# Chapter 3

## Application of Oxazolines

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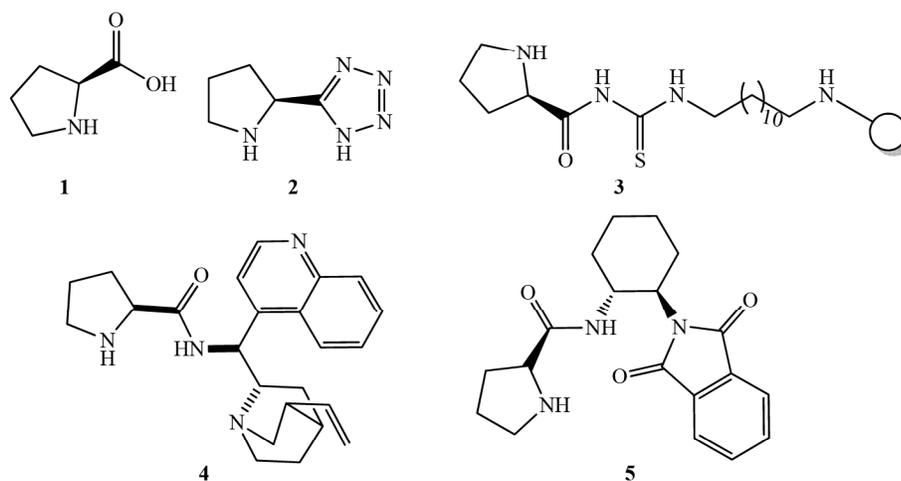
## Asymmetric Aldol Reaction

## and

## Henry Reaction

# Introduction

**Asymmetric Aldol Reaction**

The controlled creation of new stereogenic centres is of paramount importance in organic synthesis. Mainly three approaches are used to access chiral molecules, namely resolution of stereoisomers, starting from enantiomerically pure isomers and by performing asymmetric synthesis the through use of a chiral auxiliary, reagent or **catalyst**.

Use of asymmetric catalysts for accessing chirally pure organic compounds is by far the most attractive and efficient option. The developments in the field of asymmetric catalysis are inspired by the natural biochemical processes induced by biomolecules such as enzymes and antibodies. Most of the early development was based on transition metal / chiral ligand based asymmetric catalysis. Introduction of organic molecules capable of influencing the basic organic reactions has ushered in the era of "organocatalysis" in modern chemistry. The ability of organocatalyst to control the asymmetric transformation in the key step is attributed mainly to supramolecular interactions, quite similar to the enzymes in the biochemical reactions. Organocatalysts have advantages over the metal catalysed reactions, mainly it reduces the use of metals which cause problems of disposal after completion of the reaction. Elimination of the use of potentially toxic metal ion based catalysis in the wake of this development goes well wih the advent of green chemistry and realization of the commitment of the scientists towards the environmental cocerns.

The developments in the area are mostly focused on some of the carbon-carbon bond forming asymmetric reactions such as aldol condensation and its varients, Michael reaction, Baylis-Hillman reaction and Mannich reactions.[1] In this chapter we will be focussing on oganocatalytic application of chiral aminooxazolines in asymmetric aldol reaction, preparation and charactersization of aminooxazolines have already been described in Chapter 2. Since this reaction has been developed, variety of organocatalysts have been desingned to achieve good enantioselectivity in this organic transformation, most of them are prolione derived organic molecules **[Figure 1]**.

**Figure 1**: Few examples of organocatalysts used for asymmetric aldol reaction

Hence, number of reports on aldol reaction proves the considerable attention on application of organocatalysts in this carbon-carbon bond forming reaction. The major thurst in this effort began with the pioneering work by Barbas, List and others when they utilized *L*-proline to catalyse aldol reaction with excellent enantioselectivity.[2]

The *L*-proline **1** -catalyzed direct intermolecular asymmetric aldol reaction had not been described by that time. Further, there were no asymmetric small-molecule aldol catalysts that use an enamine mechanism. We initially studied the reaction of acetone with 4-nitrobenzaldehyde in presence of *L*-proline **1** (30 mol %) in DMSO/acetone (4:1) at room temperature for 4 h furnished aldol product (*R*)-**8** in 68% yield and 76% *ee* **[Scheme 1]**.[2a] Variety of commercially available chiral amino acid have also been screened for this study under the same condition. However, primary amino acids and acyclic secondary amino acids failed to give significant amounts of the desired product.
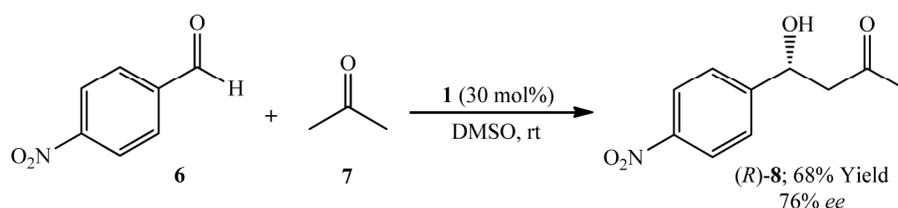


**Scheme 1**: Asymmetric Aldol Reaction using L-Proline as Organocatalyst

It is widely accepted that the organocatalysed aldol reactions follow either acid assisted enamine route **[Scheme 2]** or the base induced enol-enolate pathway **[Scheme 3]**. For aldol reaction of unactivated ketones the enamine mechanism appears favourable, while the base induced enol-enolate pathways is less likely due to the low acidity of the α-protons.
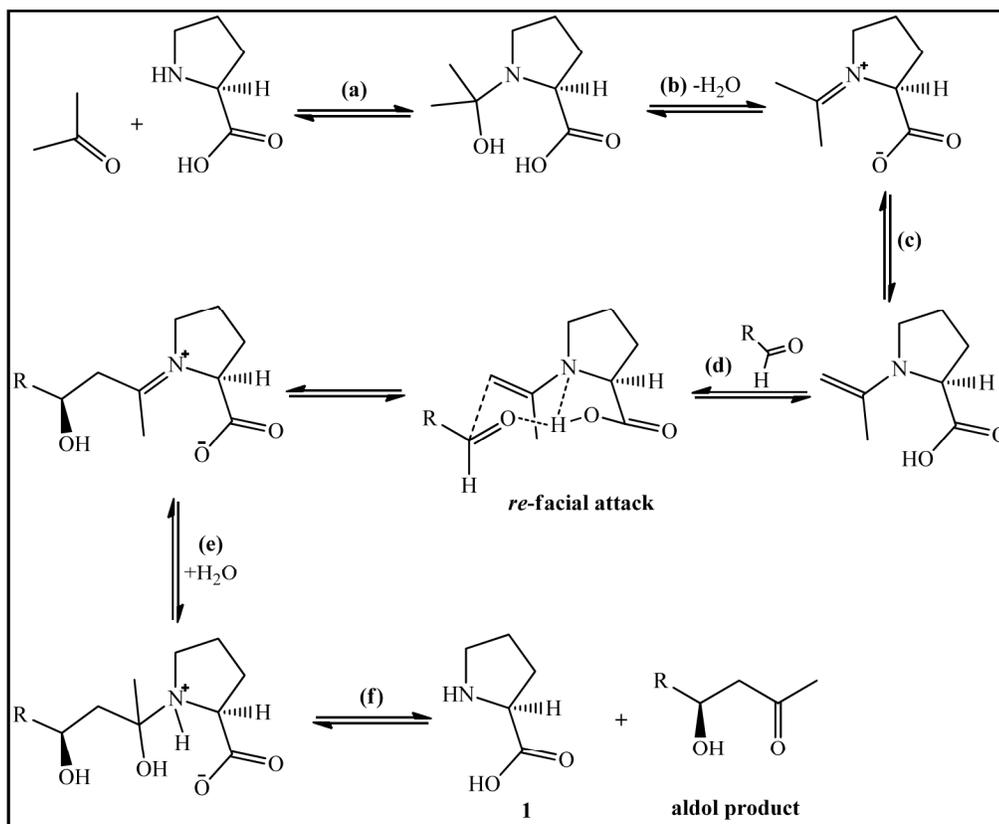
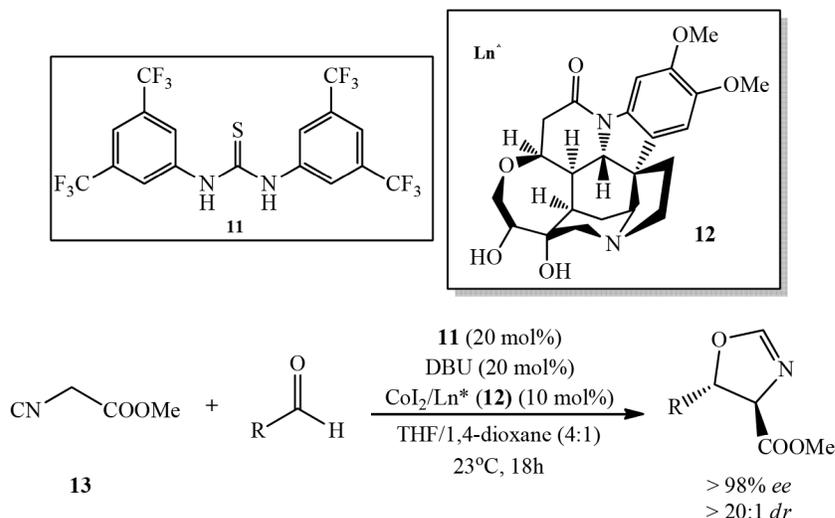**Scheme 2**: Mechanistic approach via Enamine intermediate

This mechanism involved several steps, including the nucleophilic attack of the amino group **(a)**, the dehydration of the carbinol amine intermediate **(b)**, the deprotonation of the iminium species **(c)**, the carbon-carbon bond forming step **(d)**, and both steps of the hydrolysis of the iminium-aldol intermediate **(e)** and **(f)**. The enantioselectivity can be explained with a metal free version of a Zimmerman-Traxler type transition state.17 The tricyclic hydrogen bonded framework provides for enantiofacial selectivity.
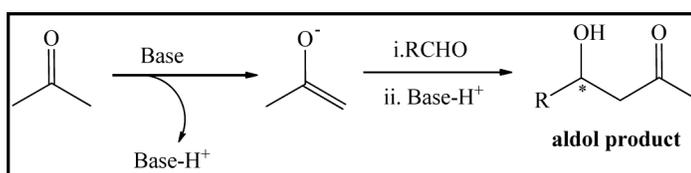


**Scheme 3**: Enol - Enolate pathway

Since these reports many applications of proline induced organocatalytic reactions have been reported with varied degree of selectivity and mechanistic investigations. Besides proline other chiral organic molecules based on thiourea,[4] thiazolidine,[5] cinchona alkaloids,[6] peptides,[7] cabohydrates[8] etc. have been screened successfully as organocatalysts for asymmetric reactions.

196

Recently an elegant combination of amino oxazoline and proline has been prepared and tested for inducing chirality in intermolecular aldol reaction.[9a] These type of prolinamide-oxazolines are amongst a series of modifications designed on the basic amino acid unit of proline where a second chiral element has been introduced. Such derivatives with two chiral units have been more selective as compared to some of the prolinamides prepared with achiral amines.[9b] This series of prolinamide-oxazolines are neutral molecules in nature as the carboxylic acid of proline is blocked by the amide group. Hansen et al. reported an interesting approach for the preparation of polymer-supported proline via acrylic copolymerization.[9c] These functionalized polymer systems have proven to be very efficient for asymmetric aldol reactions and offer an advantageous recyclability. Cui and co-workers have also developed chitosan immobilizecd proline[10] and polyvinyl chloride supported proline[11] as catalysts for direct aldol reaction with good efficiency and performance. Inspiring from these reports, Cui has utilized the ability of thiourea group being a weak Bronsted acid which able to activate the electrophilic substrate via double-hydrogen bonding, to synthesize polymer supported chiral organocatalyst **3** having incorporated L-proline and thiourea moieties in it **[Figure 1]** and **[Scheme 4]**.



$$9 \qquad 6 \xrightarrow[\text{water, rt 6 days}]{\textbf{3} \ (2 \ \text{mol\%})} 10$$

10
83% yield, *syn:anti* 34:66
97% ee for *anti* isomer

**Scheme 4**: Asymmetric aldol reaction using polymer supported thiourea based organocatalyst **3**

A cooperative catalyst system between a chiral transition-metal catalyst of the ligand **12** and achiral thiourea based Organocatalyst **11** was developed for highly diastereo- and enantioselective aldol reaction of methyl α-isocyanoacetate **13** and variety of aldehydes **[Scheme 5]**.[4]

197

**Scheme 5**: Application of thiourea based achiral Organocatalyst **11** for asymmetric aldol reaction

For strong H-bonding to the carbon in isocyanides, an anion bonding interaction I between thiourea and methyl α-isocyanoacetate was established. The thiourea assisted enolates would be capable of coordinating to a stereogenic metal centre in a more organised fashion II **[Scheme 6]**. Based on spectroscopic investigations, the anion-bonding interaction of the carbon atom of isocyanide and the N-H of the thiourea were evident.
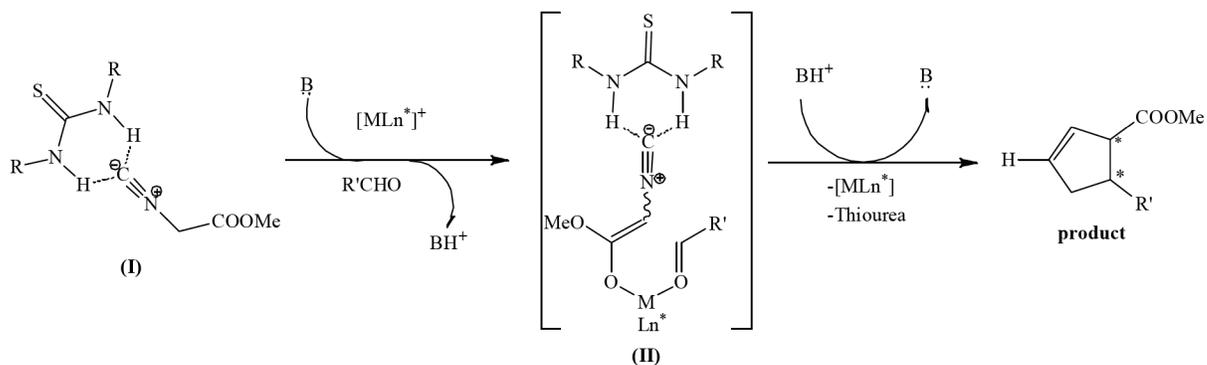


**Scheme 6**: Mechanistic approach for the application of cooperative catalyst **11**

Saccharide-derived bi-functional amine-thiourea **17** catalyst was developed by Ma *et al*. and used in direct aldol condensation of trifluoroacetaldehyde methyl hemiacetal **14** with benzaldehyde **15** to produce **16** with good stereoselectivity **[Scheme 7]**.[12]
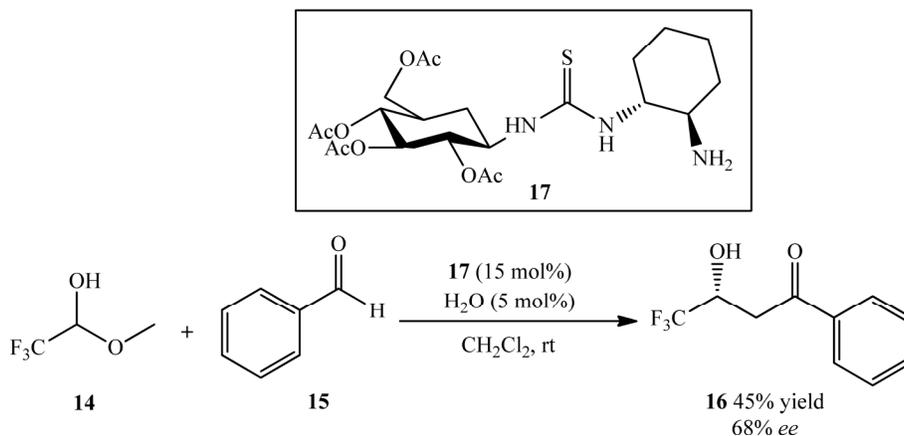
**Scheme 7**: Saccharide-derived amine-thiourea organocatalyst **17** in aldol reaction

It was also noticed that nitrosobenzene could act as an electrophilic aminooxylating reagent, inspring by this thought Hayashi and co-workers have examined the reaction between a ketone and nitrosobenzene in the presence of chiral organocatalyst **1** or **3**, and have discovered the direct asymmetric α-aminooxylation of ketones gave remarkably excellent enantioselectivity up to 98% **[Scheme 8]**.[13]
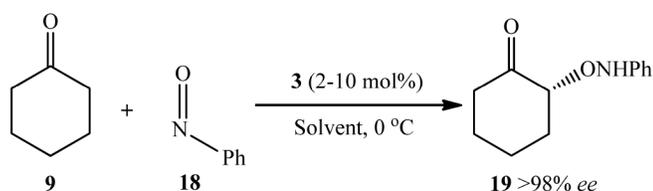
**Scheme 8**: Organocatalyzed asymmetric aminooxylation of ketones

A set of enantiopure thiazolidine-based organocatalysts have been by Schneider. In particular, organocatalyst **20** exhibited the highest catalytic performance working in an aqueous medium. It catalyzed the direct catalytic asymmetric intermolecular aldol reaction between unmodified ketones and an aldehyde with excellent stereocontrol and furnished the corresponding aldol products in up to 99% *ee* **[Scheme 9]**.[5]
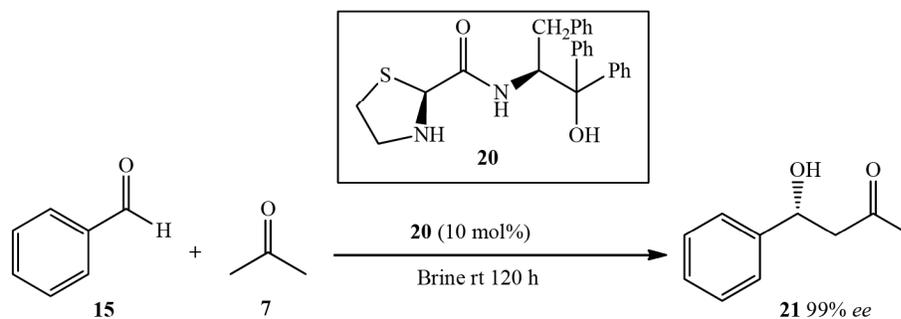
**Scheme 9**: Application of thiazolidine-based organocatalyst **20** in asymmetric aldol reaction

Over the years, number of cinchona alkaloid and their derivatives have been successfully applied in a wide diversity of organocatalytic reactions,[14] acting as chiral-base,[15]

phase transfer[16] and nucleophilic catalysts.[17] Hence, due to their extraordinary catalytic activity in organic transformations, Xiao and co-workers have developed a set of class of chiral oragnocatalysts which incorporate the properties of well established proline and cinchona alkaloid in single molecule and applied them for asymmetric aldol reaction which resulted in to high degree of enantioselectivity **[Scheme 10]**.[18]
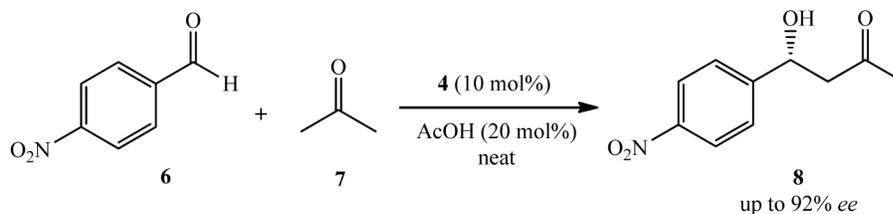


**Scheme 10**: Cinchona alkaloid based organocatalyst **4** for aldol reaction

Guan *et al.* examined the application of bi-functional recoverable and reusable L-Prolinamide oranocatalyst **5**. This Organocatalyst was applied to the aldol reactions of aromatic and heteroaromatic aldehydes with cyclic as well as acyclic ketones, and *anti*-aldol product could be obtained with up to 1:99 *syn:anti* ratio and 98% *ee*. This type of organocatalyzed asymmetric aldol reaction can be performed on a large-scale which offers the possibility for applications in industry without affecting the enantioselectivity **[Scheme 11]**.[19]
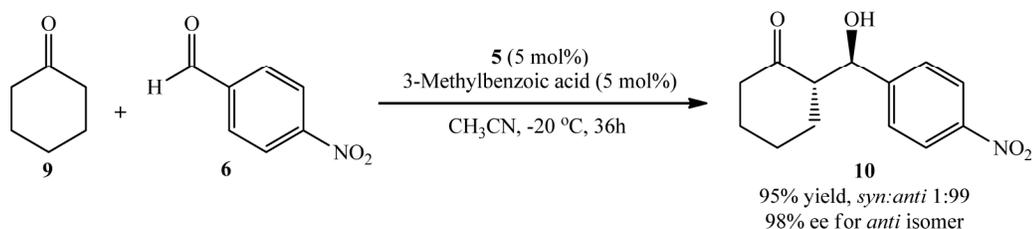


**Scheme 11**: Use of Prolinamide derived Organocatalyst **5** in aldol reaction

Interestingly, another class of carbohydrate based chiral organocatalysts **22** and **23** have also been developed to utilized the presence of the highly functionalized and having several stereogenic centres which provides additional effect on stereoselectivity in aldol reaction **[Figure 2]**.[8]
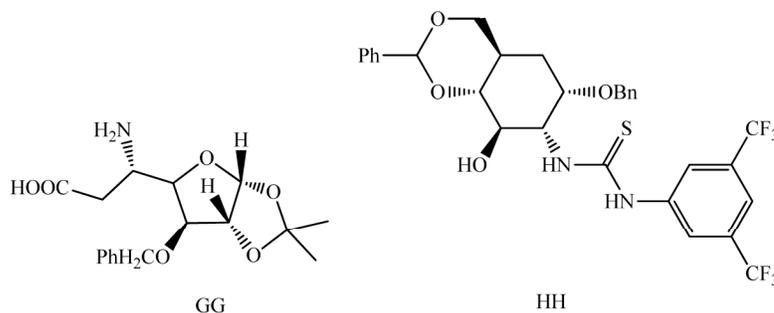


**Figure 2**: Carbohydrate based oragnocatalysts **22** and **23**

Many researchers have also studied isatin **24** as an acceptor of enolate in the asymmetric organocatalyzed aldol reaction.[7a,8b,20] Number of oragnocatalysts **25-28** have been utilized for this purpose, some of them are listed below **[Figure 3]**.[21]
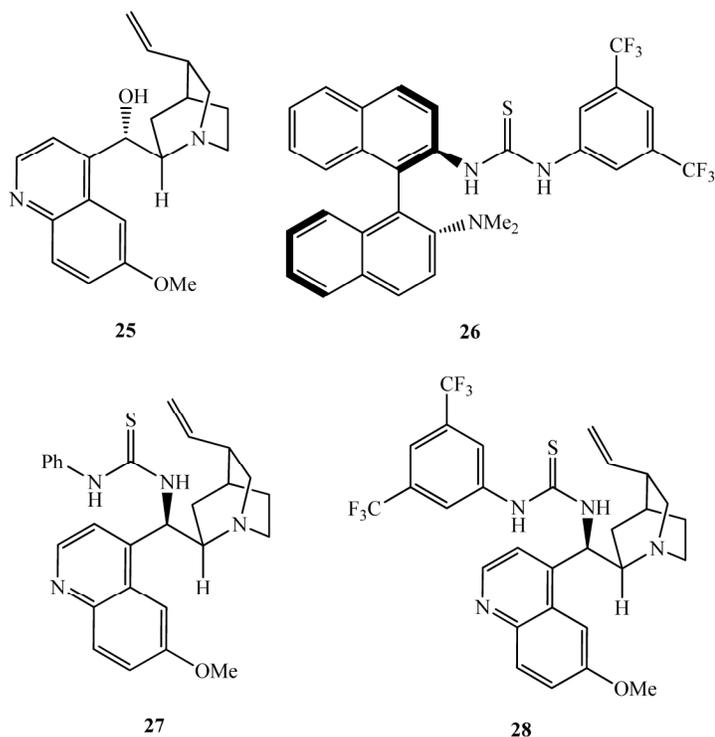


**Figure 3**: List of Organocatalysts **25-28** used for aldol reaction of isatin **24**

Using these oragnocatalysts for the asymmetric aldol reaction of isatin and acetone, **25** was found to be less effective giving only 2% *ee* for the *R*-isomeric product **29** and also catalyst **26** was not at all exhibited stereoselectivity under the same condition. But the catalysts derived by combination of thiourea and cinchona alkaloid derivatives, **27** and **28**, gave interesting results. Catalyst **27** having phenyl substituent at thiourea moiety resulted with 61% *ee* without changing stereochemistry of the chiral centre in aldol product whereas in case of catalyst **28** having comparatively bulky 3,5-ditrifluormehhylphenyl substituent at thiourea moiety exhibited same aldol product **29** with 85% *ee* **[Scheme 12]**.[21]
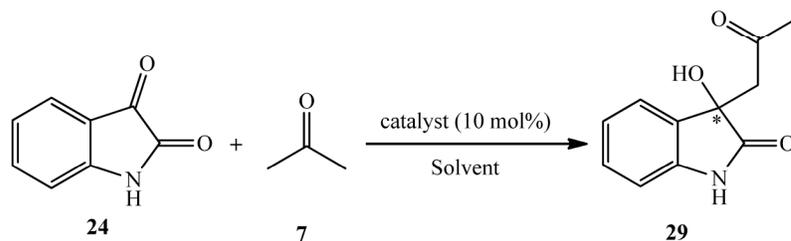


**Scheme 12**: Organocatalyzed asymmetric aldol reaction of isatin **24**

Among the C-C bond forming reactions, the nitroaldol (Henry) reaction is one of the classical reactions in organic synthesis.[22] The Henry reaction is a useful technique in the area organic chemistry due to the synthetic utility of its corresponding products, as they can be easily converted to other useful synthetic intermediates. These conversions include subsequent dehydration to yield nitroalkenes, oxidation of the secondary alcohol to yield α-nitro ketones, or reduction of the nitro group to yield β-amino alcohols. Many of these uses have been exemplified in the syntheses of various pharmaceuticals including the β-blocker (S)-propranolol,[23] HIV protease inhibitor Amprenavir, and construction of the carbohydrate subunit of the anthracycline class of antibiotics, L-Acosamine.[24] It is also well known that the nitroaldol products find increasing applications in the synthesis of natural products, polyamino alcohols and polyhydroxylated amides. Generally, the nitroaldol reaction involves the addition of a nitronate ion to a carbonyl compound. The nitronate ion can be generated *in situ* by the deprotonation of a nitroalkane with an external base. The addition is facilitated either by a Lewis acid catalyst or by a suitable bi-functional catalyst, while the former activates the carbonyl partner, the latter works as a Lewis acid- Bronsted base which activates and bring both reactants together.[25]

Many attempts to develop catalytic asymmetric nitroaldol reaction variants have therefore been made.[26] Out of the great number of metal-based catalysts, copper salts have become the most widely used examples, because copper is a relatively cheap and low-toxicity metal with excellent chelating properties.[27]

Recently, Gong has reported the synthesis of number of *N,N*-chiral ligands **30-37** derived from (-)-*exo*-bornylamine and also **38** from (+)-menthylamine **[Figure 4]**. They have screened these ligands for Cu (II)-catalyzed asymmetric Henry reaction of variety of aldehydes and nitromethane which exhibited excellent results in terms of conversion as well as stereoselectivity **[Scheme 13]**.[28]



**30**; R$^1$= Me, R$^2$= H
**31**; R$^1$= Bn, R$^2$ = H
**32**; R$^1$= H, R$^2$= H
**33**; R$^1$= Me, R$^2$= Me
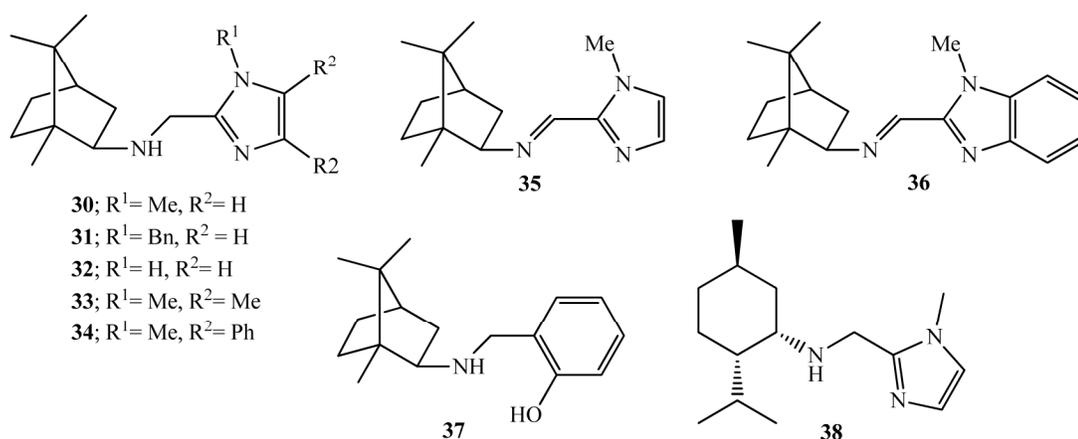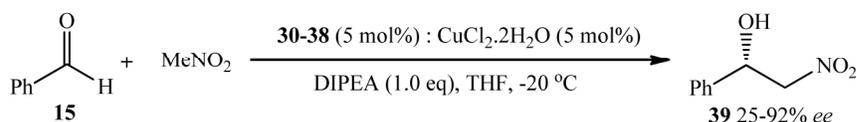**34**; R$^1$= Me, R$^2$= Ph

**Figure 4**: Ligands used for Cu-catalyzed Asymmetric Henry reaction

Among these ligands, **30-34**, **36** and **38** gave good results with enantioselectivities up to 92%, whereas ligand **35** and **37** were not showing any stereoselectivity. All the ligands produced Henry product **39** with *S*-isomeric form except ligand **38** where stereoselectivity was inversed.



**Scheme 13**: Cu-catalyzed asymmetric Henry reaction

Variety of chiral oxazolinyl ligands have also contributed for metal catalyzed asymmetric Henry reaction which showed excellent outcome for this reaction. A series of novel $C_2$-symmetric bis(thiazoline) ligands as well as bis(oxazoline) ligands have been developed and screened for Cu-catalyzed asymmetric Henry reaction to exhibit good results.[29] Another class of chiral oxazoline ligands have also been found to be successful for Cu-catalyzed Henry reaction.[30] Also certain Schiff base-Cu complexes were also reported to show remarkable input for this nitroaldol reaction.[31] Ligands derived from 1,2-diaminocyclohexane framework were also developed to contribute for asymmetric Henry reaction with excellent stereoselectivity.[32]

Considering these wide applications in organic transformations, we have screened our aminooxazolines for asymmetric aldol reaction as well as asymmetric Henry reaction and the results are encouraging which are well documented in this chapter.

# Result and Discussion

## Asymmetric Aldol Reaction

Since the chiral amino oxazoline is a weak base we have screened number of synthesized aminooxazolines **40-55** as oragnocatalysts for asymmetric aldol reaction with sufficiently activated enolate acceptors. List of the aminooxazolines are shown in **Figure 5**.
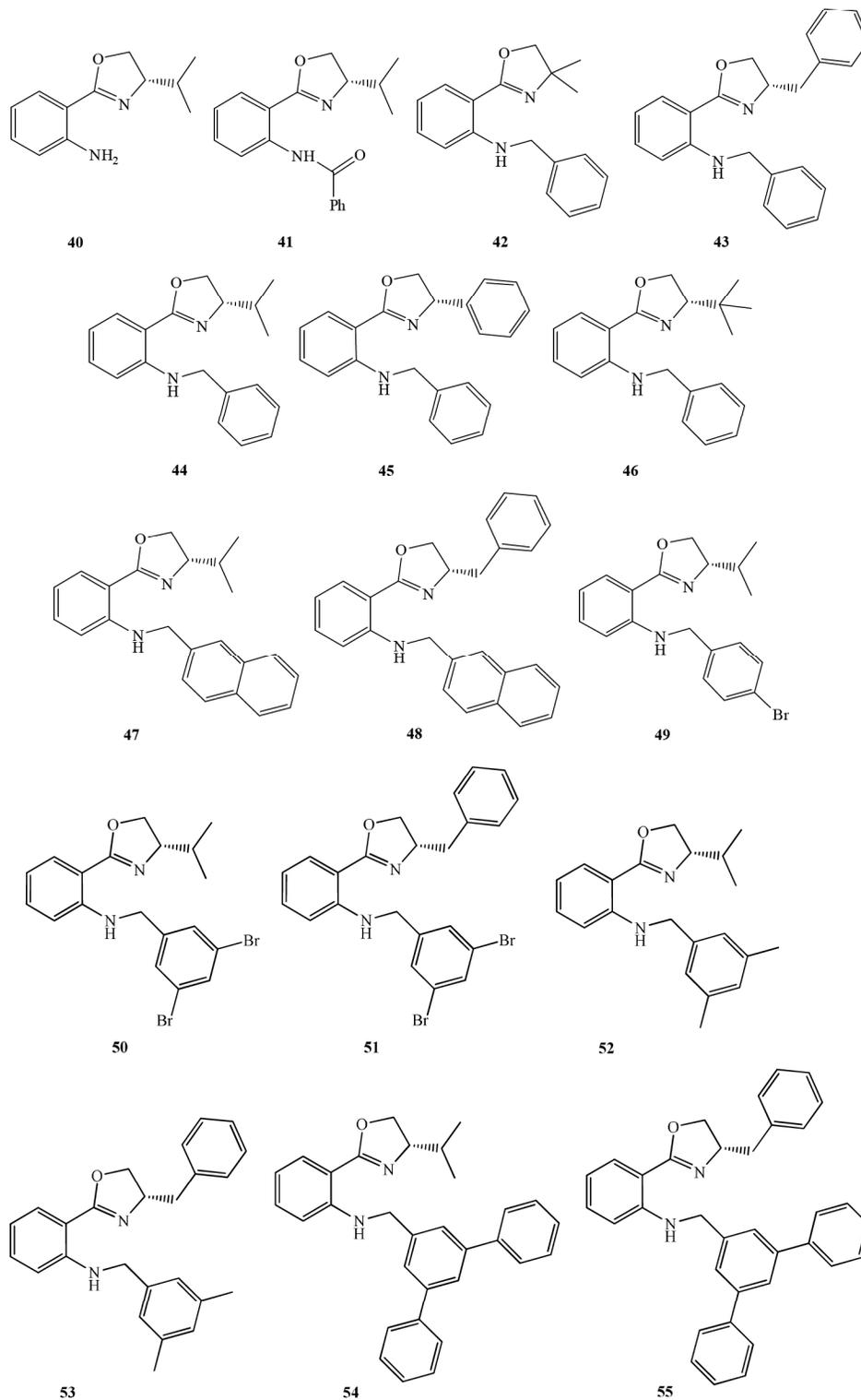


**Figure 5**: List of aminooxazolines **40-55** used as oragnocatalysts for asymmetric aldol reaction

With this concept we utilized 4-nitro benzaldehyde as the standard aldehyde and scanned the conditions with number of amino oxazolines **[Scheme 14]** and **[Table 1]**.
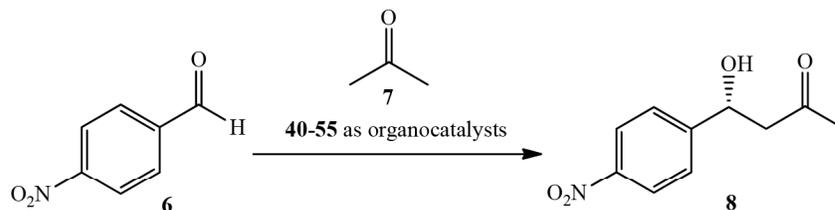


**Scheme 14**: Aminooxazoline catalyzed asymmetric aldol reaction

Recently polyethylene glycol was used as solvent for *L*-proline mediated aldol reaction.[33] Besides this we have also used other solvents **[Table 1]**. Reaction proceeded with moderate results with PEG-400 and THF, while the configuration of the β-hydroxy compound **8** was established as "*R*" by comparison of the observed optical rotation.

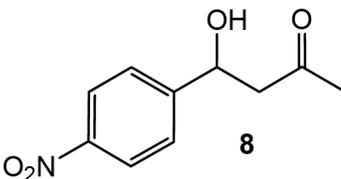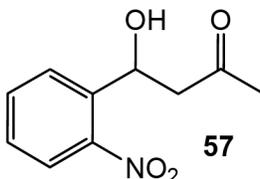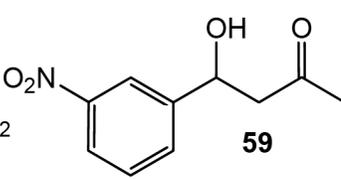**Table 1:** Screening of amino oxazoline **47** (20 mol %) for standard example of 4-nitro benzaldehyde and acetone (4 eq. Except for 3).

| No | Solvent | Temp $^{o}$C/ Ttime h | Yield/% | % ee (*R*) |
|----|---------|-----------------------|---------|------------|
| 1 | PEG-400 | 30 / 24 | 79 | 16 |
| 2 | PEG-400 | 5-8 / 24 | 61 | 51 |
| 3 | Acetone | 5-8 / 24 | 71 | 40 |
| 4 | ACN | 5-8 / 24 | 33 | 75 |
| 5 | Toluene | 5-8 / 24 | 16 | 91 |
| 6 | THF | 5-8 / 24 | 33 | 75 |
| 7 | THF | 5-8 / 72 | 48 | 71 |

205

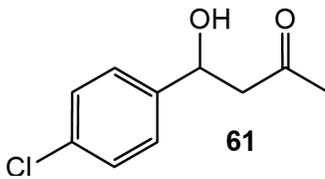The synthesized series of ligands were then scanned under the optimized condition of THF as solvent for 72 h reaction time for 4-nitro benzaldehyde **6** and acetone **7**. The results are summarised in **Table 2**, in most cases the yield and selectivity was moderate to good. The ligand with free –NH₂ group (**40**) and –NHCOPh (**41**) were both ineffective to assist this reaction, while derivatives prepared from *tert*-leucinol show good selectivity.

**Table 2:** Screening of amino oxazolines (20 mol %) for standard example of 4-nitro benzaldehyde **6** and acetone **7** (4 eq.).

| No | Amino oxazoline | Yield of **8** (%) | *ee* of **8**-(*R*) (%) | No | Amino oxazoline | Yield of **8** (%) | *ee* of **8**-(*R*) (%) |
|---|---|---|---|---|---|---|---|
| 1 | **40** | NR | -- | 9 | **49** | 59 | 39 |
| 2 | **41** | NR | -- | 10 | **50** | 57 | 63 |
| 3 | **43** | 68 | 76 | 11 | **51** | 59 | 71 |
| 4 | **44** | 66 | 76 | 12 | **52** | 60 | 76 |
| 5 | **45** | 65 | 63 | 13 | **53** | 56 | 75 |
| 6 | **46** | 52 | 86 | 14 | **54** | 60 | 75 |
| 7 | **47** | 48 | 79 | 15 | **55** | 62 | 76 |
| 8 | **48** | 51 | 71 | | | | |

For all reactions: Solvent = THF; Reaction Temp = 5-8 °C; Time 72 h.

NR = no reaction.

The amino oxazoline **46** and **47** were found to show consistent results with both good conversion and enantioselectivity. Hence, these were then investigated for a few aromatic aldehydes attached with electron withdrawing substituents, results are tabulated in **Table 3**.

**Table 3:** Screening of amines **46** and **47** for select examples.

| No | RC$_6$H$_4$CHO | β-hydroxy ketone (R) | % Yield (% ee) with **46** / with **47** |
|---|---|---|---|
| 1 | **6** R = 4-NO$_2$ | **8** | 54 (91) **48 (79)** |
| 2 | **56** R = 2-NO$_2$ | **57** | 69 (91) **72 (84)** |
| 3 | **58** R = 3-NO$_2$ | **59** | 73 (74) **68 (70)** |
| 4 | **60** R = 4-Cl | **61** | 47 (66) **52 (61)** |
| 5 | **62** R = 4-Br | **63** | 49 (84) **58 (57)** |
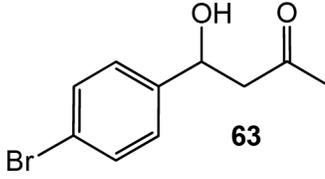
We have also tried this system for the reaction of isatin **24** and acetone **7** in presence of amino oxazoline **46** and the aldol product **29**-(*S*) was isolated in moderate enantioselectivity [**Scheme 15**].
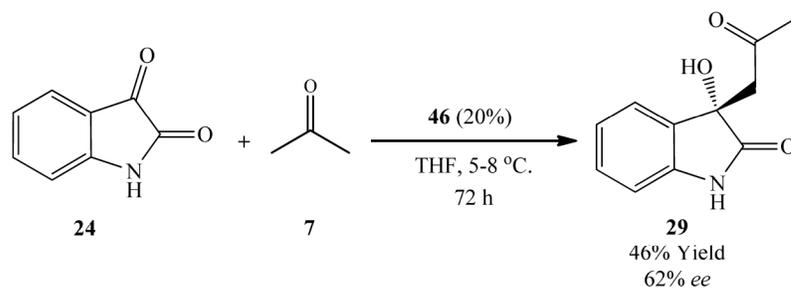


**Scheme 15:** Application for aldol reaction of isatin **24** with acetone **7**.

207

The major advantage of amino oxazolines is its high solubility in almost all routine organic solvents, unlike proline. Since the reaction is assisted by a base and condition is neutral (no acid additive is used) we propose that the reaction must be following enol-enolate pathway. The enantioselectivity of the amino oxazolines for aldol reaction is mainly controlled by the size and shape of the chiral substituent on the oxazoline ring and it is almost independent of the group attached on the amino unit. However, the derivative **40** with primary amino group as well as the benzoyl derivative **41** failed to catalyze this reaction. It is possible that in the former the condensation of aldehyde with primary amine is a competing reaction while the neutral nature of benzoyl derivative is not favoring the enol formation in the latter case.

It is also noteworthy to mention that the acid labile amino oxazoline remains intact after the reaction is complete (tlc), however, so far we have not made any attempts to recover and recycle the catalyst.

## Asymmetric Henry Reaction

We have also screened some of our chiral aminooxazolies as ligands for Cu-catalyzed asymmetric Henry reaction of 4-nitrobenzaldehyde **6** and nitromethane to afford nitroaldol product **64** with good conversion and modest enantioselectivity. We have screened **43**, **44** and **46** as ligands and Cu salts to achieve the standard condition for this reaction **[Scheme 16]** and **[Table 4]**.
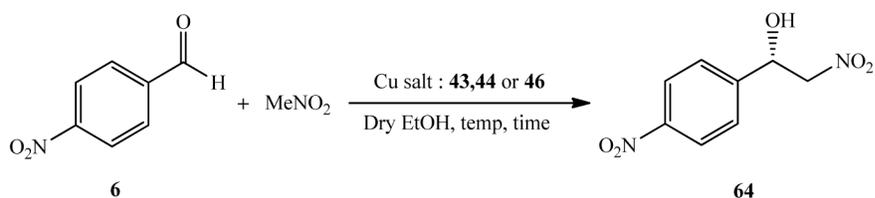


**Scheme 16**: Application of aminooxazolines in asymmetric Henry reaction

**Table 4**: Experimental parameters in search of standard conditon for Henry reaction

| No. | Cu Salt (mol%) | Ligand (mol %) | Additive (mol %) | Temperature (°C) | Time (h) | Yield of **64** (%) | *ee* of **64** (%) |
|---|---|---|---|---|---|---|---|
| 1 | Cu(OTf)$_2$ (5%) | **43** (10%) | -- | rt | 72 | 46 | Racemic |
| 2 | CuI (5%) | **43** (10%) | -- | rt | 72 | 41 | Racemic |
| 3 | Cu(OAc)$_2$.H$_2$O (5%) | **43** (10%) | -- | rt | 72 | 68 | Racemic |
| 4 | Cu(OTf)$_2$ (5%) | **43** (10%) | -- | 5-8 | 72 | trace | -- |
| 5 | Cu(OAc)$_2$.H$_2$O (5%) | **43** (10%) | -- | 5-8 | 72 | 63 | 25 (*S*) |
| 6 | CuCl$_2$.H$_2$O (5%) | **43** (10%) | -- | 5-8 | 72 | NR | -- |
| 7 | Cu(OAc)$_2$.H$_2$O (10%) | **43** (10%) | -- | 5-8 | 72 | 62 | 21(*S*) |
| 8 | Cu(OAc)$_2$.H$_2$O (5%) | **43** (10%) | DIPEA (100 mol%) | 5-8 | 72 | 81 | Racemic |
| 9 | Cu(OAc)$_2$.H$_2$O (5%) | **44** (10%) | -- | 5-8 | 72 | 69 | 26 (*S*) |
| 10 | Cu(OAc)$_2$.H$_2$O (5%) | **46** (10%) | -- | 5-8 | 72 | 74 | 31 (*S*) |

NR = no reaction. Stereochemistry was confirmed by the reportd optical rotation values in literature.

Initially we have used copper(II) triflate as a metal source and **43** as ligand in *1:2* proportion to make effective comlex to catalyse reaction of 4-nitrobenzaldehyde **6** and nitromethane in dry ethanol at room temperature. Allthough the conversion was encouraging, there was no selectivity observed in this reaction. Similar result was obtained with Cu (I) iodide under the same experiental parameters. Cu(II) acetate salt gave the racemic product but the yield was on the higher side which encouraged us to develop the condition using this system. We tried this reaction with Cu(II) acetate (5 mol%) and ligand **43** (10 mol%) at lower temperature around 5-8 °C, surprisingly it exhibited stereoselectivity of 25% *ee* for the product (*S*)-**64** in 72h. Under the same condition Cu(II) triflate and chloride were non-productive at all. We have also perfomed a reaction with equimolar ammount of salt and ligands which resulted with almost same conversion but slightly lower selectivity. Some

reports have prompted us to use DIPEA as a base with a intention to increase the stereoselectivity of the product due to its bulky nature, but on the contrary it yielded the product in racemic form with higher conversion. Hence we considered the experimental condition shown in **entry-5/Table 4** as a standard for the screening of other ligands. We have screened two more ligands **44** and **46**, earlier was having benzyl substituent at the oxazoline ring and *tert*-butyl in the later. They both were equally effective as 43 which had iso-propyl substituent at the oxazoline ring, resulted with 26% and 31% enantioselectivity respectively for the (*S*)-**64** without affecting the stereochemistry at the chiral centre.

Unfortunately, this catalyst system did not work for the other aromatic aldehydes.

# Experimental Section

Reagents were purchased from Sigma-Aldrich Chemicals Limited, SD Fine, Sisco, Qualigens, Avara Chemicals Limited etc. Tetrahydrofuran was refluxed over sodium benzophenone-ketyl and freshly distilled prior to its use. Thin Layer Chromatography was performed on Merck 60 F254 Aluminium coated plates. The spots were visualized under UV light or with iodine vapour. All the compounds were purified by column chromatography using Sisco Research Laboratory silica gel (60-120 mesh) and neutral alumina. All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. NMR Spectra were recorded on 400 MHz Bruker Avance 400 Spectrometer (400 MHz for $^1$H-NMR & 100 MHz for $^{13}$C-NMR) with CDCl$_3$ as solvent and TMS as internal standard. Signal multiplicity is denoted as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q) and multiplet (m). Mass spectra were recorded on Thermo-Fischer DSQ II GCMS instrument. IR Spectra were recorded on a Perkin-Elmer FTIR RXI spectrometer as KBr pallets. Optical rotations were measured on Jasco P-2000 polarimeter. Melting points were recorded in Thiele's tube using paraffin oil and are uncorrected. For the HPLC analysis chiral Lux 5µ Amylase – 2, chiral Diacel OD-H column and Chiralpak IC column were used on Shimadzu LC-20AD having UV-Vis detector.

## Asymmetric Aldol Reaction

## *Synthetic Procedures:*

### *(R)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (8):*
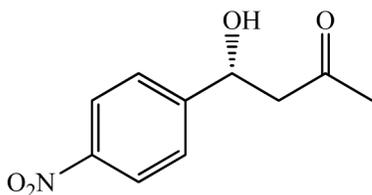


Amino oxazoline **46** (0.062 g, 0.20 mmol, 20 mol %) and acetone **7** (0.23 g, 4.0 mmol) was stirred in dry THF at 5 – 8 °C for 30 min. 4-Nitrobenzaldehyde **6** (0.151 g, 1.0 mmol) was added to the resulting solution and stirred at the same temperature for 72 hrs. Solvent was evaporated under reduced pressure then 20 mL water was added to the crude mixture and extracted 3 x 20 mL with ethylacetate, combined organic layer was dried over sodium sulfate and solvent was evaporated on rotary evaporator. The crude material was purified by column chromatography using 60 – 120 mesh silica gel and ethylacetate : petroleum ether as eluent to afford aldol product **8** (*R* isomer) with (0.111g, 54%) light yellow solid

211

**M.P.** 58 °C (Lit.[34] 59 – 61 °C). $[\alpha]_D^{30} = +35.30$ (c 0.20, CHCl$_3$). [Lit.[35] $[\alpha]_D^{25} = +35.2$ (*c* 0.20, CHCl$_3$), 81% *ee*]

**$^1$H-NMR (400 MHz, CDCl3):** δ 8.23 – 8.20 (m, 2H), 7.56 – 7.53 (dd, *J* = 2.0 & 6.4 Hz, 2H), 5.29 – 5.25 (m, 1H), 3.60 (d, *J* = 3.2 Hz, 1H), 2.92 – 2.80 (m, 2H), 2.23 (s, 3H).

**IR (KBr):** 3438, 3082, 2905, 1708, 1604, 1520, 134 cm$^{-1}$

**MS (EI):** *m/z* (%) 208.73 (51), 190.85 (100), 173.70 (76), 152.05 (30), 104.47 (10), 90.81 (11), 76.83 (14), 57.84 (11).

**Enantiomeric excess** 91% determined by HPLC [Column: Lux 5μ Amylose-2; Solvent system: Hexane/*Iso*-propanol (90:10); Flow rate: 1.0 mL/min; λmax = 254 nm; $t_R$ = 26.6 min (minor, *S* isomer), $t_R$ = 31.7 min (major, *R* isomer)].

***(S)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one (29):***
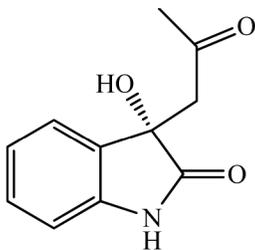


In a clean dry 25 mL flask, mixture of amino oxazoline **46** (0.063 g, 0.20 mmol, 20 mol %) and acetone **7** (0.23 g, 4.08 mmol) was mixed in dry THF at 5 – 8 °C which then stirred for 30 min. To this clear solution, isatin **24** (0.15 g, 1.02 mmol) was added and stirred at the same temperature for 72 hrs. Solvent was evaporated under reduced pressure then 20 mL Water was added to the crude mixture and extracted 3 x 20 mL with ethylacetate, combined organic layer was dried over sodium sulfate and solvent was evaporated on rotary evaporator. The crude material was purified by Column Chromatography using 60 – 120 mesh silica gel; mixture of ethylacetate and petroleum ether as eluent to afford aldol product **29** (0.097 g, 46%) as off white solid

**M.P.** 166 – 168 °C (Lit.[20] 169 – 170 °C). $[\alpha]_D^{32} = -21.11$ (*c* 0.03, CH$_3$OH)

[Lit.[21] $[\alpha]_D^{18} = -20.0$ (*c* 0.03, CH$_3$OH), 61% *ee*]

**$^1$H-NMR (400 MHz, DMSO):** δ 10.09 (s, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.12 – 7.08 (t, *J* = 7.6 Hz, 1H), 6.87 – 6.83 (t, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.92 (d, *J* = 1.6 Hz, 1H), 3.16 (d, *J* = 16.4 Hz, 1H), 2.98 (d, *J* = 16.4 Hz, 1H), 1.99 (s, 3H).

**IR (KBr):** 3362, 3260, 2358, 1718, 1621, 1472, 1365, 1077, 752 cm$^{-1}$

**MS (EI):** *m/z* (%) 204.80 (100), 161.47 (80), 147.81 (92), 120.01 (43), 91.74 (19).

**Enantiomeric excess** 62% determined by HPLC [Column: Chiralcel OD-H; Solvent system: Hexane/*Iso*-propanol (70:30); Flow rate: 1.0 mL/min; $\lambda$max = 254 nm; $t_R$ = 14.7 min (minor, *R* isomer), $t_R$ = 20.9 min (major, *S* isomer).

### *(R)-4-Hydroxy-4-(2-nitrophenyl)butan-2-one (57):*
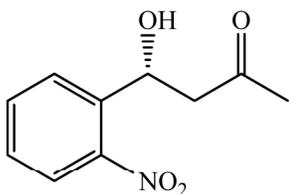


In 25 mL flask, amino oxazoline **46** (0.062 g, 0.20 mmol, 20 mol %) and acetone **7** (0.23 g, 4.0 mmol) was stirred in dry THF at 5 – 8 °C for 30 min. To the resulting solution 2-Nitrobenzaldehyde **56** (0.151 g, 1.0 mmol) was added and stirred at the same temperature for 72 hrs. Solvent was evaporated under reduced pressure then 20 mL water was added to the crude mixture and extracted 3 x 20 mL with ethylacetate, combined organic layer was dried over sodium sulfate and solvent was evaporated on rotary evaporator. The crude material was purified by column chromatography using 60 – 120 mesh silica gel and ethylacetate : petroleum ether as eluent to afford aldol product **57** (*R* isomer) (0.142 g, 69%) light yellow solid.

**M.P.** 58 – 60 °C (Lit.[36] 59 - 61 °C). $[\alpha]_D^{27}$ = -157.57 (*c* 0.3, CHCl$_3$). [lit.[37] $[\alpha]_D^{25}$ = -141.0 (*c* 0.5, CHCl$_3$), 91% *ee*]

**IR (KBr):** $\upsilon$ 3420, 3080, 2924, 1715, 1613, 1528, 1352 cm.$^{-1}$

**$^1$H-NMR (400 MHz, CDCl3):** $\delta$ 8.00 – 7.98 (dd, *J* = 1.2 & 8.4 Hz, 1H), 7.93 – 7.91 (dd, *J* = 1.6 & 8.0 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.48 – 7.44 (m, 1H), 5.71 – 5.68 (dd, *J* = 2.0 & 8.2 Hz, 1H), 3.73 (bs, 1H), 3.19 – 3.14 (m, 1H), 2.78 – 2.71 (m, 1H), 2.26 (s, 3H).

**IR (KBr):** 3420, 3080, 2924, 1715, 1613, 1528, 1352 cm$^{-1}$

**MS (EI):** *m/z* (%) 190.94 (M$^+$-18, 5), 151.17 (34), 131.78 (77), 103.98 (100), 90.83 (26), 76.61 (40).

**Enantiomeric excess** 91% determined by HPLC [Column: Lux 5$\mu$ Amylose-2; Solvent system: Hexane/*Iso*-propanol (90:10); Flow rate: 1.0 mL/min; $\lambda$max = 220 nm; $t_R$ = 36.7 min (minor, *S* isomer), $t_R$ = 40.4 min (major, *R* isomer)].

### (R)-4-Hydroxy-4-(3-nitrophenyl)butan-2-one (59):
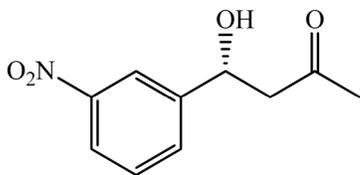


Mixture of amino oxazoline **46** (0.062 g, 0.20 mmol, 20 mol %) and acetone **7** (0.23 g, 4.0 mmol) was stirred in dry THF at 5 – 8 $^{\circ}$C for 30 min. To the resulting solution 3-Nitrobenzaldehyde **58** (0.151 g, 1.0 mmol) was added and stirred at the same temperature for 72 hrs. Solvent was evaporated under reduced pressure then 20 mL water was added to the crude mixture and extracted 3 x 20 mL with ethylacetate, combined organic layer was dried over sodium sulfate and solvent was evaporated on rotary evaporator. The crude material was purified by column chromatography using 60 – 120 mesh silica gel and ethylacetate : petroleum ether as eluent to afford aldol product **59** (*R* isomer) (0.154 g, 73%) off white solid.

**M.P.** 50 $^{\circ}$C (Lit.[38] 50 – 52 $^{\circ}$C). $[\alpha]_D^{27} = +63.13$ (*c* 0.5 in CHCl$_3$). [Lit.[39] $[\alpha]_D^{20} = +62.1$ (*c* 0.35, CHCl3), 87% *ee*]

**$^1$H-NMR (400 MHz, CDCl3):** δ 8.25 (s, 1H), 8.15 – 8.13 (m, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.52 (m, 1H), 5.28 – 5.25 (m, 1H), 3.71 (bs, 1H), 2.91 – 2.89 (m, 2H), 2.24 (s, 3H).

**IR (KBr):** 3419, 3087, 2920, 1710, 1620, 1534, 1354 cm$^{-1}$

**MS (EI)**: *m/z* (%) 191.55 (M$^+$-18, 100), 150.29 (77), 118.82 (28), 104.83 (74), 90.85 (39), 76.92 (89), 57.75 (66).

**Enantiomeric excess** 74% determined by HPLC [Column: Lux 5µ Amylose-2; Solvent system: Hexane/*Iso*-propanol (90:10); Flow rate: 1.0 mL/min; λmax = 220 nm; $t_R$ = 28.7 min (major, *R* isomer), $t_R$ = 40.4 min (major, *S* isomer)].

### (R)-4-(4-Chlorophenyl)-4-hydroxybutan-2-one (61):
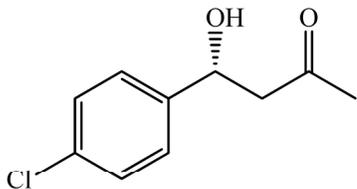


In a clean dry 25 mL flask, mixture of amino oxazoline **46** (0.062 g, 0.20 mmol, 20 mol %) and acetone **7** (0.23 g, 3.98 mmol) was stirred in dry THF at 5 – 8 $^{\circ}$C for 30 min. To the

resulting solution 4-Chlorobenzaldehyde **60** (0.14 g, 0.996 mmol) was added and stirred at the same temperature for 72 hrs. Solvent was evaporated under reduced pressure then 20 mL water was added to the crude mixture and extracted 3 x 20 mL with ethylacetate, combined organic layer was dried over sodium sulfate and solvent was evaporated on rotary evaporator. The crude material was purified by column chromatography using 60 – 120 mesh silica gel and ethylacetate : petroleum ether as eluent to afford aldol product **59** (*R* isomer) (0.093 g, 47%) as white solid.

**M.P.** 50 °C (Lit.[35] 47 – 50 °C). $[\alpha]_D^{26}$ = +55.17 (*c* 0.5, CHCl$_3$). [Lit.[37] $[\alpha]_D^{18}$ = +62.7 (c 0.48, CHCl$_3$), 93% *ee*]

**$^1$H-NMR (400 MHz, CDCl3):** δ 7.35 – 7.29 (m, 4H), 5.16 – 5.13 (m, 1H), 3.42 (d, *J* = 2.8 Hz, 1H), 2.90 – 2.78 (m, 2H), 2.22 (s, 3H).

**IR (KBr):** υ 3425, 3000, 2901, 1717, 1600, 1321, 571, 490 cm$^{-1}$

**MS (EI)**: *m/z* (%) 200 (8), 197.74 (39), 182.16 (10), 180.21 (14), 164.75 (13), 144.88 (31), 142.20 (15), 140.72 (100), 112.73 (26), 76.86 (57).

**Enantiomeric excess** 66% determined by HPLC [Column: Lux 5μ Amylose-2; Solvent system: Hexane/*Iso*-propanol (90:10); Flow rate: 1.0 mL/min; λmax = 220 nm; $t_R$ = 28.5 min (major, *R* isomer), $t_R$ = 31.3 min (major, *S* isomer).]

***(R)-4-(4-Bromophenyl)-4-hydroxybutan-2-one (63):***
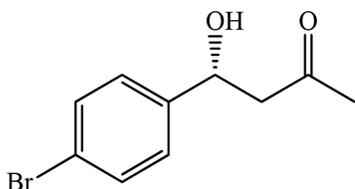


Mixture of amino oxazoline **46** (0.062 g, 0.20 mmol, 20 mol %) and acetone **7** (0.23 g, 4.0 mmol) was stirred in dry THF at 5 – 8 °C for 30 min. To the resulting solution 4-Bromobenzaldehyde **62** (0.185 g, 1.0 mmol) was added and stirred at the same temperature for 72 hrs. Solvent was evaporated under reduced pressure then 20 mL water was added to the crude mixture and extracted 3 x 20 mL with ethylacetate, combined organic layer was dried over sodium sulfate and solvent was evaporated on rotary evaporator. The crude material was purified by column chromatography using 60 – 120 mesh silica gel and ethylacetate : petroleum ether as eluent to afford aldol product **63** (*R* isomer) (0.120 g, 49%) as off white solid

**M.P.** 58 °C (Lit.[38] 58 - 60 °C). $[\alpha]_D^{27}$ = +26.61 (*c* 0.51 in CHCl₃) [Lit.[40] $[\alpha]_D^{20}$ = +47 (*c* 0.5, CHCl₃), 95% *ee*]

**¹H-NMR (400 MHz, CDCl3):** δ 7.50 – 7.48 (dd, *J* = 1.6 & 6.4 Hz, 2H), 7.27 – 7.24 (m, 2H), 5.15 – 5.12 (m, 1H), 3.40 (d, *J* = 3.2 Hz, 1H), 2.90 – 2.78 (m, 2H), 2.22 (s, 3H).

**IR (KBr):** 3247, 3067, 3027, 2844, 1718, 1605, 1322, 1077, 1051, 1028, 749, 687, 572, 544 cm⁻¹
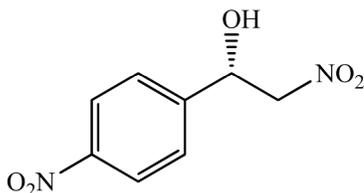
**MS (EI)**: *m/z* (%) 244 (34), 242.04 (33), 226.11 (25), 225.21 (19), 186.98 (73), 185.00 (100), 158.99 (17), 156.96 (31), 76.84 (87).

**Enantiomeric excess** 84% determined by HPLC [Column: Chiralpak IC; Solvent system: Hexane/*Iso*-propanol (90:10); Flow rate: 1.0 mL/min; λmax = 254 nm; $t_R$ = 31.4 min (minor, *S* isomer), $t_R$ = 32.4 min (major, *R* isomer)].

## *Synthetic Procedure:*

*(S)-2-Nitro-1-(4-nitrophenyl)ethanol (64):*



In a clean dry 10 mL flask, $Cu(OAc)_2.H_2O$ (0.010 g, 0.049 mmol, 5 mol%) was dissolved in dry ethanol (3 mL) at room temperature then amino oxazoline **46** (0.020 g, 0.099 mmol, 10 mol %) was added to the same flask at 5-8 $^o$C and stirred for 1 h at the same temperature. To this green coloured catalyst solution, nitromethane (0.625 g, 9.93 mmol) was added drop wise at the same temperature and stirred for additional 30 min. Then 4-nitrobenzaldehyde (0.150 g, 0.993 mmol) was added to the same flask and stirred for 72 h at 5-8 $^o$C. Solvent was evaporated under reduced pressure and resulting gummy crude product was purified by Column Chromatography using 60-120 mesh silica gel; mixture of ethylacetate and petroleum ether as eluent to afford Henry product **64** (0.157 g, 74%) as off white solid.

**M.P.** 80-82 $^o$C (Lit.[41] 80-85 $^o$C); $[\alpha]_D^{30}$ = +12.01 (*c* 1.01, $CH_2Cl_2$) [Lit.[31a] $[\alpha]_D^{25}$ = +35.9 (*c* 1.01, $CH_2Cl_2$), 92% *ee*]

**^{1}H-NMR (400 MHz, CDCl₃):** δ 8.28 – 8.26 (dd, *J* = 2.0 & 6.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 5.64 – 5.60 (m, 1H), 4.64 – 4.55 (m, 2H), 3.20 (d, *J* = 4.0 Hz, 1H).

**IR (KBr):** 3507, 2920, 2849, 1553, 1514, 1411, 1381, 1346, 1072, 849 cm$^{-1}$

**Enantiomeric excess** 31% determined by HPLC [Column: Chiralcel OD-H; Solvent system: Hexane/*Iso*-propanol (85:15); Flow rate: 0.8 mL/min; λmax = 254 nm; $t_R$ = 19.8 min (minor, *R* isomer), $t_R$ = 24.8 min (major, *S* isomer).

# Spectral Data for Asymmetric Aldol Products
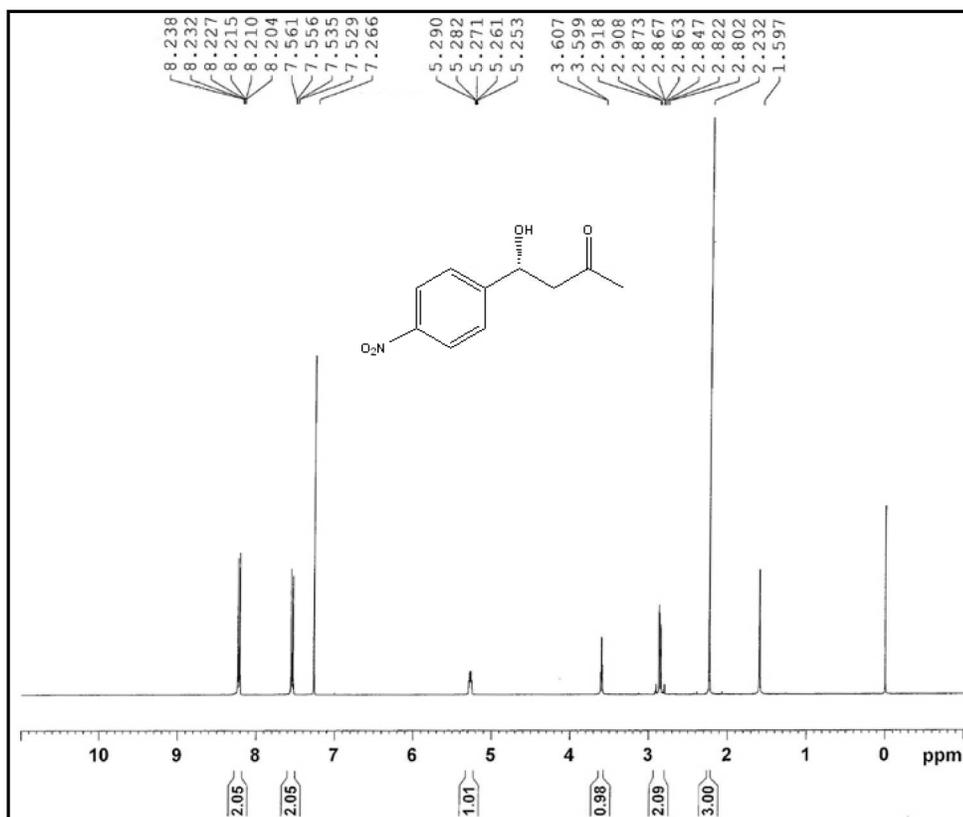


$^1$H-NMR of the compound 8 (400 MHz, CDCl$_3$)
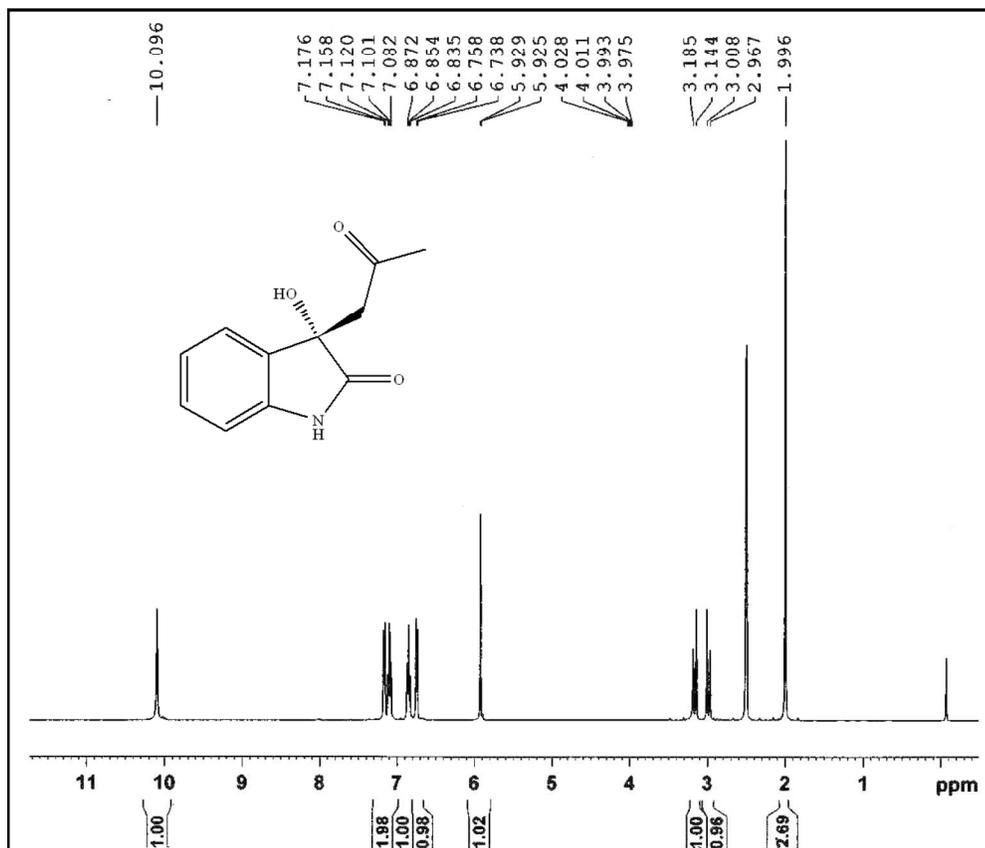


$^1$H-NMR of the compound 29 (400 MHz, DMSO)
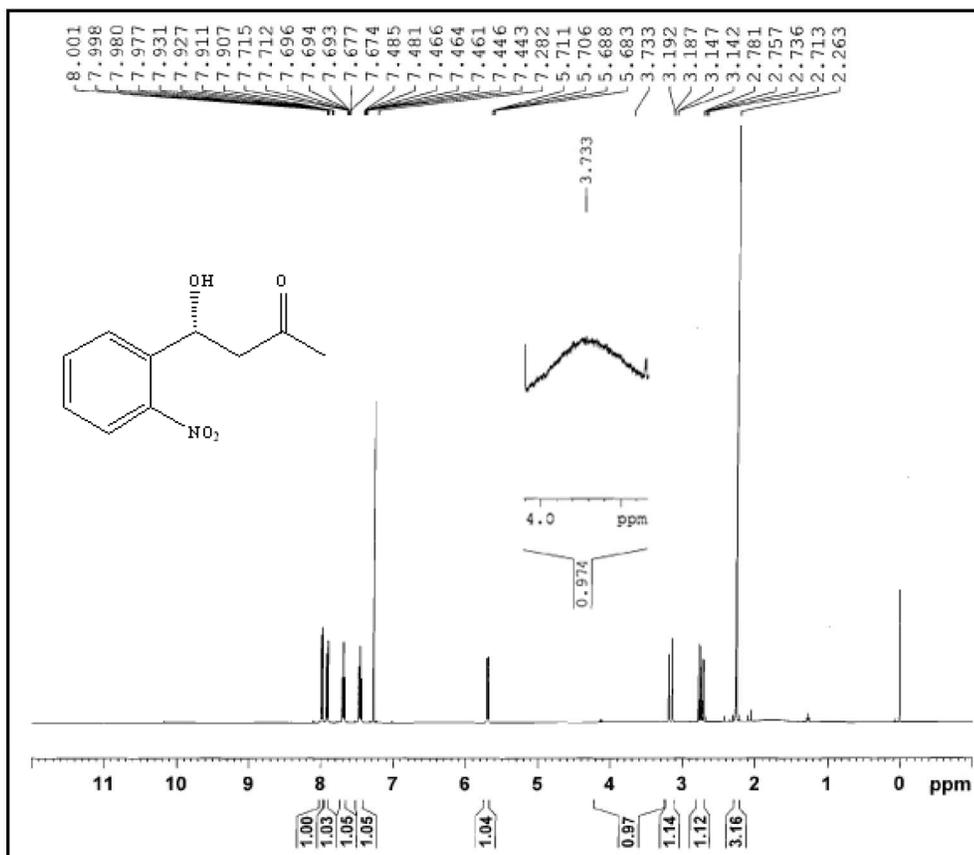
**¹H-NMR of the compound 57 (400 MHz, CDCl₃)**
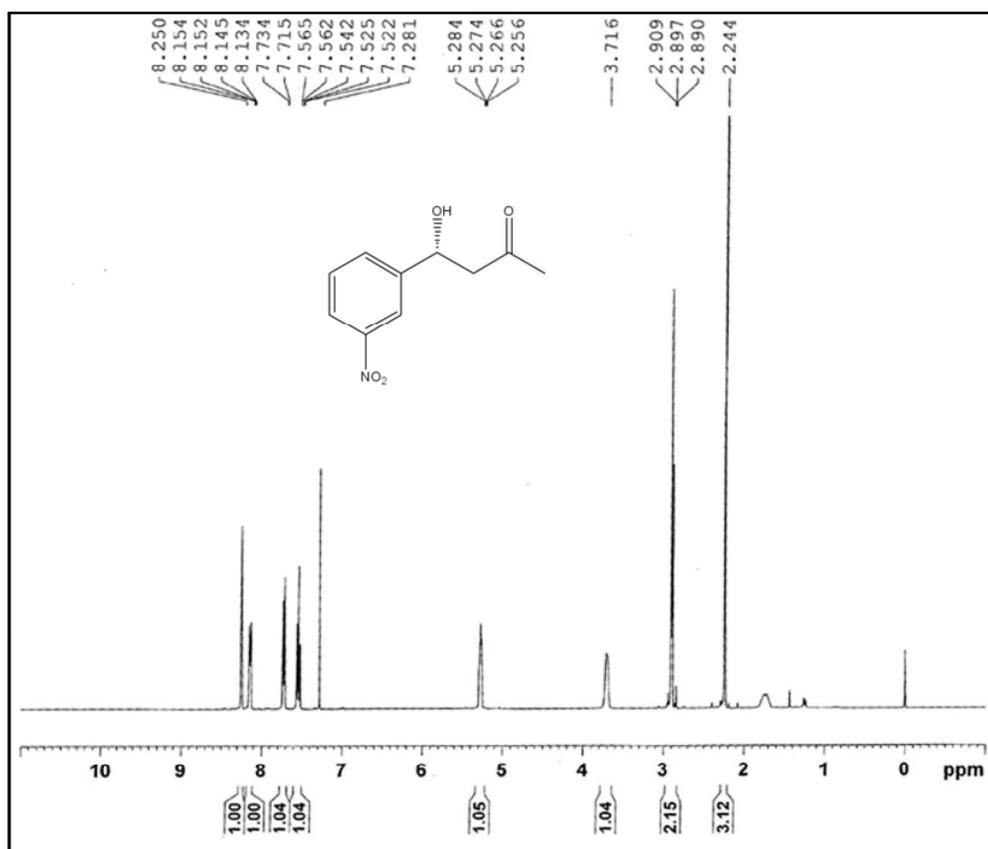


**¹H-NMR of the compound 59 (400 MHz, CDCl₃)**
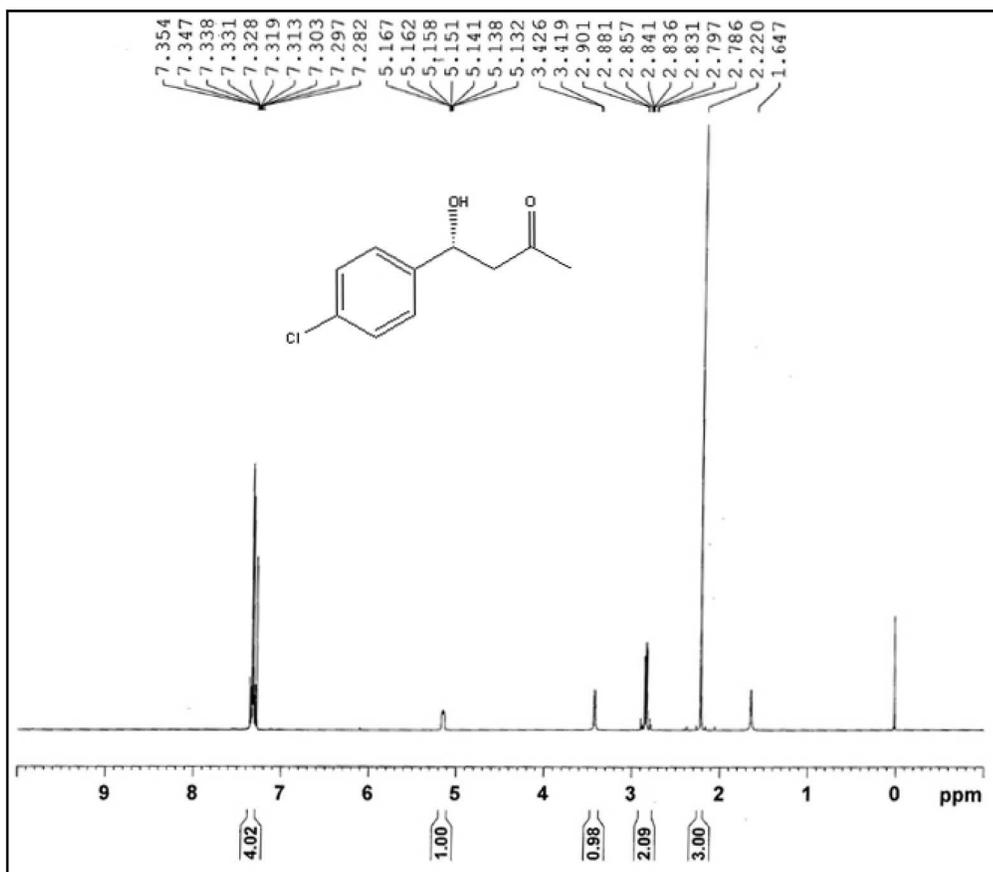
$^1$H-NMR of the compound 61 (400 MHz, CDCl$_3$)
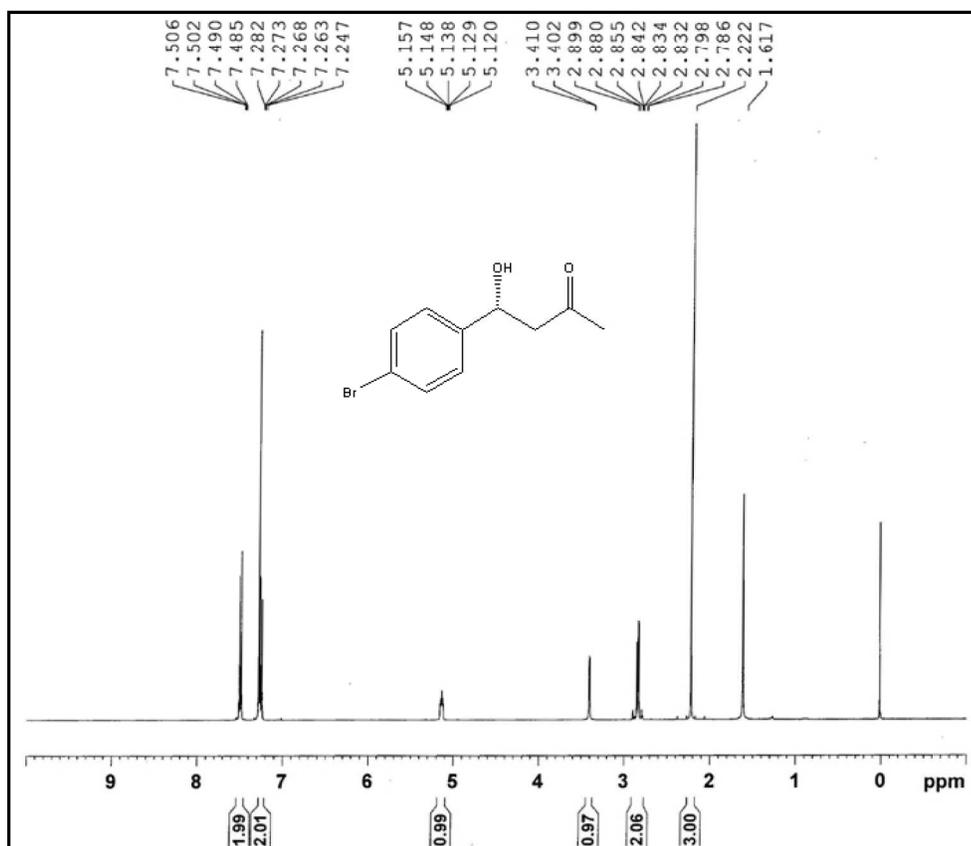


$^1$H-NMR of the compound 63 (400 MHz, CDCl$_3$)

220

# HPLC Data for Aldol Products



racemic



## PeakTable

Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 26.670 | 322480 | 6426 | 4.313 | 7.518 | RT26.670 |
| 2 | 31.750 | 7154434 | 79049 | 95.687 | 92.482 | RT31.750 |
| Total | | 7476914 | 85474 | 100.000 | 100.000 | |
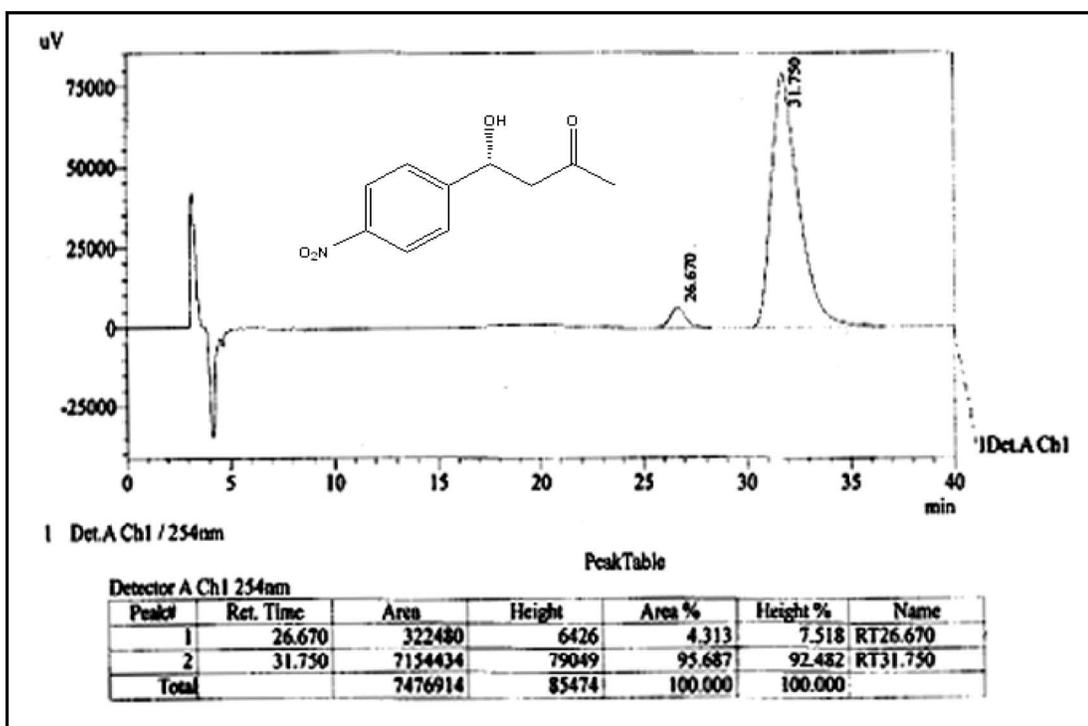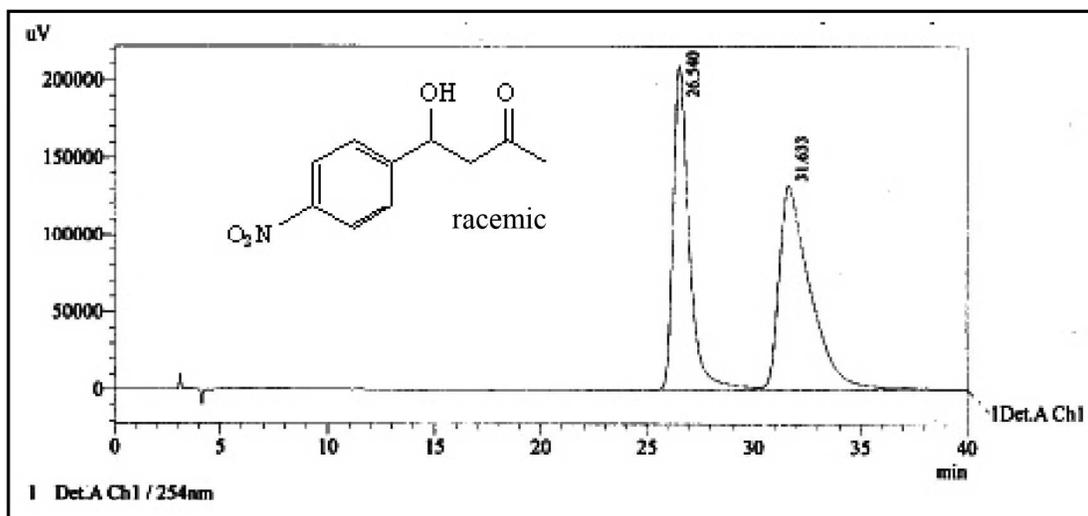
**Method For HPLC Analysis of the compound 8:**

Solvent System: *n*-Hexane: *Iso*-propanol (90:10)

Flow rate: 1 mL/min.

Detector: UV-Vis (λmax – 254 nm)

Chiral Column: Lux 5μ Amylose-2

1  Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 14.826 | 4248156 | 107038 | 50.798 | 62.562 | RT14.826 |
| 2 | 24.251 | 4114711 | 64054 | 49.202 | 37.438 | RT24.251 |
| Total | | 8362868 | 171091 | 100.000 | 100.000 | |



I  Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 14.715 | 1551022 | 40743 | 19.144 | 26.766 | RT14.715 |
| 2 | 20.887 | 6550707 | 111479 | 80.856 | 73.234 | RT20.887 |
| Total | | 8101729 | 152222 | 100.000 | 100.000 | |

**Method For HPLC Analysis of the compound 29:**

Solvent System: *n*-Hexane: *Iso*-propanol (70:30)

Flow rate: 1 mL/min.

Detector: UV-Vis (λmax – 254 nm)

Chiral Column: Chiralcel OD-H

222

| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 36.739 | 247516 | 4383 | 4.676 | 5.567 | RT36.739 |
| 2 | 40.422 | 5046366 | 74352 | 95.324 | 94.433 | RT40.422 |
| Total | | 5293882 | 78735 | 100.000 | 100.000 | |

**Method For HPLC Analysis of the compound 57:**

Solvent System: *n*-Hexane: *Iso*-propanol (90:10)

Flow rate: 1 mL/min.

Detector: UV-Vis ($\lambda$max – 220 nm)

Chiral Column: Lux 5µ Amylose-2



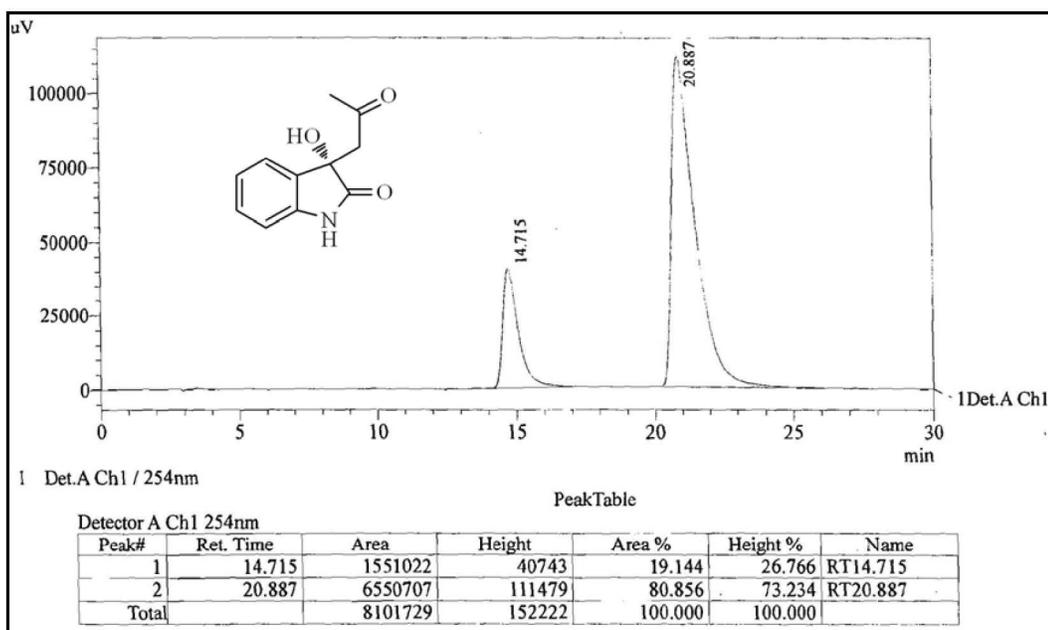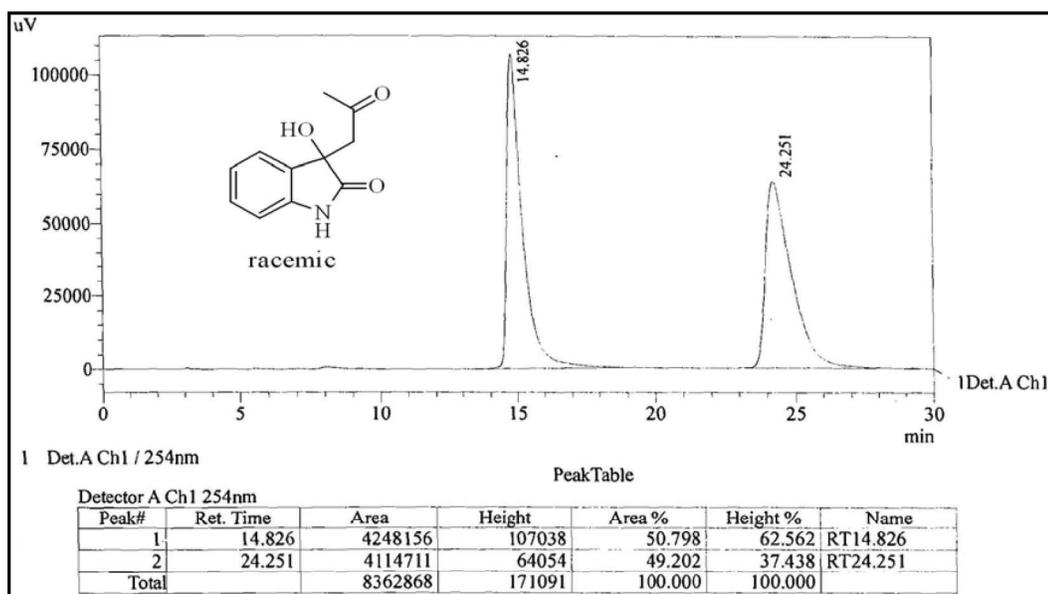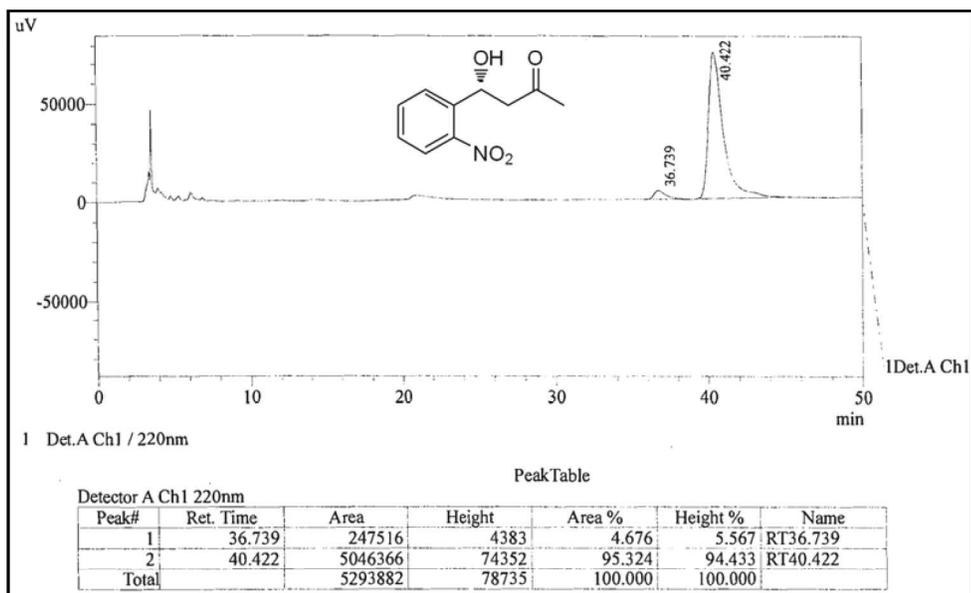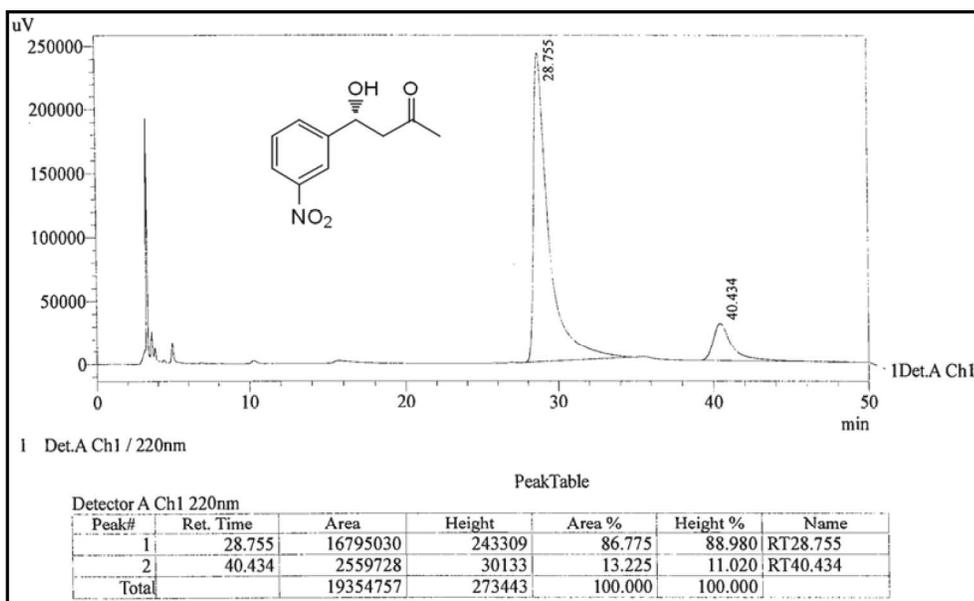| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 28.755 | 16795030 | 243309 | 86.775 | 88.980 | RT28.755 |
| 2 | 40.434 | 2559728 | 30133 | 13.225 | 11.020 | RT40.434 |
| Total | | 19354757 | 273443 | 100.000 | 100.000 | |

**Method For HPLC Analysis of the compound 59:**

Solvent System: *n*-Hexane: *Iso*-propanol (90:10)

Flow rate: 1 mL/min.

Detector: UV-Vis ($\lambda$max – 220 nm)

Chiral Column: Lux 5µ Amylose-2

223

**PeakTable**

Detector A Ch1 220nm

| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 28.522 | 18863707 | 381627 | 82.905 | 89.487 | RT28.522 |
| 2 | 31.308 | 3889634 | 44833 | 17.095 | 10.513 | RT31.308 |
| Total | | 22753341 | 426459 | 100.000 | 100.000 | |

**Method For HPLC Analysis of the compound 61:**

Solvent System: *n*-Hexane: *Iso*-propanol (90:10)

Flow rate: 1 mL/min.

Detector: UV-Vis (λmax – 220 nm)

Chiral Column: Lux 5μ Amylose-2]



**PeakTable**

Detector A Ch1 220nm

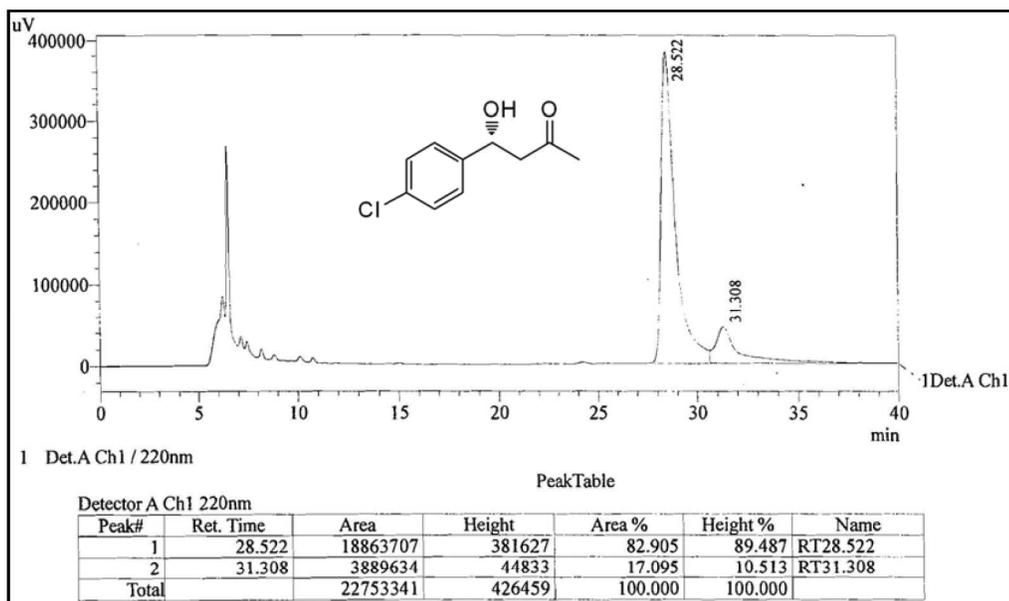| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 31.451 | 3046552 | 97378 | 8.099 | 9.062 | RT31.451 |
| 2 | 32.426 | 34568281 | 977149 | 91.901 | 90.938 | RT32.426 |
| Total | | 37614832 | 1074528 | 100.000 | 100.000 | |

**Method For HPLC Analysis of the compound 63:**

Solvent System: *n*-Hexane: *Iso*-propanol (90:10)

Flow rate: 1 mL/min.

Detector: UV-Vis (λmax – 254 nm)

Chiral Column: Chiralpak IC

224

# Spectral Data for Asymmetric Henry Product



**^{1}H-NMR of the compound 64 (400 MHz, CDCl[3])**

# HPLC Data for Henry Products



uV
500000
400000
300000
200000
100000
0

OH
NO₂

O₂N

racemic

19.980
25.085

1Det.A Ch1

0    5    10    15    20    25    30    35
min

1   Det.A Ch1 / 254nm



uV
500000
250000
0

OH
NO₂

O₂N

19.878
24.845

1Det.A Ch1

0    5    10    15    20    25    30
min

1   Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

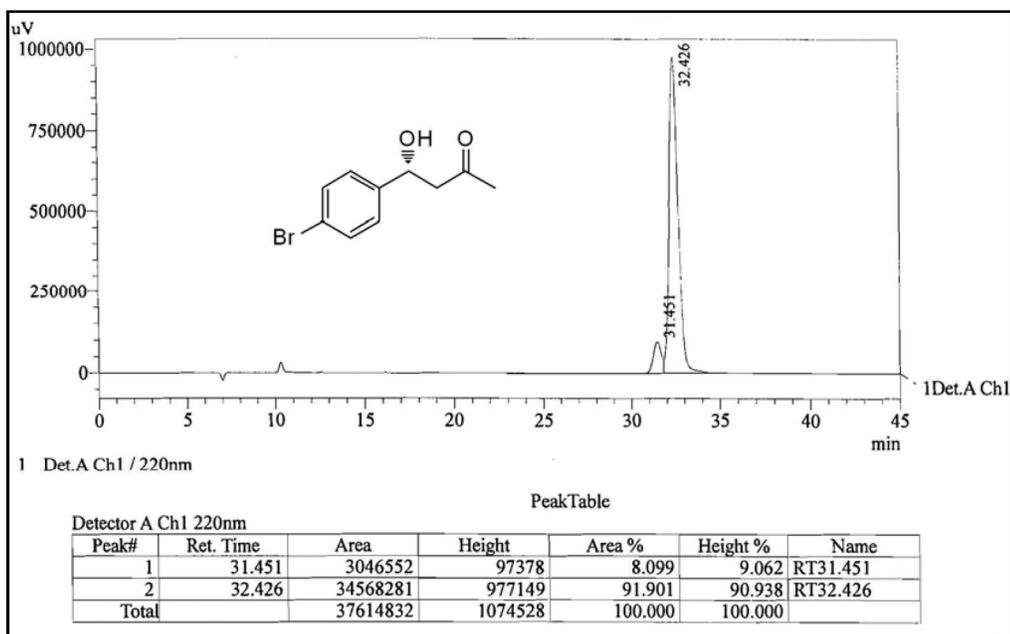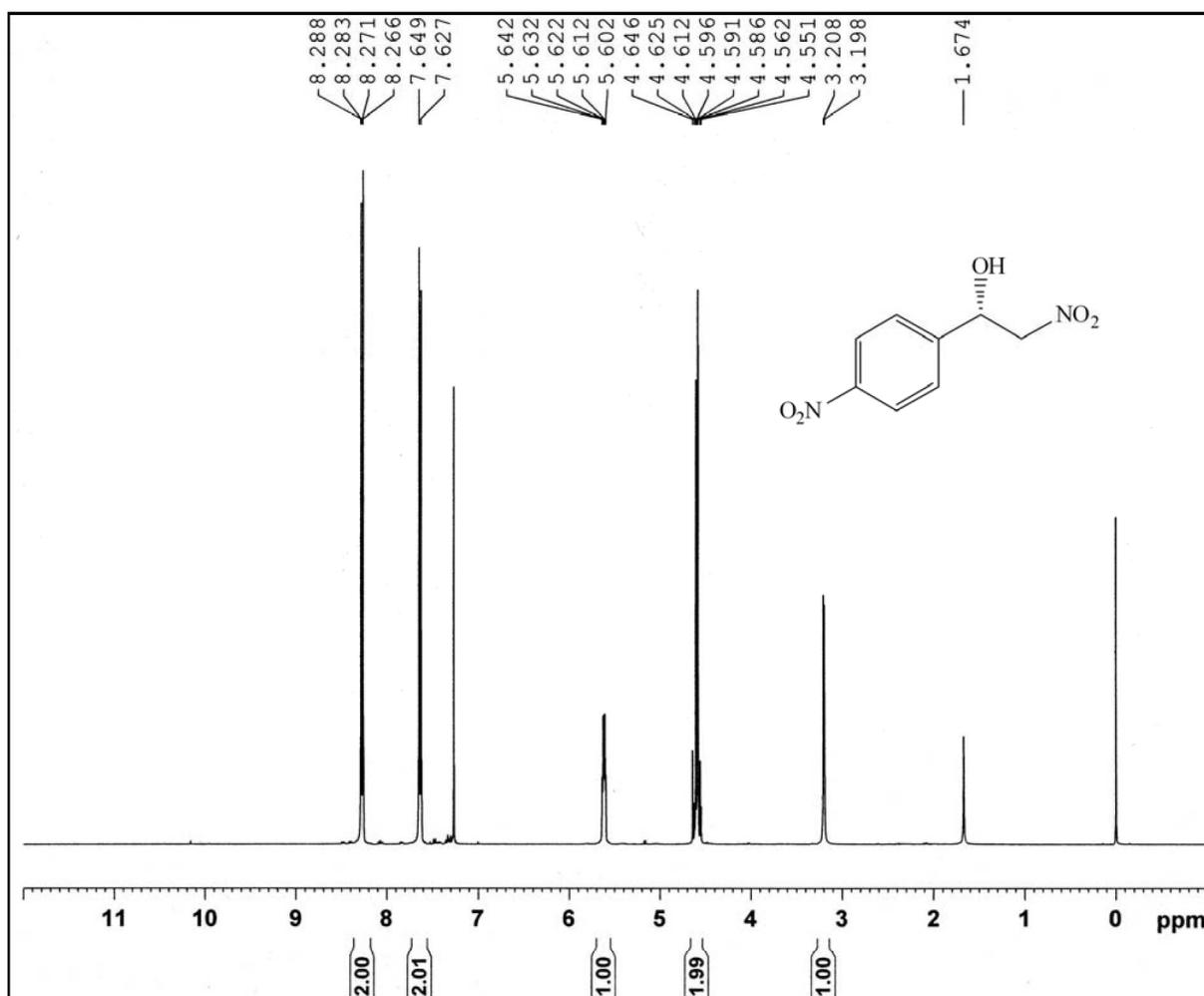| Peak# | Ret. Time | Area | Height | Area % | Height % | Name |
|---|---|---|---|---|---|---|
| 1 | 19.878 | 2448752 | 407318 | 34.419 | 41.083 | RT19.878 |
| 2 | 24.845 | 4665786 | 584133 | 65.581 | 58.916 | RT24.845 |
| Total | | 7114538 | 991451 | 100.000 | 100.000 | |

**Method For HPLC Analysis of the compound 64:**

Solvent System: *n*-Hexane: *Iso*-propanol (85:15)
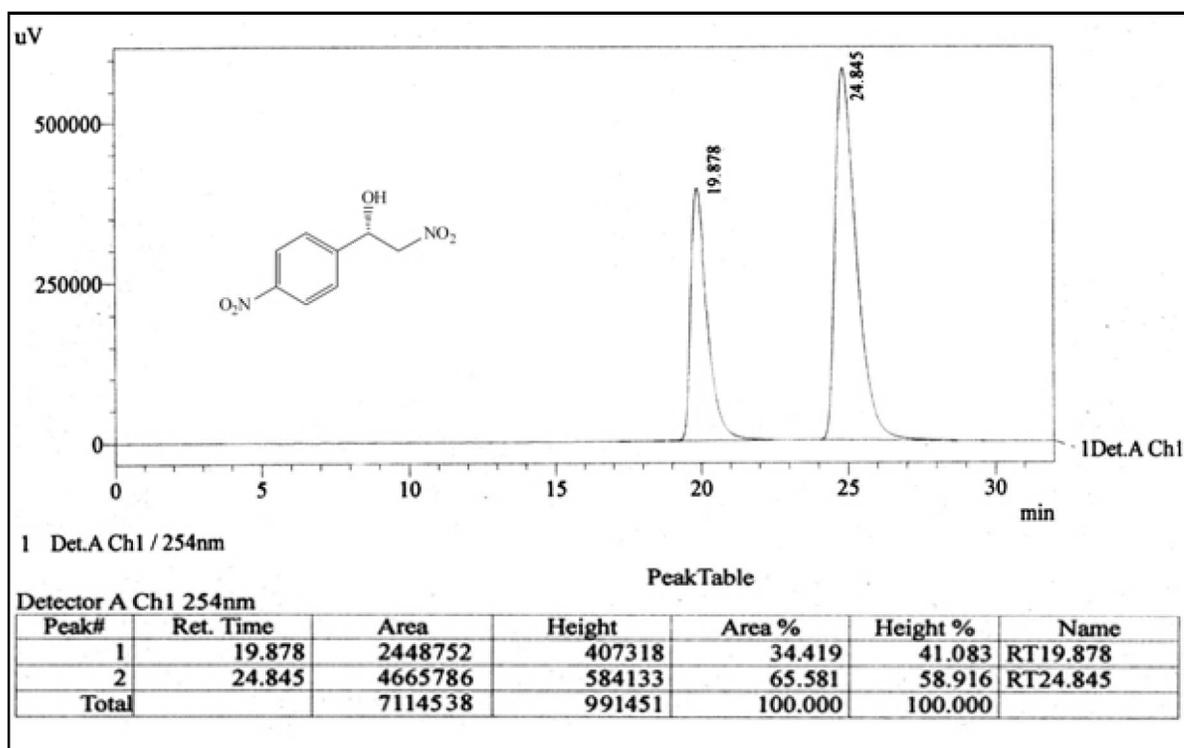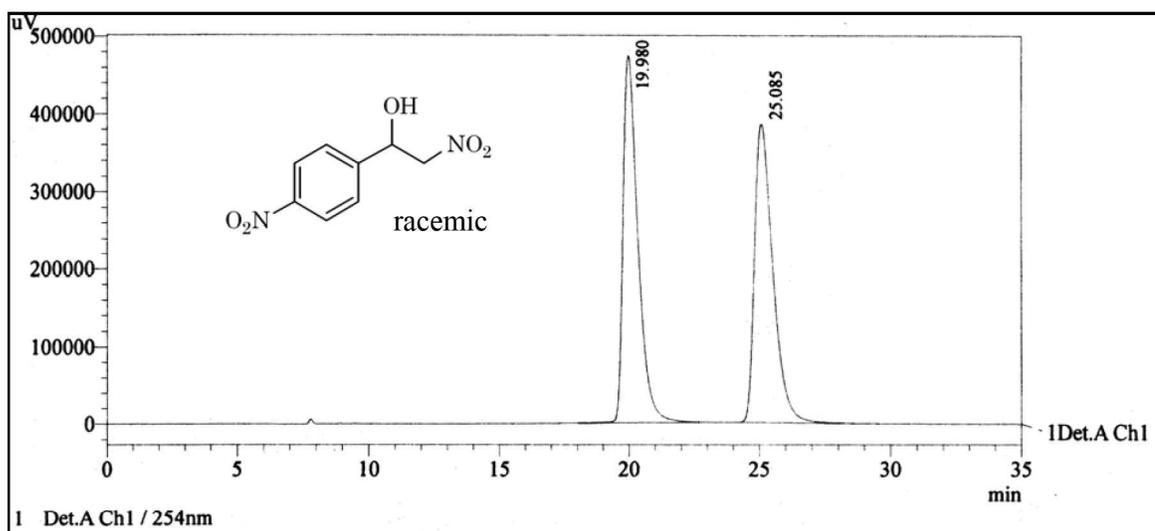
Flow rate: 0.8 mL/min.

Detector: UV-Vis (λmax – 254 nm)

Chiral Column: Chiralcel OD-H

# Conclusion

➢ A series of chiral amino oxazolines were synthesized and screened as organocatalysts for asymmetric intermolecular aldol reaction between acetone and aromatic aldehydes. The reaction works well with a range of aromatic aldehydes showing good to high selectivity. The present new system of organocatalyst was effective for the asymmetric aldol reaction for a wide range of aromatic aldehydes and isatin to accomplish the asymmetric carbon-carbon bond forming reaction with a high selectivity of up to 91 % *ee*.

➢ We have also applied some of these aminooxazolines for copper catalyzed asymmetric Henry reaction which exhibited moderate enatioinduction.

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