 1005, 1033, 1071, 1117, 1150, 1169, 1184, 1209, 1252, 1294, 1313, 1343, 1383, 1432, 1506, 1576, 1631, 2855, 2932, 3054, 3447. HRMS (ESI) Calcd. for $[M+H]^+$ $C_{58}H_{57}N_4O_6$ 905.4278, found 905.4278.

*4.3.2. 3-((E)-((2-((E)-(((S)-2,2'-dihydroxy-3'-(morpholinomethyl)-[1,1'-binaphthalen]-3-yl)methylene)amino)ethyl)imino)methyl)-3'-(morpholinomethyl)-[1,1'-binaphthalene]-2,2'-diol (**(S)-6**).* Yellow solid, 181.2 mg, 88% yield, m.p 184-185 °C. $[\alpha]_D^{20}$ -105 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.01 (s, 2H), 11.10 (br s, 2H), 8.59 (s, 2H), 7.87 (s, 2H), 7.82-7.78 (m, 4H), 7.67 (s, 2H), 7.29-7.23 (m, 7H), 7.14-7.12 (m, 5H), 4.09 (d, *J* = 13.6 Hz, 2H), 4.01-3.88 (m, 6H), 3.68 (br s, 8H), 2.63 (br s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C=N), 153.5, 152.3, 134.3, 132.8, 132.5, 127.9, 127.3, 127.3, 127.2, 126.6, 126.5, 125.3, 123.7, 123.7, 122.2, 122.2 (overlapped), 119.6, 116.1, 115.0, 65.5, 61.4, 58.7, 51.9. FT-IR (cm^{-1}): 1026, 1118, 1150, 1184, 1252, 1294, 1314, 1343, 1382, 1431, 1456, 1506, 1576, 1633, 2849, 2920, 3055, 3445. HRMS (ESI) Calcd. for $[M+H]^+$ $C_{54}H_{51}N_4O_6$ 851.3809, found 851.3806.

*4.3.3. 3-((E)-((2-((E)-(((S)-2,2'-dihydroxy-3'-(morpholinomethyl)-[1,1'-binaphthalen]-3-yl)methylene)amino)phenyl)imino)methyl)-3'-(morpholinomethyl)-[1,1'-binaphthalene]-2,2'-diol (**(S)-7**).* Yellow solid, 208.9 mg, 96% yield, m.p 195-197 °C. $[\alpha]_D^{20}$ -120 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (br s, 2H), 8.89 (s, 2H), 8.12 (s, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.69 (s, 2H), 7.32-7.08 (m, 12H), 6.82-6.73 (m, 4H), 4.06 (d, *J* = 13.6 Hz, 2H), 3.96 (d, *J* = 13.6 Hz, 2H), 3.66 (br s, 8H), 2.65 (br s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (C=N), 154.2, 153.4, 141.3, 135.7, 135.0, 134.6, 133.8, 129.1, 128.6, 128.5, 128.4, 128.3, 127.8, 126.5, 124.9, 124.8, 123.6, 123.3, 123.3, 121.6, 118.7, 118.3, 117.5, 115.9, 115.8, 66.6, 62.4, 53.0. FT-IR (cm^{-1}): 1005, 1032, 1071, 1117, 1150, 1168, 1181, 1252, 1295, 1313, 1343, 1380, 1399, 1431, 1456, 1506, 1601, 2851, 2921, 2959, 3055, 3370. HRMS (ESI) Calcd. for $[M+H]^+$ $C_{58}H_{51}N_4O_6$ 899.3809, found 899.3810.

4.4. General Procedure for the Synthesis of (S)-8[14]

(*S*)-**3** (0.48 mmol) was dissolved completely in refluxing ethanol, the yellow solution was then allowed to cool to r.t. and (-)-(*1R, 2R*)-cyclohexanediamine (0.24 mmol) was added dropwise. During this addition, the product precipitated out of solution. The mixture was then allowed to reflux for 1 h. After cooling down to r.t., the precipitate was collected by filtration, and washed with cold ethanol carefully and dried with gentle heating *in vacuo* to provide (*S*)-**8** in 85% yield as a pink-orange powder.

*4.4.1. 3-((E)-(((1R,2R)-2-((E)-(((S)-2,2'-dihydroxy-[1,1'-binaphthalen]-3-yl)methylene)amino)cyclohexyl)imino)methyl)-[1,1'-binaphthalene]-2,2'-diol (**(S)-8**).* Pink-orange powder, 145.4 mg, 85% yield, m.p 185-188 °C. $[\alpha]_D^{20}$ -342 (*c* 0.5, $CHCl_3$).[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (br s, 2H), 8.52 (s, 2H), 7.91-7.85 (m, 8H), 7.33-7.21 (m, 10H), 7.12-7.09 (m, 4H), 5.17 (br s, 2H), 3.33-3.31 (m, 2H), 1.95-1.41 (m, 8H).

4.5. General Procedure for the Synthesis of (S), or (R)-9a-m

4.5.1. General Procedure for the Synthesis of (S)-9a~m.

Ligand (*S*)-**5** (13.8 mg, 6 mol%) was dissolved in THF (0.5 mL), and the solution of cobalt acetate tetrahydrate (3.1 mg, 5 mol%) in MeOH (1.0 mL) was added dropwise. The mixture was allowed to stir at r.t. for 2 h affording a deep brown slurry, and nitromethane (125 μL, 1.25 mmol) was added for another 30 min stirring at r.t. Then aldehyde (0.25 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 15 °C for 36 h. After removal the solvent, the residue was purified by column chromatograph on silica gel eluted with petroleum ether/ethyl acetate (20:1 to 10:1) to give (*S*)-Henry adduct.

4.5.2. General Procedure for the Synthesis of (R)-9a~m.

Ligand (*S*)-**5** (13.8 mg, 6 mol%) and $Yb(O^iPr)_3$ (4.4 mg, 5 mol%) was dissolved in 1/4 MeOH-THF co-solvent. The mixture was allowed to stir at r.t. for 2 h affording a reddish orange slurry, and nitromethane (125 μL, 1.25 mmol) was added for another 30 min stirring at r.t. Then aldehyde (0.25 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 15 °C for 48 h. After removal of the solvent, the residue was purified by column chromatograph on silica gel eluted with petroleum ether/ethyl acetate (20:1 to 10:1) to give (*R*)-Henry adduct.

4.5.3. Experimental datas for (S)- or (R)-9a~m.

*4.5.3.1. (S)- or (R)- 2-nitro-1-phenylethanol (**9a**).* Colorless oil, (*S*)-product: 38.0 mg, 91% yield, (*R*)-product: 38.9 mg, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5H), 5.42-5.38 (m, 1H), 4.56 (dd, *J* = 9.6 Hz, 13.2 Hz, 1H), 4.46 (dd, *J* = 2.8 Hz, 13.2 Hz, 1H), 3.16 (br s, 1H), The ee was determined by HPLC on Chiralcel OD-H (85:15 *n*-hexane : isopropanol, 0.8 mL/min, 215 nm), t_R (minor) = 11.6 min, t_S (major) = 13.4 min,

92% ee. t_R (major) = 13.0 min, t_S (minor) = 14.9 min, 87% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[11, 20]

*4.5.3.2. (S)- or (R)- 1-(4-chlorophenyl)-2-nitroethanol (**9b**).* Pale-yellow oil, (*S*)-product: 45.2 mg, 90% yield, (*R*)-product: 38.7 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 5.41 (dd, *J* = 2.8 Hz, 9.2 Hz, 1H), 4.55 (dd, *J* = 9.2 Hz, 13.2 Hz, 1H), 4.47 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 3.32 (br s, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 14.9 min, t_S (major) = 18.7 min, 88% ee. t_R (major) = 14.6 min, t_S (minor) = 19.3 min, 37% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[11, 21-22]

*4.5.3.3. (S)- or (R)- 2-nitro-1-(4-nitrophenyl)ethanol (**9c**).* Colorless oil, (*S*)-product: 50.4 mg, 95% yield, (*R*)-product: 50.9 mg, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 5.61 (dd, *J* = 4.4 Hz, 8.4 Hz, 1H), 4.64-4.55 (m, 2H), 3.38 (br s, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 29.3 min, t_S (major) = 37.0 min, 80% ee. t_R (major) = 29.2 min, t_S (minor) = 37.1 min, 8% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[21-25]

*4.5.3.4. (S)- or (R)- 4-(1-hydroxy-2-nitroethyl)benzonitrile (**9d**).* Colorless oil, (*S*)-product: 44.2 mg, 92% yield, (*R*)-product: 47.1 mg, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 5.55 (dd, *J* = 4.0 Hz, 8.8 Hz, 1H), 4.59 (dd, *J* = 8.8 Hz, 13.6 Hz, 1H), 4.54 (dd, *J* = 4.0 Hz, 13.6 Hz, 1H), 3.36 (br s, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 30.7 min, t_S (major) = 35.4 min, 91% ee. t_R (major) = 30.3 min, t_S (minor) = 35.6 min, 12% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[7b,21]

*4.5.3.5. (S)- or (R)- 2-nitro-1-(4-(trifluoromethyl)phenyl)ethanol (**9e**).* Colorless oil, (S)-product: 52.9 mg, 90% yield, (R)-product: 50.0 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 5.54-5.52 (m, 1H), 4.59 (dd, *J* = 9.2, 13.6 Hz, 1H), 4.53 (dd, *J* = 3.6, 13.6 Hz, 1H), 3.33 (d, *J* = 4.0, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 12.1 min, t_S (major) = 15.5 min, 84 % ee. t_R (major) = 12.7 min, t_S (minor) = 16.3 min, 10% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[22]

*4.5.3.6. (S)- or (R)- 1-(4-fluorophenyl)-2-nitroethanol (**9f**).* Colorless oil, (*S*)-product: 41.2 mg, 89% yield, (*R*)-product: 38.9 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 2H), 7.09-7.05 (m, 2H), 5.42 (d, *J* = 9.2 Hz, 1H), 4.57 (dd, *J* = 9.6, 13.2 Hz, 1H), 4.48 (dd, *J* = 3.2, 13.6 Hz, 1H), 3.40 (br s, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 13.0 min, t_S (major) = 15.5 min, 90% ee. t_R (major) = 13.0 min, t_S (minor) = 15.4 min, 57% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[18, 21, 26-27]

*4.5.3.7. (S)- or (R)- 1-(2-fluorophenyl)-2-nitroethanol (**9g**).* Colorless oil, (*S*)-product: 37.9 mg, 82% yield, (*R*)-product: 42.1 mg, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.2 Hz, 1H), 7.38-7.06 (m, 3H), 5.76-5.72 (m, 1H), 4.65-4.57 (m, 2H), 3.16 (br s, 1H). The ee was determined by HPLC on Chiralcel AD-H (90:10 *n*-hexane: isopropanol, 0.9 mL/min, 215 nm), t_S (major) = 11.3 min, t_R (minor) = 12.0 min, 94% ee. t_S (minor) = 11.5 min, t_R (major) = 12.3 min, 51% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[7, 21-22]

*4.5.3.8. (S)- or (R)- 1-(3-fluorophenyl)-2-nitroethanol (**9h**).* Colorless oil, (*S*)-product: 33.3 mg, 72% yield, (*R*)-product: 42.6 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 1H), 7.27-7.13 (m, 2H), 7.07-7.02 (m, 1H), 5.47-5.43 (m, 1H), 4.60-4.49 (m, 2H), 3.27-3.24 (d, *J* = 4.0 Hz, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 13.3 min, t_S (major) = 15.7 min, 93% ee. t_R (major) = 13.0 min, t_S (minor) = 15.6 min, 65% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[21]

*4.5.3.9. (S)- or (R)- 2-nitro-1-p-tolylethanol (**9i**).* Colorless oil, (*S*)-product: 37.1 mg, 82% yield, (*R*)-product: 40.3 mg, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 8 Hz, 2H), 5.43-5.41 (m, 1H), 4.60 (dd, *J* = 9.6 Hz, 13.2 Hz, 1H), 4.48 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 2.92 (d, *J* = 3.6 Hz, 1H), 2.36 (s, 3H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 14.9 min, t_S (major) = 18.6 min, 90% ee. t_R (major) = 14.6 min, t_S (minor) = 18.9 min, 66% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[11]

*4.5.3.10. (S)- or (R)- 1-(4-methoxyphenyl)-2-nitroethanol (**9j**).* Colorless oil, (*S*)-product: 39.9 mg, 81% yield, (*R*)-product: 39.9 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 6.92-6.90 (m, 2H), 5.39 (dd, *J* = 2.4 Hz, 9.6 Hz, 1H), 4.59 (dd, *J* = 9.6 Hz, 13.2 Hz, 1H), 4.47 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 3.80 (s, 3H), 2.93 (br s, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 22.6 min, t_S (major) = 28.7 min, 87% ee. t_R (major) = 22.1 min, t_S (minor) = 28.5 min, 61% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[11, 23, 26-27]

*4.5.3.11. (S)- or (R)- 1-cyclohexyl-2-nitroethanol (**9k**).* Colorless oil, (*S*)-product: 28.1 mg, 65% yield, (*R*)-product: 29.0 mg, 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (dd, *J* = 2.8, 12.8 Hz, 1H), 4.43 (dd, *J* = 8.8, 12.8 Hz, 1H), 4.13-4.07 (m, 1H), 2.66 (br s, 1H), 1.85-1.76 (m, 3H), 1.71-1.65 (m, 2H), 1.52-1.43 (m, 1H), 1.33-1.03 (m, 5H). The ee was determined by HPLC on Chiralcel AD-H (95:5 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 21.4 min, t_S (major) = 22.6 min, 91% ee. t_R (major) = 21.3 min, t_S (minor) = 22.6 min, 51% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[23-25]

*4.5.3.12. (S)- or (R)- 1-(furan-2-yl)-2-nitroethanol (**9l**).* Colorless oil, (*S*)-product: 34.6 mg, 88% yield, (*R*)-product: 34.2 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.41 (m, 1H), 6.40-6.38 (m, 2H), 5.47-5.44 (m, 1H), 4.78 (dd, *J* = 9.2 Hz, 13.2 Hz, 1H), 4.67 (dd, *J* = 3.2 Hz, 13.2 Hz, 1H), 3.13 (br s, 1H). The ee was determined by HPLC on Chiralcel AD-H (95:5 *n*-

hexane : isopropanol, 0.9 mL/min, 215 nm), t_R (minor) = 27.8 min, t_S (major) = 29.2 min, 97% ee. t_R (major) = 28.3 min, t_S (minor) = 29.8 min, 32% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[7b, 11, 21-22]

*4.5.3.13. (S)- or (R)- (E)-1-nitro-4-phenylbut-3-en-2-ol (**9m**).* Colorless oil, (*S*)-product: 43.5 mg, 90% yield, (*R*)-product: 40.6 mg, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 6.78 (d, *J* = 16.0 Hz, 1H), 6.14 (dd, *J* = 6.4 Hz, 16.0 Hz, 1H), 5.07-5.02 (m, 1H), 4.51 (d, *J* = 6.4 Hz, 2H), 2.76 (br s, 1H). The ee was determined by HPLC on Chiralcel OD-H (90:10 *n*-hexane : isopropanol, 0.9 mL/min, 215 nm), t_S (major) = 42.9 min, t_R (minor) = 48.7 min, 81% ee. t_S (minor) = 42.3 min, t_R (major) = 48.3 min, 38% ee. Configuration assignment: Absolute configuration of major isomer was determined by comparison of the retention time with literature data.[7b, 21-23]

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Supporting Information

Design of C_2-Symmetric Salen Ligands and Their Co(II)- or Yb(III)- Complexes Controlled Reversal of Enantioselectivity in Asymmetric Henry Reaction

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[c]*These authors contributed equally to this work.*

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2. Synthesis of the chiral ligand (S)-8……....S2

3. Tables of solvent and temperature effects of Henry reaction….S2

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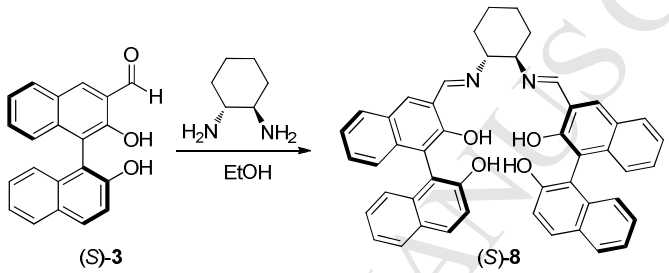
1) General information

General Methods. Unless otherwise noted, all the reactions were conducted under argon atmosphere. All reagents and solvents were dried and distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively using tetramethylsilane as an internal reference. Chemical shifts (δ) and coupling constants (J) were expressed in parts per million and hertz, respectively. Melting points were uncorrected. High-resolution mass spectrometry (HRMS) was performed with Electron Ionization (EI) resource or on an ESI-TOF spectrometer. The ee was determined by HPLC on AD, or OD column.

2) Synthesis of the chiral ligand (S)-8.



Scheme S1 Synthesis of the chiral ligand (*S*)-**8**.

3) Tables of solvent and temperature effects of Henry reaction

Table S1. Solvent screening of enantioselective Henry reaction catalyzed by Yb(^{i}PrO)$_3$/(*S*)-**5** system.[a]

Entry	Solvent	Yield(%)[b]	ee(%)[c]
1	MeOH/THF = 2/1	84	68
2	MeOH	87	66
3	EtOH	75	57
4	^{i}PrOH	40	52
5	CH_3CN	n.r	/
6	CH_2Cl_2	n.r	/
7	DMF	n.r	/
8	THF	42	3
9	MeOH/THF = 4/1	67	64
10	MeOH/THF = 3/2	84	77

11	MeOH/THF = 1/1	90	79
12	MeOH/THF = 2/3	89	80
13	**MeOH/THF = 1/4**	**93**	**87**
14	MeOH/THF = 1/5	78	79
15	MeOH/THF = 1/6	72	33
16	MeOH/THF = 1/7	57	50
17	MeOH/THF = 1/9	46	22

[a] Reaction conditions: benzaldehyde (0.25 mmol), nitromethane (1.25 mmol), ligand (6 mol%), $Yb(O^iPr)_3$ (5 mol%), solvent (1.5 mL), and 48 h for reaction time at 15 ^oC. [b] Isolated yields. [c] Determined by chiral HPLC.

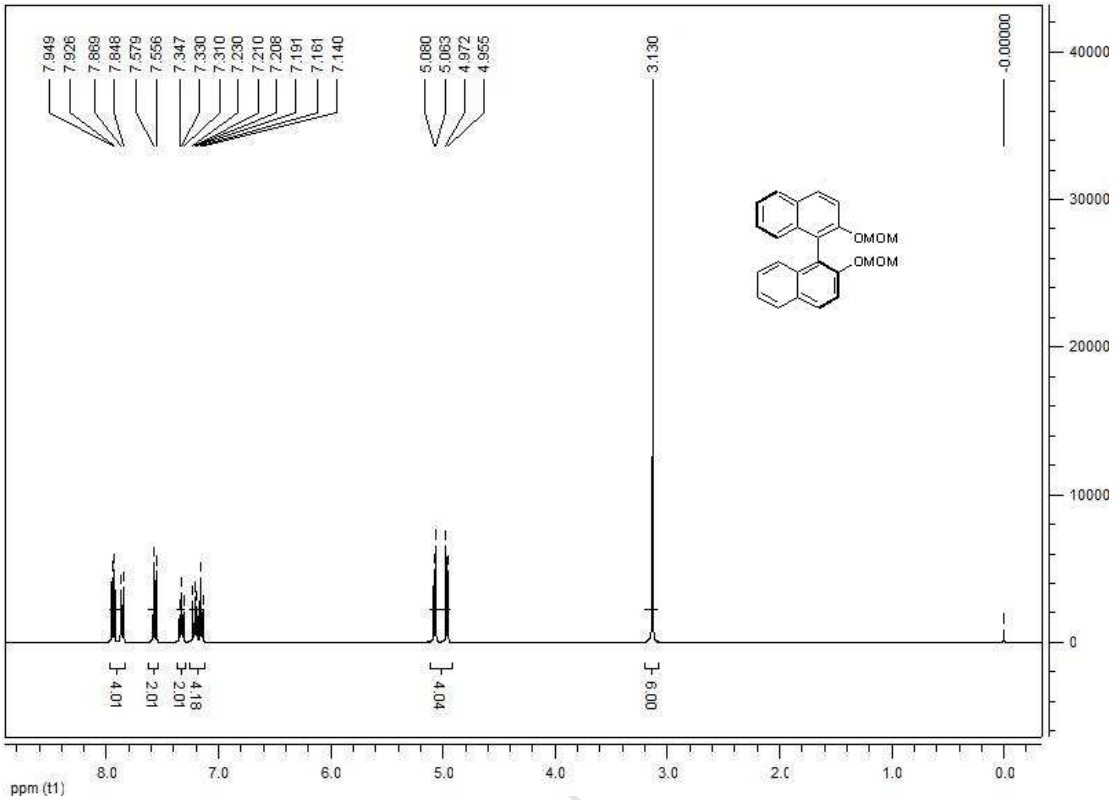
Table S2. Temperature effect of enantioselective Henry reaction catalyzed by $Yb(^iPrO)_3$/(*S*)-5 system.[a]

Entry	**Temp (^{o}C)**	**Time (h)**	**Yield (%)[b]**	**ee (%)[c]**
1	-10	84	23	76
2	0	84	70	74
3	5	72	82	79
4	**15**	**48**	**93**	**87**
5	r.t.	36	94	65
6	40	24	98	35

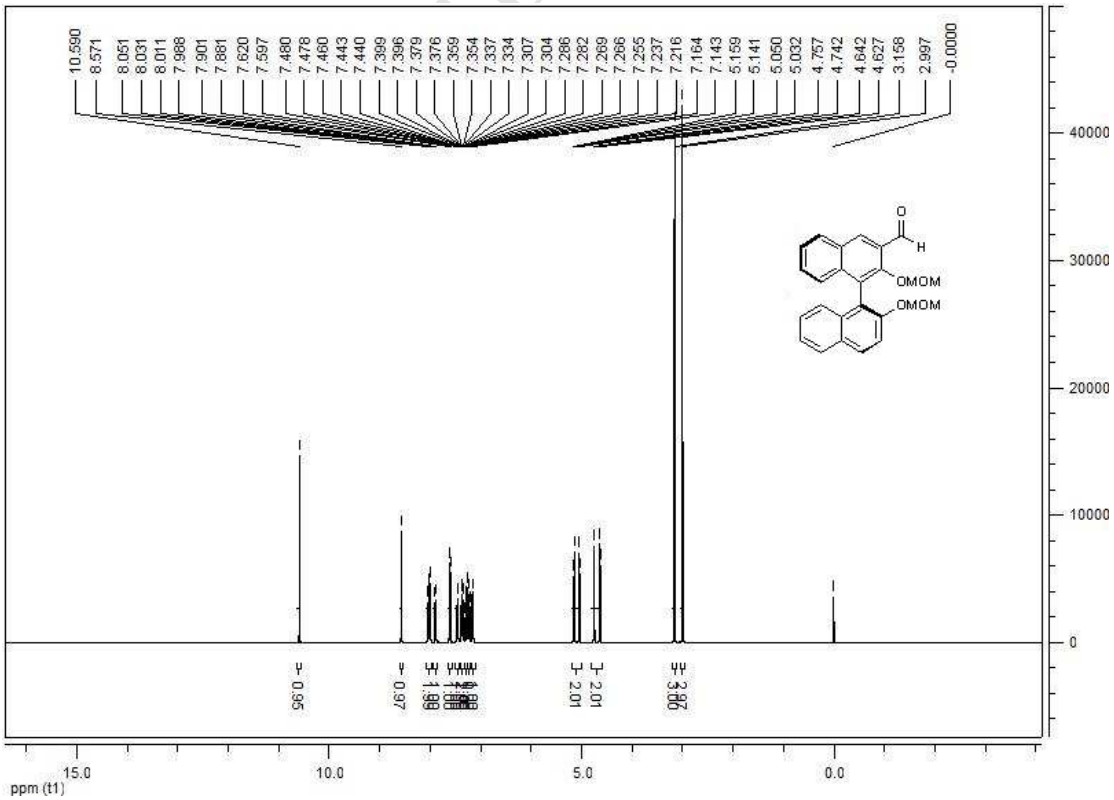
[a] Reaction conditions: benzaldehyde (0.25 mmol), nitromethane (1.25 mmol), ligand (6 mol%), $Yb(O^iPr)_3$ (5 mol%), MeOH/THF (1/4, *v/v*, 1.5 mL) at different temperature. [b] Isolated yields. [c] Determined by chiral HPLC.

4) ^{1}H and ^{13}C NMR spectra for ligands

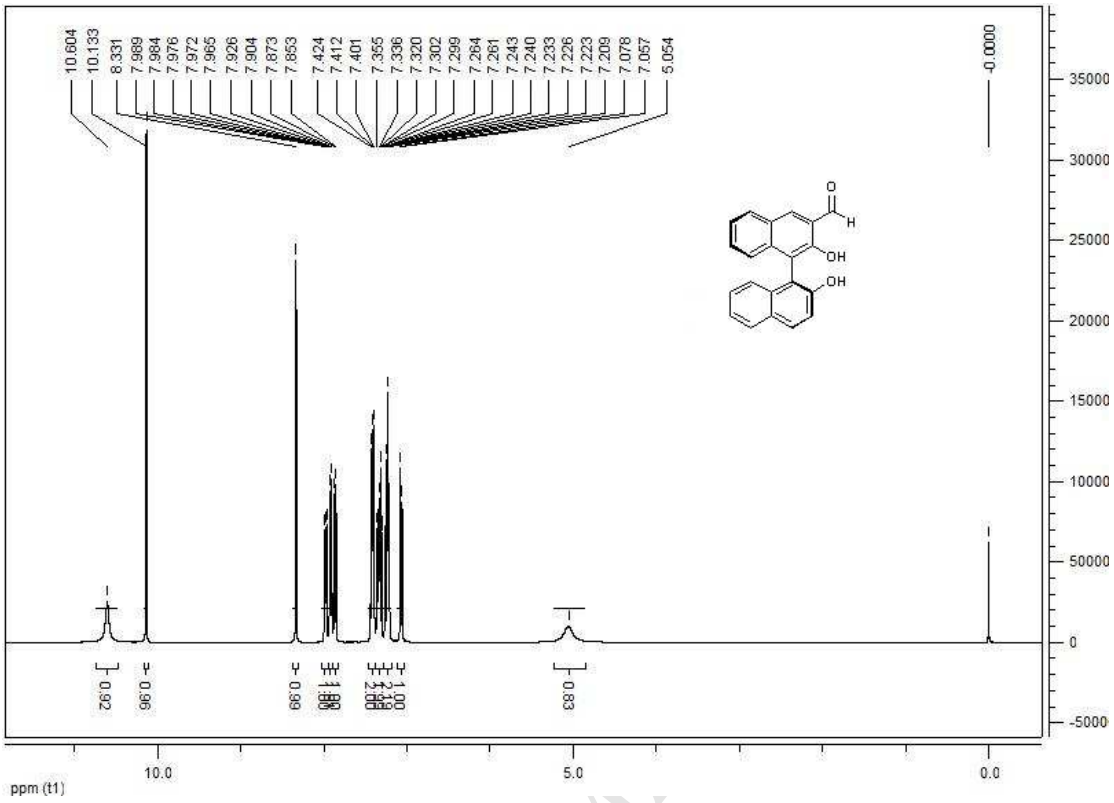
^{1}H NMR spectrum of (*S*)-**1**.



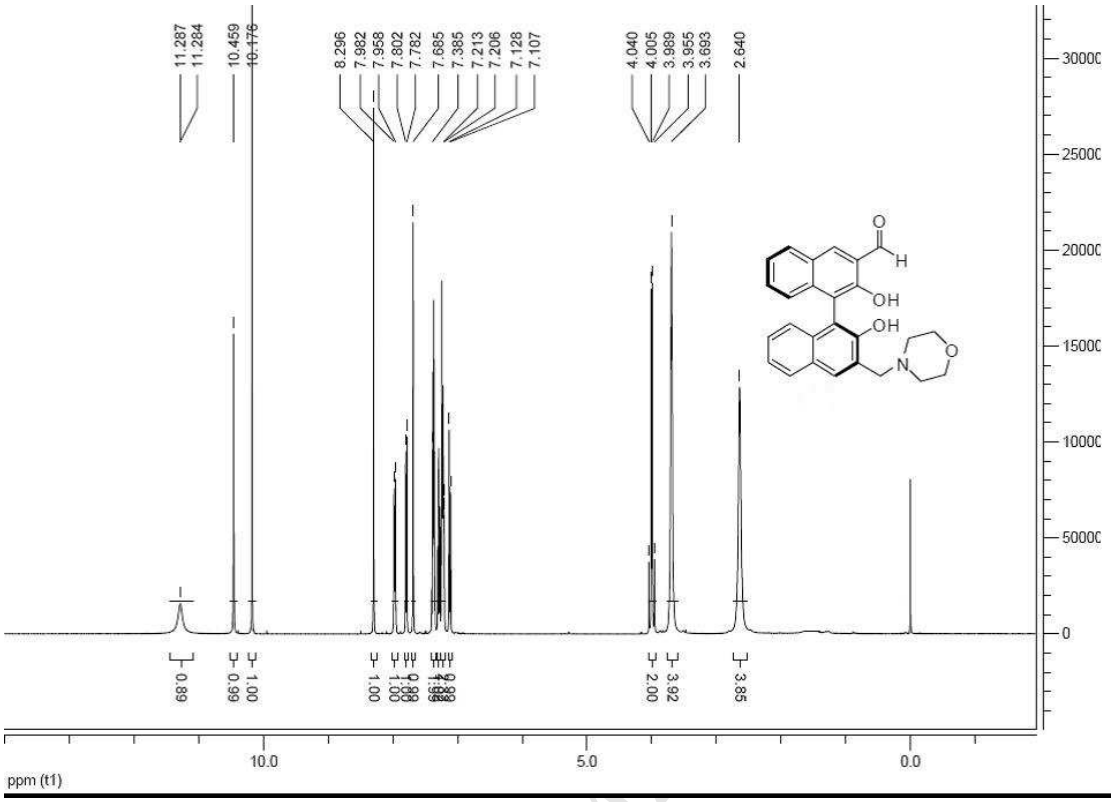
^{1}H NMR spectrum of (*S*)-**2**.



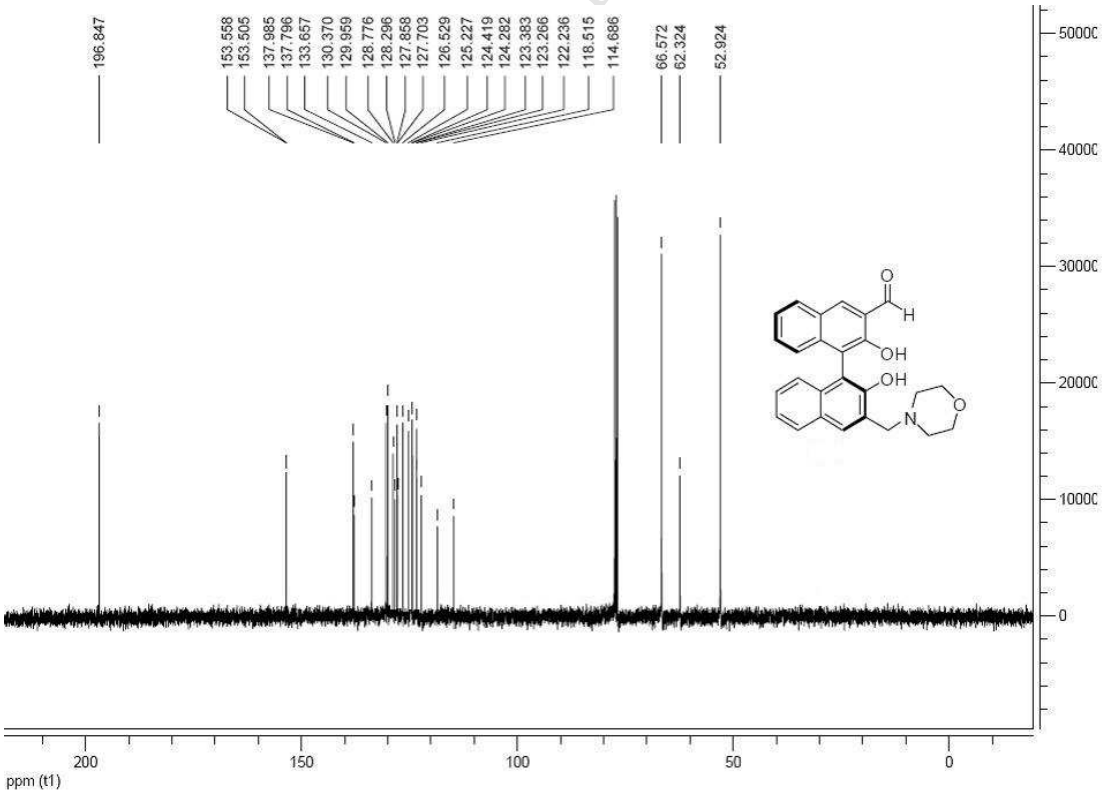
^{1}H NMR spectrum of (*S*)-**3**.



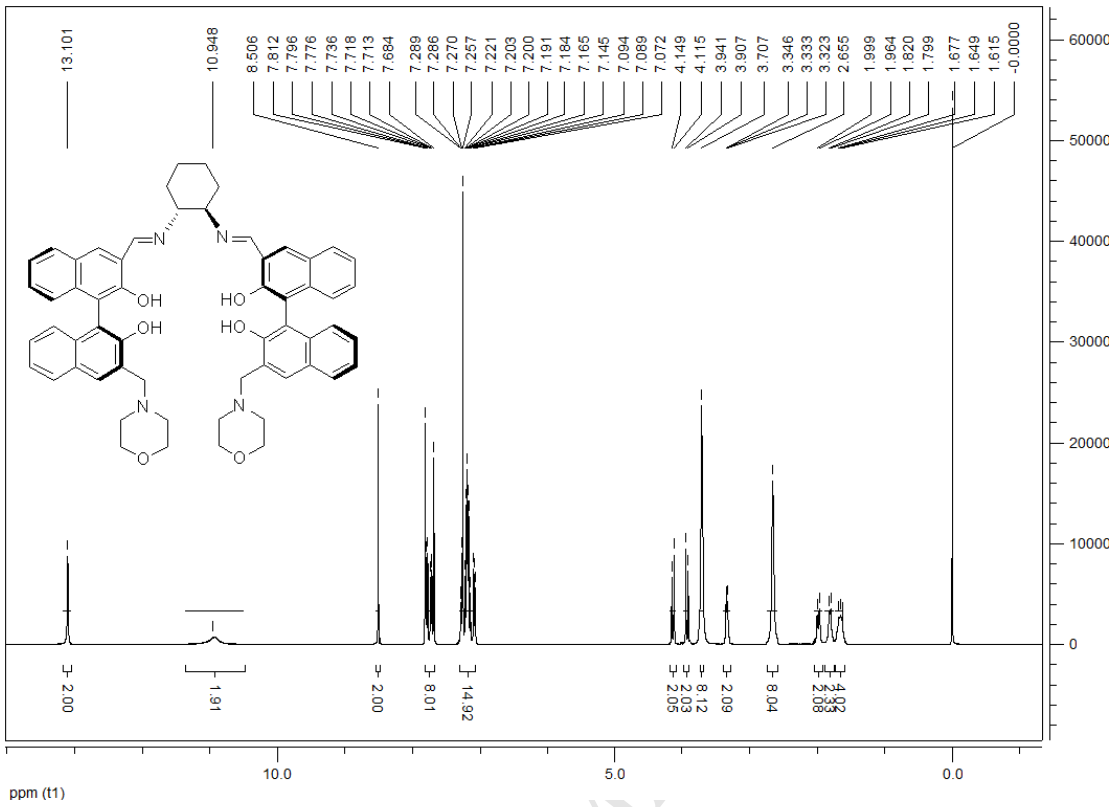
^{1}H NMR spectrum of (*S*)-**4**.



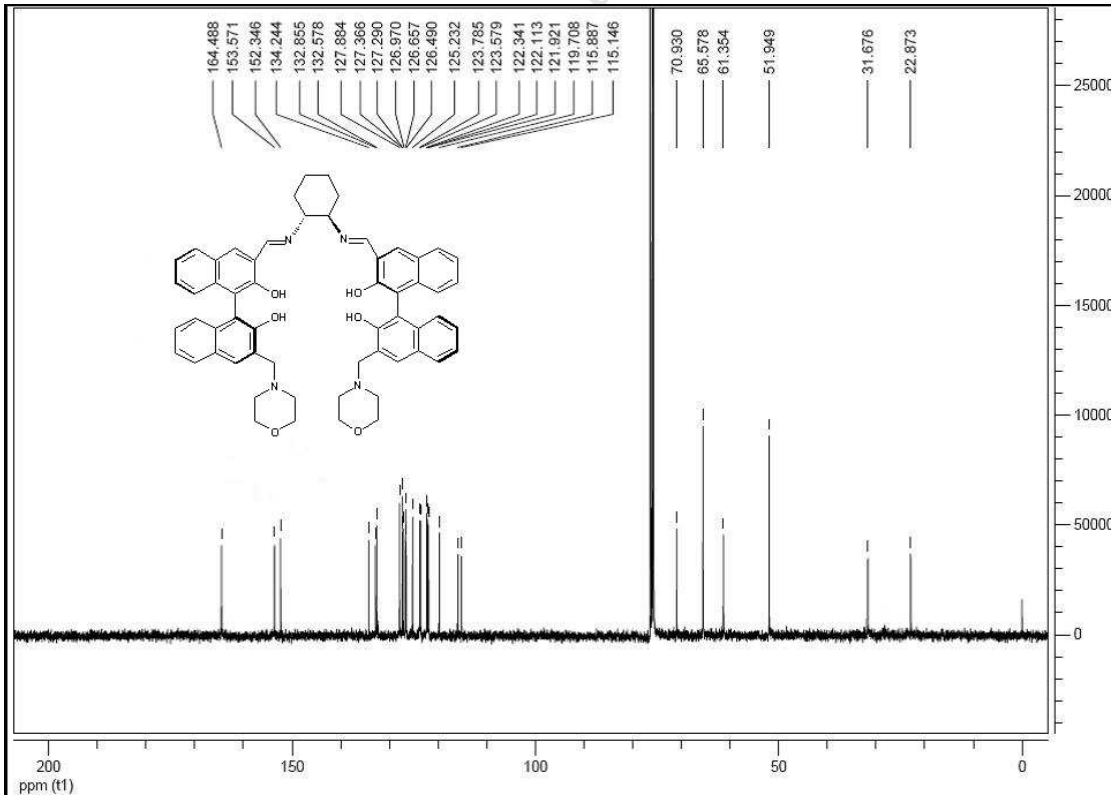
^{13}C NMR spectrum of (*S*)-**4**.



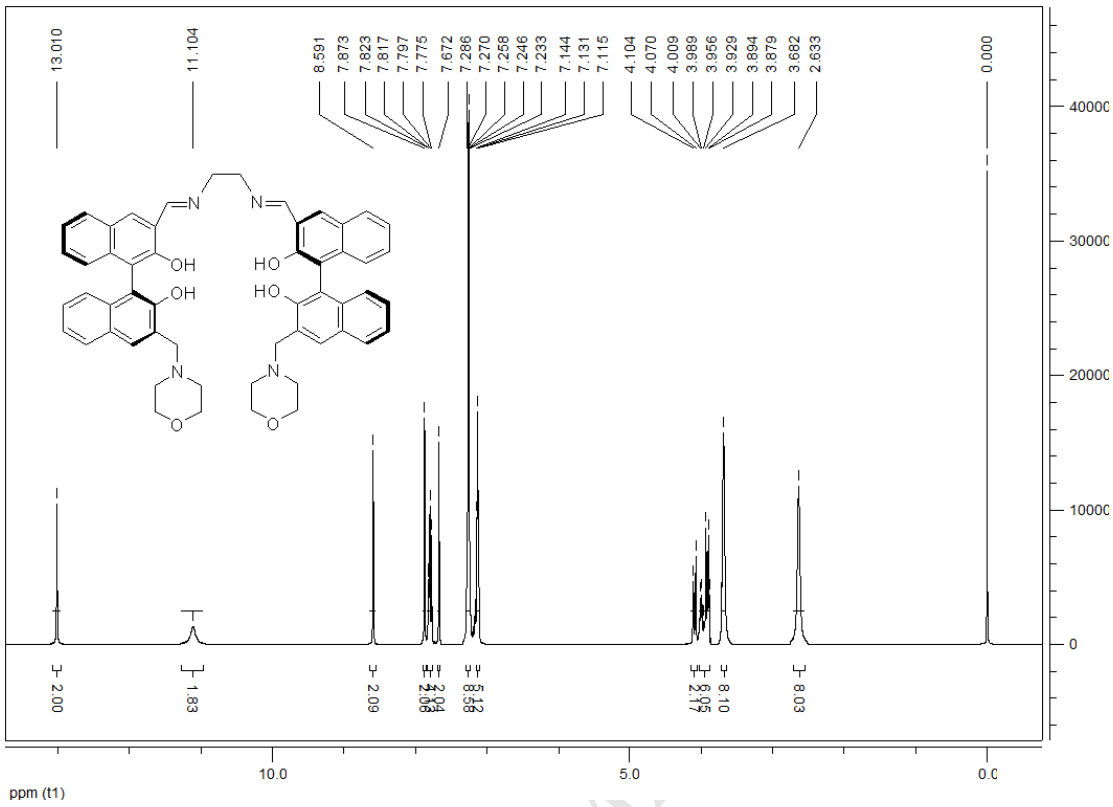
^{1}H NMR spectrum of (*S*)-**5**.



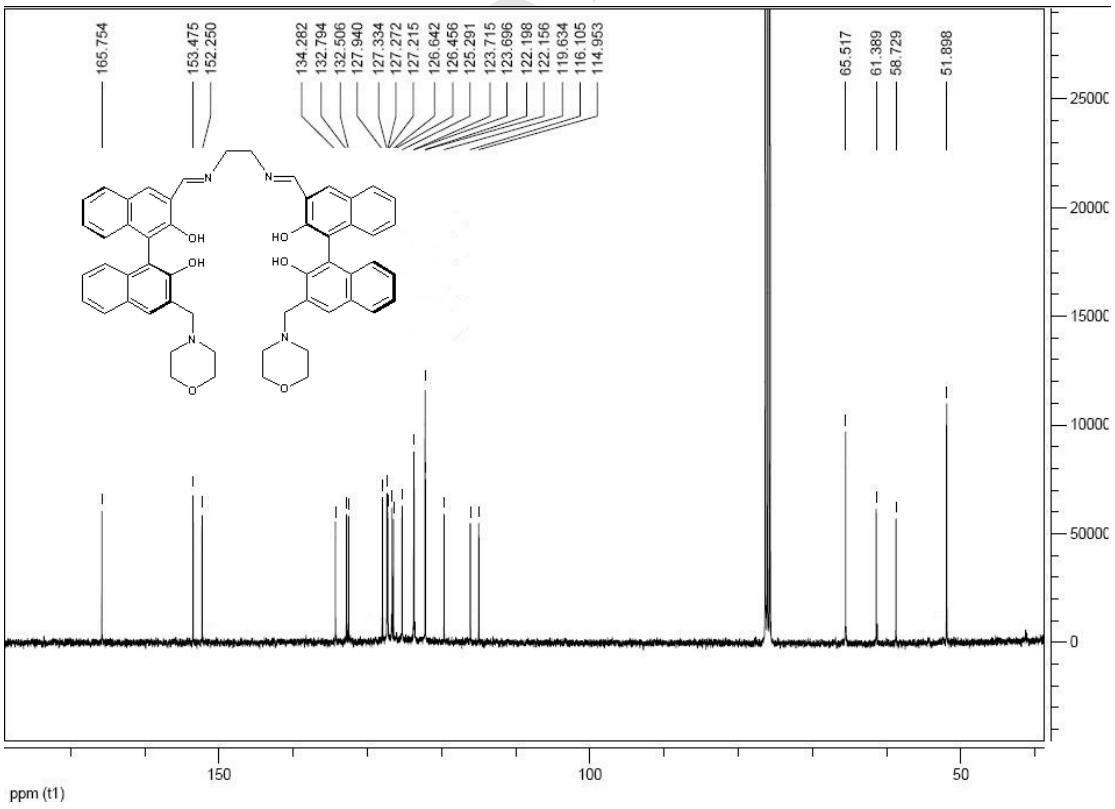
^{13}C NMR spectrum of (*S*)-**5**.



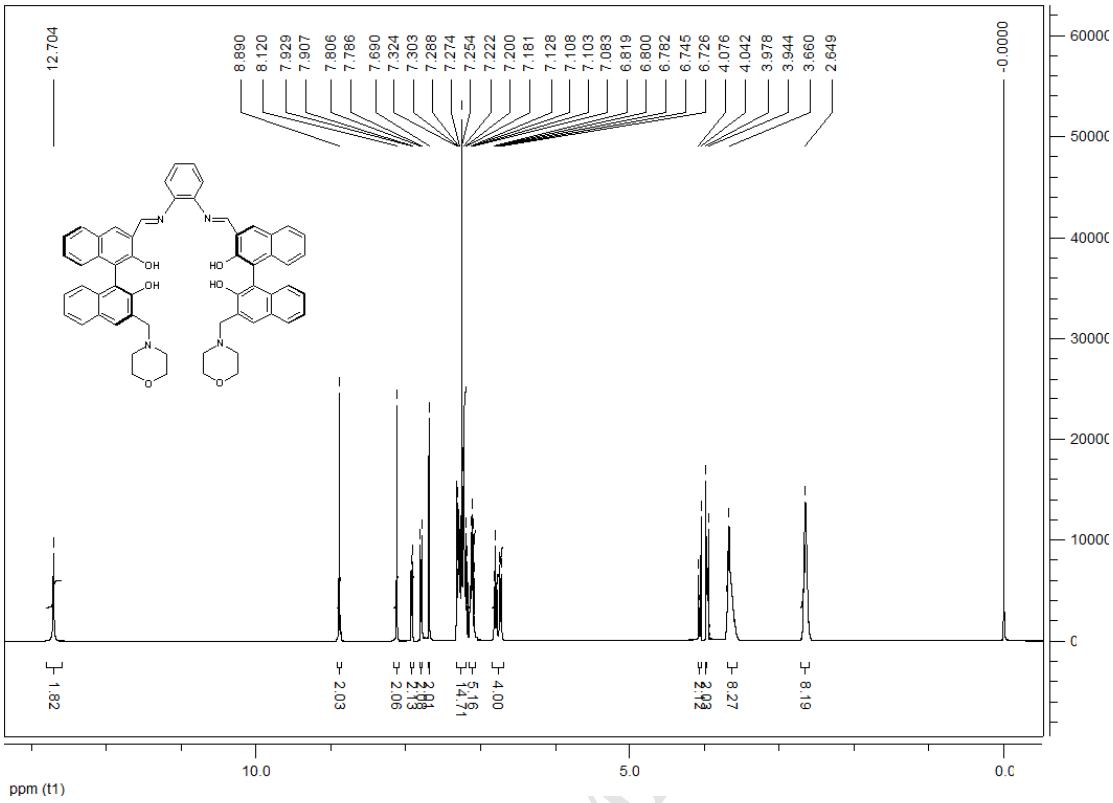
^{1}H NMR spectrum of (*S*)-**6**.



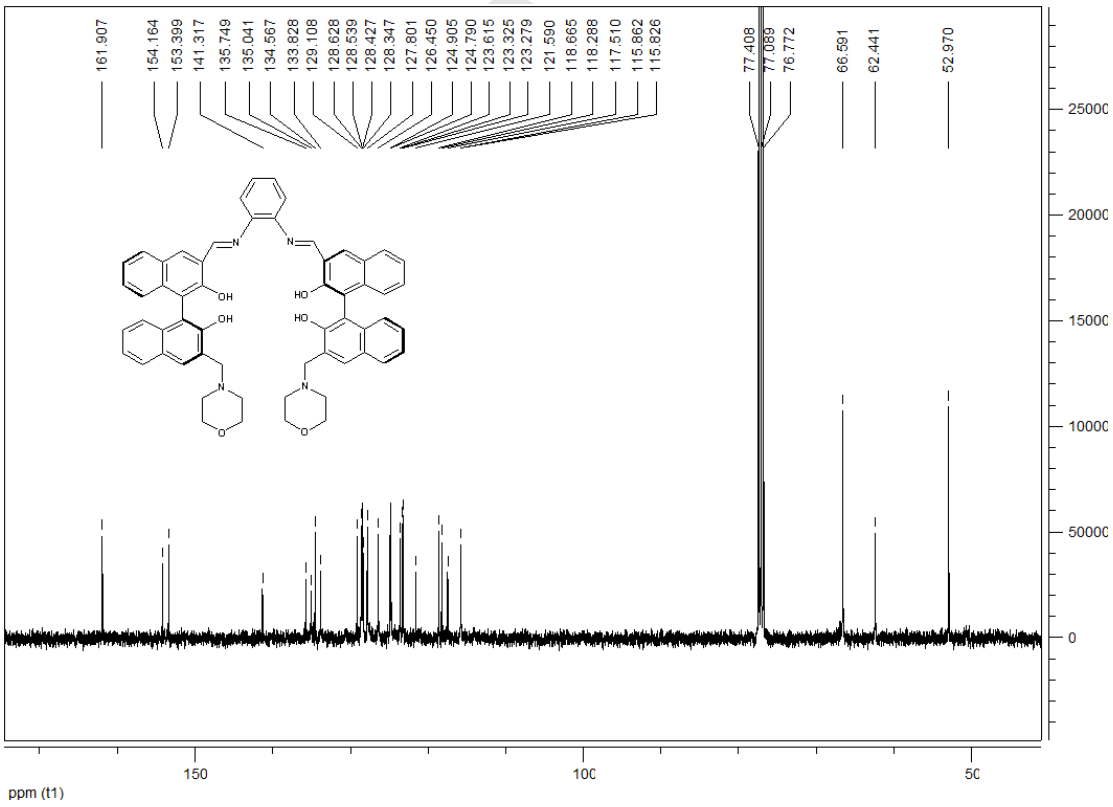
^{13}C NMR spectrum of (*S*)-**6**.



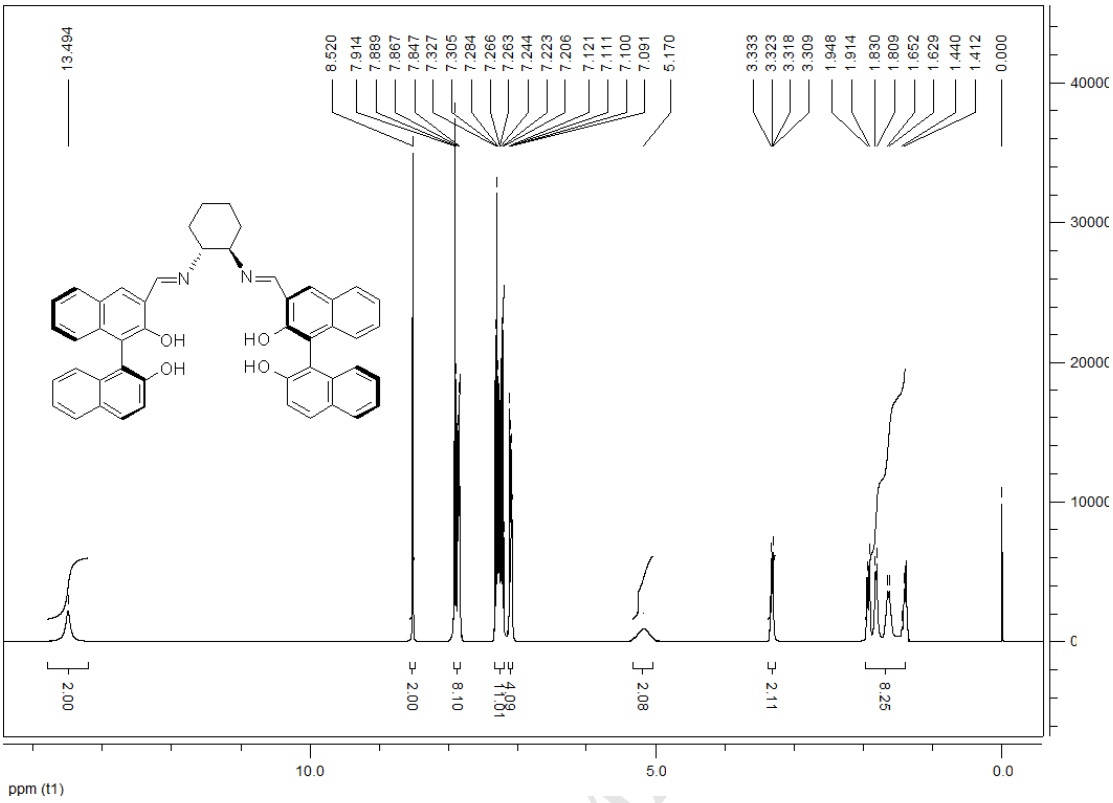
^{1}H NMR spectrum of (*S*)-**7**.



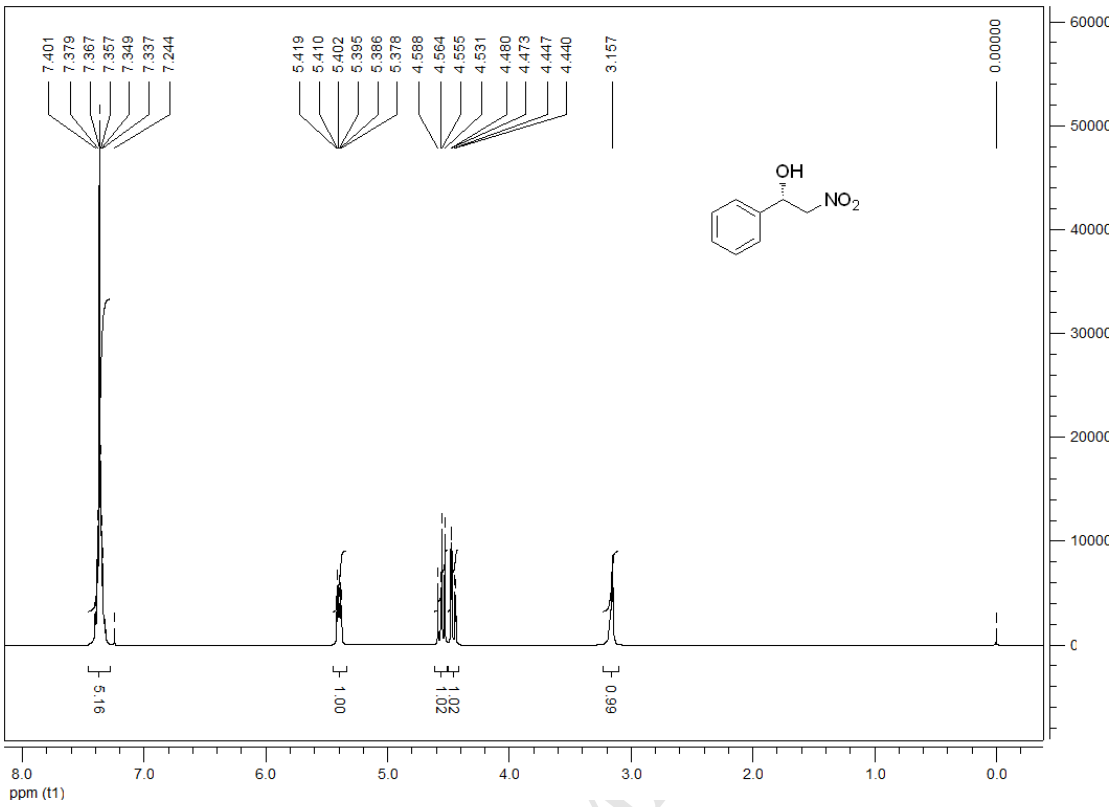
^{13}C NMR spectrum of (*S*)-**7**.

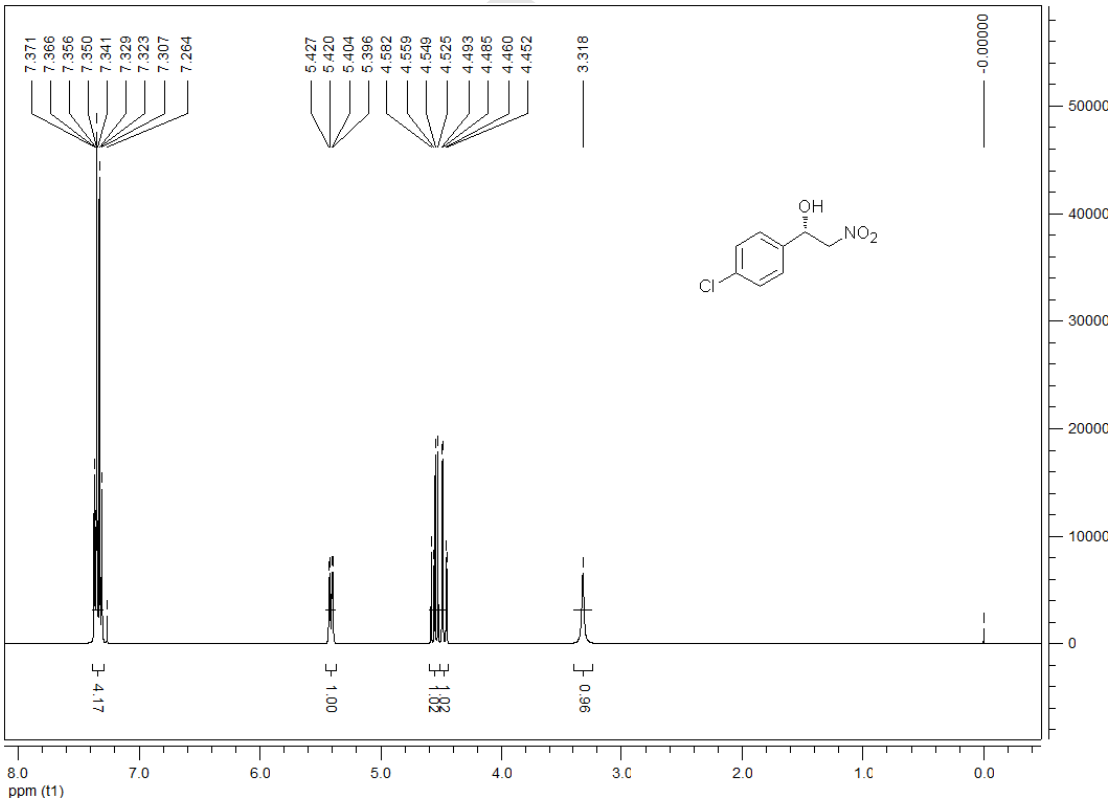


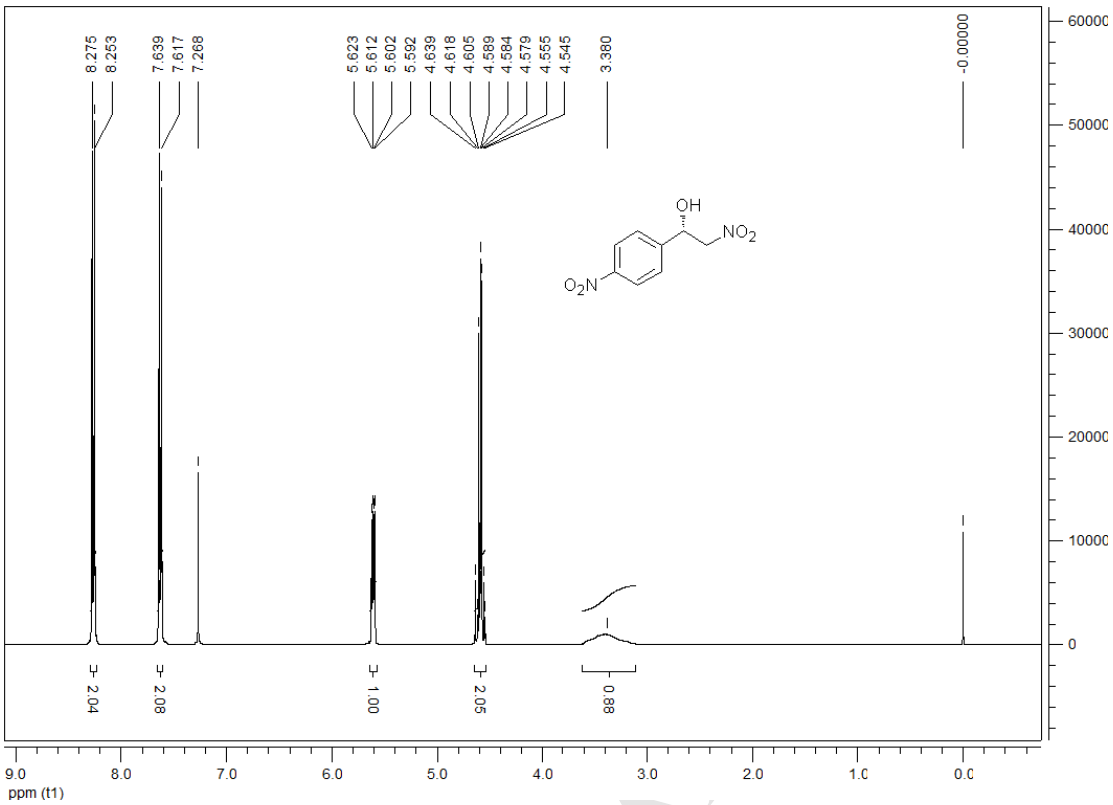
^{1}H NMR spectrum of (*S*)-**8**.



5) ^{1}H NMR spectra of Henry products



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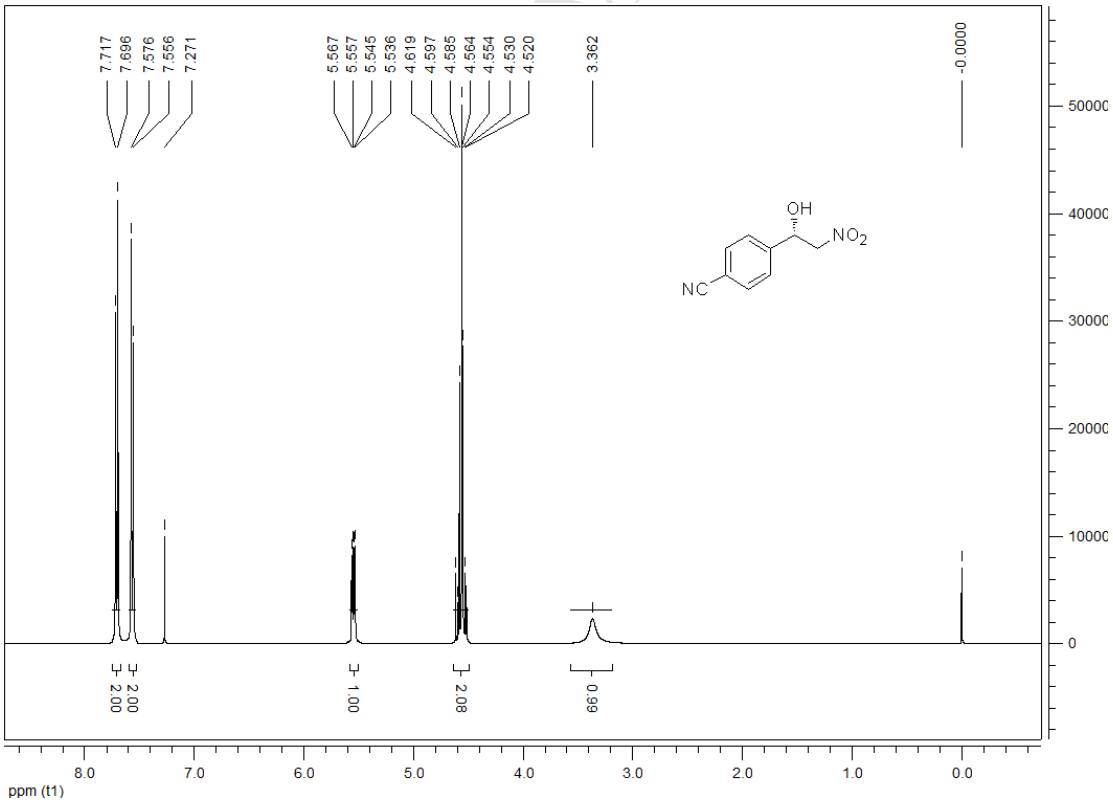
ppm (t1)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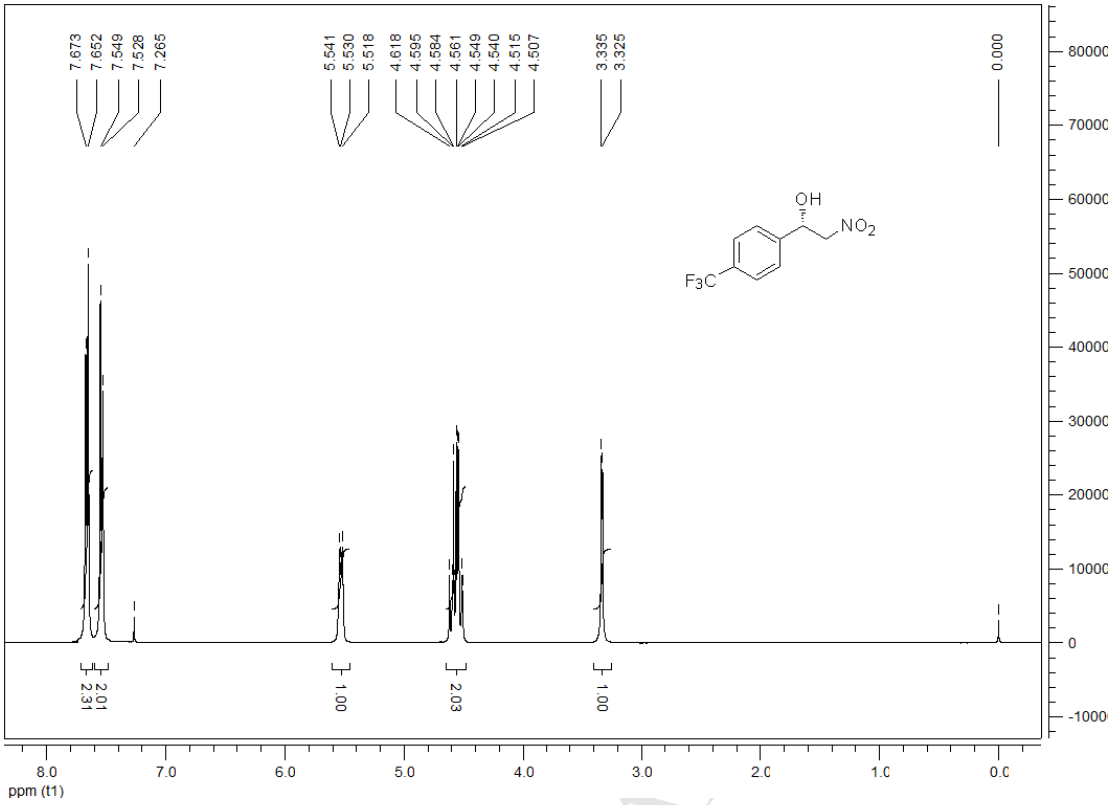
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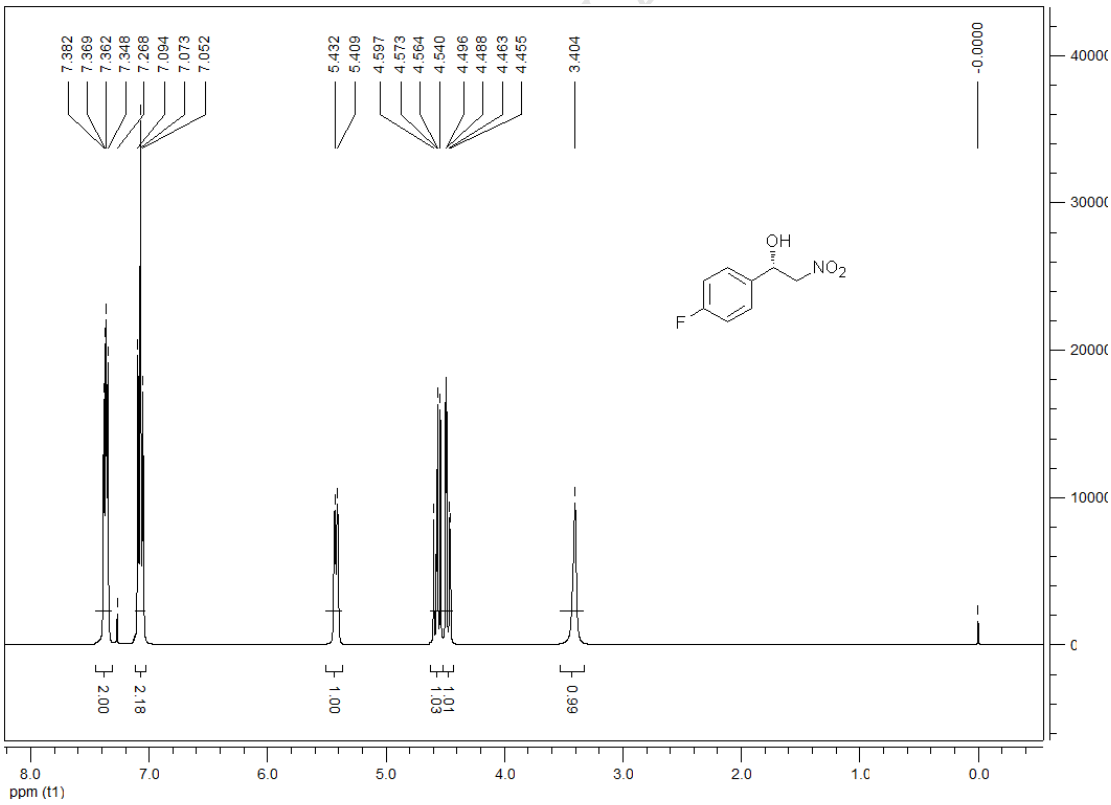
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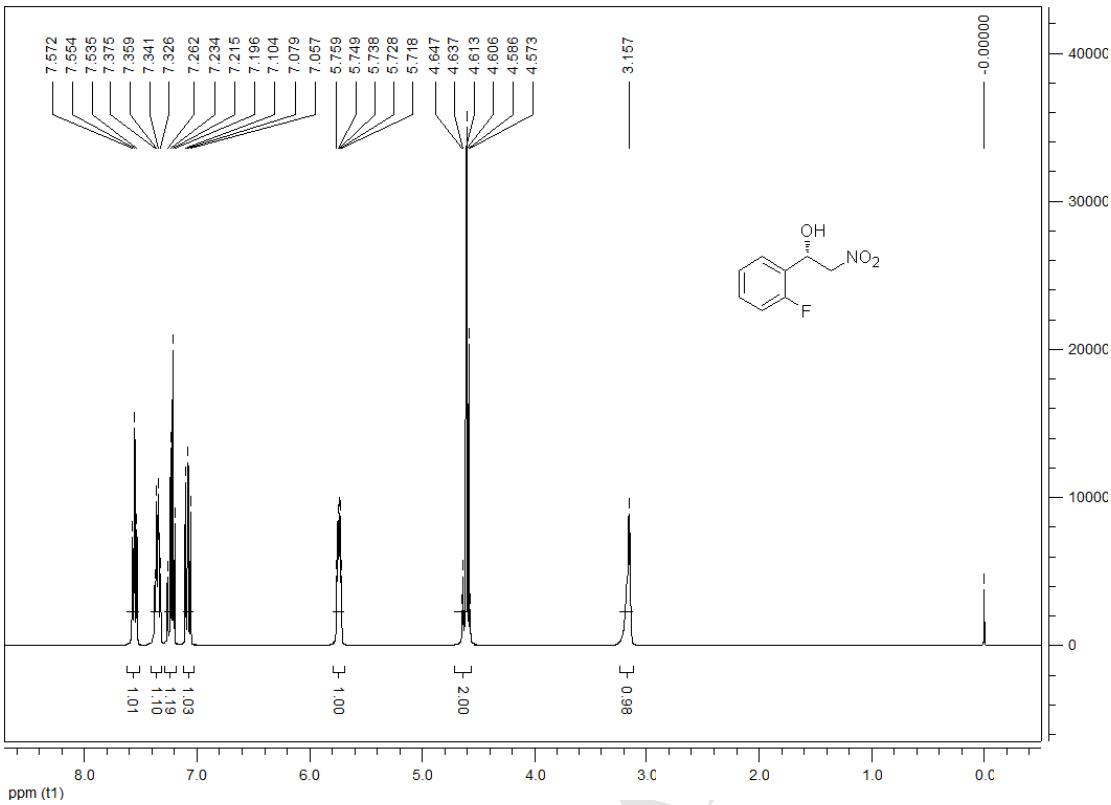
ppm (t1)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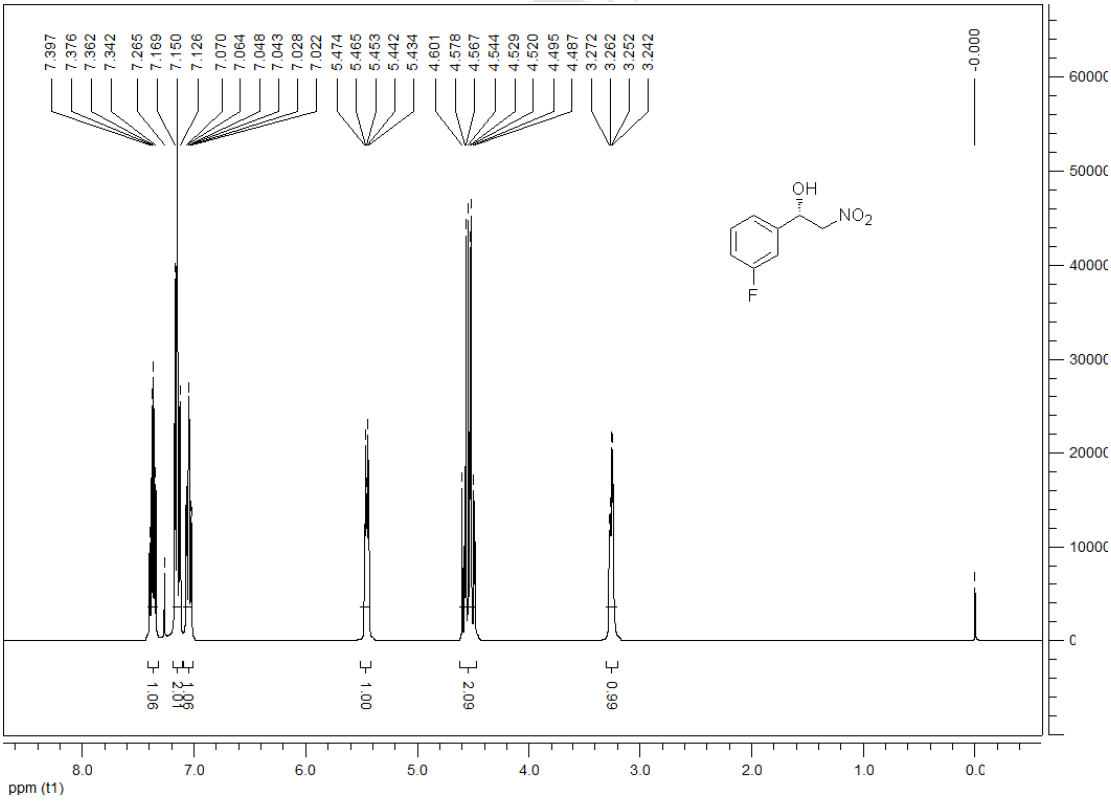
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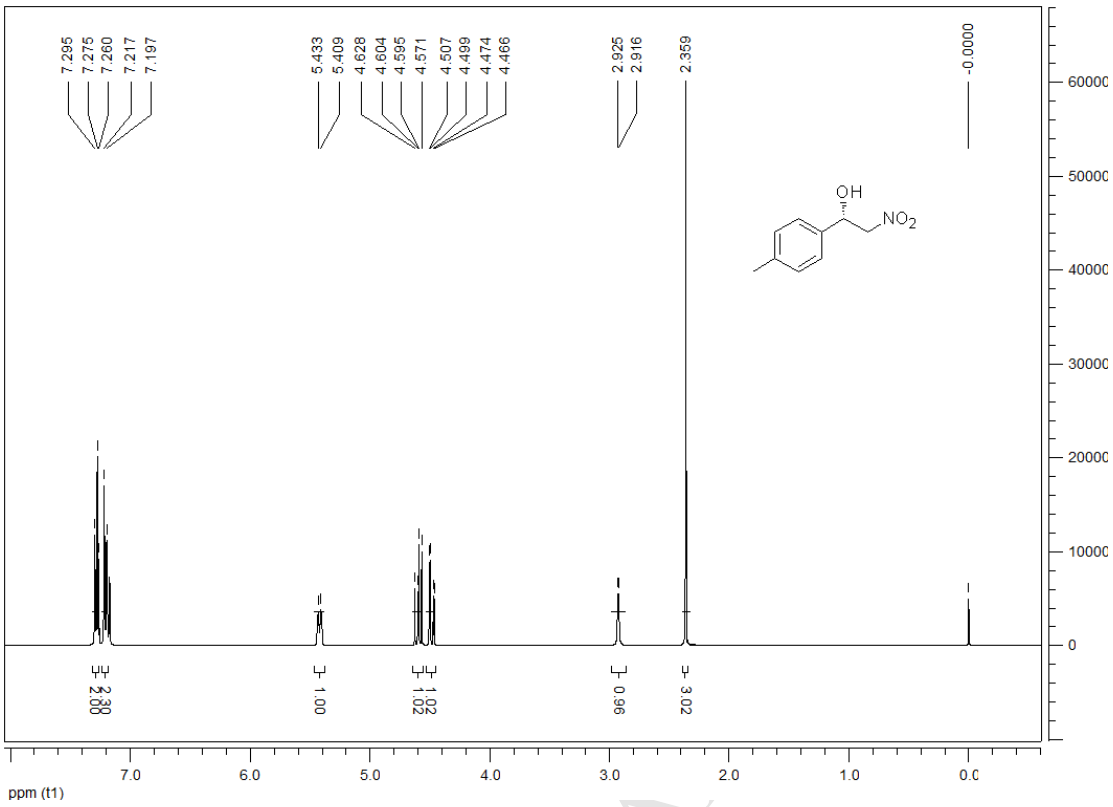
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4.466
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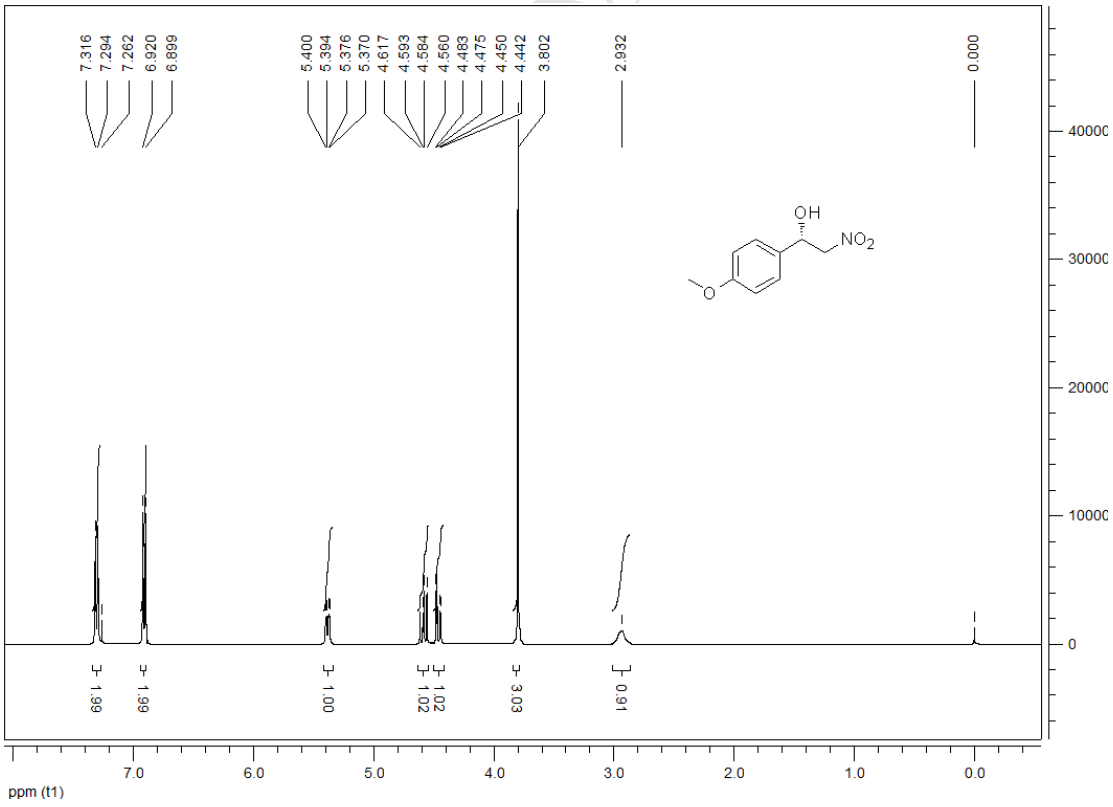
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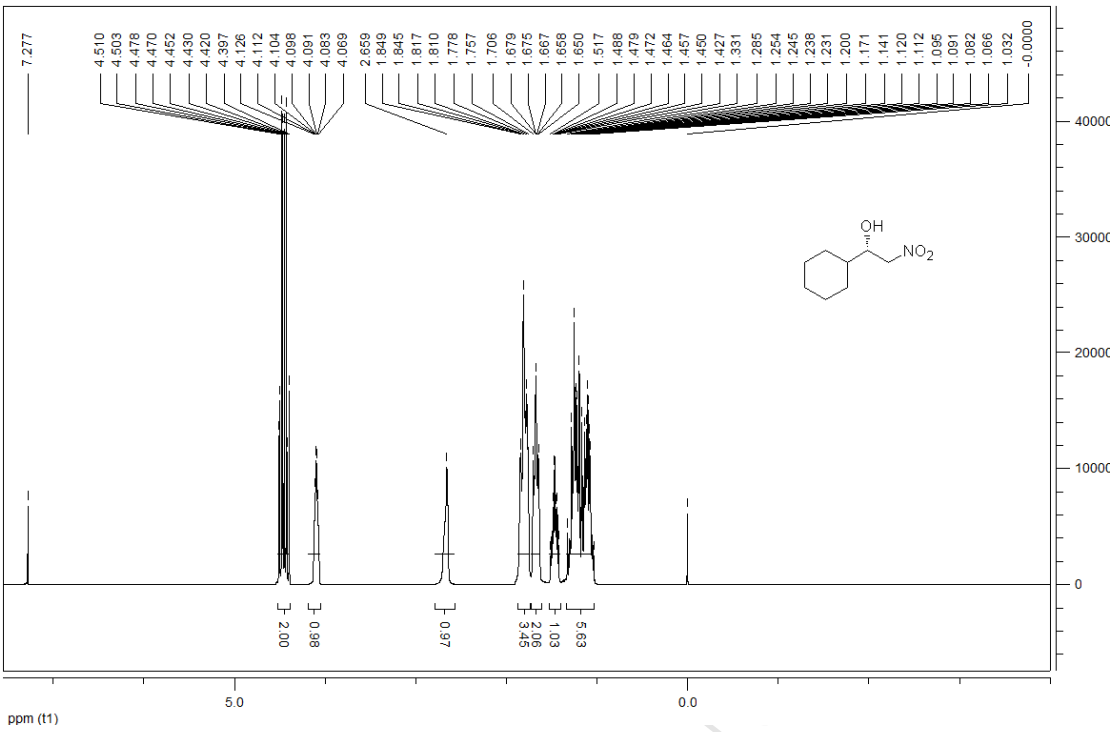
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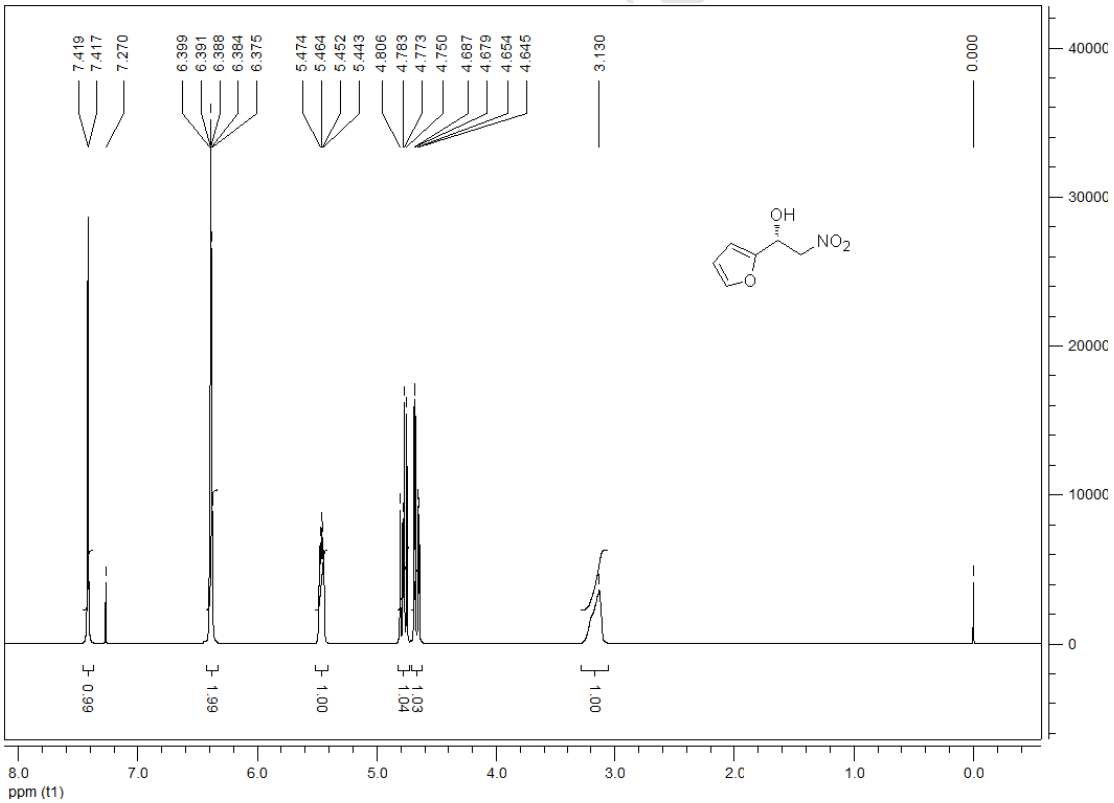
ppm (t1)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7.417
7.270
6.399
6.391
6.388
6.384
6.375
5.474
5.464
5.452
5.443
4.806
4.783
4.773
4.750
4.687
4.679
4.654
4.645
3.130
0.000
OH
NO2
O
0.99
1.99
1.00
1.04
1.03
1.00
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5.0
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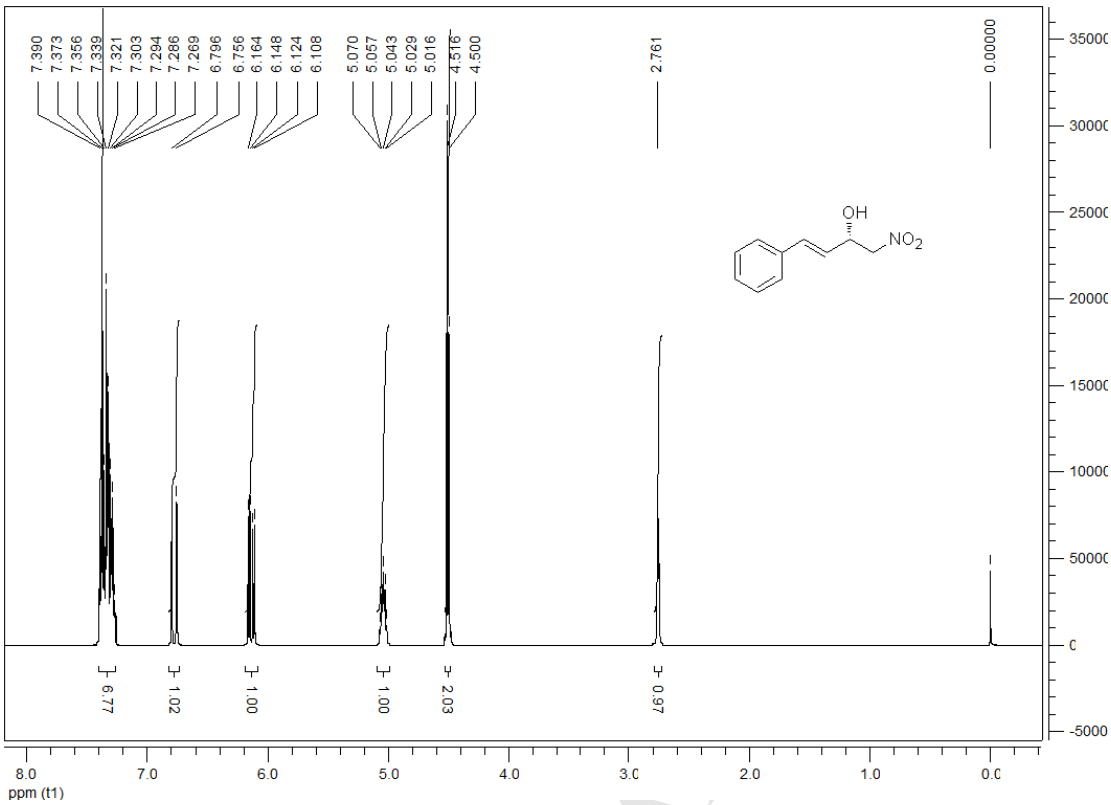
ppm (t1)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6.124
6.108
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5.057
5.043
5.029
5.016
4.516
4.500
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NO2
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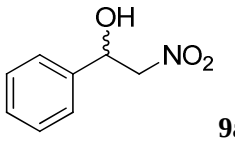
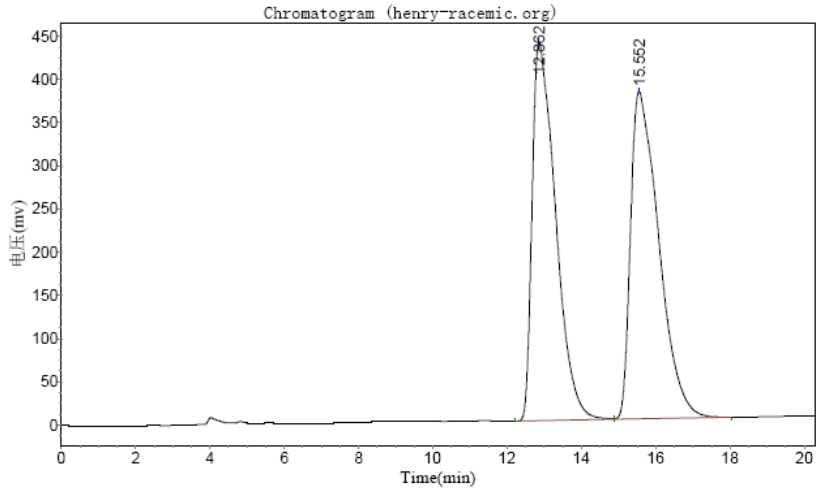
1.00
1.00
2.03
0.97
ppm (t1)

7) HPLC spectra of Henry products



9a

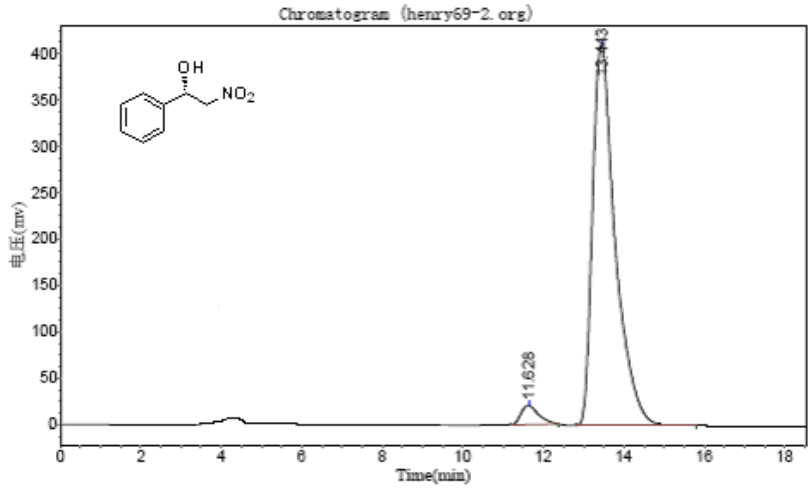
HPLC spectrum of racemic-**9a.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		12.862	437973.188	19228100.000	49.0409
2		15.552	378682.438	19980204.000	50.9591
Total			816655.625	39208304.000	100.0000

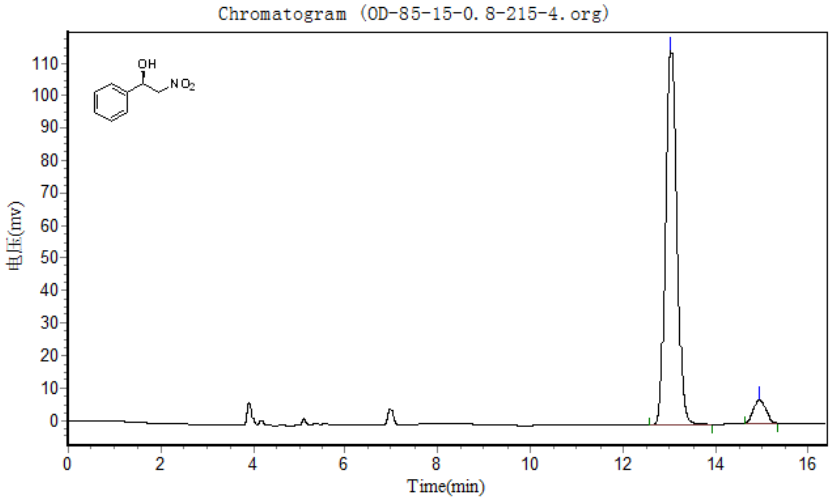
HPLC spectrum of (*S*)-**9a.**



Results

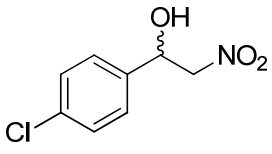
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		11.628	20821.027	640428.813	3.8397
2		13.443	410741.906	16038862.000	96.1603
Total			431562.934	16679290.813	100.0000

HPLC spectrum of (*R*)-**9a.**



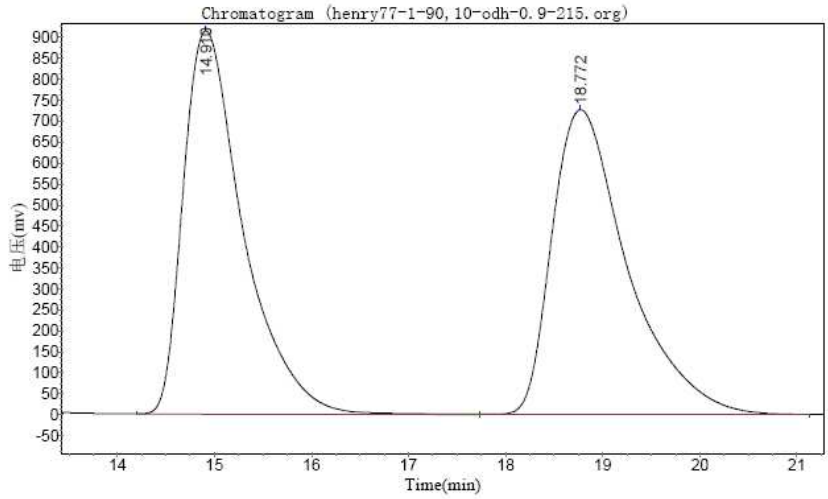
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.032	115094.211	1951055.125	93.5057
2		14.942	7421.985	135506.594	6.4943
Total			122516.196	2086561.719	100.0000



9b

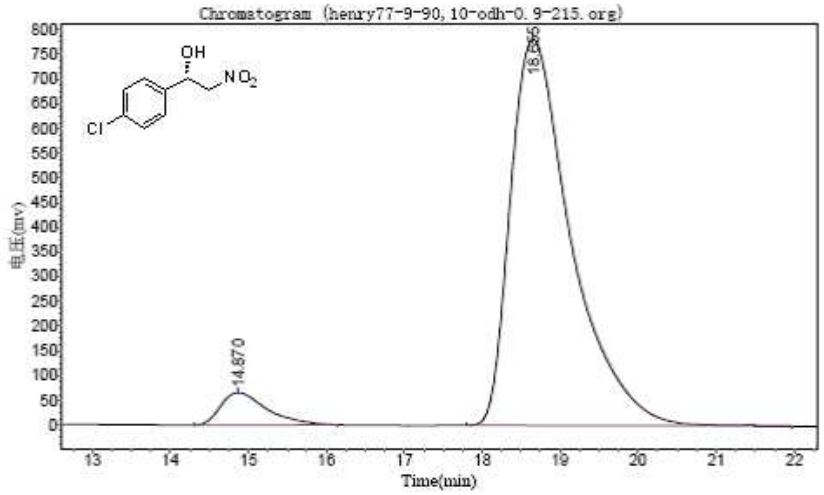
HPLC spectrum of racemic-**9b.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.910	914039.250	39189696.000	49.9120
2		18.772	726737.500	39327864.000	50.0880
Total			1640776.750	78517560.000	100.0000

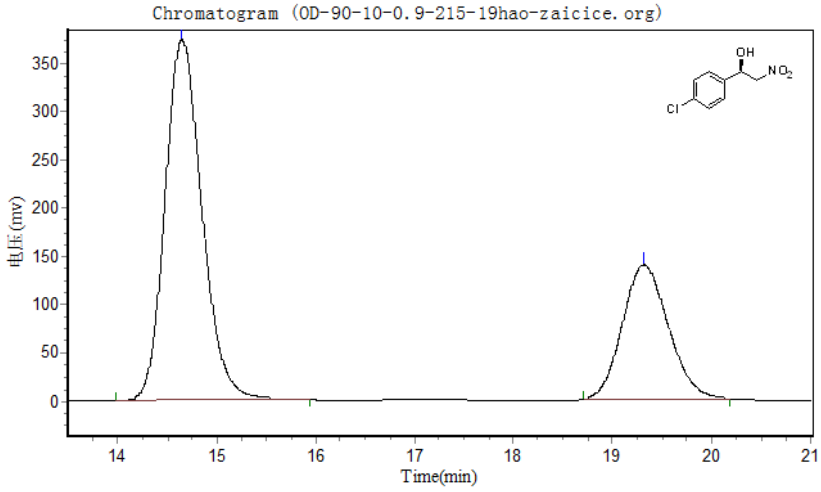
HPLC spectrum of (*S*)-**9b.**



Results

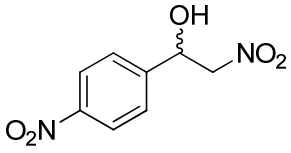
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.870	65522.977	2697721.250	6.0006
2		18.655	781683.750	42260008.000	93.9994
Total			847206.727	44957729.250	100.0000

HPLC spectrum of (*R*)-**9b.**



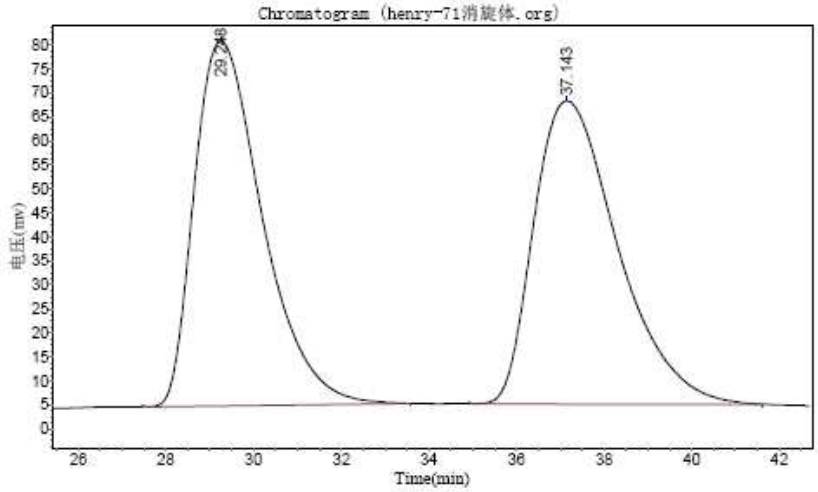
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.647	374054.125	9674820.000	68.3815
2		19.315	138695.203	4473478.000	31.6185
Total			512749.328	14148298.000	100.0000



9c

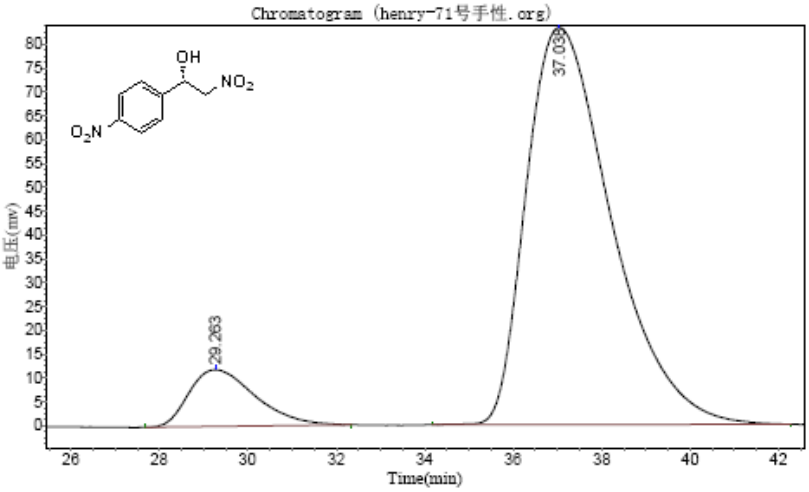
HPLC spectrum of racemic-**9c.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		29.248	75997.906	8210655.500	49.4224
2		37.143	63201.176	8402586.000	50.5776
Total			139199.082	16613241.500	100.0000

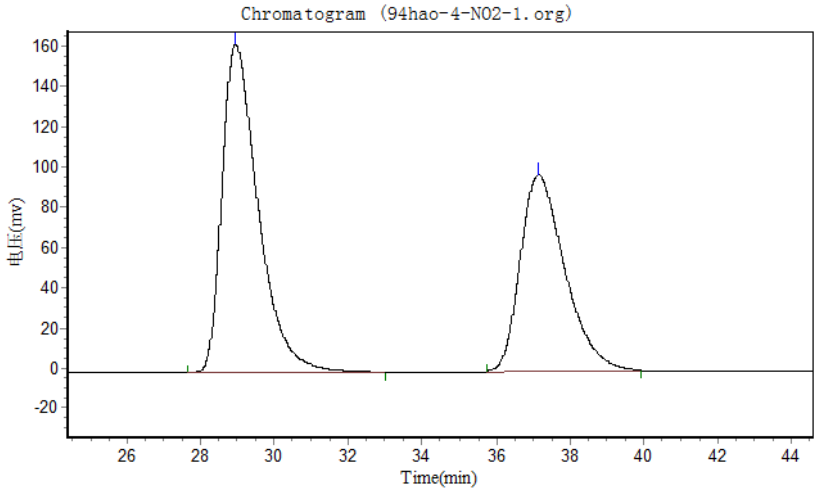
HPLC spectrum of (*S*)-**9c.**



Results

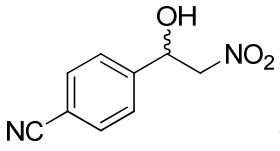
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		29.263	11892.097	1243948.125	10.0505
2		37.038	83172.508	11132979.000	89.9495
Total			95064.604	12376927.125	100.0000

HPLC spectrum of (*R*)-**9c.**



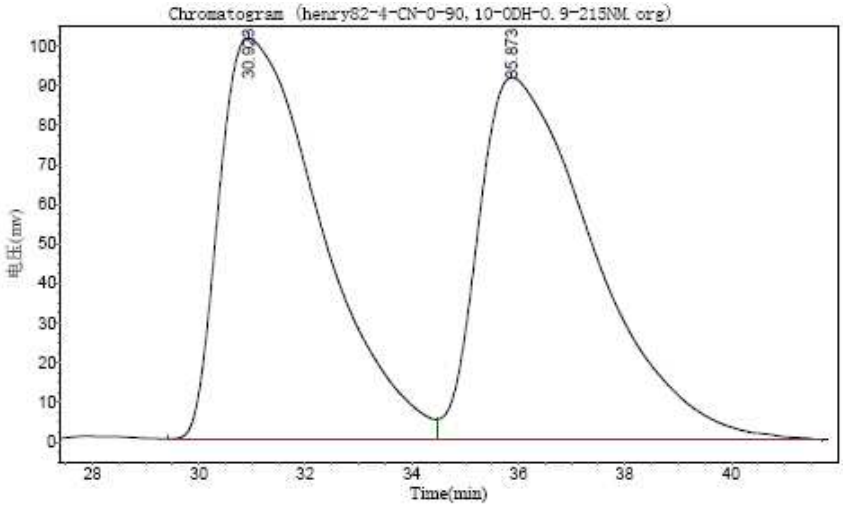
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		29.227	163822.703	11227461.000	57.8907
2		37.130	97502.570	8166769.500	42.1093
Total			261325.273	19394230.500	100.0000



9d

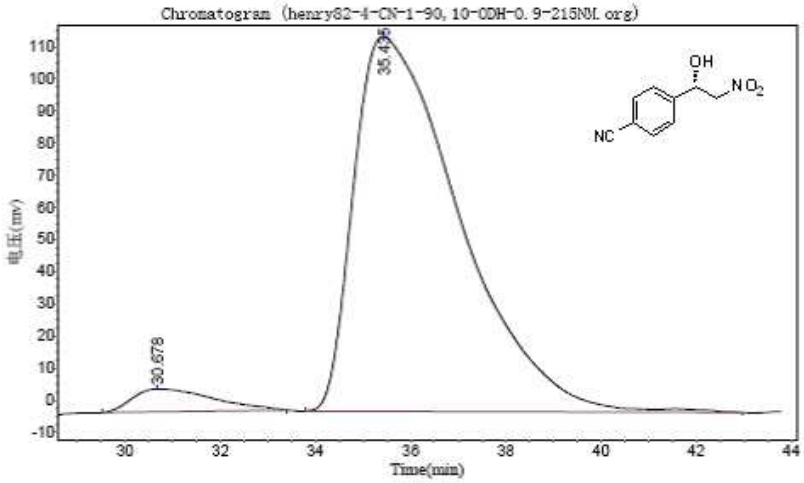
HPLC spectrum of racemic-**9d.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		30.923	101118.195	13461716.000	49.4625
2		35.873	91284.211	13754300.000	50.5375
Total			192402.406	27216016.000	100.0000

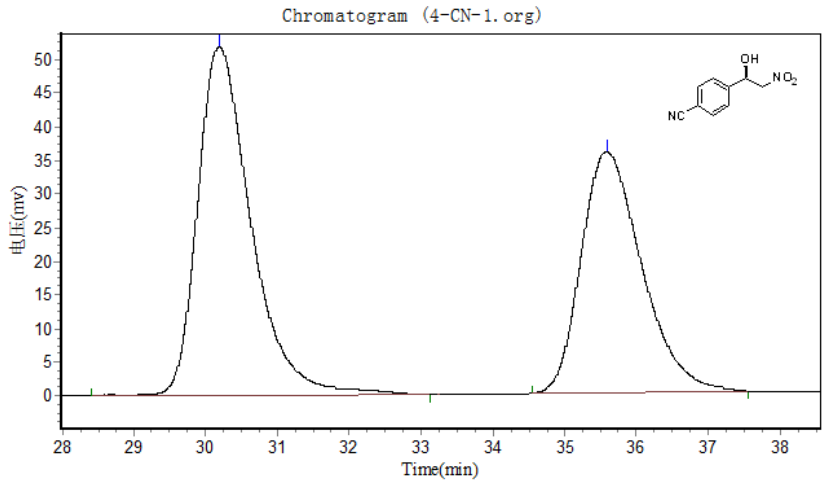
HPLC spectrum of (*S*)-**9d.**



Results

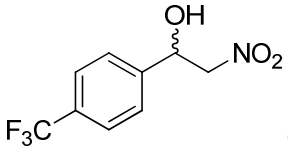
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		30.678	7168.149	845214.625	4.5009
2		35.435	116433.016	17933394.000	95.4991
Total			123601.165	18778608.625	100.0000

HPLC spectrum of (*R*)-**9d.**



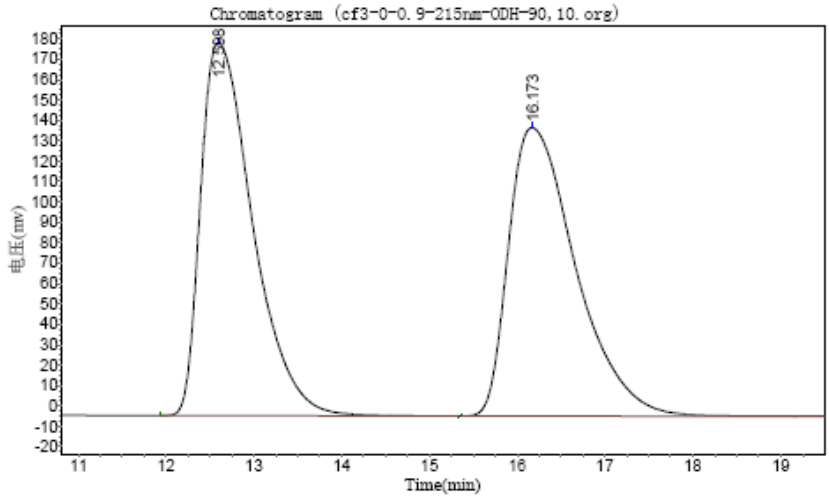
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		30.260	51795.199	3835072.500	56.0263
2		35.593	35780.547	3010059.500	43.9737
Total			87575.746	6845132.000	100.0000



9e

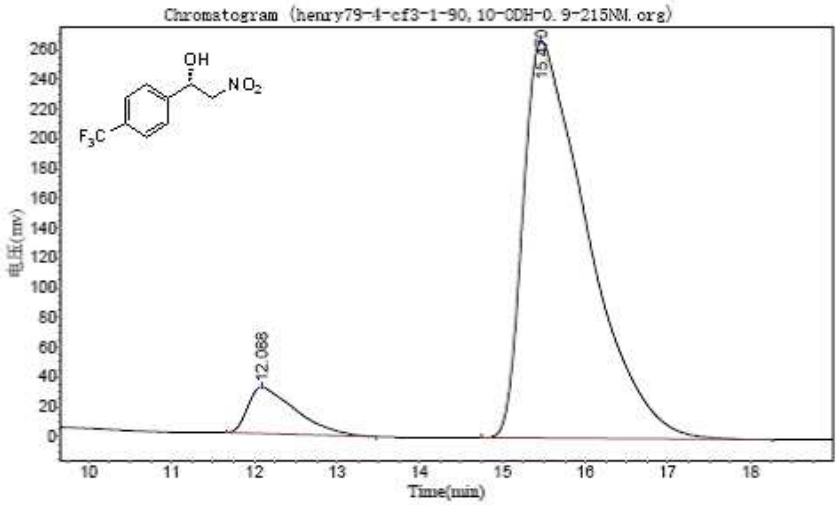
HPLC spectrum of racemic-**9e.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		12.598	182584.188	7526459.500	49.9580
2		16.173	141309.766	7539100.500	50.0420
Total			323893.953	15065560.000	100.0000

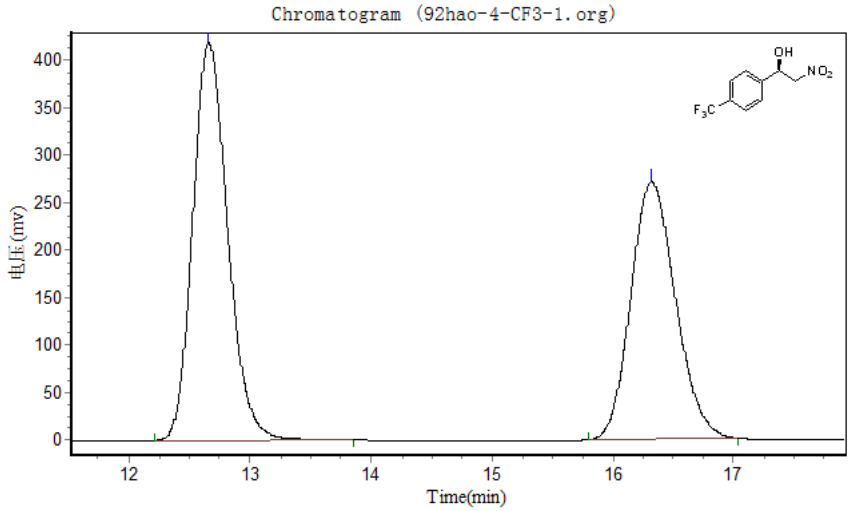
HPLC spectrum of (*S*)-**9e.**



Results

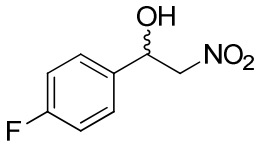
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		12.088	31250.475	1248924.625	7.9921
2		15.470	266745.375	14378056.000	92.0079
Total			297995.850	15626980.625	100.0000

HPLC spectrum of (*R*)-**9e.**



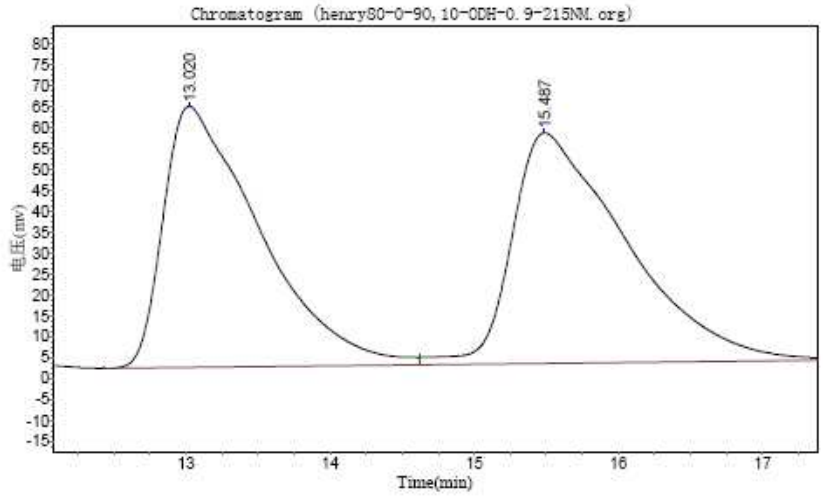
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		12.673	420110.344	8617647.000	54.7786
2		16.320	271175.844	7114117.000	45.2214
Total			691286.188	15731764.000	100.0000



9f

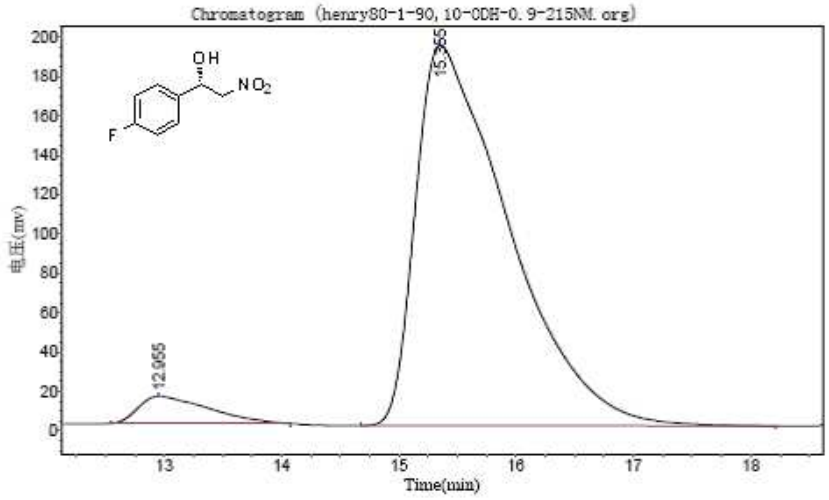
HPLC spectrum of racemic-**9f.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.020	62352.402	2894679.000	48.5830
2		15.487	55108.180	3063540.750	51.4170
Total			117460.582	5958219.750	100.0000

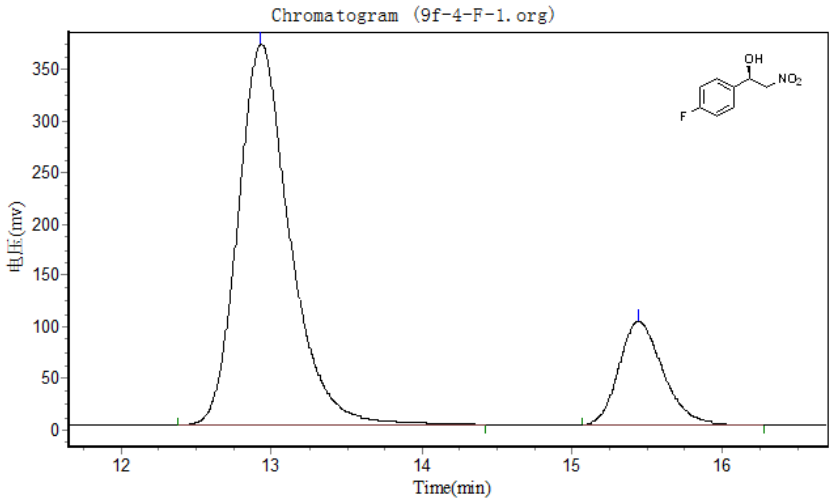
HPLC spectrum of (*S*)-**9f.**



Results

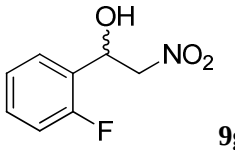
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		12.955	13935.182	576668.313	5.1240
2		15.355	193307.906	10677639.000	94.8760
Total			207243.088	11254307.313	100.0000

HPLC spectrum of (*R*)-**9f.**



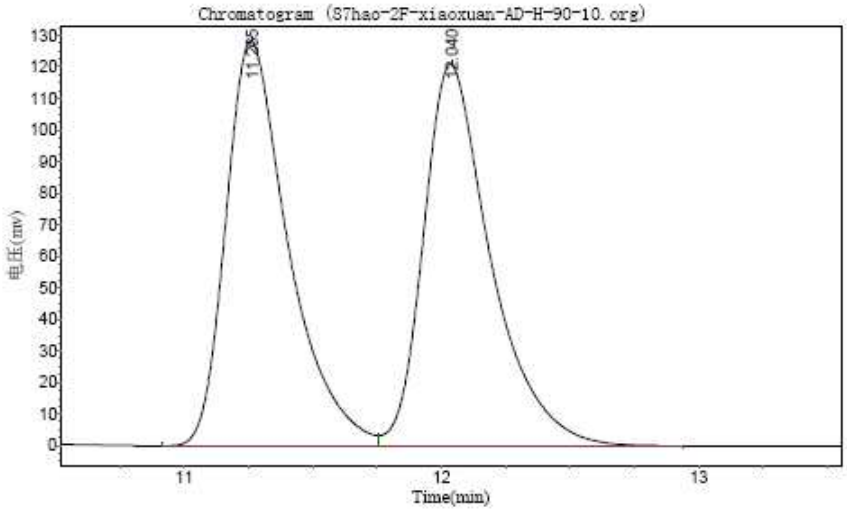
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.082	370052.500	6301129.000	79.1670
2		15.443	84460.977	1658153.500	20.8330
Total			454513.477	7959282.500	100.0000



9g

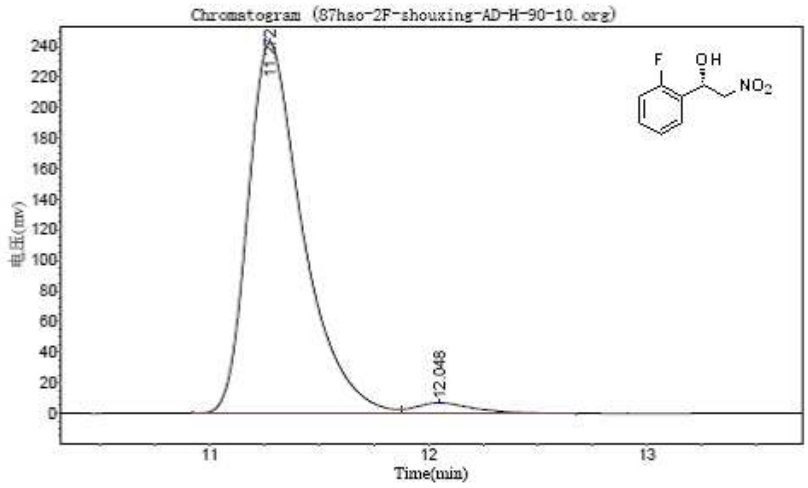
HPLC spectrum of racemic-**9g.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		11.265	128274.961	2168389.500	49.6808
2		12.040	120901.664	2196252.750	50.3192
Total			249176.625	4364642.250	100.0000

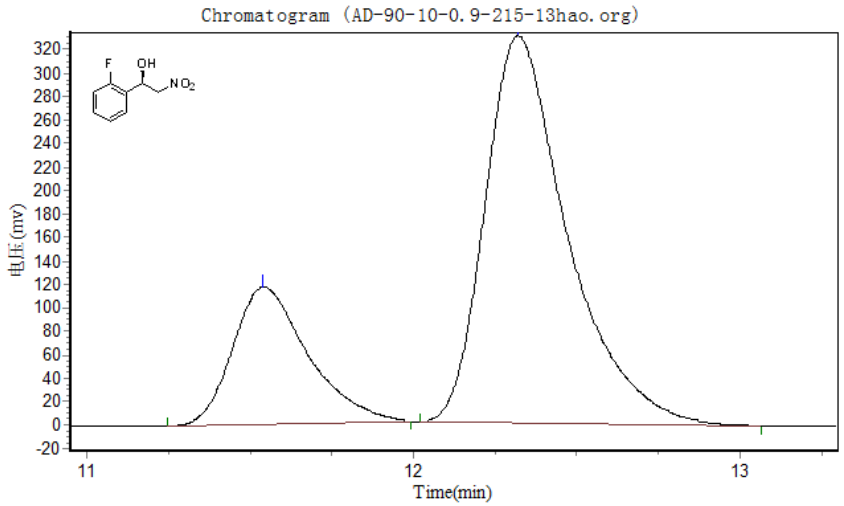
HPLC spectrum of (*S*)-**9g.**



Results

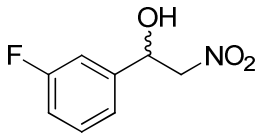
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		11.272	242593.688	4217728.000	97.0775
2		12.048	6832.703	126972.719	2.9225
Total			249426.390	4344700.719	100.0000

HPLC spectrum of (*R*)-**9g.**



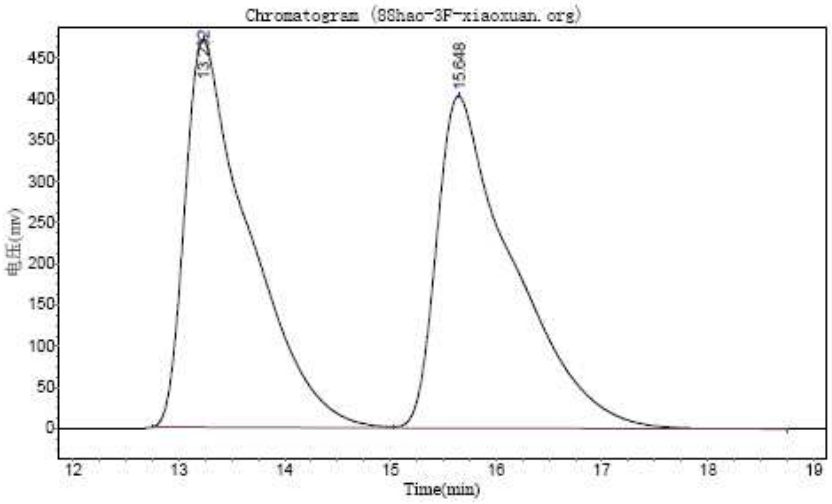
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		11.540	116932.711	1870694.500	24.3944
2		12.320	329873.031	5797830.500	75.6056
Total			446805.742	7668525.000	100.0000



9h

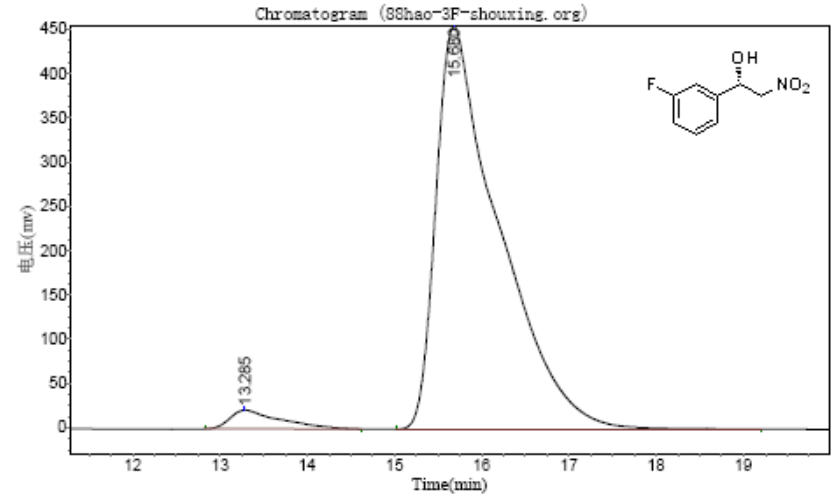
HPLC spectrum of racemic-**9h.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.232	470188.938	19902638.000	49.6544
2		15.648	402729.000	20179658.000	50.3456
Total			872917.938	40082296.000	100.0000

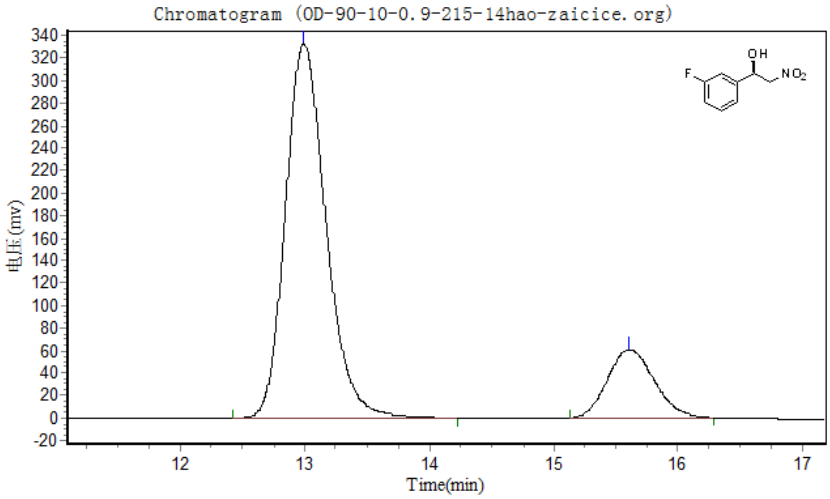
HPLC spectrum of (*S*)-**9h.**



Results

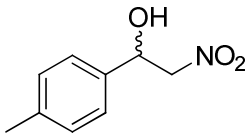
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		13.285	21086.215	845009.750	3.5684
2		15.680	454412.875	22835264.000	96.4316
Total			475499.090	23680273.750	100.0000

HPLC spectrum of (*R*)-**9h.**



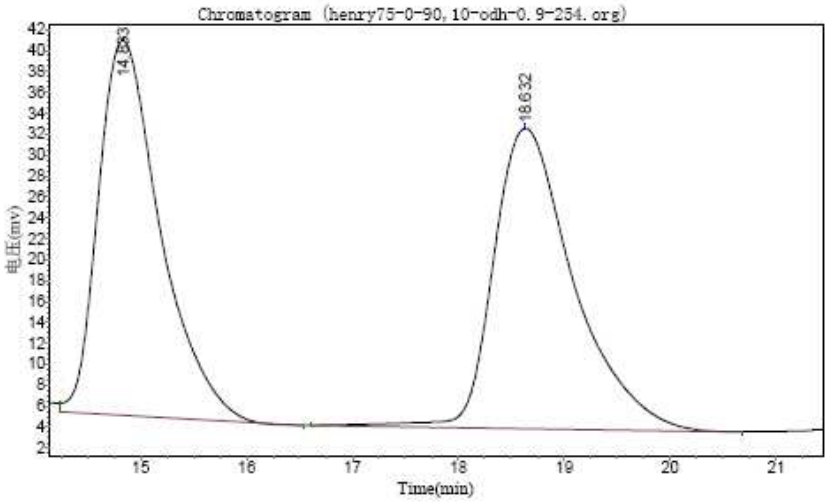
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		12.998	333075.438	7544098.000	82.5732
2		15.610	61108.023	1592153.750	17.4268
Total			394183.461	9136251.750	100.0000



9i

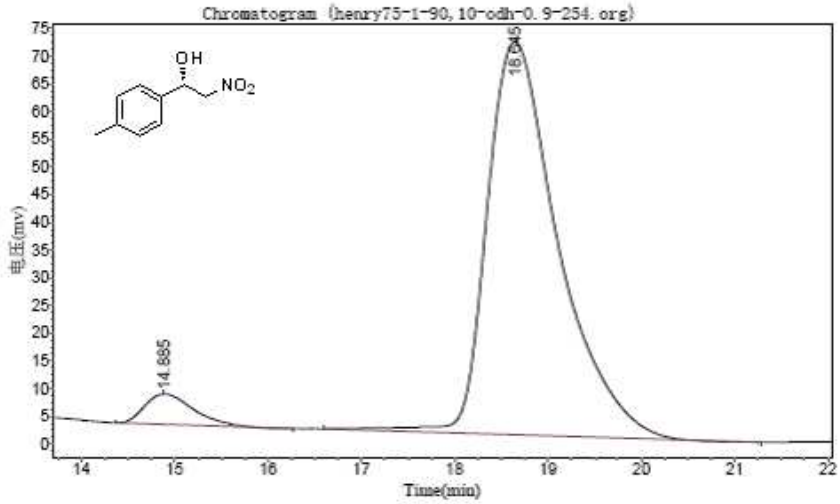
HPLC spectrum of racemic-**9i.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.833	35801.543	1454022.750	49.1036
2		18.632	28698.625	1507108.250	50.8964
Total			64500.168	2961131.000	100.0000

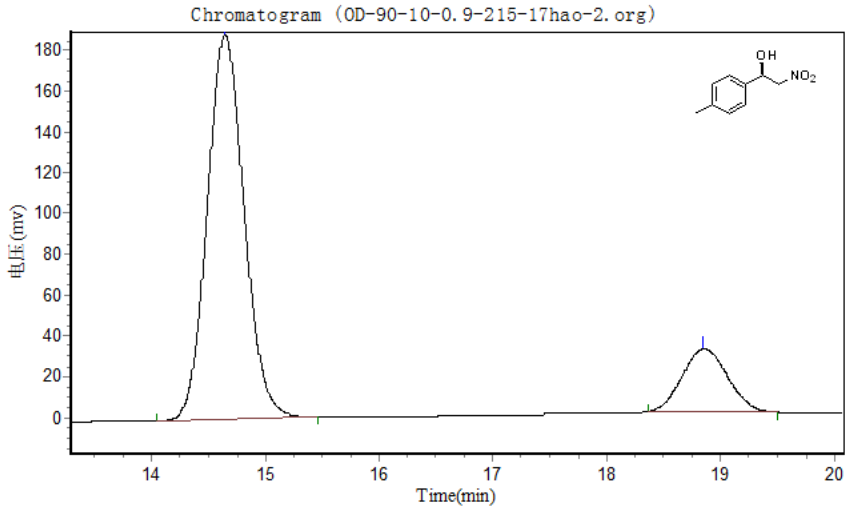
HPLC spectrum of (*S*)-**9i.**



Results

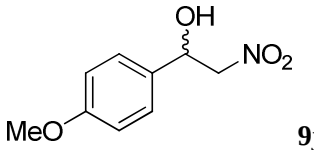
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.885	5470.380	198703.297	5.0457
2		18.645	70933.070	3739359.000	94.9543
Total			76403.451	3938062.297	100.0000

HPLC spectrum of (*R*)-**9i.**



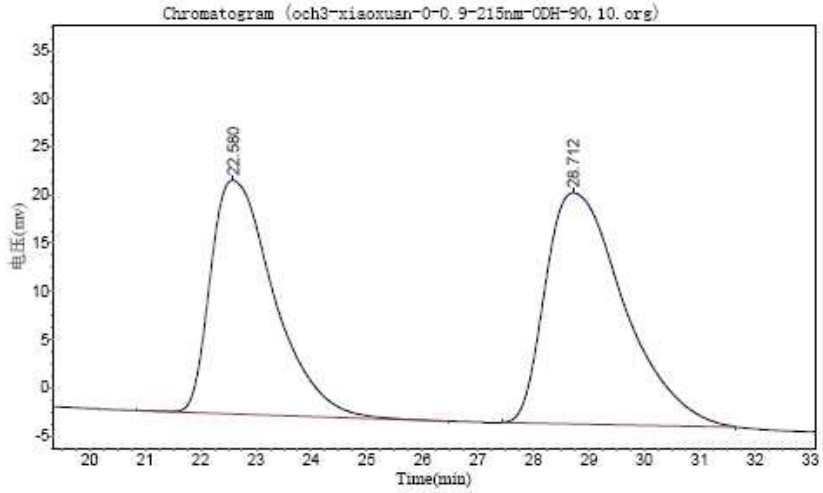
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.645	188785.672	4262967.000	83.0879
2		18.852	31176.322	867704.625	16.9121
Total			219961.994	5130671.625	100.0000



9j

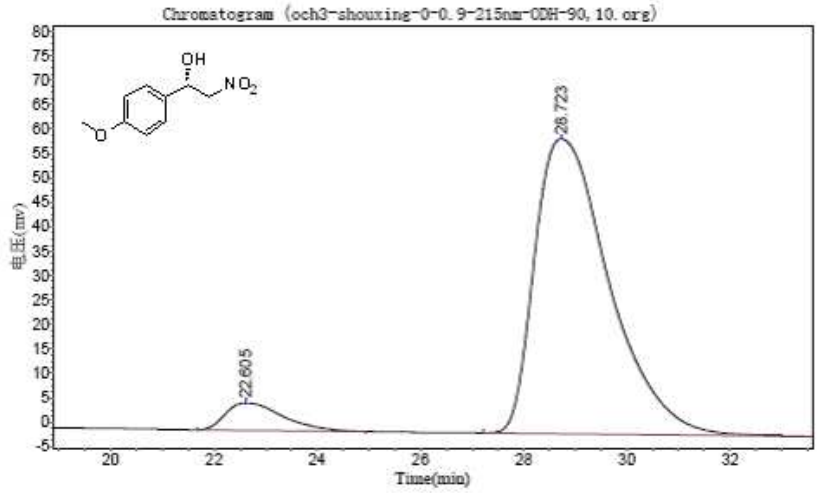
HPLC spectrum of racemic-**9j.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		22.580	24200.846	1920716.625	44.9211
2		28.712	23945.600	2355035.750	55.0789
Total			48146.445	4275752.375	100.0000

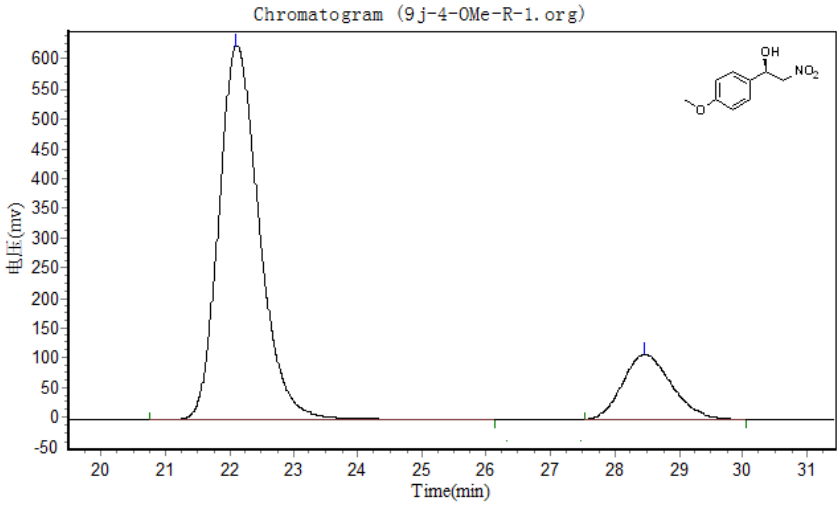
HPLC spectrum of (*S*)-**9j.**



Results

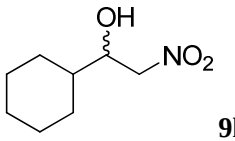
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		22.605	5559.411	427759.500	6.6164
2		28.723	60266.629	6037336.000	93.3836
Total			65826.040	6465095.500	100.0000

HPLC spectrum of (*R*)-**9j.**



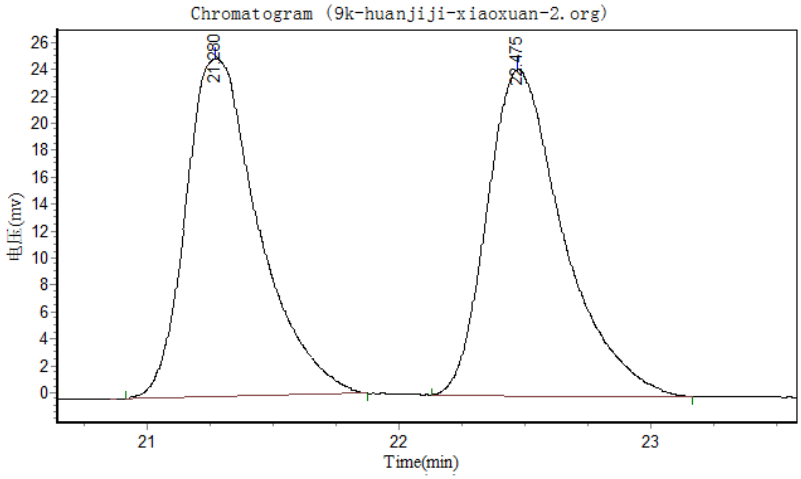
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		22.065	626794.313	14068708.000	80.9710
2		28.490	123142.969	3306279.500	19.0290
Total			749937.281	17374987.500	100.0000



9k

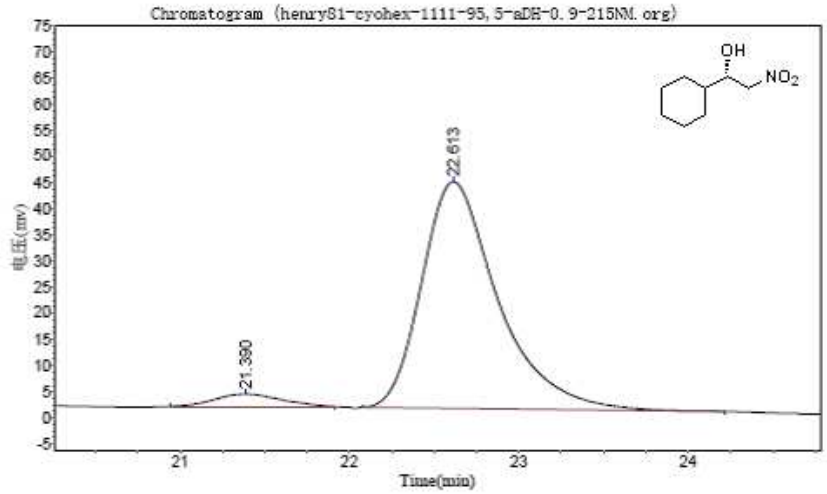
HPLC spectrum of racemic-**9k.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		21.280	26405.838	791561.625	49.9272
2		22.475	24747.223	793870.125	50.0728
Total			51153.061	1585431.750	100.0000

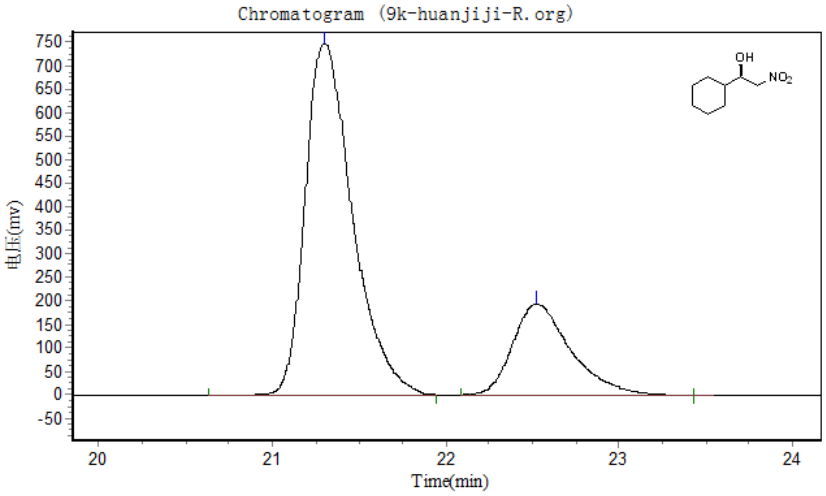
HPLC spectrum of (*S*)-**9k.**



Results

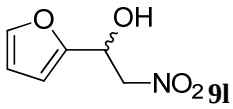
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		21.390	2400.834	65106.398	4.5923
2		22.613	43358.570	1352620.000	95.4077
Total			45759.405	1417726.398	100.0000

HPLC spectrum of (*R*)-**9k.**



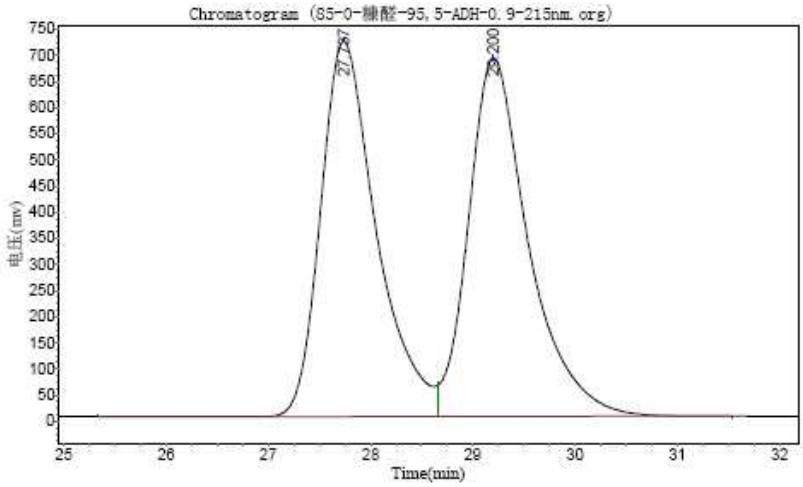
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		21.348	752469.813	12906871.000	76.0634
2		22.582	207610.938	4061696.750	23.9366
Total			960080.750	16968567.750	100.0000



9l

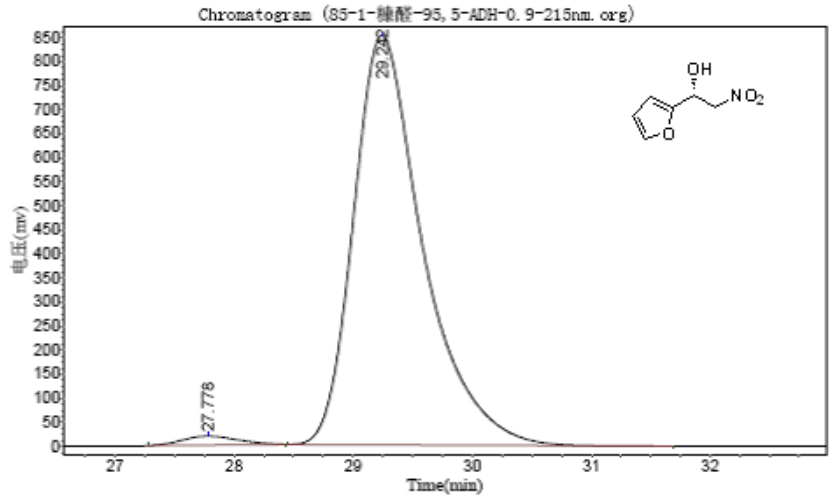
HPLC spectrum of racemic-**9l.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		27.737	717752.688	27228748.000	49.3703
2		29.200	685807.188	27923282.000	50.6297
Total			1403559.875	55152030.000	100.0000

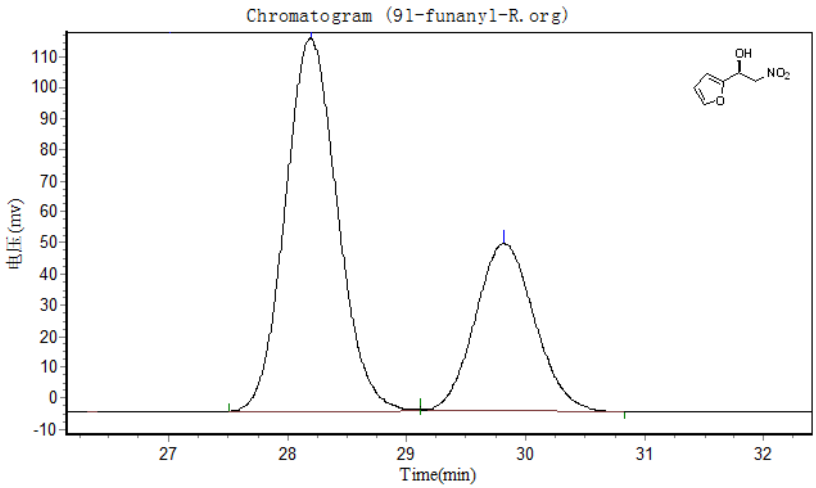
HPLC spectrum of (*S*)-**9l.**



Results

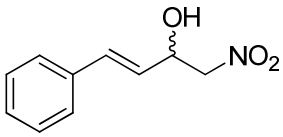
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		27.778	18740.982	603623.563	1.7269
2		29.242	851264.438	34350488.000	98.2731
Total			870005.420	34954111.563	100.0000

HPLC spectrum of (*R*)-**9l.**



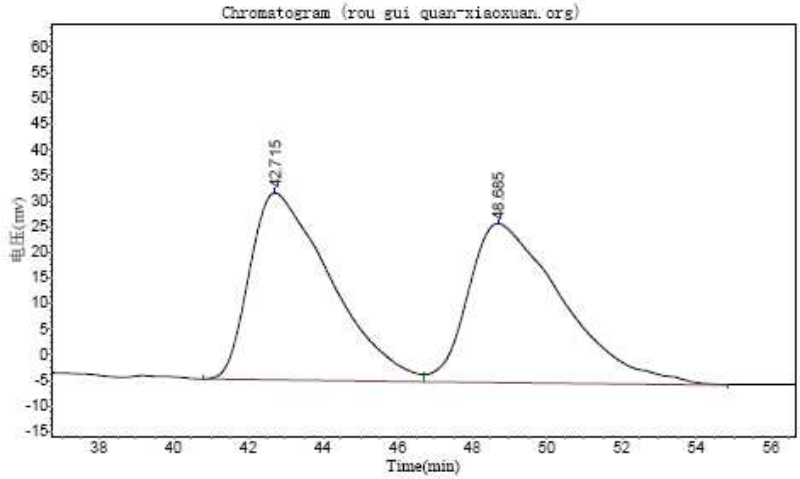
Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		28.298	120072.344	2173793.500	66.2746
2		29.848	54079.875	1106185.500	33.7254
Total			174152.219	3279979.000	100.0000



9m

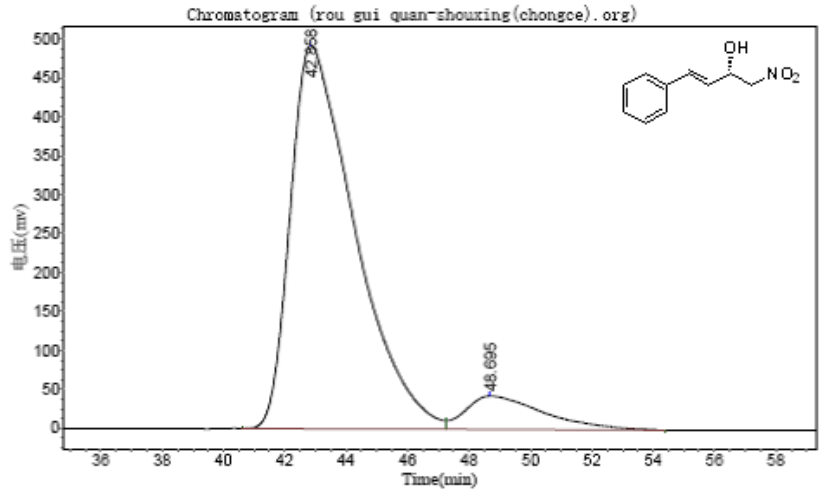
HPLC spectrum of racemic-**9m.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		42.715	36443.344	5477262.500	50.2379
2		48.685	30982.951	5425379.000	49.7621
Total			67426.295	10902641.500	100.0000

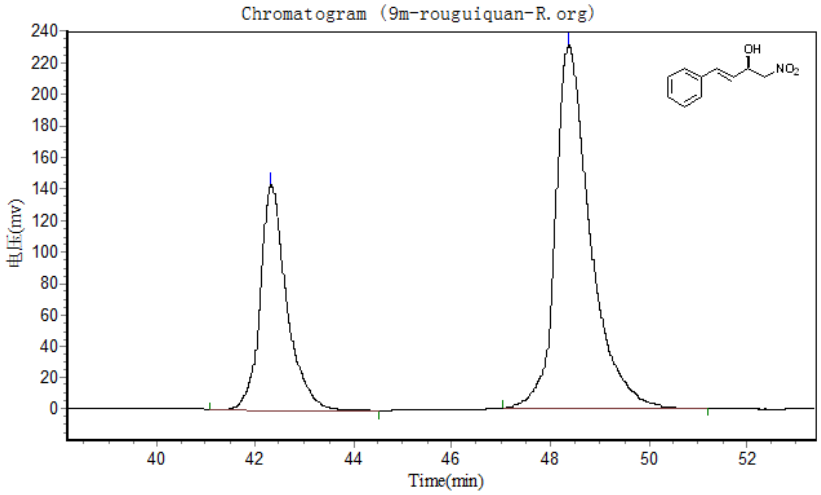
HPLC spectrum of (*S*)-**9m.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		42.858	491846.719	71857920.000	90.5360
2		48.695	43019.402	7511556.000	9.4640
Total			534866.121	79369476.000	100.0000

HPLC spectrum of (*R*)-**9m.**



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		42.315	141151.734	4682093.000	31.0634
2		48.315	231098.266	10390602.000	68.9366
Total			372250.000	15072695.000	100.0000