Supporting Information

L-Proline supported on ionic liquid-modified magnetic nanoparticles as a highly efficient and reusable organocatalyst for direct asymmetric aldol reaction in water

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Experimental

General Procedure for the Direct Asymmetric Aldol Reaction

The selected catalyst (10 mol%, based on L-proline content in the catalyst), ketone (2.5 mmol), aldehyde (0.25 mmol) and deionized water (2 mL) were added in a 10 mL round-bottom flask in turn. The mixture was allowed to react at room temperature for 12 h. The reaction was monitored constantly by TLC. After completion of the reaction, the magnetic catalyst was separated by a magnet near the bottle. The reaction solution was removed from the reaction vessel by decantation while the external magnet held the magnetic catalyst inside the bottle. The magnetic catalyst was then washed with ethyl acetate, separated by magnetic decantation as described above, dried under vacuum overnight at room temperature for the recycle experiment. Ethyl acetate (3 × 10 mL) was used to extract the aldols from the reaction solution. The combined organic layers were washed with brine and died with Na_2SO_4. After the evaporation of ethyl acetate, the residue was purified by column chromatography on silica gel (Acros, 40–60 μm, 60 Å, eluent *n*-hexane/ethyl acetate = 3/1 (V/V)) to afford the desired aldol products. Enantiomeric excess of the corresponding aldol products was determined by HPLC analysis with a UV-vis detector using the Daicel chiralpak AD-H, OB-H or AD column. All the aldol products have been identified by comparison with those corresponding authentic samples in detailed HPLC analysis. NMR spectra for the aldol products **1-6** are in agreement with those reported in references.[1] The syn and anti diastereomers of the aldols **1-6** were readily distinguished in ^1H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton.

(2R,10S)-2-(Hydroxy-(2-nitrophenyl)methyl)cyclohexan-1-one (1).

Enantiomeric excess (85% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane =15: 85 (V/V) eluent) UV 254 nm, flow rate 1.0 mL/min, major enantiomer t_R = 13.4 min and minor enantiomer t_R = 14.2 min (see Fig. S1 and S2).

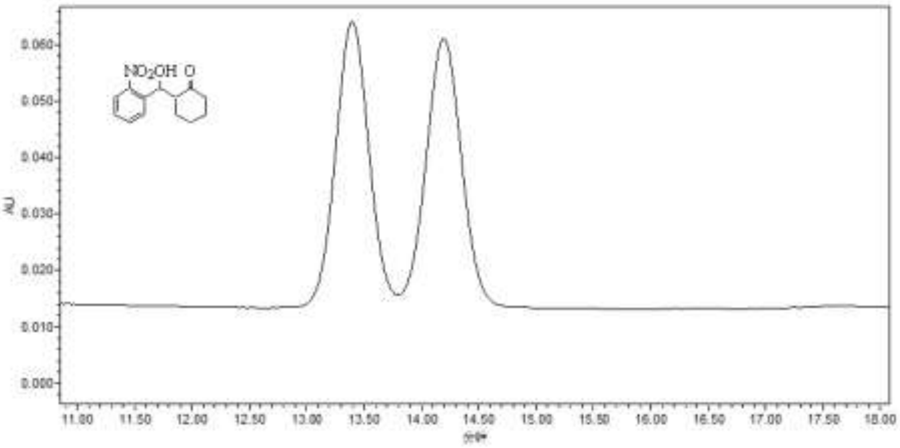


Fig. S1 HLPC of the authentic sample **1**

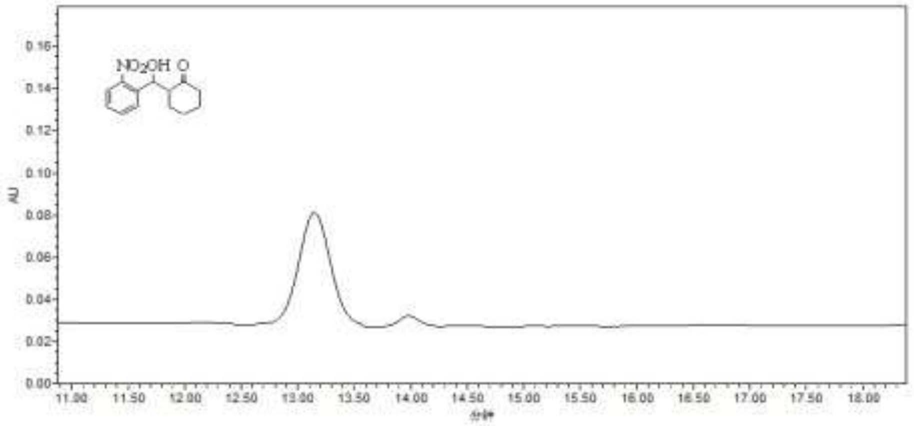


Fig. S2 HLPC of the as-obtained product **1**

The aldol product **1** has been identified by ^{1}H NMR spectrum, which is in agreement with the reported data.[1a] The syn and anti diastereomers of the aldol **1** were distinguished in ^{1}H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton according to the corresponding chemical shifts published in the reference.[1b] (see Fig. S3)

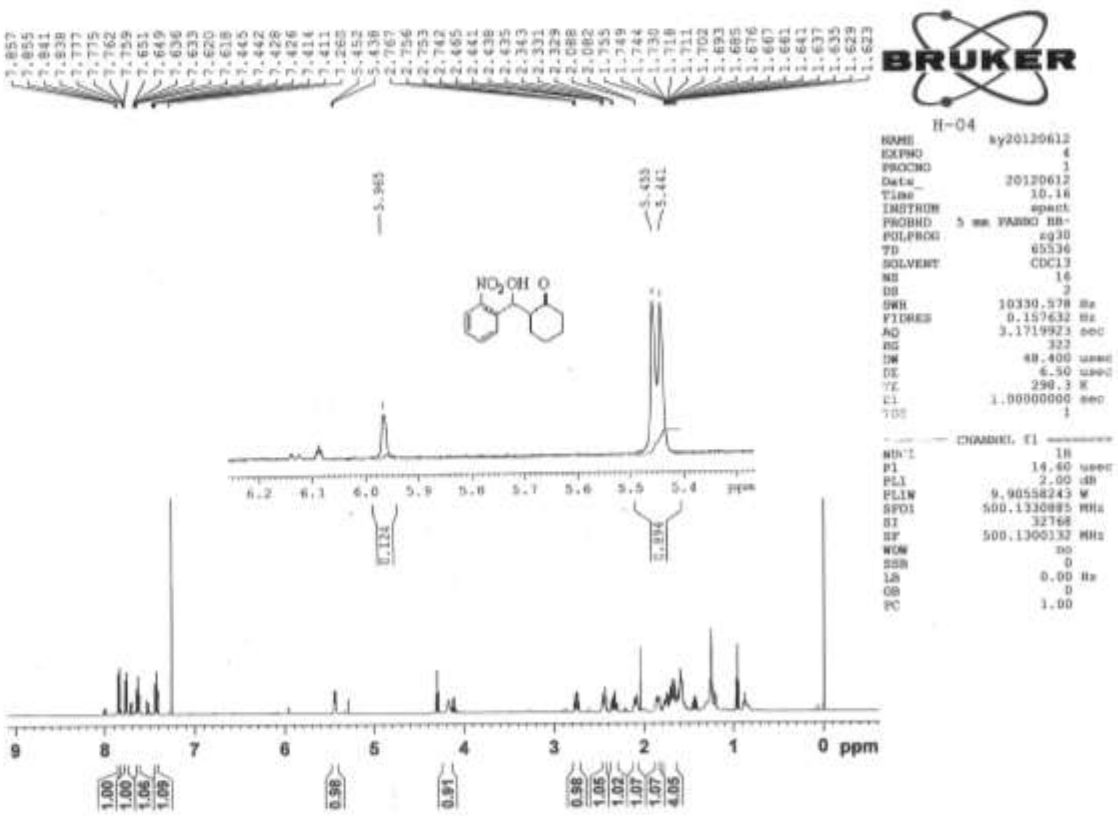


Fig. S3 ^{1}H NMR of the as-obtained product **1** (inset: Chemical shifts of –C*H*OH– proton in sample **1** (anti/syn) =88: 12)

(2R,10S)-2-(Hydroxy-(4-nitrophenyl)methyl)cyclohexan-1-one (2).

Enantiomeric excess (75% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane =15: 85 (V/V) eluent) UV 254 nm, flow rate 1.0 mL/min, major enantiomer t_R = 16.2 min and minor enantiomer t_R = 21.4 min (see Fig. S4 and S5).

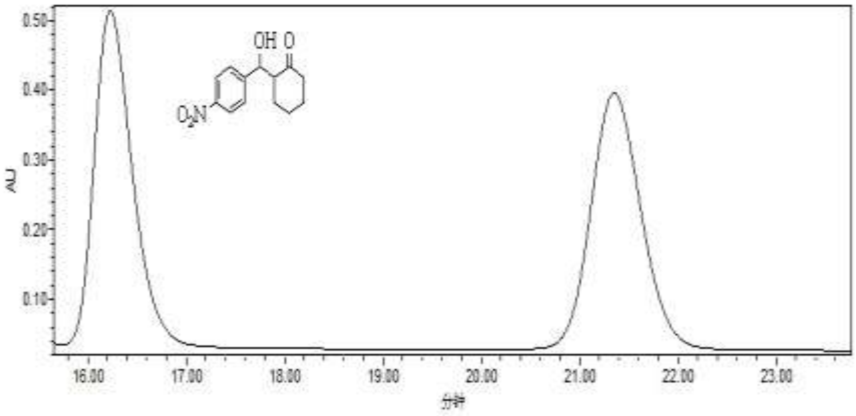


Fig. S4 HLPC of the authentic sample **2**

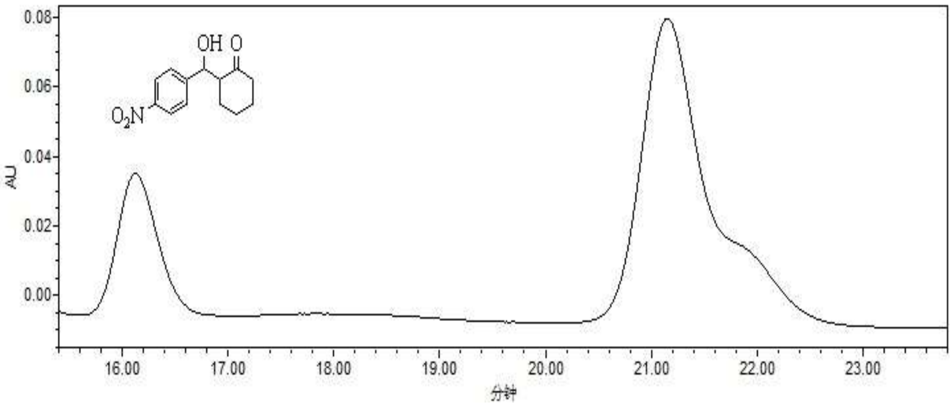


Fig. S5 HLPC of the as-obtained product **2**

The aldol product **2** has been identified by ^{1}H NMR spectrum, which is in agreement with the reported data. [1a, 1c] The syn and anti diastereomers of the aldol **2** were distinguished in ^{1}H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton according to the corresponding chemical shifts published in the reference.[1b] (see Fig. S6)

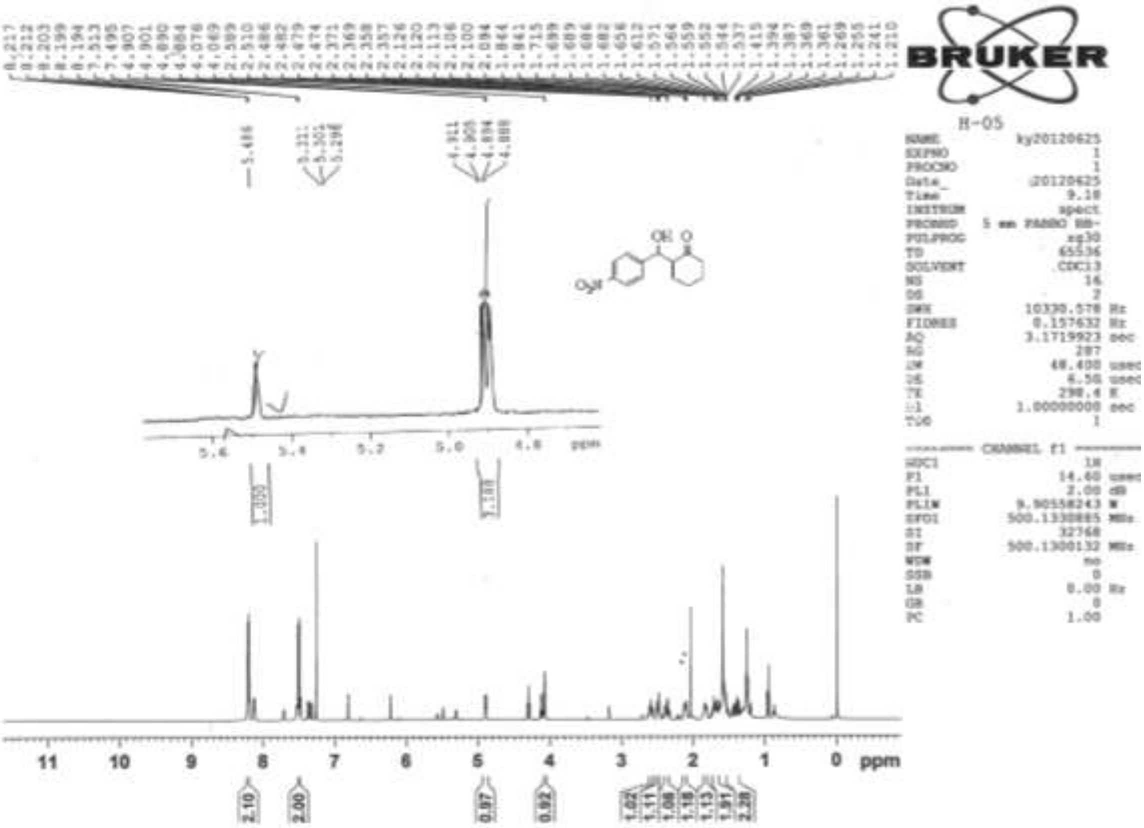


Fig. S6 ^{1}H NMR of the as-obtained product **2** (inset: Chemical shifts of –C*H*OH– proton in sample **2** (anti/syn) = 76: 24)

(2R,10S)-2-(Hydroxy-(2-chlorophenyl)methyl)cyclohexa -n-1-one (3).

Enantiomeric excess (89% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane =10: 90 (V/V) eluent) UV 220 nm, flow rate 1.0 mL/min, major enantiomer t_R = 9.9 min and minor enantiomer t_R = 11.1 min (see Fig. S7 and S8).

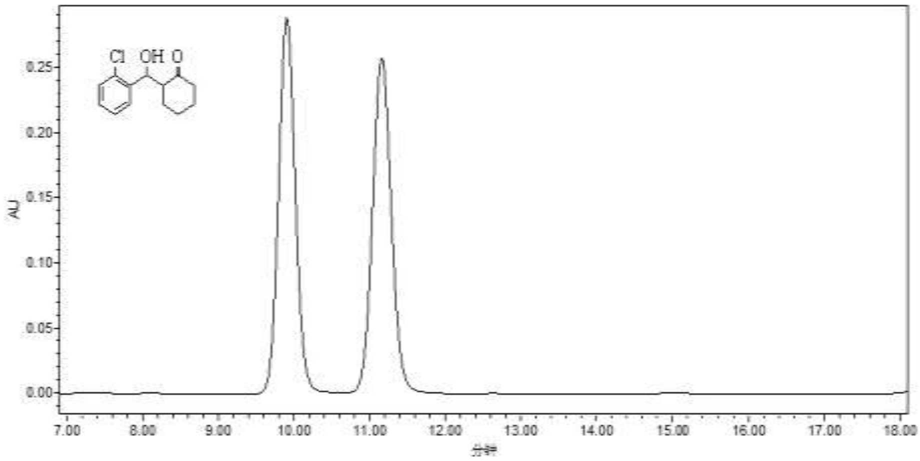


Fig. S7 HLPC of the authentic sample **3**

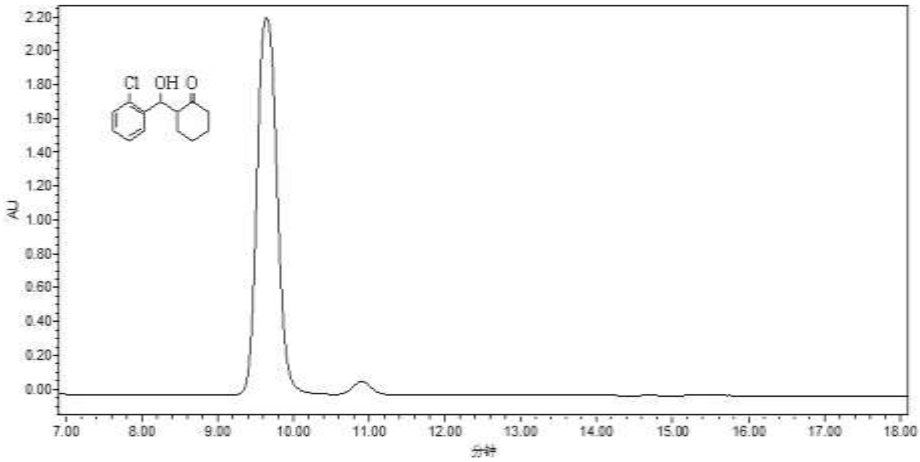


Fig. S8 HLPC of the as-obtained product **3**

The aldol product **3** has been identified by ^{1}H NMR spectrum, which is in agreement with the reported data. [1a, 1c] The syn and anti diastereomers of the aldol **3** were distinguished in ^{1}H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton according to the corresponding chemical shifts published in the reference. [1a, 1c] (see Fig. S9)

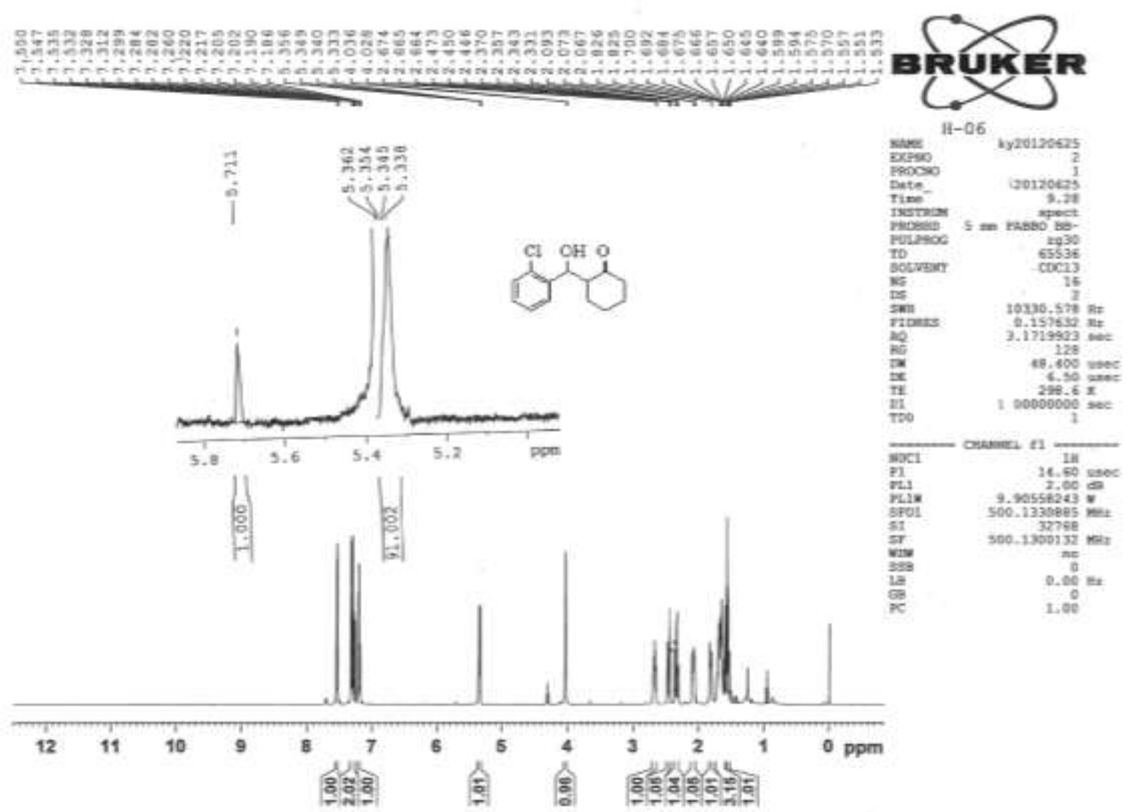


Fig. S9 ^{1}H NMR of the as-obtained product **3** (inset: Chemical shifts of –C*H*OH– proton in sample **3** (anti/syn) = 99: 1)

(2R,10S)-2-(Hydroxy-(4-bromophenyl)methyl)cyclohexan-1-one (4).

Enantiomeric excess (89% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane =10: 90 (V/V) eluent) UV 220 nm, flow rate 1.0 mL/min, major enantiomer t_R = 16.1 min and minor enantiomer t_R = 13.2 min (see Fig. S10 and S11).

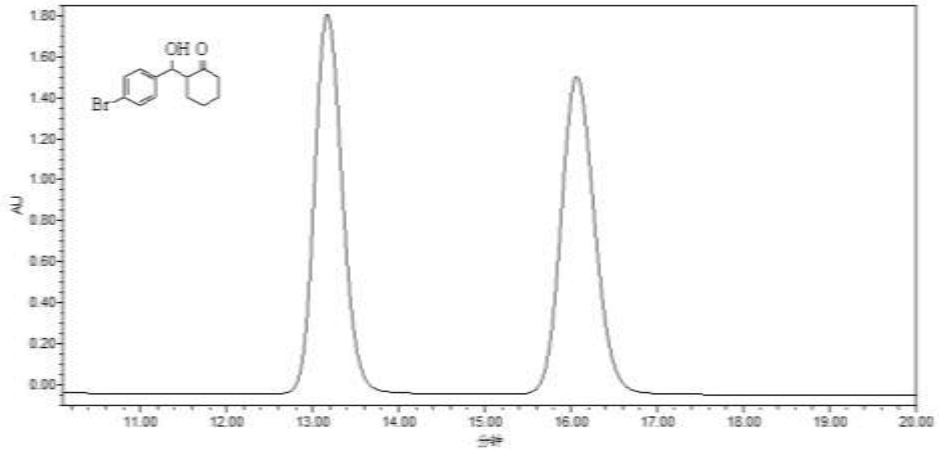


Fig. S10 HLPC of the authentic sample **4**

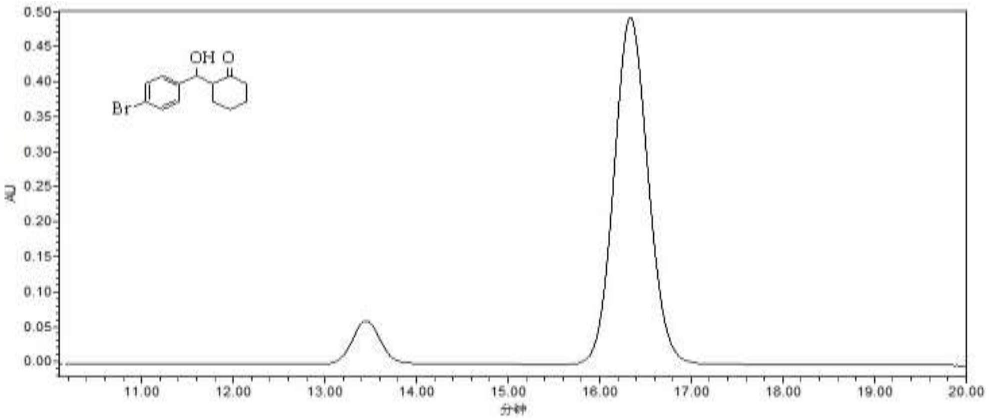
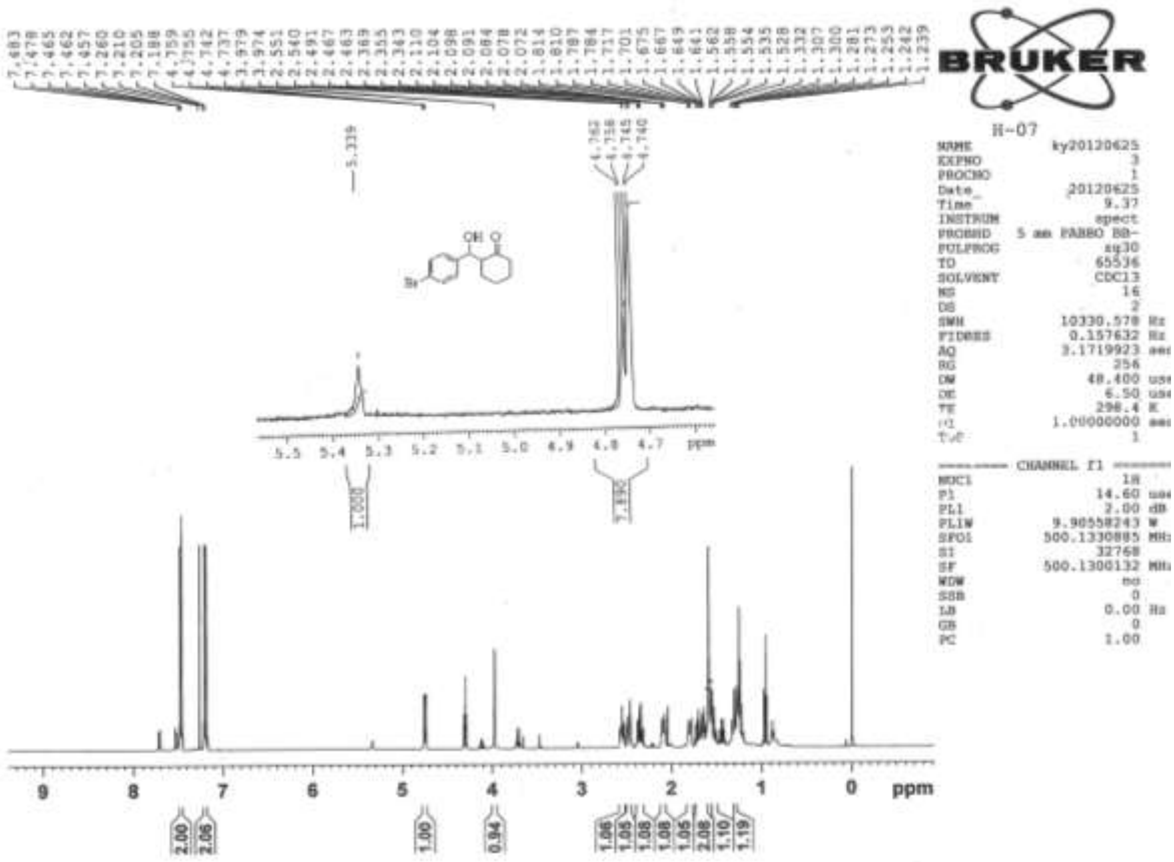


Fig. S11 HLPC of the as-obtained product **4**

The aldol product **4** has been identified by ^{1}H NMR spectrum, which is in agreement with the reported data.[1a, 1c] The syn and anti diastereomers of the aldol **4** were distinguished in ^{1}H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton according to the corresponding chemical shifts published in the reference.[1b] (see Fig. S12)



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TD0 1

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SF 500.1300132 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

Fig. S12 ^{1}H NMR of the as-obtained product **4** (inset: Chemical shifts of –C*H*OH– proton in sample **4** (anti/syn) = 89: 11)

(2R,10S)-2-(Hydroxy-(2-naphthyl)methyl)cyclohexan-1-one (5).

The aldol product **5** has been identified by comparison of the HPLC retention times with reported values.[1d] Enantiomeric excess (45% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane = 2: 98 (V/V) eluent) UV 220 nm, flow rate 1.0 mL/min, major enantiomer t_R = 26.2 min and minor enantiomer t_R = 29.6 min (see Fig. S13).

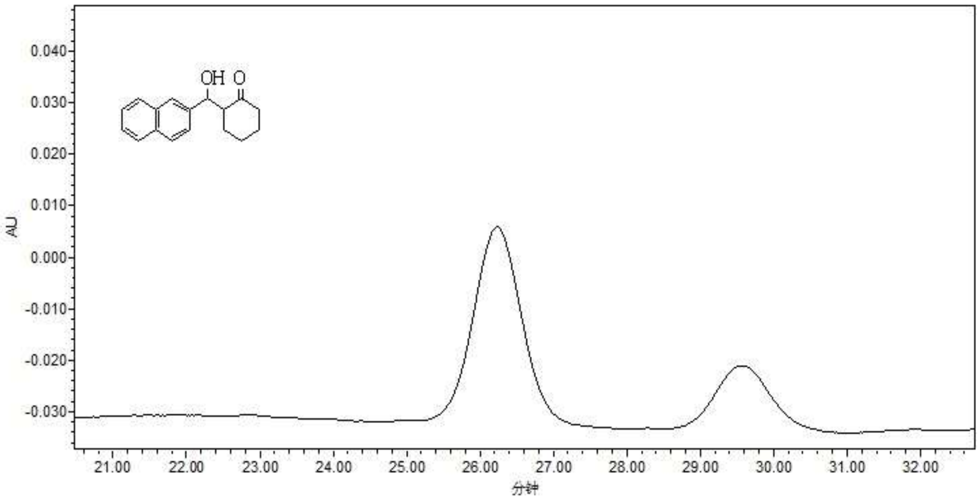

Fig. S13 HLPC of the as-obtained product **5**

The aldol product **5** has been identified by ^{1}H NMR spectrum, which is in agreement with the reported data.[1c, 1d] The syn and anti diastereomers of the aldol **5** were distinguished in ^{1}H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton according to the corresponding chemical shifts published in the reference.[1c] (see Fig. S14)

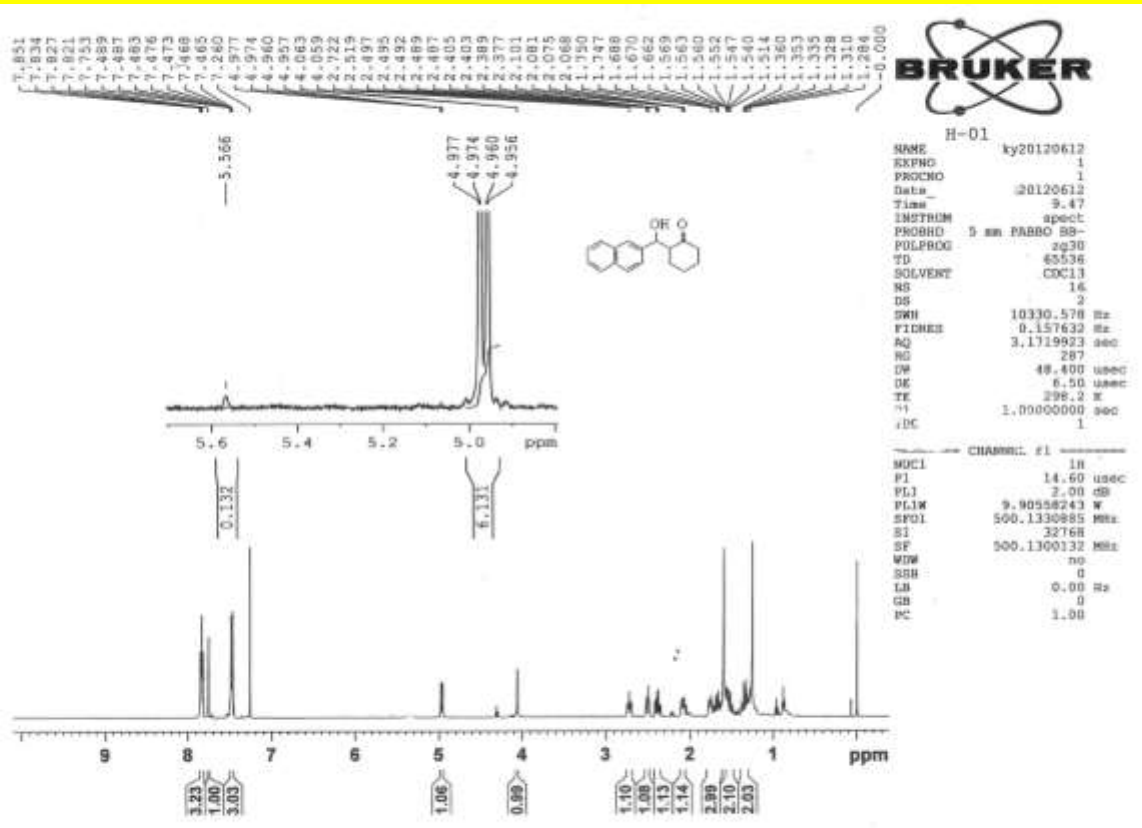

Fig. S14 ^{1}H NMR of the as-obtained product **5** (inset: Chemical shifts of –C*H*OH– proton in sample **5** (anti/syn) = 98: 2)

(2R,10S)-2-(Hydroxy-(4-nitrophenyl)methyl)cyclopentanone-1-one (6).

Enantiomeric excess (86% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane = 10: 90 (V/V) eluent) UV 220 nm, flow rate 1.0 mL/min, major enantiomer t_R = 12.9 min and minor enantiomer t_R = 16.7 min (see Fig. S15 and S16).

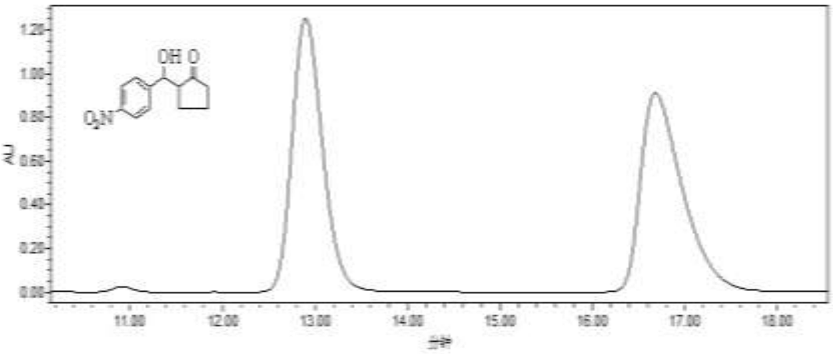

Fig. S15 HLPC of the authentic sample **6**

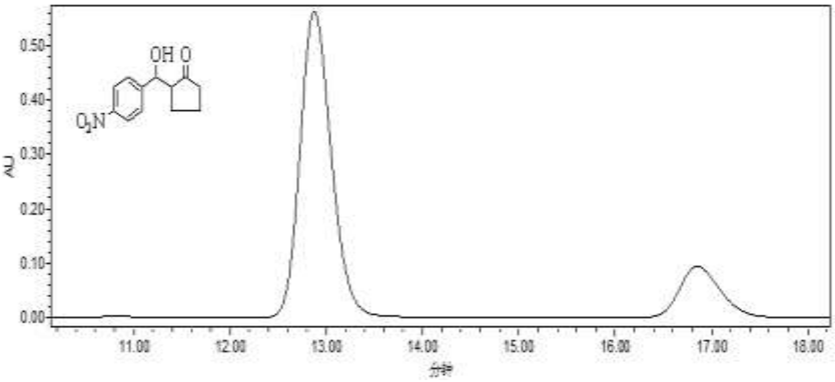

Fig. S16 HLPC of the as-obtained sample **6**

The aldol product **6** has been identified by ^{1}H NMR spectrum, which is in agreement with the reported data.[1e] The syn and anti diastereomers of the aldol **6** were distinguished in ^{1}H NMR spectroscopy by the diagnostic chemical shifts of –C*H*OH– proton according to the corresponding chemical shifts published in the reference.[1b] (see Fig. S17)

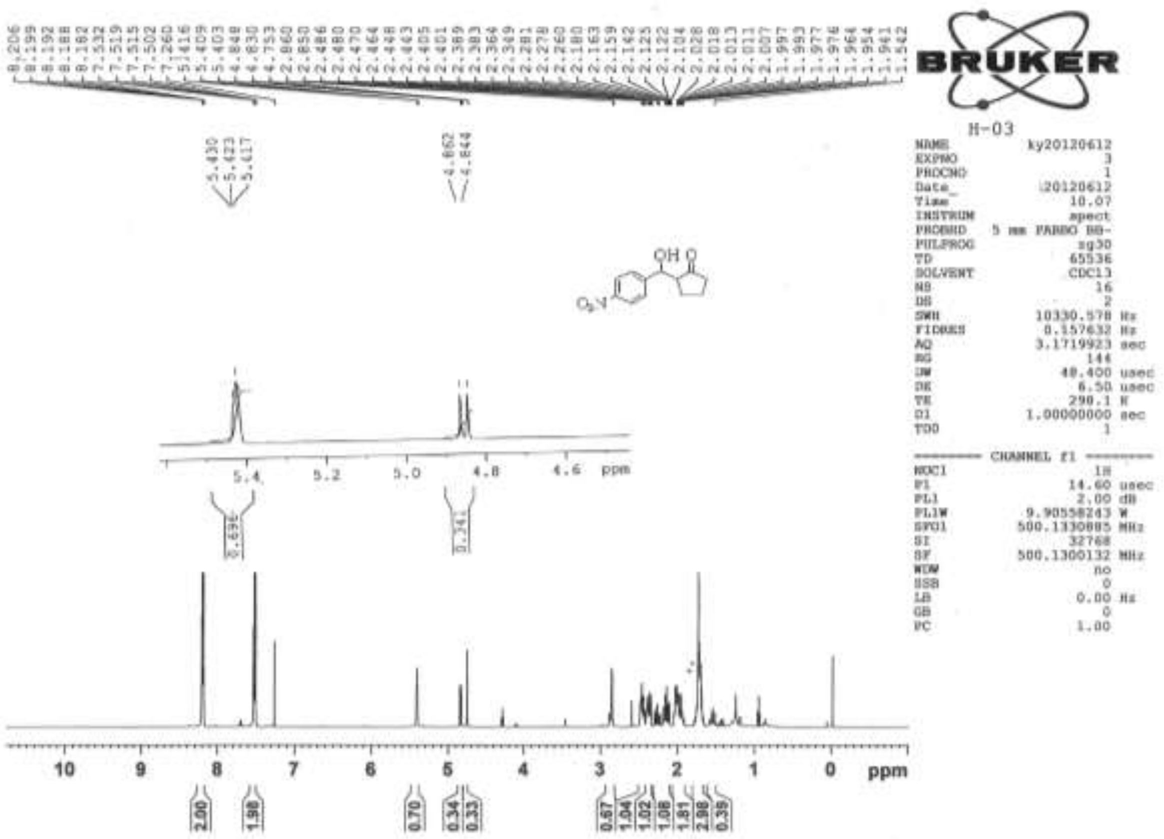

Fig. S17 ^{1}H NMR of the as-obtained product **6** (inset: Chemical shifts of –C*H*OH– proton in sample **6** (anti/syn) =33: 67)

(4R)-Hydroxy-4-(2-nitrophenyl)-butan-2-one (7).

Enantiomeric excess (77% ee) was determined by HPLC with a Chiralpak OB-H column (2-propanol/*n*-hexane = 15: 85 (V/V) eluent) UV 254 nm, flow rate 1.0 mL/min, major enantiomer t_R = 8.4 min and minor enantiomer t_R = 7.3 min (see Fig. S18 and S19).

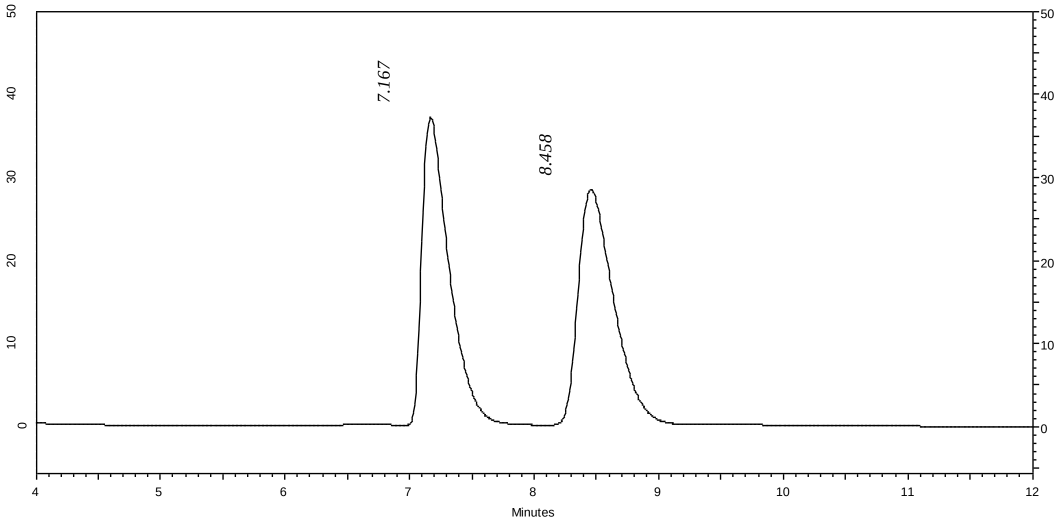

Fig. S18 HLPC of the authentic sample **7**

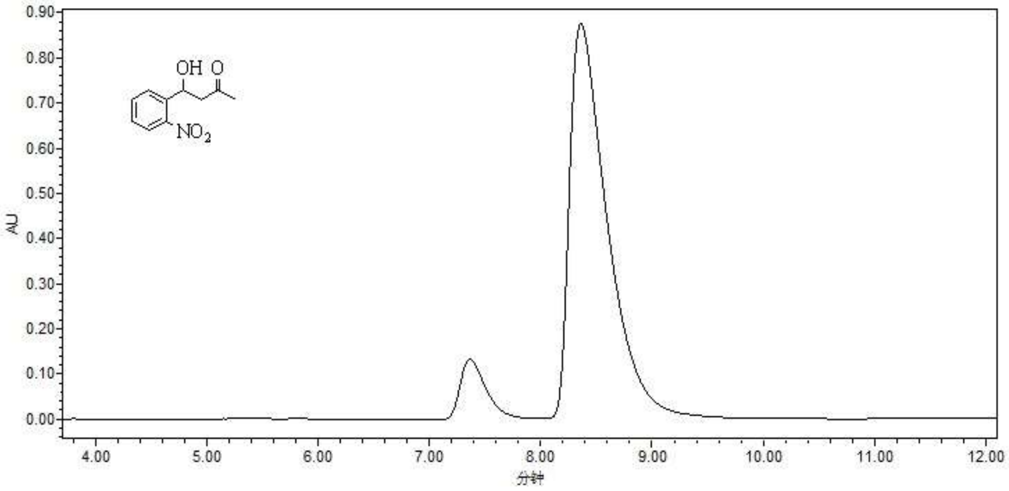

Fig. S19 HLPC of the as-obtained sample **7**

The aldol product **7** has been identified by ^{1}H NMR and ^{13}C NMR spectra (see Fig. S20 and S21).

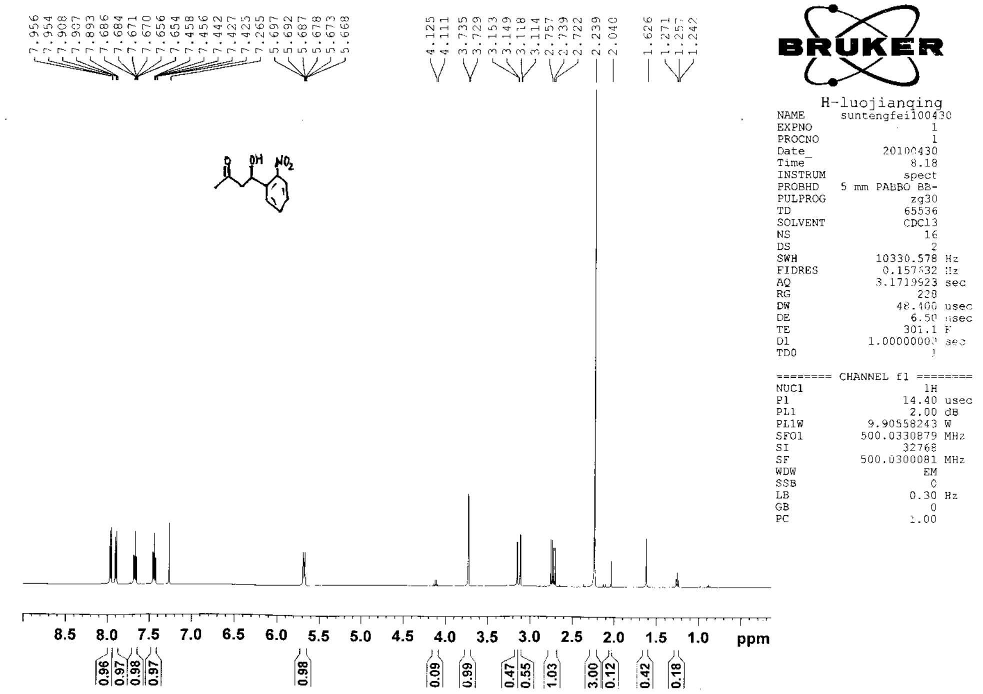

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Fig. S20 ^{1}H NMR of the as-obtained product **7**

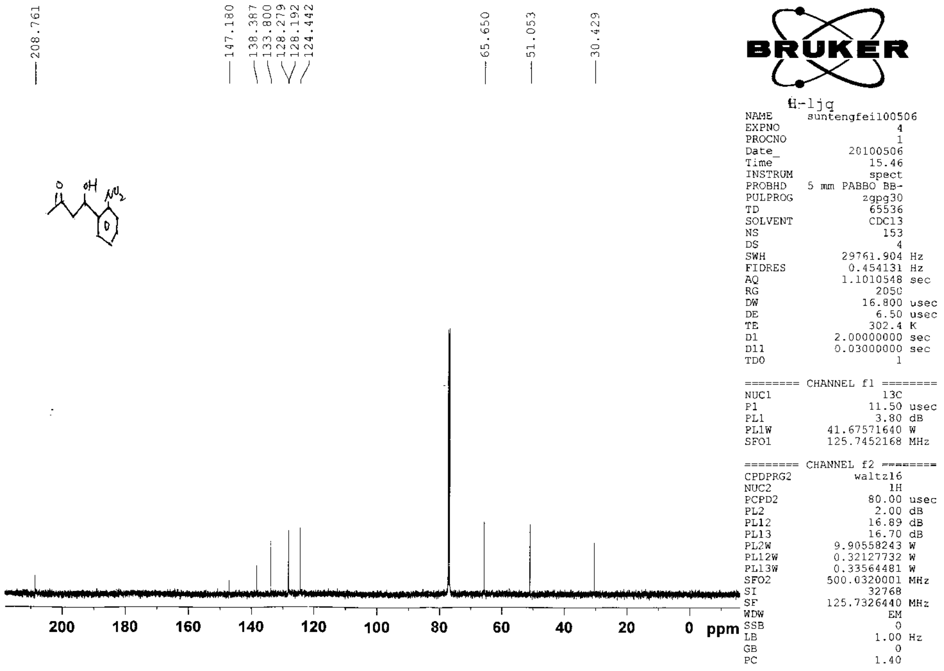

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Fig. S21 ^{13}C NMR of the as-obtained product **7**

(4R)-Hydroxy-4-(4-nitrophenyl)-butan-2-one (8).

Enantiomeric excess (70% ee) was determined by HPLC with a Chiralpak OB-H column (2-propanol/*n*-hexane = 15: 85 (V/V) eluent) UV 254 nm, flow rate 1.0 mL/min, major enantiomer t_R = 14.7 min and minor enantiomer t_R = 16.9 min (see Fig. S22 and S23).

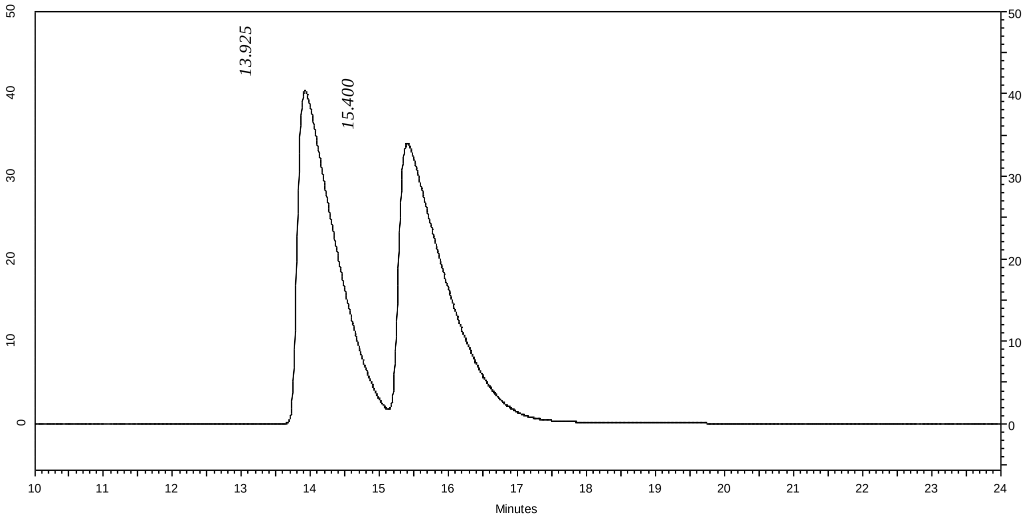

Fig. S22 HLPC of the authentic sample **8**

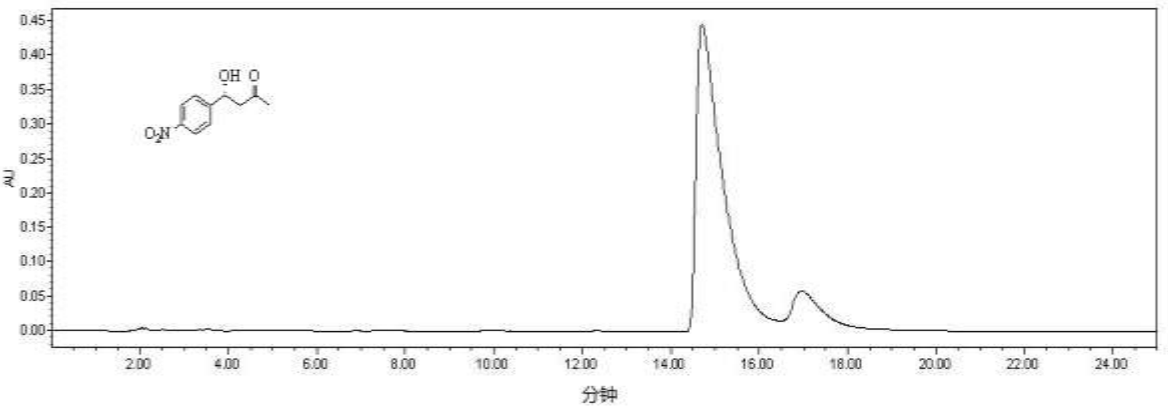

Fig. S23 HLPC of the as-obtained sample **8**

The aldol product **8** has been identified by ^{1}H NMR and ^{13}C NMR spectra (see Fig. S24 and S25).

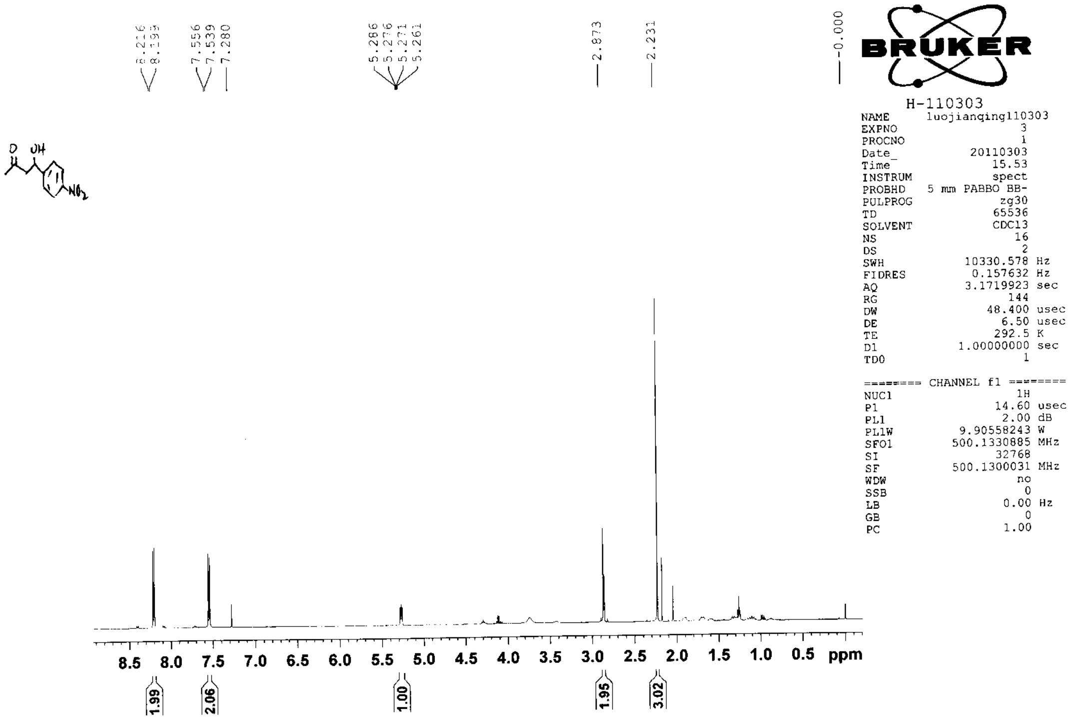

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Fig. S24 ^{1}H NMR of the as-obtained product **8**

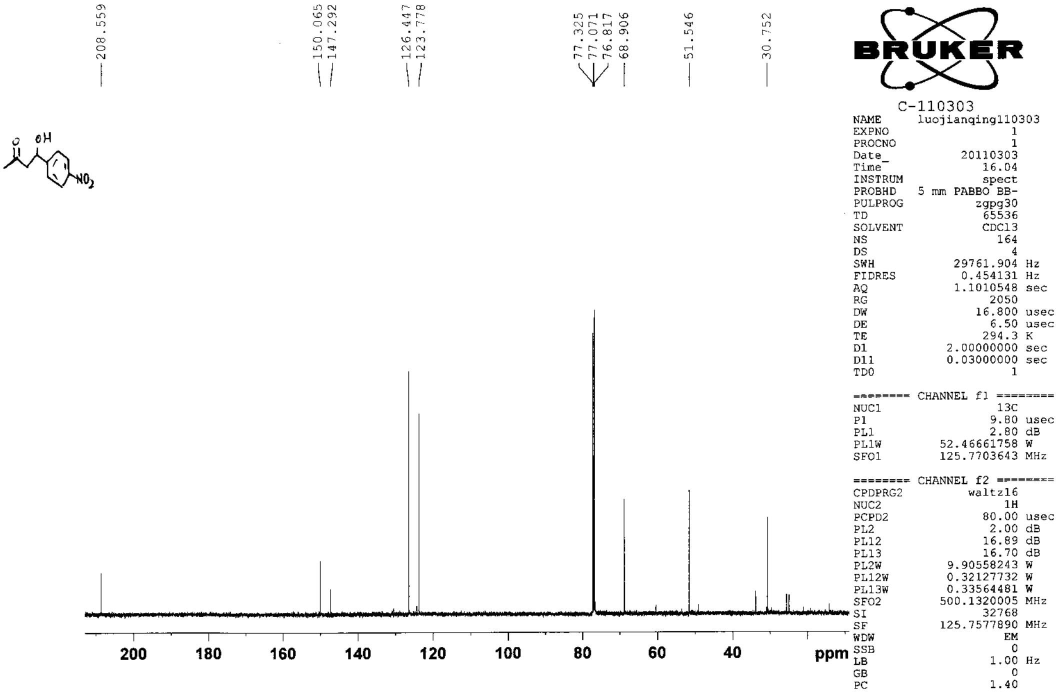

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Fig. S25 ^{13}C NMR of the as-obtained product **8**

(4R)-(2-Chlorophenyl)-4-hydroxy-2-butanone (9).

Enantiomeric excess (77% ee) was determined by HPLC with a Chiralpak AD column

(2-propanol/*n*-hexane = 7.5: 92.5 (V/V) eluent) UV 254 nm, flow rate 0.8 mL/min, major enantiomer t_R = 10.9 min and minor enantiomer t_R = 12.3 min (see Fig. S26 and S27).

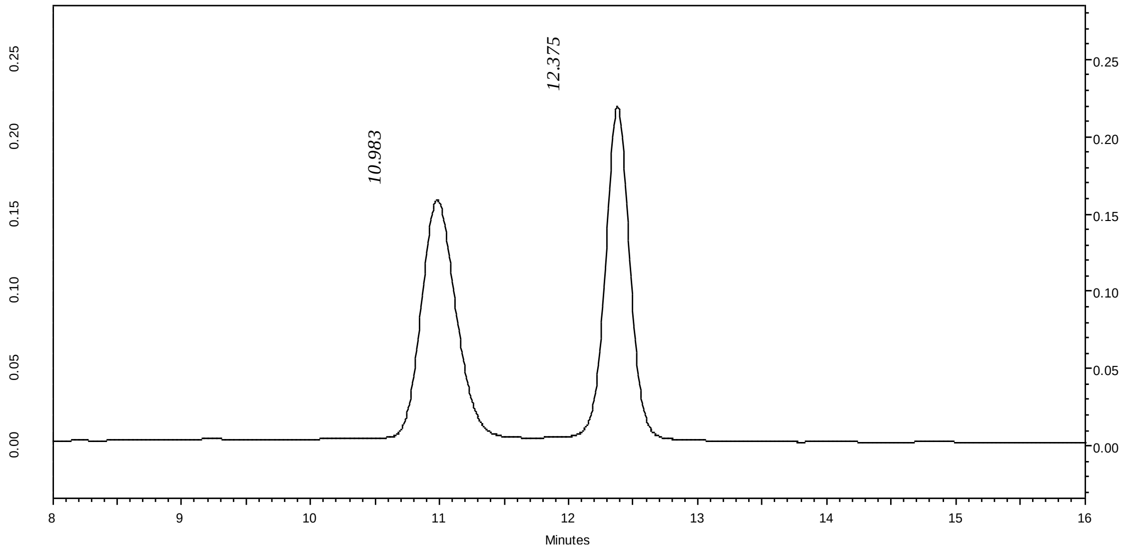

Fig. S26 HLPC of the authentic sample **9**

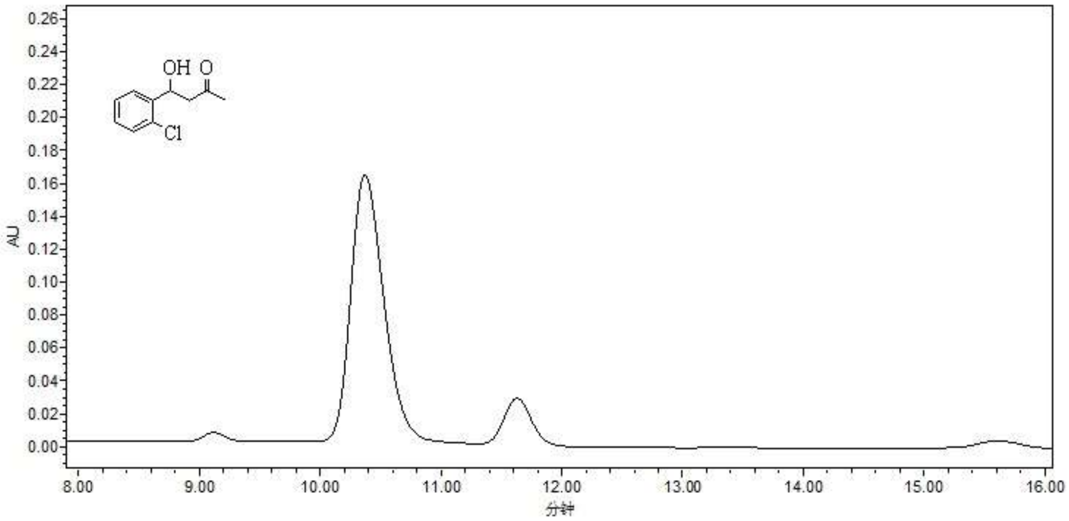

Fig. S27 HLPC of the as-obtained sample **9**

The aldol product **9** has been identified by ^{1}H NMR and ^{13}C NMR spectra (see Fig. S28 and S29).

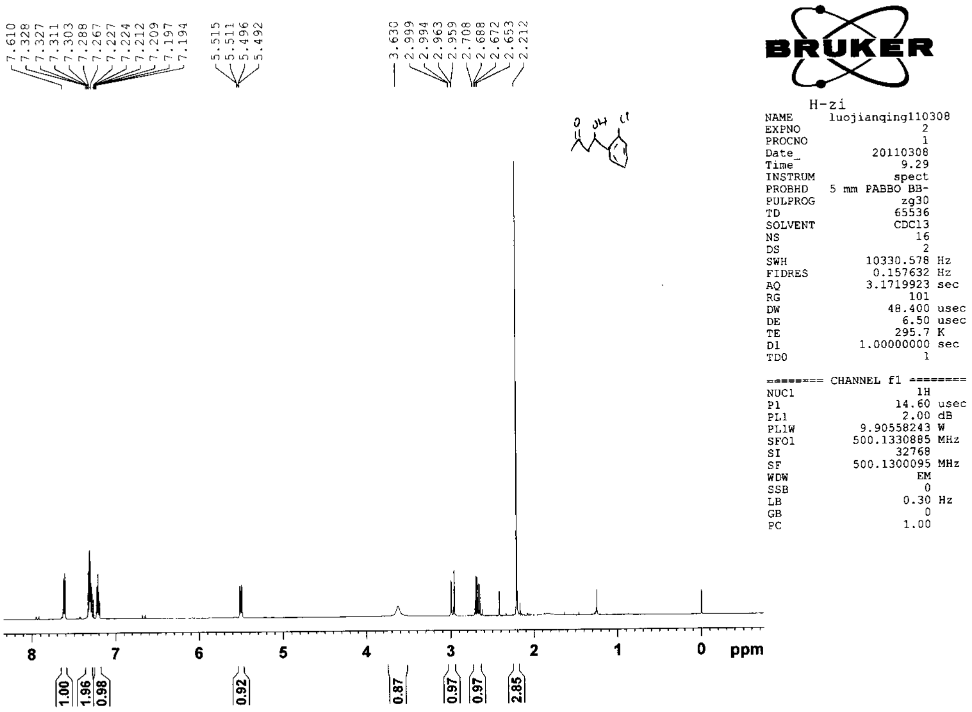

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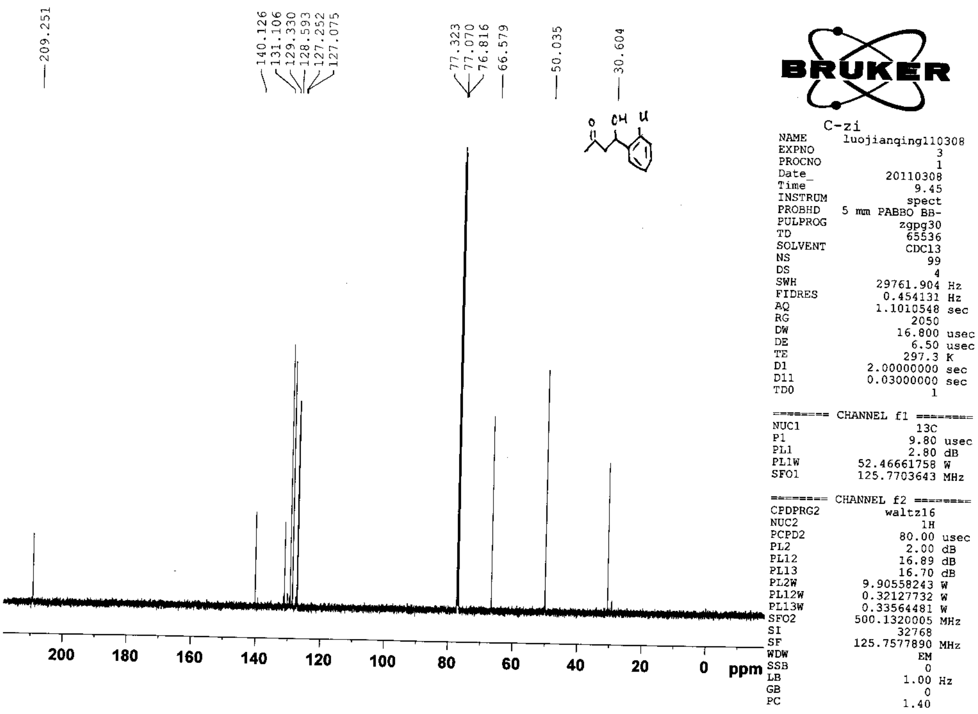
Fig. S28 ^{1}H NMR of the as-obtained product **9**



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SOLVENT            CDC13
NS                    99
DS                     4
SWH            29761.904 Hz
FIDRES          0.454131 Hz
AQ             1.1010548 sec
RG                  2050
DW                16.800 usec
DE                  6.50 usec
TE                 297.3 K
D1            2.00000000 sec
D11           0.03000000 sec
TDO                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                  9.80 usec
PL1                 2.80 dB
PL1W         52.46661758 W
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 2.00 dB
PL12               16.89 dB
PL13               16.70 dB
PL2W          9.90558243 W
PL12W         0.32127732 W
PL13W         0.33564481 W
SFO2         500.1320005 MHz
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

Fig. S29 ^{13}C NMR of the as-obtained product **9**

(4R)-(4-Bromophenyl)-4-hydroxy-2-butanone (10).

Enantiomeric excess (77% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane = 7.5: 92.5 (V/V) eluent) UV 254 nm, flow rate 0.8 mL/min, major enantiomer t_R = 15.2 min and minor enantiomer t_R = 16.1 min (see Fig. S30 and S31).

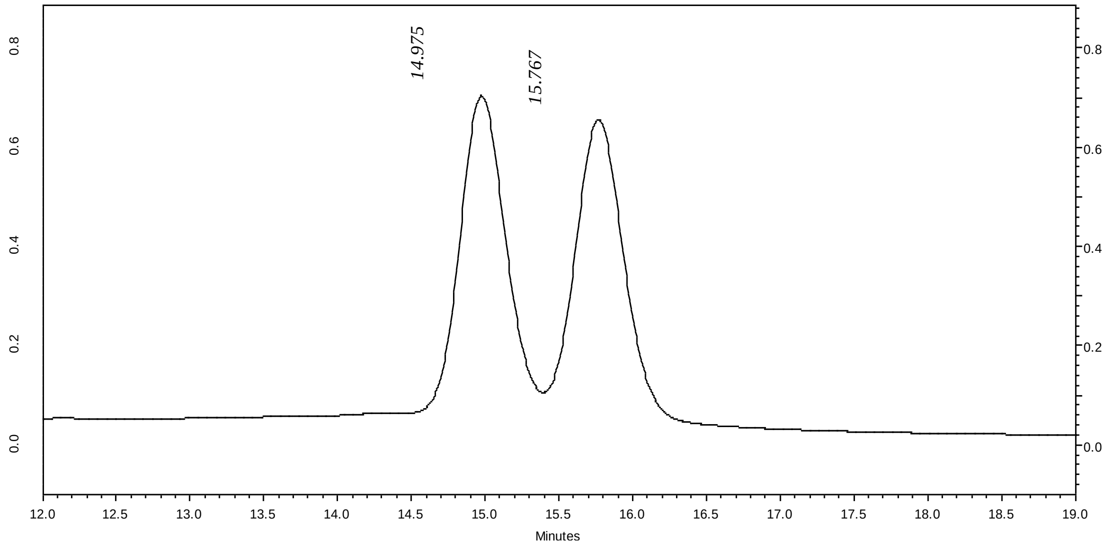

Fig. S30 HLPC of the authentic sample **10**

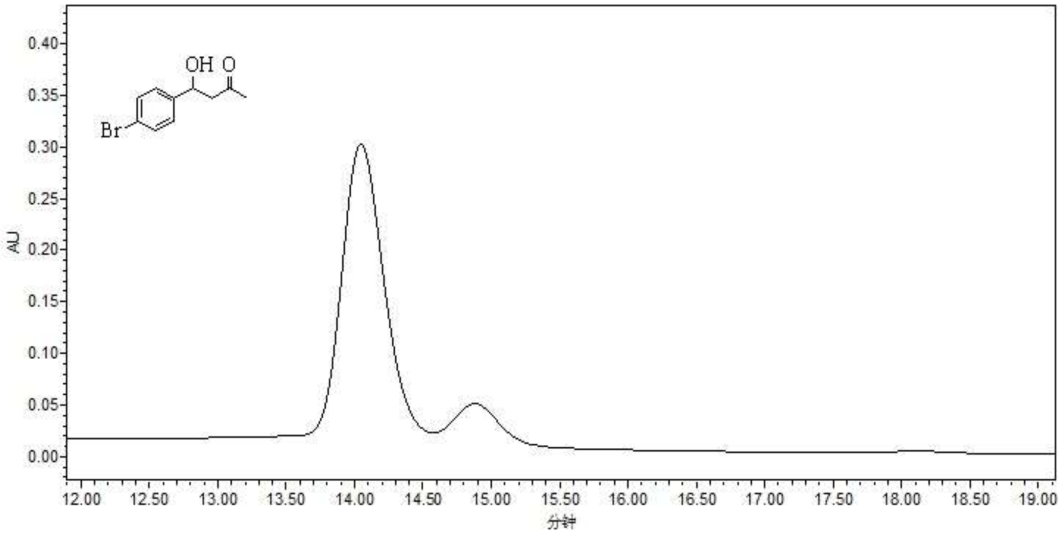

Fig. S31 HLPC of the as-obtained sample **10**

The aldol product **10** has been identified by ^{1}H NMR and ^{13}C NMR spectra (see Fig. S32 and S33).

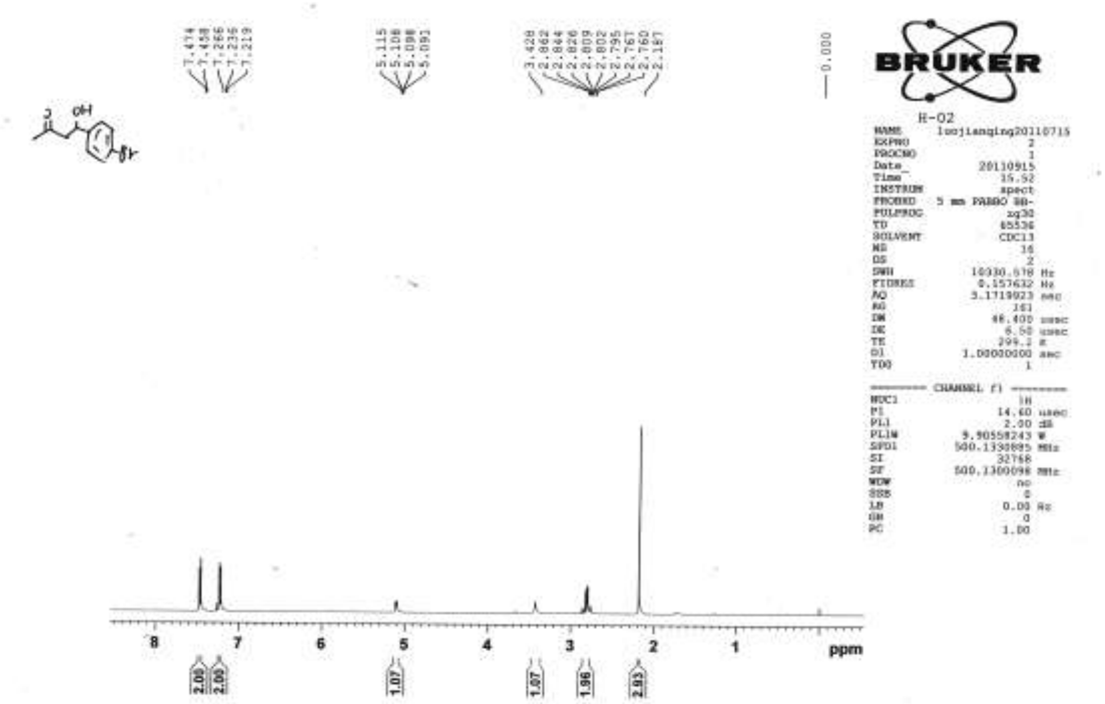

Fig. S32 ^{1}H NMR of the as-obtained product **10**

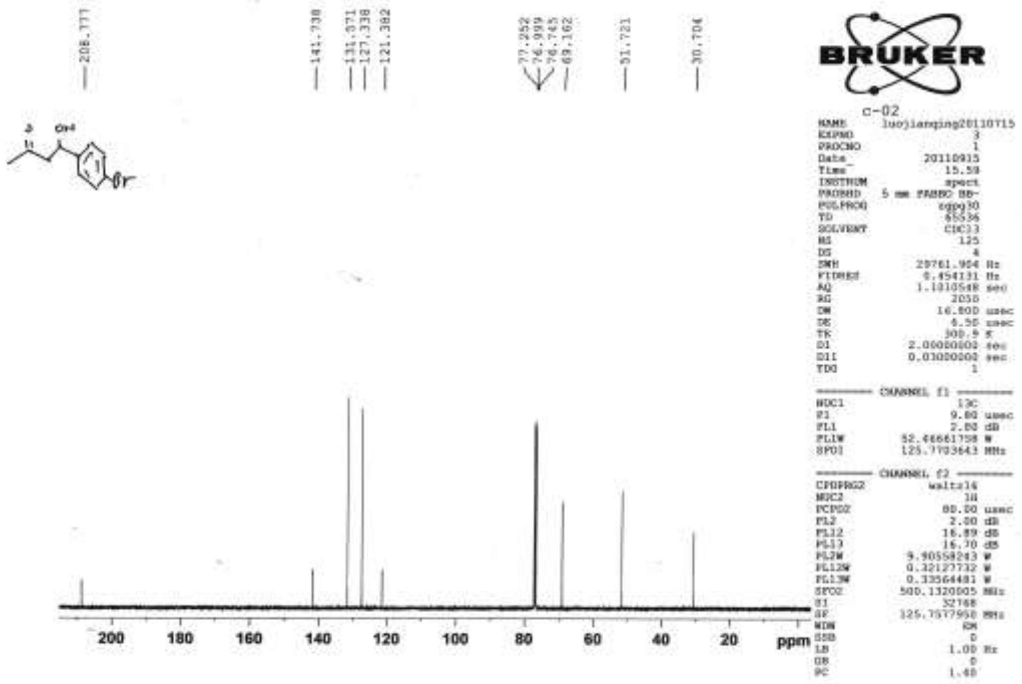

Fig. S33 ^{13}C NMR of the as-obtained product **10**

(4R)-(4-Acetamidophenyl)-4-hydroxy-2-butanone (11).

Enantiomeric excess (83% ee) was determined by HPLC with a Chiralpak AD column

(2-propanol/*n*-hexane = 10: 90 (V/V) eluent) UV 254 nm, flow rate 0.8 mL/min, major enantiomer t_R = 50.0 min and minor enantiomer t_R = 55.7 min (see Fig. S34 and S35).

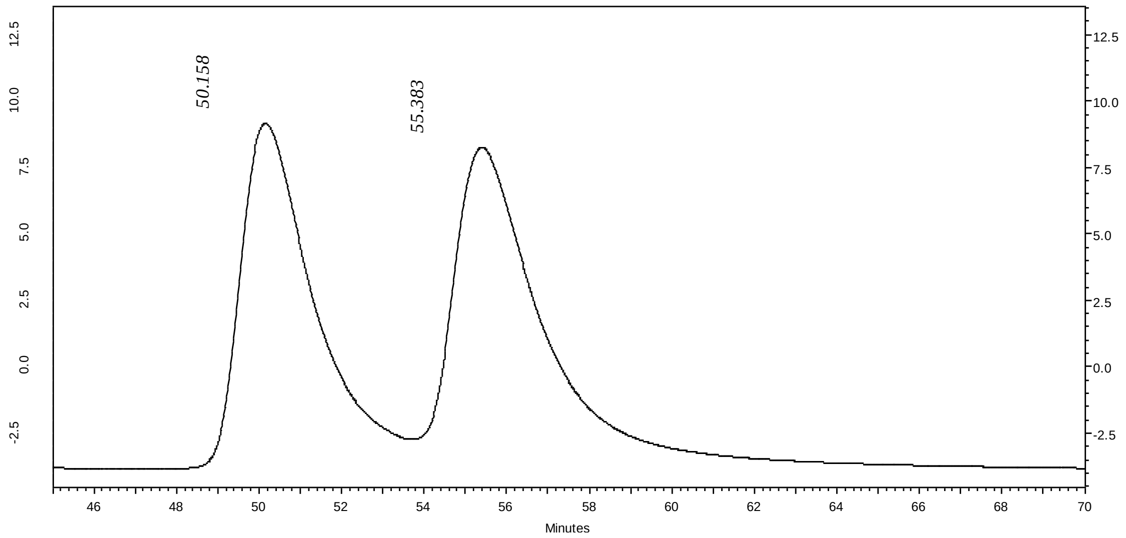

Fig. S34 HLPC of the authentic sample **11**

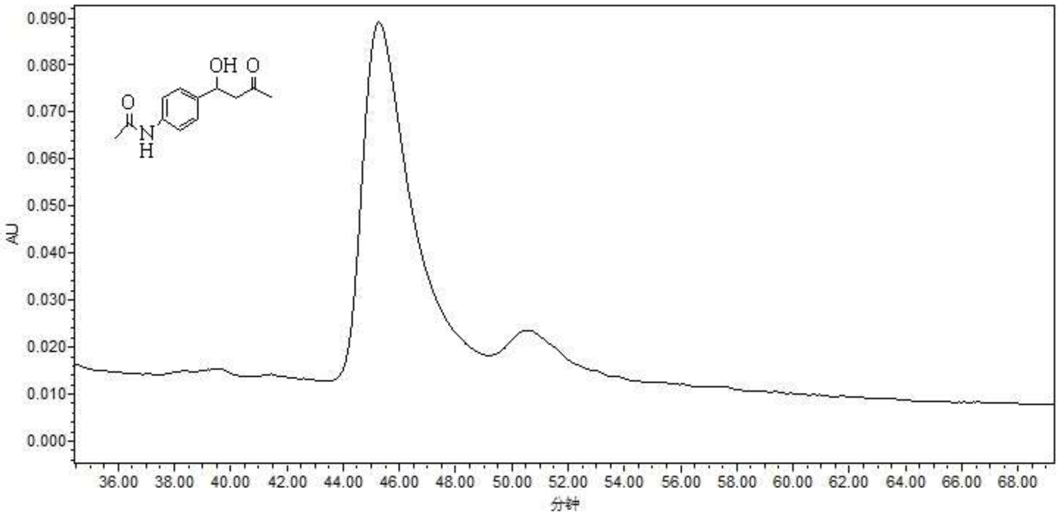

Fig. S35 HLPC of the as-obtained sample **11**

The aldol product **11** has been identified by ^{1}H NMR and ^{13}C NMR spectra (see Fig. S36 and S37).

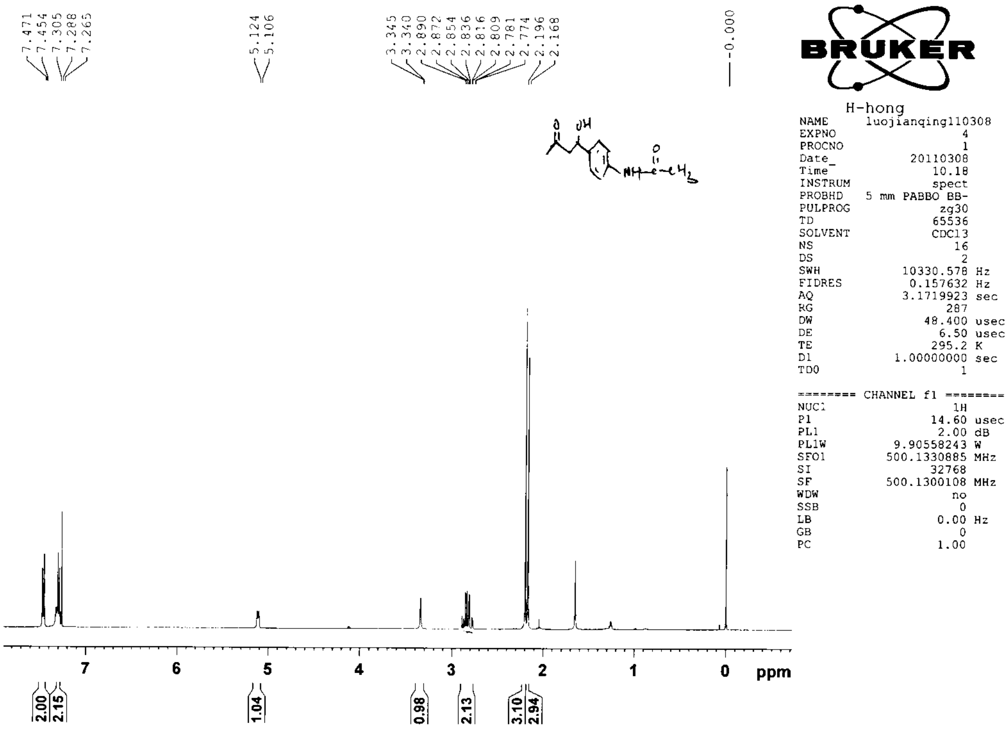

Fig. S36 ^{1}H NMR of the as-obtained product **11**

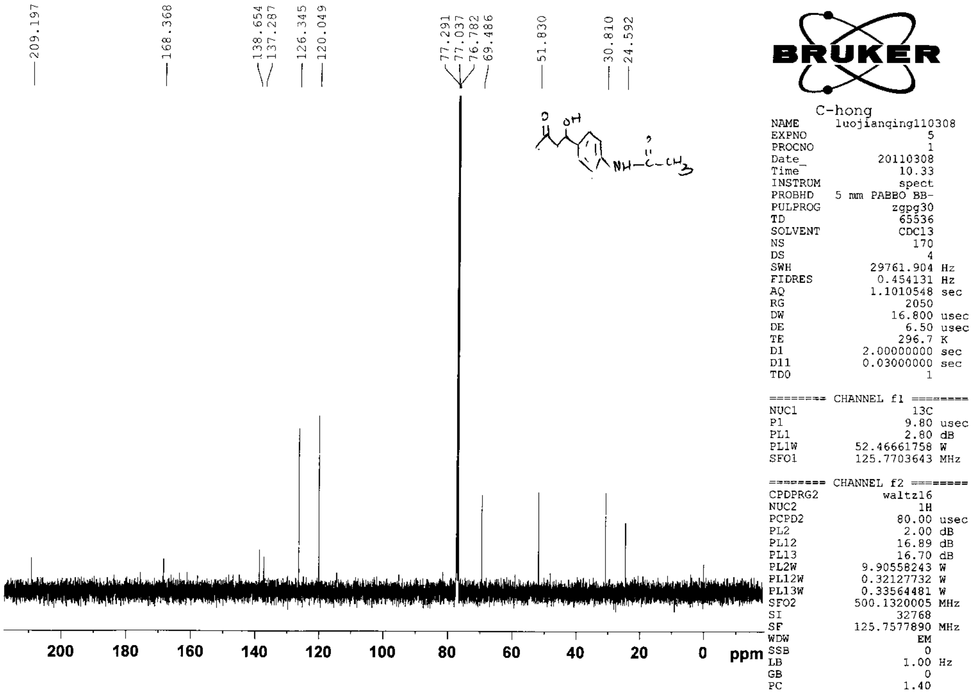

Fig. S37 ^{13}C NMR of the as-obtained product **11**

(4R)-Hydroxy-4-(2-naphthyl)-2-butanone (12).

Enantiomeric excess (83% ee) was determined by HPLC with a Chiralpak AD column (2-propanol/*n*-hexane = 7.5: 92.5 (V/V) eluent) UV 254 nm, flow rate 0.8 mL/min, major enantiomer t_R = 20.9 min and minor enantiomer t_R = 25.2 min (see Fig. S38 and S39).

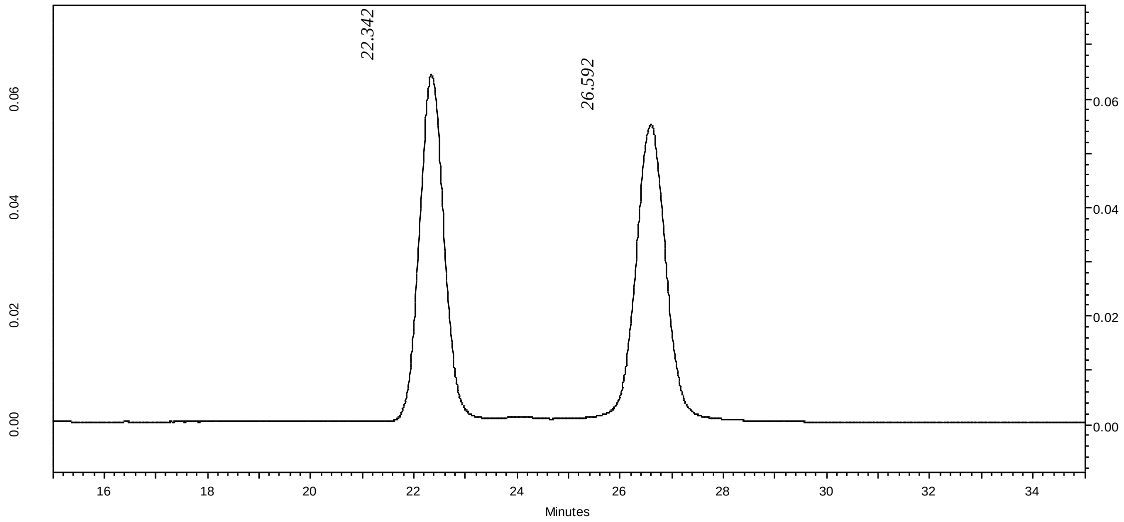

Fig. S38 HLPC of the authentic sample **12**

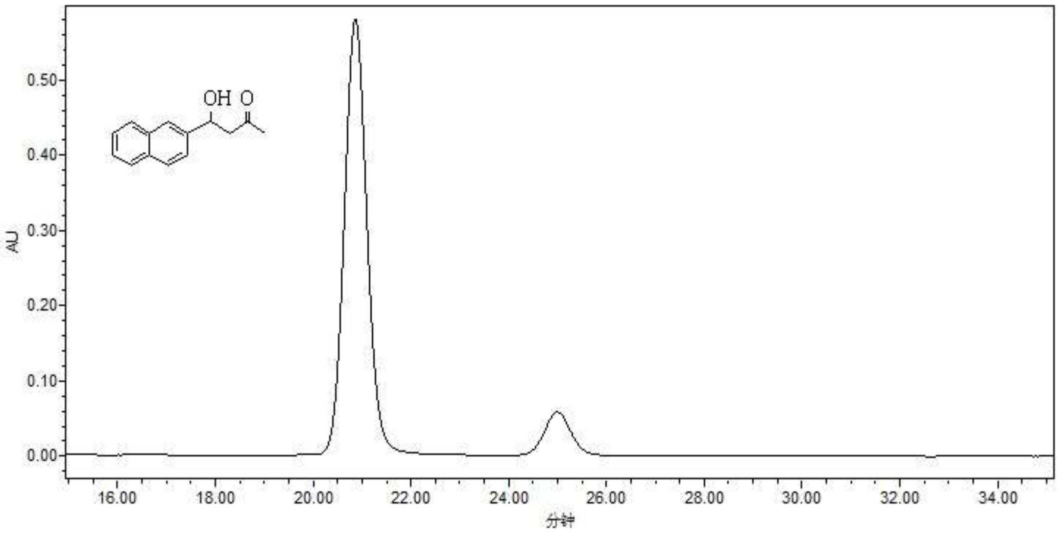

Fig. S39 HLPC of the as-obtained sample **12**

The aldol product **12** has been identified by ^{1}H NMR and ^{13}C NMR spectra (see Fig. S40 and S41).

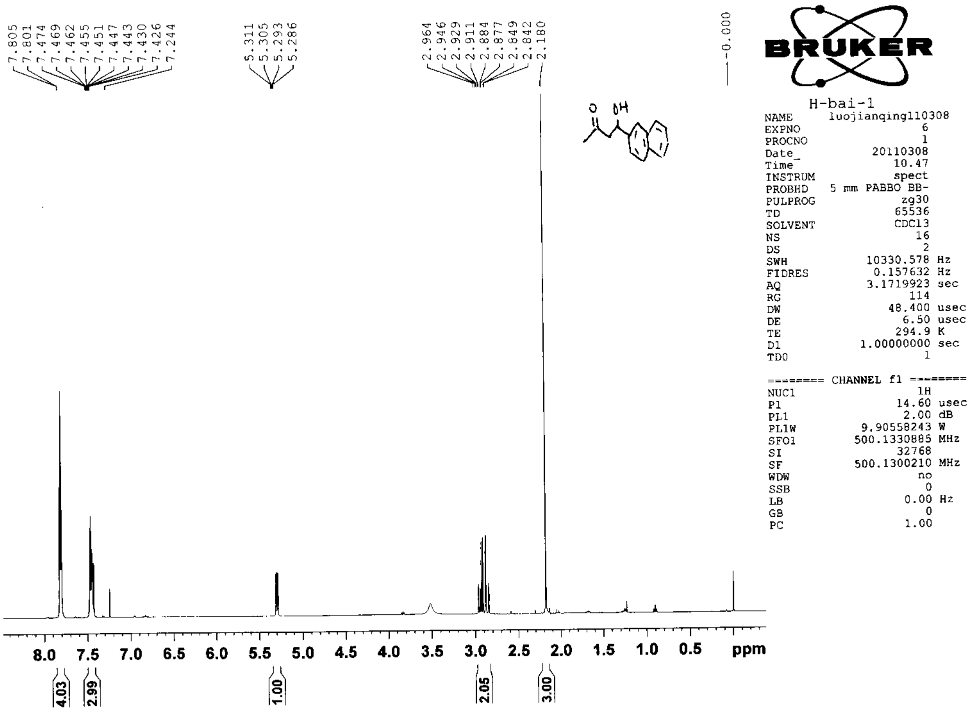

Fig. S40 ^{1}H NMR of the as-obtained product **12**

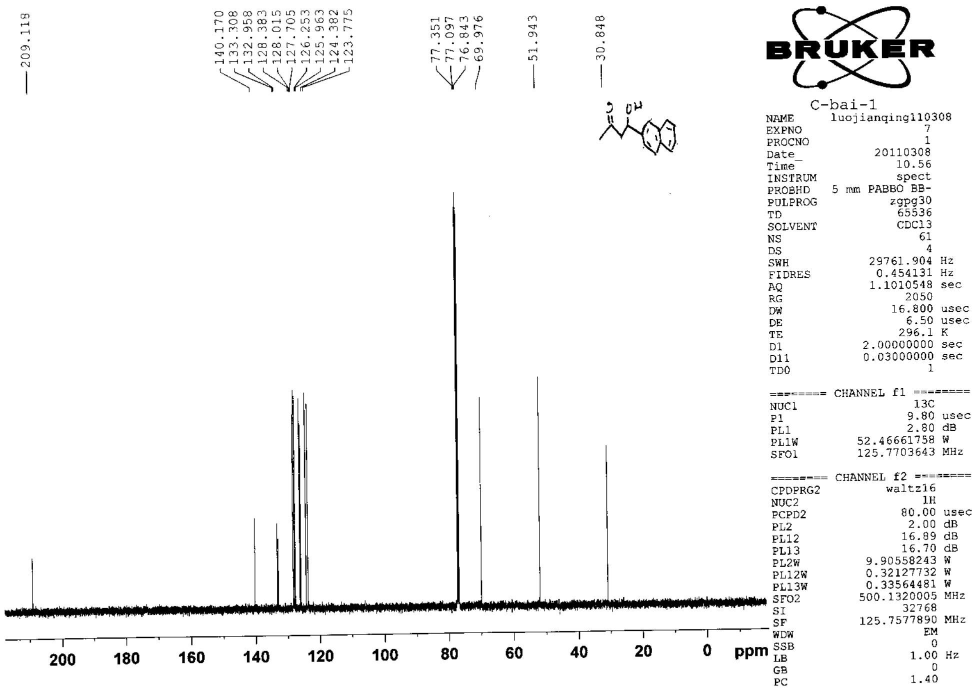

Fig. S41 ^{13}C NMR of the as-obtained product **12**

Characterization of Samples

TG-DTG curves

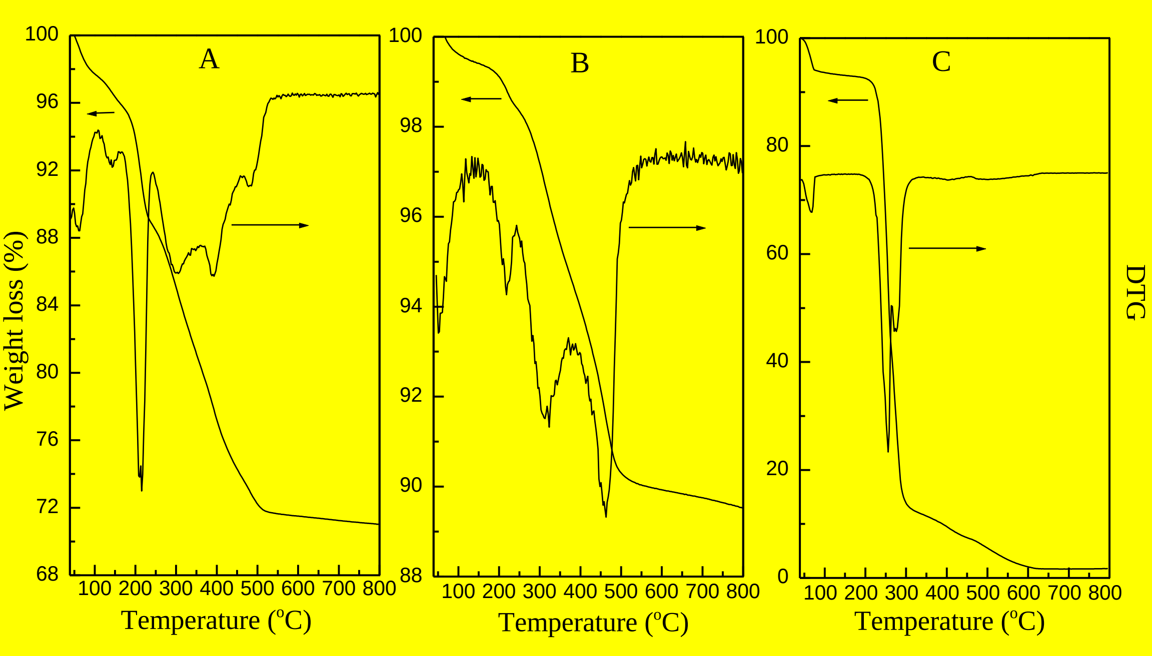

Fig. S42 Thermogravimetric and differential thermogravimetric curves of the **catalyst 1** (A), **catalyst 2** (B) and pristine L -proline (C).

References

[1] (a) G. Chen, X. Fu, C. Li, C. Wu and Q. Miao, *J. Organomet. Chem*. 2012, **702**, 19; (b) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc*. 2006, **128**, 734; (c) W. Miao and T. H. Chan, *Adv. Synth. Catal.* 2006, **348**, 1711; (d) M. Lombardo, F. Pasi, S. Easwar and C. Trombini, *Adv. Synth. Catal.* 2007, **349**, 2061; (e) S. V. Kochetkov, A. S. Kucherenko, G. V. Kryshtal, G. M. Zhdankina and S. G. Zlotin, *Eur. J. Org. Chem.* 2012, 7129.