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Asymmetric Henry Reaction of Nitromethane with Substituted Aldehydes Catalyzed by Novel In Situ Generated Chiral Bis(β-Amino Alcohol-Cu(OAc)$_2$·H$_2$O Complex

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Abstract: Novel chiral thiophene-2,5-bis(β-amino alcohol) ligands (**L1**–**L5**) were designed and synthesized from thiophene-2,5-dicarbaldehyde (**3**) with chiral β-amino alcohols (**4a–e**) in 4 steps with overall 23% yields. An in situ generated **L**-Cu(OAc)$_2$·H$_2$O catalyst system was found to be highly capable catalyst for the asymmetric Henry reaction of nitromethane (**7**) with various substituted aromatic aldehydes (**6a–m**) producing chiral nitroaldols product (**8a–m**) with excellent enantiomeric purity (up to 94.6% ee) and up to >99% chemical yields. 20 mol% of **L4**-Cu(OAc)$_2$ catalyst complex in EtOH was effective for the asymmetric Henry transformation in 24 h, at ambient temperature. Ease of ligand synthesis, use of green solvent, base free reaction, mild reaction conditions, high yields and excellent enantioselectivity are all key factors that make this catalytic system robust and highly desirable for the access of versatile building block β-nitro alcohol in practical catalytic usage via asymmetric Henry reaction.

Keywords: asymmetric catalysis; Henry reaction; Lewis acid; amino alcohols; chiral thiophene-2,5-bis-(β-amino alcohol) ligands

Citation: Alammari, A.S.; Al-Majid, A.M.; Barakat, A.; Alshahrani, S.; Ali, M.; Islam, M.S. Asymmetric Henry Reaction of Nitromethane with Substituted Aldehydes Catalyzed by Novel In Situ Generated Chiral Bis(β-Amino Alcohol-Cu(OAc)$_2$·H$_2$O Complex. *Catalysts* **2021**, *11*, 1208. https://doi.org/10.3390/catal11101208

Academic Editor: Takeshi Ohkuma

Received: 29 August 2021
Accepted: 1 October 2021
Published: 8 October 2021

1. Introduction

The catalytic synthesis of chiral building blocks is highly desirable to many researchers worldwide because enantiomeric enriched molecules have numerous medicinal importance and applications [1–5]. In recent years, significant improvement has been made in the development of newly synthesized and designed stereoselective catalytic systems in order to access enantiomerically enriched molecules [2,6,7].

Lewis-acid metal catalyzed nucleophilic addition of nitroalkane to carbonyl compound is an important aspect allowing us to furnace a large number of important molecular frameworks [8,9]. Henry reaction [10] (i.e., nitroaldol condensation) is one of the prominent transformations to access a wide range of strategically fundamental molecular structures such as β-hydroxy nitro alkanes, α-hydroxy carboxylic acids and 1,2-amino-alcohols, etc., in a forthright fashion [9,11]. Henry reaction also provides a facile and direct access of various versatile building block β-nitro alcohols [10,12,13] which are the vital skeleton found in many biologically active compounds, such as antibiotics L-acosamine [14], anti-asthmatic drug (*R*)-salmeterol [15], fungicide (*S*)-spirobrassinin [16] and bestatin [17]. Due to the dual functionality of β-nitro alcohol, it can be easily transformed into various functionalities via a several roots such as reduction of nitro group into amine, dehydration leads to nitro-olefin, denitration, or other transformations such as Nef reaction and retro-Henry reaction (Figure 1) [18]. Asymmetric Henry approach has been widely reported in the literature; for example, Suami and coworkers employed the asymmetric Henry reaction as a key step during the total synthesis of nucleoside antibiotics 'tunicamycin-V' [12,19].

The total synthesis of tetrodotoxin from D-glucose, using two-step Henry reactions was developed by Sato group [20]. Of late, Dixon et al. reported an efficient process for the total synthesis of natural products marine alkaloid 'manzamine A', and '(−)-nakadomarin A' involving aza-Henry and Henry reaction [21,22] (Figure 2). It is evident from the above facts that we should emphasize the great utility of the Henry reaction in practical organic transformation.

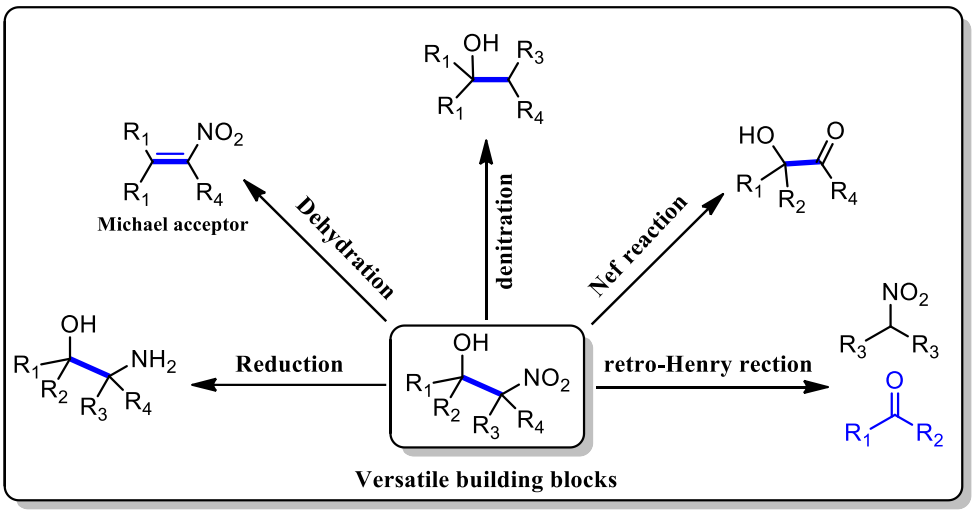


Figure 1. Versatile building blocks can be formulated from Henry-aldol products.

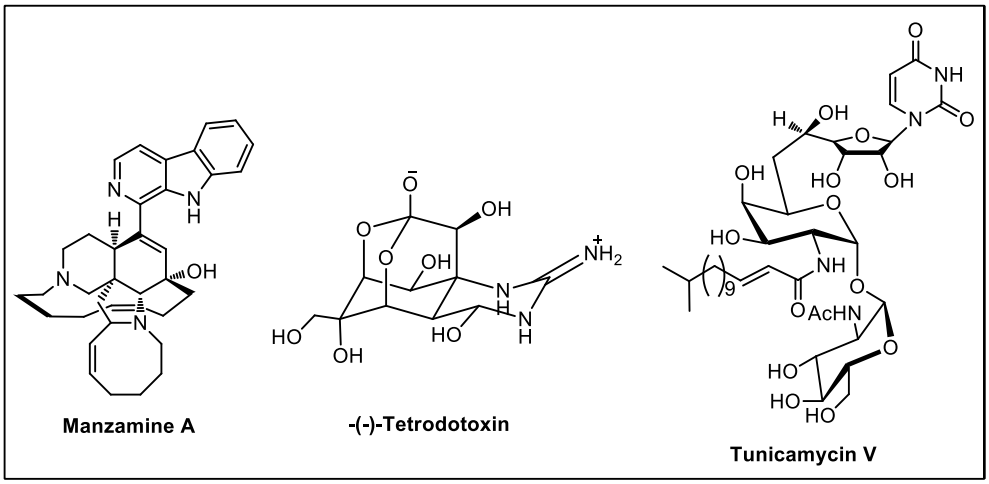


Figure 2. The application of Henry reaction in natural products.

The catalytic-controlled enantioselective Henry reaction was developed and reported for the first time by Shibasaki [23]. Since then, significant efforts have been made for the development of an efficient catalytic system including both metal catalysts [24], as well as organocatalysts [25]. For example, copper(II) complexes of chiral ethane-1,2-diamine derivatives [26,27], bis(oxazolidine)ligands-copper(II) complexes [28], 1,10-binaphthalene-2,20-diol based lanthanide complexes [29], and C_2-symmetric alcohols induced dinuclear zinc(II) complexes [30] were used as a metal-based catalyst in asymmetric Henry reaction applied successfully, while chiral cinchona alkaloids [31], bis(thioureas) [32,33] and guanidines [34] were explored as examples of organocatalysts for Henry reaction which have proved to be work efficiently.

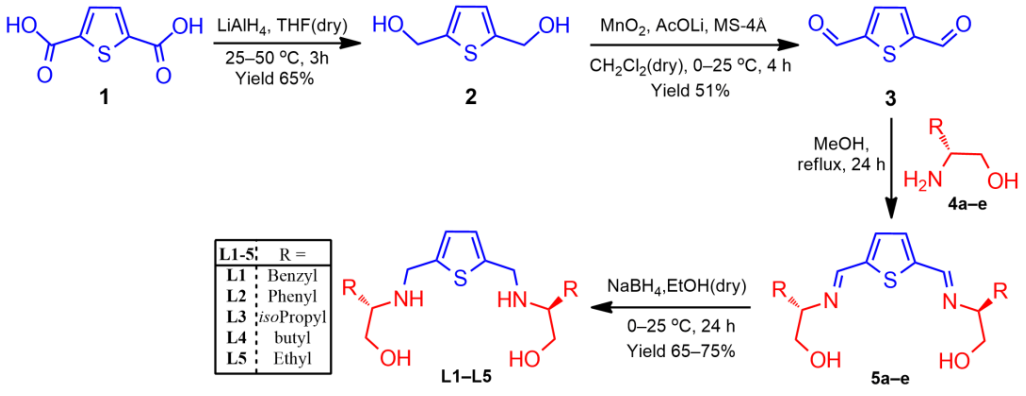
Several enantioselective Henry reactions have been documented recently, such as application of chiral trans-cyclohexane-1,2-diamine-copper complexes described in the asymmetric Henry reaction in modest to excellent enantioselectivity [35–42]. Formation

of binuclear copper(II) complexes of two chiral β-amino alcohols connected to benzene ring in 1,4-positions to the central backbone developed and explored in asymmetric Henry reaction by Zhang et al. [43]. Moreover, transition metal catalyzed asymmetric Henry reactions summarized by Velmathi et al. prior to 2011 have been well documented [33,44–49]. Many reports suggested that the chiral bi-functional coordination complexes system efficiently controls the stereochemical outcomes of the reaction (Shibasaki [23], Jørgensen [50], Trost [30], Yamada [51] and Palomo [52]). However, in their findings some genuine limitations have been found, such as use of organic bases like nucleophilic silyl nitronates as additives, low reaction temperatures (even lower than −20 °C) and comparatively high catalyst loadings, etc. Evans and coworkers have developed a catalytic system based on copper acetate-chiral bis-oxazoline ligand for Henry reaction affording nitroaldol in high yield with excellent enantioselectivity [28]. In general, readily available, cheap, effective catalytic system, mild reaction conditions, low catalyst loading, and a high degree of stereo-induction are still a challenging task for the development of sustainable catalytic systems [53]. Therefore, design, synthesis and development of new chiral ligand based on an optically active system is still desirable for the catalytic asymmetric Henry reactions [43].

Since the main family of successful chiral ligands predominantly belongs to diphosphine, diamine, di-ol etc, i.e., phosphorous, nitrogen and oxygen-containing substrate, large amount of work has been done on these areas. From the past few years, researchers have been eagerly keen to develop chiral ligands for enantioselective catalysis, based on sulfur containing compounds due to high coordination ability of sulfur atom to most of the transition metals. The sulfur atom is considered as a soft atom which can form strong bonds with soft metals like Cu(II). In addition, sulfur ligands are poor σ-donor and poor π-acceptor ligands as compared to phosphine ligands which results in strong metal-sulfur bond strength. Moreover, sulfur-containing compounds are easily accessible and easy to handle as well as store due to their more tolerance to air as compared to phosphine containing ligands, and therefore they are highly stable [54].

In this article, we report the synthesis of chiral ligands based on thiophene framework and their applications in asymmetric henry reaction as part of our ongoing research project in our laboratory.

Based on these facts, we synthesized a new chiral thiophene-2,5-bis (β-amino alcohol) ligands (**L1**–**L5**) (Scheme 1) possessing two trans-β-hydroxy amine units attached to C1 and C4 carbon of thiophene ring and we explored their utilities for asymmetric Henry reaction (nitroaldol condensation).



Scheme 1. Synthesis of New amino alcohol chiral Ligands **(L1–L5)**.

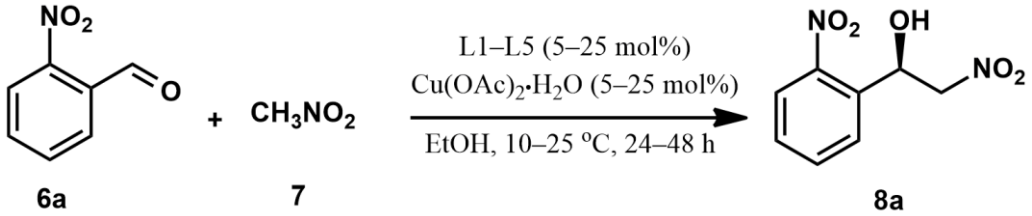
2. Results and Discussion

*2.1. Synthesis of Ligand **L1–L5***

A series of C_2-symmetric thiophene based chiral bis (β-amino alcohol) ligands (**L1–L5**) have been synthesized in 4 steps from a commercially available starting material thiophene-2,5-dicarboxlyic acid (**1**) and variety of chiral β-amino alcohols (**4a–e**) with good yield and excellent optical purity as depicted in Scheme 1. Initially, thiophene-2,5-dicarboxlyic acid (**1**) was reduced into thiophene-2,5-diyldimethanol (**2**) by 2.5 eq. of $LiAlH_4$ in dry THF with 65% chemical yield, followed by reported literature procedure [55,56]. The product thiophene-2,5-dicarbaldehyde (**3**) was obtained as dark red solid in 51% isolated yield from the oxidation of thiophene-2,5-diyldimethanol (**2**) using the mixture of MnO_2 (2.2 eq.) and Lithium acetate (2.2 eq.) in dry CH_2Cl_2 as oxidizing agent with 30 mg pre-treated 4Å molecular sieve as reported in the literature [57,58]. Thiophene-2,5-dicarbaldehyde (**3**) was then allowed to react with various chiral β-amino alcohols (2.2 eq. **4a–e**) in methanol under reflux for 24 h afforded the corresponding enamines (**4a–e**) those were successfully reduced by $NaBH_4$ (2.6 eq.) [59], in ethanol to yield the desired chiral bis (β-amino alcohol) ligands (**L1–L5**) in 65–75% isolated yield and excellent optical purity (Scheme 1). All the intermediates (**2, 3, 5a–e**) and final ligands (**L1–L5**) were characterized by NMR, LCMS and FT-IR techniques.

2.2. Catalytic Studies of the Henry Reaction

At the very outset, in order to achieve isolated crystalline material of the metal-ligand complex, several metal salts including ($Cu(OAc)_2 \cdot H_2O$, $CuBr_2$, $CuCl_2$, $Cu(OTf)_2$, $Zn(OTf)_2$) were allowed to react with pure ligands (**L1–L5**) in various solvents (ethanol, methanol, toluene, diethylether, and THF) under inert atmosphere using Schlenk tube technique. Despite multiple attempts were carried out, but the desired ligand metal complexes were unsuccessfully isolated. Therefore, we decided to test the catalytic activity of our ligand and in situ generated complex with metal salt. Initially, we tested the efficiency of our newly synthesized ligands (**L1–L5**) for asymmetric Henry reaction (Scheme 2) in the presence of $Cu(OAc)_2 \cdot H_2O$ in ethanol by choosing nitromethane (**7**) and 2-nitrobenzaldehyde (**6a**) as model substrate (Table 1). The first attempt, equimolar of ligands (**L1–L5**) and $Cu(OAc)_2 \cdot H_2O$ (20 mol%) in ethanol (2 mL) were stirred at 25 °C under inert atmosphere for 2h to generate blue colored solution of **L**-$Cu(OAc)_2.H_2O$ complex followed by addition of the model substrate 2-nitrobenzaldehyde (**6a**). After 20 min of stirring at room temperature nitromethane (**7**) was added to the reaction and further stirred for 24–48 h at ambient temperature to produce nitroaldol Henry product (**8a**) and the results were summarized in Table 1. Surprisingly, our initial results exhibits that all the ligands (**L1–L5**) under the above reaction parameters performed very well to induce excellent enantioselectivity (89.9–94.6% ee) with high chemical yields (90–99%) (Table 1, entries 1–5). However, Ligand **L4** was found to be the best choice for the asymmetric Henry reaction which yielded 99% chemical yield and high enantioselectivity 94.6% ee in 24h (Table 1, entry 4) at ambient temperature. In order to optimize the catalyst loading, we further perform the Henry reaction by employing the most efficacy catalyst system i.e., **L4**-$Cu(OAc)_2 \cdot H_2O$ complex under different catalyst loading (5, 10, 25 mol%) in ethanol for 24 h but unfortunately no further improvements were observed (Table 1, entries 7–9). To achieve higher enantioselectivity, the Henry reaction was carried out at lower temperature 10 °C for 48 h which produces 87% chemical yields and 90.4% ee (Table 1, entries 6). It was obvious that 20 mol% of the catalytic system **L4**-$Cu(OAc)_2 \cdot H_2O$ in ethanol at 25 °C for 24 h was found to be the best catalytic system for asymmetric Henry reaction.



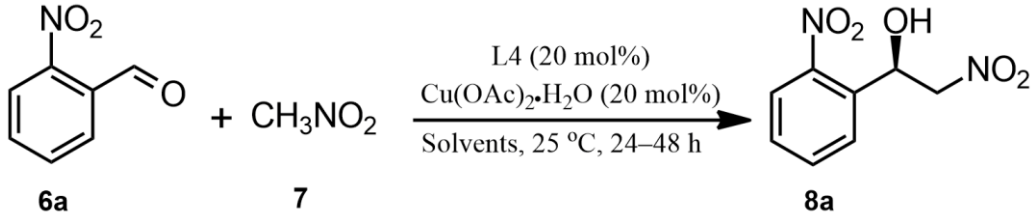
Scheme 2. Asymmetric Henry Reaction of nitromethane (**7**) with 2-nitrobenzaldehyde (**6a**), ligands screening.

Table 1. Henry reaction investigation of nitromethane (**7**) with 2-nitrobenzaldehyde (**6a**) as model substrate; Ligand screening.

Entry [a]	Ligands	L:Cu(OAc)$_2$·H$_2$O (mol%)	Temp [t]	Time [T/h]	Yield (%) [b]	ee % [c]
1.	L1	20	25 °C	24	99	92.3
2.	L2	20	25 °C	24	90	94.0
3.	L3	20	25 °C	48	91	89.9
4.	L4	20	25 °C	24	99	94.6
5.	L5	20	25 °C	48	89	90.0
6.	L4	20	10 °C	48	87	90.4
7.	L4	5	25 °C	24	80	87.1
8.	L4	10	25 °C	24	88	85.2
9.	L4	25	25 °C	24	99	94.0

[a] Reaction was performed on a 0.2 mmol scale of aldehyde and 2 mmol of nitromethane; [b] Yield of the isolated product after flash column chromatography; [c] Determined by HPLC analysis on a Daicel Chiralcel OD-H column (25 cm × 4.6 mm × 5 µm).

Next, aiming to find out the best medium for Henry reaction (Scheme 3), several solvents were examined like methanol, isopropanol, isobutanol, and tetrahydrofuran using best reaction condition 20 mol% **L4**-Cu(OAc)$_2$·H$_2$O at room temperature for 24–48 h and the results are shown in Table 2. Almost in all solvent's reaction proceeded very well with commendable yields (79–99%) and enantioselectivity (68.3–86.6% ee) (Table 2, entries 1–4). However, in methanol high yield (88%) and high enantioselectivity (85.3% ee) were observed, on the contrary in THF lowest yield (79%) and lowest enantiomeric excess (68.3% ee) was obtained (Table 2, entries 1 & 4). Moderate to excellent yield (80% & 99%) and enantiomeric excess (86.6%, 82.6% ee) were achieved when the reaction was performed in isopropanol, isobutanol respectively (Table 2, entries 2 & 3). However, ethanol remains the best choice for the asymmetric Henry reaction.



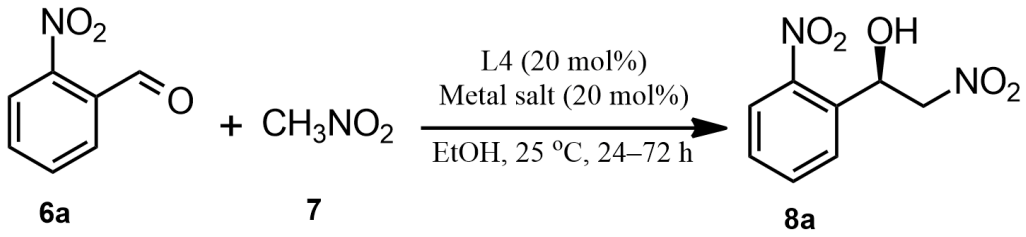
Scheme 3. Asymmetric Henry Reaction of nitromethane (**7**) with 2-nitrobenzaldehyde (**6a**), solvent screening.

Table 2. Solvent screening on the enantioselective Henry Reaction of nitromethane (**7**) with 2-nitrobenzaldehyde (**6a**).

Entry [a]	Solvent	Time (h)	Yield (%) [b]	ee % [c]
1.	MeOH	24	88	85.3
2.	*i*-PrOH	48	80	86.6
3.	*t*-BuOH	48	99	82.6
4.	THF	48	79	68.3

[a] Reaction was performed on a 0.2 mmol scale of aldehyde and 2 mmol of nitromethane; [b] Yield of the isolated product after flash column chromatography; [c] Determined by HPLC analysis on a Daicel Chiralcel OD-H column (25 cm × 4.6 mm × 5 µm).

Further, we investigated the effects of various metal salts such as $Cu(OAc)_2 \cdot nH_2O$, $Zn(OTf)_2$, $Cu(OTf)_2$, $CuBr_2$, $CuCl_2$ and $Zn(OAc)_2 \cdot 2H_2O$ as a Lewis acid with keeping in mind that the other reaction parameters unchanged with prolonged reaction time up to 72 h (Scheme 4), the results are summarized in Table 3. From these results it can be infer that the ligand **L4** with Cu(II)acetate complex is the only choice for the asymmetric Henry reaction which is capable of inducing chirality (up to 94.6%) into the nitroaldol product **8a** in high chemical yield (Table 3, entry 1). The best performance of copper(II) acetate perhaps could be attributed to its high effectiveness in chelate formation with ligands than the other tested copper(II) salts [60]. Although **L4**-$Zn(OTf)_2$ system produced excellent chemical yield but failed to induce enantioselectivity (only 6.6% ee) (Table 3, entry 3), while **L4**-$Zn(OAc)_2 \cdot 2H_2O$ complex produce 50% yield with 19% ee (Table 3, entry 7) which is obviously insignificant. The metal salts $Cu(OTf)_2$, $CuBr_2$ and $CuCl_2$ in combination with **L4** were found to inactive in catalyzing the Henry reaction (Table 2, entries 4–6).



Scheme 4. Asymmetric Henry Reaction of nitromethane (**7**) with 2-nitrobenzaldehyde (**6a**), metal salts screening.

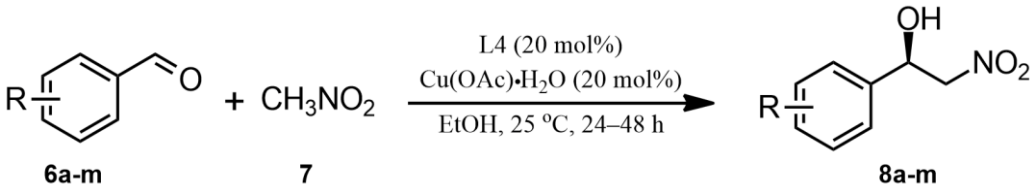
Table 3. Effect of metal salt on the enantioselective Henry Reaction of nitromethane with 2-nitrobenzaldehyde.

Entry [a]	Metal Salt	Time [T/h]	Yield (%) [b]	ee (%) [c]
1.	$Cu(OAc)_2 \cdot H_2O$	24	99	94.6
2.	$Cu(OAc)_2 \cdot nH_2O$	24	97	94.3
3.	$Zn(OTf)_2$	48	99	6.6
4.	$Cu(OTf)_2$	72	20	1
5.	$CuBr_2$	72	-	-
6.	$CuCl_2$	72	-	-
7.	$Zn(OAc)_2 \cdot 2H_2O$	72	50	19.0

[a] Reaction was performed on a 0.2 mmol scale of aldehyde and 2 mmol of nitromethane; [b] Yield of the isolated product after flash column chromatography; [c] Determined by HPLC analysis on a Daicel Chiralcel OD-H column (25 cm × 4.6 mm × 5 µm).

To illustrate the generality of this catalytic approach, asymmetric Henry reaction (Scheme 5) was performed with a variety of aromatic aldehydes (**6a**–**m,** 13 examples) and nitromethane (**7**) utilizing the optimized reaction conditions (20 mol% **L4**-$Cu(OAc)_2 \cdot H_2O$ in ethanol for 24–48 h at rt). All of the screened aromatic aldehydes produced corresponding nitroaldol product (**8a**–**m**) predominantly with enriched of *(R)*-enantiomer with moder-

ate to excellent isolated yields (66–99%) and enantioselectivities (53–95% ee) (Scheme 5, Table 4). Although, higher enantioselectivities (81–94% ee) and yields (82–99%) were found corresponding to the *ortho*, *meta*, *para* nitro-benzaldehyde, *p*-tolualdehyde and benzaldehyde (Table 4, entry 1–3, 11, 13), However, there is no clear, conclusive evidence which suggests that there is any kind of influence in the enantioselectivity due to steric factor as well as electronic environments of the substituents in the aromatic ring (Table 4, entries 1–13). Previously asymmetric Henry reaction has been reported by Lu et al. [59] with very good yield (89–98% ee) in 24–48 h at 10 °C, using similar type of amino alcohol chiral ligand- $Cu(OAc)_2 \cdot H_2O$. Jin et al. reported asymmetric Henry reaction with excellent enantiomeric excess using CuBr-diamine catalyst in the presence of another additive like pyridine [40]. Amino Alcohol–Cu(II) complex has been used to catalyze asymmetric Henry reaction by Qin et al. and very high ee % obtained with prolonged time 48–72 h. However, in our study we have optimized the reaction at room temperature in ethanol as green solvent, good to high enantiomeric access were achieved without using any additives within reasonable timeframe (24–48 h) at ambient temperature. Several Literature suggest that the retention time of the *R* enantiomer is lesser than the *S* enantiomer for the nitroaldol products. Therefore, the absolute configuration of all the newly synthesized chiral nitroaldol product (**8a**–**m**) were assigned as *R* respectively by comparing their retention time found in reported literature [40,59,61,62].



Scheme 5. Asymmetric Henry Reaction of nitromethane substrate scope.

Table 4. Substrate scope of aldehydes and nitromethane in the asymmetric Henry reaction.

Entry [a]	R (6a–m)	Products	Time (h)	Yield (%) [b]	ee % [c]
1.	2-NO_2	**8a**	24	99	94.6 (*R*)
2.	4-NO_2	**8b**	24	96	81.3 (*R*)
3.	3-NO_2	**8c**	48	91	81.2 (*R*)
4.	4-Br	**8d**	48	80	76.4 (*R*)
5.	Naph	**8e**	48	66	75.1 (*R*)
6.	4-CF_3	**8f**	24	82	58.9 (*R*)
7.	2,4-Cl	**8g**	48	86	53.0 (*R*)
8.	4-Cl	**8h**	48	66	73.1 (*R*)
9.	4-F	**8i**	48	75	60.9 (*R*) [d]
10.	4-OCH_3	**8j**	24	77	63.9 (*R*) [d]
11.	4-CH_3	**8k**	24	85	81.3 (*R*)
12.	3-CH_3	**8l**	48	88	60.8 (*R*) [d]
13.	H	**8m**	48	82	89.2 (*R*)

[a] Reactions were performed with the aldehyde (0.2 mmol) and nitromethane (1 mmol) in 2 mL of ethanol; [b] Isolated yield after column chromatography; [c] Determined by chiral HPLC analysis on a Daicel Chiralcel OD-H column (25 cm × 4.6 mm × 5 µm). [d] Due to some impurities altered the ee %.

3. Experiments

3.1. General

Reagents obtained from commercial suppliers were used without further purification. Preparation of bis(β-amino alcohol) ligands was performed in flask dried glassware under a static pressure of nitrogen. Solvents were dried prior to use following standard procedures. Reactions were monitored by thin layer chromatography using Merck (silica gel 60 Kieselgel F254 TLC (Merck, Kenilworth, NJ, USA) and column chromatography was performed on silica gel 100–200 mesh (40–63 µm, 200 mesh, ASTM) from Merck using the indicated

solvents. ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Jeol Spectrometer (Jeol, Tokyo, Japan) (400 MHz and 500 MHz). The chemical shifts are reported in ppm relative to $CDCl_3$ (δ(ppm) = 7.26) or d_6-DMSO (δ(ppm) = 2.50) for ^{1}H-NMR. For the ^{13}C-NMR spectra, the residual $CDCl_3$ (δ(ppm) = 77.16 in ppm) or d_6-DMSO (δ(ppm) = 39.5 in ppm). All the racemic products were freshly prepared as per the method reported in the literature [61]. Infrared spectra were recorded on a Thermo Scientific Nicolet iS10 FT-IR spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Enantiomeric ratios were determined by analytical chiral HPLC analysis on a Shimadzu LC-20A Prominence instrument (Shimadzu, Kuoto, Japan) with a chiral stationary phase using Daicel Chiralcel OD-H columns (Chiral Technologies Europe, Illkirch Graffenstaden, France) (80–95% *n*-hexane/*iso*-propanol) (Supplementary Materials). Optical rotations were obtained with a Perkin-Elmer 343 polarimeter (Perkin-Elmer, Waltham, MA, USA). Melting points (m.p.) were recorded on a Thomas–Hoover (Thomas–Hoover, Keller, TX, USA) capillary melting point apparatus and were not corrected. Mass spectrometric analysis was done using ESI mode on AGILENT Technologies 6410-triple quad LC/MS instrument (Agilent, Santa Clara, CA, USA). Elemental analyses were performed on Perkin-Elmer PE 2400 CHN Elemental Analyzer with autosampler, CHN mode.

*3.2. Synthesis of thiophene-2,5-diyldimethanol (**2**)*

A solution of thiophene-2,5-dicarboxylic acid (1.40 g, 8.14 mmol) in dry THF (50 mL) were added slowly to a the pre stirred suspension of lithium aluminum hydride (0.76 g, 20.00 mmol) in dry tetrahydrofuran (100 mL) at 0 °C [55,56]. The reaction was then warmed up to 50 °C and stirred for 3h followed by cooling of temperature to ambient temperature. The reaction was then neutralized with saturated Na_2SO_4 solution and filtered through celite bed. The filtrate was concentrated in vacuum to afford thiophene-2,5-diyldimethanol (**2**) was obtained as red oil (0.76 g, 65%); IR (KBr, cm^{-1}): 3364, 3082, 3066, 2956, 1613, 1543, 1515, 1464, 1023, 741; ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 6.86 (s, 2H, thiophene-**H**), 4.78 (s, 4H, C**H**$_2$), 2.00 (s, 2H, O**H**); ^{13}C-NMR (126 MHz, $CDCl_3$) δ(ppm) = 144.46, 125.42, 60.33; LC/MS (ESI, m/z): found 145.02 $[M+H]^+$, exact mass 144.02 for $C_6H_8O_2S$; Anal. calcd. for $C_6H_8O_2S$: C, 49.98; H, 5.59 found C, 49.73; H, 5.44.

*3.3. Synthesis of thiophene-2,5-dicarbaldehyde (**3**)*

A suspension solution of thiophene-2,5-diyldimethanol (**2**) (144 mg, 1 mmol) in dry CH_2Cl_2 (35 mL) were added to a previously stirred suspension solution of MnO_2 (191.25 mg, 2.2 mmol), Lithium acetate (145.18 mg, 2.2 mmol) and pre-activated molecular sieve 4Å (30 mg) in dry CH_2Cl_2 (20 mL) at room temperature. After 4h, the reaction turned into dark red suspension which was then filtered through grit-glass filter with Celite 521. The solvents were then removed under reduced pressure to afford crude product. The crude material was purified by column chromatography using silica gel (100–200 mesh) and ethyl acetate/*n*-hexane (40%) as an eluent to obtain the pure compound (**3**) as dark red solid (yield 71.5mg, 51%) [57,58]; m.p. 114–115 °C; IR (KBr, cm^{-1}): 3083, 3075, 2942, 1721, 1541, 1511, 1461, 1033, 741 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 10.02 (s, 2H, C**H**O), 7.83 (s, 2H, thiophene-**H**), 4.76 (s, 4H, C**H**$_2$). ^{13}C-NMR (126 MHz, $CDCl_3$) δ(ppm) = 183.58, 149.25, 135.29; LC/MS (ESI, m/z): found 139.99 $[M+H]^+$, exact mass for $C_6H_8O_2S$ is140.16; Anal. calcd. for $C_6H_4O_2S$: C, 51.42; H, 2.88; found C, 51.22; H, 2.94.

*3.4. General Procedure for Synthesis of Chiral Diamine Alcohol Ligands (**L1**–**L5**)*

General Procedure (**GP1**): In a 100 mL round bottom flask, thiophene-2,5-dicarbaldehyde (**3**) (140 mg; 1 mmol) and chiral β-amino alcohol (**4a**–**e**) (2.2 mmol) were dissolved in dry methanol (25 mL). The reaction was then vigorously stirred for 24 h under reflux condition in an inert atmosphere. Then the solvents were evaporated and washed with cold diethyl ether (2 × 20 mL) and dried to avail chiral enamine Schiff base (**5a**–**e**). The chiral enamines (**5a**–**e**) (1 mmol) suspended in dry ethanol (20 mL) followed by portion wise addition of $NaBH_4$ (2.6 eq.) in four equal parts and kept on stirring at ambient temperature for 24 h [59].

After completion of the reaction (approximately 24h), solvent was completely removed under reduced pressure and added plenty of water, solid precipitate comes out which was filtrated and further purified by column chromatography using silica gel (100 mesh) and 7–10% ($MeOH/CH_2Cl_2$) as eluent to obtain the desired Ligands (**L1**–**L5**) in good yield (65–75%).

3.4.1. ((2*S*,2′*S*)-2,2′-((Thiophene-2,5-diylbis(methylene))bis(azanediyl))bis(3-phenylpropan-1-ol) (**L1**)

Following **GP1**, thiophene-2,5-dicarboaldehyde (**3**) and (*S*)-2-amino-3-phenylpropan-1-ol (**4a**) were reacted to produce diamine alcohol (**L1**) as pale brown solid (308 mg, 75%); m.p. 124–125 °C; $[\alpha]_D^{25}$ = +1.39° (c 0.064, MeOH); IR (KBr, cm^{-1}): 3390, 3287, 3131, 3058, 2924, 2855, 1604, 1494, 1451, 1384, 1027, 747 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ(ppm) = 7.25 (t, *J* = 7.5 Hz, 4H, Ar–**H**), 7.17 (t, *J* = 6.0 Hz, 6H, Ar–**H**), 6.69 (s, 2H, thiophene-**H**), 4.55 (t, *J* = 5.5 Hz, 2H, O**H**), 3.85 (d, *J* = 3.1 Hz, 4H, C$\mathbf{H}_2$NH), 3.32 (dd, *J* = 10.9, 5.1 Hz, 2H, C$\mathbf{H}_2$OH), 3.23 (dd, *J* = 10.9, 5.1 Hz, 2H, C$\mathbf{H}_2$-OH), 2.75 (q, *J* = 5.8 Hz, 2H, C**H**NH), 2.68 (*J* = 13.4, 5.8 Hz, 2H, C$\mathbf{H}_2$–Ph), 2.62 (*J* = 13.4, 5.8 Hz, 2H, C$\mathbf{H}_2$-Ph), 1.93 (br, 2H, N**H**); ^{13}C-NMR (126 MHz, DMSO-d_6) δ(ppm) = ^{13}C NMR (126 MHz, DMSO-D6) δ(ppm) 143.60, 139.69, 129.32, 128.10, 125.79, 123.66, 62.20, 59.69, 45.77, 37.28; LCMS (ESI, m/z): found 410.20 $[M+H]^+$, exact mass 410.20 for $C_{24}H_{30}N_2O_2S$; Anal. calcd. for $C_{24}H_{30}N_2O_2S$: C, 70.21; H, 7.37; N, 6.82; found C, 70.15; H, 7.33; N, 6.78.

3.4.2. (2*S*,2′*S*)-2,2′-((Thiophene-2,5-diylbis (methylene))bis(azanediyl))bis(2-phenylethan-1-ol) (**L2**)

Following **GP1**, thiophene-2,5-dicarboaldehyde (**3**) and (*S*)-2-amino-2-phenylethan-1-ol (**4b**) were reacted to produce chiral diamine alcohol (**L2**) as pale brown solid (256 mg, 67%); m.p. 100–103 °C; $[\alpha]_D^{25}$ = +87.13° (c 0.124, MeOH); IR (KBr, cm^{-1}): 3292, 3061, 3030, 2918, 2863, 1602, 1492, 1453, 1337, 1025, 761 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ(ppm) = 7.41–7.31 (m, 6H, Ar–**H**), 7.28–7.21 (m, 2H, Ar–**H**), 6.67 (s, 2H, thiophene-**H**), 4.88 (s, 2H, O**H**), 3.72 (dt, *J* = 8.4, 4.3 Hz, 2H, C**H**NH), 3.63 (t, *J* = 7.7 Hz, 4H, C$\mathbf{H}_2$NH), 3.58(d, *J* = 6.0 Hz, 2H, C$\mathbf{H}_2$N), 3.45 (dd, *J* = 10.6, 4.6 Hz, 2H, C$\mathbf{H}_2$OH), 2.55 (td, *J* = 7.3, 3.7 Hz, 2H, N**H**). ^{13}C-NMR (126 MHz, DMSO-d_6) δ(ppm) = 143.07, 141.54, 128.25, 127.54, 127.04, 123.97, 66.44, 63.66, 45.67; LCMS (ESI, m/z): found 383.20 $[M+H]^+$, exact mass 382.17 for $C_{22}H_{26}N_2O_2S$; Anal. calcd. for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.85; N, 7.32; found C, 69.13; H, 6.81; N, 7.27.

3.4.3. (2*S*,2′*S*)-2,2′-((Thiophene-2,5-diylbis(methylene))bis(azanediyl))bis(3-methyl butan-1-ol) (**L3**)

Following **GP1**, thiophene-2,5-dicarboaldehyde (**3**) and (*S*)-2-amino-3-methylbutan-1-ol (**4c**) were reacted to produce chiral diamine alcohol **(L3**) as pale brown solid (204 mg, 65%); $[\alpha]_D^{25}$ = −3.76° (c 0.158, MeOH); IR (KBr, cm^{-1}): 3412, 3061, 3030, 2975, 2874, 1602, 1466, 1336, 1025, 763 cm^{-1}; 1H-NMR (500 MHz, DMSO-d_6): δ(ppm) = 6.72 (s, 2H, thiophene-**H**), 4.37 (t, *J* = 5.3 Hz, 2H, O**H**), 3.88 (d, *J* = 14.1 Hz, 2H, C$\mathbf{H}_2$NH), 3.80 (d, *J* = 14.1 Hz, 2H, C$\mathbf{H}_2$NH) 3.44 (dd, *J* = 10.8, 4.3 Hz, 2H, C$\mathbf{H}_2$OH), 3.32–3.27 (m, 2H, C**H**$(CH_3)_2$, 3.29 (dd, *J* = 10.8, 4.3 Hz, 2H, C$\mathbf{H}_2$OH), 2.29 (dt, *J* = 6.1, 5.0 Hz, 2H, C**H**-N), 1.80 (s, 2H, N**H**), 1.73 (m, 2H, C**H**), 0.85 (dd, *J* = 10.2, 6.9 Hz, 12H, C$\mathbf{H}_3$). ^{13}C-NMR (126 MHz, DMSO-d_6): δ(ppm) = 144.02, 123.39, 63.06, 60.09, 46.42, 28.25, 18.77, 18.62; LCMS (ESI, m/z): found 315.20 $[M+H]^+$, exact mass 314.20 for $C_{16}H_{30}N_2O_2S$; Anal. calcd. for $C_{16}H_{30}N_2O_2S$: C, 61.11; H, 9.62; N, 8.91; found C, 60.99; H, 9.69; N, 8.93.

3.4.4. (2*S*,2′*S*)-2,2′-((Thiophene-2,5-diylbis(methylene))bis(azanediyl))bis(3,3-dimethyl butan-1-ol) (**L4**)

Following **GP1**, thiophene-2,5-dicarboaldehyde (**3**) and (S)-2-amino-3,3-dimethylbutan-1-ol (**4d**) were reacted to produce chiral diamine alcohol (**L4**) as pale yellow solid (229mg, 67%); m.p. 72–174 °C; $[\alpha]_D^{25}$= −96.31° (c 0.072, MeOH); IR (KBr, cm^{-1}): 3330, 3201, 3131, 3058, 2951, 2866, 1604, 1481, 1392, 1002, 742 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ(ppm) = 6.72 (s, 2H, thiophene-**H**), 4.36 (t, *J* = 5.2 Hz, 2H, O**H**), 4.06 (dd, *J* = 13.9,

5.1 Hz, 2H, C**H**$_2$NH), 3.77 (dd, *J* = 13.9, 8.3 Hz, 2H, C**H**$_2$NH) 3.63 (dd, *J* = 11.3, 4.4 Hz, 2H, C**H**$_2$OH), 3.34 (dd, *J* = 10.2, 4.0 Hz, 2H, C**H**$_2$OH), 2.12 (ddd, *J* = 7.2, 5.9, 4.0 Hz, 2H, C**H**NH), 1.73 (td, *J* = 7.9, 5.3 Hz, 2H, N**H**), 0.87 (s, 18H, C**H**$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6): δ(ppm) = 144.08, 123.27, 66.71, 60.22, 48.61, 34.19, 27.26; LCMS (ESI, m/z): found 343.25 $[M+H]^+$, exact mass 342.23 for $C_{18}H_{34}N_2O_2S$; Anal. calcd. for $C_{18}H_{34}N_2O_2S$: C, 63.12; H, 10.01; N, 8.18; found C, 62.98; H, 10.11; N, 8.15.

3.4.5. (2*S*,2′*S*)-2,2′-((Thiophene-2,5-diylbis(methylene))bis(azanediyl))bis(butan-1-ol) (**L5**)

Following **GP1**, thiophene-2,5-dicarboaldehyde (**3**) and (*S*)-2-aminobutan-1-ol (**4e**) were reacted to produce chiral diamine alcohol (**L5**) as a pale yellow solid (200 mg, 70%); m.p. 94–95 °C; $[\alpha]_D^{25}$= +32.73° (c 0.107, MeOH); IR (KBr, cm^{-1}): 3309, 3089, 3131, 3058, 2958, 2855, 1604, 1458, 1428, 1021, 764 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ(ppm) = 6.75 (s, 2H, thiophene-**H**), 4.44 (br, 2H, O**H**), 3.85 (s, 4H, C**H**$_2$NH), 3.39 (dd, *J* = 10.7, 5.0 Hz, 2H, C**H**$_2$OH), 3.29 (dd, *J* = 10.7, 5.8 Hz, 2H, C**H**$_2$OH), 2.45 (p, *J* = 5.8 Hz, 2H, C**H**NH), 1.44–1.30 (m, 4H, C**H**$_2$CH$_3$), 0.84 (t, *J* = 7.5 Hz, 6H, C**H**$_3$); ^{13}C-NMR (126 MHz, DMSO-d_6) δ(ppm) = 143.67, 123.65, 62.17, 59.06, 45.47, 23.41, 10.00; LCMS (ESI, m/z): found 287.20 $[M+H]^+$, exact mass 286.17 for $C_{14}H_{26}N_2O_2S$; Anal. calcd. for $C_{14}H_{26}N_2O_2S$: C, 58.71; H, 9.15; N, 9.78; found C, 58.61; H, 9.29; N, 9.71.

*3.5. General Procedures for the Synthesis of Racemic Nitroaldol Products (Rac **8a–m**)*

General Procedure (**GP2**): To a solution of aldehyde **6a**–**m** (1.0 equiv.) and nitromethane **7** (1.4 equiv.) in ethanol (3 mL) sodiumacetate trihydrate (0.6 equiv.) was added at room temperature as per the literature [61]. The resulting suspension was stirred for 72 h and then filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography using 10–15% ethylacetate/*n*-hexane as eluent to afford racemic products *rac***8a**–**m**, in excellent yields (≥0%).

*3.6. General Procedure for the Catalytic Asymmetric Henry Reaction (**8a–m**)*

General Procedure (**GP3**): A small 8 mL vial under nitrogen atmosphere was charged with ligand **4** (14mg, 0.041mmol, 20 mol%), Cu(OAc)$_2$·H$_2$O (8 mg, 0.04 mmol, 20 mol%) and ethanol (2 mL). The solution was stirred for 2h at room temperature to obtain a blue solution of **L4**-Cu(OAc)$_2$·H$_2$O complex. The aldehyde **6a**–**m** (0.2 mmol) were then added to this blue colored solution of **L4**-Cu(OAc)$_2$·H$_2$O complex and stirred for 20 min at room temperature followed by addition of nitromethane **7** (122 mg, 2 mmol) and the reaction mixture was left stirring for the 24–48 h. The solvent was then removed under reduced pressure and the residue was directly purified on 100 mesh silica gel column eluting by 10–15% EtOAc/petroleum ether to obtain the corresponding product chiral nitroaldol product **8a**–**m**.

3.6.1. (*R*)-(+)-2-Nitro-1-(2-nitrophenyl)ethan-1-ol (**8a**)

2-Nitrobenzaldehyde **6a** (30.22 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8a** as yellow oil, isolated yield (42 mg, 99%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 90.0% *n*-hexane/*i*-PrOH, 0.8 mL/min.; t_{major} = 18.19 min.; t_{minor} = 20.56 min.; λ = 254 nm]; 94.56% ee; $[\alpha]_D^{20}$ = +239.3º (c 1.0, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20}$ = +237.0º (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 8.07 (d, *J* = 8.2 Hz, 1H, Ar–**H**), 7.95 (d, *J* = 7.9 Hz, 1H, Ar–**H**), 7.77–7.72 (m, 1H, Ar–**H**), 7.58–7.52 (m, 1H, Ar–**H**), 6.04 (d, *J* = 9.2 Hz, 1H, C**H**OH), 4.86 (dd, 1H, *J* = 13.89, 2.43 Hz, C**H**$_2$NO$_2$), 4.55 (dd, 1H, *J* = 13.75, 9.02 Hz, C**H**$_2$NO$_2$), 3.28 (s, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 147.28, 134.54, 134.13, 129.83, 128.83, 125.15, 80.17, 66.91; all the analytical data are in accordance with the reported literature [62].

3.6.2. (*R*)-(−)-2-Nitro-1-(4-nitrophenyl)ethan-1-ol (**8b**)

4-Nitrobenzaldehyde **6b** (30.22mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8b** as yellow oil, isolated yield (40.7 mg,

96%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 85.0% *n*-hexane/*i*-PrOH, 1.0 mL/min.; t_{major} = 15.89 min.; t_{minor} = 20.19 min.; λ = 254 nm]; 81.32% ee; $[\alpha]_D^{20} = -18.7^o$ (c 0.5, CH_2Cl_2); Ref. [40] $[\alpha]_D^{20} = -39.1^o$ (c 0.98, CH_2Cl_2); δ(ppm) = 8.24 (d, *J* = 8.2 Hz, 2H, Ar–**H**), 7.62 (d, *J* = 8.7 Hz, 2H, Ar–**H**), 5.60 (dd, *J* = 8.5, 3.9 Hz, 1H, C**H**OH), 4.64–4.54 (m, 2H, C$\mathbf{H}_2$$NO_2$), 3.48–3.40 (m, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 148.27, 145.11, 127.09, 124.33, 80.73, 70.10. All the analytical data are in accordance with the reported literature [40,61].

3.6.3. (*R*)-(−)-2-Nitro-1-(3-nitrophenyl)ethan-1-ol (**8c**)

3-Nitrobenzaldehyde **6c** (30.22 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8c** as yellow oil, isolated yield (38.61 mg, 91%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 85.0% *n*-hexane/*i*-PrOH, 1.0 mL/min.; t_{major} = 15.51 min.; t_{minor} = 17.73 min.; λ = 254 nm]; 81.20% ee; $[\alpha]_D^{20} = -17.4^o$ (c 0.5, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20} = -32.5^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 8.32 (s, 1H, Ar–**H**), 8.21 (d, *J* = 8.2 Hz, 1H, Ar–**H**), 7.77 (d, *J* = 9.5 Hz, 1H, Ar–**H**), 7.60 (td, *J* = 7.9, 2.0 Hz, 1H, Ar–**H**), 5.61 (d, *J* = 9.4 Hz, 1H, C**H**OH), 4.66–4.56 (m, 2H, C$\mathbf{H}_2$$NO_2$), 3.43 (brs, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 148.70, 140.44, 132.14, 130.25, 123.93, 121.28, 80.84, 69.96; all the analytical data are in accordance with reported literature [62].

3.6.4. (*R*)-(−)-1-(4-Bromophenyl)-2-nitroethan-1-ol (**8d**)

4-Bromobenzaldehyde **6d** (37 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8d** as yellow oil, isolated yield (39.4 mg, 80%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 85.0% *n*-hexane/*i*-PrOH, 0.8 mL/min.; t_{major} = 13.95 min.; t_{minor} = 18.25 min.; λ = 254 nm]; 76.36% ee; $[\alpha]_D^{20} = -8.8^o$ (c 0.25, CH_2Cl_2); Ref. [40] $[\alpha]_D^{20} = -48.0^o$ (c 0.95, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.54 (d, *J* = 8.4 Hz, 2H, Ar–**H**), 7.30 (d, *J* = 8.2 Hz, 2H, Ar–**H**), 5.44 (dd, *J* = 9.5, 3 Hz, 1H, C**H**OH), 4.57 (dd, *J* = 13.5, 9.5 Hz, 1H, C$\mathbf{H}_2$$NO_2$), 4.49 (dd, *J* = 13.5, 9.5 Hz, 1H, C$\mathbf{H}_2$$NO_2$), 2.94 (s, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 137.17, 132.34, 127.76, 123.12, 81.04, 70.48. all the analytical data are in accordance with the reported literature [40,61].

3.6.5. (*R*)-(−)-1-(Naphthalen-2-yl)-2-nitroethan-1-ol (**8e**)

2-Naphthaldehyde **6e** (31.24 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product 8e as yellow oil, isolated yield (28.67 mg, 66%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 80.0% *n*-hexane/*i*-PrOH, 1.0 mL/min.; t_{major} = 21.35 min.; t_{minor} = 30.55 min.; λ = 254 nm]; 75.12% ee; $[\alpha]_D^{20} = -21.6^o$ (c 0.5, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20} = -51.5^o$ (c 1.11, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.65–7.57 (m, 4H, Ar–**H**), 7.31–7.17 (m, 3H, Ar–**H**), 5.37 (d, *J* = 9.6 Hz, 1H, C**H**OH), 4.43 (dd, *J* = 13.5, 9.6 Hz, 1H, C$\mathbf{H}_2$$NO_2$), 4.34 (dd, *J* = 13.5, 9.6 Hz, 1H, C$\mathbf{H}_2$$NO_2$), 2.76 (s, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 135.54, 133.56, 133.32, 129.17, 128.20, 127.94, 126.87, 126.83, 125.48, 123.34, 81.34, 71.29. All the analytical data are in accordance with the reported literature [40,62].

3.6.6. (*R*)-(−)-2-Nitro-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (**8f**)

4-(Trifluoromethyl) benzaldehyde **6f** (34.82 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8f** as yellow oil, isolated yield (38.57 mg, 82%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 85.0% *n*-hexane/*i*-PrOH, 0.8 mL/min.; t_{major} = 9.26 min.; t_{minor} = 11.62 min; λ = 254 nm]; 58.91% ee; $[\alpha]_D^{20} = -32.7^o$ (c 0.5, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20} = -24.5^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.68 (d, *J* = 8.4 Hz, 2H, Ar–**H**), 7.55 (d, *J* = 8.0 Hz, 2H, Ar–**H**), 5.55 (d, *J* = 9.2 Hz, 1H, C**H**OH), 4.62–4.52 (m, 2H, C$\mathbf{H}_2$$NO_2$), 3.06 (s,

1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 142.03, 126.50, 126.17, 126.15, 81.00, 70.44. All the analytical data are in accordance with the reported literature [61,62].

3.6.7. (*R*)-(−)-1-(2,4-Dichlorophenyl)-2-nitroethan-1-ol (**8g**)

2,4-Dichlorobenzaldehyde **6g** (35mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8g** as yellow oil, isolated yield (40.60 mg, 86%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 95.0% *n*-hexane/*i*-PrOH, 0.8 mL/min.; t_{major} = 18.45 min.; t_{minor} = 19.31 min.; λ = 254 nm]; 53.02% ee; $[\alpha]_D^{20} = -13.7^o$ (c 0.5, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20} = -50.7^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.62 (d, *J* = 8.4 Hz, 1H, Ar–**H**), 7.41 (d, *J* = 2.1 Hz, H, Ar–**H**), 7.34 (dd, *J* = 8.4, 2.1 Hz, 1H, Ar–**H**) 5.80 (d, *J* = 9.5 Hz, 1H, C**H**OH), 4.65 (dd, *J* = 13.7, 2.4 Hz, 1H, C**H**$_2$NO$_2$), 4.42 (dd, *J* = 13.7, 9.5 Hz, 1H, C**H**$_2$NO$_2$) 3.08 (d, *J* = 4.3 Hz, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 135.40, 134.24, 132.22, 129.65, 128.73, 128.13, 79.18, 67.56. All the analytical data are in accordance with the reported literature [61,62].

3.6.8. (*R*)-(−)-1-(4-Chlorophenyl)-2-nitroethan-1-ol (**8h**)

4-Chlorobenzaldehyde **6h** (28mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8h** as yellow oil, isolated yield (26.61 mg, 66%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 90.0% *n*-hexane/*i*-PrOH, 0.8 mL/min.; t_{major} = 17.49 min.; t_{minor} = 22.25 min.; λ = 254 nm]; 73.05% ee; $[\alpha]_D^{20} = -11.6^o$ (c 0.5, CH_2Cl_2); Ref. [61] $[\alpha]_D^{20} = -34.7^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.37 (d, *J* = 8.7 Hz, 2H, Ar–**H**), 7.41 (d, *J* = 7.0 Hz, 2H, Ar–**H**), 5.44 (d, *J* = 9.6 Hz, 1H, C**H**OH), 4.57 (ddd, *J* = 13.3, 9.5, 1.1 Hz, 1H, C**H**$_2$NO$_2$), 4.49 (ddd, *J* = 13.3, 3.0, 1.1 Hz, 1H, C**H**$_2$NO$_2$), 3.06 (s, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 136.67, 134.95, 129.35, 127.46, 81.11, 70.42. All the analytical data are in accordance with the reported literature [40,61].

3.6.9. (*R*)-(−)-1-(4-Fluorophenyl)-2-nitroethan-1-ol (**8i**)

4-Fluorbenzaldehyde **6i** (24.82 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8i** as yellow oil, isolated yield (27.77 mg, 75%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 85.0% *n*-hexane/*i*-PrOH, 0.5 mL/min.; t_{major} = 16.20 min.; t_{minor} = 18.89 min.; λ = 254 nm]; 60.89% ee; $[\alpha]_D^{20} = -19.1^o$ (c 0.5, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20} = -25.7^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.44–7.36 (m, 2H, Ar–**H**), 7.10 (m, 2H, Ar–**H**), 5.46 (d, *J* = 9.6 Hz, 1H, C**H**OH), 4.59 (dd, *J* = 13.4, 9.5 Hz, 1H, C**H**$_2$NO$_2$), 4.50 (dd, *J* = 13.4, 9.5 Hz, 1H, C**H**$_2$NO$_2$), 2.89 (s, 1H, O**H**).; ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 164.05, 162.08, 133.99, 127.96, 127.89, 116.28, 116.10, 81.25, 70.47. All the analytical data are in accordance with the reported literature [49,62].

3.6.10. (*R*)-(−)-1-(4-Methoxyphenyl)-2-nitroethan-1-ol (**8j**)

4-Methoxybenzaldehyde **6j** (27.3 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8j** as yellow oil, isolated yield (30.37 mg, 77%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 90.0% *n*-hexane/*i*-PrOH, 1.0 mL/min.; t_{major} = 20.51 min.; t_{minor} = 26.77 min.; λ = 254 nm]; 63.89% ee; $[\alpha]_D^{20} = -9.8^o$ (c 0.5, CH_3OH); Ref. [61] $[\alpha]_D^{20} = -33.3^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.33 (d, *J* = 8.6 Hz, 2H, Ar–**H**), 6.93 (d, *J* = 8.7 Hz, 2H, Ar–**H**), 5.42 (d, *J* = 9.7 Hz, 1H, C**H**OH), 4.61 (dd, *J* = 13.2, 9.7 Hz, 1H C**H**$_2$NO$_2$), 4.48 (dd, *J* = 13.2, 9.7 Hz, 1H, C**H**$_2$NO$_2$), 3.81 (s, 3H, OC**H**$_3$) 2.74 (s, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 160.21, 130.29, 127.43, 114.55, 81.39, 70.82, 55.50. All the analytical data are in accordance with the reported literature [40,61].

3.6.11. (*R*)-(−)-2-Nitro-1-(*p*-tolyl)ethan-1-ol (**8k**)

4-Methybenzaldehyde **6k** (24 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8k** as yellow oil, isolated yield (30.80 mg,

85%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 85.0% *n*-hexane/*i*-PrOH, 0.5 mL/min.; t_{major} = 20.96 min.; t_{mino}r = 26.99 min.; λ = 254 nm]; 81.29% ee; $[\alpha]_D^{20} = -25.9^o$ (c 0.5, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20} = -31.5^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = 7.29 (d, *J* = 8.2 Hz, 2H, Ar–**H**), 7.21 (d, *J* = 8.2 Hz, 2H, Ar–**H**), 5.43 (d, *J* = 9.8 Hz, 1H, C**H**OH), 4.60 (dd, *J* = 13.3, 9.6 Hz, 1H, C$\mathbf{H}_2NO_2$), 4.49 (dd, *J* = 13.3, 9.6 Hz, 1H, C$\mathbf{H}_2NO_2$), 2.79 (s, 1H, O**H**), 2.36 (s, 1H, C$\mathbf{H}_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 139.08, 135.30, 129.84, 126.01, 81.39, 71.04, 21.30. All the analytical data are in accordance with the reported literature [61,62].

3.6.12. (*R*)-(−)-2-Nitro-1-(*m*-tolyl)ethan-1-ol (**8l**)

3-Methybenzaldehyde **6l** (24 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8l** as yellow oil, isolated yield (31.89 mg, 88%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 90.0% *n*-hexane/*i*-PrOH, 0.5 mL/min.; t_{major} = 24.72 min.; t_{minor} = 29.21 min.; λ = 254 nm]; 60.81% ee; $[\alpha]_D^{20} = -36.9^o$ (c 0.5, CH_2Cl_2); Ref. [62] $[\alpha]_D^{20} = -92.3^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = δ(ppm) 7.32 (q, *J* = 7.5 Hz, 2H, Ar–**H**), 7.26 (s, 1H, Ar–**H**) 7.24 (d, *J* = 7.7 Hz, 2H, Ar–**H**), 5.47 (d, *J* = 9.7 Hz, 1H, C**H**OH), 4.64 (dd, *J* = 13.3, 9.6 Hz, 1H, C$\mathbf{H}_2NO_2$), 4.54 (dd, *J* = 13.3, 9.6 Hz, 1H, C$\mathbf{H}_2NO_2$), 2.88 (s, 1H, O**H**), 2.41 (s, 1H, C$\mathbf{H}_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 139.03, 138.20, 129.86, 129.07, 126.72, 123.11, 81.40, 71.18, 21.54. All the analytical data are in accordance with the reported literature [61,62].

3.6.13. (*R*)-(−)-2-Nitro-1-phenylethan-1-ol (**8m**)

Benzaldehyde **6m** (21.22 mg, 0.2 mmol) and nitromethane **7** (122 mg, 2 mmol) were reacted according to the **GP3** to yield product **8m** as yellow oil, isolated yield (27.41 mg, 82%). Enantiomeric excess (ee) was determined by chiral HPLC [Chiracel OD-H column), 90.0% *n*-hexane/*i*-PrOH, 0.8 mL/min.; t_{major} = 17.94 min.; t_{minor} = 22.72 min.; λ = 254 nm]; 89.22% ee; $[\alpha]_D^{20} = -14.7^o$ (c 0.5, CH_2Cl_2); Ref. [61] $[\alpha]_D^{20} = -35.2^o$ (c 1.0, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ(ppm) = δ(ppm) 7.44–7.34 (m, 5H, Ar–**H**), 5.44 (d, *J* = 9.7 Hz, 1H, C**H**OH), 4.57 (dd, *J* = 13.7, 3.5 Hz, 1H, C$\mathbf{H}_2NO_2$), 4.49 (dd, *J* = 13.7, 3.5 Hz, 1H, C$\mathbf{H}_2NO_2$), 3.08 (s, 1H, O**H**); ^{13}C-NMR (125 MHz, $CDCl_3$): δ(ppm) = 138.24, 129.12, 129.06, 126.05, 81.29, 71.08. All the analytical data are in accordance with the reported literature [40,61].

4. Conclusions

In conclusion, a series of newly design and developed C_2-symmetric bis(β-amino alcohol) ligands **(L1–L5)** have been synthesized based on thiophene framework, and their asymmetric catalytic efficiency has been examined in asymmetric Henry reaction of nitromethane with a variety of substituted aromatic aldehydes successfully. 20 mol % of **L4**:$Cu(OAc)_2 \cdot H_2O$ complex catalytic system was found to be the most efficient catalyst for asymmetric Henry reaction in ethanol at 25 °C. Our newly developed catalytic system is one of the robust processes which are capable of inducing chirality into nitroaldol condensation of nitromethane with several substituted aldehydes with moderate to excellent isolate yields (66–99%) and enantioselectivity (53–95% ee) at room temperature in ethanol as a green solvent. The easy catalyst synthesis, mild conditions, high enantioselectivity and chemical yield enhanced the potential application for this catalyst system. Our further investigations are currently ongoing for other chiral transformations using this catalytic system, and henceforth the outcome of this research will be communicated in the near future.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11101208/s1, Figure S1: ^{1}H-NMR and ^{13}C-NMR for thiophene-2,5-diyldimethanol-**2**, Figure S2: ^{1}H-NMR and ^{13}C-NMR for thiophene-2,5-dicarbaldehyde-**3**, Figure S3: ^{1}H-NMR and ^{13}C-NMR for thiophene-2,5-bis-(β-amino alcohol) ligand-**L1**, Figure S4: ^{1}H-NMR and ^{13}C-NMR for thiophene-2,5-bis-(β-amino alcohol) ligand-**L2**, Figure S5: ^{1}H-NMR and ^{13}C-NMR for thiophene-2,5-bis-(β-amino alcohol) ligand-**L3**, Figure S6: ^{1}H-NMR and ^{13}C-NMR for thiophene-2,5-bis-(β-amino

alcohol) ligand-**L4**, Figure S7: ^{1}H-NMR and ^{13}C-NMR for thiophene-2,5-bis-(β-amino alcohol) ligand-**L5**, Figure S8: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8a**, Figure S9: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8b**, Figure S10: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8c**, Figure S11: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8d**, Figure S12: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8e**, Figure S13: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8f**, Figure S14: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8g**, Figure S15: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8h**, Figure S16: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8i**, Figure S17: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8j**, Figure S18: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8k**, Figure S19: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8l**, Figure S20: ^{1}H-NMR and ^{13}C-NMR for Henry product-**8m**, Figure S21: Chiral HPLC for Henry product-**8a**, Figure S22: Chiral HPLC for for Friedel Craft product-**8b**, Figure S23: Chiral HPLC for for Friedel Craft product-**8c,** Figure S24: Chiral HPLC for for Friedel Craft product-**8d,** Figure S25: Chiral HPLC for for Friedel Craft product-**8e,** Figure S26: Chiral HPLC for for Friedel Craft product-**8f,** Figure S27: Chiral HPLC for for Friedel Craft product-**8g,** Figure S28: Chiral HPLC for for Friedel Craft product-**8h,** Figure S29: Chiral HPLC for for Friedel Craft product-**8i,** Figure S30: Chiral HPLC for for Friedel Craft product-**8j,** Figure S31: Chiral HPLC for for Friedel Craft product-**8k,** Figure S32: Chiral HPLC for for Friedel Craft product-**8l,** Figure S33: Chiral HPLC for for Friedel Craft product-**8m.**

Author Contributions: Conceptualization, A.M.A.-M. and A.B.; Supervision, A.M.A.-M., A.B. and M.S.I.; methodology, A.S.A., M.S.I., M.A. and A.M.A.-M.; validation, M.S.I., A.S.A., S.A., M.A. and A.M.A.-M.; formal analysis, A.S.A.; M.S.I., M.A. and S.A.; investigation, A.S.A.; M.S.I., M.A. and S.A.; resources, A.M.A.-M. and A.B.; data cu-ration, A.S.A., M.S.I. and A.B.; writing—original draft preparation, M.S.I., A.B. and A.S.A.; writing—review and editing, M.S.I., A.B. and A.M.A.-M.; visualization, A.B., M.S.I., S.A. and M.A.; project administration, A.M.A.-M. and A.B.; funding acquisition, A.M.A.-M. and A.B.; Software A.S.A., M.S.I., M.A. and A.B.; All authors have read and agreed to the published version of the manuscript.

Funding: Researchers Supporting Project number (RSP-2021/64), King Saud University, Riyadh, Saudi Arabia.

Data Availability Statement: The data presented in this study are available in Supplementary Material.

Acknowledgments: The authors would like to extend their sincere appreciation to the Researchers Supporting Project (RSP-2021/64), King Saud University, Riyadh, Saudi Arabia.

Conflicts of Interest: The authors declare no conflict of interest.

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