

Supporting Information

A novel poly (*N*-isopropyl-acrylamine-*co*-*L*-proline) catalyst for aldol reaction: synthesis, catalytic performance and recyclability

Yubing Liu,^{a,b} Qing Tong,^{a,b} Liya Ge,^{d,e} Yu Zhang,^b Lin Hua^{**b,c} and Yining Fan^{*a,b}

^a Key Laboratory of Mesoscopic Chemistry of MOE, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, Jiangsu Province, China

^b Nanjing University-Yangzhou Institute of Chemistry and Chemical Engineering, Yizheng 211400, Jiangsu Province, China

^c Linovus Technology Pte Ltd, 8 Chang Charn Road, Link (THM) Building #02-11, Singapore 159637, Singapore

^d Residues and Resource Reclamation Centre, Nanyang Environment and Water Research Institute, Nanyang Technological University, 1 Cleantech Loop, Clean Tech One, Singapore 637141, Singapore

^e Natural Sciences and Science Education Academic Group, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616, Singapore

Materials: DMF was distilled prior to use. *N*-Isopropylacrylamide (NIPAM, 98%, obtained from Linovus Technology, Singapore.) was recrystallized from *n*-hexane. 2,2'-Azo-bis-isobutyronitrile (AIBN, Sigma-Aldrich) was purified by recrystallization from methanol. *trans*-4-Hydroxyl-*L*-proline (99%, Energy Chemical) was dried at 65 °C for 24 h prior to use. All other reagents were A. R. grade and used as received unless otherwise specified.

Instrumentation: ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DRX 500 spectrometer using deuterated solvents. Chemical shifts are reported as δ in parts per million relative to Chloroform-d (7.26 ppm for ¹H and 77.2 ppm for ¹³C), Methanol-d₄ (4.87 ppm for ¹H and 49.0 ppm for ¹³C) or Deuterium Oxide (4.79 ppm for ¹H). All HPLC experiments were performed on a Wufeng Scientific Instruments using Chiralomix SA-5 (Sepax Technologies, Inc) equipped with a UV/VIS detector, with hexane and isopropyl alcohol (*i*-PrOH) as the eluting solvents. The molecular weights were determined by GPC (Wyatt Technology Corporation) with a Shodex SB806+803 columns. The column was calibrated with PEG standards (Sigma-Aldrich). 0.1M NaNO₃ aqueous solution was used as solvent at a flow rate of 0.8 mL/min. Ultraviolet-visible (UV-vis) spectra were recorded with Shimadzu UV-3600 spectrophotometer. CD spectra were obtained using JASCO J-810 CD spectrometers. Specific rotation was determined with a Ruololph Research Analytical Autopol I. TGA was recorded with Perkin-Elmer Pyris 1 DSC. FT-IR spectra were taken on a Thermo Scientific Nicolet iS10 spectrometer. Elemental analyses of C, H and N were performed on an Elementary Vario MICRO analyzer.

Experimental Procedure

Synthesis of *O*-Acryloyl-*trans*-4-hydroxy-*L*-proline hydrochloride (AHP) monomer:^[1]

Dried *trans*-4-hydroxy-*L*-proline (16.42 g, 125 mmol) was added in small portions to CF₃CO₂H (60 mL) with vigorous stirring at 0°C. Then CF₃SO₃H (2.0 mL, 22.9 mmol) was added, followed 5 min later by acryloyl chloride (20.31 mL, 250 mmol). The reaction was stirred for 2 h and 40 min at room temperature and then cooled with an ice/water bath. Et₂O (180 mL) was added slowly to the reaction. The resulting product (18.32 g, 66%) was vacuum-filtered, washed twice with Et₂O and dried at room temperature. [α]_D²⁰ = -18 (c = 0.1, MeOH); ¹H NMR (500 MHz, MeOD): δ 6.46 (dd, J = 17.3, 1.3 Hz, 1H), 6.18 (dd, J = 17.3, 10.5 Hz, 1H), 5.95 (dd, J = 10.5, 1.3 Hz, 1H), 5.50 (t, J = 4.8 Hz, 1H), 4.60 (dd, J = 10.4, 7.9 Hz, 1H), 3.69 (dd, J = 13.3, 4.7 Hz, 1H), 3.52 (dt, J = 13.3, 1.5 Hz, 1H), 2.62 (ddt, J = 14.6, 7.8, 1.5 Hz, 1H), 2.50 – 2.41 (m, 1H). ¹³C NMR (126 MHz, MeOD): δ 170.59, 166.41, 133.02, 128.76, 74.15, 59.63, 52.31, 35.83.

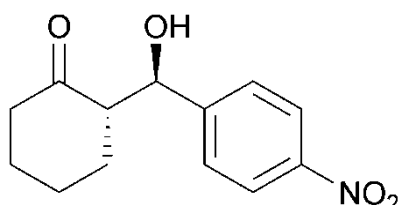
Copolymerization of *O*-Acryloyl-*trans*-4-hydroxy-*L*-proline hydrochloride monomer with NIPAM: NIPAM (90 eq), *O*-Acryloyl-*trans*-4-hydroxy-*L*-proline hydrochloride monomer (10 eq) and AIBN (1 eq) were dissolved in 15 mL DMF. The mixture was degassed via three freeze-pump-thaw cycles, back filled with nitrogen gas and then placed into a pre-heated oil bath at 70 °C. After 8 h, the mixture was dropwise into rapidly stirred Et₂O, and the precipitated product was isolated by centrifugation. The sediment was sequentially purified by reprecipitation from CH₃OH and DMF. Finally, the polymer washed with Et₂O for several times and dried under vacuum overnight. IR (ν cm⁻¹): 2978, 1731, 1632, 1539, 1460, 1361, 1254, 1166. Anal. Calcd for C₆₂H₁₁₀O₁₃N₁₀: C,

61.89; H, 9.15; N, 11.65. Found: C, 63.37; H, 9.21; N 12.34. M_n : 35892; PDI: 2.73.

General procedure for the aldol reaction:

Polymer (0.5000 g, 0.0117 mmol) was dissolved in a solvent (DMF/H₂O = 2.1/0.7 mL). *p*-Nitrobenzaldehyde (0.0756 g, 0.50 mmol), cyclohexanone (2.0 mL), were added to the solution and the homogeneous solution was stirred at room temperature for 24 h. After this time, Et₂O was added into the mixture, and the polymer was isolated by centrifugation. The polymer was washed with additional Et₂O for 3 times and then dried under vacuum. The filtrate was dried over MgSO₄ and concentrated under vacuum. The crude product was purified by flash chromatography (hexane/ethyl acetate = 80/20, v/v). The diastereomeric ratio (*anti:syn* ratio) was determined by ¹H NMR analysis of the crude product and enantiomeric excess (ee %) determined by HPLC with chiral column Chiralomix SA-5.

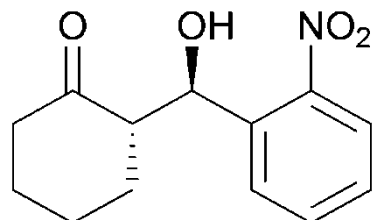
2-(Hydroxy (4-nitrophenyl) methyl) cyclohexan-1-one:



$[\alpha]_D^{20} = + 8.8$ (c = 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 8.20 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 4.89 (dd, J = 8.3, 2.6 Hz, 1H), 4.07 (d, J = 3.0 Hz, 1H), 2.59-2.36 (m, 3H), 2.19-2.02 (m, 1H), 1.83-1.27 (m, 5H). ¹³C NMR (126 MHz, CDCl₃): δ 214.81, 148.52, 147.69, 127.99, 123.67, 74.11, 57.30, 42.78, 30.87, 27.75, 24.80.

HPLC: hexane/*i*-PrOH = 85/15, $\lambda = 254$ nm, 1.0 mL/min, minor enantiomer $R_t = 33.3$ min and major enantiomer $R_t = 42.8$ min.

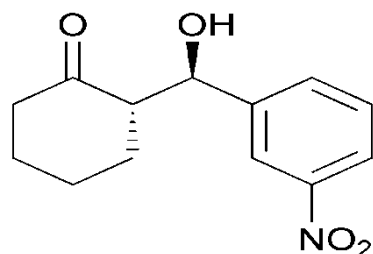
2-(Hydroxy (2-nitrophenyl) methyl) cyclohexan-1-one:



$[\alpha]_D^{20} = + 15.3$ (c = 0.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 7.85 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 5.45 (d, J = 6.9 Hz, 1H), 4.16 (s, 1H), 2.75 (dt, J = 12.4, 6.1 Hz, 1H), 2.45-2.34 (m, 2H), 2.10-1.66(m, 6H). ¹³C NMR (126 MHz, CDCl₃): δ 215.04, 148.92, 136.78, 133.19, 129.16, 128.54,

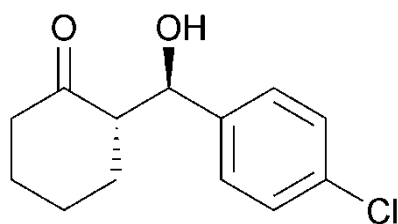
124.22, 69.95, 57.46, 42.97, 31.27, 27.90, 25.13. HPLC: hexane/*i*-PrOH = 90/10, $\lambda = 254$ nm, 0.7 mL/min, minor enantiomer $R_t = 38.9$ min and major enantiomer $R_t = 43.5$ min.

2-(Hydroxy (3-nitrophenyl) methyl) cyclohexan-1-one:



$[\alpha]_D^{20} = + 35.3$ (c = 0.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 8.21 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 4.89 (d, J = 8.4 Hz, 1H), 4.09(s, 1H), 2.62-2.38 (m, 3H), 2.11-1.57 (m, 4H), 1.41-1.25 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 214.95, 148.48, 143.45, 133.32, 129.44, 123.01, 122.18, 74.19, 57.29, 42.81, 30.90, 27.77, 24.82. HPLC: hexane/*i*-PrOH = 80/20, $\lambda = 254$ nm, 0.5 mL/min, minor enantiomer $R_t = 21.6$ min and major enantiomer $R_t = 24.2$ min.

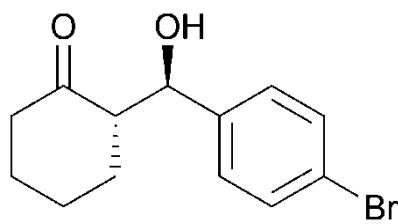
2-(Hydroxy (4-chlorophenyl) methyl) cyclohexan-1-one:



$[\alpha]_{\text{D}}^{20} = + 18.7$ ($c = 0.1$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.32 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 4.76 (d, $J = 8.7$ Hz, 1H), 3.98 (s, 1H), 2.59-2.40 (m, 2H), 2.35-2.07 (m, 2H), 1.71-1.19 (m, 5H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 215.37, 139.67, 133.73, 128.68, 128.53, 74.28, 57.52, 42.80, 30.90, 27.86, 24.85. HPLC: hexane/*i*-PrOH =

90/10, $\lambda = 220$ nm, 1.0 mL/min, minor enantiomer $R_t = 15.6$ min and major enantiomer $R_t = 18.5$ min.

2-(Hydroxy (4-bromophenyl) methyl) cyclohexan-1-one:



$[\alpha]_{\text{D}}^{20} = + 19.3$ ($c = 0.1$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.47 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.2$ Hz, 2H), 4.75 (d, $J = 8.7$ Hz, 1H), 3.97 (s, 1H), 2.63-2.40 (m, 3H), 2.13-1.61 (m, 4H), 1.54-1.23 (m, 2H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 215.36, 140.19, 131.65, 128.89, 121.87, 74.35, 57.49, 42.81, 30.91, 27.86, 24.87. HPLC: hexane/*i*-PrOH =

90/10, $\lambda = 220$ nm, 1.0 mL/min, minor enantiomer $R_t = 16.1$ min and major enantiomer $R_t = 19.6$ min.

Recycling:

After the reaction, the mixture was added saturated brine to form three phases, aqueous phase, organic phase and sediment. The polymer was isolated by centrifugation, washed with Et_2O , dried under vacuum overnight and reused in the next experiment. The separated organic phase was added Et_2O filtrate and then dried over MgSO_4 and concentrated under vacuum. The aqueous phase was reused directly in the next recycling.

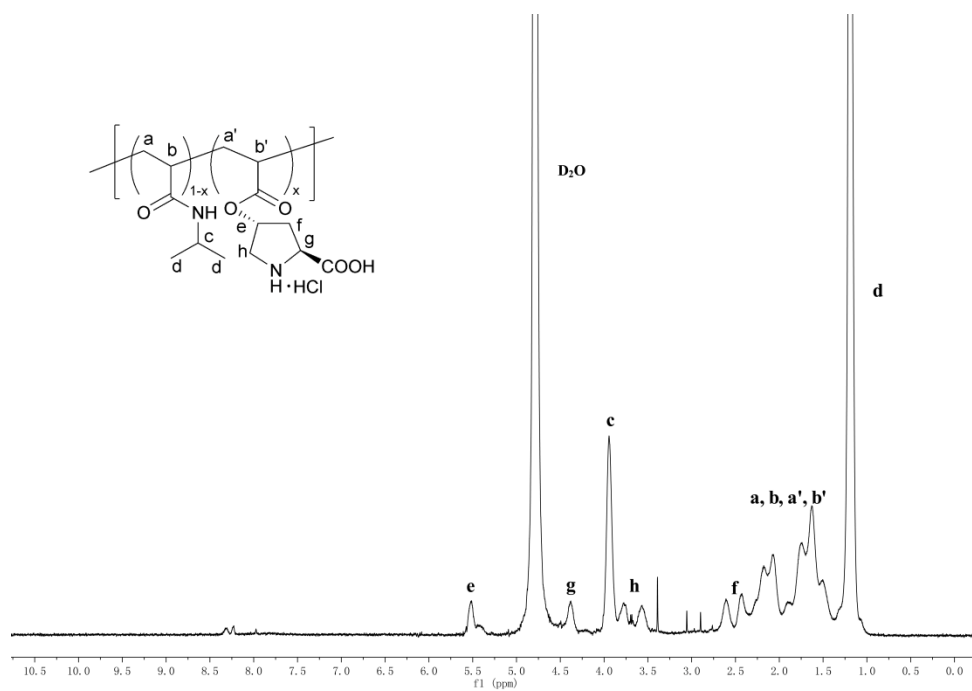


Fig S1. ¹H NMR spectrum of copolymer catalyst.^[2]

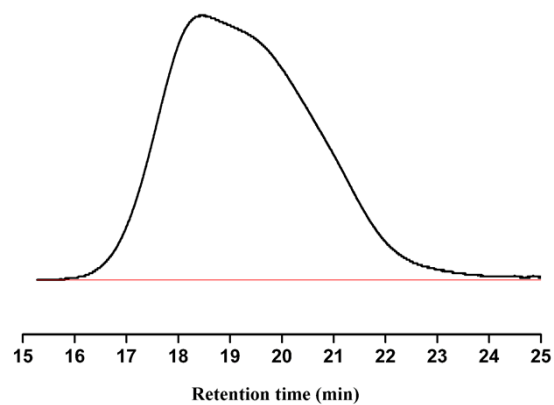


Fig S2. GPC traces recorded for copolymer catalyst

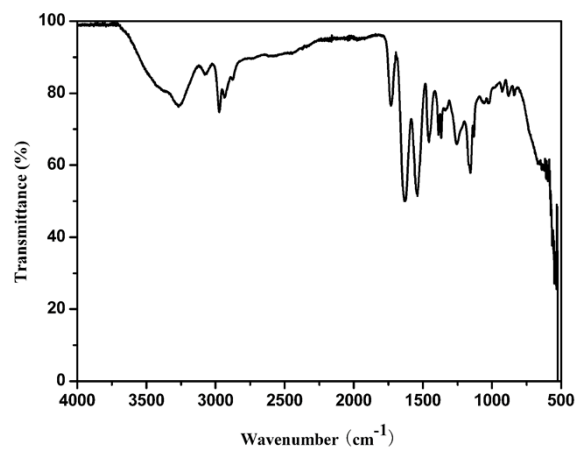


Fig S3. IR spectrum of copolymer catalyst

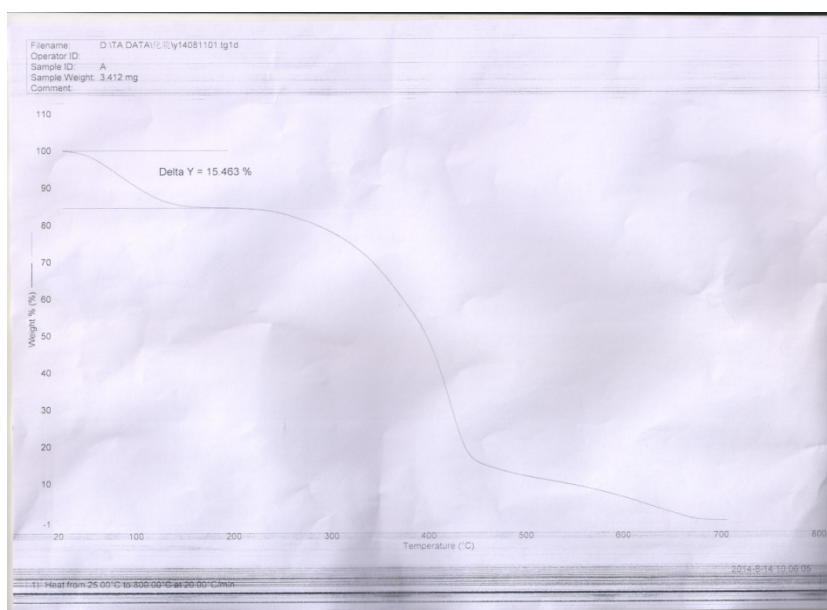


Fig S4. TGA curve of copolymer catalyst

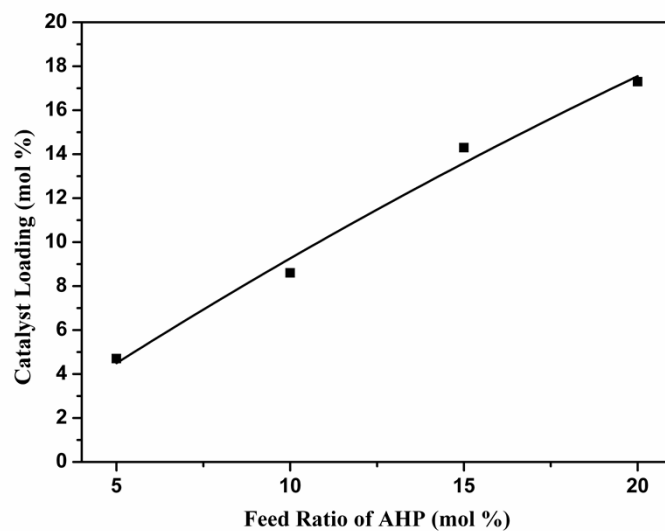


Fig S5. Plot of feed ratio against catalyst loading. Calculated by ^1H NMR spectroscopy.

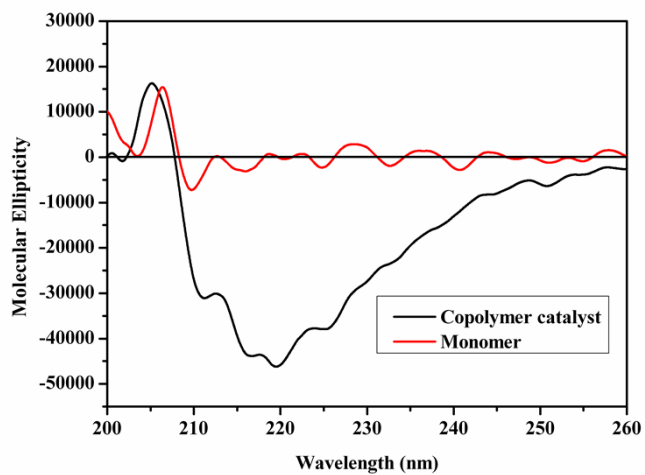


Fig S6. CD spectra of copolymer catalyst ($1.0 \times 10^{-5} \text{ mol} \cdot \text{L}^{-1}$) and monomer ($1.0 \times 10^{-5} \text{ mol} \cdot \text{L}^{-1}$) in CH_3OH .

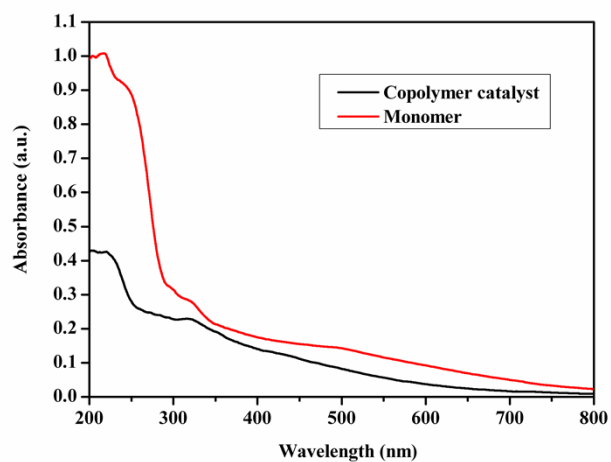


Fig S7. UV-vis absorption spectra of the copolymer catalyst and monomer

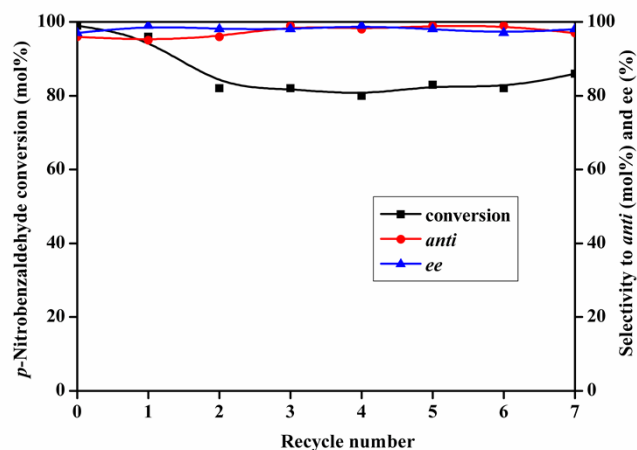
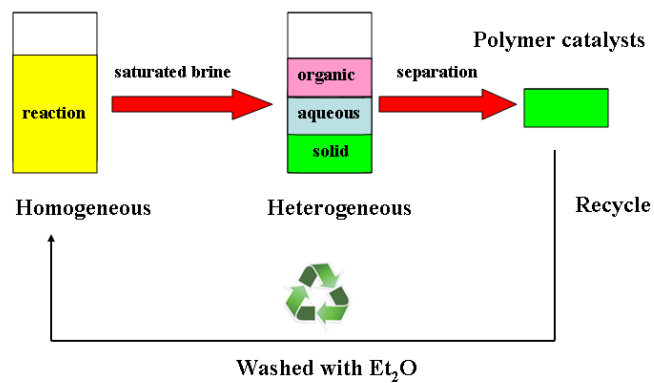


Fig S8. Recyclability of the copolymer catalyst (saturated brine as precipitant)



Scheme S1. The recycling process of catalysts

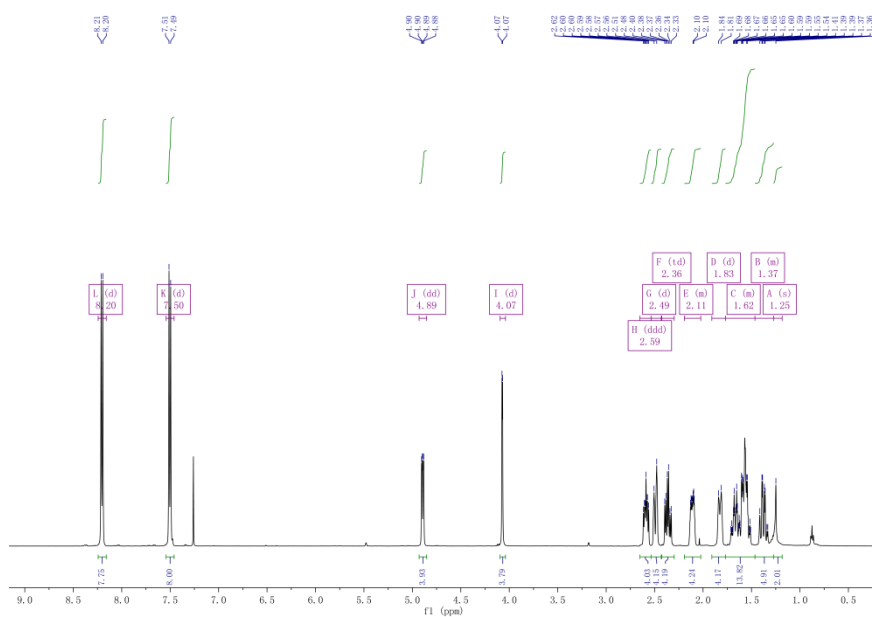


Fig S9. ^1H NMR spectra of 2-(Hydroxy (4-nitrophenyl) methyl) cyclohexan-1-one

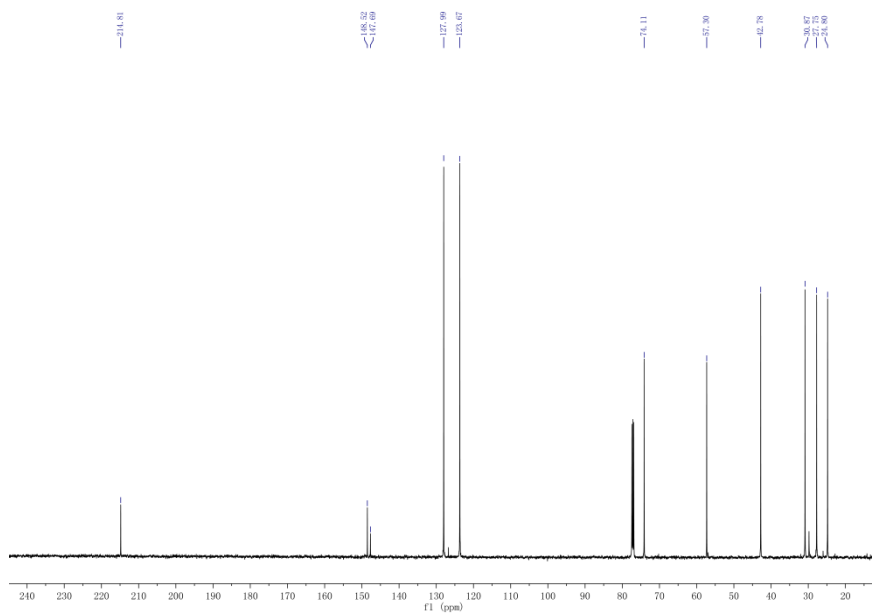


Fig S10. ^{13}C NMR spectra of 2-(Hydroxy (4-nitrophenyl) methyl) cyclohexan-1-one

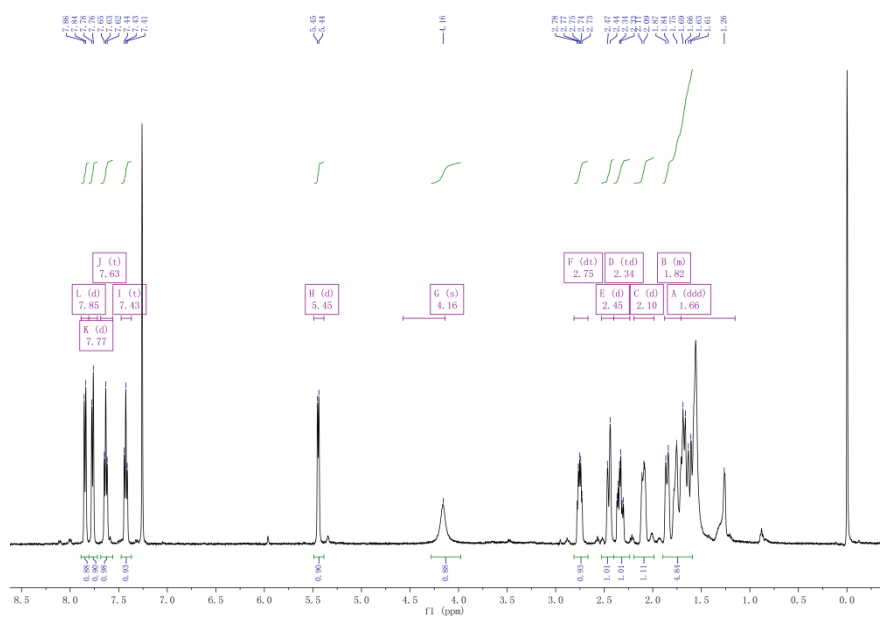


Fig S11. ¹H NMR spectra of 2-(Hydroxy (2-nitrophenyl) methyl) cyclohexan-1-one

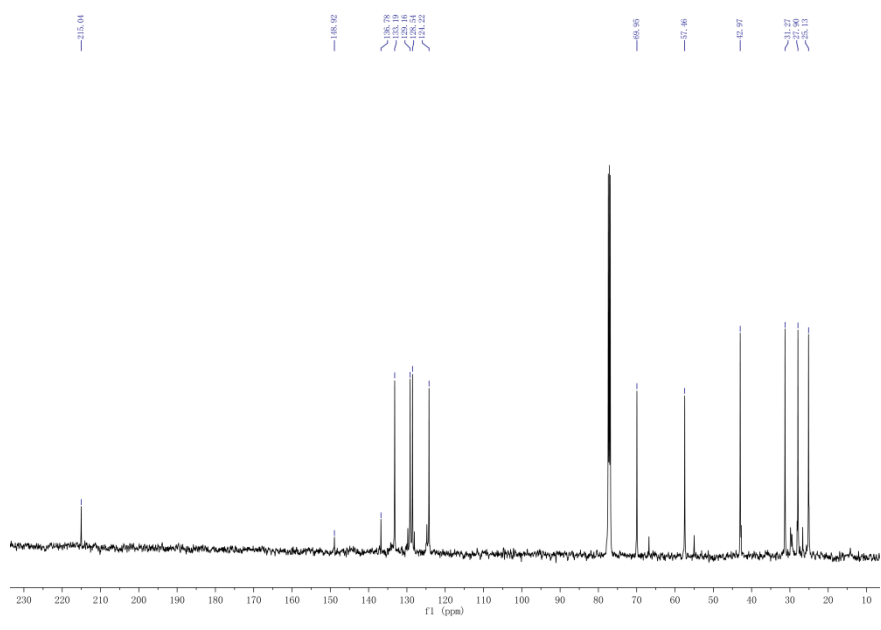


Fig S12. ¹³C NMR spectra of 2-(Hydroxy (2-nitrophenyl) methyl) cyclohexan-1-one

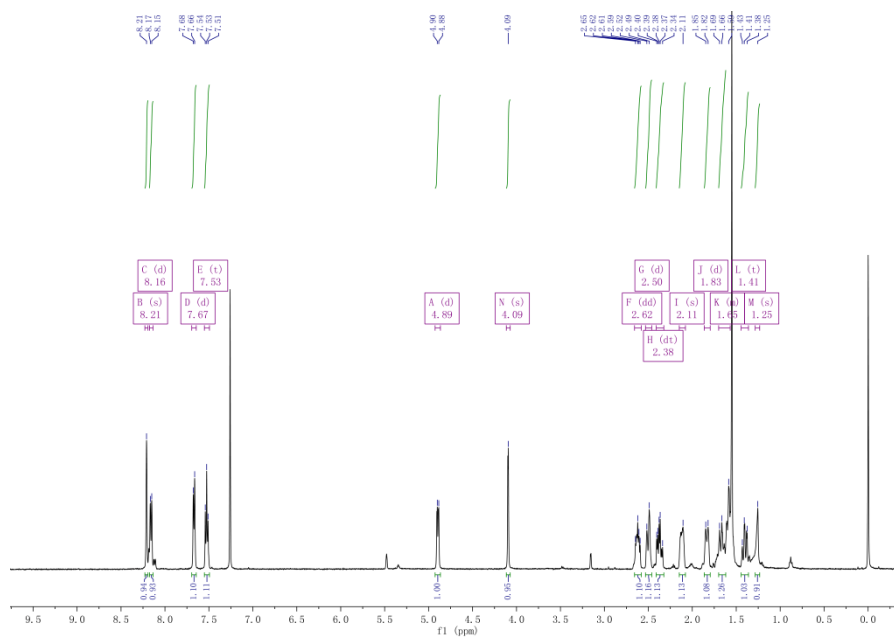


Fig S13. ¹H NMR spectra of 2-(Hydroxy (3-nitrophenyl) methyl) cyclohexan-1-one

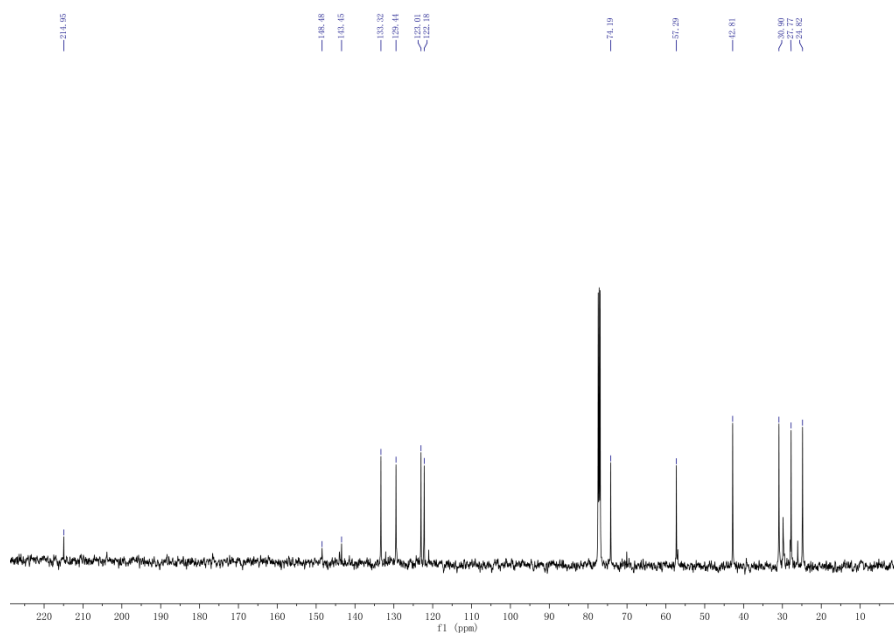


Fig S14. ¹³C NMR spectra of 2-(Hydroxy (3-nitrophenyl) methyl) cyclohexan-1-one

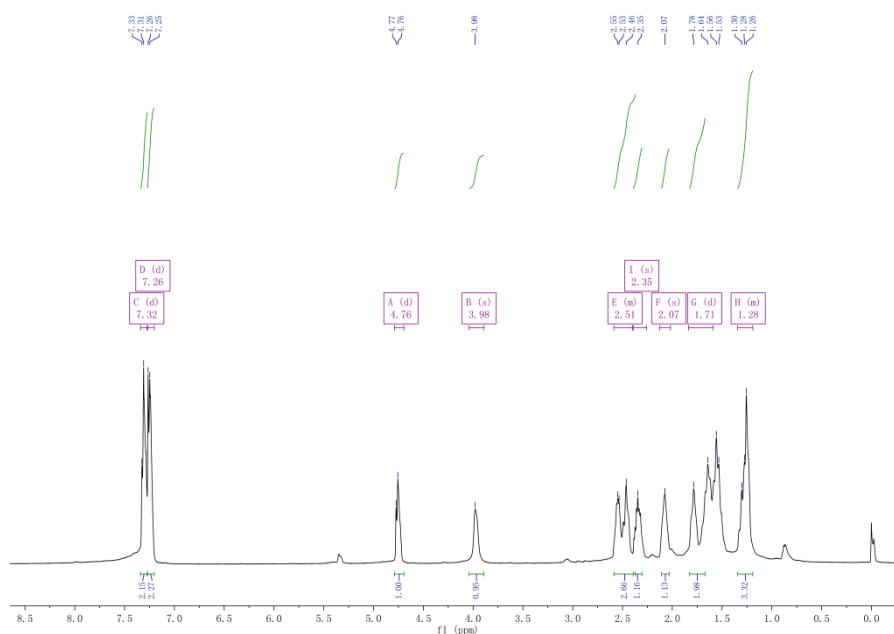


Fig S15. ^1H NMR spectra of 2-(Hydroxy (4-chlorophenyl) methyl) cyclohexan-1-one

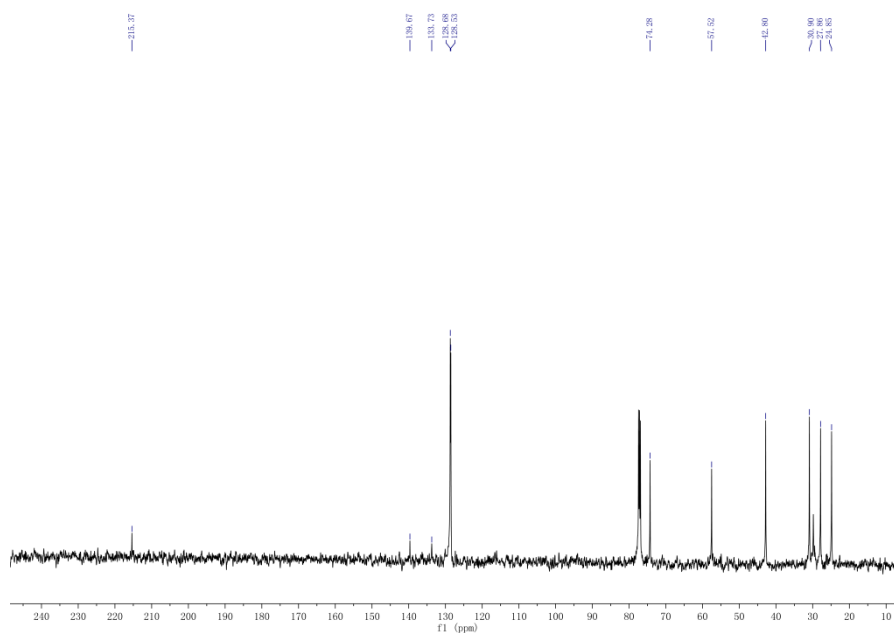


Fig S16. ^{13}C NMR spectra of 2-(Hydroxy (4-chlorophenyl) methyl) cyclohexan-1-one

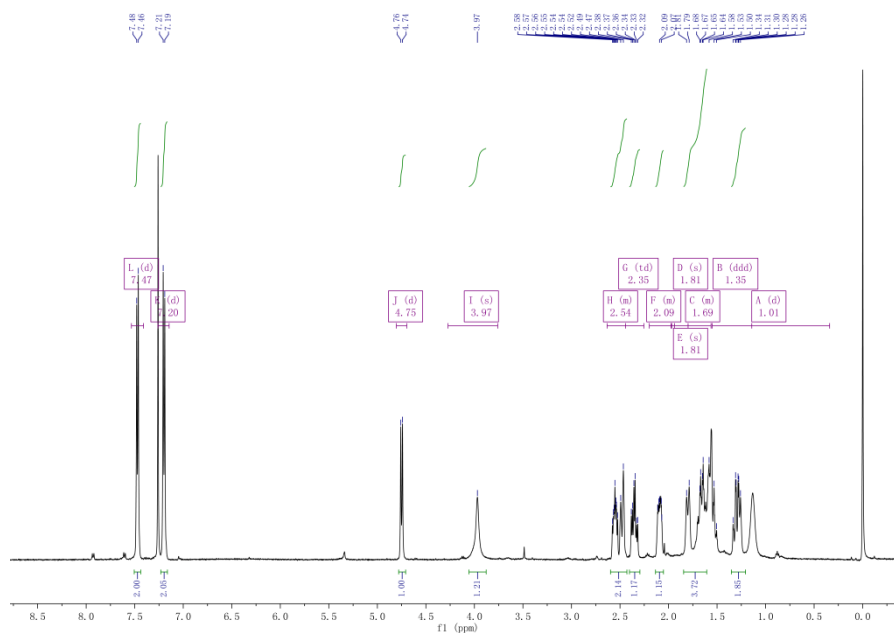


Fig S17. ^1H NMR spectra of 2-(Hydroxy (4-bromophenyl) methyl) cyclohexan-1-one

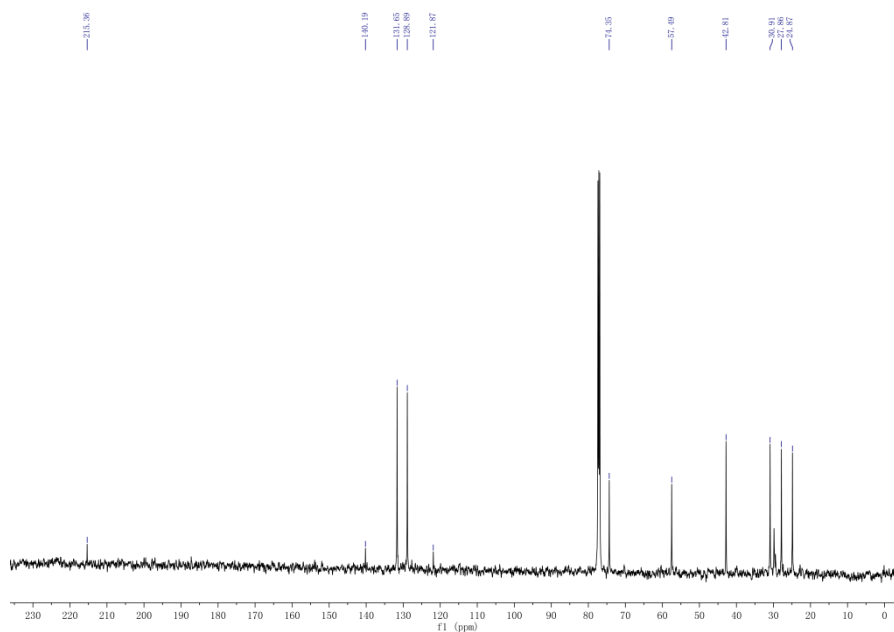
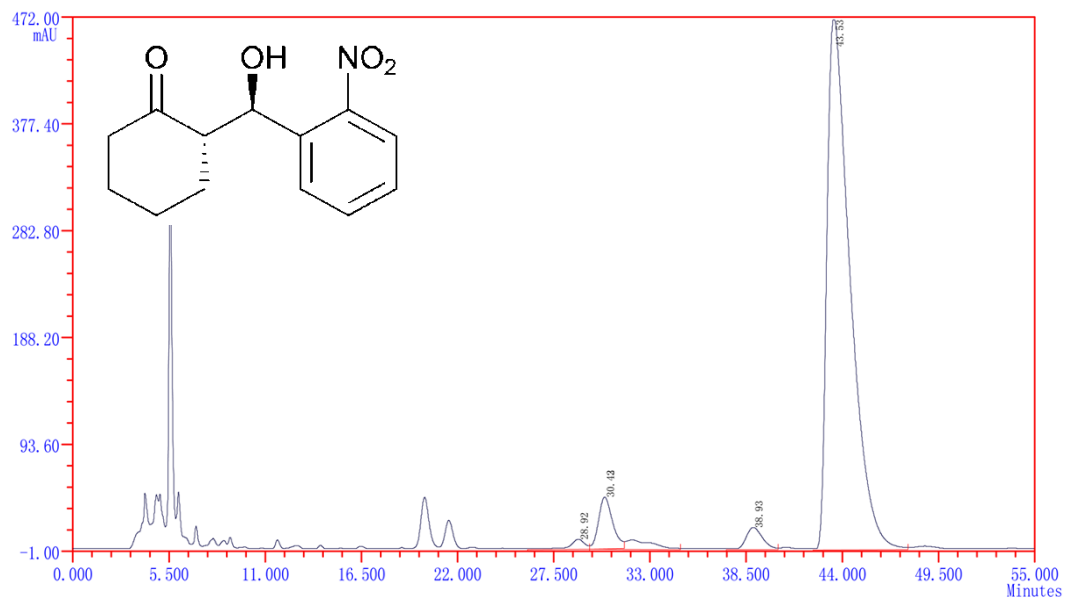
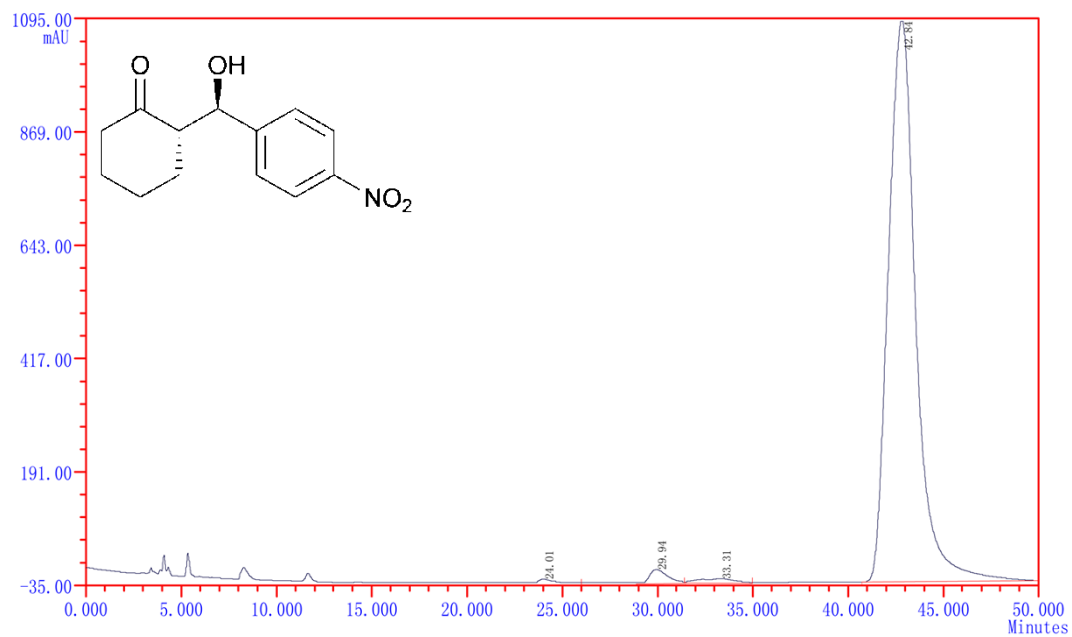
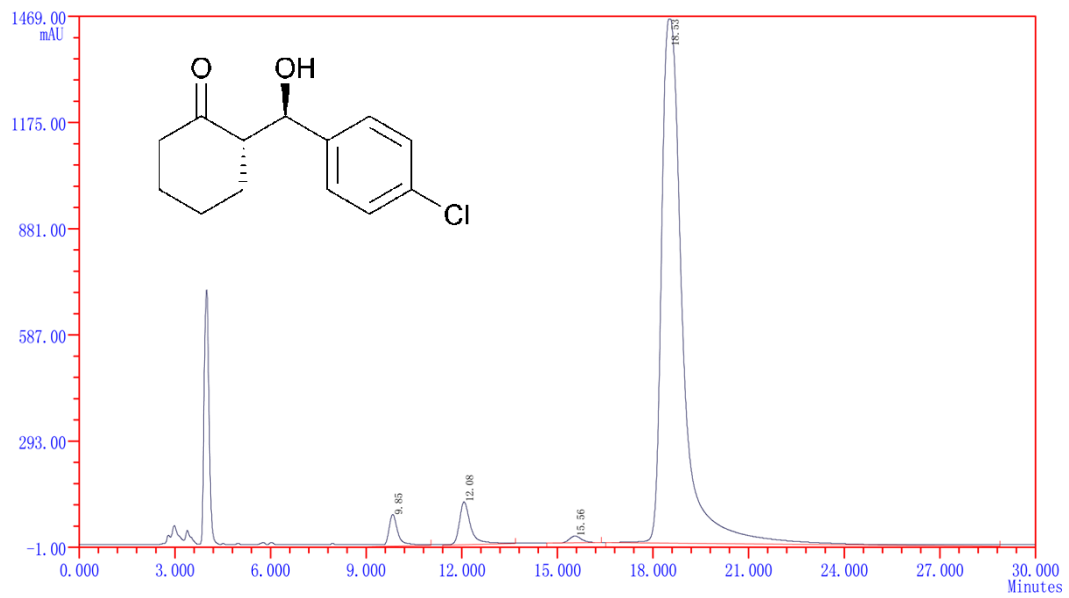
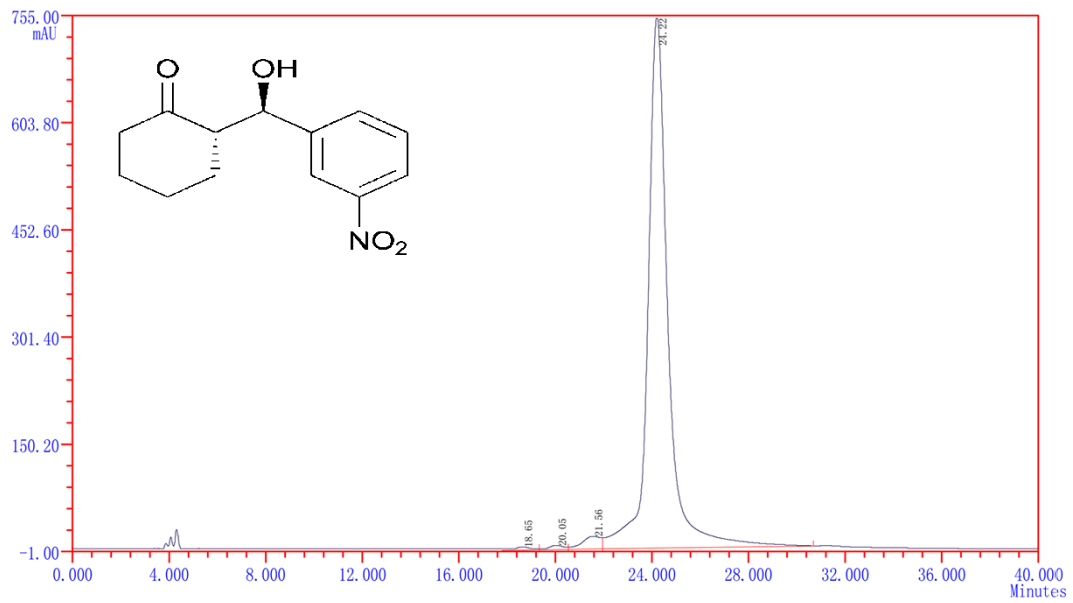
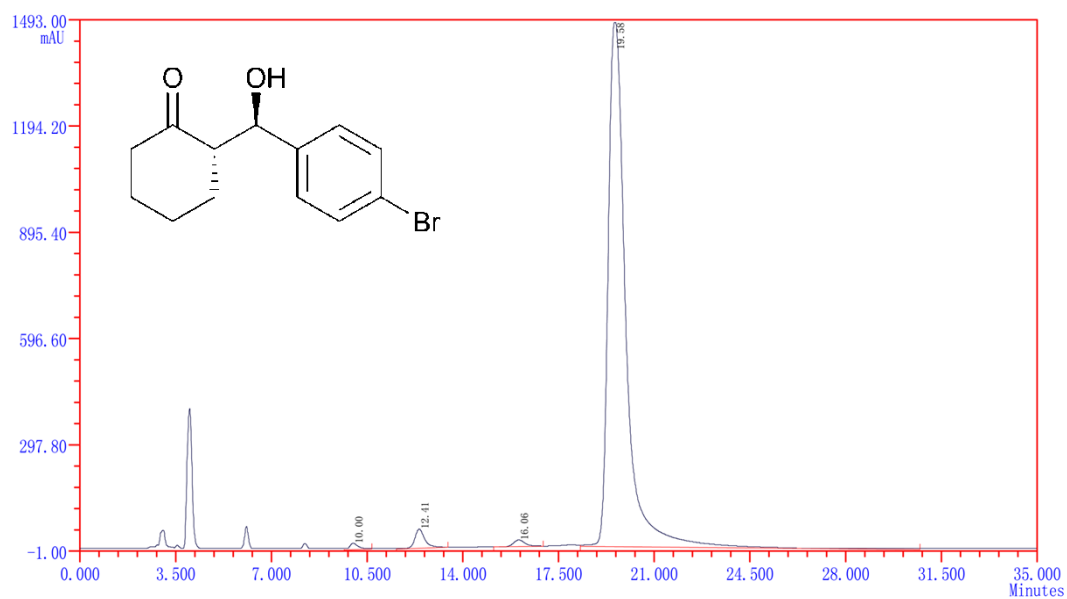


Fig S18. ^{13}C NMR spectra of 2-(Hydroxy (4-bromophenyl) methyl) cyclohexan-1-one

Fig S19. The HPLC chromatograms of reaction products







References

- [1] T. E. Kristensen, F. K. Hansen, T. Hansen, *Eur. J. Org. Chem.* **2009**, 387-395.
- [2] a) T. Tokuhiro, T. Amiya, A. Mamada, T. Tanaka, *Macromolecules* **1991**, *24*, 2936-2943;
b) J. Xu, J. Ye, S. Liu, *Macromolecules* **2007**, *40*, 9103-9110.