Accepted Manuscript

Research paper

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PII:	S0020-1693(18)30063-X
DOI:	https://doi.org/10.1016/j.ica.2018.04.048
Reference:	ICA 18239

To appear in: Inorganica Chimica Acta

Received Date:12 January 2018Revised Date:20 April 2018Accepted Date:24 April 2018



Please cite this article as: A. Dixit, P. Kumar, G.D. Yadav, S. Singh, Asymmetric Henry reaction catalyzed by chiral Cu(II) salalen and salan complexes derived from (S)-proline, *Inorganica Chimica Acta* (2018), doi: https://doi.org/10.1016/j.ica.2018.04.048

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Asymmetric Henry reaction catalyzed by chiral Cu(II) salalen and salan complexes derived from (S)-proline

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Abstract: Single chiral center C₁ symmetric salalen and salan ligands were synthesized from (*S*)-proline and their Cu(II) complexes were used as catalysts for the asymmetric Henry reaction between aromatic aldehydes and nitromethane/nitroethane. The reaction of 4-nitrobenzaldehyde and nitromethane using salalen ligand (10 mol%) and Cu(OAc)₂.H₂O (10 mol%) in isopropanol with 4-methoxyphenol (10 mol%) as an additive at room temperature, afforded the (*S*)-2-nitro-1-(4-nitrophenyl)ethanol in 82% yield and 81% *ee*. We have also generalized the catalysis of nitro-aldol reaction for a variety of substrates using nitromethane, gave 67–94% yields with 46–98% *ee* after 96–120h. The absolute configuration of nitro-aldol product was governed by the use of the metal, Mn(III) complex of the ligand **2** gives (*R*)-enantiomer while Cu(II) complex of same ligand gives the (*S*)-enantiomer.

Key words: Cu(II) Salalen complex, Henry reaction, (*S*)-Proline, Asymmetric Nitro-aldol reaction and C₁-Symmetric ligand

1. Introduction

The Henry reaction (nitro-aldol reaction) is very efficient and atom economic method for the formation of C-C bond.¹⁻² The asymmetric version of this reaction attracts more attention of the chemists since 1992, when Shibasaki and co-workers reported the reaction.³ The products of nitro-aldol reactions are β -nitro alcohols, which contains two functional groups (i.e. nitro and hydroxyl groups), can easily be transformed to the β -amino alcohols, α -hydroxy acids, α -hydroxy ketones, and other various biological active compounds.⁴⁻⁸

Asymmetric nitro-aldol reaction catalyzed by various transition metal complexes⁹⁻³⁰ as well as rare earth metal complexes³⁰⁻³³ been developed in last two decades. Beside chiral metal complexes, organocatalysts³⁵⁻⁴⁰ and biocatalysts⁴¹⁻⁴² were also used in asymmetric nitro-aldol raection. Salen ligands are one of the most privileged ligands in asymmetric catalysis and Cu(II) complexes of salen and salan were largely used for this reaction because these can be generated *in situ* and efficiently working at mild reaction conditions.⁴³⁻⁵² (*S*)-Proline based single chiral center salalen and salan ligands are useful for the asymmetric epoxidation of non-functionalised alkenes,⁵³ polymerisation of α -olefins⁵⁴ and stereoselective polymerization of lactide.^{55,56} Recently we have reported the Mn(III) salalen and salan complexes derived from (*S*)-proline for asymmetric Strecker and Henry reactions.^{57,58} Herein, we wish to report Cu(II) salalen and salan complexes for asymmetric nitro-aldol reaction at room temperature.

2. Experimental

2.1. Materials and Methods

All reagents were purchased commercially and used as received. HPLC grade isopropyl alcohol was used as solvent for the reactions. Proton and carbon nuclear magnetic resonance spectra (¹H and ¹³C NMR, respectively) were recorded on 400 MHz (operating frequencies: ¹H, 400.13 MHz; ¹³C, 100.61 MHz) Jeol-FT-NMR spectrometers at ambient temperature. In the case of ¹H and ¹³C NMR spectra, the chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform (CDCl₃) were 7.26 and 77.00 ppm for ¹H and ¹³C NMR spectra, respectively. High resolution mass spectra were measured on an Agilent instrument. Optical rotation values were measured on a Rudolph digital polarimeter. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F254 silica gel plates. Column chromatographic separations were performed using silica gel (200-400 mesh). All the new compounds were characterized by ¹H and ¹³C NMR and mass spectroscopy and the known compounds was characterized by ¹H-NMR. The enantiomeric excess was determined using Schimadzu 2010 HPLC using Chiralpak AD-H, Chiralcel OD-H and Chiralpak IC as chiral columns. The details on the crystal structure data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.chem.ac.uk/data request/cif, on quoting the depository numbers CCDC 1411751.

2.2. Synthesis of Ligands 1-6

Synthesis of ligands **1-6** were carried out using our earlier reported procedures.⁵⁷ Here we are giving procedure of the synthesis ligand **2** and its spectroscopic data. Synthesis of precursors of the ligands was also reported in our earlier report.⁵⁷

2.2.1. (S)-2-*tert*-butyl-6-(((1-(3-*tert*-butyl-2-hydroxybenzyl)pyrrolidin-2-yl)methylimino)methyl)phenol (2)

(*S*)-2-((2-(Aminomethyl)pyrrolidin-1-yl)methyl)-6-*tert*-butylphenol (498 mg, 1.9 mmol) was taken in methanol (10 mL) and 3-*tert*-butyl-2-hydroxy-benzaldehyde (338 mg, 1.9 mmol, in methanol (5 mL)) was added drop wise over a period of 30 min. Reaction mixture was stirred for 30 min at room temperature to give a yellow precipitate of ligand **2** (627 mg, 78%). M.p. = 102.4 °C. $[\alpha]_D^{27} = -29.69$ (c 1 in CH₂Cl₂). ¹H NMR (CDCl₃, 400 MHz): $\delta = 13.73$ (s, 1H), 7.31 (d, J = 8.05 Hz, 1H), 7.17 (d, J = 7.32 Hz, 1H), 7.10 (d, J = 7.32 Hz, 1H), 6.85 (d, J = 7.32 Hz, 1H), 6.80 (t , J = 7.32 Hz, 1H), 6.70 (t, J = 7.32 Hz, 1H), 4.21 (d, J = 13.91 Hz, 1H), 3.85–3.78 (m, 1H), 3.68–3.62 (m, 1H), 3.58 (d, J = 13.91 Hz, 1H), 3.10–2.92 (m, 2H), 2.43–2.30 (m, 1H), 2.17–2.03 (m, 1H), 1.90–1.74 (m, 3H), 1.43 (s, 9H), 1.38 (s, 9H) ppm. ¹³C NMR (CDCl₃, 100 MHz): $\delta = 167.11$, 160.28, 156.76, 137.26, 129.81, 129.41, 126.08, 125.76, 122.70, 118.58, 118.14, 117.78, 64.70, 62.97, 58.63, 54.31, 34.79, 34.59, 29.40, 29.28, 22.96 ppm. FTIR (KBr) v = 3051, 2959, 1635, 1046 cm⁻¹. ESI MS calcd. for C₂₇H₃₉N₂O₂⁺ [M+H]⁺ 423.3006; found 423.3030.

2.3. General procedure for the catalytic asymmetric nitro-aldol reaction

The mixture of salalen ligand 2 (21.1 mg, 10 mol%), Cu(OAc)₂.H₂O (9.9 mg, 10 mol%) and CH₃NO₂ (265 μ L, 10 eq.) was stirred for 1 h at room temperature in *iso*-propanol (2.0 mL), then 4-methoxyphenol (6.2 mg, 10 mol%) was added and reaction mixture further stirred for 0.5 h, at the end benzaldehydes/substituted benzaldehydes (0.5 mmol) was added. Reaction mixture was stirred for specified time and monitored by TLC. Solvent was evaporated by rotary evaporator and nitro-aldol product was purified by column chromatography on silica gel (hexane/ethyl acetate 80:20). The *ee's* were determined by HPLC using Chiralcel OD-H, AD-H and IC column. HPLC chromatogram and copy of ¹H-NMR and ¹³C-NMR spectra of the nitro-aldol products are given in SI.

2.3.1. 2-Nitro-1-phenylethanol (Table 3, entry 1)³⁰

Yellow oil, Yield: 122 mg (73%), *ee*: 95%. HPLC Conditions: Chiralcel OD-H, hexane/*i*PrOH, 90:10 *v*/*v*, 0.8mL/min, 25 °C, UV λ max 230 nm): t_r (minor) = 15.46 min, t_r(major) = 17.36 min. t_{al25} = +21.26 (C 0.40 CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ = 7.60-7.30 (m, 5H), 4.44 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.59 (dd, *J* = 13.2, 9.2 Hz, 1H), 4.49 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.90 (brs, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 138.1, 129.0 (2C), 128.9, 125.9 (2C), 80.2, 70.9 ppm.

3. Results and Discussion

The C₁-symmetric chiral salalen (1–3) and salan (4–6) ligands shown in figure 1 were synthesized from (*S*)-proline and detailed procedure for synthesis is reported in our earlier report.⁵⁷ The Cu(II) complexes of these ligands (1–6) were generated *in situ* with Cu(OAc)₂.H₂O in *iso*-propanol (IPA) and used as catalysts for asymmetric Henry (nitro-aldol) reaction.



Figure 1. Structures of ligands 1-6.

3.1. Crystal structure of the Cu(II) complex of ligand 2

Copper complex of ligand 2 was prepared in *iso*-propanol by using $Cu(OAc)_2.H_2O$: ligand 2 (1:1) at room temperature and after removal of *iso*-propanol, single crystal of complex was obtained by crystalizing in dichloromethane. The structure of Cu(II) complex of ligand 2 was confirmed by single crystal X-ray study. Complex of ligand 2 crystallizes in the chiral space

group *P*₂₁ and consists of one Cu(II) ion and one dianoinic L (Fig 2). The distorted square planar Cu(II) is coordinated by two oxygen atoms and two nitrogen atoms from ligand **2** (L²⁻). The Cu(II) atom deviates by 0.036 Å from the mean plane constituted by four ligating atoms. Thus L²⁻ acts as a tetratopic chelating unit. The bond lengths of Cu-O [Cu-O1 = 1.896(2) Å, Cu-O2 = 1.888(2) Å] and for Cu-N [Cu-N1 = 2.026(2), Cu-N2 = 1.916(2) Å], are similar to the many of Cu(II) salen complexes.⁵⁷⁻⁵⁹ From the X-ray structure of complex of ligand **2**, it is confirmed that pyrrolidine ring adopted the envelop-shaped conformation with nitrogen atom out of the plane from the remaining four carbon atoms. In the crystal structure each molecule interacts with a neighboring molecule through C-H..... π interaction [$d(C21\cdots C26\pi) = 3.755$ Å; C-H… $\pi = 162.96^{\circ}$] resulting in the formation of zig-zag chain. Ligand **2** showed absorption band at 272 nm and 338 nm, the 338 nm absorption may be assigned to n- π^* transition in ligand. The crystal of the isolated Cu(II) complex of ligand **2** the band at 338 nm was shifted to 388 nm (red shift), which may be due to ligand to metal charge transfer of non-bonding lone pair of the phenoxide oxygen to the d-orbital of the Cu(II) *i.e.*, LMCT. It affirms the complex formation of the ligand **2** with the Cu(OAc)₂.H₂O.



Figure 2. Crystal structure of Cu(II) complex of ligand 2.

3.2. Optimization of the reaction conditions for Henry reaction 3.2.1. Screening of different ligands

Initially, we have screened the ligands 1-6 (5 mol%) with Cu(OAc)₂.H₂O (5 mol%) in *iso*propanol (IPA) for the reaction of 4-nitrobenzaldehyde (7) and nitromethane at 25 °C. Yields of the (*S*)-2-nitro-1-(4-nitrophenyl)ethanol (8) were better with salen ligands (4–6) compared to salalen ligands (1–3) but the enantiomeric excesses (*ee's*) were better in case of salalen ligands (1–3) (Table 1, entries 1–6). The *ee* of product (*S*)-2-nitro-1-(4-nitrophenyl)ethanol (8) was better with salalen ligand 2 compared to other salalen ligands 1 and 3. These preliminary results show that bulky group like *tert*-butyl group(s) at different position on phenol in a ligand made a significant influence on yield and *ee* of the product 8. 2-*tert*-Butyl group on phenol in salalen ligand (2) induced better *ee* compared to 2,4-di-*tert*-butyl group on phenol in salalen ligand (1) and 4-*tert*-butyl group on phenol in a salalen ligand (3). Similar trends were observed with salan ligands 4–6 (Table 1, entries 4–6). We have also screened Cu(II) salts with salalen ligand 2 for the asymmetric nitro-aldol reaction at room temperature in IPA. The Cu(OAc)₂.H₂O was only

found to be good source of Cu(II) for the nitro-aldol reaction compared to other salts, $Cu(NO_3)_2.3H_2O$ and $CuCl_2.2H_2O$ did not catalyze the reaction (entries 2, 7 and 8).

Table 1. Screening of different ligands for asymmetric nitro-aldol reaction.^a

C	HO + CH ₃ NO ₂	ligand 1-6 Cu source	OH	NO ₂
O ₂ N		IPA, rt (25 °C)	D ₂ N	
7			8	
Entw	Ligand	Cu couroo	Viold ^b	20 (9/) ^c
				<i>ee</i> (70)
1	1	$Cu(OAc)_2.H_2O$	19	50
2	2	$Cu(OAc)_2.H_2O$	30	67
3	3	$Cu(OAc)_2.H_2O$	53	33
4	4	$Cu(OAc)_2.H_2O$	62	17
5	5	Cu(OAc) ₂ .H ₂ O	86	22
6	6	Cu(OAc) ₂ .H ₂ O	90	15
7	2	CuCl ₂ .2H ₂ O	No	-
			reaction	
8	2	$Cu(NO_3)_2.3H_2O$	No	-
			reaction	
9	-	Mn(III) complex of	81	-17
		ligand 2		

^a Ligand **1-6** (5 mol %) was dissolved in *iso*-propanol (2 mL), Cu(OAc)₂.H₂O (5 mol %), CH₃NO₂ (10 eq., 5 mmol) and nitrobenzaldehyde (0.5 mmol) were added and stirred at 25 °C for 20 h. ^b Yield of isolated product after purification by column chromatography. ^c Enantiomeric excess was determined by HPLC using a Chiralpak OD-H column and absolute configuration of product was determined by comparison of optical rotation with literature value.

The interesting observation is that the nitro-aldol reaction using Mn(III) salalen complex of ligand **2** giving opposite enantiomer of product **8** in 81% yield with 17% *ee* (Table 1, entry 9).⁵⁸ The absolute configuration of the nitro-aldol product is governed by the metal (Mn and Cu) with same configuration of (*S*)-ligand (**2**). It is worthy that different metal complex of same ligand **2** can give two different enantiomers. Reversible enantioselectivity in Henry reaction also observed by Wu et al using complex of C₂-symmetric ligand by changing Co(II) to Yb(III).⁶²

3.2.2. Effect of solvent, temperature and additive on catalysis of Henry Reaction

Effect of temperature, solvent, catalyst loading and additive on asymmetric Henry reaction using 4-nitrobenzaldehyde and nitromethane as substrate catalyzed by Cu(II) complex of ligand **2** were evaluated. Initially, we have varied reaction temperature in a range of 20–35 °C for the asymmetric nitro-addol reaction of 4-nitrobenzaldehyde (**7**) with nitromethane using ligand **2** (5 mol%) and Cu(OAc)₂.H₂O (5 mol%) in IPA at 20 °C, gave product (*S*)-2-nitro-1-(4-nitrophenyl)ethanol (**8**) in lower yield 19%, than room temperature 25 °C (Table 2, entries 1 and

2). When temperature was increased from 25 °C to 35 °C, yield of the product 8 was slightly improved but ee was decreased (entry 3). In order to improve the catalytic activity, the loading of catalyst increased to 10 mol% at 25 °C and yield of nitro-aldol product (8) improved up to 43% with 65% ee (entry 4). Solvent makes a significant influence on the yield as well as on ee. We have screened different solvent or solvent systems for the reaction and IPA was found to be best choice of solvent for the reaction (entries 5-8). These investigation, led us to use ligand 2 and Cu(OAc)₂.H₂O (10 mol%) in IPA at room temperature (25 °C) for this reaction. The literature reports show that additives like bases and phenols were known to influence the yield and ee.⁴⁸ Initially, we used various bases as additives (10 mol%) like CsCO₃, lutidine, triethylamine (TEA) and diisopropylethylenediamine (DIPEA), afforded racemic products in 60-91% yields after 3-20 h. Racemic product formation is due to background reaction of nitromethane and 4nitrobenzaldehyde catalyzed by base at room temperature (entries 9–12).⁶¹ We also tested benzoic acid as an additive and product 8 obtained in 64% yield after 50 h but again ee was lower (entry 13). Later we used some phenolic additives such as 4-methoxyphenol and 4-tertbutylphenol, afforded product in 47–70% yields but in case of 4-methoxyphenol the ee was 74% (entries 14 and 15). Additive phenol may form the hydrogen bonding with oxygen of enolate of nitromethane which shown in figure 3 and results of these two additive show that strong hydrogen bonding is stabilizes the nitroenolate therefore increases the reactivity.



Figure 3. Hydrogen bonding between nitro enolate and 4-methoxyphenol and 4-tert-butylphenol.

Table 2. Optimization of reaction conditions.^a



Entry	Additive	Solvent	Time	Yield ^b	ee ^c
			(h)		
1	-	IPA	20	19	67 ^d
2	-	IPA	20	30	67 ^e
3	-	IPA	20	43	55 ^f
4	-	IPA	20	53	65
5	-	IPA/DCM (1/0.5)	20	43	66
6	-	MeOH	20	23	50
7	-	IPA/THF (1/0.5)	20	55	33
8	-	Toluene	40	-	
9	CsCO ₃	IPA	7	91	0
10	DIPEA	IPA	13	60	0
11	Lutidine	IPA	20	84	0
12	TEA	IPA	3	91	0
13	Triphenylphosphine	IPA	21	47	0
13	Benzoic acid	IPA	50	64	51
14	4-tert-butylphenol	IPA	50	70	44
15	4-methoxyphenol	IPA	50	47	74

^aLigand **2** (10 mol %) was dissolved in solvent (2.0 mL), Cu(OAc)₂.H₂O (10 mol %), CH₃NO₂ (10 eq., 5 mmol), additive (10 mol%) and nitrobenzaldehyde (0.5 mmol) were added and stirred at 25 °C for 20 h. ^b Yield of isolated product after purification by column chromatography. ^c Enantiomeric excess was determined by HPLC using a Chiralpak OD-H column and absolute configuration of product was determined by comparison of optical rotation with literature value. ^d Ligand (5 mol%) and Cu(OAc)₂.H₂O (5 mol%) was used at 20 °C. ^e Ligand (5 mol%) and Cu(OAc)₂.2H₂O (5 mol%) was used at 25 °C.

3.2.3. Plausible mechanism for Henry reaction

We have proposed the plausible mechanism for the Henry reaction between 4-nitrobenzaldehyde and nitromethane catalyzed by *in situ* generated Cu complex of ligand **2** (Figure 4). Ligand **2** treated with Cu(CH₃COO)₂.H₂O to generate a complex CuL^{*} and acetate anions. Acetate anion acts as base to abstract a proton of the nitromethane to form nitro enolate. The oxygen of nitro enolate and oxygen of 4-nitrobenzaldehyde interact with CuL^{*}. The transition state (a) of figure 5 indicate that the *Si*-face arrangement of 4-nitrobenzaldehyde is hindered by the imine part of ligand and found to be disfavored. Another transition sate (b) in figure 5 is favorable since 4-nitrobenzaldehyde is far away from the imine part of ligand and attacks of nucleophile nitro enolate on the *Re*-face of 4-nitrobenzaldehyde giving the (*S*)-enantiomer of the nitro-aldol product **8**.



Figure 4. Plausible mechanism for Henry reaction catalyzed by Cu(II) complex.



Figure 5. Transition state for *in situ* generated complex of Cu(OAc)₂.2H₂O and salalen ligand **2** catalysed Henry reaction

Nitro-aldol reaction between 4-nitrobenzaldehyde catalyzed by salalen Mn(III)-Cl complex is giving an opposite enantiomer of nitroaldol product compared to its salalen Cu(II) complex. Mn(III) in salalen complex is penta-coordinated and the chloride is in apical position this restricts interaction of 4-nitrobenzaldehyde and nitro enolate from the plane where Cl is located.

As a result, the substrates approaches Mn(III) in a plane opposite to Cl which enables the formation of opposite enantiomer (Figure 6).



Figure 6. Crystal structures of Mn(III)Cl salalen complex⁵⁷

The interaction of 4-nitrobenzaldehyde and nitro enolate approaches Mn(III) in a plane opposite to Cl and nitro enolate is attacking on the Re-face of the 4-nitrobenzaldehyde which give (*R*)-enantiomer of product **8** (Figure 7).



Figure 7. Transition state for Mn(III)salan complex catalyzed Henry reaction

3.2.4. Scope and limitation of the catalytic system

After optimizing the reaction conditions, the scope and limitations of methodology was examined with a variety substrates (aldehydes) for the asymmetric nitro-aldol reaction by using ligand **2** (10 mol%), Cu(OAc)₂.H₂O (10 mol%) and 4-methoxyphenol (10 mol%) as an additive in IPA at 25 °C, in all the cases we have obtained (*S*)- β -nitro alcohols as nitro-aldol products (Table 3). The simplest aromatic aldehyde such as benzaldehyde gave β -nitro alcohol in a 73% yield with 95% *ee* after 120 h (Table 3, entry 1). Benzaldehyde substituted with electron withdrawing group like 4-nitro and 2-nitro took less reaction time (96 h) and yielded corresponding products in 82-84% with 61-81% *ee's* (entries 2 and 3). Benzaldehyde substituted with electron donating group like 4-methoxy and 2- methoxy took longer reaction time, gave corresponding nitro-aldol products in 67–68% yields with 49–88% *ee's* after 120 h (entries 4 and 5). Nitro-aldol products of 2-methyl and 4-methylbenzaldehyde were obtained in 67–71% yields with excellent *ee* up to 98% after 120 h. The halogenated benzaldehyde like 2-bromo and 4-bromobenzaldehyde gave 72–78% yields with 64–76% *ee* (entries 8 and 9). In case of chloro and fluoro substituted benzaldehyde gave corresponding nitro-aldol products in better *ee's* compared

to nitro-aldol products obtained from bromo substituted benzaldehyde (entries 8–13). We have also used 1-napthaldehyde as substrate and gave 82% yield of the product but *ee* was poor compared to nitro-aldol product of benzaldehyde (entry 14).

Table 3. Nitro-aldol reaction of variety of aldehydes with nitromethane.^a

R⁄

	IPA, 4-methoxypl 25 °C	IPA, 4-methoxyphenol, 25 °C			
Entry	R	Time (h)	Yield ^b (%)	<i>ee</i> ^c (%)	
1	C ₆ H ₅	120	73	95	
2	$4-NO_2C_6H_4$	96	82	81	
3	$2-NO_2C_6H_4$	96	84	61	
4	4-OMeC ₆ H ₄	120	68	49	
5	2-OMeC ₆ H ₄	120	67	88	
6	4-MeC ₆ H ₄	120	67	97	
7	$2-MeC_6H_4$	120	71	98	
8	$4-BrC_6H_4$	96	78	64	
9	$2-BrC_6H_4$	96	72	76	
10	$4-FC_6H_4$	96	80	91	
11	$2-FC_6H_4$	96	94	90	
12	4-ClC ₆ H ₄	96	70	90	
13	$2-ClC_6H_4$	96	76	90	
14	1-Napthyl	96	82	49	

^aLigand **2** (10 mol %) was dissolved in *iso*-propanol (2.0 mL), Cu(OAc)₂.H₂O (10 mol %), CH₃NO₂ (10 eq., 5 mmol), 4-methoxyphenol (10 mol%) and benzaldehyde derivatives (0.5 mmol) were added and stirred at 25 °C for specified time. ^bYield of isolated product after purification by column chromatography. ^c Enantiomeric excess was determined by HPLC using a Chiralpak OD-H and AD-H columns and absolute configuration of products were determined by comparison of optical rotation with literature value.

The effect of catalyst on the diastereoselectivity and enantioselectivity of the nitro-aldol reaction between benzaldehyde or substituted benzaldehydes with nitroethane was also studided at 25°C using ligand 2 (10 mol%), Cu(CH₃COO)₂.H₂O (10 mol%) and 4-methoxyphenol (10 mol%) as additive. We obtained the *anti*-diastereomer of β -nitro alcohols as major products. *Anti*-selective asymmetric Henry reaction catalyzed by Cu(I)-amine-imine complex and heterobimetallic Cu-Sm-aminophenol sulfonamide complexes are reported in literature.^{64,65} The *anti* and *syn* ratio of nitro-aldol products were determined by ¹H-NMR of the crude products by comparing literature value of chemical shift and coupling constant of proton (–CHOH-).^{30,41} The best diastereomeric ratio (*dr*) *anti/syn* (98/2) and 71% *ee* of *anti*-product (*1S*, *2R*) was obtained with benzaldehyde (Table 4, entry 1). Electron withdrawing group on benzaldehyde like -NO₂ gave product in 90% yield *anti/syn* (81/19) with poor *ee* of both diastereomer (entries 2 and 3). Benzaldehyde having electron donating group like methoxy at 4-positions gave only 16% yield after 120 h and *anti/syn*

(90/10) (entry 3). Halogenated benzaldehydes afforded corresponding products in 54-81% yields and best *dr* and *ee* was obtained in case of 4-fluorobenzaldehyde compared to the other halogenated benzaldehydes (entries 4-6).

Table 4. Scope of substrates with nitroethane.^a



^aLigand **2** (10 mol %) was dissolved in *iso*-propanol (2.0 mL), Cu(OAc)₂.H₂O (10 mol %), CH₃CH₂NO₂ (10 eq., 5 mmol), 4-methoxyphenol (10 mol%) and substituted benzaldehyde (0.5 mmol) were added and stirred at 25 °C for 120 h. ^b Yield of isolated product after purification by column chromatography. ^c Diastereomeric ratio was determined by ¹H-NMR. ^d Enantiomeric excess was determined by HPLC using a Chiralpak OD-H and AD-H columns and absolute configuration of products were determined by comparison of optical rotation with literature value.

4. Conclusions

In summary, C₁-symmetric salalen and salan ligands derived from (*S*)-proline and their *in situ* generated Cu (II) complexes by Cu(OAc)₂.H₂O, act as catalysts for asymmetric Henry reaction. The Cu(II) complex generated in situ from ligand **2** (10 mol%) and Cu(OAc)₂.H₂O (10 mol%) in *iso*-propanol demonstrated as an efficient catalyst for the asymmetric nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane using 4-methoxyphenol (10 mol%) as an additive at 25°C, gave corresponding nitro-aldol product in 82% yield and 81% *ee*. Additives like base giving the racemic product at room temperature but 4-methoxyphenol is choice of additive which improved the *ee* of the product. The catalytic system was found to be an efficient for various aromatic aldehydes and gave 67–94% yields with 49–98% *ee*'s of the corresponding products. The nitro-aldol reaction of a variety of 4-substituted benzaldehydes with nitroethane were also carried out and *anti*-nitro-aldol products were obtained as major products with best *anti:syn* 98:2 with 71% *ee*. Development of new C₁ symmetric ligands derived from proline for asymmetric Henry reaction will be reported in due course.

Acknowledgement

SS thanks to CSIR for research grant 02(0152)/13/EMR-II. We are also thankful to University Science Instrumentation Centre (USIC), University of Delhi, for providing instrumental facilities. PK is thankful to UGC for awarding JRF and SRF.

References

- 1. L.C.R. Henry, Hebd. Seances, Acad. Sci. 120 (1895) 1265-1265.
- 2. C. Palomo, M. Oiarbide, A. Laso, Eur. J. Org. Chem. (2007) 2561-2574.
- H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, J. Am. Chem. Soc. 114 (1992) 4418– 4420.
- 4. N. Ono, The Nitro Group in Organic Synthesis, Wiley-VCH: New York, 2001.
- 5. F. A. Luzzio, *Tetrahedron* 57 (2001) 915–945.
- 6. J. Boruwa, N. Gogoi, P. Saikia, N. C. Barua, *Tetrahedron:Asymmetry* 173 (2006) 315–3326.
- 7. M. Bandini, F. Piccinelli, S. Tommasi, A. U. Ronchi, C. Ventrici, *Chem. Commun.*, 2007, 616–618.
- 8. G. Blay, V. H. Olmos, J. R. Pedro, Synlett 19 (2011) 1195-1211.
- 9. B. M. Trost, Y. S. C. Yeh, Angew. Chem., 114 (2002) 889-891.
- 10. B. M. Trost, Y. S. C. Yeh, H. Ito, N. Bremeyer, Org. Lett. 4 (2002) 2621-2623.
- 11. Y. Kogami, T. Ikeno, T. Yamada, Synthesis (2004) 1947–1950.
- R. Kowalczyk, L. Sidorowicz, J. Skarżewski, *Tetrahedron: Asymmetry*, 18 (2007) 2581– 2586.
- 13. T. Arai, M. Watanabe, A. Yanagisawa, Org. Lett. 9 (2007) 3595-3597.
- 14. B. Quin, X. Xiao, X. Liu, J. Huang, Y. Wen. X. Feng, J. Org. Chem. 72 (2007) 9323– 9328.
- 15. J. Park, K. Lang, K. A. Abboud, S. Hong, J. Am. Chem. Soc. 130 (2008) 16484–16485.
- 16. S. Jammi, M. A. Ali, S. Sakthivel, L. Rout, T. Punniyamurthy, *Chem.–Asian J.*, 4 (2008) 314–320.
- 17. S. Jammi, P. Saha, S. Sanyashi, T. Punniyamurthy, Tetrahedron 64 (2008) 11724–11731.
- 18. A. Bulut, A. Aslan, O. Dogan, J. Org. Chem. 73 (2008) 7373-7375.
- 19. G. Blay, V. H. Olmos, J. R. Pedro, Chem. Commun. (2008) 4840-4842.
- 20. M. Bandini, S. Cabiddu, E. Cadoni, P. Olivelli, R. Sinisi, A. U. Ronchiand, M. Usai, *Chirality* 21 (2009) 239–244.
- 21. N. Sanjeevkumar, M. Periasamy, Tetrahedron: Asymmetry 20 (2009) 1842-1847.
- 22. R. Kowalczyk, R. Skarżewski, Tetrahedron: Asymmetry 20 (2009) 2467–2473.
- 23. M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem. Eur. J.* 15 (2009) 12764–12769.
- 24. A. Zulauf, M. Mellah, E. Schulz, J. Org. Chem. 74 (2009) 2242-2245.
- 25. A. Noole, K. Lippur, A. Metsala, M. Lopp, T. Kanger, J. Org. Chem. 75 (2010) 1313– 1316.
- 26. M. Steurer, C. Bolm, J. Org. Chem. 75 (2010) 3301-3310.

- 27. K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen, Z. Wang, Chem-Eur J. 18 (2012) 12357–12362.
- 28. G. Blay, R. L. Domingo, V. H. Olmos, J. R. Pedro, Chem-Eur J. 14 (2008) 4725–4720.
- 29. T. Arai, K. Suzuki, Synlett, 20 (2009), 3167-3170.
- I. Panov, Pavel Drabina, Z. Padêlková, P. Šimůnek, M. Sedlák, J. Org. Chem. 76 (2011) 4787–4793.
- 31. T. Arai, Y. M. A. Yamada, N. Yamamato, H. Sasai, M. Shibasaki, *Chem-Eur. J.* 2 (1996) 1368–1372.
- 32. M. Shibasaki, N. Yoshikawa, Chem. Rev. 102 (2002) 2187-2210.
- 33. H. Sasai, S. Watanabe, T. Suzuki, M. Shibasaki, Org. Synth. 10 (2004) 571-577.
- 34. B. M. Choudary, K. V. S. Ranganath, U. Pal, M. L. Kantam, B. J. Sreedhar, Am. Chem. Soc. 127 (2005) 13167–13171.
- 35. E. J. Corey, F. Y. Zhang, Angew. Chem. Int. Ed. 38 (1999) 1931-1934.
- 36. T. Ooi, K. Doda, K. Maruoka, J. Am. Chem. Soc. 125 (2003) 2054-2055.
- 37. H. Li, B. Wang, L. Deng, J. Am. Chem. Soc. 128 (2006) 732-733.
- 38. T. Marcelli, R. N. S. Vander-Haas, J. H. V. Maarseveen, H. Hiemstra, Angew. Chem. Int. Ed., 45 (2006) 929–931.
- 39. T. Mandal, S. Samanta, C. G. Zhao, Org. Lett. 9 (2007) 943-945.
- 40. T. Nitabaru, N. Kumagai, M. Shibasaki, Angew. Chem. Int. Ed. 51 (2012) 1644–1647.
- 41. T. Purkarthofer, K. Gruber, M. Khadjawi, K. Waich, W. Skrane, D. Mink, H. Griengl, *Angew. Chem.* 118 (2006) 3532–3535.
- 42. M. Gruber-Khadjawi, T. Purkarthofer, W. Skrane, H. Griengl, *Adv. Synth. Catal.* 349 (2007) 1445–1950.
- 43. C. Palomo, M. Oiarbide, A. Mielgo, Angew. Chem. Int. Ed. 43 (2004) 5442-5444.
- M. Colak, T. Aral, H. Hosgoren, N. Demirel, *Tetrahedron: Asymmetry*, 18 (2007) 1129– 1133.
- 45. T. M. Suzuki, M. Yamamato, K. Fukumoto, K. Yano, J. Cat. 251 (2007) 249-257.
- N. H. Khan, E. A. Prasetyanto, Y. K. Kim, B. M. Ansari, *Catal. Lett.* 140 (2010) 189– 196.
- 47. K. Dhahagani, J. Rajesh, R. Kannan, G. Rajagopal, *Tetrahedron:Asymmetry*, 22 (2011) 857–865.
- 48. R. I. Kureshy, B. Dangi, A. Das, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Applied Catalysis A: General*, 439-440 (2012) 74–79.
- 49. J. D. White, S. Shaw, Org. Lett. 24 (2012) 6270-6273.
- 50. R. Boobalan, G. H. Lee, C. Chena, Adv. Synth. Catal., 354 (2012) 2511–2520.
- A. Das, R. I. Kureshy, K. J. Prathap, M. K. Choudhary, G. V. S. Rao, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Applied Catalysis A: General* 459 (2013) 97–105.
- 52. A. Das, R.I. Kureshy, P. S. Subramanian, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Catal. Sci. Technol.* 4 (2014) 411–418.
- 53. K. Matsumoto, T. Oguma, T. Katsuki, Angew. Chem. Int. Ed. 48 (2009) 7432-7435.
- 54. M. Kol, K. Press, A. Cohen, US patent: US 2013/0096271 A1.

- 55. K. Press, A. Cohen, I. Goldberg, V. Venditto, M. Mazzeo, M. Kol, *Angew. Chem. Int. Ed.*, 50 (2011) 3529–3532.
- 56. A. Pilone, K. Press, I. Goldberg, M. Kol, M. Mazzeo, M. Lamberti, J. Am. Chem. Soc., 136 (2014) 2940–2943.
- 57. P. Kumar, S. Sarvanan, N. H. Khan, F. Hussain, S. Singh, Eur. J. Inorg. Chem. 29 (2014) 5077–5083.
- 58. P. Kumar, M. S. Chauhan, G. D. Yadav, S. Singh, Synlett 27 (2016) 267–271.
- 59. W. K. Dong, J. G. Duan, Y. H. Guan, J. Y. Shi, C. Y. Zhao, *Inorganica Chimica Acta*, 362 (2009) 1129–1135.
- M. Orio, O. Jarjayes, H. Kanso, C. Philouze, F. Neese, F. Thomas, *Angew. Chem.* 122 (2010) 5109–5112.
- P. Adao, S. Barroso, F. Avecilla, M.C. Oliveira, J. C. Pessoa, *Journal of Organometallic Chemistry* 760 (2014) 212–223.
- S. Wu, J. Tang, J. Han, D. Mao, X. Gao, J. Yu, L. Wang, *Tetrahedron* 70 (2014) 5986– 5992.
- 63. A. Majhi, S. T. Kadam, S. S. Kim, Bull. Korean Chem. Soc. 30 (2009) 1767–1770
- 64. Y. Q. Ji, G. Qi, Z. M. A. Judeh, Tetrahedron: Asymmetry 22 (2011) 2065–2070.
- 65. Y. Li, P. Dang, Y. Zeng, Y. Xiong, H. Zhou, Org. Lett., 18 (2016) 1578-1581.

Graphical Abstract



Highlights

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- Chiral Salalen ligands were derived from readily available (*L*)-proline
- ▶ The *in situ* generated Cu(II) complex of Ligand and Cu(OAC)₂.H₂O was used as a catalyst and 4-methoxyphenol as an additive for asymmetric Henry reaction.
- The *in situ* generated Cu(II) complex of ligand 2 are found to be efficient catalyst for

Henry reaction of a variety of aromatic aldehydes with nitromethane and nitroethane

> The absolute configuration of nitro-aldol product was governed by the use of the metal, Mn(III) complex of the ligand 2 gives (R)-enantiomer while Cu(II) complex of same ligand gives the (S)-enantiomer MAN