Supporting Information

Atom-Efficient Aldol Condensations via Magnetically Recyclable Nanoreactors: Sol-Gel Imprinting Enables Template-Switchable Triple-Selectivity

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Contents

1. More experimental details for nanoreactor synthesis and characterization

1.1 Reagents and materials

All organic solvents and reagents were of analytical grade or higher grade and used without treatment. Ferric chloride crystals ($FeCl_3 \cdot 6H_2O$), sodium borohydride ($NaBH_4$), ethylene glycol (EG), glutaraldehyde (GA), 1,6-hexadiamine (HDM), anhydrous sodium acetate were supplied by Xi'an Chemicals Ltd. Polyethylenimine (PEI), 4-formylphenylboronic acid (FPBA), L-5-bromotryptophan (L-5-bromo-Trp), phenyltrimethoxysilane (PTMOS), *n*-octyltrimethoxysilane (OTMS) and 2-Methyltetrahydrofuran (2-MeTHF), Diethyl succinate (DES) and Acetal as well as benzaldehyde substrate (*p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, *o*-cyanobenzaldehyde, *m*-cyanobenzaldehyde, *p*-cyanobenzaldehyde, ect.), cyclohexanone were purchased from Aladdin Industrial Corporation. Flash column chromatography was performed on SiliFlash P60 silica gel (30-60 μm, 60 Å)

1.2 Measurements and characterizations

Transmission electron microscopy (TEM) analysis was conducted on a JEM-2100 transmission electron microscope (JEOL Co., Japan). The zeta potentials were determined by a Zeta Potential analyzer (Zetasizer Nano S90, Malvern). Fourier-transform infrared spectra (FT-IR) were carried out on via a Nicolet AVATAR 330 spectrophotometer (Thermo Electron Co., USA) in the region of 4000–400 cm^{-1}. N_2 adsorption–desorption isotherms were obtained using a Micromeritics ASAP 2020 with an outgassing temperature of 200°C. The X-ray diffraction (XRD) patterns were recorded on a Rigaku D/max/2500v/pc X-ray diffractometer (Rigaku Co., Japan) with Cu K_α radiation. The magnetic properties were determined by an MPMS-squid VSM-094 vibrating sample magnetometer (VSM). The weight loss in high temperature was recorded in thermogravimetric analyzer (TGA, Xi'an Jinyi Technology Co., Ltd). All new compounds characterized by ^1H NMR were determined on 400 MHz Bruker AV400 spectrometer. Chemical shifts are reported in

ppm relative to residual solvent peaks (chloroform-*d,* 7.26 ppm for ^{1}H NMR). Coupling constants are reported in hertz with multiplicities denoted as s (singlet), d (doublet), t (triplet), *q* (quartet), m (multiplet).The HPLC analysis was reported by Shimadzu LC-20AT on Chiral Daicel Chiralpak AD-H, AS-H columns.

1.3 Preparation of benzylboric acid modified magnetic nanoparticles (Fe_3O_4-PBA)

Briefly, $FeCl_3 \cdot 6H_2O$ (1.0 g), NaOAc (3.6 g) and HDM (6.0 g) were dissolved in 30 mL of ethylene glycol in a Teflon-lined stainless-steel autoclave, which was heated at 200 °C for 7 h. Then, the obtained nanoparticles were rinsed several times with ultrapure water and collected with a magnet. Finally, the Fe_3O_4-NH_2 were dried under vacuum for further use.

Subsequently, PEI was covalently grafted onto Fe_3O_4-NH_2 using GA as the linker. Fe_3O_4-NH_2 (200 mg), PEI (1 mg/mL, 30 mL) and $NaBH_4$ (90 mg) were dissolved in 30 mL GA solution (1%, v/v). After stirring at room temperature for 3 h, the amino hyperbranched nanoparticles (Fe_3O_4-PEI) were magnetically separated and transferred into methanol solution containing FPBA (300 mg) and $NaBH_4$ (225 mg). After 24 h of stirring at room temperature, the phenylboronic acid hyperbranched nanoparticles (Fe_3O_4-PBA) were separated magnetically, rinsed with highly purified water and finally dried under vacuum.

1.4 Synthesis of the molecularly imprinted nanoreactor

The subsequent immobilization of L-tryptophan (L-Trp) active sites was achieved through a water-based Suzuki cross-coupling reaction between the Fe_3O_4-PBA support and L-5-bromotryptophan. In brief, a reaction mixture containing Fe_3O_4-PBA (100 mg), L-5-bromotryptophan (200 mg, 0.76 mmol), sodium tetrachloropalladate(II) (Na_2PdCl_4, 142 mg, 0.38 mmol), trisodium tri(3-sulfonatophenyl)phosphine (TPPTS, 355 mg, 0.61 mmol) as the stabilizing ligand, and K_2CO_3 (485 mg, 3.51 mmol) was added to a 100 mL three-neck round-bottom flask equipped with a reflux condenser. The reaction flask was purged with N_2 for 30 min before adding 60 mL of degassed deionized water via syringe. The

reaction was carried out under an inert atmosphere at 85 ℃ with stirring for 24 h. The resulting Fe_3O_4-Trp catalyst was magnetically separated, sequentially washed with deionized water and ethanol to remove unreacted precursors, and then vacuum-dried at 60 ℃ for 12 h.

Subsequently, the highly selective molecularly imprinted nanoreactor (P-MMIP) was prepared using sol-gel method. Fe_3O_4-Trp (100 mg), polyvinylpyrrolidone (PVP, 5.0 g) and template [(*S*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one, **1a**, 50 mg] were added to a solution of 50 mL ethanol and water (4:1, v/v). The mixture was then stirred at room temperature for 30 min. Next, $NH_3 \cdot H_2O$ (1.5 mL), OTMOS (670 μL) and PTMOS (330 μL) were introduced and the mixture was continuously stirred at room temperature for 12 h to form the imprinted network. The obtained nanoparticles were collected by magnetic separation, washed with deionized water and ethanol, and finally dried in a vacuum oven at 50 ℃. A mixture of methanol-acetic acid (90:10, v/v) was used to elute the template until no absorption peak at 272 nm was observed via UV-vis spectroscopy. The non-molecularly imprinted catalyst (P-MNIP) was synthesized using the same procedure, but in the absence of template molecules.

2. Catalytic performance on imprinted nanoreactor

Cyclohexanone (0.25 mL, 2.5 mmol) was dissolved in 1.8 mL solvent containing a dispersed amount of P-MMIP nanoreactor. After stirring at room temperature for 15 min, the *p*-nitrobenzaldehyde (75.5 mg, 0.5 mmol) was introduced. The mixture was maintained at different temperature under mechanical agitation (300 rpm) and monitored by thin-layer chromatography (TLC). Subsequently, the catalyst was removed by magnetic separation and washed with methanol-acetic acid (90:10, v/v). The reaction mixture was then extracted multiple times with dichloromethane. The combined organic layer was concentrated, and the resulting residue was purified by flash chromatography on silica gel (EtOAc:n-hexane = 1:6) to obtain the final product. For the comparative catalytic experiment, an equal amount of free L-tryptophan (10.2 mg, ~10 mol%) served as the catalytic species under identical reaction parameters.

Furthermore, the catalytic performance of P-MMIP nanoreactor in mixed isomers was investigated. Approximately 10 mol% of catalyst (L-Trp, P-MNIP or P-MMIP) was added to a substrate mixture consisting of isomers (equal amounts of *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde and *m*-nitrobenzaldehyde, 0.5 mmol) and cyclohexanone (excess). The reaction was carried out at 35 ℃ for 48 h. After catalyst separation and extraction with dichloromethane, the organic layers were concentrated and analyzed by HPLC.

3. The adsorption experiments of *p*-nitrobenzaldehyde on P-MMIP

5.0 mg of P-MNIP or P-MMIP was added to a solution of *p*-nitrobenzaldehyde (50 μg mL^{-1}, 20 mL) for adsorption experiments. The kinetic studies were conducted for a duration of 0 to 72 h. The obtained supernatant was separated using magnetic separation, and its concentration was analyzed using UV-vis spectroscopy (λ=272 nm). Additionally, the adsorption capacity of *p*-nitrobenzaldehyde (Q, mg g^{-1}) was calculated using equation (S1). The kinetic results are fitted with *pseudo-first-order* and *pseudo-second-order* kinetic models according to equation (S2) and (S3).

$$Q=\frac{(C_0-C_e)V}{M} \tag{S1}$$

$$\ln(Q_e-Q_t)=\ln Q_e-k_1 t \tag{S2}$$

$$\frac{t}{Q_t}=\frac{1}{k_2 Q_e^2}+\frac{t}{Q_e}=\frac{1}{v_0}+\frac{t}{Q_e} \tag{S3}$$

Where C_0 and C_e (μg mL^{-1}) are the initial and equilibrium concentrations of *p*-nitrobenzaldehyde. V (mL) and M (mg) are the volume of the *p*-nitrobenzaldehyde solution and the mass of nanoreactors, respectively. In addition, k_1 and k_2 (g mg^{-1} h^{-1}) refer to the equilibrium rate constants. The initial rate of absorption is represented by V_0 (mg g^{-1} h^{-1}). Q_e is the adsorption capacity at equilibrium. Q_t represents the adsorption capacity at different adsorption times, t (h).

Thermodynamic adsorption experiments were carried out by increasing the initial concentration of *p*-nitrobenzaldehyde solution from 20 to 90 μg mL^{-1} and maintaining the adsorption time for 24 h. The *Langmuir* and *Freundlich* thermodynamic models were applied to analyze the thermodynamic data as indicated in equation (S4) and (S5).

$$\frac{C_e}{Q}=\frac{1}{K_L Q_m}+\frac{C_e}{Q_m} \tag{S4}$$

$$\log Q=m\log C_e+\log K_F \tag{S5}$$

where K_F (mg g^{-1}) and K_L (mL mg^{-1}) are the constants of two thermodynamic models. C_e (μg mL^{-1}) represents the equilibrium concentration of *p*-nitrobenzaldehyde. Q_{max} (mg g^{-1}) stands for the optimum adsorption capacity of nanoreactors, and m represents the *Freundlich* exponent.

Furthermore, the substrate selectivity of P-MMIP and P-MNIP was examined using five competing aldehydes (*o*-nitrobenzaldehyde, *m*-nitrobenzaldehyde, *o*-cyanobenzaldehyde, *m*-cyanobenzaldehyde and *p*-cyanobenzaldehyde). For each experiment, 5 mg of catalyst (P-MMIP or P-MNIP) was dispersed in 20 mL of competitor solution (50 μg mL^{-1}) and agitated for 24 h.

4. Optimization of P-MMIP preparation conditions

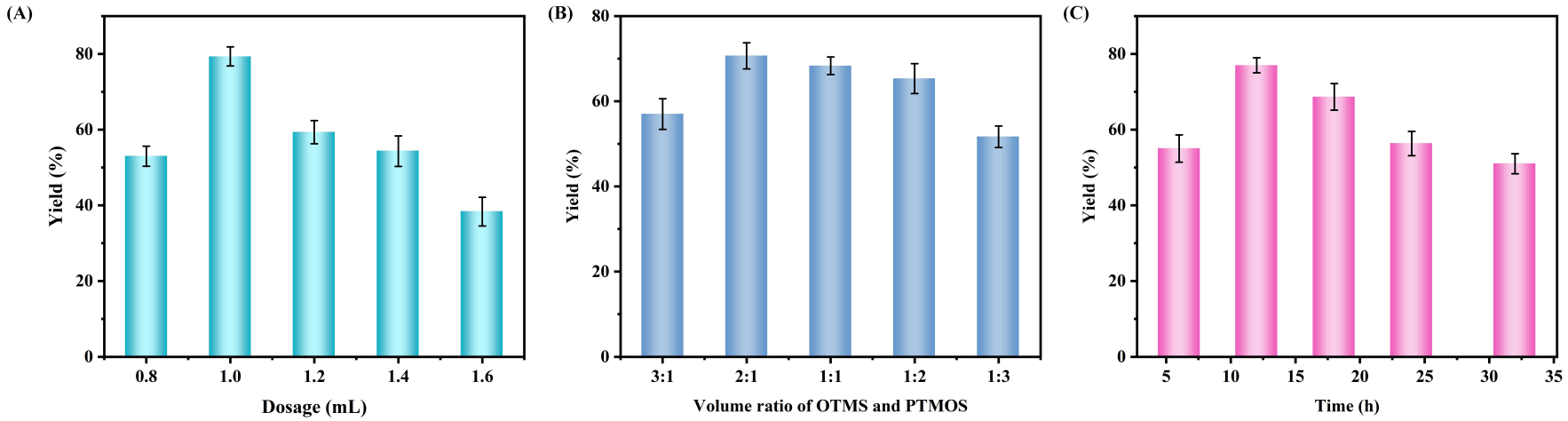


Fig. S1 The effects of (A) the dosage of functional monomers, (B) the volume ratio of OTMOS and PTMOS, and (C) the reaction time during preparation procedure on catalytic performance of P-MMIP.

5. N_2 adsorption–desorption isotherms of P-MMIP

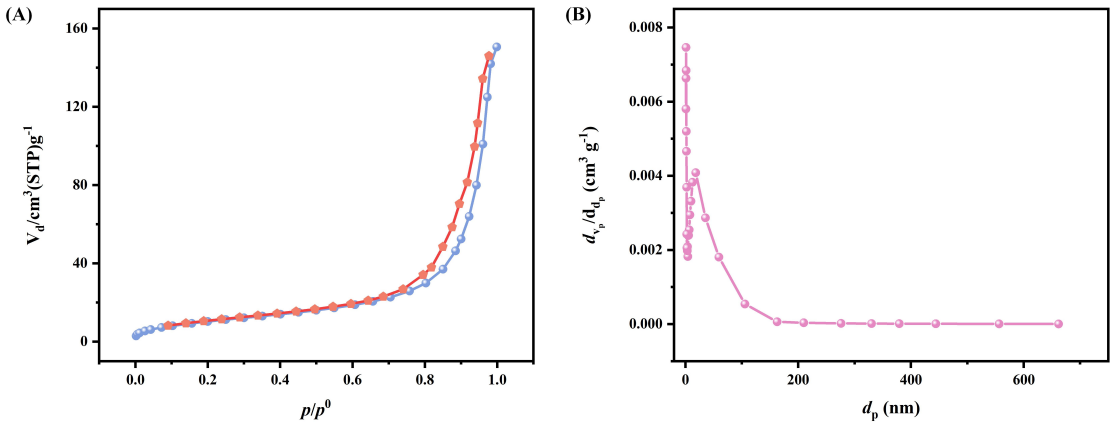


Fig. S2 N_2 adsorption–desorption isotherms (A) and pore diameter distribution (B) of P-MMIP.

6. Water contact angle and weight loss analysis

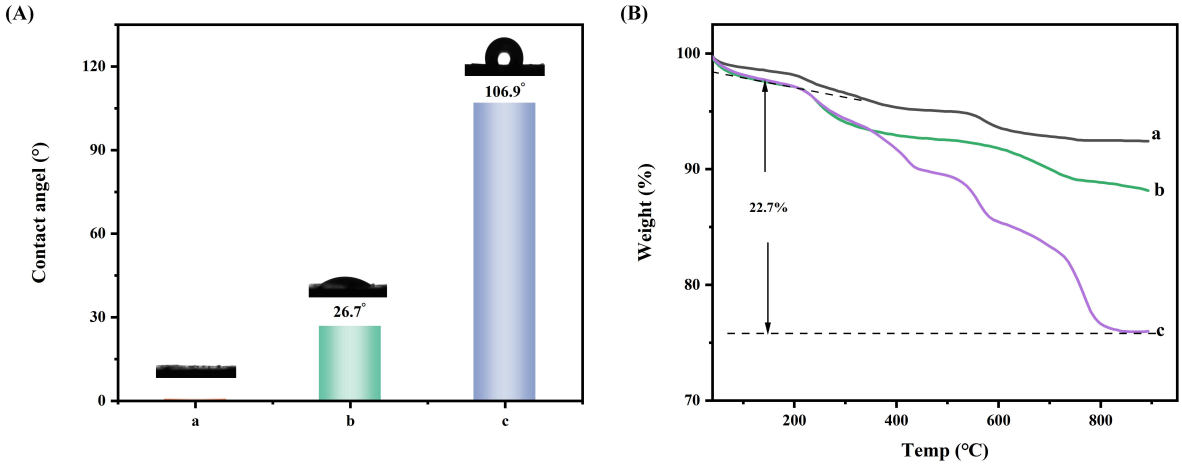


Fig. S3 Water contact angle (A) and Weight loss (B) measurements of (a) Fe_3O_4-NH_2, (b) Fe_3O_4-Trp and (c) P-MMIP.

7. UV-vis analysis before and after Suzuki reaction

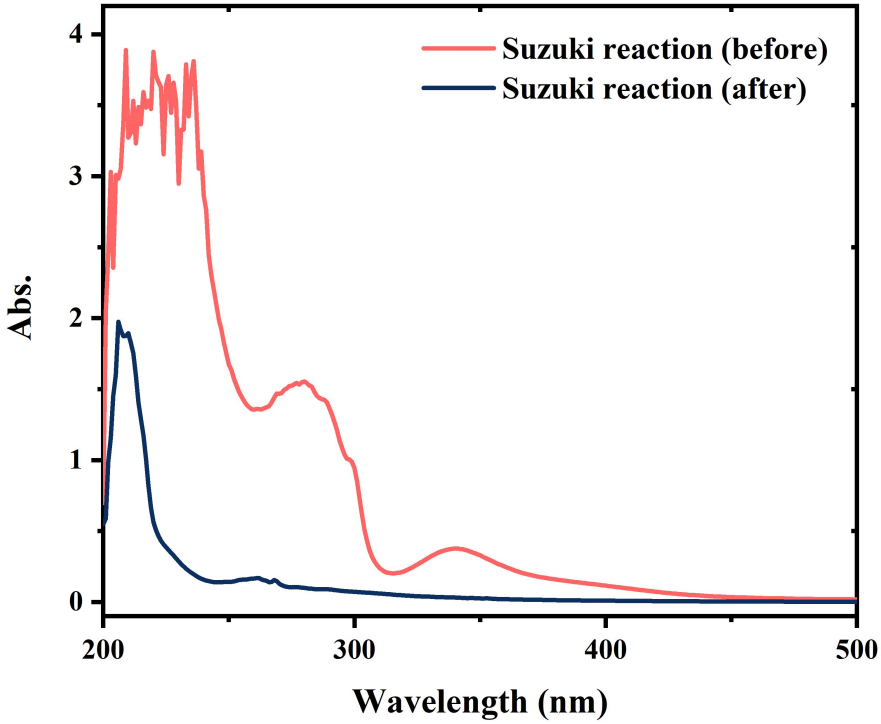


Fig. S4 The UV-vis detection of L-5-bromotryptophan before and after Suzuki reaction in P-MMIP preparation.

8. The adsorption analysis of *p*-nitrobenzaldehyde on P-MMIP

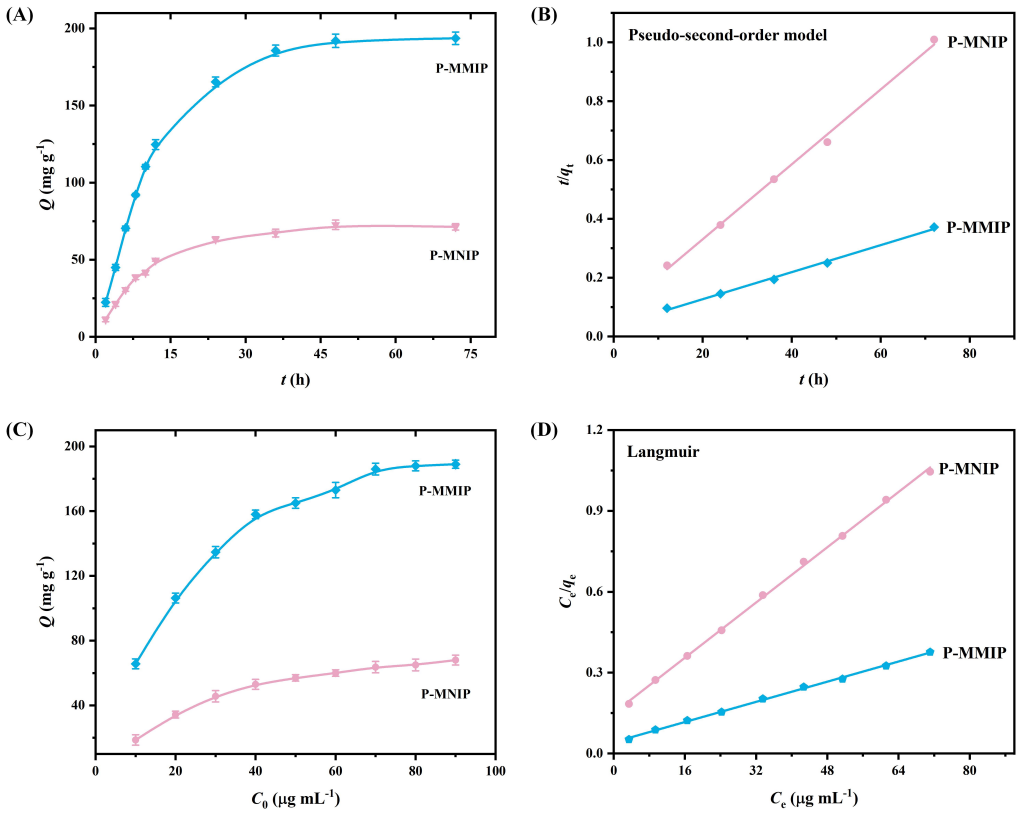
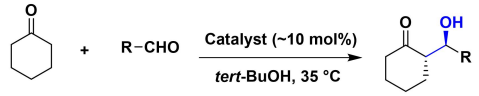


Fig. S5 The adsorption kinetic curves (A),*pseudo-second-order model* (B), adsorption isothermal curves (C) and *Langmuir* isotherms model (D) of *p*-nitrobenzaldehyde on P-MNIP and P-MMIP.

Table S1 The parameters of adsorption isotherms and kinetics.

Adsorbent	*Langmuir* isotherm			*Freundlich* isotherm		
	K_L (L mg^{-1})	Q_m (mg g^{-1})	R^2	K_F	m	R^2
P-MNIP	0.029	95.12	0.9932	8.55	0.47	0.9567
P-MMIP	0.039	247.94	0.9914	33.04	0.40	0.9421
Adsorbent	*Pseudo-first-order* model			*Pseudo-second-order* model		
	K_1 (g mg^{-1}min^{-1})	Q_e (mg g^{-1})	R^2	K_2 (g mg^{-1}min^{-1})	Q_e (mg g^{-1})	R^2
P-MNIP	0.095	71.66	0.9825	9.18×10^{-4}	94.45	0.9940
P-MMIP	0.076	199.70	0.9805	2.34×10^{-4}	270.59	0.9905

9. Catalytic performance on L-Trp, P-MNIP and P-MMIP



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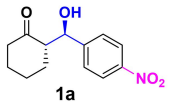

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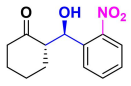

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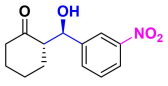

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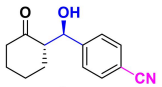

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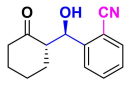
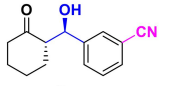


2b

Cat.	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%
L-Trp	93	6:1	90	78	55:1	92	79	14:1	89	80	3:1	87	65	77:1	90
PA-MNIP	25	7:1	85	13	54:1	93	16	14:1	90	20	2:1	93	11	74:1	93
PA-MMIP	89	7:1	81	10	57:1	95	15	17:1	93	55	1:1	99	12	71:1	99



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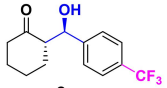

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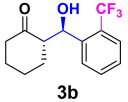

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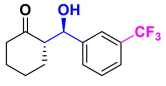

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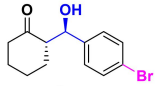
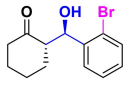


4a

Cat.	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%
L-Trp	72	5:1	79	65	26:1	76	26	5:1	66	75	26:1	70	66	18:1	84
PA-MNIP	12	3:1	73	14	24:1	80	5	7:1	72	22	19:1	75	18	17:1	85
PA-MMIP	10	2:1	56	35	1:1	93	8	11:1	87	27	1:1	97	32	4:1	81



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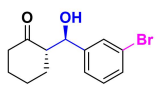

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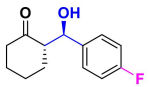

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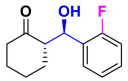

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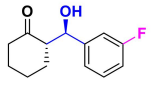


5c

Cat.	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%
L-Trp	44	12:1	79	49	85:1	77	65	15:1	89	52	5:1	79	57	87:1	77
PA-MNIP	10	9:1	73	8	83:1	73	12	13:1	83	7	7:1	80	10	83:1	79
PA-MMIP	9	7:1	98	17	79:1	81	22	14:1	93	5	8:1	89	10	85:1	85

Fig. S6 The direct aldol reactions between various ketones and aldehydes catalyzed by L-Trp, P-MNIP and P-MMIP. The diastereometric ratio (dr) and enantiomeric excess (ee) was determined by HPLC data.

10. Catalytic selectivity of mixed cyanobenzaldehyde and *p*-nitrobenzaldehyde

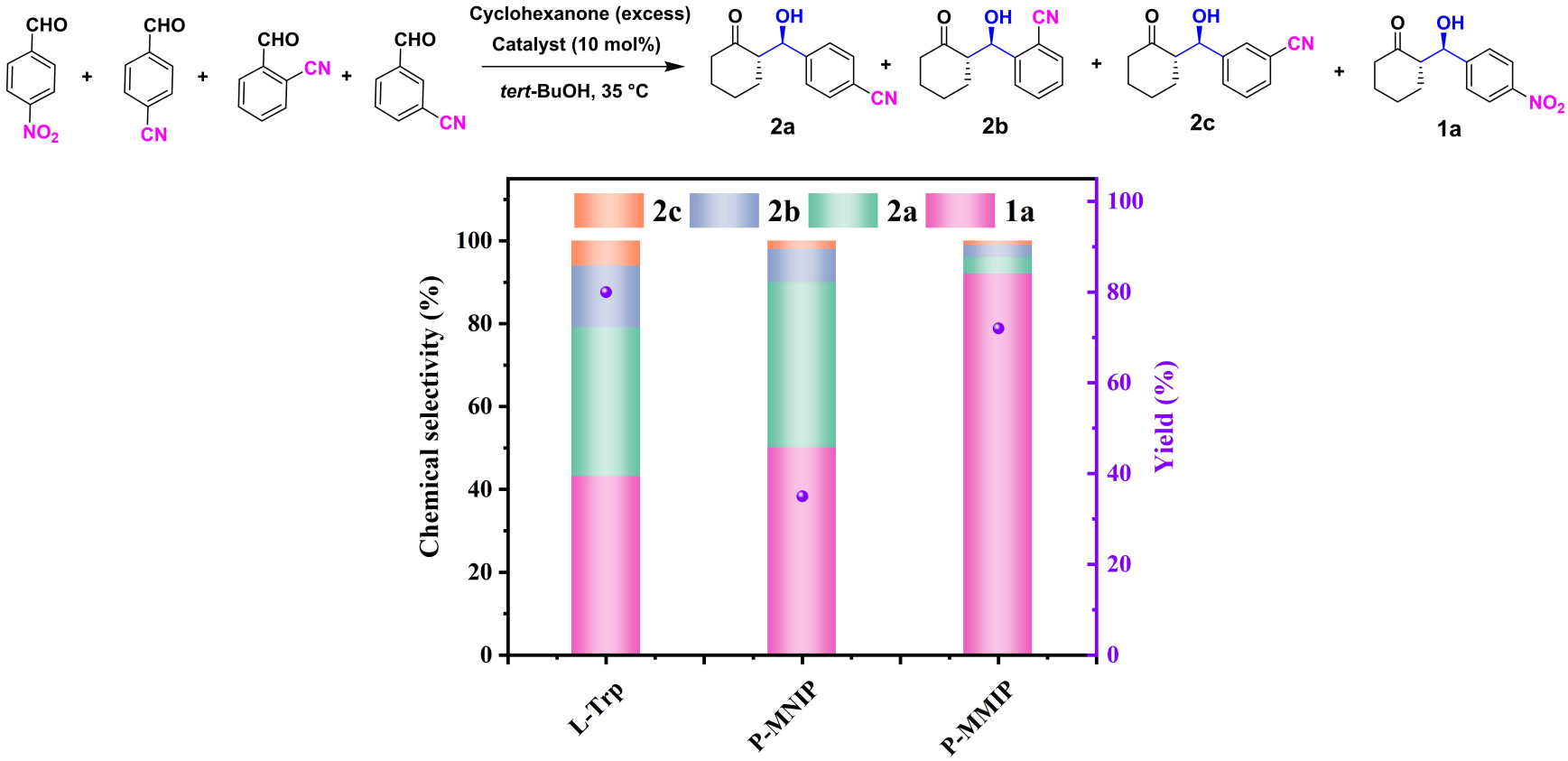


Fig. S7 Reaction profiles of molar mixtures of *ortho*-, *meta*- and *para*-cyanobenzaldehyde and their mixtures with *p*-nitrophenylaldehydes catalyzed by L-Trp, P-MNIP and P-MMIP.

11. Catalytic selectivity on m'-MMIP in single-substrate system

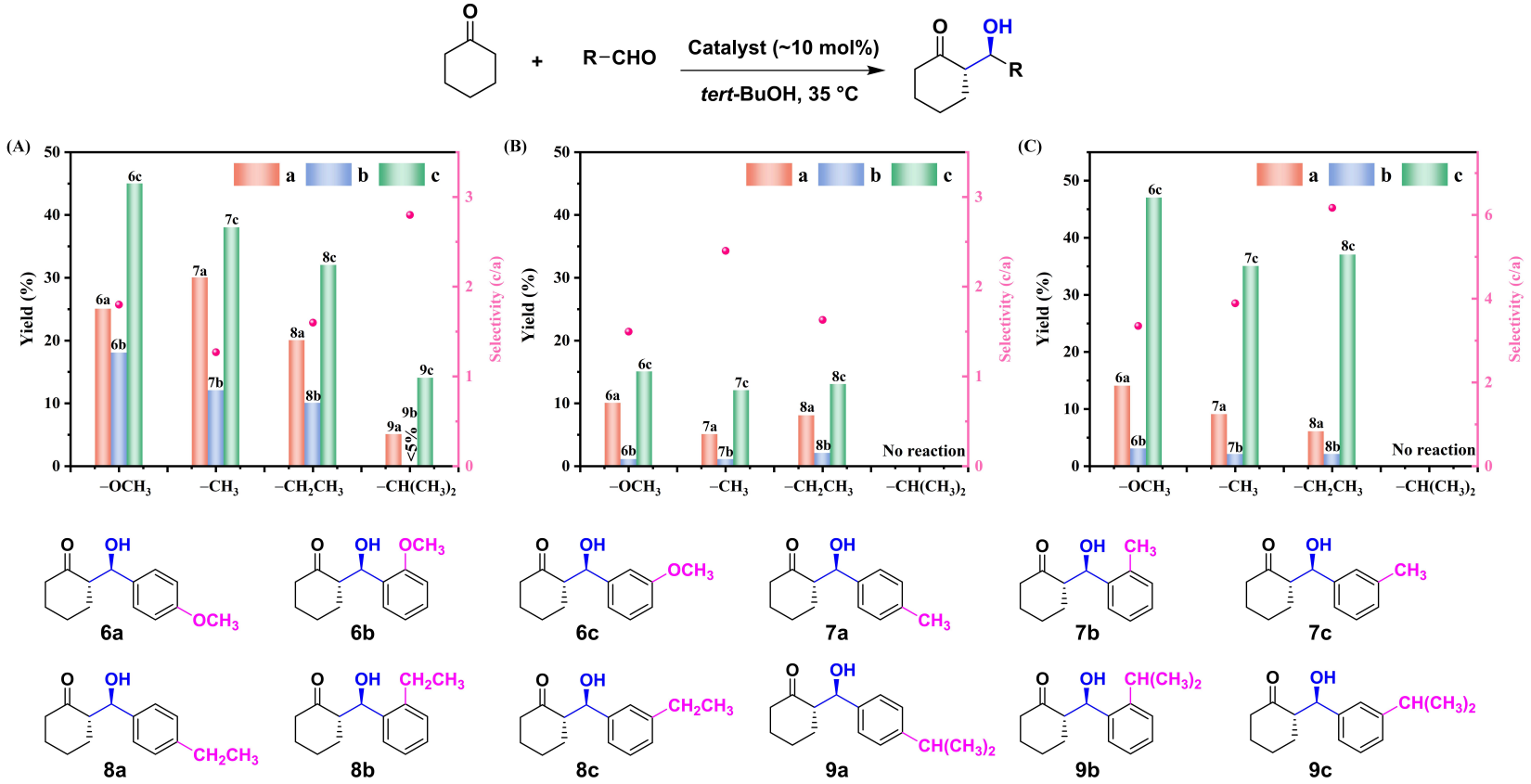
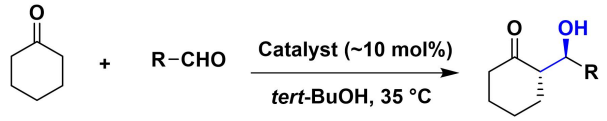


Fig. S8 Benzaldehyde substrates by *para*-, *ortho*-, and *meta*-substituted groups (-OCH_3, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$) catalyzed by L-Trp (A) , m'-MNIP (B) and m'-MMIP (C)

12. Catalytic performance on L-Trp, MNIP and m'-MMIP



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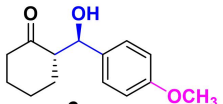

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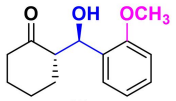

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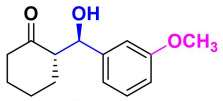

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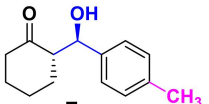
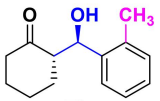
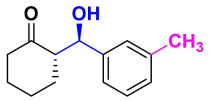


7a

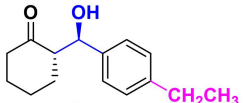


7b

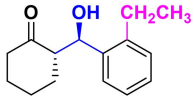


7c

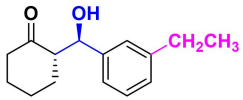
Cat.	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%
L-Trp	25	56:1	89	18	52:1	89	45	16:1	87	30	73:1	87	12	197:1	80	38	35:1	80
MNIP	10	54:1	85	<5	54:1	87	15	14:1	89	5	72:1	93	<5	194:1	83	12	30:1	73
m'-MMIP	14	51:1	88	<5	49:1	88	47	18:1	97	9	66:1	98	<5	210:1	77	15	28:1	69



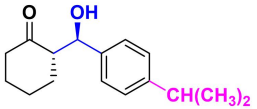
8a



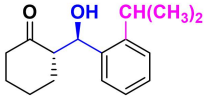
8b



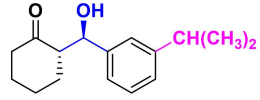
8c



9a



9b



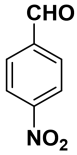
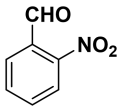
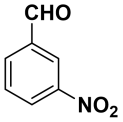
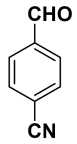
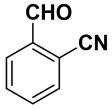
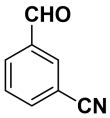
9c

Cat.	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%	Yield/%	dr	ee/%
L-Trp	20	65:1	89	10	28:1	79	32	25:1	66	<5	26:1	70	-	-	-	14	28:1	74
MNIP	8	63:1	93	-	-	-	13	27:1	62	-	-	-	-	-	-	-	-	-
m'-MMIP	6	63:1	98	-	-	-	37	23:1	56	-	-	-	-	-	-	-	-	-

Fig. S9 The direct aldol reactions between various ketones and aldehydes catalyzed by L-Trp, MNIP and m'-MMIP. The dr and ee was determined by HPLC data

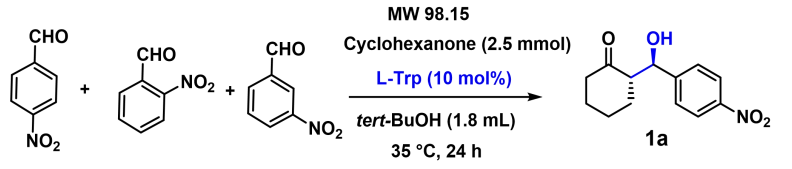
13. Adsorption selectivity of *p*-nitrobenzaldehyde on P-MMIP nanoreactor

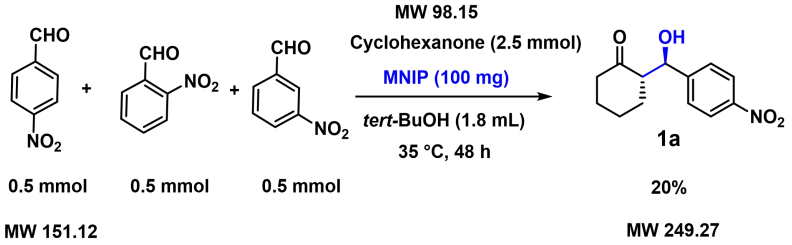
Table S2 The parameters of adsorption selectivity on P-MMIP under single-/multi-substrate system

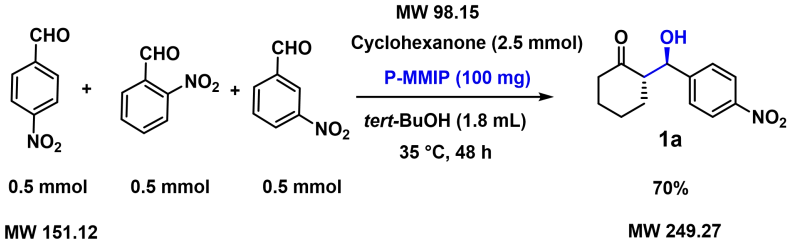
Adsorption selectivity on P-MMIP under single-substrate system					Adsorption selectivity on P-MMIP under mixed isomers system			
Substrate	$Q_{P\text{-}MMIP}$ (mg g^{-1})	$Q_{P\text{-}MNIP}$ (mg g^{-1})	*IF*	*SC*	$Q_{P\text{-}MMIP}$ (mg g^{-1})	$Q_{P\text{-}MNIP}$ (mg g^{-1})	*IF*	*SC*
	187.21	64.02	2.92	-	168.50	45.42	3.71	-
	60.03	48.67	1.23	2.37	48.03	42.32	1.13	3.28
	50.05	42.33	1.18	2.47	36.05	28.33	1.27	2.92
	70.11	52.67	1.33	2.20	35.60	32.67	1.09	3.40
	44.67	38.22	1.17	2.50	28.67	25.22	1.14	3.25
	32.33	28.33	1.14	2.56	22.33	20.33	1.1	3.37

14. Environmental perspectives

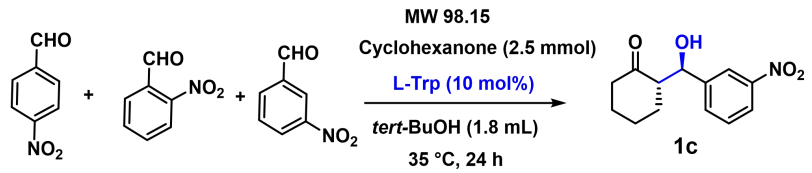
System 1: The aldol reaction between molar mixture of *ortho*-, *meta*- and *para*-nitrosubstituted benzaldehyde (*o*/*m*/*p*-NO_2) and cyclohexanone catalyzed by L-Trp, MNIP and P-MMIP, the ideal product is **1a;**

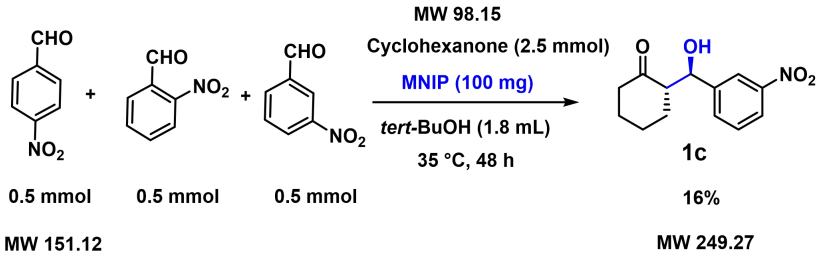


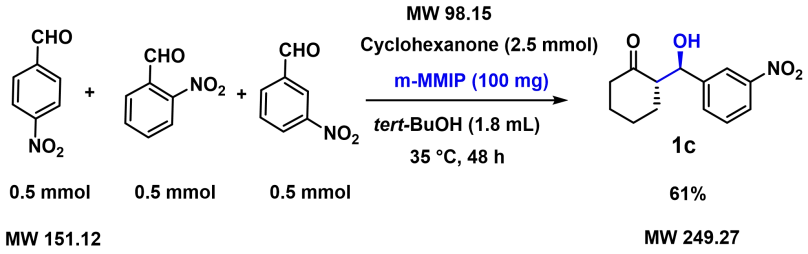




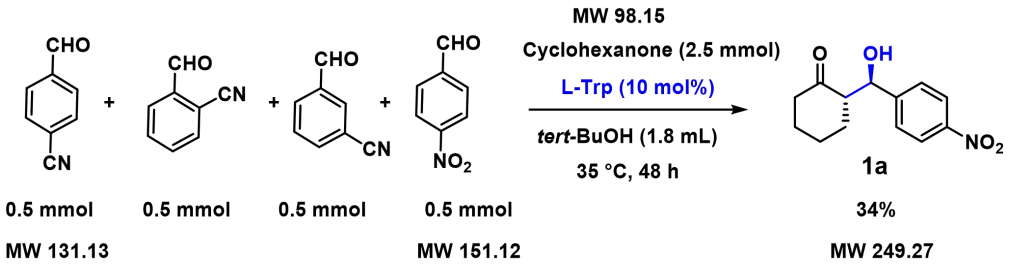
System 2: The aldol reaction between molar mixture of *ortho*-, *meta*- and *para*-nitrosubstituted benzaldehyde (*o*/*m*/*p*-NO_2) and cyclohexanone catalyzed by L-Trp, MNIP and m-MMIP, the ideal product is **1c;**

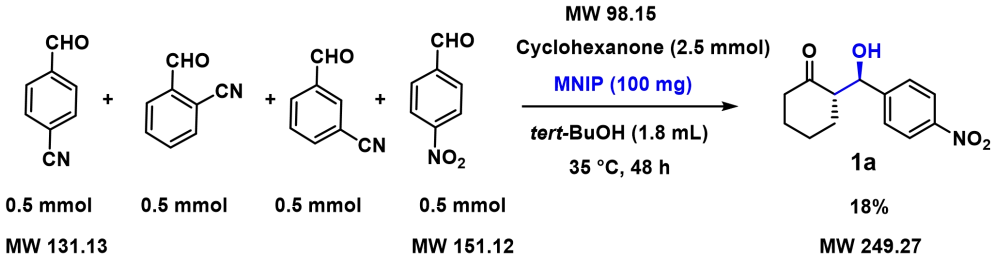


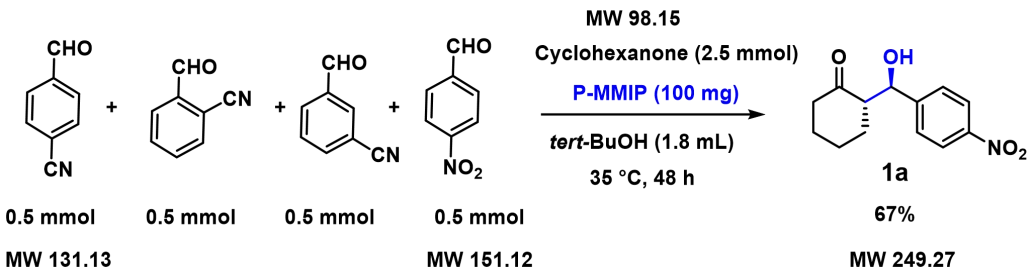




System 3: The aldol reaction between molar mixtures of *ortho*-, *meta*- and *para*-cyanobenzaldehyde and their mixtures with *p*-nitrophenylaldehydes (*o*/*m*/*p*-CN+*p*-NO_2) and cyclohexanone catalyzed by L-Trp, MNIP and p-MMIP, the ideal product is **1a;**







15. Characterizations of original and used P-MMIP nanoreactors

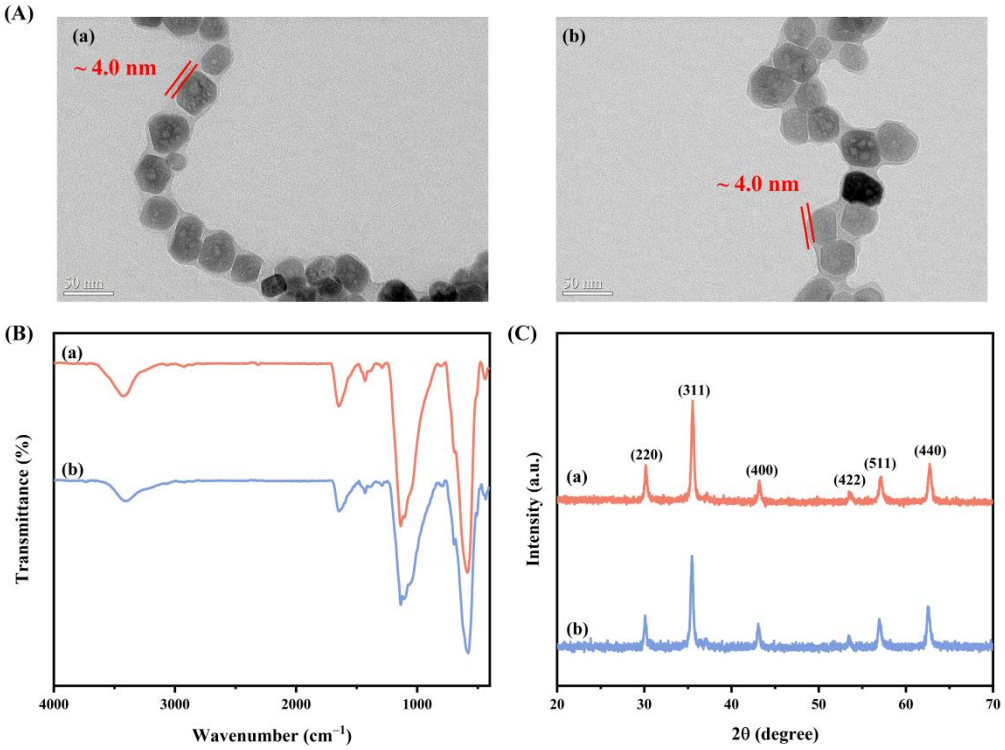
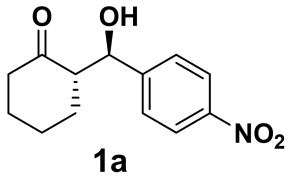


Fig. S10 TEM (A), FT-IR (B), and XRD (C) characterizations of original (a) and used (b) P-MMIP.

16. Analytical data and HPLC spectra of the aldol products

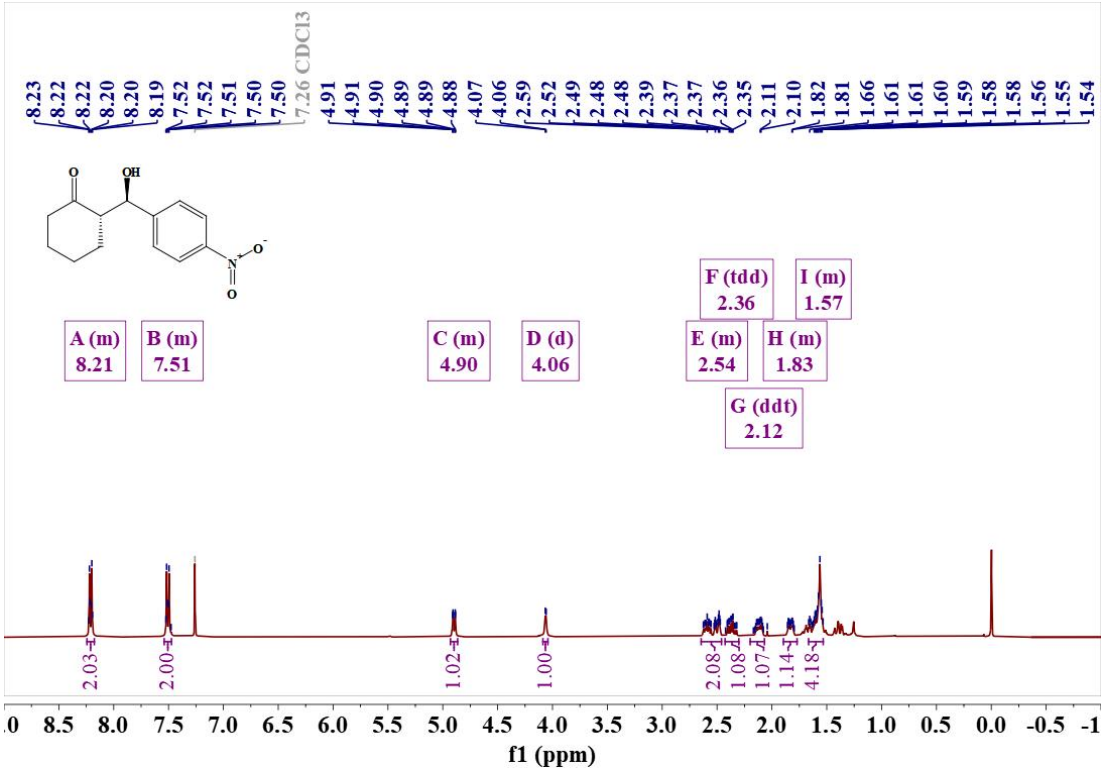
Compounds **7a**-**8c** are new, all the other aldol products are known compounds[22].

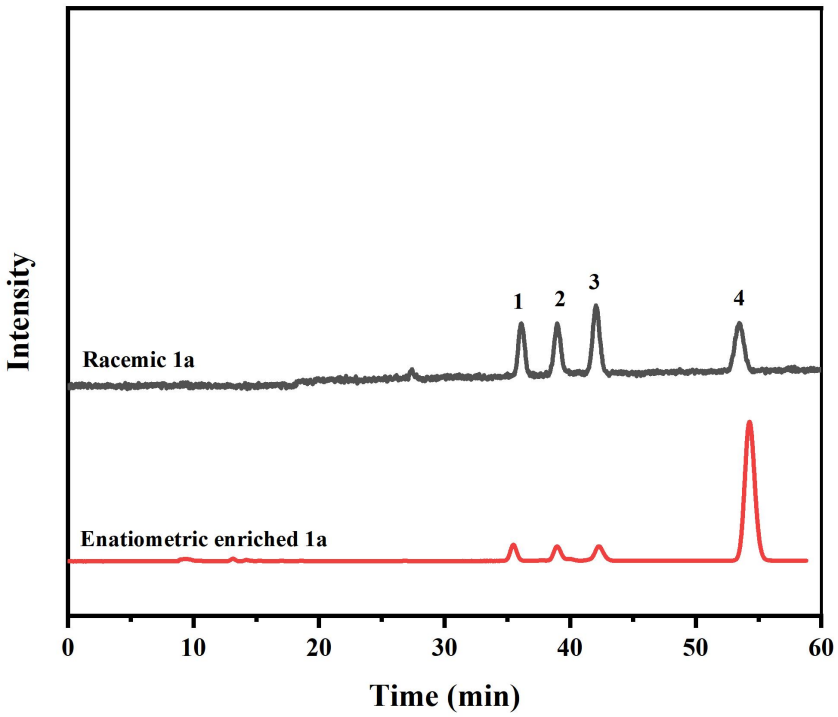
(*S*)-2-((*R*)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (**1a**)



1a

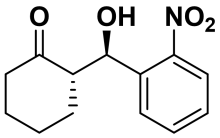
Compound **1a**: a yellow solid; Chiralcel AD-H column, λ = 254 nm, *i*-PrOH:Hexane = 20:80, 0.5 mL/min, t_R= 42.344 min (minor) t_R= 54.26 min (major) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.18 (m, 2H, ArH), 7.54 – 7.47 (m, 2H, ArH), 4.93 – 4.86 (m, 1H, CH), 4.06 (d, *J* = 3.1 Hz, 1H, OH), 2.64 – 2.46 (m, 2H, CH_2), 2.36 (tdd, *J* = 13.6, 6.2, 1.3 Hz, 1H, CH), 2.12 (ddt, *J* = 12.1, 5.8, 2.9 Hz, 1H, CH), 1.89 – 1.77 (m, 1H, CH), 1.67 – 1.53 (m, 4H, $2CH_2$).





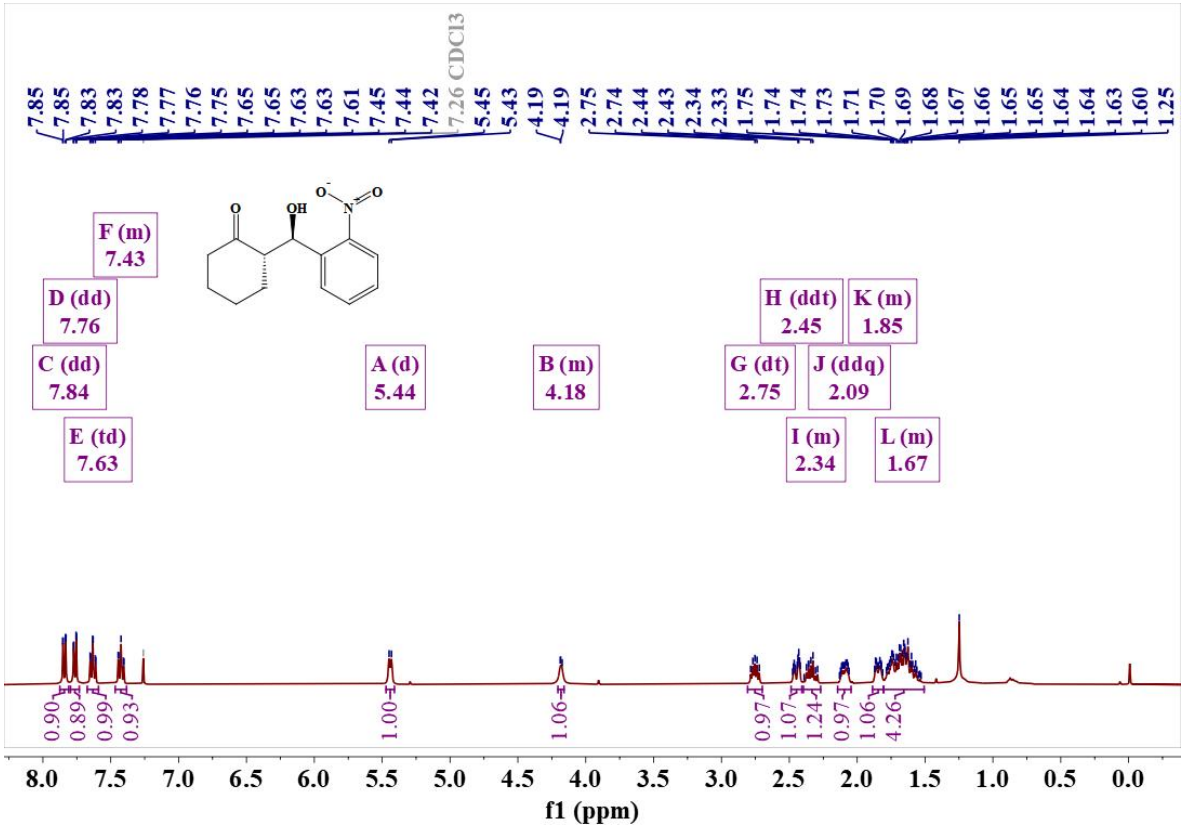
Product	Peak	t_R	Area	Height	%Area
Racemic **1a**	1	35.947	338207	5947	24.51
	2	39.466	326207	5736	23.64
	3	42.791	369201	6492	26.76
	4	54.783	346282	6089	25.09
Enatiometric enriched **1a**	1	35.563	110695	3009	6.03
	2	39.133	113486	2684	6.18
	3	42.344	135243	2695	7.37
	4	54.26	1476807	25968	80.43

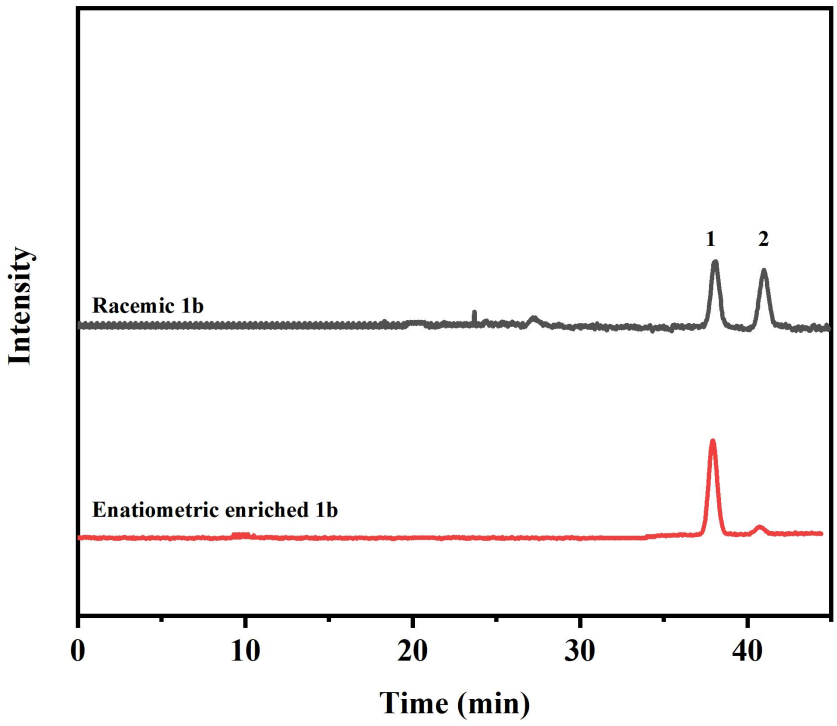
(*S*)-2-((*R*)-hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (**1b**)



1b

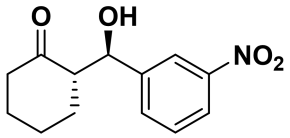
Compound **1b**: a yellow oil; Chiralcel AD-H column, λ = 254 nm, *i*-PrOH:Hexane = 20:80, 0.5 mL/min,t_R= 37.931 min (major). t_R= 40.572 min (minor). 1H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.76 (dd, *J* = 8.0, 1.4 Hz, 1H, ArH), 7.63 (td, *J* = 7.7, 1.3 Hz, 1H,ArH), 7.47 – 7.38 (m, 1H, ArH), 5.44 (d, *J* = 7.0 Hz, 1H, CH), 4.20 – 4.16 (m, 1H, OH), 2.75 (dt, *J* = 12.8, 6.5 Hz, 1H, CH), 2.45 (ddt, *J* = 13.8, 4.4, 2.2 Hz, 1H, CH), 2.40 – 2.27 (m, 1H, CH), 2.09 (ddq, *J* = 12.1, 5.7, 3.0 Hz, 1H, CH), 1.89 – 1.80 (m, 1H, CH), 1.81 – 1.51 (m, 4H, 2CH_2).





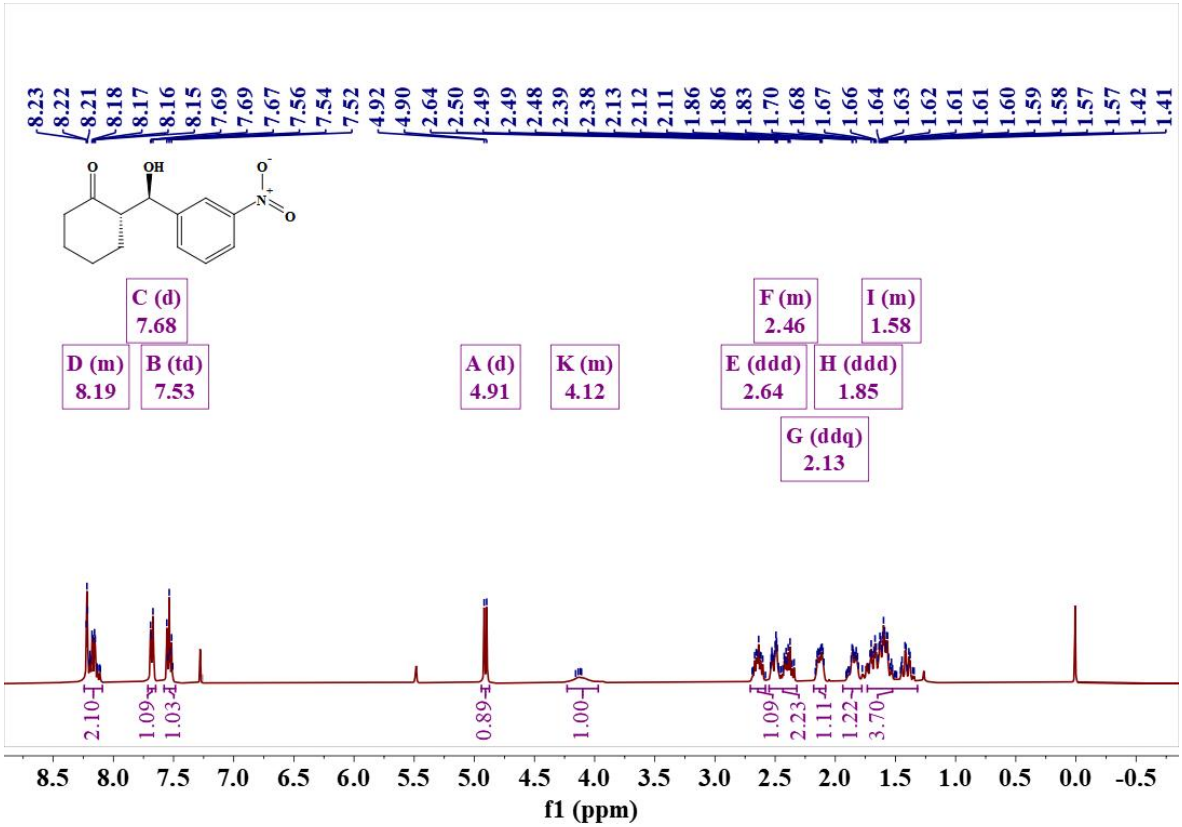
Product	Peak	t_R	Area	Height	%Area
Racemic **1b**	1	38.087	9678	284	50.69
	2	40.98	9416	254	49.31
Enatiometric	1	37.931	9891	326	97.56
enriched **1b**	2	40.752	247	46	2.44

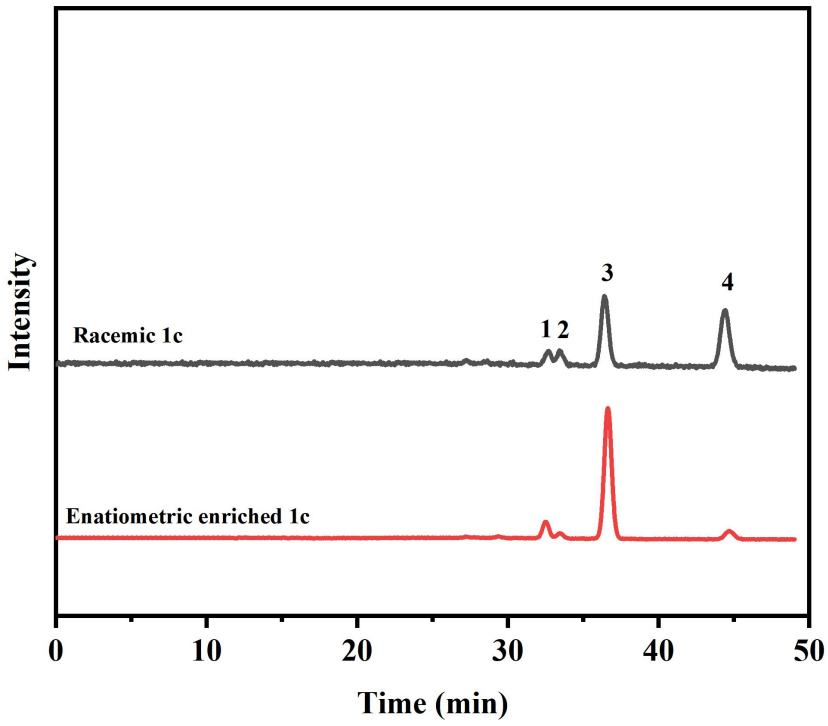
(*S*)-2-((*R*)-hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (**1c**)



1c

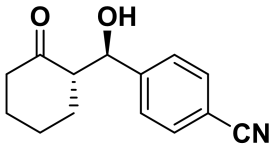
Compound **1c**: a yellow oil; Chiralcel AD-H column, λ = 254 nm, *i*-PrOH:Hexane =20:80, 0.5 mL/min, t_R =37.927 min. (major), t_R =44.732 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.09 (m, 2H, ArH), 7.68 (d, *J* = 8.0 Hz, 1H, ArH), 7.53 (td, *J* = 7.9, 3.7 Hz, 1H, ArH), 4.91 (d, *J* = 8.4 Hz, 1H, CH), 4.23 – 3.97 (m, 1H, OH), 2.64 (ddd, *J* = 13.7, 8.6, 5.4 Hz, 1H, CH), 2.55 – 2.32 (m, 2H, CH_2), 2.13 (ddq, *J* = 12.2, 6.0, 3.1 Hz, 1H, CH), 1.85 (ddd, *J* = 13.3, 10.2, 6.9 Hz, 1H, CH), 1.73 – 1.32 (m, 4H, $2CH_2$).





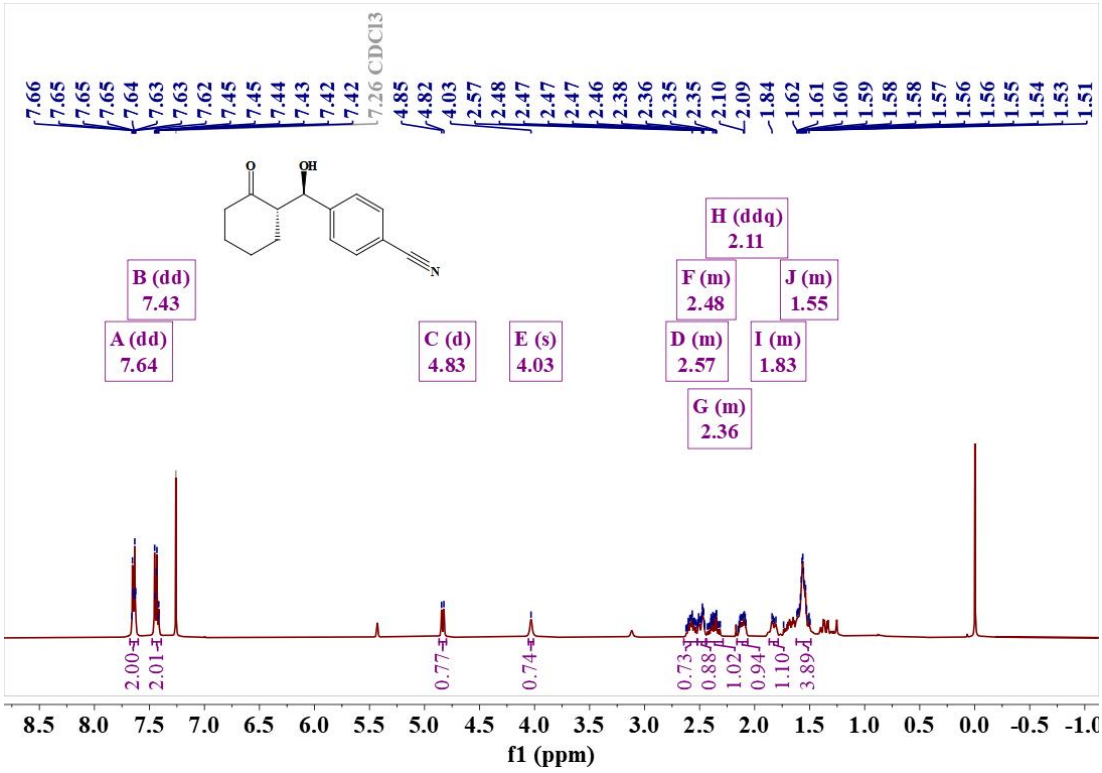
Product	Peak	t_R	Area	Height	%Area
Racemic **1c**	1	32.695	2644	153	6.50
	2	34.344	2187	154	5.37
	3	36.45	17919	522	44.02
	4	44.39	17953	419	44.11
Enatiometric enriched **1c**	1	32.866	2963	146	3.98
	2	34.997	1145	109	1.54
	3	37.929	67916	1841	91.17
	4	44.732	2473	112	3.32

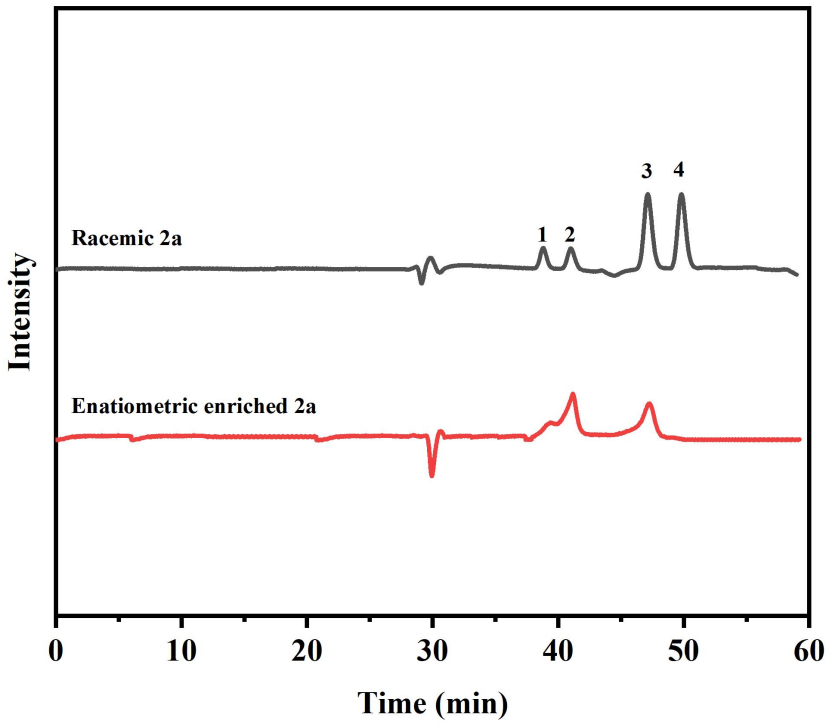
4-((*R*)-hydroxy((*S*)-2-oxocyclohexyl)methyl)benzonitrile (**2a**)



2a

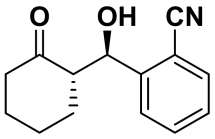
Compound **2a**: a yellow solid; Chiralcel AS-H column, λ= 254 nm, *i*-PrOH:Hexane =20:80, 0.5 mL/min, t_R =47.346 min (major), t_R =49.987 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (dd, *J* = 8.3, 3.4 Hz, 2H, ArH), 7.43 (dd, *J* = 8.3, 6.5 Hz, 2H, ArH), 4.83 (d, *J* = 8.4 Hz, 1H, CH), 4.03 (s, 1H, OH), 2.64 – 2.52 (m, 1H, CH), 2.52 – 2.44 (m, 1H, CH), 2.44 – 2.29 (m, 1H, CH), 2.11 (ddq, *J* = 12.2, 5.7, 3.0 Hz, 1H, CH), 1.87 – 1.79 (m, 1H, CH), 1.62 – 1.49 (m, 4H, 2CH_2).





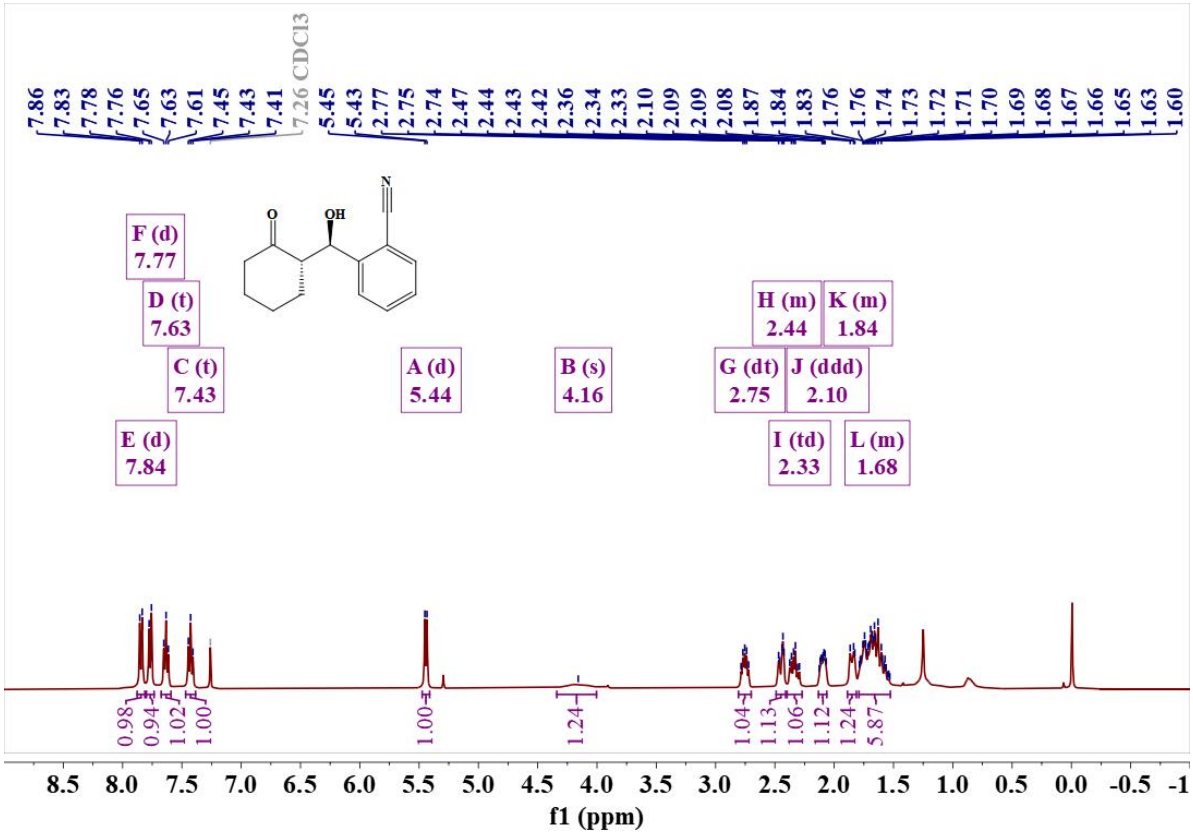
Product	Peak	t_R	Area	Height	%Area
Racemic **2a**	1	38.727	7781	238	8.74
	2	41.121	7808	251	8.77
	3	47.127	36668	977	41.19
	4	49.877	36772	967	41.30
Enatiometric enriched **2a**	1	39.233	2075	131	0.57
	2	41.258	209095	4590	57.05
	3	47.346	155243	3546	42.35
	4	49.987	129	8	0.04

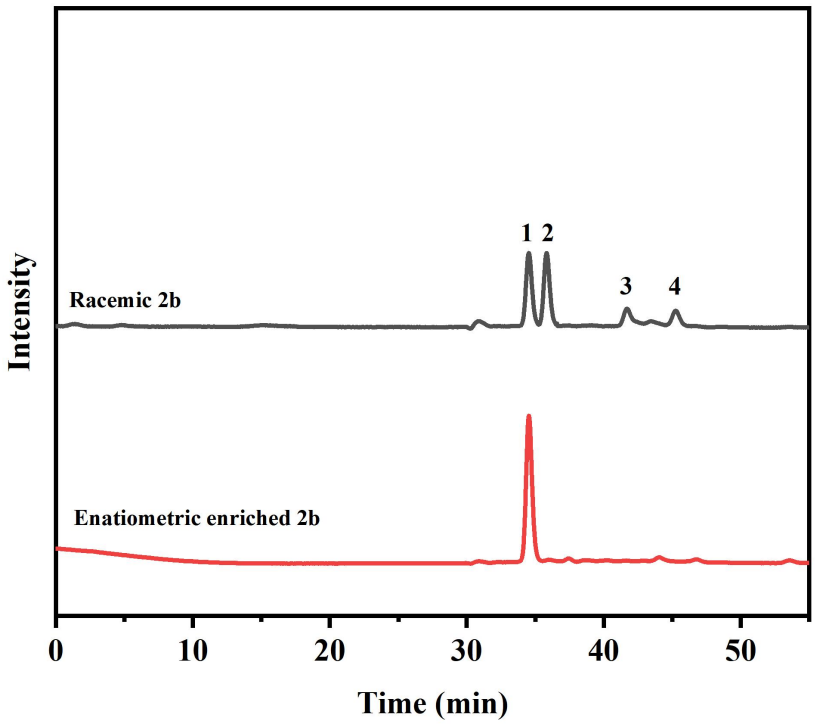
2-((*R*)-hydroxy((*S*)-2-oxocyclohexyl)methyl)benzonitrile (**2b**)



2b

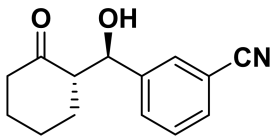
Compound **2b**: a yellow solid; Chiralcel AD-H column,λ= 254 nm, *i*-PrOH:Hexane =20:80, 0.5 mL/min, t_R =34.434 min (major), t_R =37.42 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.2 Hz, 1H, ArH), 7.77 (d, *J* = 7.9 Hz, 1H, ArH), 7.63 (t, *J* = 7.6 Hz, 1H, ArH), 7.43 (t, *J* = 7.7 Hz, 1H, ArH), 5.44 (d, *J* = 7.0 Hz, 1H, CH), 4.16 (s, 1H, OH), 2.75 (dt, *J* = 12.8, 6.4 Hz, 1H, CH), 2.49 – 2.41 (m, 1H, CH), 2.33 (td, *J* = 13.3, 6.1 Hz, 1H, CH), 2.10 (ddd, *J* = 13.8, 6.7, 3.5 Hz, 1H, CH), 1.89 – 1.81 (m, 1H, CH), 1.79 – 1.53 (m, 4H, 2CH_2).





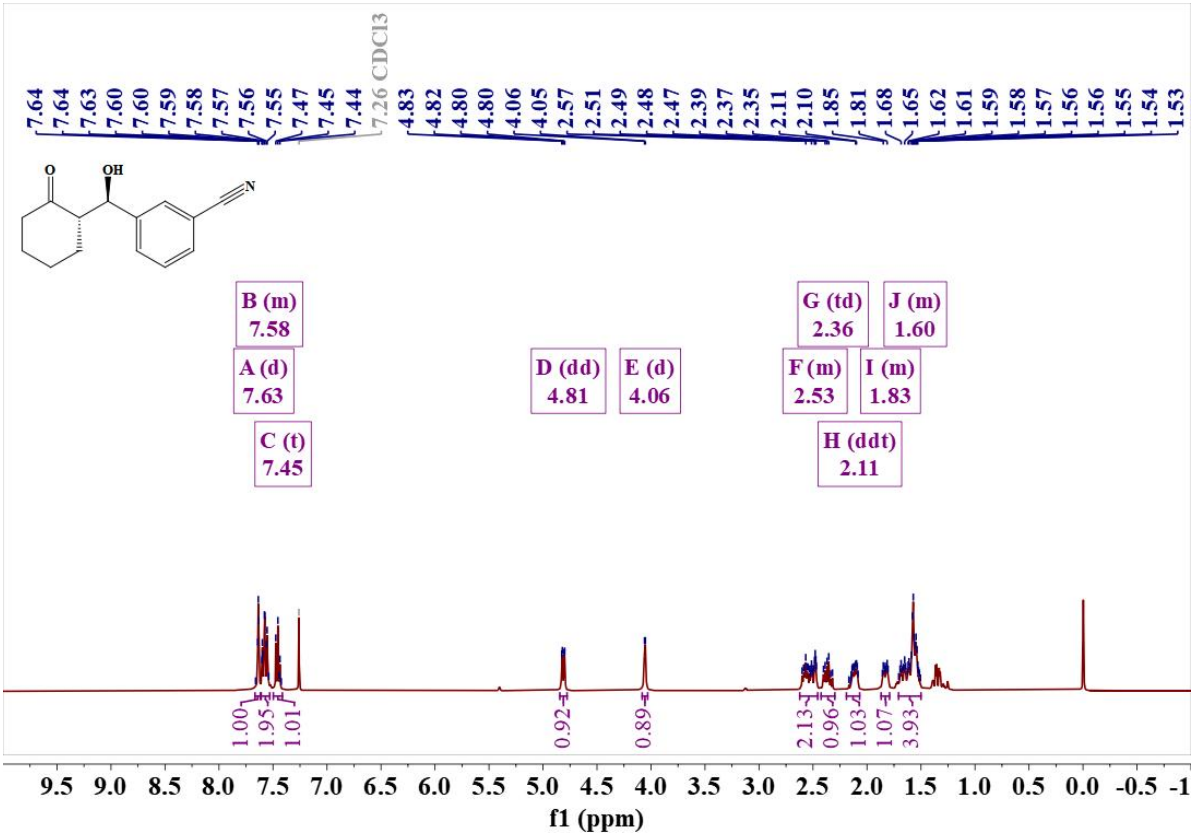
Product	Peak	t_R	Area	Height	%Area
Racemic **2b**	1	34.37	167865	3583	48.76
	2	35.762	168262	3584	48.87
	3	41.607	4210	113	1.22
	4	45.120	3949	107	1.15
Enatiometric enriched **2b**	1	34.434	399927	4929	98.34
	2	37.42	1085	80	0.27
	3	42.127	2908	74	0.72
	4	46.91	2745	73	0.68

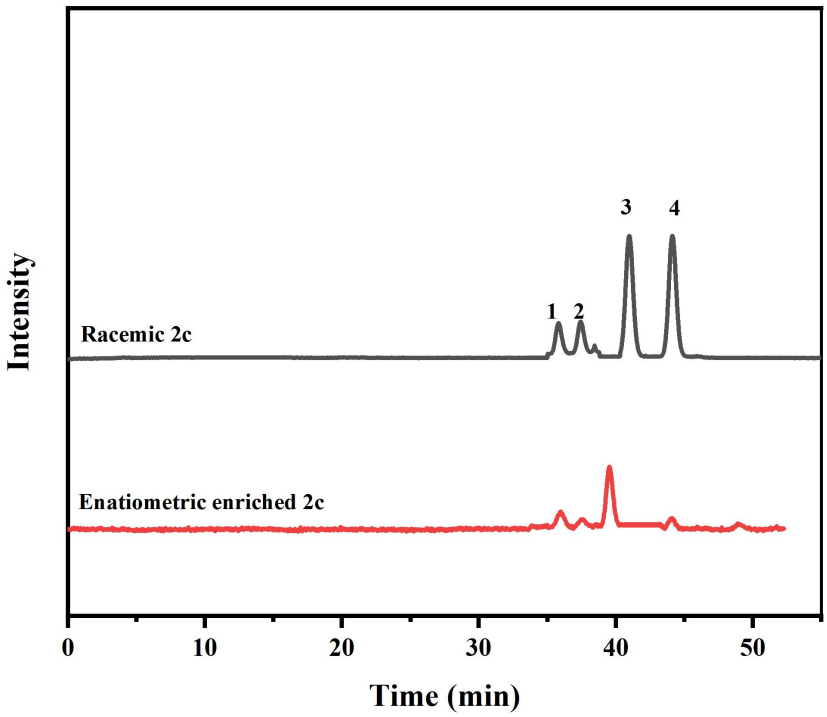
3-((*R*)-hydroxy((*S*)-2-oxocyclohexyl)methyl)benzonitrile (**2c**)



2c

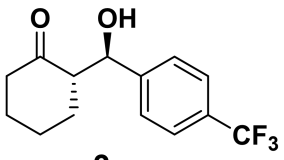
Compound **2c**: a yellow solid; Chiralcel AD-H column,λ= 254 nm, *i*-PrOH:Hexane =20:80, 0.5 mL/min, t_R=39.579 min (major), t_R=44.09 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 1.8 Hz, 1H, ArH), 7.61 – 7.53 (m, 2H, ArH), 7.45 (t, *J* = 7.7 Hz, 1H, ArH), 4.81 (dd, *J* = 8.6, 2.2 Hz, 1H, CH), 4.06 (d, *J* = 2.9 Hz, 1H, OH), 2.62 – 2.46 (m, 2H, CH_2), 2.36 (td, *J* = 13.3, 6.2 Hz, 1H, CH), 2.11 (ddt, *J* = 12.2, 5.9, 3.0 Hz, 1H, CH), 1.87 – 1.79 (m, 1H, CH), 1.71 – 1.50 (m, 4H, 2CH_2).





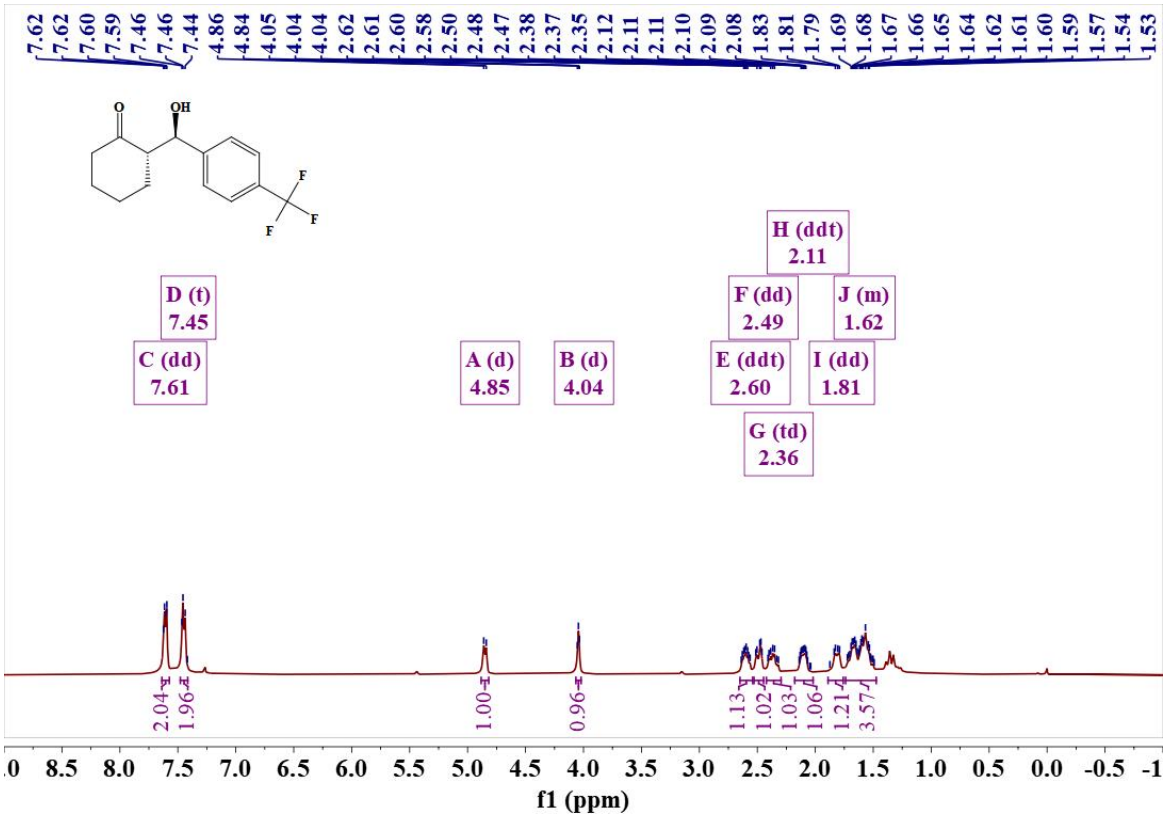
Product	Peak	t_R	Area	Height	%Area
Racemic **2c**	1	35.851	12781	357	7.80
	2	37.44	14733	396	8.99
	3	40.997	68329	1513	41.71
	4	45.41	67989	1505	41.50
Enatiometric enriched **2c**	1	35.99	5795	194	16.74
	2	37.519	5210	134	15.05
	3	39.579	18445	406	53.28
	4	44.09	5166	140	14.92

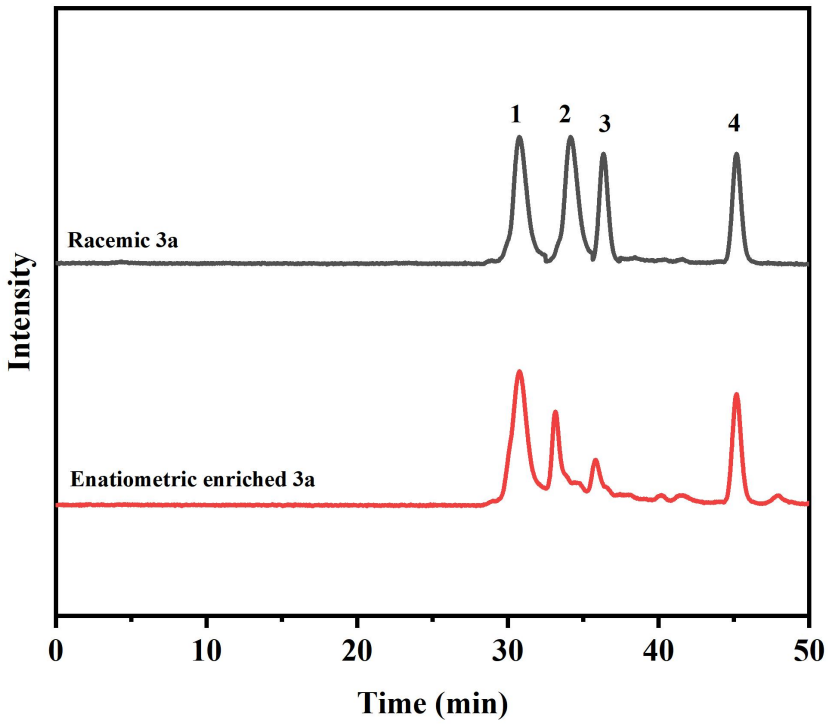
(*S*)-2-((*R*)-hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (**3a**)



3a

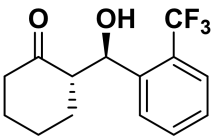
Compound **3a**: a white solid; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH:Hexane = 20:80, 0.5 mL/min, t_R=35.809 min (minor), t_R=45.138 min (major). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.61 (dd, *J* = 8.3, 3.3 Hz, 2H, ArH), 7.45 (t, *J* = 5.6 Hz, 2H, ArH), 4.85 (d, *J* = 8.6 Hz, 1H, CH), 4.04 (d, J = 3.3 Hz, 1H, OH), 2.60 (ddt, *J* = 13.6, 8.5, 4.3 Hz, 1H, CH), 2.49 (dd, *J* = 13.7, 4.0 Hz, 1H, CH), 2.36 (td, *J* = 13.2, 5.8 Hz, 1H, CH), 2.11 (ddt, *J* = 13.2, 6.6, 3.2 Hz, 1H, CH), 1.81 (dd, *J* = 13.5, 5.1 Hz, 1H, CH), 1.74–1.47 (m, 4H, 2CH_2).





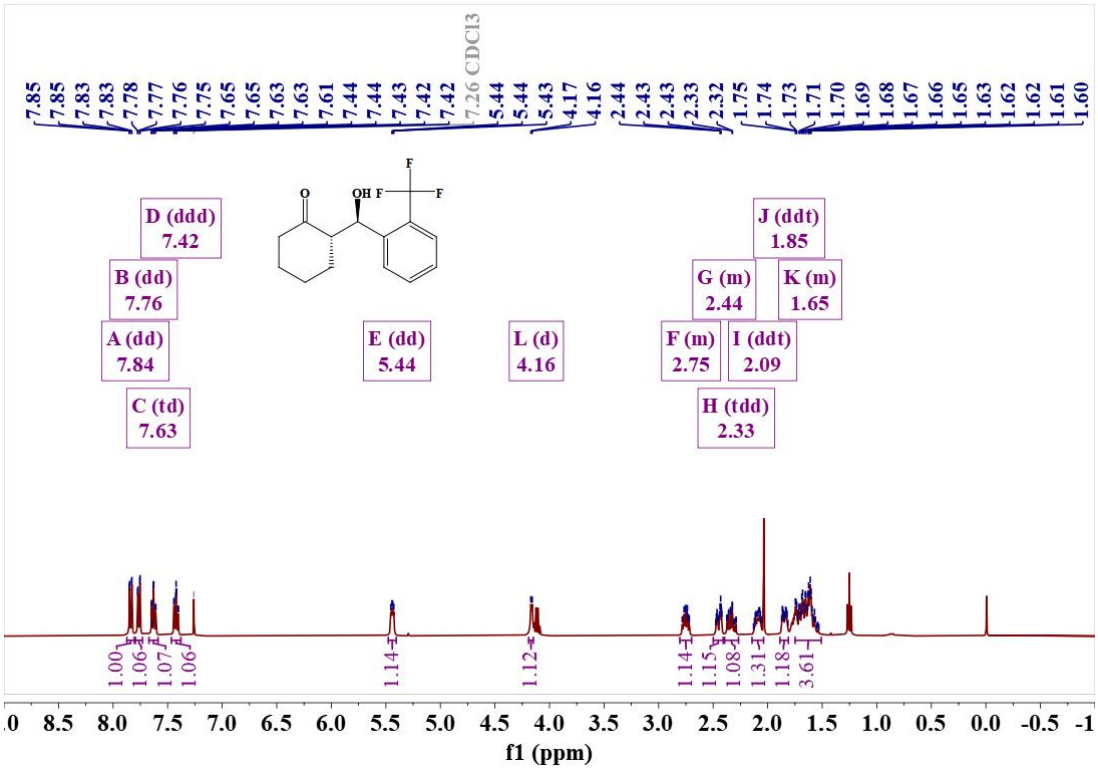
Product	Peak	t_R	Area	Height	%Area
Racemic **3a**	1	30.742	44609	1278	29.96
	2	33.188	43648	1250	29.31
	3	35.822	30648	1021	20.58
	4	45.126	30007	1001	20.15
Enatiometric enriched **3a**	1	30.725	52714	1294	48.17
	2	33.132	8842	408	8.08
	3	35.809	1652	196	1.51
	4	45.138	46230	1270	42.24

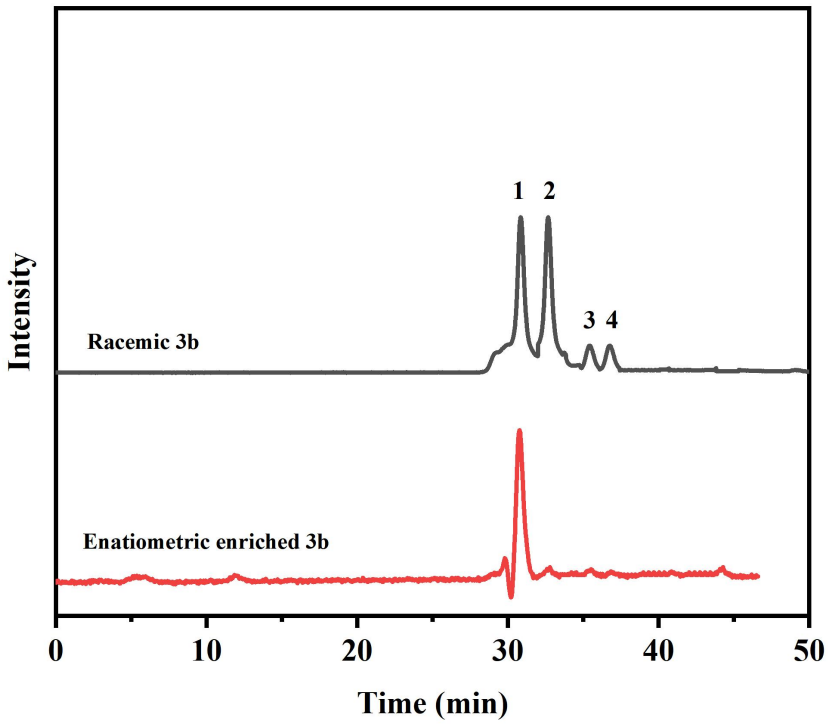
(*S*)-2-((*R*)-hydroxy(2-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (**3b**)



3b

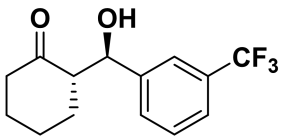
Compound **3b**: a colorless oil; Chiralcel AD-H column, λ= 254 nm, *i*-PrOH:Hexane = 20:80, 0.5 mL/min, t_R= 30.77 min (major), t_R = 32.471 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH), 7.76 (dd, *J* = 7.8, 1.4 Hz, 1H, ArH), 7.63 (td, *J* = 7.7, 1.3 Hz, 1H, ArH), 7.42 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H, ArH), 5.44 (dd, *J* = 7.1, 4.0 Hz, 1H, CH), 4.16 (d, *J* = 5.0 Hz, 1H, OH), 2.81 – 2.70 (m, 1H, CH), 2.50 – 2.41 (m, 1H, CH), 2.33 (tdd, *J* = 13.4, 6.1, 1.3 Hz, 1H, CH), 2.09 (ddt, *J* = 11.9, 5.6, 2.8 Hz, 1H, CH), 1.85 (ddt, *J* = 12.4, 3.6, 2.0 Hz, 1H, CH), 1.75 – 1.51 (m, 4H, 2CH_2).





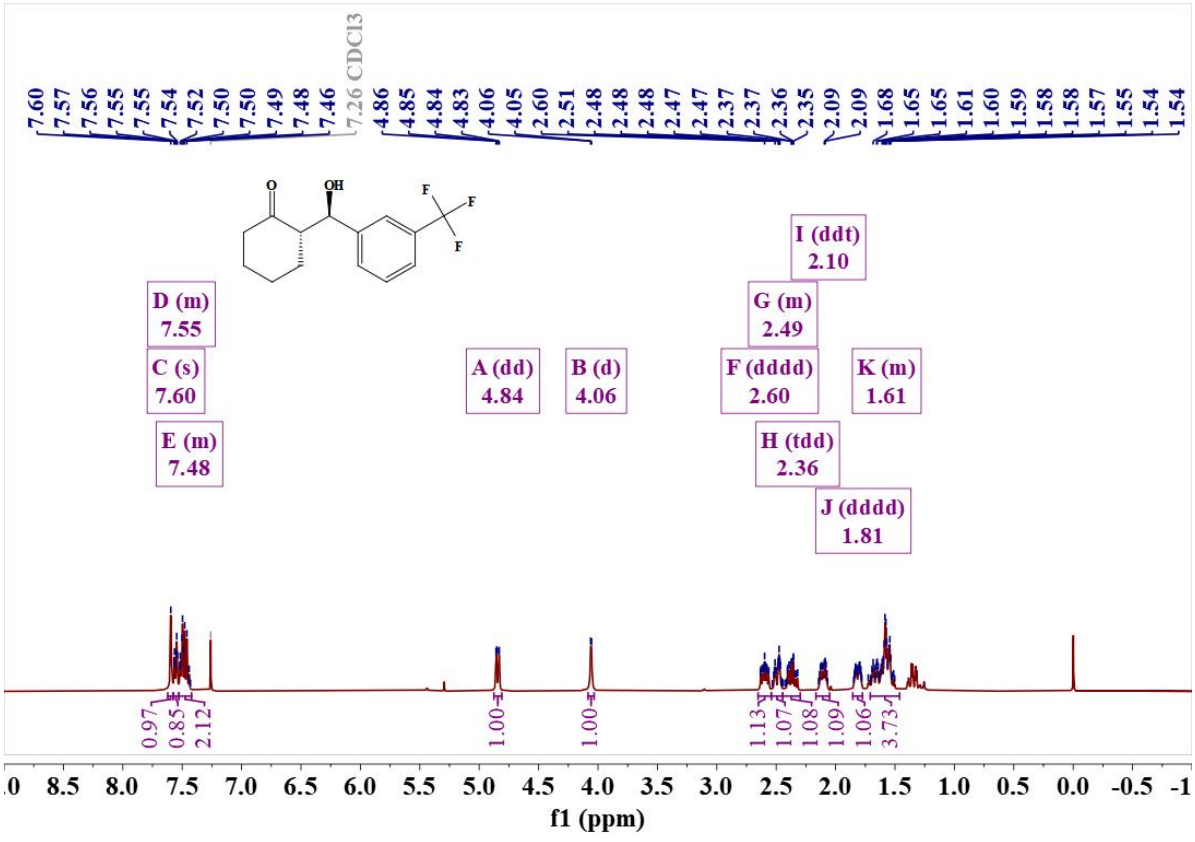
Product	Peak	t_R	Area	Height	%Area
Racemic **3b**	1	30.846	39975	1126	42.01
	2	32.616	40021	1117	42.06
	3	35.215	7447	271	7.83
	4	36.575	7717	273	8.11
Enatiometric enriched **3b**	1	30.77	46844	1249	85.85
	2	32.471	3127	108	5.73
	3	35.046	2516	105	4.61
	4	36.609	2080	104	3.81

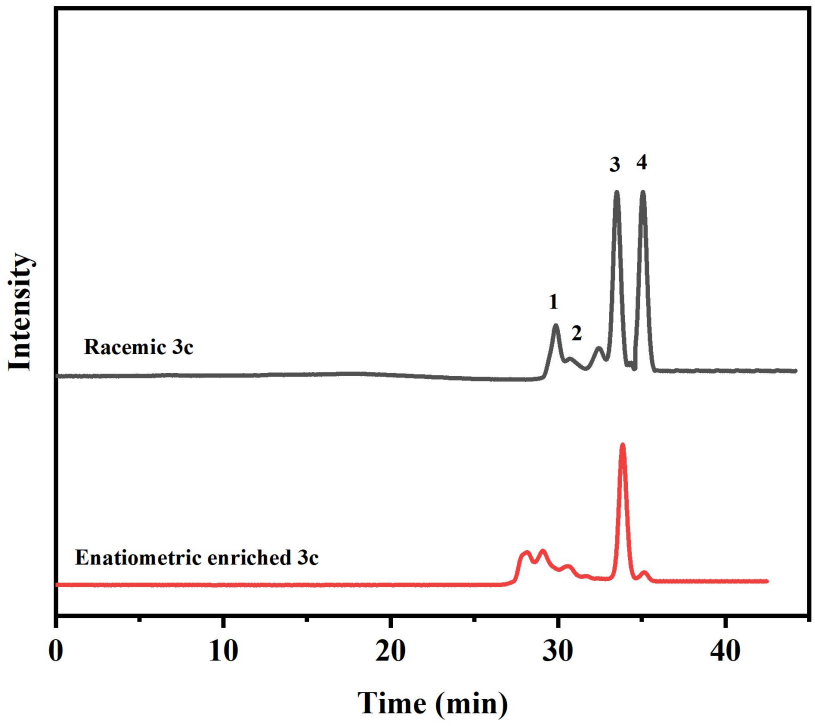
(*S*)-2-((*R*)-hydroxy(3-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (**3c**)



3c

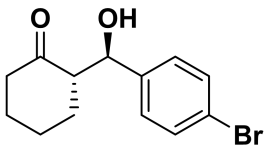
Compound **3c**: a white solid; Chiralcel AS-H column, λ= 254 nm, *i*-PrOH:Hexane = 5:95, 0.5 mL/min, t_R =32.299 min (major), t_R = 35.582 (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 (s, 1H, ArH), 7.58 – 7.53 (m, 1H, ArH), 7.53 – 7.42 (m, 2H, ArH), 4.84 (dd, *J* = 8.6, 2.1 Hz, 1H, ArH), 4.06 (d, *J* = 2.9 Hz, 1H, OH), 2.60 (dddd, *J* = 12.8, 8.6, 5.5, 1.3 Hz, 1H, CH), 2.54 – 2.44 (m, 1H, CH), 2.36 (tdd, *J* = 13.5, 6.1, 1.3 Hz, 1H, CH), 2.10 (ddt, *J* = 12.1, 5.8, 2.9 Hz, 1H, CH), 1.81 (dddd, *J* = 13.3, 6.8, 3.4, 1.7 Hz, 1H, CH), 1.71 – 1.46 (m, 4H, 2CH_2).





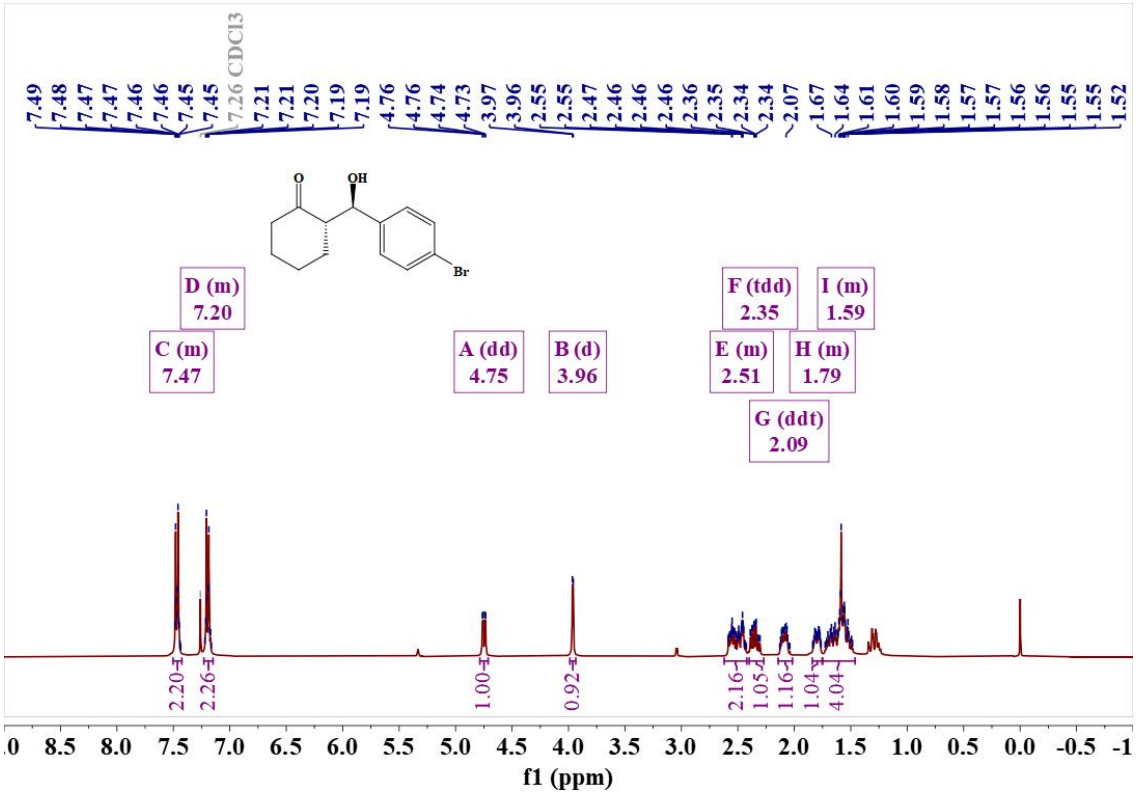
Product	Peak	t_R	Area	Height	%Area
Racemic **3c**	1	29.861	97907	1975	9.10
	2	30.678	73881	1326	6.86
	3	33.506	445282	12720	41.37
	4	35.586	459344	12848	42.67
Enatiometric enriched **3c**	1	29.878	132371	2318	21.85
	2	30.818	160380	2420	26.47
	3	32.299	308718	9338	50.96
	4	35.582	4344	209	0.72

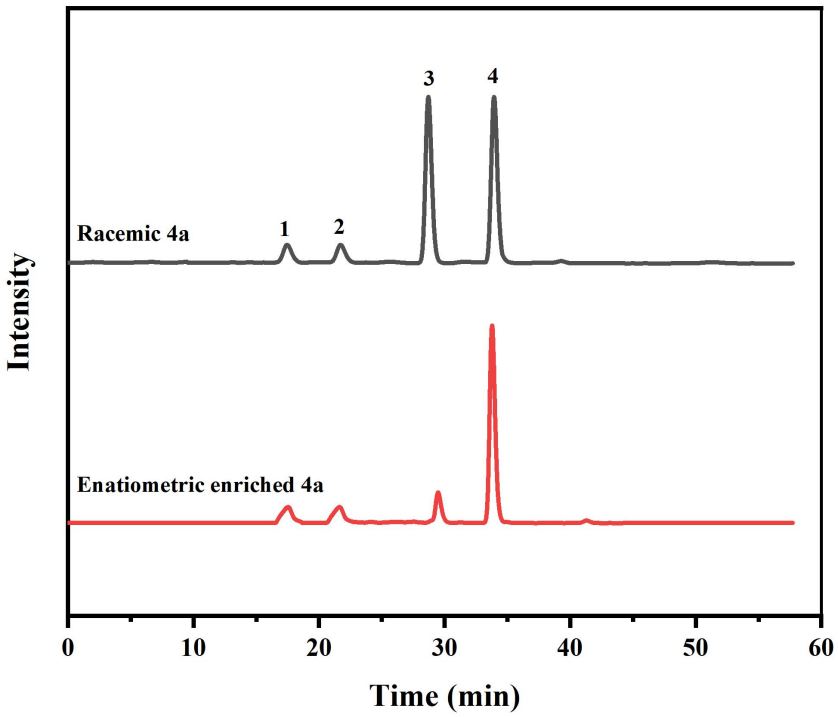
(*S*)-2-((*R*)-(4-bromophenyl)(hydroxy)methyl)cyclohexan-1-one (**4a**)



4a

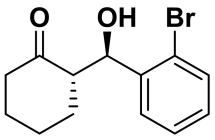
Compound **4a**: a yellow solid; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 28.707 min (minor). t_R = 34.168 min (major). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.42 (m, 2H, ArH), 7.23 – 7.15 (m, 2H, ArH), 4.75 (dd, *J* = 8.7, 2.7 Hz, 1H, CH), 3.96 (d, *J* = 2.9 Hz, 1H, OH), 2.62 – 2.42 (m, 2H, CH_2), 2.35 (tdd, *J* = 13.6, 6.1, 1.3 Hz, 1H, CH), 2.09 (ddt, *J* = 12.2, 5.8, 3.0 Hz, 1H, CH), 1.84 – 1.75 (m, 1H, CH), 1.75 – 1.46 (m, 4H, $2CH_2$).





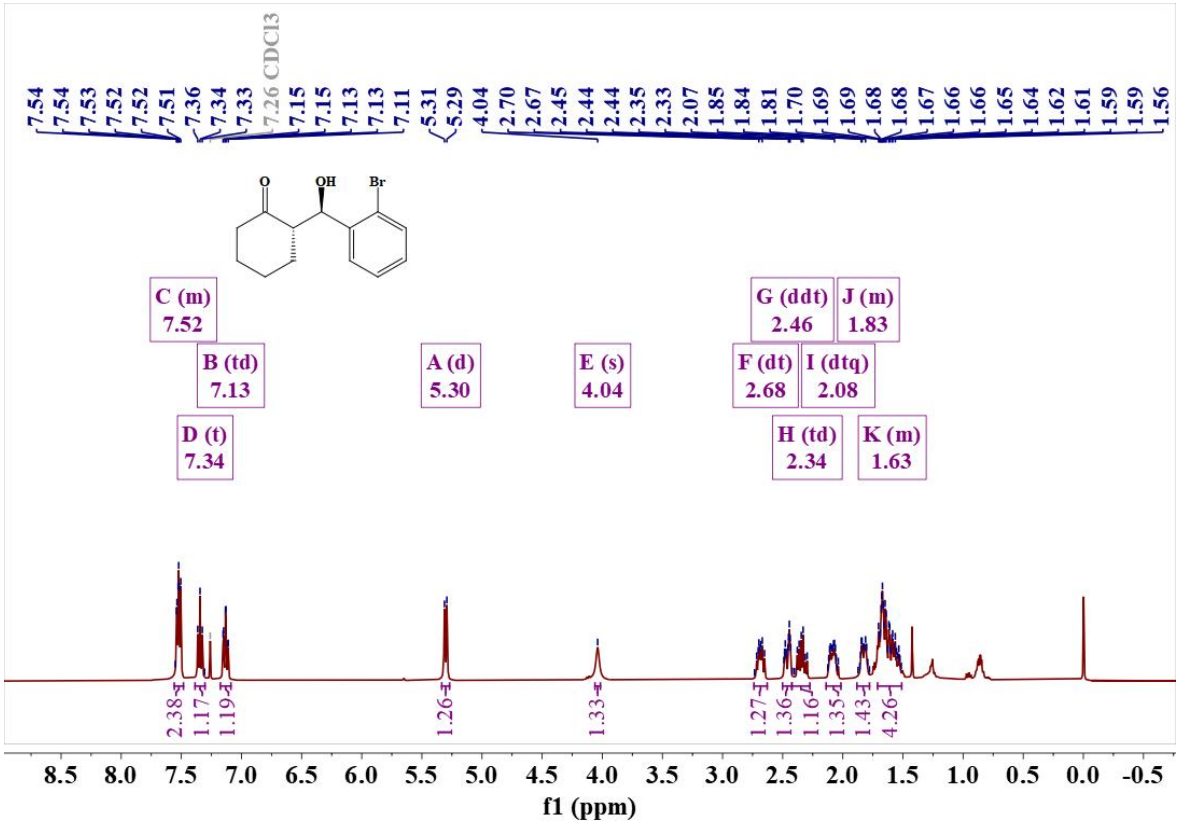
Product	Peak	t_R	Area	Height	%Area
Racemic **4a**	1	17.625	51846	1084	6.25
	2	21.583	51909	1083	6.25
	3	28.708	363135	10255	43.75
	4	33.941	363115	10256	43.75
Enatiometric enriched **4a**	1	15.563	54756	954	10.05
	2	19.133	55973	961	10.27
	3	28.707	60795	1869	11.16
	4	34.168	373260	12160	68.52

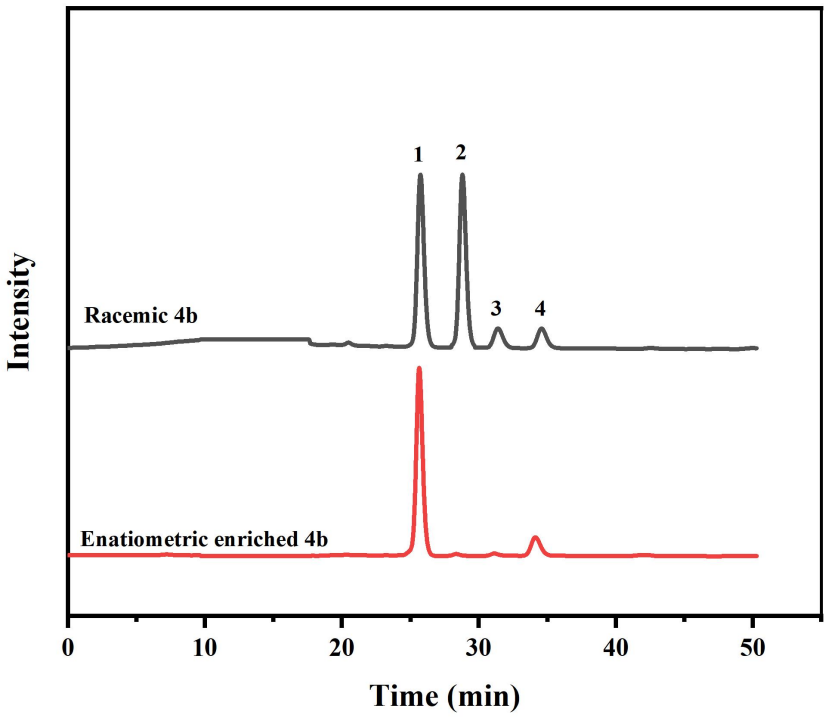
(*S*)-2-((*R*)-(2-bromophenyl)(hydroxy)methyl)cyclohexan-1-one (**4b**)



4b

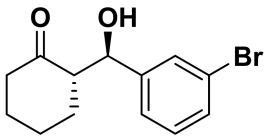
Compound **4b**: a yellow solid; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 25.65 min (major). t_R = 28.34 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.48 (m, 2H, ArH), 7.34 (t, *J* = 7.5 Hz, 1H, ArH), 7.13 (td, *J* = 7.7, 1.7 Hz, 1H, ArH), 5.30 (d, *J* = 8.0 Hz, 1H, CH), 4.04 (s, 1H, OH), 2.68 (dt, *J* = 12.7, 7.3 Hz, 1H, CH), 2.46 (ddt, *J* = 13.6, 4.5, 2.2 Hz, 1H, CH), 2.34 (td, *J* = 13.3, 6.1 Hz, 1H, CH), 2.08 (dtq, *J* = 12.5, 6.5, 3.4 Hz, 1H, CH), 1.88 – 1.78 (m, 1H, CH), 1.71 – 1.51 (m, 4H, 2CH_2).





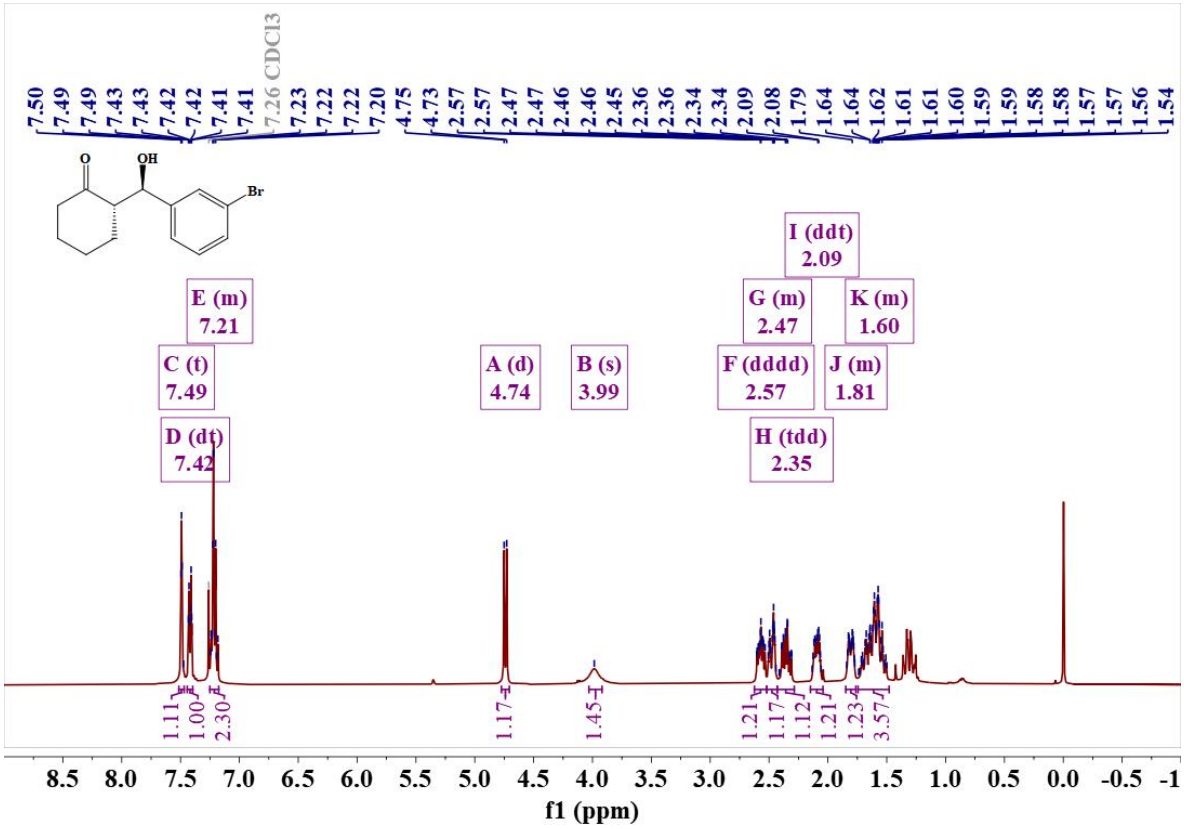
Product	Peak	t_R	Area	Height	%Area
Racemic **4b**	1	25.738	348150	9916	43.43
	2	28.537	348340	9918	43.45
	3	31.148	52282	1122	6.52
	4	34.581	52864	1124	6.59
Enatiometric enriched **4b**	1	25.65	368661	10816	86.52
	2	28.34	2797	91	0.66
	3	31.125	4202	118	0.99
	4	34.134	50448	1055	11.84

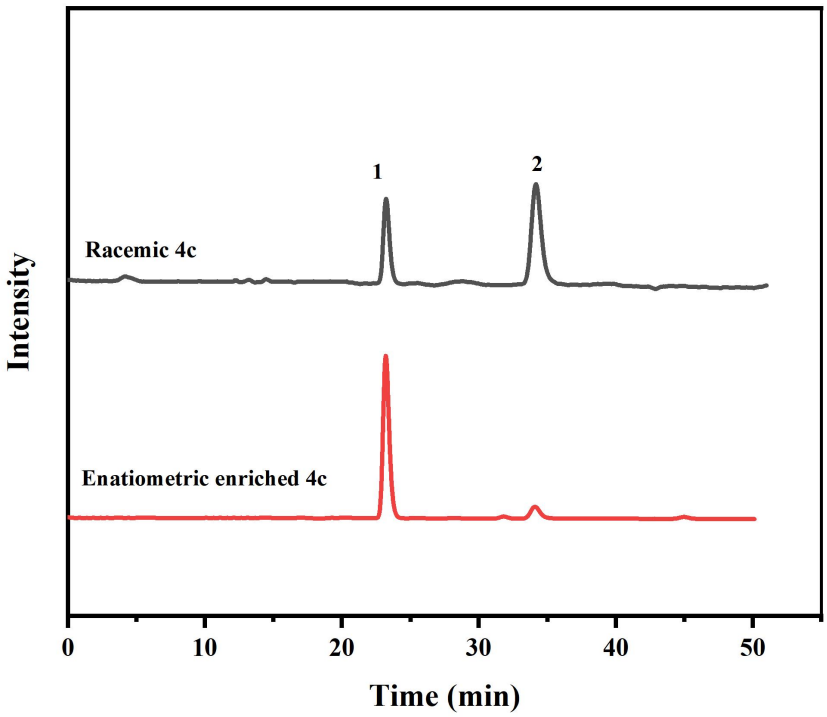
(*S*)-2-((*R*)-(3-bromophenyl)(hydroxy)methyl)cyclohexan-1-one (**4c**)



4c

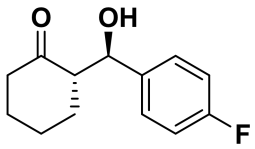
Compound **4c**: a yellow solid; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH: Hexane = 15:85, 0.5 mL/min, t_R = 23.207 min (major). t_R = 34.089 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 (t, *J* = 1.8 Hz, 1H, ArH), 7.42 (dt, *J* = 7.0, 2.0 Hz, 1H, ArH), 7.25 – 7.18 (m, 2H, ArH), 4.74 (d, *J* = 8.7 Hz, 1H, CH), 3.99 (s, 1H, OH), 2.57 (dddd, *J* = 14.2, 8.7, 5.5, 1.3 Hz, 1H, CH), 2.52 – 2.43 (m, 1H, CH), 2.35 (tdd, *J* = 13.6, 6.1, 1.3 Hz, 1H, CH), 2.09 (ddt, *J* = 12.1, 5.8, 3.0 Hz, 1H, CH), 1.85 – 1.76 (m, 1H, CH), 1.74 – 1.48 (m, 4H, 2CH_2).





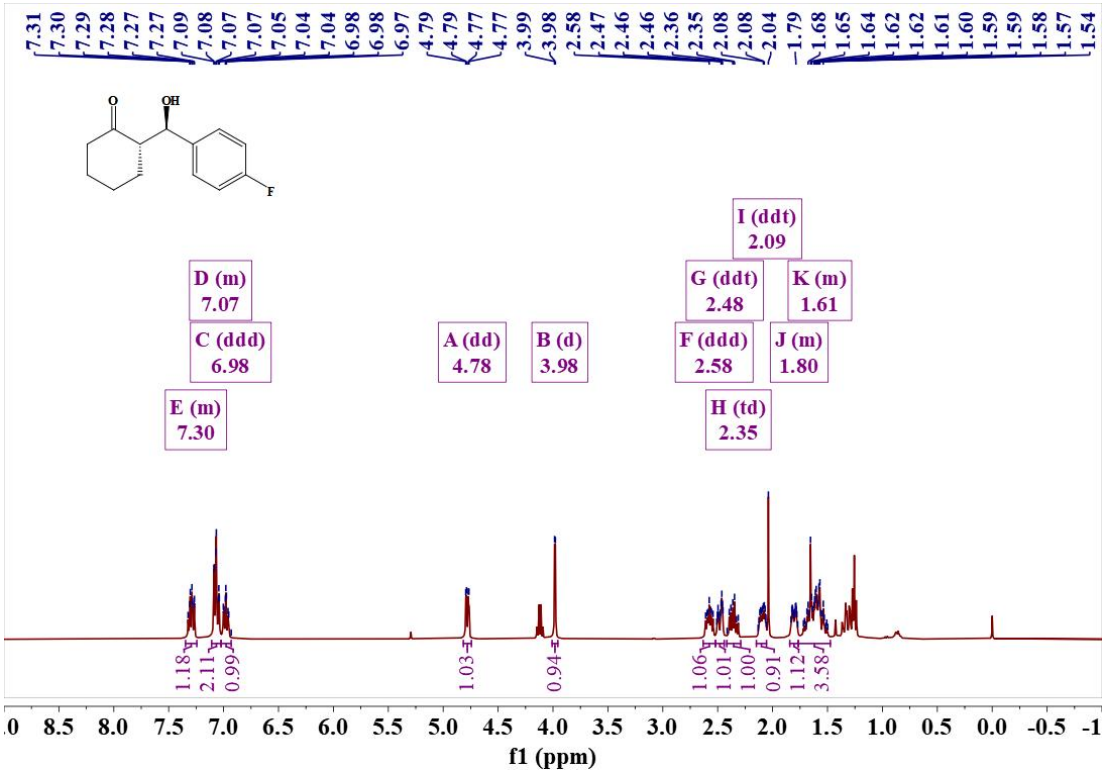
Product	Peak	t_R	Area	Height	%Area
Racemic **4c**	1	23.231	28968	922	34.52
	2	34.168	54951	1088	65.48
Enatiometric	1	23.207	489347	15273	90.32
enriched **4c**	2	34.089	52455	1093	9.68

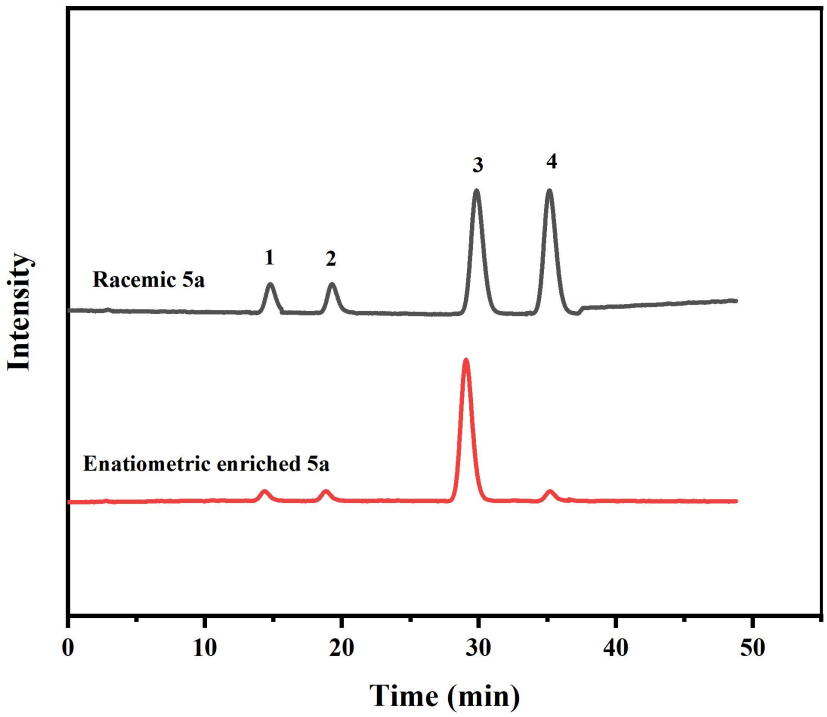
(*S*)-2-((*R*)-(4-fluorophenyl)(hydroxy)methyl)cyclohexan-1-one (**5a**)



5a

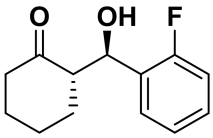
Compound **5a**: a colorless oil; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 29.058 min (major). t_R = 35.108 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.24 (m, 1H, ArH), 7.11 – 7.02 (m, 2H, ArH), 6.98 (ddd, *J* = 10.6, 8.0, 2.6 Hz, 1H, ArH), 4.78 (dd, *J* = 8.7, 2.9 Hz, 1H, CH), 3.98 (d, *J* = 2.9 Hz, 1H, OH), 2.58 (ddd, *J* = 13.8, 8.6, 5.4 Hz, 1H, CH), 2.48 (ddt, *J* = 13.7, 4.2, 2.1 Hz, 1H, CH), 2.35 (td, *J* = 13.2, 6.1 Hz, 1H, CH), 2.09 (ddt, *J* = 12.2, 5.9, 3.0 Hz, 1H, CH), 1.84 – 1.77 (m, 1H, CH), 1.76 – 1.47 (m, 4H, 2CH_2).





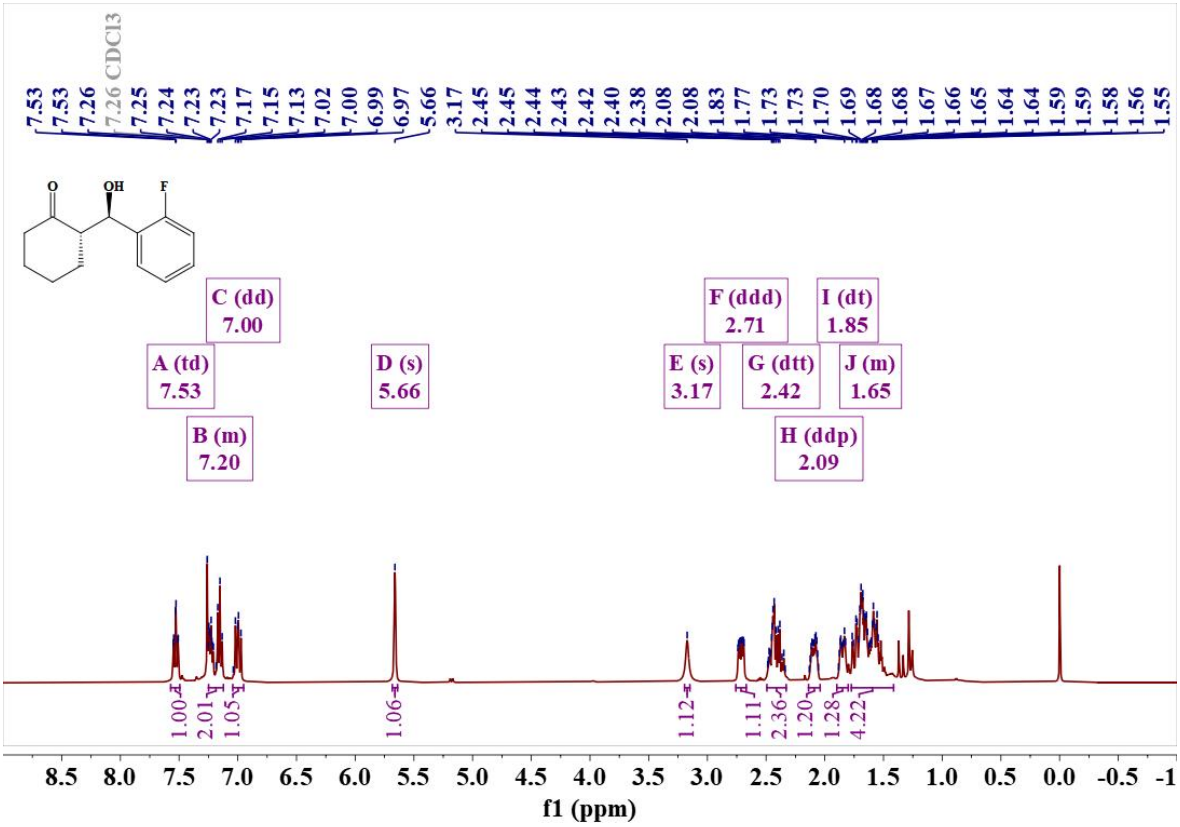
Product	Peak	t_R	Area	Height	%Area
Racemic **5a**	1	14.7	42846	1004	5.28
	2	19.275	41909	1003	5.17
	3	29.867	363135	8925	44.78
	4	35.217	363115	8916	44.77
Enatiometric enriched **5a**	1	14.517	14556	354	3.25
	2	18.825	15923	361	3.55
	3	29.058	403260	10160	90.02
	4	35.108	14231	357	3.18

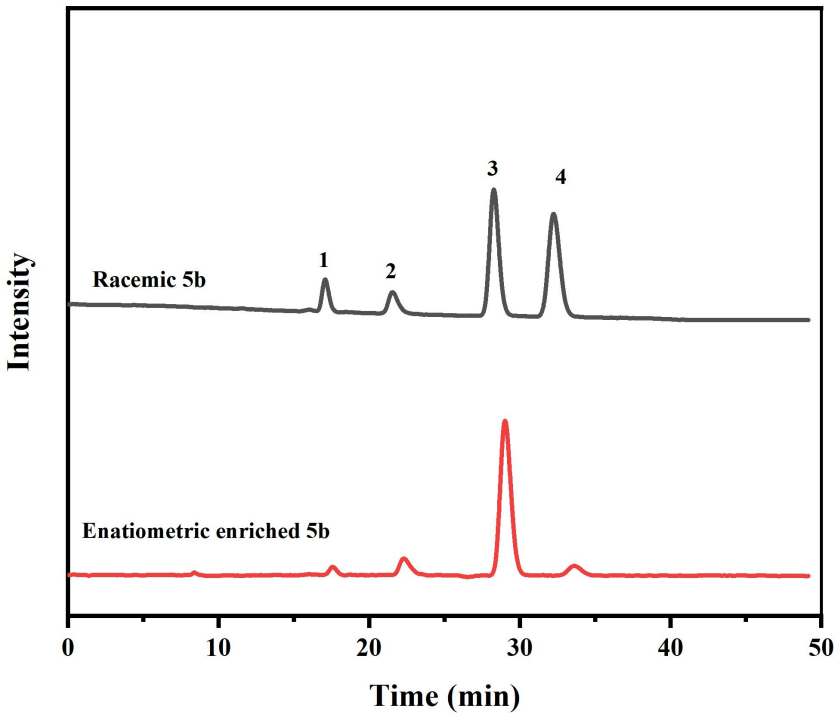
(*S*)-2-((*R*)-(2-fluorophenyl)(hydroxy)methyl)cyclohexan-1-one (**5b**)



5b

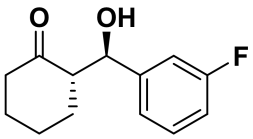
Compound **5b**: a yellow solid; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 28.975 min (major). t_R = 33.633 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (td, *J* = 7.5, 1.9 Hz, 1H, ArH), 7.25 – 7.12 (m, 2H, ArH), 7.00 (dd, *J* = 10.8, 8.1 Hz, 1H, ArH), 5.66 (s, 1H, CH), 3.17 (s, 1H, OH), 2.71 (ddd, *J* = 12.4, 6.1, 2.2 Hz, 1H, CH), 2.42 (dtt, *J* = 19.5, 13.5, 7.3 Hz, 2H, CH_2), 2.09 (ddp, *J* = 11.5, 5.6, 2.9 Hz, 1H, CH), 1.85 (dt, *J* = 13.3, 2.7 Hz, 1H, CH), 1.77 – 1.41 (m, 4H, $2CH_2$).





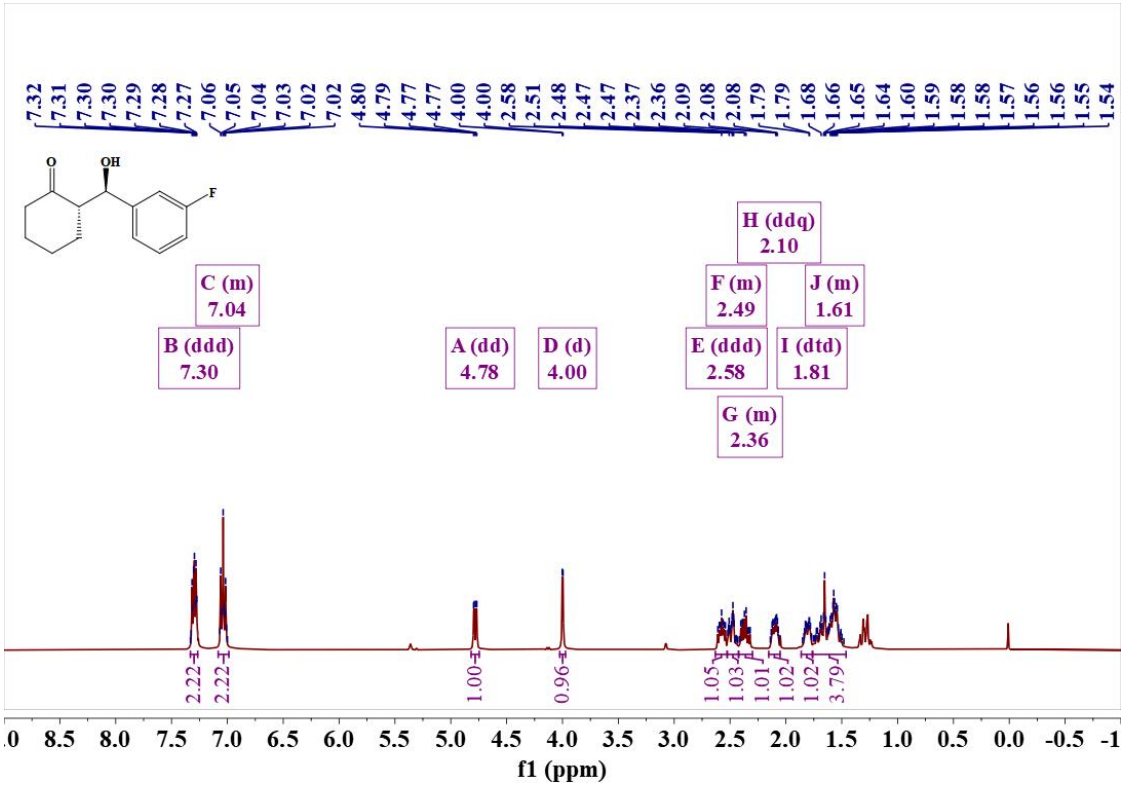
Product	Peak	t_R	Area	Height	%Area
Racemic **5b**	1	17.025	26447	553	5.98
	2	21.533	22875	534	5.17
	3	28.235	197019	2922	44.54
	4	32.292	196001	2419	44.31
Enatiometric enriched **5b**	1	17.583	13963	386	4.41
	2	22.483	20963	509	6.62
	3	28.975	257916	3284	81.47
	4	33.633	23731	438	7.50

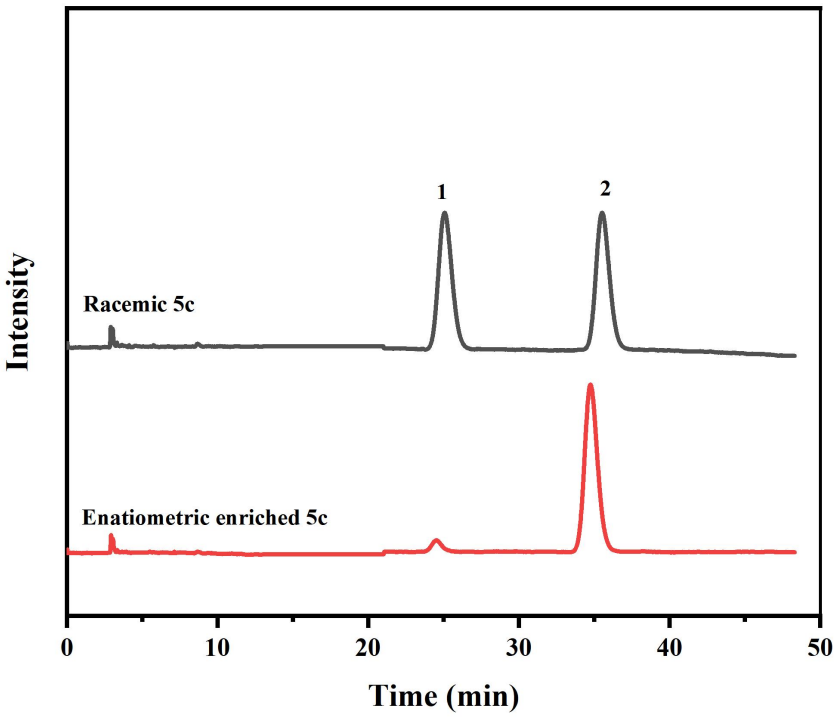
(*S*)-2-((*R*)-(3-fluorophenyl)(hydroxy)methyl)cyclohexan-1-one (**5c**)



5c

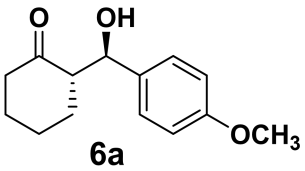
Compound **5c**: a yellow oil; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 24.50 min (minor). t_R = 34.68 min (major). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (ddd, *J* = 8.4, 5.4, 2.5 Hz, 2H, ArH), 7.08 – 6.99 (m, 2H, ArH), 4.78 (dd, *J* = 8.8, 2.5 Hz, 1H, CH), 4.00 (d, *J* = 2.7 Hz, 1H, OH), 2.58 (ddd, *J* = 13.6, 8.7, 5.3 Hz, 1H, CH), 2.53 – 2.42 (m, 1H, CH), 2.42 – 2.30 (m, 1H, CH), 2.10 (ddq, *J* = 12.2, 5.8, 3.0 Hz, 1H, CH), 1.81 (dtd, *J* = 12.8, 5.0, 2.8 Hz, 1H, CH), 1.76 – 1.46 (m, 4H, 2CH_2).





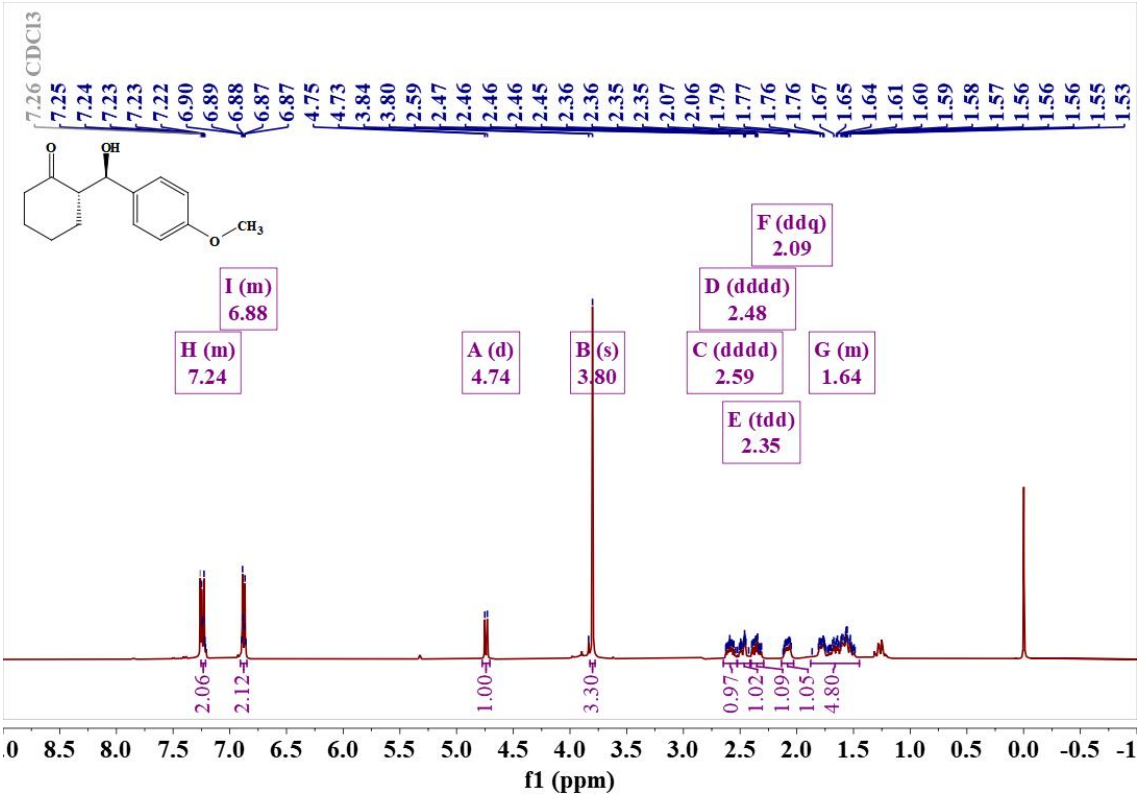
Product	Peak	t_R	Area	Height	%Area
Racemic **5c**	1	25.00	54968	1086	49.98
	2	35.55	54951	1088	50.02
Enatiometric	1	24.50	4347	173	7.27
enriched **5c**	2	34.68	55460	1099	92.73

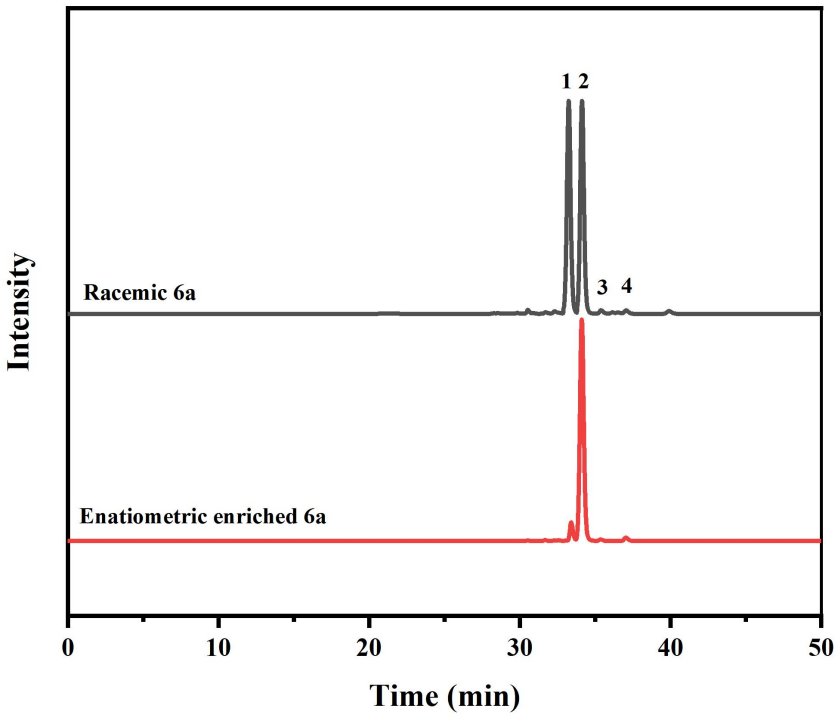
(*S*)-2-((*R*)-hydroxy(4-methoxyphenyl)methyl)cyclohexan-1-one (**6a**)



6a

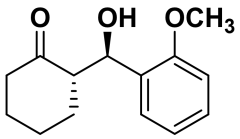
Compound **6a**: a yellow oil; Chiralcel AS-H column, λ= 230 nm, i-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 33.223 min (minor). t_R = 34.053 min (major).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.21 (m, 2H, ArH), 6.91 – 6.85 (m, 2H, ArH), 4.74 (d, *J* = 8.9 Hz, 1H, CH), 3.80 (s, 3H,CH_3), 2.59 (dddd, *J* = 12.9, 8.9, 5.5, 1.2 Hz, 1H, CH), 2.48 (dddd, *J* = 13.7, 4.5, 3.0, 1.7 Hz, 1H, CH), 2.35 (tdd, *J* = 13.6, 6.1, 1.3 Hz, 1H, CH), 2.09 (ddq, *J* = 12.2, 5.9, 3.0 Hz, 1H, CH), 1.88 – 1.45 (m, 5H, CH, 2CH_2).





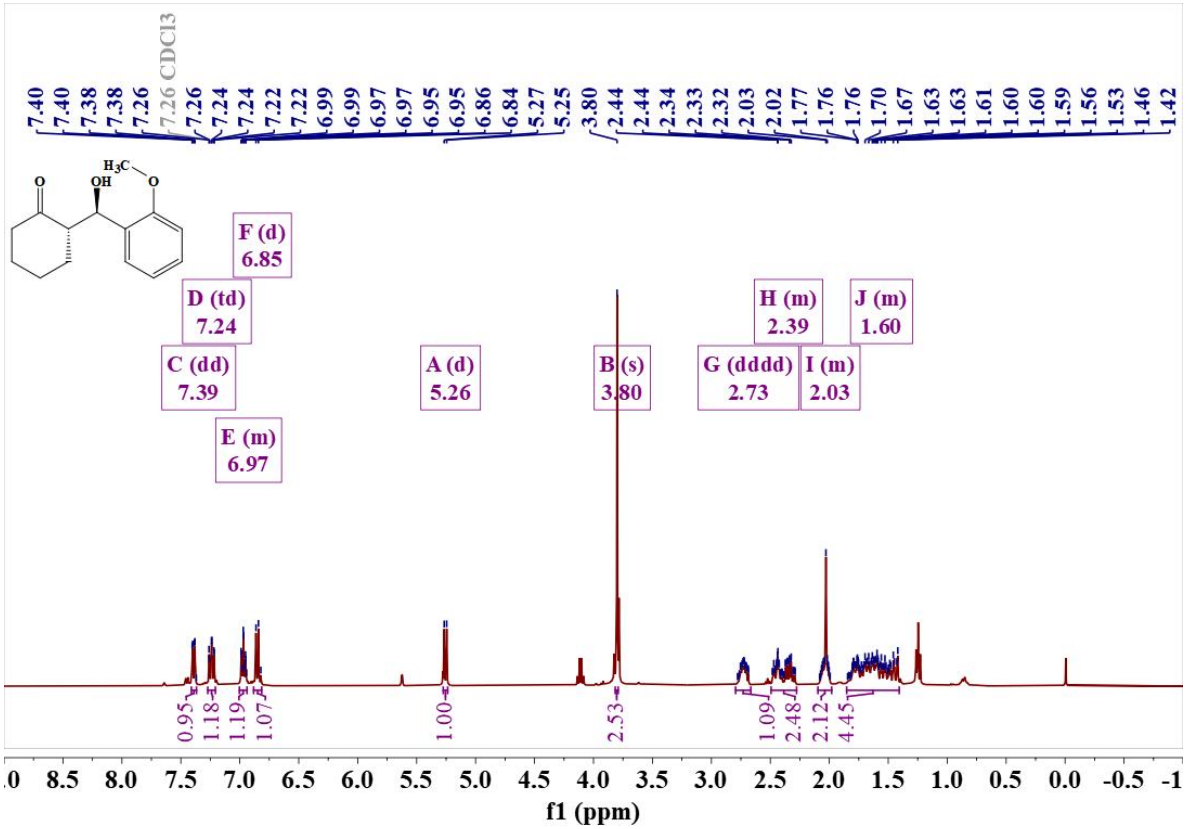
Product	Peak	t_R	Area	Height	%Area
Racemic **6a**	1	33.233	1220282	74216	45.99
	2	34.102	1346582	72957	50.75
	3	35.58	23537	1543	1.01
	4	36.824	52217	2013	2.24
Enatiometric enriched 6**a**	1	33.223	141860	11733	5.92
	2	34.053	2209949	121110	92.16
	3	35.585	22671	1451	0.95
	4	36.848	23375	1407	0.97

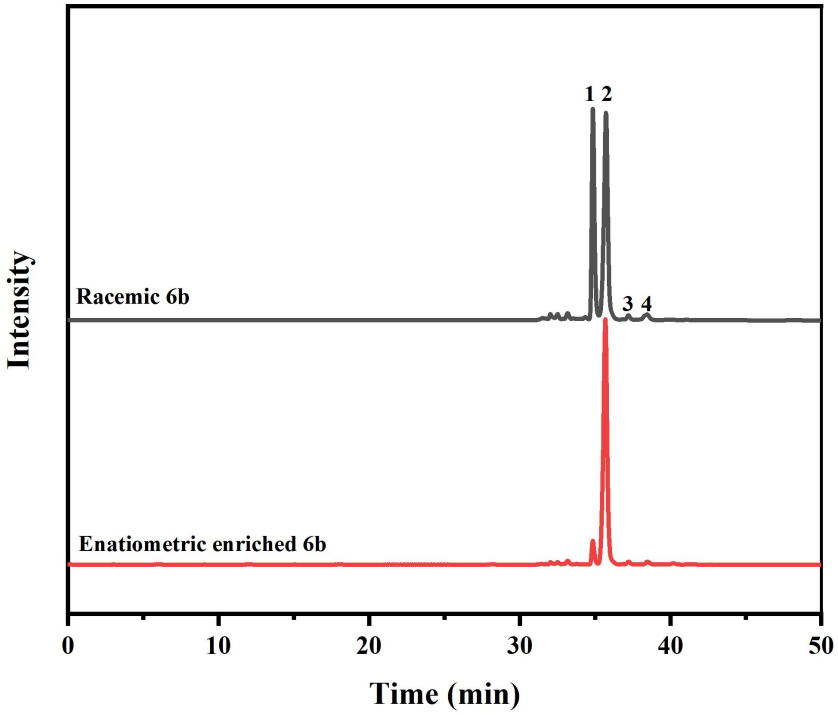
(*S*)-2-((*R*)-hydroxy(2-methoxyphenyl)methyl)cyclohexan-1-one (**6b**)



6b

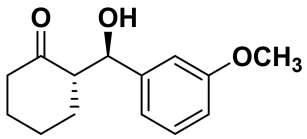
Compound **6b**: a yellow oil; Chiralcel AS-H column, λ= 230 nm, *i*-PrOH: Hexane = 20:80, 0.5 mL/min, t_R = 33.367 min (minor). t_R = 34.117 min (major).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (dd, *J* = 7.5, 1.8 Hz, 1H, ArH), 7.24 (td, *J* = 8.0, 1.9 Hz, 1H, ArH), 7.00 – 6.94 (m, 1H, ArH), 6.85 (d, *J* = 8.2 Hz, 1H, ArH), 5.26 (d, *J* = 8.5 Hz, 1H, CH), 3.80 (s, 3H, CH_3), 2.73 (dddd, *J* = 13.8, 9.5, 5.7, 1.8 Hz, 1H, CH), 2.49 – 2.28 (m, 2H, CH_2), 2.10 – 1.98 (m, 2H, CH_2), 1.85 – 1.41 (m, 4H, $2CH_2$).





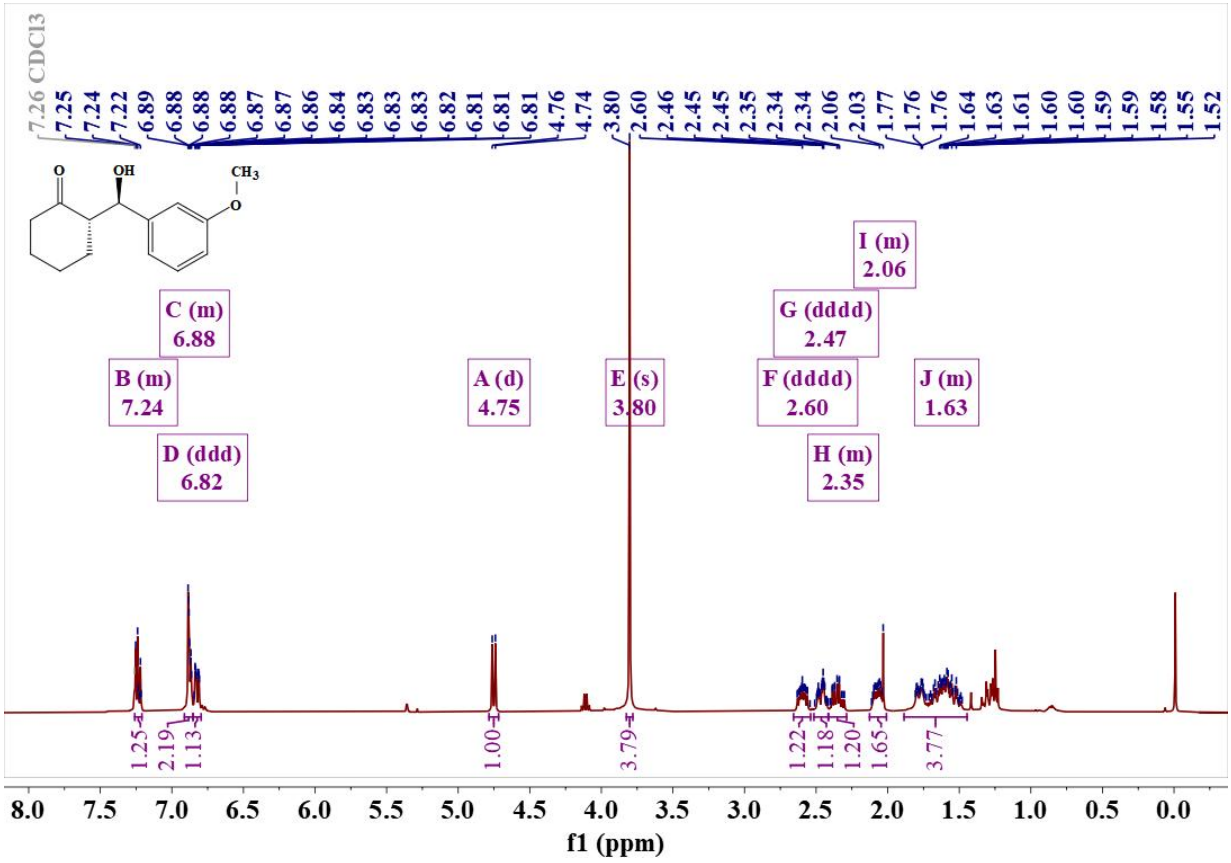
Product	Peak	t_R	Area	Height	%Area
Racemic **6b**	1	33.233	1598281	89450	49.20
	2	34.116	1602180	90069	49.23
	3	35.4	24380	1468	0.75
	4	37.133	26781	1445	0.82
Enatiometric enriched **6b**	1	33.367	259666	18256	5.98
	2	34.117	4011543	218671	92.05
	3	35.367	25742	1469	0.59
	4	37.1	61153	3248	1.40

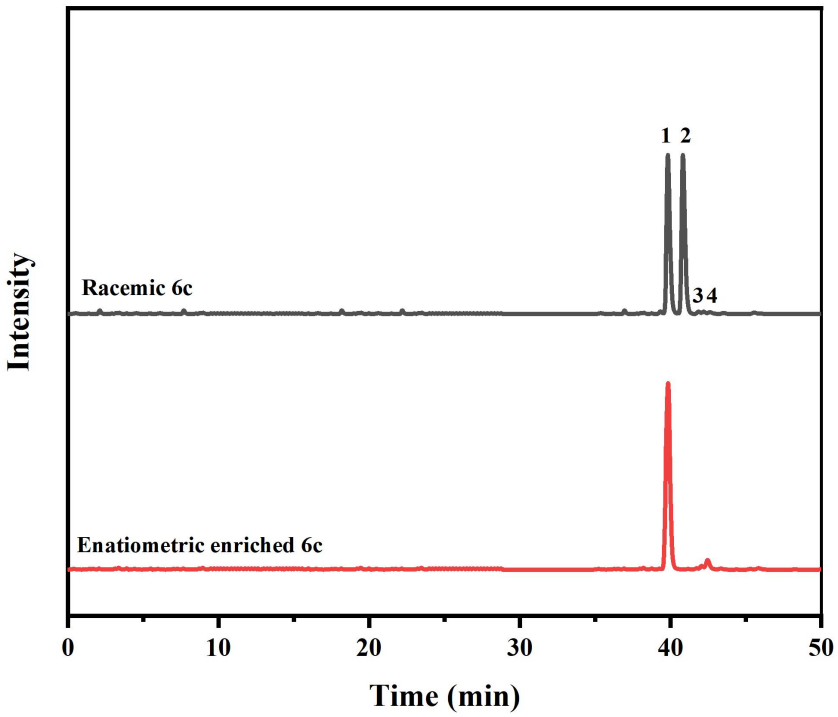
(*S*)-2-((*R*)-hydroxy(3-methoxyphenyl)methyl)cyclohexan-1-one (**6c**)



6c

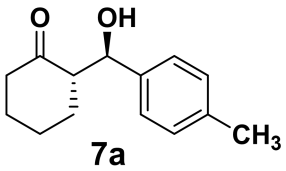
Compound **6c**: a yellow oil; Chiralcel AS-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 39.31 min (major). t_R = 39.799 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.21 (m, 1H, ArH), 6.91 – 6.85 (m, 2H, ArH), 6.82 (ddd, *J* = 8.2, 2.5, 1.1 Hz, 1H, ArH), 4.75 (d, *J* = 8.8 Hz, 1H, CH), 3.80 (s, 3H, CH_3), 2.60 (dddd, *J* = 12.8, 8.9, 5.5, 1.2 Hz, 1H, CH), 2.47 (dddd, *J* = 13.7, 4.6, 3.0, 1.7 Hz, 1H, CH), 2.42 – 2.29 (m, 1H, CH), 2.13 – 2.01 (m, 2H, CH_2), 1.89 – 1.45 (m, 4H, $2CH_2$).





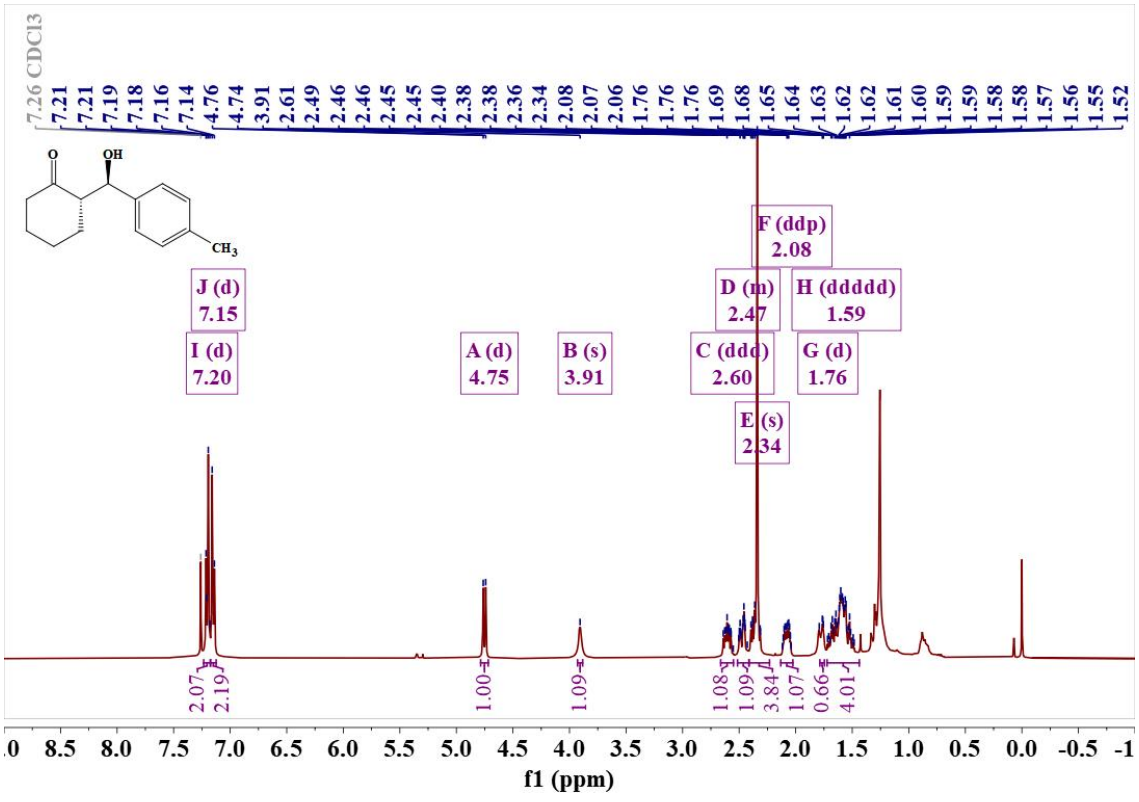
Product	Peak	t_R	Area	Height	%Area
Racemic **6c**	1	39.291	1664523	104586	49.41
	2	39.784	1663173	104501	49.37
	3	42.573	25178	1261	0.75
	4	43.518	15879	890	0.47
Enatiometric enriched **6c**	1	39.31	27247	1849	1.34
	2	39.799	1904170	98132	93.36
	3	42.422	13795	676	0.68
	4	43.799	93906	5046	4.61

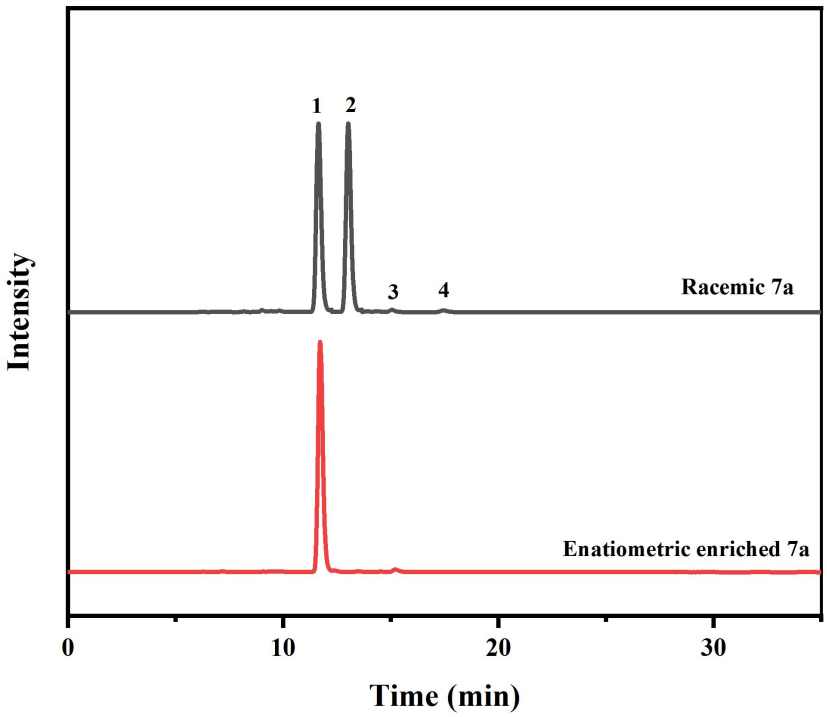
(*S*)-2-((*R*)-hydroxy(p-tolyl)methyl)cyclohexan-1-one (**7a**)



7a

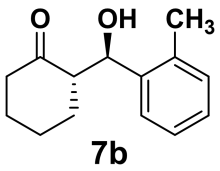
Compound **7a**: a colorless oil; Chiralcel AS-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 11.720 min (major). t_R = 12.383 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 8.0 Hz, 2H, ArH), 7.15 (d, *J* = 7.9 Hz, 2H, ArH), 4.75 (d, *J* = 8.8 Hz, 1H, CH), 3.91 (s, 1H, OH), 2.60 (ddd, *J* = 14.4, 7.8, 3.2 Hz, 1H, CH), 2.51 – 2.41 (m, 1H, CH), 2.34 (s, 4H, CH, CH_3), 2.08 (ddp, *J* = 11.9, 5.8, 3.0 Hz, 1H, CH), 1.76 (d, *J* = 3.7 Hz, 1H, CH), 1.59 (ddddd, *J* = 31.8, 28.7, 16.2, 9.9, 3.9 Hz, 4H, 2CH_2).





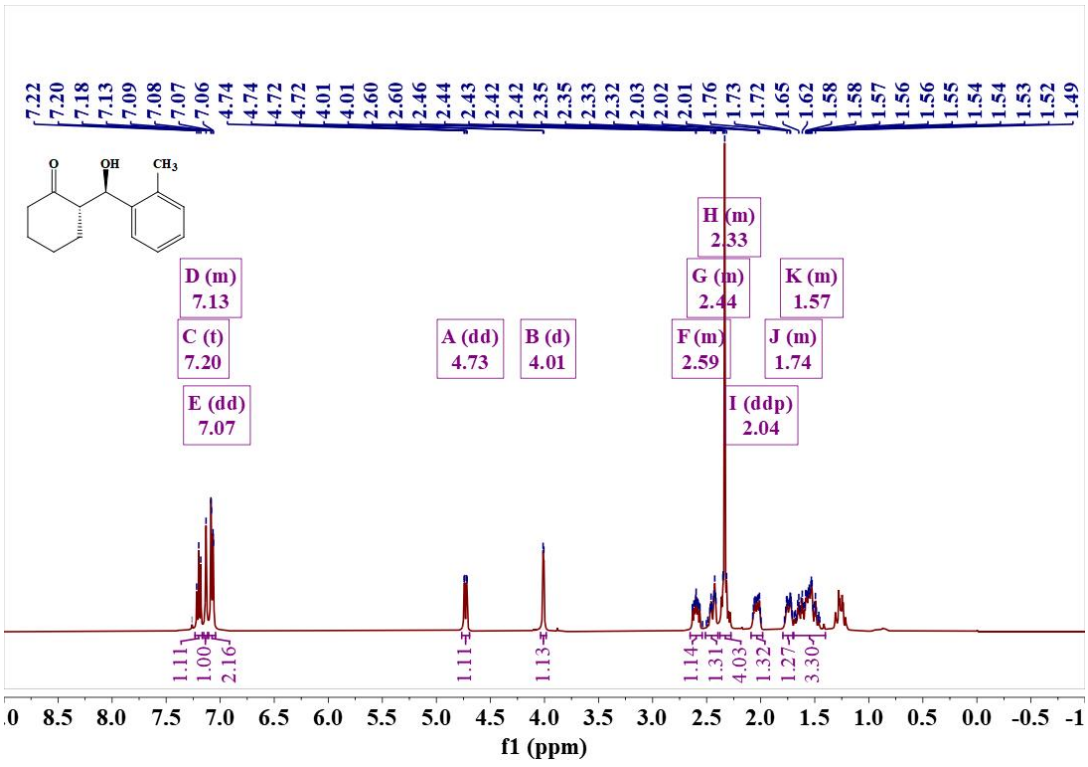
Product	Peak	t_R	Area	Height	%Area
Racemic **7a**	1	11.642	3020415	186630	49.36
	2	12.265	3021211	186856	49.42
	3	15.052	38043	2206	0.62
	4	17.450	37197	1726	0.60
Enatiometric enriched **7a**	1	11.720	3175644	200628	97.85
	2	12.383	21524	1383	0.66
	3	14.592	5579	227	0.17
	4	16.707	42652	2204	1.31

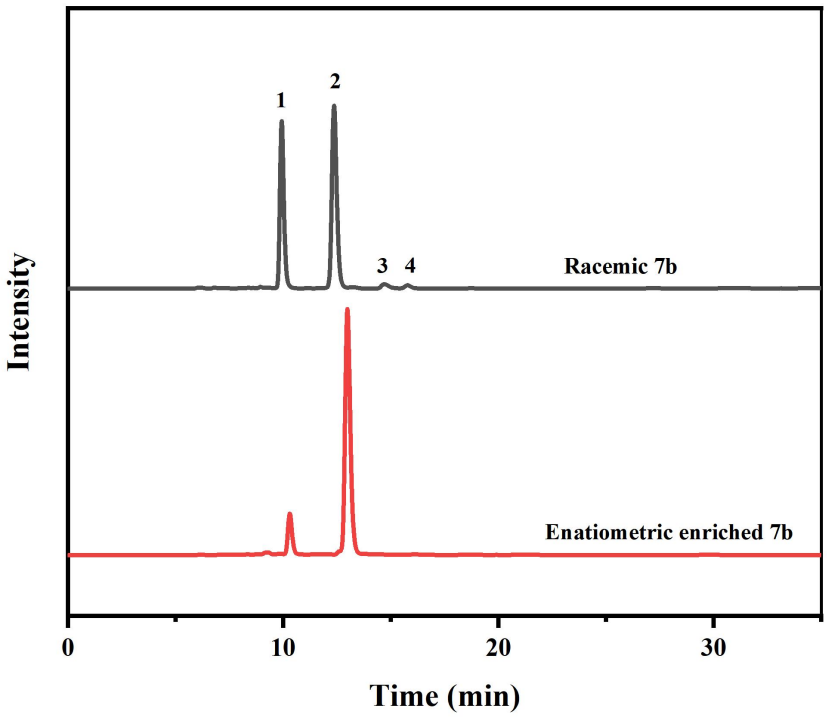
(*S*)-2-((*R*)-hydroxy(o-tolyl)methyl)cyclohexan-1-one (**7b**)



7b

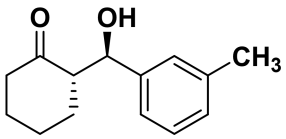
Compound **7b**: a colorless oil; Chiralcel AS-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 10.038 min (minor). t_R = 12.786 min (major). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 (t, *J* = 7.5 Hz, 1H, ArH), 7.13 (m, 1H, ArH), 7.07 (dd, *J* = 7.6, 1.8 Hz, 2H, ArH), 4.73 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.01 (d, *J* = 2.8 Hz, 1H, OH), 2.65 – 2.54 (m, 1H, CH), 2.51 – 2.40 (m, 1H, CH), 2.38 – 2.28 (m, 4H,CH, CH_3), 2.04 (ddp, *J* = 12.1, 5.8, 2.8 Hz, 1H, CH), 1.79 – 1.70 (m, 1H, CH), 1.69 – 1.40 (m, 4H, $2CH_2$).





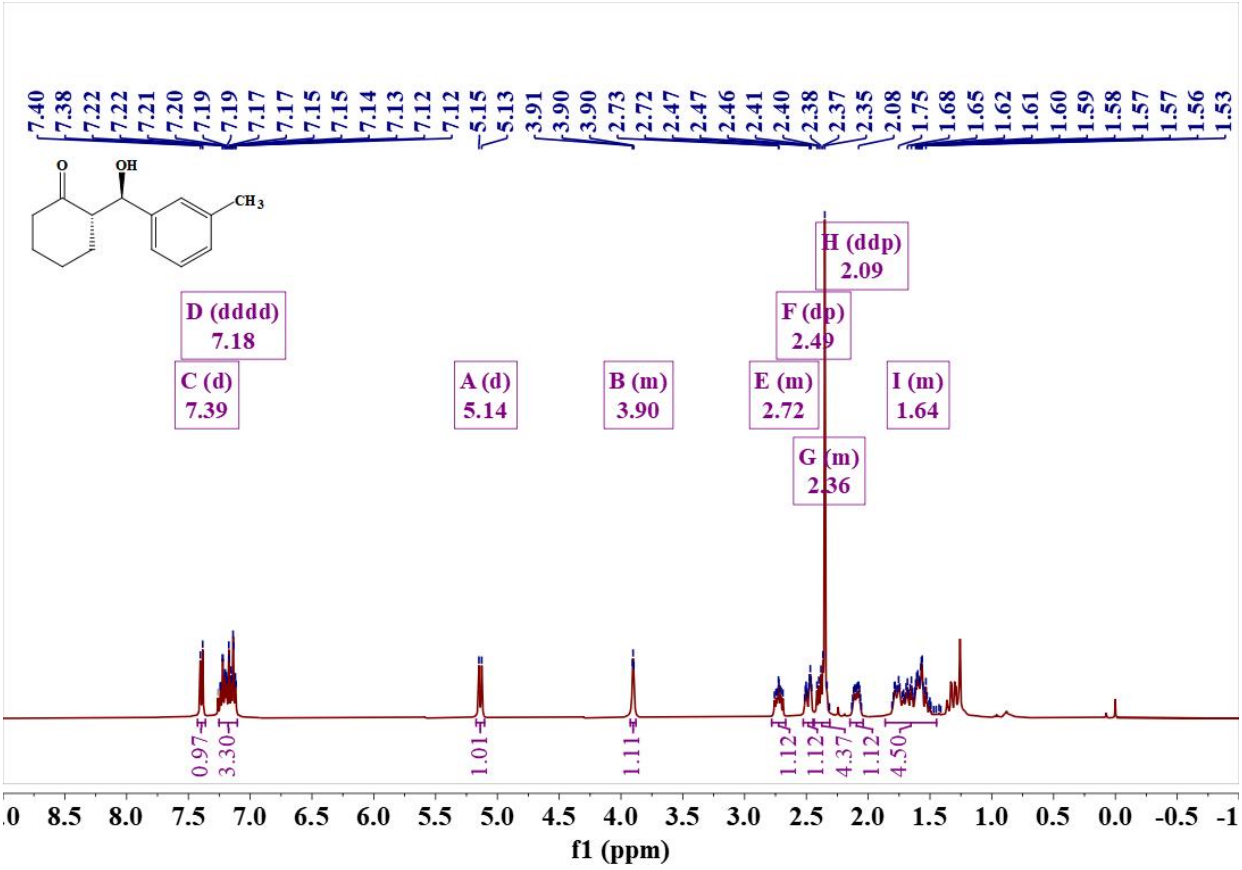
Product	Peak	t_R	Area	Height	%Area
Racemic **7b**	1	9.931	916186	71260	40.77
	2	12.365	1260273	78162	56.08
	3	14.699	44125	1848	1.96
	4	15.762	26689	135	1.19
Enatiometric enriched **7b**	1	10.038	396446	29144	11.60
	2	12.786	3006317	175193	87.93
	3	14.710	8245	416	0.24
	4	16.108	7955	410	0.23

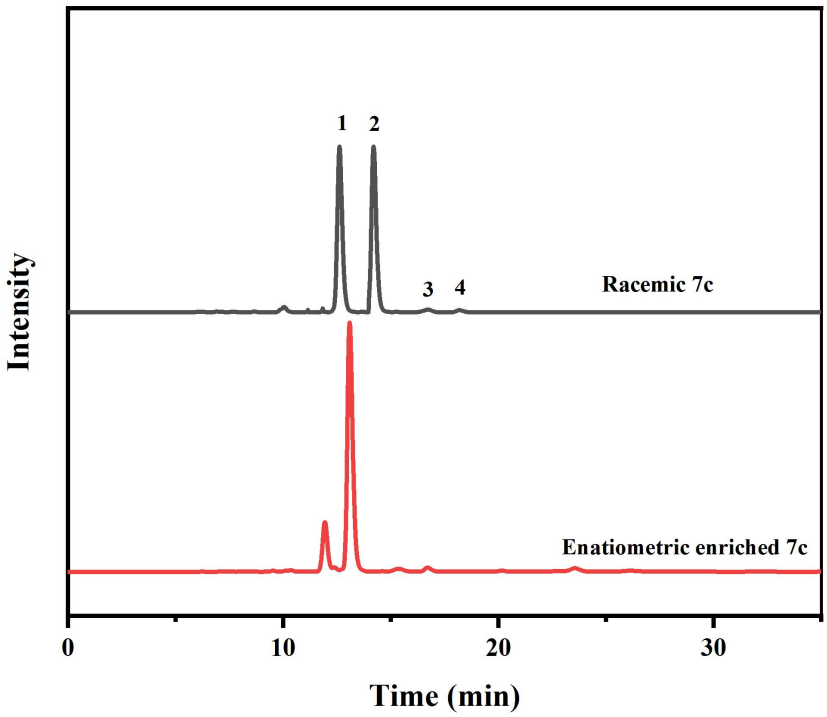
(*S*)-2-((*R*)-hydroxy(m-tolyl)methyl)cyclohexan-1-one (**7c**)



7c

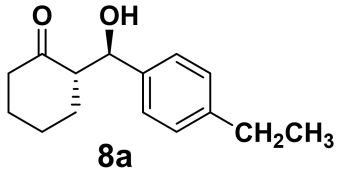
Compound **7c**: a colorless oil; Chiralcel AS-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 11.140 min (minor). t_R = 12.290 min (major). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 7.5 Hz, 1H, ArH), 7.18 (dddd, *J* = 28.9, 14.2, 7.3, 1.6 Hz, 3H, ArH), 5.14 (d, *J* = 9.0 Hz, 1H, CH), 3.92 – 3.88 (m, 1H, OH), 2.78 – 2.67 (m, 1H, CH), 2.49 (dp, *J* = 13.7, 2.1 Hz, 1H, CH), 2.44 – 2.31 (m, 4H, CH, CH_3), 2.09 (ddp, *J* = 12.0, 5.8, 3.0 Hz, 1H, CH), 1.86 – 1.45 (m, 5H, CH, $2CH_2$).





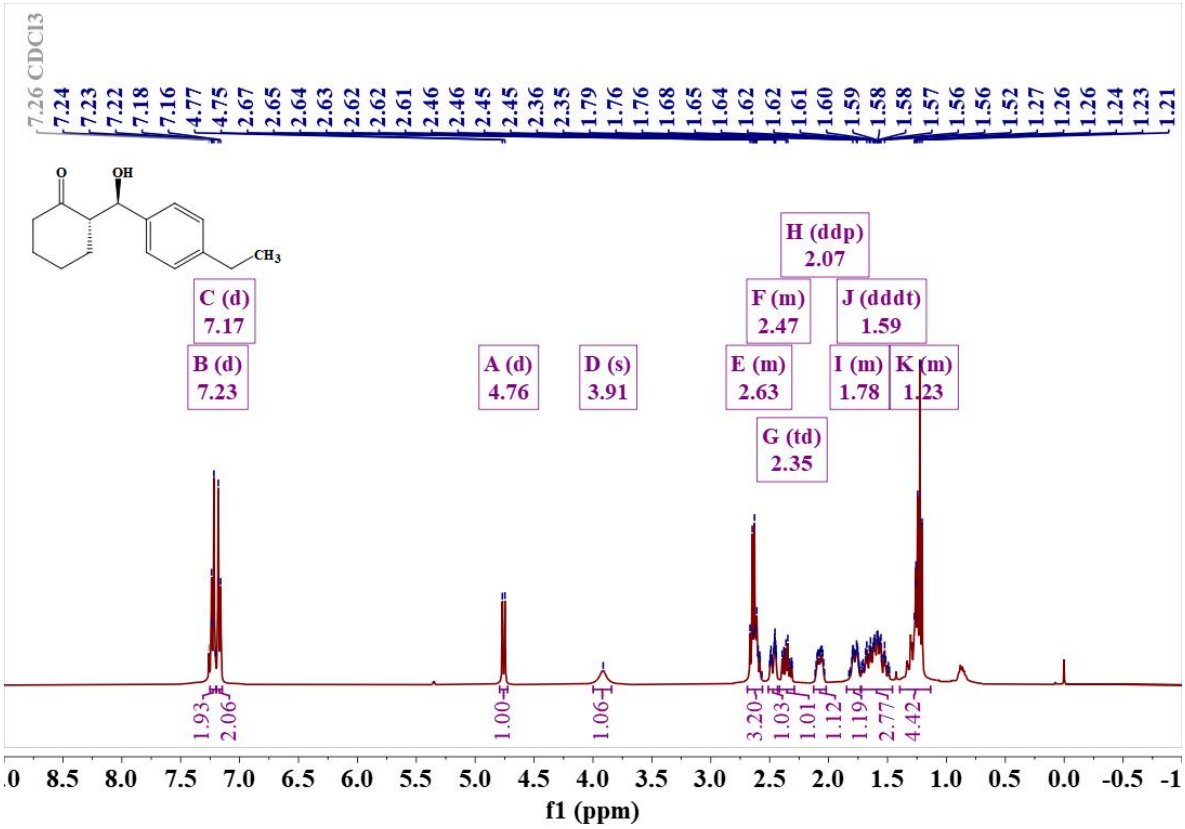
Product	Peak	t_R	Area	Height	%Area
Racemic **7c**	1	11.369	456898	30091	47.95
	2	12.619	456974	30097	47.96
	3	14.598	22869	1506	2.40
	4	16.737	16103	1060	1.69
Enatiometric enriched **7c**	1	11.140	810410	49090	15.13
	2	12.290	4360111	246486	81.43
	3	14.572	92511	2932	1.73
	4	16.707	91557	4111	1.71

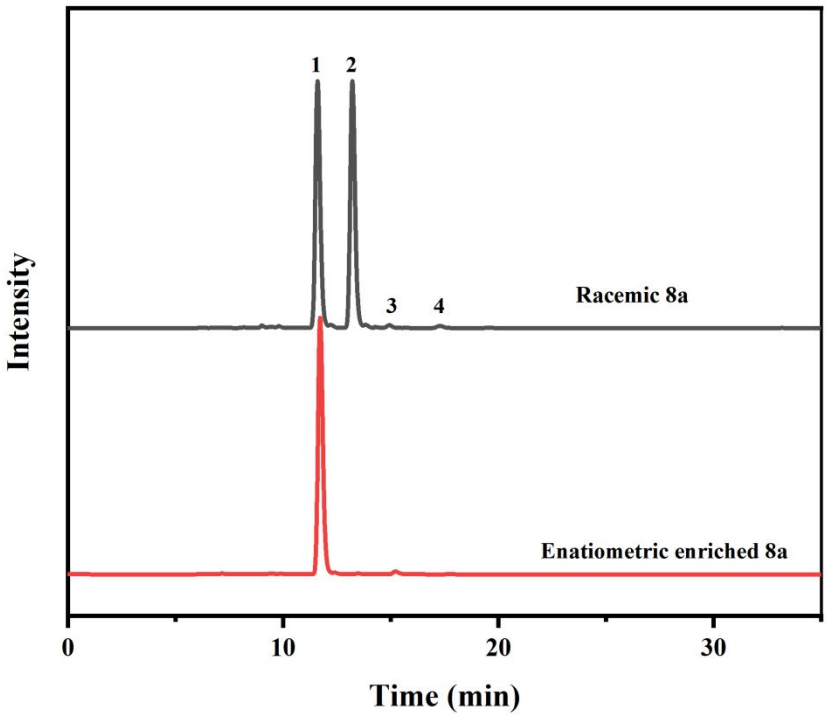
(*S*)-2-((*R*)-(4-ethylphenyl)(hydroxy)methyl)cyclohexan-1-one (**8a**)



8a

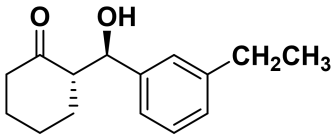
Compound **8a**: a colorless oil; Chiralcel AD-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 11.720 min (major). t_R = 12.388 min (minor). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 8.0 Hz, 2H, ArH), 7.17 (d, *J* = 7.9 Hz, 2H, ArH), 4.76 (d, *J* = 8.8 Hz, 1H, CH), 3.91 (s, 1H, OH), 2.69 – 2.56 (m, 3H, CH, CH_2), 2.51 – 2.43 (m, 1H, CH), 2.35 (td, *J* = 13.0, 5.9 Hz, 1H, CH), 2.07 (ddp, *J* = 12.1, 5.9, 3.2 Hz, 1H, CH), 1.85 – 1.72 (m, 1H, CH), 1.59 (dddt, *J* = 28.6, 25.3, 16.2, 6.6 Hz, 3H, CH, CH_2), 1.40 – 1.13 (m, 4H, CH, CH_3).





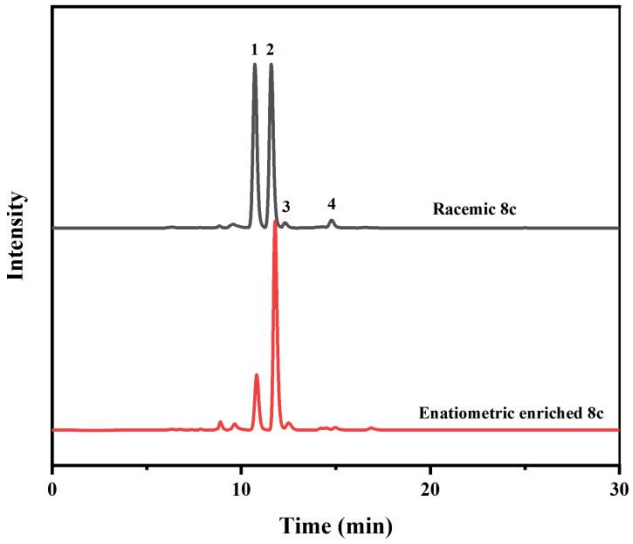
Product	Peak	t_R	Area	Height	%Area
Racemic **8a**	1	11.601	3058023	193024	49.38
	2	12.212	3059881	193102	49.40
	3	14.931	39233	2329	0.63
	4	17.278	36414	1751	0.59
Enatiometric enriched **8a**	1	11.720	3175213	200621	97.78
	2	12.388	21159	1372	0.65
	3	15.214	39971	2144	1.23
	4	17.485	10914	659	0.34

(*S*)-2-((*R*)-(3-ethylphenyl)(hydroxy)methyl)cyclohexan-1-one (**8c**)



8c

Compound **8c**: a colorless oil; Chiralcel AS-H column, λ= 230 nm, *i*-PrOH: Hexane = 10:90, 0.5 mL/min, t_R = 10.816 min (minor). t_R = 11.785 min (major). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 7.5 Hz, 1H, ArH), 7.26–7.06 (m, 3H, ArH), 4.75 (d, *J* = 8.8 Hz, 1H, CH), 3.91 (s, 1H, OH), 2.60 (ddd, *J* = 14.4, 7.8, 3.2 Hz, 1H, CH), 2.51–2.41 (m, 1H, CH), 2.34 (m, 3H, CH, CH_2), 2.08 (ddp, *J* = 11.9, 5.8, 3.0 Hz, 1H, CH), 1.85–1.74 (m, 1H, CH), 1.72–1.47 (m, 4H, $2CH_2$), 1.35–1.18 (m, 3H, CH_3).



Product	Peak	t_R	Area	Height	%Area
Racemic **8c**	1	10.723	896254	58088	47.74
	2	11.649	902541	58247	47.87
	3	12.318	29483	1792	1.56
	4	14.774	47673	2691	2.83
Enatiometric enriched **8c**	1	10.816	300805	19567	21.22
	2	11.785	1058431	73958	74.66
	3	12.504	49078	2470	3.46
	4	14.976	9363	680	0.66

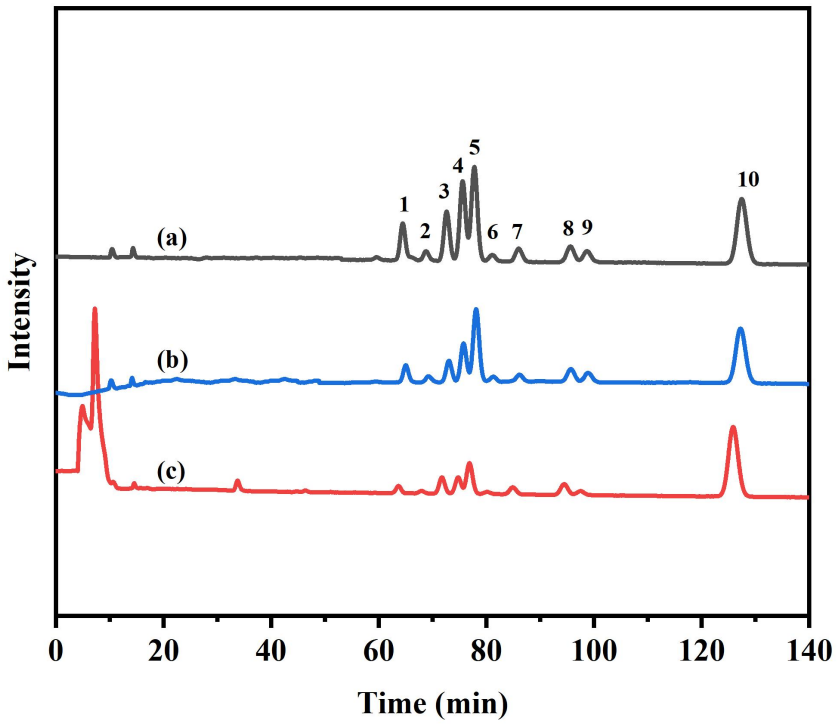


Fig. S11 HPLC analysis of mixed nitro-substituted benzaldehyde reaction: (a) L-Trp catalysis; (b) L-Trp and P-MMIP catalysis; (c) P-MMIP catalysis (Chiralcel AD-H column, λ= 254 nm, *i*-PrOH: Hexane = 5:95, 0.5 mL/min, injection volume 10 μL, column temperature 30℃)

Catalyst	Product	Peak	t_R	Area	Height	%Area
(a)	**1c**	1	64.163	18123	442	9.36
	1c	2	68.454	5950	190	3.07
	1a	3	72.248	22024	734	11.37
	1c	4	75.246	12454	342	6.43
	1b	5	77.41	23252	752	12.00
	1a	6	80.713	1975	89	1.02
	1b	7	85.563	8752	752	4.52
	1a	8	95.121	29930	784	15.45
	1c	9	98.196	11802	245	6.09
	1a	10	126.7	59435	1592	30.68

Catalyst	Product	Peak	t_R	Area	Height	%Area
(b)	**1c**	1	63.638	13396	362	2.45
	1c	2	67.963	5425	191	0.99
	1a	3	71.73	37702	895	6.90
	1c	4	74.75	39791	924	7.29
	1b	5	76.853	83701	1618	15.32
	1a	6	80.029	4117	310	0.75
	1b	7	84.909	19825	453	3.63
	1a	8	94.452	31015	797	5.68
	1c	9	97.504	10223	240	1.87
	1a	10	125.846	300981	7066	55.11
(c)	**1c**	1	63.625	5427	212	1.49
	1c	2	67.921	465	12	0.13
	1a	3	71.896	27954	776	7.67
	1c	4	74.954	4181	310	1.15
	1b	5	77.292	7217	225	1.98
	1a	6	79.354	2837	267	0.78
	1b	7	85.757	15659	497	4.30
	1a	8	95.626	26338	773	7.23
	1c	9	98.879	2308	232	0.63
	1a	10	126.056	271945	6384	74.64

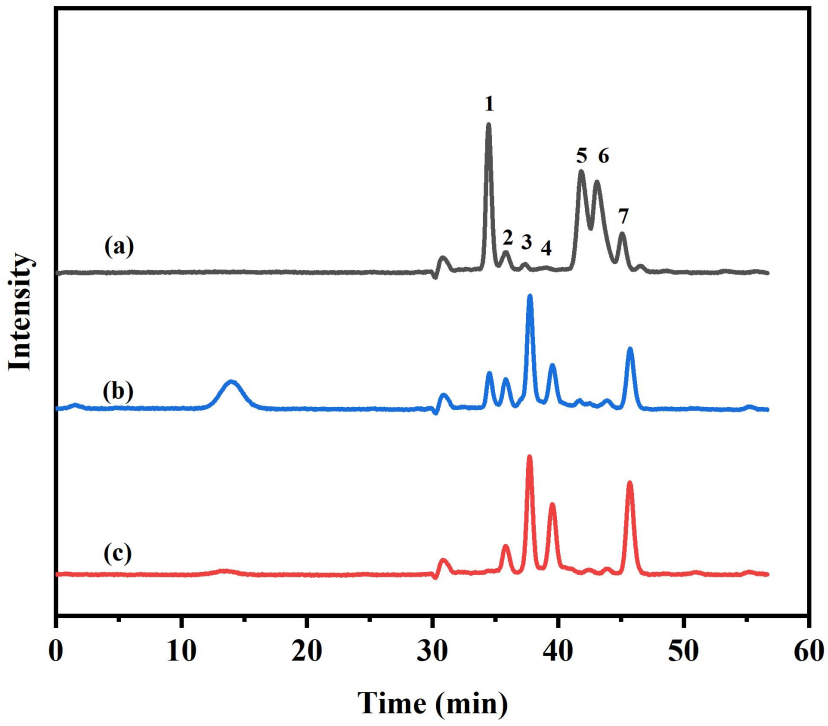


Fig. S12 HPLC analysis of mixed cyanosubstituted benzaldehyde reaction: (a) L-Trp catalysis; (b) P-MNIP catalysis; (c) P-MMIP catalysis (Chiralcel AD-H column, λ= 254 nm, *i*-PrOH: Hexane = 20:80, 0.5 mL/min, injection volume 10 μL, column temperature 30°C)

Catalyst	Product	Peak	t_R	Area	Height	%Area
(a)	**2b**	1	34.458	97564	3099	25.92
	2a	2	35.823	11535	313	3.06
	2a	3	37.313	2463	123	0.65
	3c	4	40.208	1322	106	0.35
	3c	5	41.838	114623	2103	30.45
	2b	6	43.097	116665	1872	31.00
	2a	7	45.118	32199	781	8.56
(b)	**2b**	1	34.53	22642	541	10.42
	2a	2	35.892	19216	2354	8.84
	2a	3	37.753	83718	825	38.51
	3c	4	40.532	31689	103	14.58
	3c	5	42.707	2636	141	1.21
	2b	6	43.963	5384	1268	2.48
	2a	7	45.739	52101	541	23.97
(c)	**2a**	1	35.79	20313	573	8.48
	2a	3	37.729	81054	1807	33.86
	3c	4	39.548	51983	1097	21.71
	3c	5	42.513	2162	71	0.90
	2b	6	43.871	2893	74	1.21
	2a	7	45.711	81008	2058	33.84

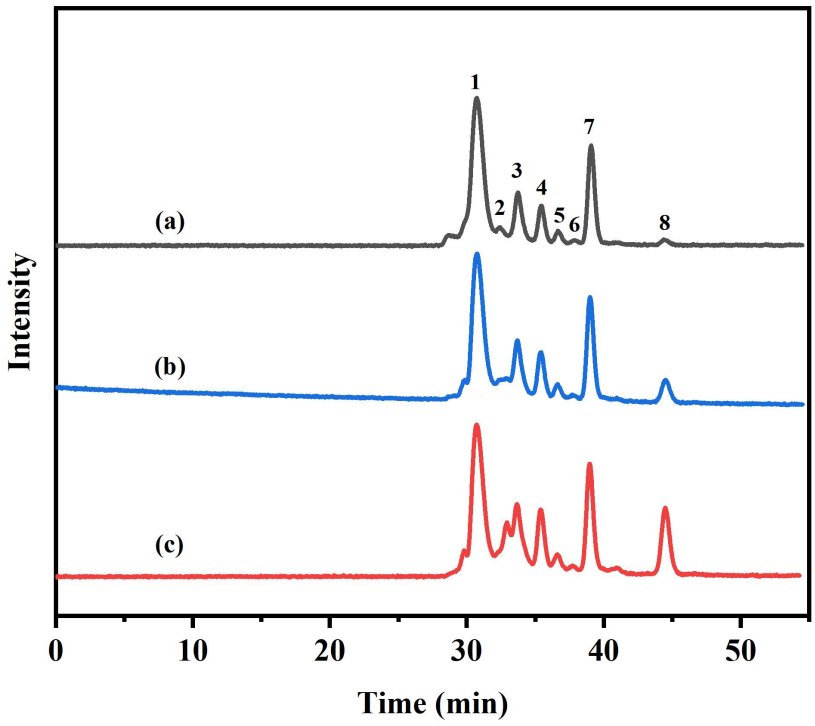


Fig. S13 HPLC analysis of mixed cyanosubstituted benzaldehyde reaction: (a) L-Trp catalysis; (b) P-MNIP catalysis; (c) P-MMIP catalysis (Chiralcel AD-H column, λ= 254 nm, *i*-PrOH: Hexane = 20:80, 0.5 mL/min, injection volume 10 μL, column temperature 30°C)

Catalyst	Product	Peak	t_R	Area	Height	%Area
(a)	**3a**	1	30.723	132189	2100	50.09
	3b	2	32.431	10464	226	3.96
	3a	3	33.722	23493	670	8.90
	3c	4	35.448	16143	512	6.12
	3c	5	36.649	11587	285	4.39
	3b	6	37.3	5570	189	2.11
	3b	7	39.082	51239	1448	19.41
	3a	8	44.523	3233	81	1.23
(b)	**3a**	1	30.764	111926	541	47.99
	3b	2	32.441	5031	202	2.16
	3a	3	33.701	23095	666	9.90
	3c	4	35.419	21467	630	9.20
	3c	5	36.636	3684	185	1.58
	3b	6	37.775	1621	144	0.70
	3b	7	38.993	52316	1496	22.43
	3a	8	44.512	14097	331	6.04
(c)	**3a**	1	30.71	135892	2229	37.01
	3b	2	32.932	29160	768	7.94
	3a	3	33.679	51590	1037	14.05
	3c	4	35.4	37479	951	10.21
	3c	5	36.577	10217	267	2.78
	3b	6	37.783	1204	94	0.33
	3b	7	38.973	58175	1592	15.84
	3a	8	44.497	43457	986	11.84

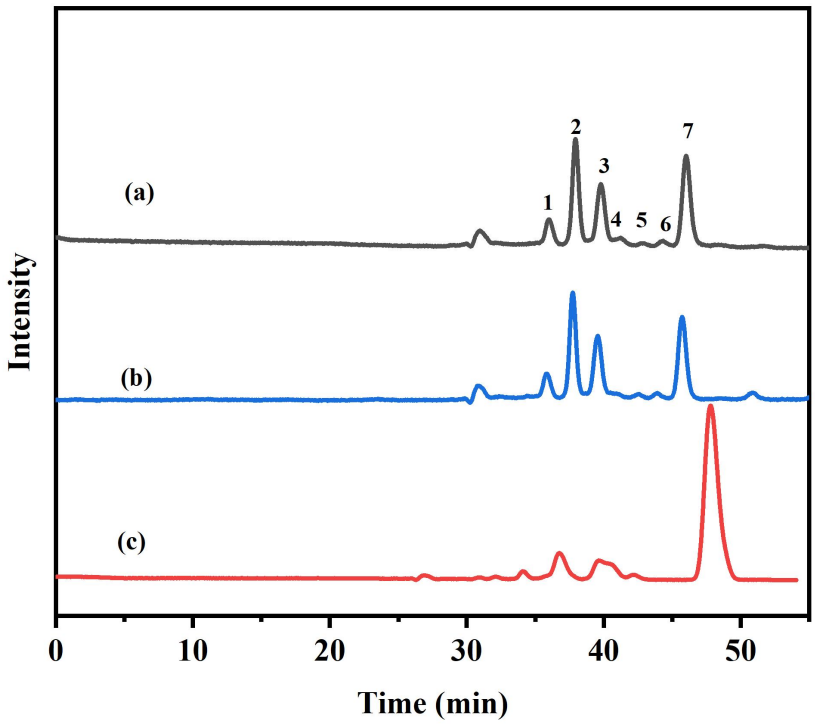


Fig. S14 HPLC analysis of mixed substituted benzaldehyde and *p*-nitrosubstituted benzaldehyde reaction: (a) L-Trp catalysis; (b) P-MNIP catalysis; (c) P-MMIP catalysis (Chiralcel AD-H column, λ= 254 nm, *i*-PrOH: Hexane = 20:80, 0.5 mL/min, injection volume 10 μL, column temperature 30℃)

Catalyst	Product	Peak	t_R	Area	Height	%Area
	2a	1	35.978	22054	584	8.70
	2a	2	37.937	80841	2422	31.90
	2c	3	39.792	50581	1302	19.96
(a)	**1a**	4	41.198	1361	63	0.54
	2b	5	42.762	4322	101	1.71
	2b	6	44.247	5732	147	2.26
	1a	7	46	88499	2077	34.93
	2a	1	35.831	20154	540	8.43
	2a	2	37.732	79989	2405	33.45
	2c	3	39.562	53506	1349	22.37
(b)	**1a**	4	42.518	1988	88	0.83
	2b	5	43.901	1237	114	0.52
	2b	6	44.025	1271	94	0.53
	1a	7	45.719	81019	1910	33.88
	2a	1	38.107	21047	537	1.81
	2a	2	40.767	114527	1793	9.86
	2c	3	43.657	74845	1294	6.44
(c)	**1a**	4	44.208	10941	1113	0.94
	2b	5	44.392	45733	1086	3.94
	2b	6	46.229	15176	321	1.31
	1a	7	49.79	879794	12210	75.71

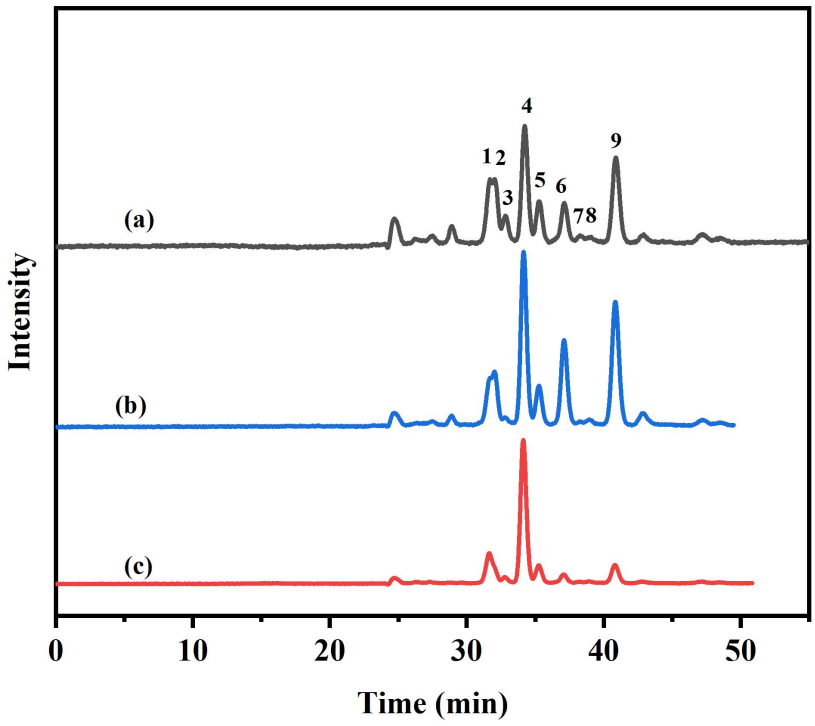


Fig. S15 HPLC analysis of mixed nitro-substituted benzaldehyde reaction: (a) L-Trp catalysis; (b) m-MMIP catalysis; (c) m-MMIP catalysis (Chiralcel AD-H column, λ= 254 nm, i-PrOH: Hexane = 20:80, 0.5 mL/min, injection volume 10 μL, column temperature 30℃)

Catalyst	Product	Peak	t_R	Area	Height	%Area
	1c	1	31.749	19576	712	12.10
	1c	2	32.066	19048	719	11.77
	1a	3	32.822	7691	283	4.75
	1c	4	34.213	42399	1314	26.21
(a)	**1b**	5	35.306	14275	455	8.82
	1b	6	37.132	14212	442	8.79
	1a	7	38.257	4718	104	2.92
	1c	8	39.028	3538	117	2.19
	1a	9	40.873	36318	974	22.45
	1c	1	31.667	28081	1076	7.18
	1c	2	32.006	35274	1225	9.02
	1a	3	32.769	4207	169	1.08
	1c	4	34.146	124137	3983	31.73
(b)	**1b**	5	35.255	27990	882	7.15
	1b	6	37.108	63194	1913	16.15
	1a	7	37.997	1016	77	0.26
	1c	8	38.986	1069	79	0.27
	1a	9	40.836	106246	2831	27.16
	1c	1	31.644	74831	1747	17.33
	1c	2	32.783	10283	344	2.38
	1c	4	34.121	256953	8239	59.50
	1b	5	35.258	33034	1024	7.65
(c)	**1b**	6	37.068	15803	489	3.66
	1a	7	38.15	1546	77	0.36
	1c	8	39.025	1056	71	0.24
	1a	9	40.794	38323	1035	8.87