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Synthesis of chiral salalen ligands and their in-situ generated Cu-complexes for asymmetric Henry reaction

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Abstract

Chiral salalen ligands derived from (*S*)-proline and derivatives of salicyaldehydes were synthesized, and their in-situ generated Cu (II) complexes were evaluated in the asymmetric Henry reaction. Salalen ligand of different substituents on the phenyl moiety showed remarkable effect on the enantioselectivity of nitro-aldol product of 4-nitrobenzaldehyde and nitromethane. Cu (II) complex generated in situ with (*S*)-2-(*tert*-butyl)-6-((2-(((2-hydroxy-3-methylbenzylidene)amino)methyl)pyrrolidin-1-yl)methyl) phenol (10 mol%) and Cu $(OAc)_2.H_2O$ (10 mol%), found to be better catalyst for nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane, gave corresponding product in 85% yield and 88% enantiomeric excess (*ee*) in isopropanol at 35°C after 40 hours. The catalyst also used for the Henry reaction with different substituted benzaldehydes and corresponding products were obtained in 22% to 99% yields with 66% to 92% *ee*. Henry reaction of 4-nitrobenzaldehyde and prochiral nitroethane gave *anti*-selective product (*dr* = 79/21; *anti/syn*) in a 91% yield with 80% *ee*.

KEYWORDS

asymmetric Henry reaction, C_1-symmetric salalen ligand, Cu-salalen complex, nitro-aldol reaction, proline

1 | INTRODUCTION

The Henry reaction (nitro-aldol reaction) is a very efficient and atom economic method for the formation of C—C bond which afford β-nitro alcohols containing two functional groups (ie, nitro and hydroxyl groups) and can easily be transformed to the β-amino alcohols, α-hydroxy acids, α-hydroxy ketones, and other various biological active compounds.[1-5] Asymmetric version of this reaction attracted more attention of the chemists since 1992, when Shibasaki and co-workers reported the reaction.[6] In the last two decades, various chiral transition metal complexes and rare earth metal complexes have been developed for asymmetric nitro-aldol reaction.[7-32,33-37] Besides chiral metal complexes, organocatalysts and biocatalysts were also used in asymmetric nitro-aldol raection.[38-46] Diastereo- and enantioselective nitro aldol reaction using prochiral nitroethane and other nitroalkanes are limited in the literature, and *syn*-selective asymmetric nitro aldol reactions have been established by Shibasaki and others.[47-52] *Anti*-selective reaction in basic conditions is reported by Ooi and co-workers and later reported by other researchers.[53-61] Salen ligands are one of the most privileged ligands for the asymmetric catalysis, and Cu (II) complexes of salen and salan ligands were largely used for nitro-aldol reaction and efficiently active at mild reaction conditions.[62-72] (*S*)-Proline-based single chiral center salalen and salan ligands were first reported by Katsuki and co-workers for the asymmetric epoxidation of non-functionalised alkenes.[73] These ligands were also used by Kol and co-workers for polymerisation of

α-olefins and stereoselective polymerization of lactide.[74-76] We have already reported Mn (III) and Cu (II) salalen and salan complexes of ligands derived from (*S*)-proline and derivatives of salicyaldehyde for asymmetric Strecker and Henry reactions.[77-79] Herein, we wish to report the synthesis of salalen ligands and their in situ generated Cu (II) salalen complexes for diastereo- and enantioselective nitro-aldol reaction.

2 | MATERIALS AND METHODS

2.1 | Instruments and materials

All reagents were purchased commercially and used as received. HPLC grade isopropyl alcohol was used as solvent for the reactions. The synthesis of compound 1 and ligand 4g was reported in literature.[77,78] Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR, respectively) were recorded on 400 MHz (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) Jeol-FT-NMR spectrometers at ambient temperature. In the case of ^{1}H and ^{13}C NMR spectra, the chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane as an internal reference in the NMR solvent. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.00 ppm for ^{1}H and ^{13}C 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 ^{1}H and ^{13}C NMR and mass spectrometry (HRMS), and known compounds were characterized by ^{1}H-NMR and ^{13}C-NMR. The enantiomeric excess was determined using Schimadzu 2010 HPLC using Chiralpak AD-H, Chiralcel OD-H, and Chiralpak IC as chiral columns.

2.2 | General procedure for synthesis of ligand 4b

(*S*)-2-((2-(Aminomethyl)pyrrolidin-1-yl)methyl)-6-(*tert*-butyl) phenol (2) (0.262 g, 1 mmol) was dissolved in ethanol (2 mL); then, 2-methylsalicylaldehyde (3b) (0.136 g, 1 mmol) dissolved in ethanol (3 mL) was added to it dropwise, and reaction mixture was stirred for 16 hours at room temperature. Solvent was removed on rotavapor under reduced pressure, and product was purified from column chromatography by passing on short column on silica gel using ethyl acetate:hexane (10:90) as a mobile phase to yield ligand 4b as yellow oil. Spectroscopic data of ligands 4a-f are given below.

- (4a): Yield (0.615 g, 70%, yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.80 (brs, 1H), 8.41 (s, 1H), 7.6 (d, *J* = 7.2 Hz, 2H), 7.43 to 7.37 (m, 3H), 7.33 to 7.30 (m, 1H), 7.25 to 7.24 (m, 1H), 7.13 (d, *J* = 8 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 4.17 (d, *J* = 12.8 Hz, 1H), 3.82 (dd, *J* = 4 Hz, 12.4 Hz, 1H), 3.63 (dd, *J* = 6.8 Hz, 12.4 Hz, 1H), 3.54 (d, *J* = 13.6 Hz, 1H),3.05 to 2.90 (m, 2H), 2.34 (q, *J* = 8.4 Hz, 1H), 2.11 to 2.02 (m, 1H), 1.86 to 1.75 (m, 3H), 1.36 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.73, 158.33, 156.70, 137.72, 136.34, 133.27, 130.96, 129.59, 129.29, 128.05, 127.00, 126.06, 125.75, 122.62, 118.84, 118.52, 118.15, 64.68, 62.87, 58.66, 54.27, 34.56, 29.39, 22.99 ppm. $[\alpha]_D^{25} = -42.5$ (*c* 0.5 in CH_2Cl_2). FT-IR ($CHCl_3$, Film) $\bar{\upsilon}$ = 2953, 1630 cm^{-1}. HRMS (ESI): m/z $[M + H]^+$ calcd. For $C_{29}H_{35}N_2O_2$: 443.2698; found 443.2699.
- (4b): Yield (0.308 g, 81%, yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.54(brs, 1H), 8.41 (s, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 6.8 Hz, 1H), 6.84 (t, *J* = 7.6 Hz,1H), 6.75 (t, *J* = 7.6 Hz, 1H), 4.25 (d, *J* = 13.6 Hz, 1H), 3.88 (dd, *J* = 4.4 Hz, 12.4 Hz, 1H), 3.7 to 3.61 (m, 2H), 3.13 to 2.98 (m, 2H), 2.46 to 2.39 (m, 1H), 2.32 (s, 3H), 2.19 to 2.09 (m, 1H), 1.93 to 1.83 (m, 3H), 1.43 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =166.66, 159.23, 156.73, 136.36, 133.28, 129.16, 126.07, 125.79, 125.76, 122.67, 118.14, 118.09, 117.92, 64.76, 63.09, 58.75, 54.32, 34.56, 29.45, 29.38, 23.05, 15.47 ppm. $[\alpha]_D^{25} = -17.2$ (*c* 0.378 in CH_2Cl_2). FT-IR ($CHCl_3$, Film) $\bar{\upsilon}$ = 2953, 1628, 1042 cm^{-1}. HRMS (ESI): m/z $[M + H]^+$ calcd. $C_{24}H_{33}N_2O_2$: 381.2542; found 381.2542.
- (4c): Yield (0.331 g, 61%). M.p. = 91°C to 93°C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.15 (brs, 1H), 8.30 (s, 1H), 7.49 (s, 1H), 7.24 to 7.13 (m, 7H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.66 (t, *J* = 7.6 Hz, 1H), 4.12 (d, *J* = 13.6 Hz, 1H), 3.75 to 3.70 (m, 1H), 3.50 to 3.43 (m, 3H), 2.99 to 2.86 (m, 2H), 2.29 (q, *J* = 8.4 Hz, 1H), 2.00 to 1.88 (m, 1H), 1.74 to 1.70 (m, 8H), 1.34 (d, *J* = 15.2 Hz, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.08, 157.36, 156.74, 150.76, 139.87, 136.27, 135.90, 127.71, 127.45, 126.37, 126.07, 125.67, 125.62, 124.95, 122.73, 118.08, 117.95, 64.65, 63.29, 58.71, 54.27, 42.21, 34.58, 34.11, 31.50, 29.61, 29.44, 29.26, 22.95 ppm. $[\alpha]_D^{25} = -26.45$ (*c* 0.24 in CH_2Cl_2). FT-IR ($CHCl_3$, Film) $\bar{\upsilon}$ = 2958, 1631 cm^{-1}. HRMS (ESI): m/z $[M + H]^+$ calcd. For $C_{36}H_{49}N_2O_2$: 541.3794; found 541.3777.

- (4d): (0.340 g, 86%, yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.72 (brs, 1H), 8.34 (s, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.91 to 6.76 (m, 4H), 6.67 (t, J = 8 Hz, 1H), 4.15 d, J = 13.6 Hz, 1H), 3.88 (s, 3H), 3.81 (dd, J = 4.8 Hz, 13.2 Hz, 1H), 3.63 to 3.55 (m, 2H), 3.08 to 2.91 (m, 2H), 2.35 (q, J = 8.4 Hz, 1H), 2.16 to 2.03 (m, 1H), 1.88 to 1.76 (m, 3H), 1.33 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.59, 156.66, 151.56, 148.26, 136.29, 126.05, 125.71, 123.05, 122.63, 118.46, 118.12, 117.88, 113.86, 64.65, 62.63, 58.73, 55.97, 54.38, 34.51, 29.35, 29.18, 23.14 ppm. $[\alpha]_D^{25}$ = −29.0 (*c* 0.62 in CH_2Cl_2). FT-IR ($CHCl_3$, Film) $\bar{\upsilon}$ = 2953, 1631, 1083 cm^{-1}. HRMS (ESI): m/z $[M + H]^+$ calcd. For $C_{24}H_{33}N_2O_3$: 397.2491; found 397.2489.
- (4e): Yield (0.333 g, 91%, yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1H), 7.29 to 7.23 (m, 2H), 7.23 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.87 to 6.82 (m, 2H), 6.68 (t, J = 7.6 Hz, 1H), 4.18 (d, J = 14 Hz, 1H), 3.82 (dd, J = 4 Hz, 12.4 Hz, 1H), 3.72 to 3.55 (m, 2H), 3.05 to 2.97 (m, 2H), 2.40 to 2.34 (m, 1H), 2.15 to 2.02 (m, 1H), 1.87 to 1.76 (m, 3H), 1.37 to 1.34 (m, 9H) ppm. ^{13}C NMR (100 MHz, CDCl3): δ = 166.49, 160.89, 156.65, 136.26, 132.19, 131.43, 126.02, 125.69, 122.58, 118.66, 118.50, 118.12, 116.79, 64.63, 63.02, 58.65, 54.25, 34.49, 29.36, 29.28, 23.02 ppm. $[\alpha]_D^{25}$ = −22.7 (*c* 0.892, CH_2Cl_2). FT-IR ($CHCl_3$, Film) $\bar{\upsilon}$ = 2953, 1631 cm^{-1}. HRMS (ESI): m/z $[M + H]^+$ calcd. For $C_{24}H_{33}N_2O_3$: 367.2385; found 367.2380.
- (4f): Yield (0.377 g, 85%, yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.42 (brs, 1H), 10.98 (brs, 1H), 8.33 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 7.6 Hz, 20.8 Hz, 2H), 6.86 (d, J = 7.6 Hz, 1H), 6.79 to 6.69 (m, 2H), 4.16 (d, J = 13.2 Hz, 1H), 3.85 (dd, J = 4.4 Hz, 12 Hz, 1H), 3.68 to 3.59 (m, 2H), 3.08 to 2.96 (m, 2H), 2.40 (q, J = 8.4 Hz, 1H), 2.20 to 2.08 (m, 1H), 1.93 to 1.80 (m, 3H), 1.37 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.96, 158.54, 156.58, 136.32, 135.61, 130.73, 126.05, 125.78, 122.49, 119.19, 119.00, 118.21, 111.01, 64.57, 62.16, 58.71, 54.32, 34.51, 29.35, 23.11 ppm. $[\alpha]_D^{25}$ = −75.3 (c = 0.2, CH_2Cl_2). FT-IR ($CHCl_3$, Film) $\bar{\upsilon}$ = 2954, 1632 cm^{-1}. HRMS (ESI): m/z $[M + H]^+$ calcd. For $C_{23}H_{30}BrN_2O_2$: 445.1490; found 445.1488.

2.3 | Synthesis of derivatives of salicyaldehyde 3a-c

2.3.1 | 2-Phenylsalicylaldehyde (3a)

2-Phenylphenol (10 g, 58.8 mmol) was dissolved in dry THF (100 mL), and then $MgCl_2$ (8.38 g, 88.2 mmol) and triethylamine (11.87 g, 117.6 mmol) were added to the reaction mixture and stirred at room temperature for 1 hour, then paraformaldehyde (8.82 g, 294 mmol) was added to it. The resulting mixture was refluxed for 24 hours. Solvent was removed on reduced pressure by rotavapor, and it was then acidified with 11.16 N HCl, and resulting mixture was extracted with ethyl acetate, dried over Na_2SO_4. Solvent was recovered at the reduced pressure by rotavapor to yield yellowish oil which was then purified by column chromatography on silica gel using hexane as an eluent to give light greenish solid product (3a) (8.0 g, 69%). M.p. = 44°C.^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.46 (s, 1H), 9.87 (s, 1H), 7.55 to 7.47 (m, 4H), 7.37 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.84, 158.83, 137.79, 136.23, 133.16, 130.42, 129.22, 128.25, 127.64, 120.80, 119.89 ppm.

2.3.2 | 2-Methylsalicylaldehyde (3b)

2-Methylphenol (4 g, 36.9 mmol) was taken in dry THF (50 mL); then, $MgCl_2$ (5.25 g, 55.3 mmol) and triethylamine (7.47 g, 73.9 mmol) were added to it and stirred for 30 minutes at room temperature. Then, paraformaldehyde (5.54 g, 184.9 mmol) was added, and resulting reaction mixture was refluxed for 24 hours. Solvent was removed under reduced pressure by rotavapor, and it was acidified with 11.16 N HCl. The resulting mixture was extracted with ethyl acetate, dried over Na_2SO_4. Solvent was recovered at the reduced pressure on rotavapour to yield yellowish oil which was purified by column chromatography on silica gel using hexane as an eluent to give product (3b) as greenish oil (1.9 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.25 (s, 1H), 9.84 (s, 1H), 7.36 (d, J = 7.6 Hz, 2H), 6.90 (t, J = 7.6 Hz, 1H), 2.25 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.65, 159.85, 137.72, 131.27, 126.69, 119.90, 119.26, 14.92 ppm.

2.3.3 | 5-(*tert*-Butyl)-2-hydroxy-3-(2-phenylpropan-2-yl) benzaldehyde (3c)

4-(*tert*-Butyl)-2-(2-phenylpropan-2-yl) phenol (2.06 g, 7.66 mmol) was dissolved in dry THF (50 mL); then, $MgCl_2$ (1.09 g, 11.4 mmol) and triethylamine (1.54 g, 15.3 mmol) were added to it and stirred for 30 minutes at room temperature, and later paraformaldeyde (1.14 g, 38.3 mmol) was added and refluxed for 24 hours. Solvent was removed under reduced pressure by rotavapor, and it was acidified with 11.16 N HCl. The resulting mixture was extracted with ethyl acetate, dried over Na_2SO_4. Solvent was recovered at the reduced pressure on rotavapour to yield yellowish oil which was purified by column chromatography on silica gel using hexane as an eluent to

give product (3c) as light greenish oil (1.2 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.13 (s, 1H), 9.75 (s, 1H), 7.66 (d, *J* = 2 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.20 to 7.07 (m, 5H), 1.67 (s, 6H), 1.29 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.94, 158.30, 149.78, 141.55, 137.04, 132.07, 128.13, 127.87, 125.56, 125.37, 120.09, 42.08, 34.27, 31.33, 29.21 ppm.

2.4 | General procedure for asymmetric Henry (nitro-aldol) reaction

The mixture of salalen ligand 4b (19 mg, 10 mol%) and Cu $(OAc)_2.H_2O$ (9.9 mg, 10 mol%) in isopropanol (2.0 mL) was stirred for 30 minutes; then, CH_3NO_2 (267 μL, 5 mmol, 10 equiv.) was added, and resulting reaction mixture was stirred for 30 minutes at 35°C, at the end benzaldehyde/substituted benzaldehydes (0.5 mmol) was added. Reaction mixture was stirred for specified time and monitored by TLC. Solvent was evaporated on rotavapor and nitro-aldol product was purified by column chromatography on silica gel using hexane/ethyl acetate as a mobile phase. Enantiomeric excess was determined by HPLC using Chiracel OD-H, AD-H and IC columns. HPLC chromatogram and ^{1}H-NMR and ^{13}C-NMR spectra of the nitro-aldol products are given in SI.

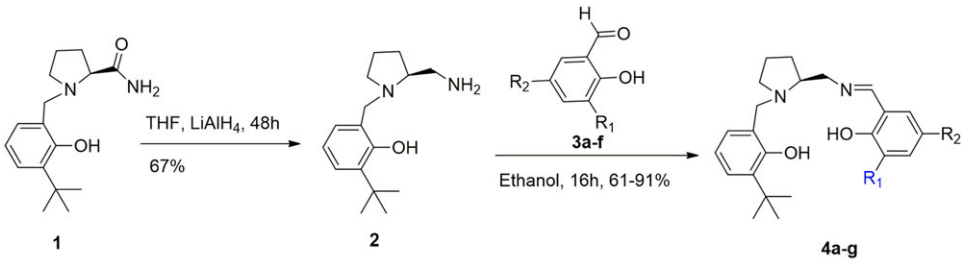
2.4.1 | 2-Nitro-1-(4-nitrophenyl) ethanol (7)[19]

Yellow oil, yield: 90.1 mg (85%), *ee*: 88%. HPLC conditions: Chiralcel OD-H (hexane/*i*PrOH, 80:20 *v*/*v*, 1.00 mL/min, 25°C, UV 230 nm), t_r (minor) = 10.5 minutes and t_r (major) = 12.7 minutes. $[\alpha]_D^{25}$ = +19.7 (*c* 0.63 CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 5.58 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.58 to 4.53 (m, 2H), 3.20 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 144.9, 126.9 (2C), 124.2 (2C), 80.6, 69.9 ppm.

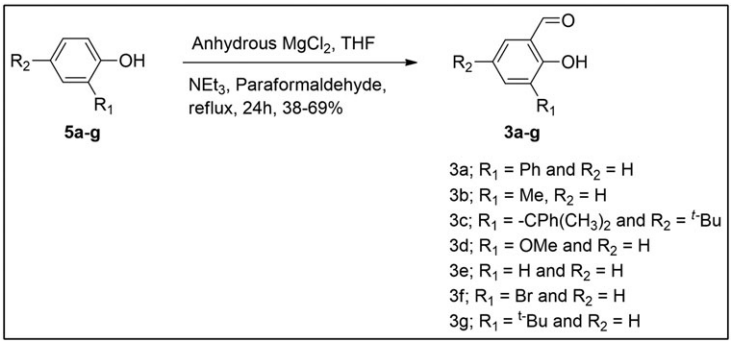
3 | RESULTS AND DISCUSSION

Chiral salalen ligands (**4a-g**) were synthesized in 61% to 91% yields from reaction of (*S*)-2-((2-(aminomethyl) pyrrolidin-1-yl)methyl)-6-(*tert*-butyl) phenol (**2**) and derivatives of salicyaldehyde **3a-g** in ethanol (Scheme 1). (*S*)-2-((2-(Aminomethyl)pyrrolidin-1-yl)methyl)-6-(*tert*-butyl) phenol (**2**) was synthesized by the reduction of (*S*)-1-(3-(*tert*-butyl)-2-hydroxybenzyl)pyrrolidine-2-carboxamide (**1**) with $LiAlH_4$.[73] (*S*)-1-(3-(*tert*-Butyl)-2-hydroxybenzyl) pyrrolidine-2-carboxamide (**1**) was synthesized from (*S*)-proline as a starting material according to literature reports.[73,77] The synthesis of derivatives of salicyaldehyde (**3a-g**) was carried out according to scheme 2.[80] Substituted phenols were reacted with paraformaldehyde in the presence of anhydrous $MgCl_2$ and triethylamine in THF under reflux condition for 24 hours to afford corresponding salicyaldehyde derivatives **3a-c** in 38% to 69% yields. All salalen ligands were characterized by ^{1}H, ^{13}C NMR, IR, and HRMS.

In our initial investigation, we have evaluated in situ generated Cu (II) complexes of the ligands **4a-g** (5 mol%) and Cu $(OAc)_2.H_2O$ (5 mol%) for Henry (nitro-aldol) reaction between 4-nitrobenzaldehyde and nitromethane in isopropanol at 25°C. The results shown in Table 1 indicate that the R^1 group on the phenol influences the yield and *ee* of product **7**. Yield of the product **7** was found to be better in case of ligand **4e** (R^1 = H and R^2 = H), but when bulky and electron donating group was attached to imine contained phenyl ring, yield of product **7** was decreased (Table 1, entries 2, 3, 4, 6, and 7).

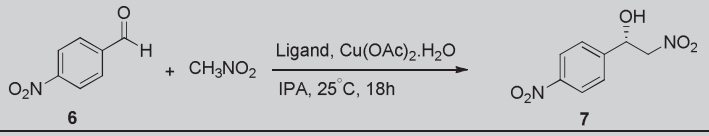


SCHEME 1 Synthesis of chiral salalen ligands **4a-g**



SCHEME 2 Synthesis of salicyaldehyde derivatives **3a-g**

TABLE 1 Screening of different ligands for Henry reaction[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	4a	74	71
2	4b	26	91
3	4c	31	66
4	4d	44	79
5	4e	83	24
6	4f	38	53
7	4g	30	66

[a]Ligand **4a-g** (5 mol%) and Cu $(OAc)_2.H_2O$ (5 mol%) was stirred in isopropanol (2 mL) at 25°C for 30 min, and then nitromethane (5 mmol) was added to it and again stirred for 30 min; finally, 4-nitrobenzaldehyde (0.5 mmol) was added, and the reaction was carried out for 18 h at same temperature.

[b]Yield after purification by column chromatography.

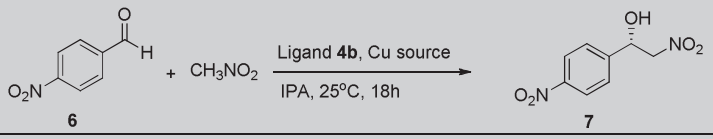
[c]Enantiomeric excess was determined by HPLC on Chiralpak OD-H column.

In our recent report we have used ligand **4g** (R^1 = -C $(CH_3)_3$) and product was obtained in a 66% ee (Table 1, entry 7).[79] Bulkiness of substituents R_1 = —C $(CH_3)_2$Ph and R_2 = —C $(CH_3)_3$ in the ligands **4c** also gave the product in 66% *ee* (Table 1, entry 3 and 7). Enantiomeric excess of nitroaldol product was better in case of ligand **4b** (R^1 = CH_3, Table 1, entry 2) compared with other ligand (**4a**, **4c**, **4d**, **4f**, and **4g**) bearing bulky groups (Table 1, entries 1, 3, 4, 6, and 7). Product was obtained with (*S*)-absolute configuration which was determined by comparing the optical rotation of literature reports.[79]

After screening of the ligands, we found that ligand **4b** is a better ligand among all the ligands. Then, we varied Cu sources with ligand **4b** for catalysis in Henry reaction of 4-nitrobenzaldehyde (**6**) and nitromethane, and Cu $(OAc)_2.H_2O$ gave best yield and *ee* compared to CuCl, $CuSO_4.5H_2O$, and CuCN (Table 2, entries 1-4,) whereas in case of Cu $(NO_3)_2.3H_2O$, $CuCl_2.2H_2O$, and Cu $(OTf)_2$ did not form desired product **7** at 25°C (Table 2, entries 5-7).

Reaction conditions of Henry reaction between 4-nitrobenzaldehyde (**6**) and nitromethane were optimized by varying catalyst loading, temperature, and additive. We have increased the in situ generated catalyst loading (ligand **4b** (10 mol%) with Cu $(OAc)_2.H_2O$ (10 mol%)) at 25°C and increased the yield of the product **7** up to 41%. Low loading of in-situ generated Cu (II) catalyst (2 mol%) gave 15% yield and poor *ee* of the product **7** (Table 3, entries 1 and 2). We also increased the reaction temperature from 25°C to 35°C using in-situ generated Cu (II) catalyst (10 mol%) which improved yield and *ee* of the product **7** (Table 3, entry 3), but further increase of temperature up to 45°C enhanced the yield of the product up to 91% but *ee* was decreased (Table 3, entry 5). The yield of product **7** was increased with longer reaction time, but slight drop in ee was observed (Table 3, entries 4). At this stage again, we have increased the in-situ generated catalyst loading up to 20 mol%, and results show that yield of product **7** was improved but *ee* decreased (Table 3, entries 6 and 7). We examined the efficacy of nitrogen containing

TABLE 2 Screening of various cu source with ligands **4b** for Henry reaction[a]



6 7

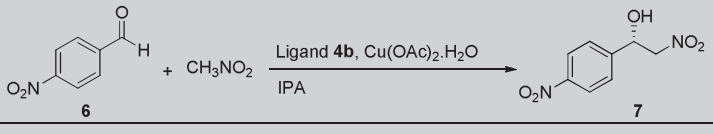
Entry	Cu Source	Yield[b], %	ee[c], %
1	Cu $(OAc)_2.H_2O$	26	91
2	CuCl	8	79
3	Cu $(SO_4).5H_2O$	11	77
4	CuCN	5	40
5	Cu $(NO_3)_2.3H_2O$	-	-
6	$CuCl_2.2H_2O$	-	-
7	Cu $(OTf)_2$	-	-

[a]Ligand **4b** (5 mol%) and Cu source (5 mol%) were stirred in isopropanol (2 mL) at 25°C for 30 min, and then nitromethane (5 mmol) was added to it and again stirred for 30 min; finally, 4-nitrobenzaldehyde (0.5 mmol) was added, and reaction was carried out for 18 h at same temperature.

[b]Yield after purification by column chromatography.

[c]Enantiomeric excess was determined by HPLC on Chiralpak OD-H column.

TABLE 3 Optimization of reaction conditions[a]



6 7

Entry	Additive, mol%	Mol% of 4b and Cu $(OAc)_2.H_2O$	Time, h	Temp., °C	Yield[b], %	ee[c], %
1	-	10	18	25	41	91
2	-	2	18	25	15	43
3(4)	-	10	18 (40)[d]	35	58 (85)	94 (88)
5	-	10	18	45	91	68
6	-	15	18	35	80	74
7	-	20	18	35	89	77
8	NEt_3	10	2	35	95	0
9	DIEPA	10	2	35	98	0
10	NMO	10	21	35	90	50
11	4-methylphenol	10	21	35	76	70
12	4-methoxyphenol	10	40	35	77	90

[a]Ligand **4b** and Cu $(OAc)_2.H_2O$ were stirred in isopropanol (2 mL) for 30 min; additive (10 mol%) and nitromethane (5 mmol) were added to it and stirred for 30 min. Then, 4-nitrobenzaldehyde (0.5 mmol) was added to it, and reaction mixture was stirred for respective time at specified temperature.

[b]Yield after purification by column chromatography.

[c]Enantiomeric excess was determined by HPLC on chiralpak OD-H column.

[d]Result in parenthesis is given for reaction time 40 h.

bases as additive, and it worked well in very short span of time to get the desired nitro-aldol product **7** in good yield, but poor enantiomeric excess was observed (Table 3, entry 8, 9, and 10). We also study the effect of O-donor additives like 4-methylphenol and 4-methoxyphenol. In the presence of additive 4-methoxyphenol, the nitroaldol product **7** was obtained in slight low yield and comparable ee which indicate that additive is not playing a significant role in catalysis (Table 3, entries 11 and 12). These experiments provided optimized reaction conditions for nitro-aldol reaction that is ligand **4b** (10 mol%) and Cu $(OAc)_2.H_2O$ (10 mol%) in isopropanol (2 mL) at 35°C.

We also checked the dependency of enantiomeric excess (ee) with time during the course of reaction (Figure 1). For this, we have carried out asymmetric Henry reaction between 4-nitrobenzaldehyde (**6**) and nitromethane using ligand **4b** (10 mol%) and Cu $(OAc)_2$. H_2O (10 mol%) in isopropanol at 35°C, and *ee* of the reaction was monitored for different interval of time. When reaction was started, *ee* of product **7** was found to be high 90%, but the ee of product **7** slightly decreased with respect to reaction time. After 24 hours, the reaction proceeds with constant enantioselectivity till 44 hours. The results show that decrease in enantioselectivity may be due to formation of thermodynamically more stable product over kinetically stable product because of retro-Henry reaction.[81]

We are proposing the plausible reaction mechanism for the Henry reaction between 4-nitrobenzaldehyde and nitromethane catalyzed by in situ generated Cu (II) complex of ligand **4b** (Figure 2). Ligand **4b** was reacted with Cu $(CH_3COO)_2.H_2O$ in isopropanol which generate a complex Cu (II)L^* and acetate anions. Acetate anion acts as a base and abstracts a proton of the nitromethane and forming a nitro enolate. The Cu metal center of this complex is interacting with nitro enolate and oxygen of 4-nitrobenzaldehyde. The transition state (a) of Figure 3 found to be disfavored because the *Si*-face arrangement of 4-nitrobenzaldehyde is hindered by the imine part of the in situ generated complex (Cu (II)L^*) from ligand **4b** and Cu $(CH_3COO)_2.H_2O$. Another transition state (b) in the Figure 3 is favorable since 4-nitrobenzaldehyde is far away from the imine part of in situ generated Cu (II)L^* complex of ligand **4b** and nucleophile nitro enolate is attacking on the *Re*-face of 4-nitrobenzaldehyde which is giving the (*S*)-enantiomer of the nitro-aldol product **7**.

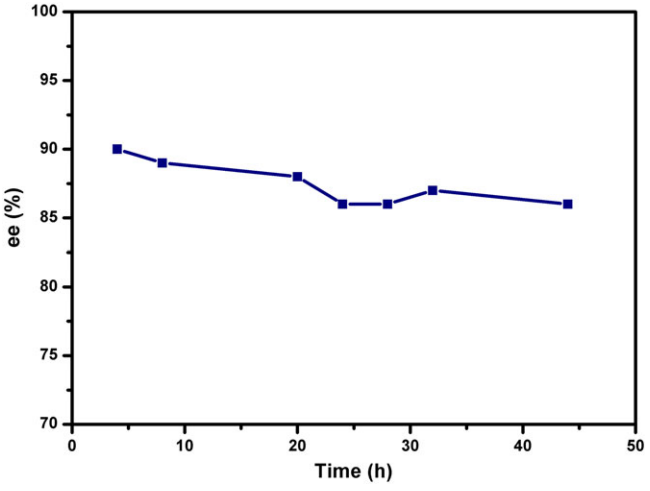


FIGURE 1 Graph represents the enantiomeric excess (ee) of product **7** v/s reaction time

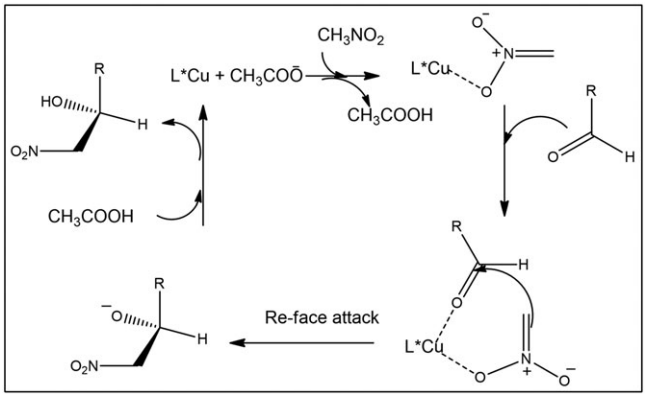


FIGURE 2 Plausible mechanism for Henry reaction catalyzed by Cu (II) complex

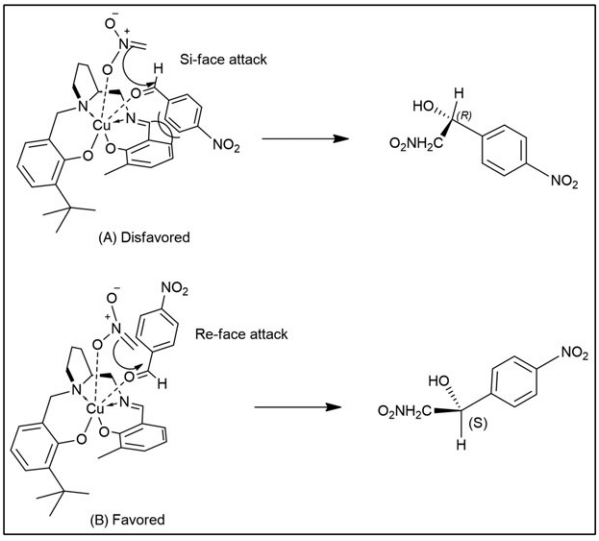
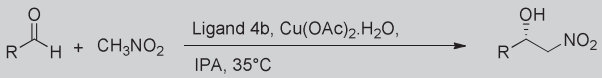


FIGURE 3 Transition state of Henry reaction catalyzed by in situ generated Cu (II) complex of salalen ligand **4b** and Cu $(OAc)_2.H_2O$

Scope and limitations of asymmetric Henry reaction catalyzed by in situ generated Cu(II) complex was studied for a variety of substituted benzaldehydes with nitromethane (Table 4). Electron withdrawing group on benzaldehyde such as nitro reacted fastest to afford the corresponding nitro-aldol products in excellent yields and good enantiomeric excesses (Table 4, entries 1 and 2). Electron withdrawing group makes the carbonyl group of benzaldehyde more electrophilic and found to be more reactive for nitro-aldol reaction, while electron donating group reduces the electrophilicity of the carbonyl group and therefore found to be less reactive. The nitro-aldol reaction of halo-benzaldehydes gave corresponding products in good yields and *ee*. The reactivity of 4-halobenzaldehyde was found to be in order Br > Cl > F but poor than 4-nitrobenzaldehydes (Table 4, entries 1, 3,

TABLE 4 Scope and limitations of in situ generated Cu (II) salalen complex as a catalyst for nitro-aldol reaction[a]



Entry	R	Time, h	Yield[b], %	ee[c], %
1	4-NO_2-Ph	40	85	88
2	2-NO_2-Ph	40	91	85
3	4-Br-Ph	72	81	72
4	2-Br-Ph	72	95	91
5	4-Cl-Ph	72	68	77
6	2-Cl-Ph	72	99	92
7	4-F-Ph	72	53	66
8	2-F-Ph	72	90	85
9	4-MeO-Ph	72	22	72
10	2-MeO-Ph	72	69	87
11	4-Me-Ph	72	50	69
12	2-Me-Ph	72	61	69
13	Ph	72	69	69
14	Cinnamyl	72	32	74
15	Ethyl	72	80	73

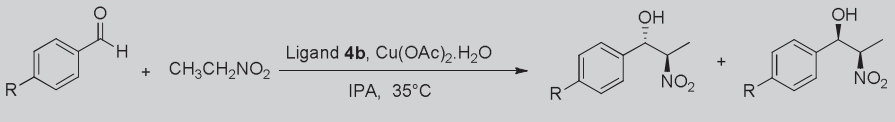
[a]Ligand **4b** (10 mol%) and Cu $(OAc)_2.H_2O$ (10 mol%) were stirred in isopropanol (2 mL) for 30 min, and nitromethane (5 mmol) was added to it and stirred for 30 min; then, substituted benzaldehyde (0.5 mmol) was added to it, and reaction mixture was stirred at 35°C for respective time.

[b]Yield after purification by column chromatography.

[c]Enantiomeric excess was determined by HPLC on chiralpak OD-H and AD-H column.

5, and 7). 2-Halobenzaldehydes after 72 hours afforded corresponding products in better yields and *ee* compared with corresponding products of 4-halobenzaldehydes (Table 4, entries 3-8). Electron donating group on benzaldehyde such as methoxy and methyl was found to be less reactive than benzaldehyde and 4-nitrobenzaldehyde and afforded corresponding products in 22% to 69% yields with 69% to 87% *ee* (Table 4, entries 9-13). We also used conjugated aldehydes cinnamaldehyde for nitro-aldol reaction, and poor yield of product was obtained with moderate *ee* (Table 4, entry 14). Aliphatic aldehyde like propanal was also efficiently catalyzed to give the corresponding product in an 80% yield with 73% *ee* (Table 4, entry 15). The results show that the better *ee* was obtained with most of the 2-substituted benzaldehydes, which may be due to steric effect of substrate and the ligand **4b**.

TABLE 5 Asymmetric Henry reaction between substituted benzaldehydes and prochiral nitroethane[a]



11a 11b

Entry	R	Time, h	Yield, %[b]	dr (*anti/syn*)[d]	ee, %[c] (*anti/syn*)
1	NO_2	48	91	79/21	80/66
2	Br	72	76	65/35	52/58
3	OMe	96	38	47/53	3/45

[a]Ligand **4b** and Cu $(OAc)_2.4H_2O$ (10 mol%) were stirred in isopropanol (2 mL) for 30 min; nitroethane was added to it and further stirred for 30 min. Then, substituted benzaldehyde (0.5 mmol) was added to it, and reaction mixture was stirred respective time at 35°C.

[b]Yield after purification by column chromatography.

[c]Enantiomeric excess (*ee*) was determined by HPLC on chiralpak IC and AD-H column.

[d]Diasteiomeric ratio (*dr*) was determined from ^1H NMR.

We also carried out the Henry reaction between 4-substituted benzaldehydes and prochiral nitroethane to know the diastereoselectivity of the corresponding products (Table 5). In case of electron withdrawing group such as nitro, it gave *anti* diastereomer as a major product with 91% yield and dr (79/21, *anti/syn*) with 80% *ee* of the *anti*-product (Table 5, entry 1). The diastereomeric ratio was determined by ^{1}H-NMR considering the area of the peak of the benzylic proton in *anti* and *syn* products. In case of 4-bromobenazaldehyde, poor *dr* and *ee* were obtained compared with 4-nitrobenzaldehyde (Table 5, entry 1 and 2). The electron donating group on benzaldehyde like 4-methoxy was found to be less reactive; *anti*-selectivity of diastereomer was also reduced, and dr *anti/syn* (47/53) and only 3% *ee* were obtained for *anti*-product (Table 5, entry 3).2

4 | CONCLUSIONS

Complexes of Cu (II) generated in situ from the chiral salalen ligands derived from (*S*)-proline were evaluated as catalyst in the asymmetric Henry reaction. Cu (II) complex generated in situ from ligand **4b** (10 mol%) and Cu $(OAc)_2.H_2O$ (10 mol%) was acting as a catalyst for nitro-aldol reaction of 4-nitrobenzaldehyde and nitromethane in isopropanol at 35°C; the corresponding nitro-aldol product was obtained in an 85% yield with 88% *ee*. Substrate scope for Henry reaction with derivatives of benzaldehydes and nitromethane using in-situ generated Cu (II) complex (10 mol%) was investigated and the corresponding products obtained in 22% to 99% yields with 66% to 92% *ee's*. Catalyst was found to be more active in nitro-aldol reaction of nitromethane with benzaldehydes that contain electron withdrawing group compared with benzaldehydes that contain electron donating group. Diastereo- and enantio-selective Henry reaction of benzaldehyde derivatives with prochiral nitroethane was performed, and *anti*-selective product was obtained for electron withdrawing group with yield up to 91% and dr 79/21 (*anti/syn*), while electron donating group on benzaldehyde showed poor *anti*-selectivity.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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