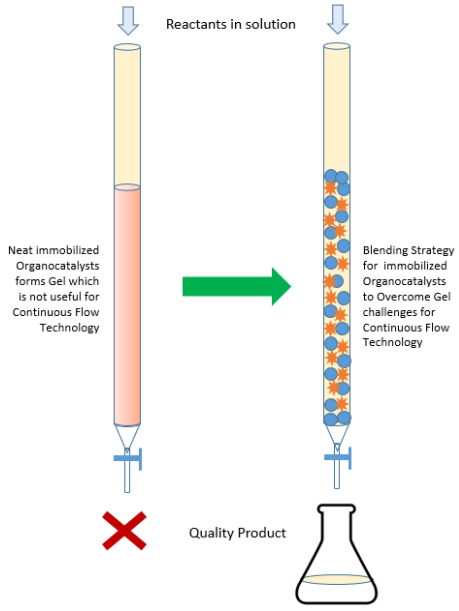
Chapter 4

L-proline based Sustainable Material for Continuous Flow Processes :



A case of Asymmetric Aldol Reaction

4.1 Introduction

Nowadays industrial vision towards sustainability and green processes preferred in alignment with 4th industrial revolution. Continuous flow technologies have lots of benefits, some of the benefits are (1) it increases the rate of production than batch processes due to avoiding intermediate operations (2) it is more safer than batch processes as reactions between molecules divided in to multiple small reactions through continuous column. Hence, chemical exposure to the person and potential risks are reduces (3) it makes ease to challenging operations for plant scale (4) it improves the product quality along with increase in the production rate because starting raw materials are converted in to product through the flow and the product is separated out from the output, side products formation are less compared to the batch process as the product molecule is not hold up for more time in the continuous flow, it has less probability to convert into side products or reactants (5) along with the economical perspective, it is sustainable because it reduces carbon footprint at every steps of the operations (Fig. 1).

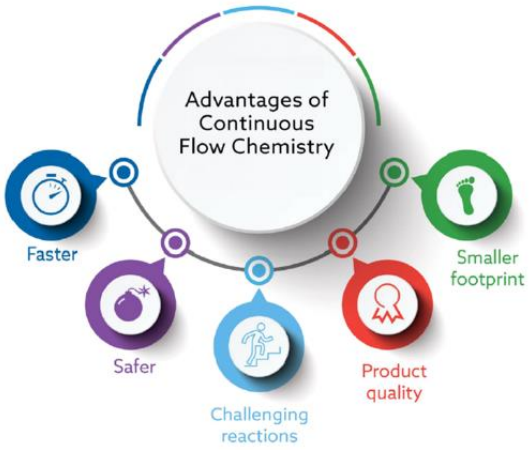


Fig.1. Strategic drivers for adoption of continuous flow approaches for synthesis of chemicals.[1]

Although it has lots of benefits than batch processes, the identification of opportunities to apply flow solutions to current processes is very critical to the success of this new continuous flow technology for pharmaceutical and fine chemical companies as per requirements of stringent operation conditions.

Generally, there are four types of continuous flow technology. (I) No catalyst system: it is a simple column or capillary which can be used for the reactions having no catalyst required. (II) Supported

reagent system: one of the reactant is supported on inert solid material which act as stationary phase in column. Remaining reactant/s pass through this stationary phase. At the output of the column, product is obtained. This type is also applicable for those reactions which has no requirement of catalyst. (III) Homogeneous catalyst system: it is quite similar with 'No catalyst system', the only difference is it has catalyst along with the reagents. One of the limitations is, catalyst will be present with the product. Additionally, catalyst separation process is applicable for this type of flow system. (IV) Heterogeneous catalyst system: it is the most important and broad application scope system among all these four systems. In this type, catalyst or immobilized catalysts supported materials used as a stationary phase. Reagents are passing through it and formed product at the output. There is no requirement of catalyst separation process and the product can be directly used for the next step of the operation. Describing the fourth type considering that no side product and without stringent conditions. Type IV (heterogeneous catalyst system) is regarded as the best method for continuous-flow synthesis. Heterogeneous catalysts without metal components is rarely reported for the continuous flow system (Fig. 2).

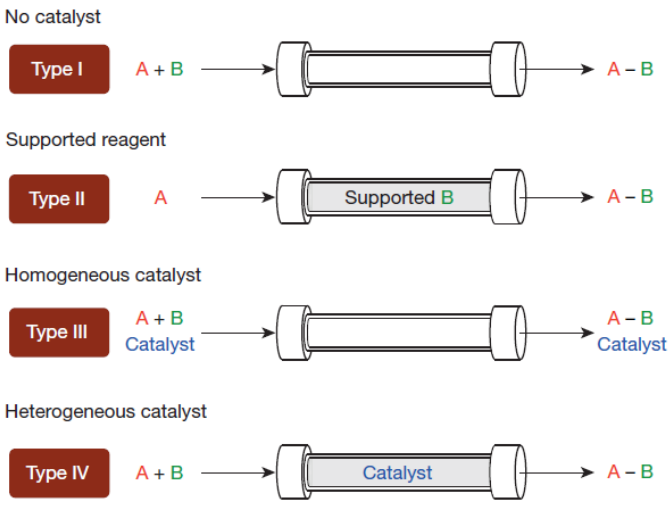


Fig. 2. Types of continuous flow systems.[2]

Proline is widely used and proven as an efficient catalyst for many asymmetric organic transformations. Proline and its derivatives are also make immobilized by metallic and polymeric supports for the purpose of easy recovery and recyclability of the catalysts. Metallic supported L-proline can be used for the flow process but there is challenge of leaching out the L-proline from the support. Polymeric supported L-proline has challenge of gel formation with most of solvents.

Here mentioned some examples of polymeric supported L-proline and its derivatives as an organocatalysts for recovery and recyclability purpose.

L. Gu et al. synthesized PEG supported L-proline for easy recovery of the catalysts in 2007. They reported Michael reaction of cyclohexanone and 2-nitrostyrene with 5 mole% of the catalyst, the products of the Michael reactions, reported 94% and high diastereo-selectivity up to 98:2 (*syn*:*anti)* (Fig. 3).[3]

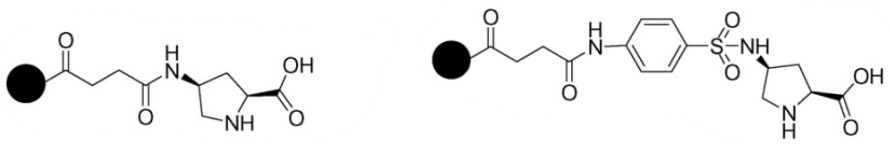


Fig. 3. PEG supported immobilized L-proline.[3]

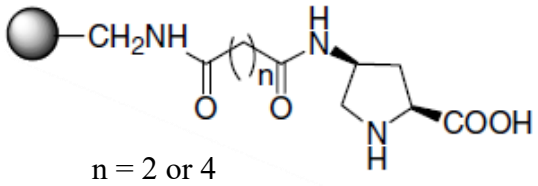


Fig. 4. Polystyrene supported immobilized L-proline.[4]

Y. -X. Liu et al. reported the linear polystyrene anchored L-proline as a catalyst for the Aldol reaction was evaluated in aqueous DMF and a ketone/water mixture. Good yields and high stereoselectivities, 94% yield, 96:4 (*anti: syn)* ratio, 96% ee in DMF: water (15:1) and 76% yield, 93:7 (*anti: syn)* ratio, 95% ee in ketone: water (1:1) mixture, obtained for the reactions of aromatic aldehydes with ketones. It was also reported that water could play a special role in improving the reactivity and stereoselectivity in the Aldol reaction (Fig. 4).[4]

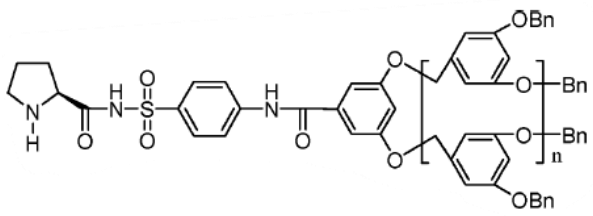


Fig. 5. Dendritic catalysts derived from N-prolylsulfonamide.[5]

Y. Wu reported in 2006 that the direct Aldol reaction of 4-nitrobenzaldehye and cyclohexanone catalysed by chiral dendritic catalysts derived from N-prolylsulfonamide gave the corresponding products in high isolated yields (up to 99%) with excellent *anti* diastereoselectivities (up to >99:1) and enantioselectivities (up to >99% ee) in water. In addition, the catalyst reused for at least five times without loss of catalytic activity (Fig. 5).[5]

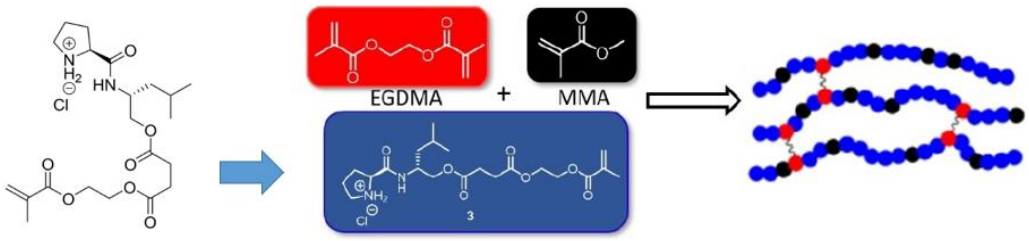


Fig. 6. Components of polymer gel. Methyl methacrylate (MMA), ethylene glycol dimethacrylate (EGDMA) as cross-linker and the catalyst.[6]

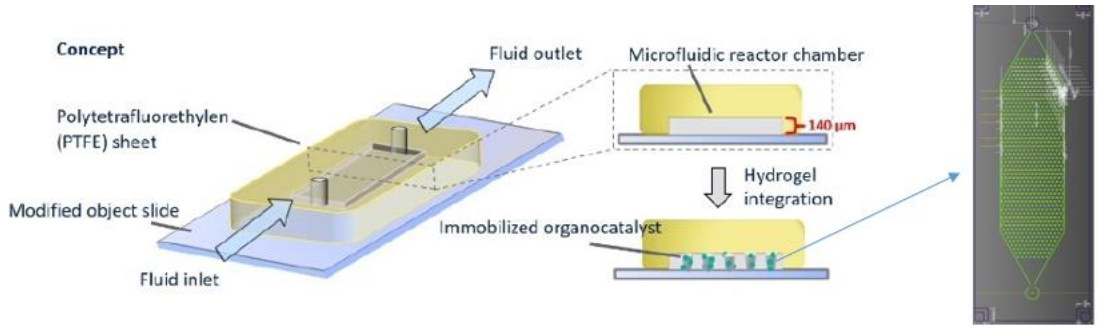


Fig. 7. Schematic diagram of gel-bound organocatalyst with micro-fluid reactor for continuous flow technology.[6]

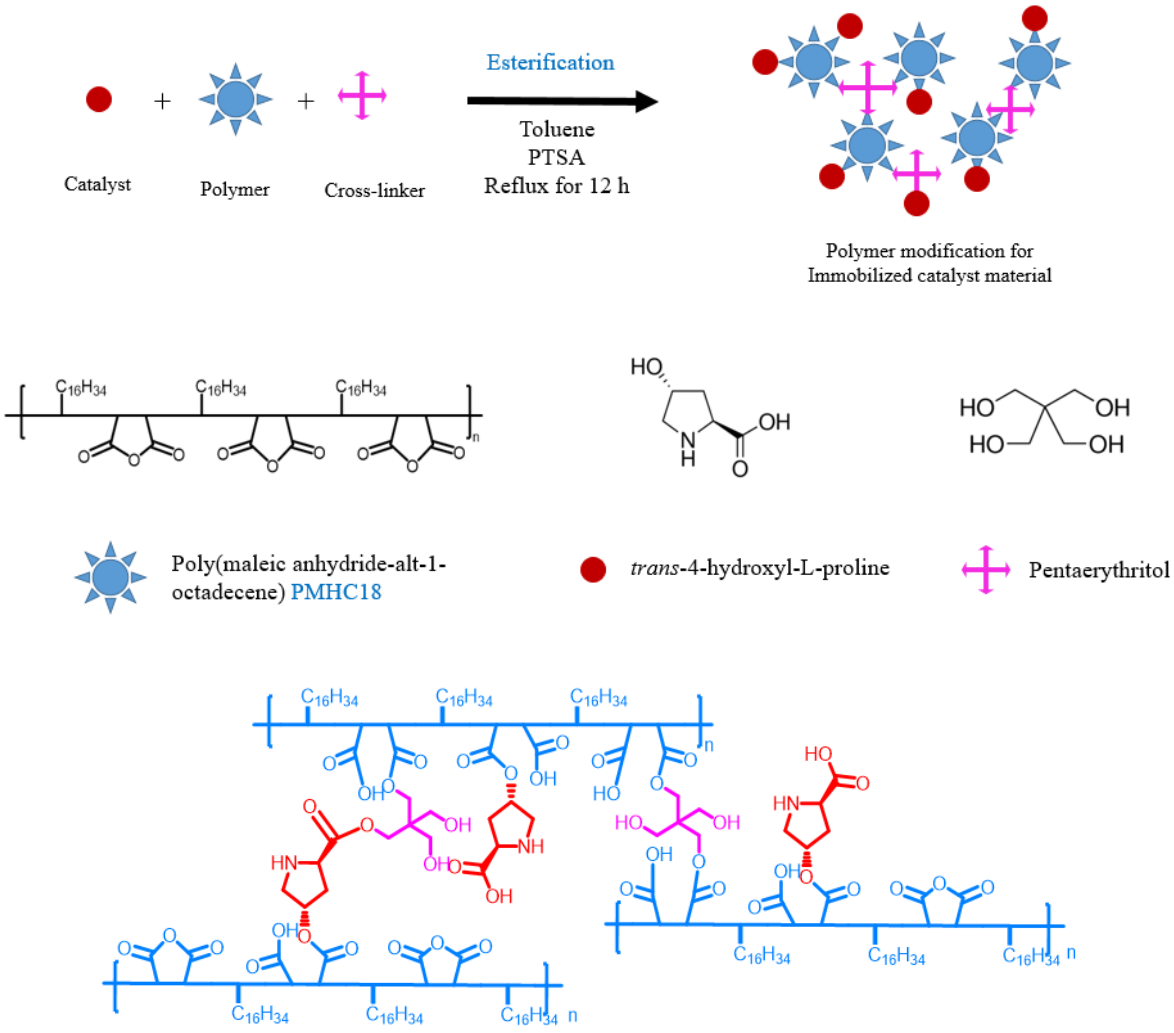
Recently in 2021, C. J. Schmiegel et al. reported direct asymmetric Aldol reaction of 4-nitrobenzaldehyde and cyclohexanone in continuous flow using gel-bound organocatalyst with micro-fluid reactor. They reported Aldol reaction of 4-nitrobenzaldehyde and cyclohexanone with DMSO: water (9:1) at room temperature for 144 h in continuous flow method. They obtained 95% conversion with *syn: anti* ratio 33:67 (Fig. 6 and 7).[6] Immobilized L-proline polymers as organocatalysts are rarely reported for continuous flow system due to challenge of gel formation with solvents. It is very technically challenged task for using gel for continuous flow method as it requires high pump pressure and other challenges of operations. In this study, we design immobilized-L-proline material PMHC18-L-pro-CL and blended with other stable and inert material for the overcome the gel formation challenges for continuous flow techniques.

4.2 Experimental

Materials

Poly (maleic anhydride-alt-octadecene; PMHC18), p-toluene sulfonic acid (PTSA) were purchased from Sigma Aldrich Ltd and 4-hydroxy-L-proline and azobis-isobutyronitrile (AIBN) from Loba Chemie Pvt. Ltd. Toluene and dimethylsulfoxide (DMSO) were procured from S. D. Fine chemicals. Sawdust were collected from local saw mill. Other solvents were purchased from Loba Chemie. All the materials and solvents were used as received.

Synthesis of cross-linked polymeric immobilized L-proline (PMHC18-L-pro-CL)



PMHC18-L-pro-CL

Scheme 1: Strategy to design polymeric supported immobilized-L-proline.

15 g of PMHC18 polymer was added in 75 mL of toluene in a 250 mL round bottom flask, stirred with magnetic bar and heated to 80 ºC in an oil bath. To this solution, 5.44 g 4-hydroxy-L-proline and 3 g of p-toluene sulfonic acid were added. Then, 0.75 g of pentaerythritol was introduced as a cross-linker in the solution. Reflux condition was set by increasing the reaction temperature to 120 ºC and maintained the same for 24 h. The light pink cross linked polymer appear to settle at the bottom of the flask was isolated from the supernatant liquid. The powder was washed with toluene followed by methanol to remove the unreacted reactants and dried in oven at 80 ºC. Free flow dried powder obtained was used for the characterization and as a catalyst for the model Aldol reaction (Scheme 1).

Pre-treatment of sawdust

50 g of raw sawdust taken in a petri dish to spread and remove bigger particles from it. The material was transferred in a 500 mL of beaker and added water into it. It was stirred for 5 min. and filtered through 100 micron mesh to remove fine particles. This process was repeated for five times. The wet material further treated with 50 mL of DMSO and filtered it. This DMSO treatment was repeated for 3 times to remove unwanted stuffs from sawdust. DMSO was chosen as a treatment part as it was going to be used for the mobile phase for the continuous flow process. Then the treatment followed by methanol and acetone to washed out organic impurities. The treated wet material was dried in oven at 60-120 ºC. Dried pre-treated sawdust was used as blending material with PMHC18-L-pro-CL.

Establishing the model Aldol reaction by continuous flow process

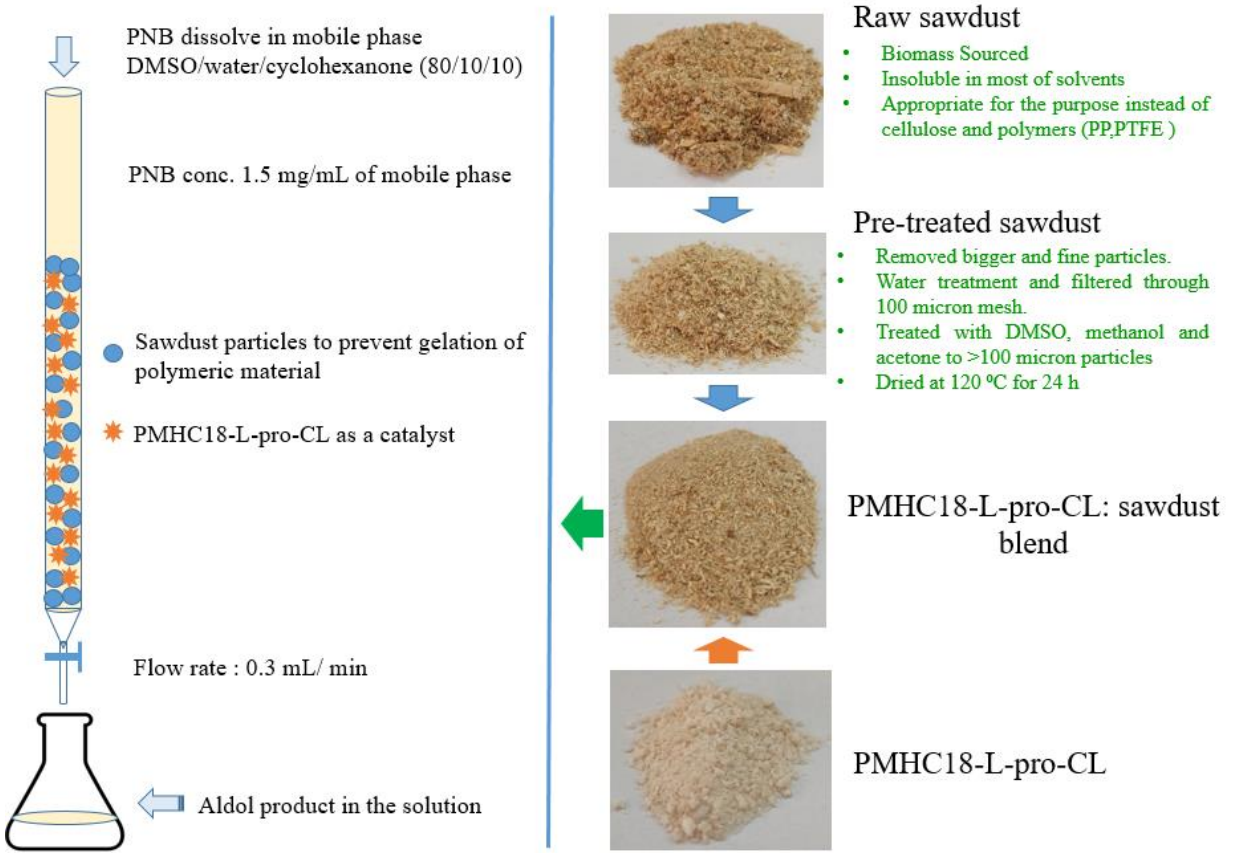


Fig. 8. Preparing continuous flow experiment by using saw dust as a blending material.

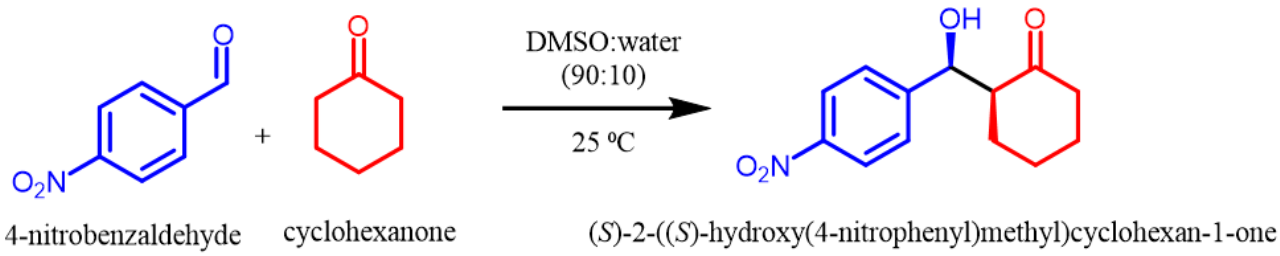
6 g of PMHC18-L-Pro-CL was blended with 6 g of pre-treated sawdust with 50:50 or other blending compositions. Blending was carried out by using rotary equipment for making the homogenous mixture. This blended mixture was used as a stationary phase for the continuous flow process experiment. Column was compactly packed with the blended material by mechanical tapping. The reaction mixture was prepared in a conical flask having 40 mL of dimethylsulfoxide, 5 mL of water, 5 mL of cyclohexanone and 75 mg of p-nitrobenzaldehyde (PNB) which was acted as a mobile phase for the continuous flow. The mixture was stirred until clear transparent solution obtained. The purpose of addition of water to the reaction mixture was to maintain the polarity of the stationary phase to avoid gel formation. The reaction mixture was passed through the above prepared packed column and flow was adjusted by the gravitational force (0.3 mL/min) without using external pumping system (Fig. 8). The Aldol product was monitored by TLC. Chiral HPLC

analysis of the reaction mixture was done at the end of the column. The product was isolated by column chromatography using petroleum ether/ethyl acetate (80:20).

Model Aldol reaction by batch process in presence of PMHC18-L-pro-CL

75 mg of p-nitrobenzaldehyde was added in a solution of 2 mL of dimethylsulfoxide, 0.5 mL of cyclohexanone and 0.5 mL of water (70:15:15), in a RBF having 25 mL capacity. 50 mg of PMHC18-L-Pro-CL was added as a catalyst for the batch process. The reaction mixture was stirred for 24 h at RT. The Aldol product monitored on TLC plate and isolated by column chromatography by using petroleum ether/ethyl acetate (80:20). The isolated product was used for characterization.

4.3 Results and Discussion



Scheme 2. The model Aldol reaction for continuous flow process.

Table 1. Optimization of solvent system for the model Aldol reaction through batch process.

Sr. No.	Solvent	Reaction system	Catalyst[a] (mole%)	Time (h)	Yield (%)[b]	dr[c] *(syn:anti)*	ee (%)[d]
1	DMSO	homogeneous	PMHC18-L-Pro-CL	24	60	93:7	13
2	water	emulsion*	PMHC18-L-Pro-CL	48	-	-	-
3	-	homogeneous	PMHC18-L-Pro-CL	48	-	-	-
4	DMSO	homogeneous	PMHC18	48	-	-	-
5	DMSO	homogeneous	Pre-treated sawdust	48	-	-	-

*[a] calculated as considering 30 mole% of L-hydroxyl proline loaded in the catalyst [b] isolated yield [c] determine from ^{1}H NMR [d] calculated from chiral HPLC analysis * Emulsion of cyclohexanone and water (w/o).*

Before applying PMHC18-L-pro-CL for the continuous flow process. It was required to observe the catalyst effectiveness in the batch process for the optimization of the reaction conditions. The synthesized material was used as a catalyst for the model Aldol reaction between p-nitrobenzaldehyde and cyclohexanone in dimethylsulfoxide as a solvent for 24 h at RT. It resulted 60% yield having 93:7 dr (*syn:anti*) and 13% ee (Table 1, entry 1). It was observed that the catalyst was effective to catalyze the model Aldol reaction and its catalytic site available for the interactions are responsible for the outcome. The catalyst was not showing its effect without DMSO solvent (Table 1, entry 2 and 3). During the batch process, it was also observed that the cross-linked polymeric catalysts formed gel in DMSO solvent. The gel behavior of PMHC18-L-pro-CL was also studied in different solvents. It was observed that gel was formed with different non-polar solvents like chloroform, dichloromethane, ethyl acetate, hexane, cyclohexane, and cyclohexanone. However, it was stable with the polar solvents like water, methanol, acetone, and dimethylsulfoxide. The control experiments were also carried out with PMHC18 and laboratory treated saw dust separately to confirm the effect of the catalyst on the model Aldol reaction (Table 1, entry 4 and 5).

Table 2. Optimization of parameters for the continuous flow process for the model Aldol reaction.

Sr. No.	Solvent	System	PMHC18-L-pro-CL:sawdust	Time (h)	Yield[a] (%)	dr[b] (*syn:anti*)	ee[c] (%)
1	DMSO	Batch process	100:0	24	60	93:7	13
2	DMSO:water	Continuous flow	70:30	No flow	-	-	-
3	DMSO:water	Continuous flow	50:50	1 run	99	97:3	92
4	DMSO:water	Continuous flow	30:70	3 run	99	97:3	91
5	Methanol:water	Continuous flow	70:30	8 run	40	97:3	20

[a] isolated yield [b] determine from ^{1}H NMR [c] calculated from chiral HPLC analysis.

PMHC18-L-pro-CL as such forms gel with cyclohexanone. Hence, avoiding the hindrance in the flow of the mobile phase through the column, the PMHC18-L-pro-CL was blended with the treated saw dust which make the ease in the flow of the mobile phase simultaneously increases the free volume of the material. Saw dust was selected as the blending material as it serves many purposes

like (i) it is generated as a waste in the saw mill (ii) it is a bio-sourced and non-toxic material (iii) it is an inert material to satisfy the requirement of the process like it must be insoluble and stable in most of solvents (iv) there are also some synthetic polymers available like polytetrafluoroethylene (PTFE), polypropylene (PP) which can fulfill these requirements, however, they are costly and environmentally not advisable (v) cellulose is also one of the green sourced material for the purpose but, it forms very fine particles and it is a second layer green sourced material as it is the processed product of bio-mass.

For the composition of PMHC18-L-pro-CL:sawdust (70:30), it was challenge to make a flow of the mobile phase from the packed column. The flow was effectively set for the 50:50 composition and the model Aldol product observed with complete conversion of p-nitrobenzaldehyde on TLC plate in a single run of the mobile phase. The model Aldol product found with 99% conversion, 92% ee and 97:3 *syn:anti* dr. To optimize the catalyst effectiveness, the composition was changed to 30:70 ratio and it required three complete cycles of the mobile phase to run through the column to complete the reaction. It took place with 99% conversion having 91% ee and 97:3 *syn:anti* dr. Towards the more sustainable approach, DMSO was replaced with methanol. However, it required multiple runs (eight runs) of the mobile phase resulting 40% conversion, 97:3 *syn:anti* dr and 20% ee (Table 2). From the experimental data, batch process and methanol based continuous flow process showed lower conversion and stereoselectivity. In the case of batch process, insufficient number of the catalytic sites available compared to the continuous flow process. While alcohol based process having more compacted PMHC18-L-pro-CL has less interacting catalytic sites due to high polarity of the mobile phase, responsible for the less conversion and more reaction time also affect the stereoselectivity due to epimerization of the product.

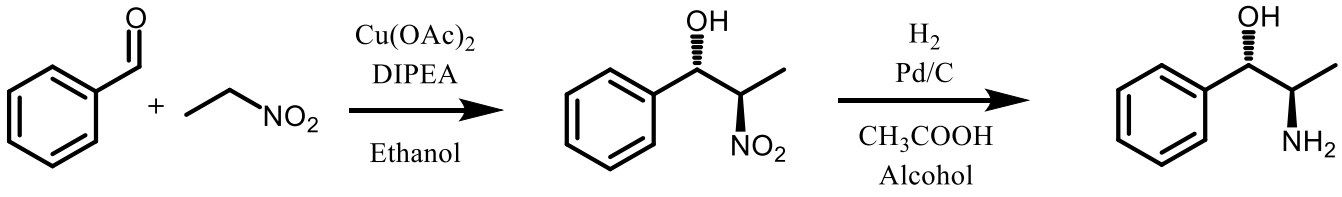
Table 3. Catalyst recyclability for the model Aldol reaction in continuous flow process under the optimized conditions (Table 2, entry 3).

No. of catalytic cycle	Yield[a] (%)	dr[b] *(syn:anti)*	ee[c] (%)
1	99	97:3	92
2	99	97:3	91
3	99	97:3	97
4	99	97:3	97
5	99	97:3	97

[a] Isolated yield [b] determined from ^{1}H NMR [c] calculated from chiral HPLC analysis

The recycling experiments were carried out for five times by following the process mentioned in Table 2, entry 3 for continuous flow system. It was observed that the system was capable to produce the model Aldol product without affecting the %conversion (99%) and stereoselectivity (97%) (Table 3).

4.4 Applications of similar continuous flow process reported in the literature



Norephedrine

Scheme 3. Synthesis of Norephedrine by continuous flow process. [7]

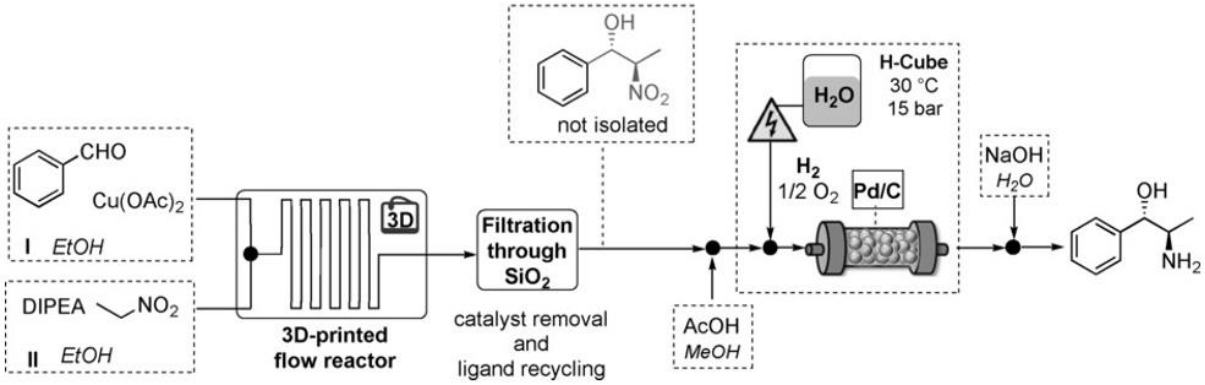


Fig. 9. Continuous flow process diagram for Norephedrine synthesis. [7]

Norephedrine is generally synthesized by Nitro-Aldol reaction also known as Henry reaction followed by the reduction of nitro functional group to amine (Fig. 8). It is used as a decongestant and appetite suppressant drug. This drug synthesis process is reported with type III (homogeneous system) continuous flow process as mentioned in introduction section. As per reported process, metal based catalyst was separated by filtration through SiO_2 bed. The filtered product solution was further used for the next step of reduction without isolating the product (Fig. 9). The as-synthesized catalyst PMHC18-L-pro-CL, application for continuous flow process have potential to improve the reported process of Norephedrine. It may improve it by two ways (i) it requires less reagent (ii) eliminating the catalyst removal step from the operation. The second step, reduction of nitro group, would be same as the reported process.

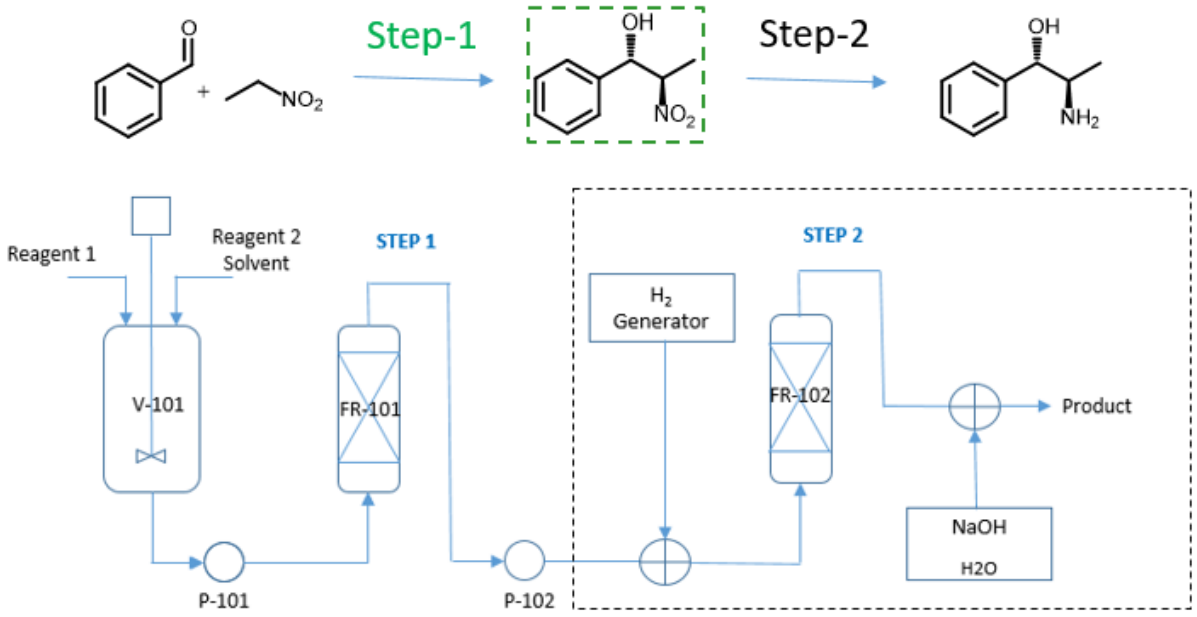


Fig. 10. Proposed process flow diagram of continuous flow for Norephedrine.

Based on this reports, we propose the flow diagram for the synthesis of Norephedrine with PMHC18-L-pro-CL, an organocatalyst for type-IV continuous flow system (Fig. 10). There are possibilities to synthesize Nitro-Aldol reaction based drugs like Metaraminol, Methoxamine, Levonordefrine, etc. similar to Norephedrine (Fig. 11).[7]

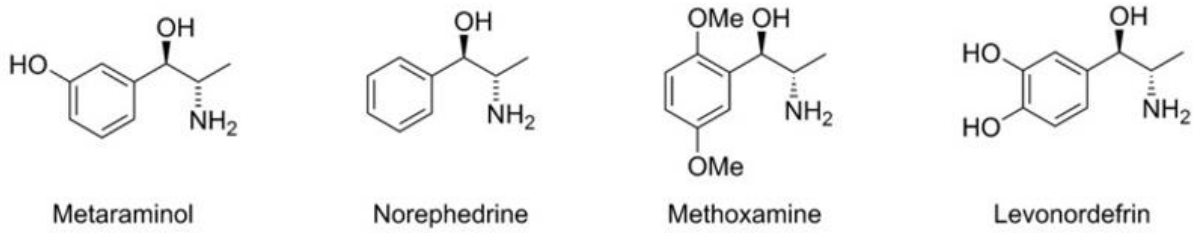


Fig. 11. Examples of APIs synthesized by Nitro-Aldol reaction.[7]

Multi Tubular Packed Bed Reactor: Estimation for Industrial Scale [11-14]

Based on the optimized reaction parameters and experimental set up conditions, we did the chemical engineering calculations and estimated the number of tubes required for the large scale production of model Aldol product by the continuous flow process.

Experimental set up parameters:

- Bulk volume occupied by the catalyst bed : 37 cm3
- Flow rate : 0.3 mL/min
- Hold up volume : 16 mL
- Porosity of bed ; 16/37 = 0.432
- Residence time : volume / flow rate = 16/0.3 = 53.33 min (considering 100% conversion)
- Density of the catalyst : mass/volume = 11/37 = 0.297 g/mL

If scale up capacity = 500 ton/annum (for working days = 330 days)

Production rate: (500*1000)/(330*24) = 63.13 kg/h

Assuming the production rate: 70 kg/h

Reactant mass flow rate from the stoichiometry = Mol. wt. of limiting reactant* Production rate/Mol.wt. of the product

= (151.12*70000)/249.27 = 42437.51 gm/h = 43 kg/h

As per experiment, the amount of limiting reactant (4-nitrobenzaldehyde) in kg/h for 0.3 mL/min flow rate = $2.7* 10^{-5}$ kg limiting reactant in 18 mL for 1 hour.

Catalyst amount, 5 g = 0.005 kg

Proportionality constant $M_w/ M_f = C_p$ = (kg of catalyst/ kg of limiting reactant in kg/h) =

$= 0.005/ 2.7*10^{-5} = 185.18$

Mass of catalyst require for the commercial scale = C_p * 43 kg/h = 185.18* 43= 7962 kg

The volume of catalyst based on density = mass/ density = 7962/297 = 26.8 m^3

Volume of catalyst for scale up

$V_1 = \pi/4 * D^2* h$

considering, column height 7 m, diameter will be 2.21 m

Total cross sectional area (A_1) = $\pi/4 * D^2 = \pi r^2 = 3.83$ m^2

Considering 10 cm = 0.1 m diameter for each tube, cross section area of each tube will be

$A_2 = \pi/4 * D^2 = 0.00785$ m^2

Number of tubes required = A_1/A_2 = 3.83/0.00785 = **488 Tubes**

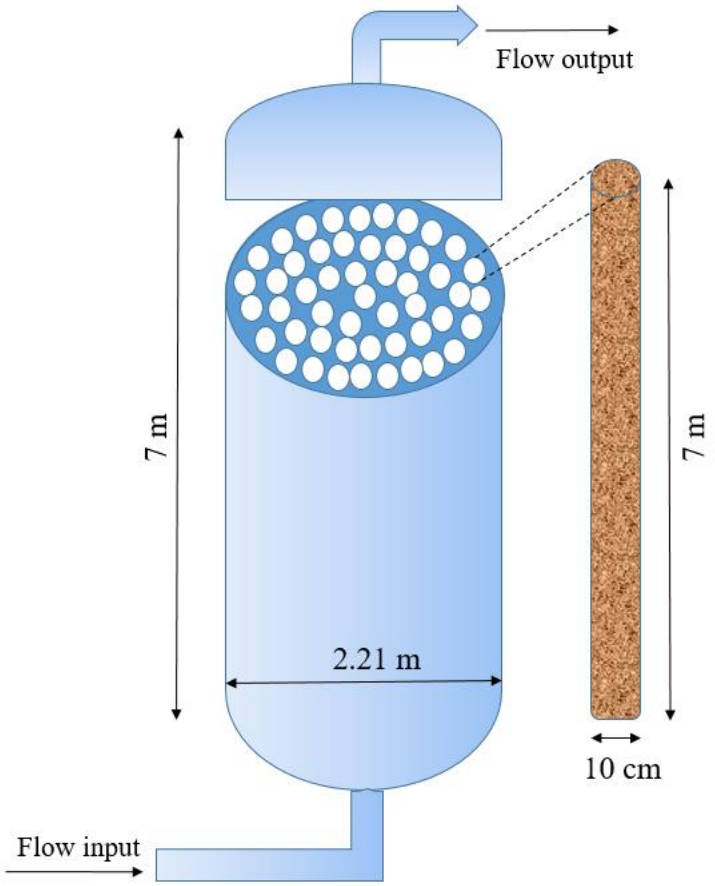


Fig. 12. Multi tubular packed bed reactor graphical design for industrial scale production of the model Aldol product.

4.5 Conclusion

Polymer based immobilized L-Proline with cross linking strategy (PMHC18-L-pro-CL) effectively works for the model Aldol reaction. Aqueous DMSO observed the most suitable solvent for PMHC18-L-Pro catalysed Aldol process. Strategy regarding the blending of saw dust with the synthesized cross-linked polymer (PMHC18-L-pro-CL) for continuous flow system, found successful for the model Aldol reaction. Continuous flow process showed better results in terms of stereoselectivity and conversion than batch process. Recyclability and effectiveness of the catalyst validated for five times with consistency. This process could be explored for the synthesis of APIs like Norephedrine etc. It has also potential to explore further for industrial scale production with a sustainability point of view.

4.6 Characterization

PMHC18-L-pro-CL: FTIR (cm^{-1}): 2923, 2853 (C-H stretching), 1852 (C=O Anhydride), 1783 (C=O Ester), 1727 (C=O Acid), 1637 (N-H bending), 1595 (C-N bending). 46 % of L-hydroxy proline linkage determined by elemental analysis. 75 % crosslinking of the chains determined by Titration method. Thermal stability of the cross linked polymer increases from 215 ºC to 260 ºC and PMHC18-L-pro-CL Phase transition was not significantly observed at 132 ºC by TGA and DSC analysis which was observed in PMHC18.

4.6.1. Characterization of PMHC18-L-pro-CL

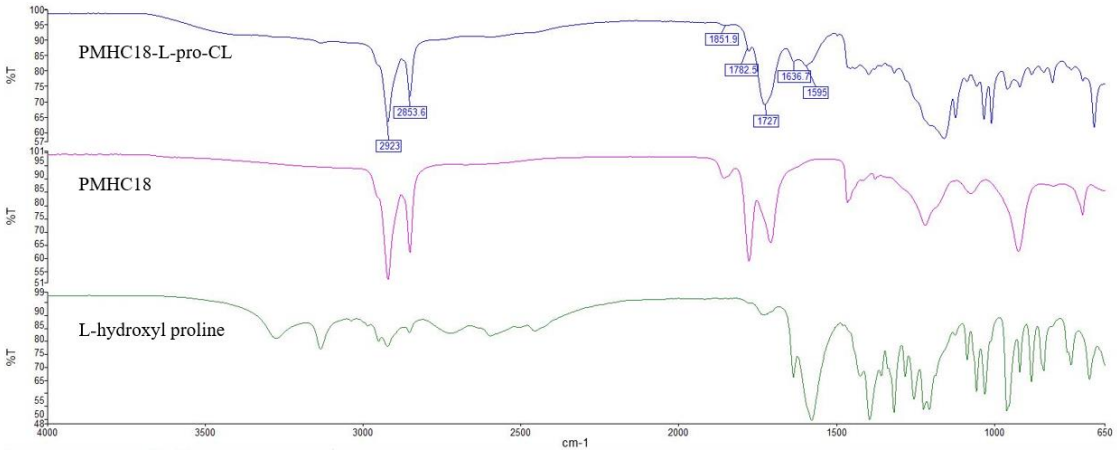


Fig. S1. FTIR Analysis of (a) PMHC18-L-pro-CL and its comparison with (b) PMHC18 and (c) L-hydroxy proline.

Table S1. Elemental analysis of PMHC18-L-pro-CL.

SAMPLE	%N	%C	%H
4-Hydroxyl L-Proline	10.64	45.91	7.09
PMHC18	0.00	72.15	10.82
PMHC18-L-Pro-CL	4.93	57.13	8.80

% Proline linkage in PMHC18-L-Pro-CL**: 46.16 %***

**Calculation From on basis of %N present in the compound*

Table S2. Acid number analysis of PMHC18-L-pro-CL.

Polymer	Acid Number[#]	% non-cross linkage	Remarks
PMHC18	256	100	Soluble in $CHCl_3$
PMHC18-L-Pro-CL	63	24.61	Insoluble in $CHCl_3$

%Cross-linkage in PMHC18-L-Pro-CL = **75.39 %***

[#] KOH mg/g of sample * *Insoluble material in solvent was considered as cross-linked material.*

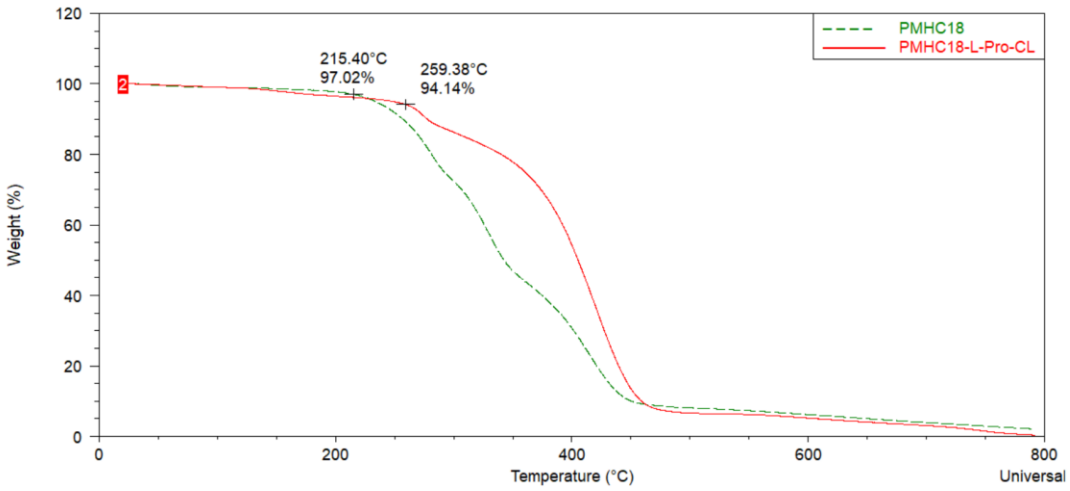


Fig. S2. TG analysis of PMHC18-L-Pro-CL and PMHC18.

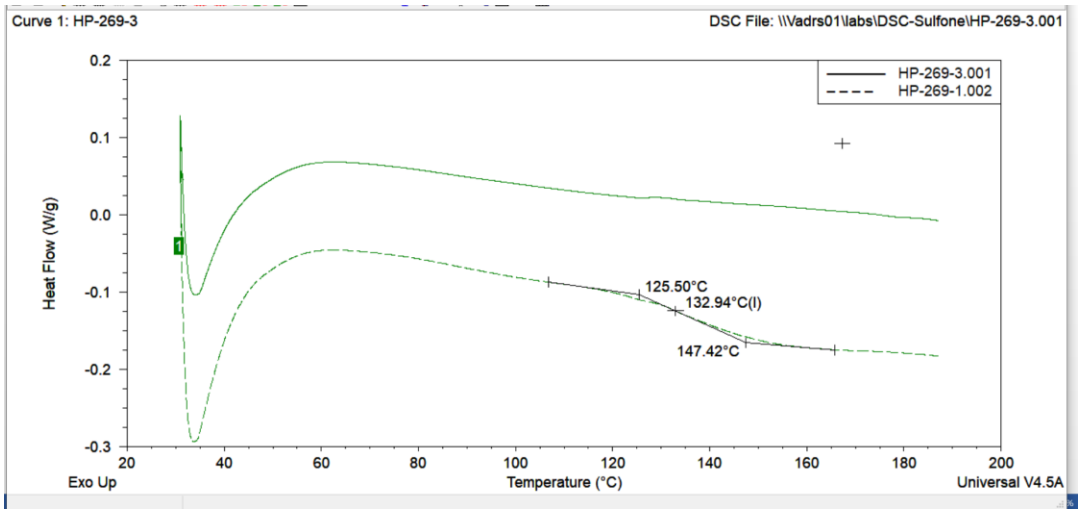


Fig. S3. DSC analysis of PMHC18-L-Pro-CL and PMHC18.

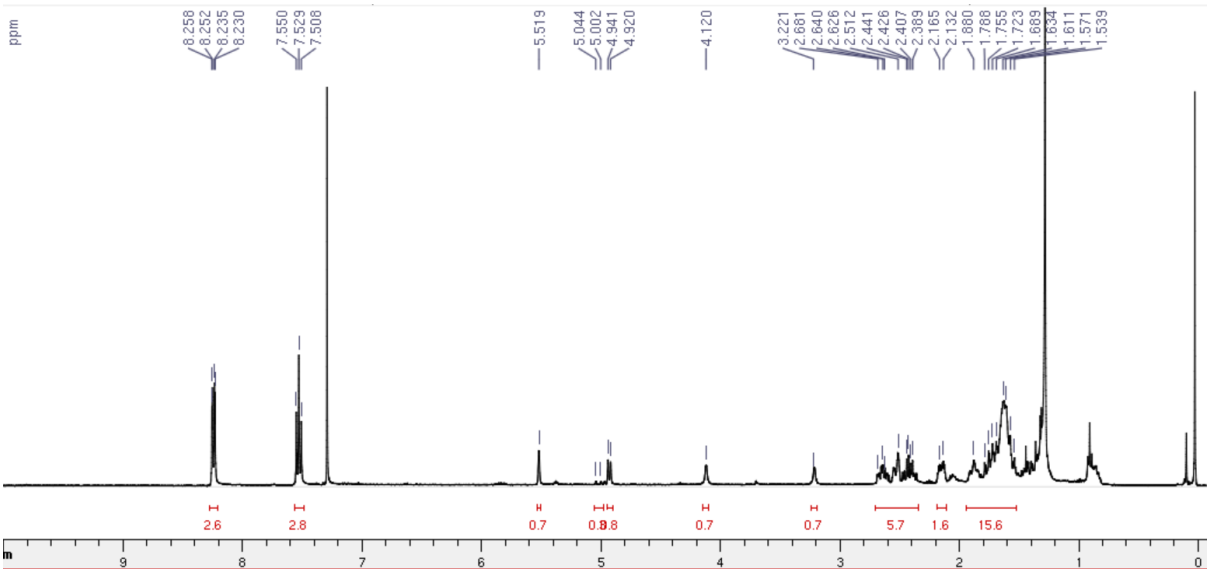


Fig. S4. [1]H NMR of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one, the model Aldol product (Table 1, entry 1).

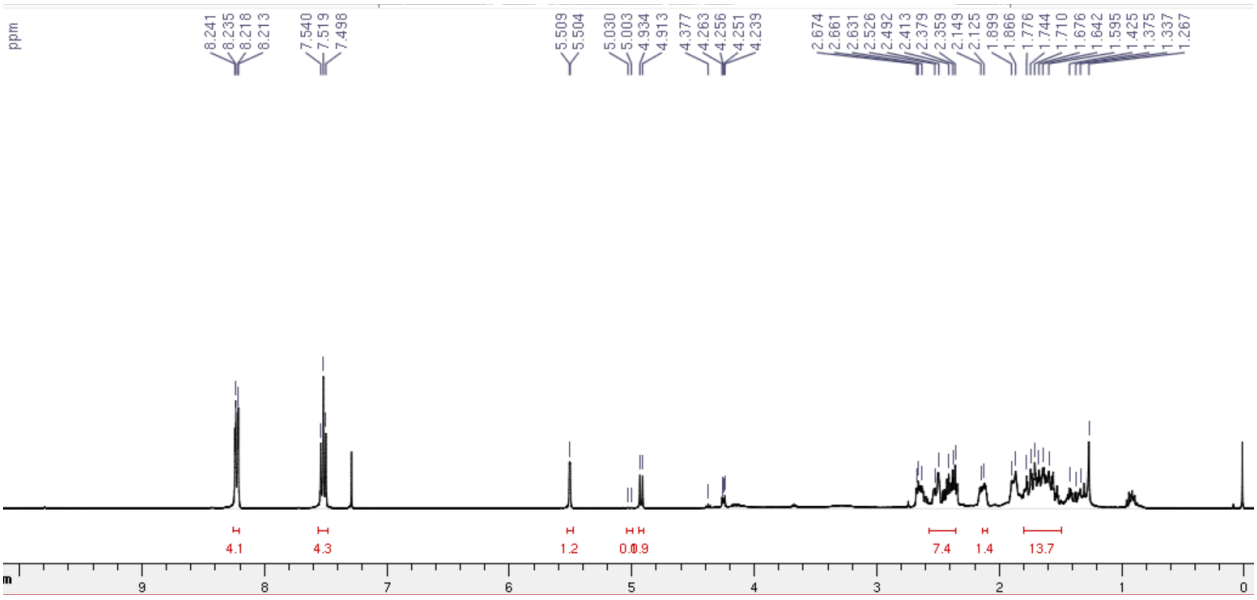


Fig. S5. 1H NMR of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one, the model Aldol product, (Table 2, entry 1).

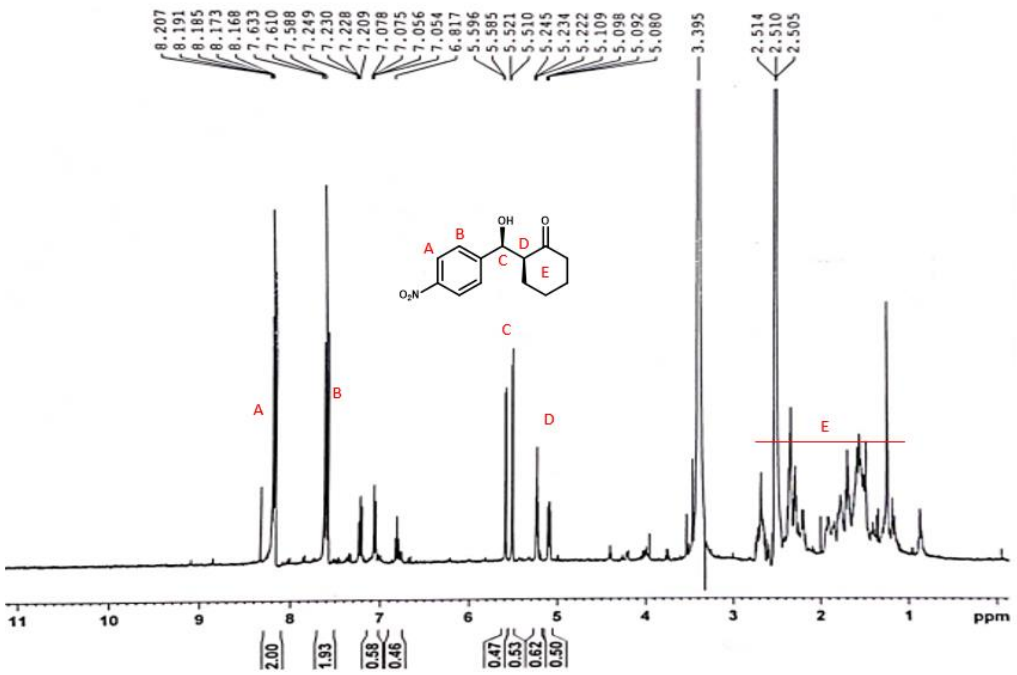
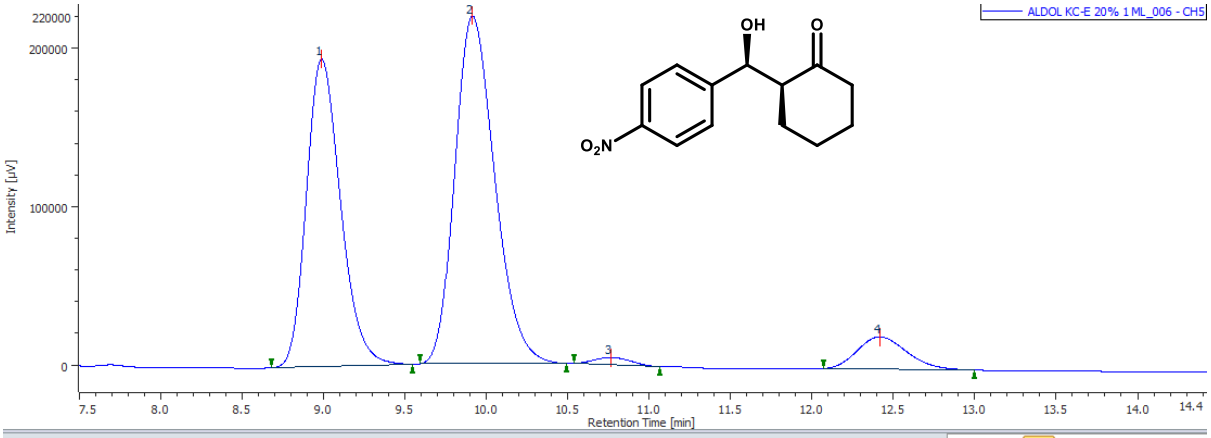
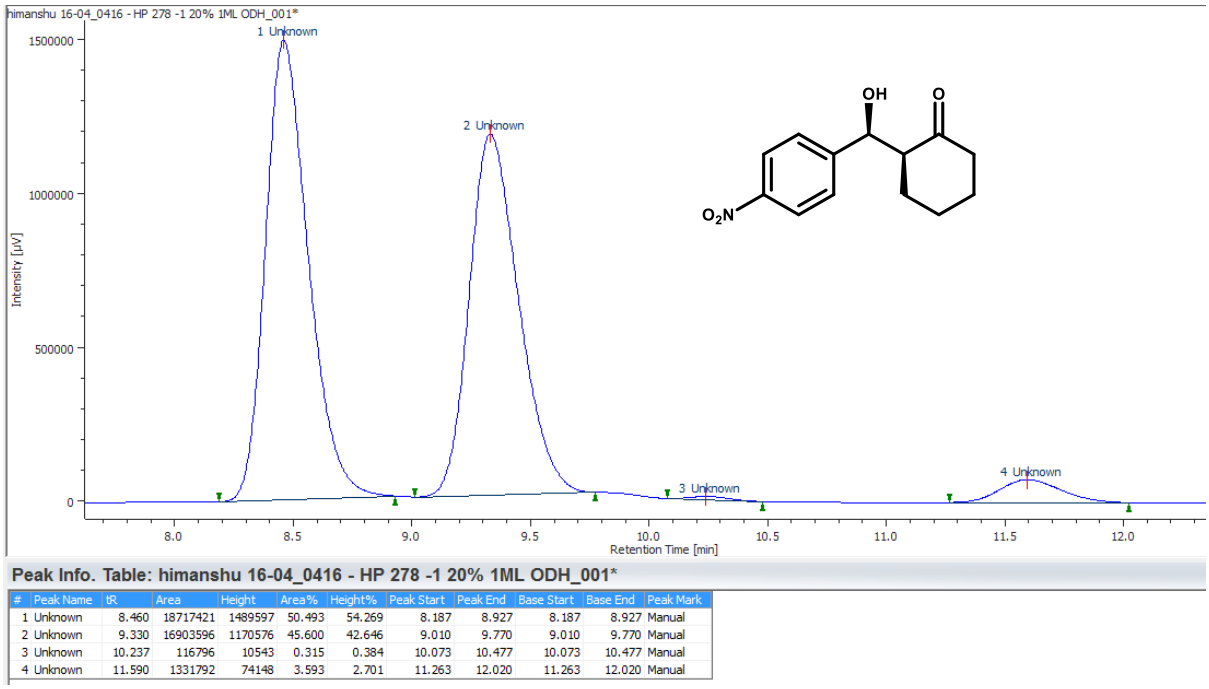


Fig. S6. [1]H NMR of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one, the model Aldol product using DMSO-d6 (Table 2, entry 5).



#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	8.987	2835411	193617	40.118	44.244	N/A	8886	2.236	1.237	
2	Unknown	5	9.910	3724520	218881	52.698	50.018	N/A	7879	1.929	1.251	
3	Unknown	5	10.760	74373	4731	1.052	1.081	N/A	9704	3.307	1.123	
4	Unknown	5	12.410	433339	20378	6.131	4.657	N/A	7755	N/A	1.208	

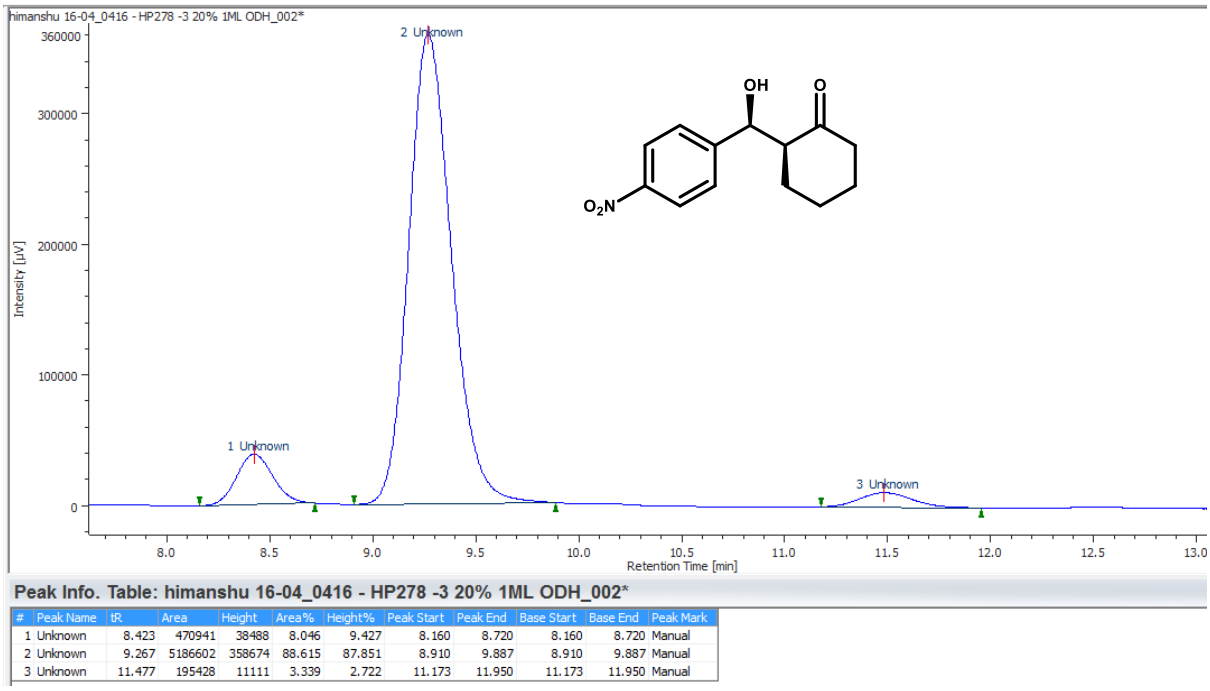
Fig. S7. Chiral HPLC chromatogram of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one (Table 1, entry 1).



Peak Info. Table: himanshu 16-04_0416 - HP 278 -1 20% 1ML ODH_001*

#	Peak Name	tR	Area	Height	Area%	Height%	Peak Start	Peak End	Base Start	Base End	Peak Mark
1	Unknown	8.460	18717421	1489597	50.493	54.269	8.187	8.927	8.187	8.927	Manual
2	Unknown	9.330	16903596	1170576	45.600	42.646	9.010	9.770	9.010	9.770	Manual
3	Unknown	10.237	116796	10543	0.315	0.384	10.073	10.477	10.073	10.477	Manual
4	Unknown	11.590	1331792	74148	3.593	2.701	11.263	12.020	11.263	12.020	Manual

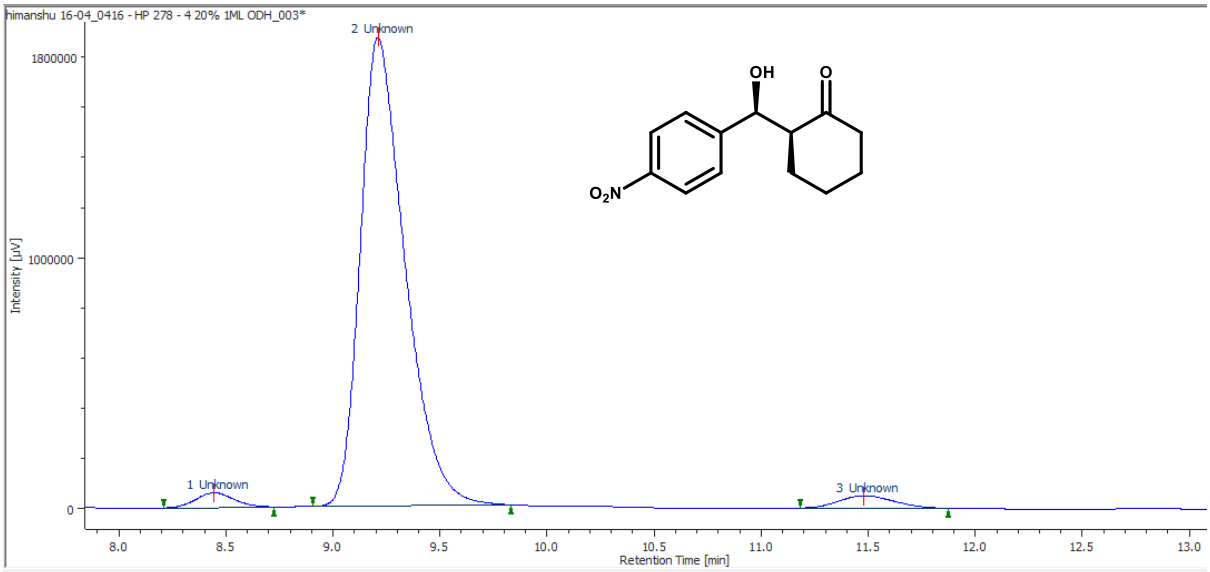
Fig. S8. Chiral HPLC chromatogram of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 5).



Peak Info. Table: himanshu 16-04_0416 - HP278 -3 20% 1ML ODH_002*

#	Peak Name	tR	Area	Height	Area%	Height%	Peak Start	Peak End	Base Start	Base End	Peak Mark
1	Unknown	8.423	470941	38488	8.046	9.427	8.160	8.720	8.160	8.720	Manual
2	Unknown	9.267	5186602	358674	88.615	87.851	8.910	9.887	8.910	9.887	Manual
3	Unknown	11.477	195428	11111	3.339	2.722	11.173	11.950	11.173	11.950	Manual

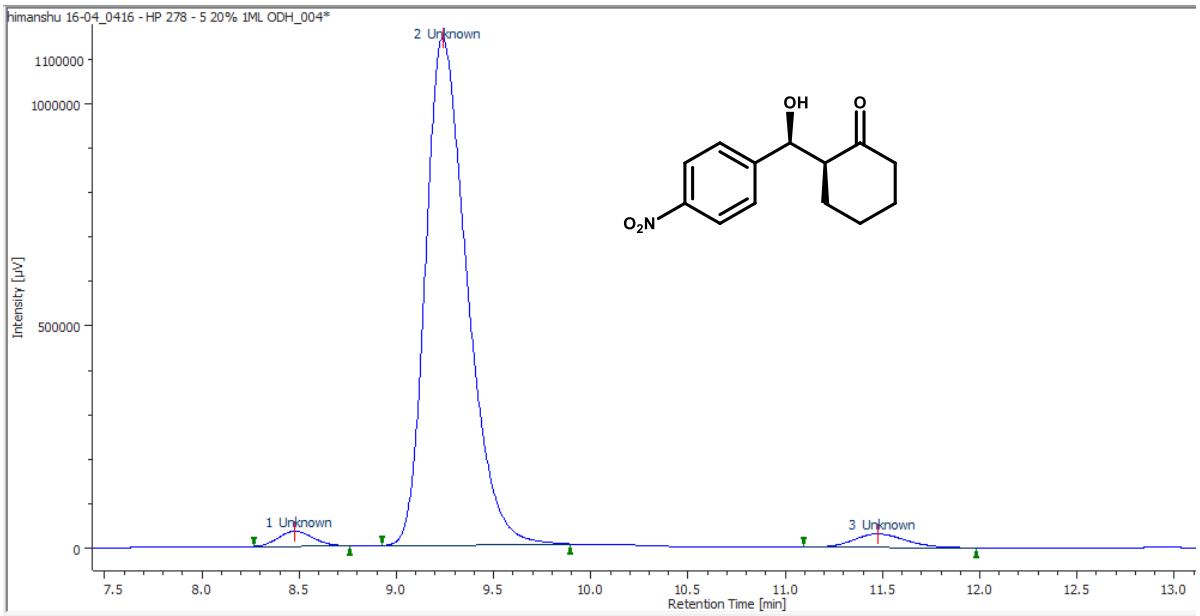
Fig. S9. Chiral HPLC chromatogram of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 3).



Peak Info. Table: himanshu 16-04_0416 - HP 278 - 4 20% 1ML ODH_003*

#	Peak Name	tR	Area	Height	Area%	Height%	Peak Start	Peak End	Base Start	Base End	Peak Mark
1	Unknown	8.443	716989	57988	2.505	2.941	8.210	8.723	8.210	8.723	Manual
2	Unknown	9.210	27024196	1864441	94.413	94.549	8.907	9.830	8.907	9.830	Manual
3	Unknown	11.477	882199	49496	3.082	2.510	11.180	11.870	11.180	11.870	Manual

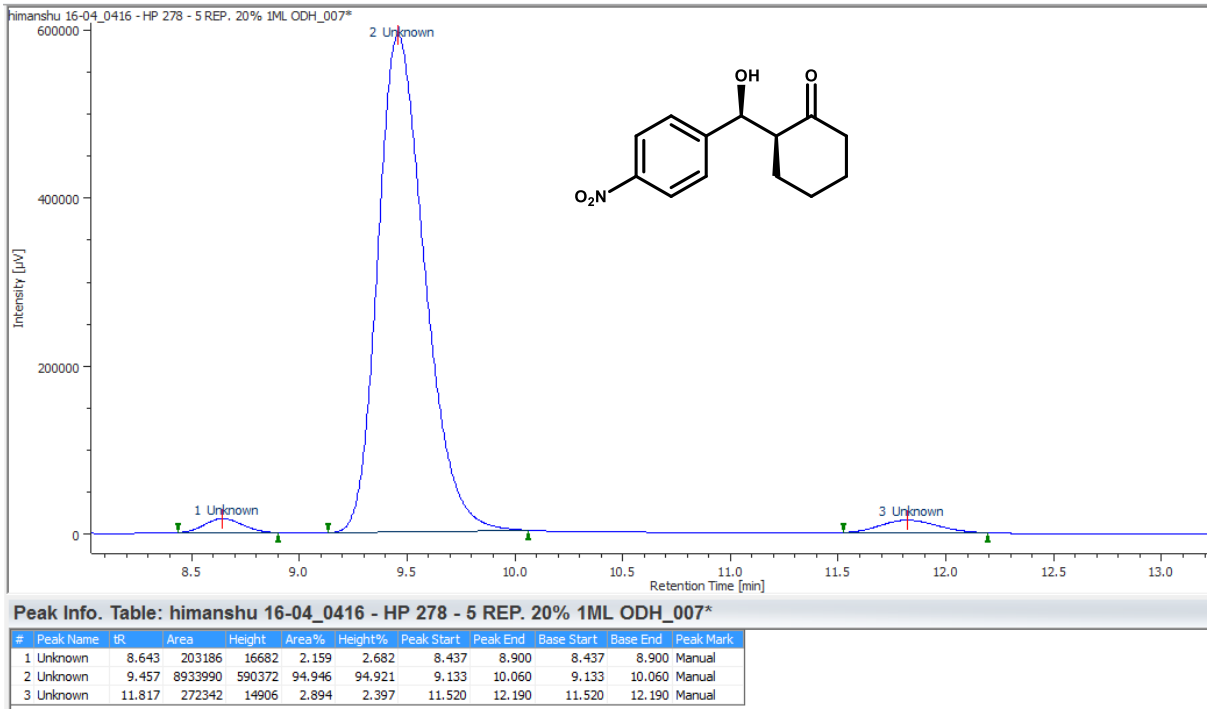
Fig. S10. Chiral HPLC chromatogram of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 4).



Peak Info. Table: himanshu 16-04_0416 - HP 278 - 5 20% 1ML ODH_004*

#	Peak Name	tR	Area	Height	Area%	Height%	Peak Start	Peak End	Base Start	Base End	Peak Mark
1	Unknown	8.477	413806	33720	2.320	2.801	8.267	8.760	8.267	8.760	Manual
2	Unknown	9.237	16856816	1139931	94.520	94.677	8.923	9.890	8.923	9.890	Manual
3	Unknown	11.470	563484	30368	3.160	2.522	11.090	11.977	11.090	11.977	Manual

Fig. S11. Chiral HPLC chromatogram of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one (Table 3, entry 2).



#	Peak Name	tR	Area	Height	Area%	Height%	Peak Start	Peak End	Base Start	Base End	Peak Mark
1	Unknown	8.643	203186	16682	2.159	2.682	8.437	8.900	8.437	8.900	Manual
2	Unknown	9.457	8933990	590372	94.946	94.921	9.133	10.060	9.133	10.060	Manual
3	Unknown	11.817	272342	14906	2.894	2.397	11.520	12.190	11.520	12.190	Manual

Fig. S12. Chiral HPLC chromatogram of 2-(hydroxy (4-nitrophenyl)methyl)cyclohexan-1-one (Table 3, entry 5).

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