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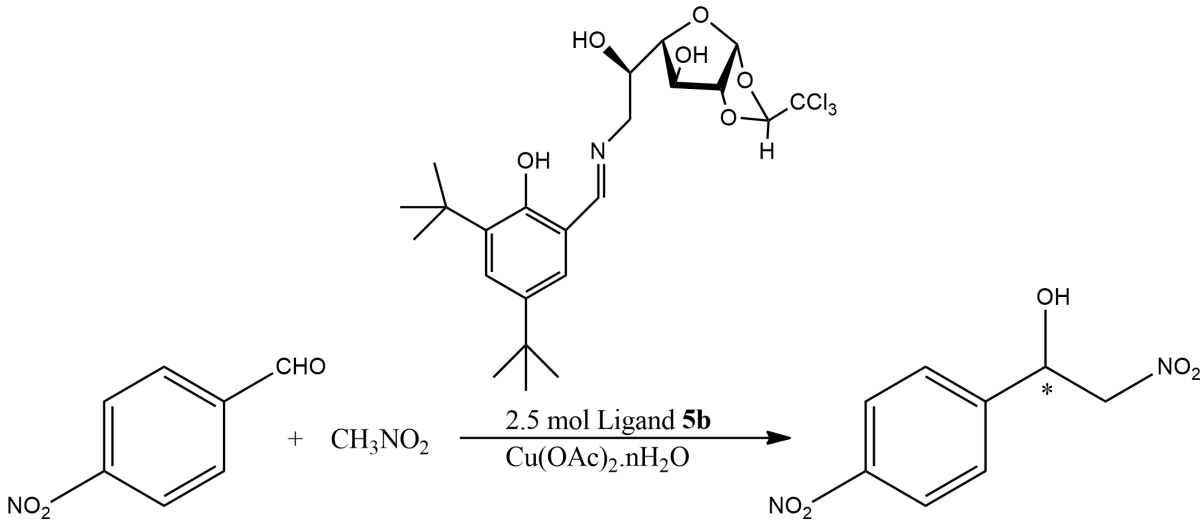


Synthesis of Novel Schiff Base Ligands from Gluco- and Galactochloraloses for the Cu(II) Catalysed Asymmetric Henry Reaction

Sevda Alkan, Fatma Ç. Telli, Yeşim Salman* and Stephen T. Astley*

Ege University, Faculty of Science, Department of Chemistry, Bornova, İzmir 35100, Turkey

Key Words: Chloralose, Asymmetric Henry reaction, Chiral Schiff base, Amino sugar

* Corresponding authors. Tel.:+902323115451; fax:+902323888264

Email: stephen.thomas.astley@ege.edu.tr, yesim.salman@ege.edu.tr

Abstract

A series of chiral Schiff base ligands has been prepared using aminochloralose derivatives of glucose and galactose. These ligands were used as catalysts in the asymmetric Henry reaction in the presence of Cu(II) ions giving yields of up to 95%. An interesting solvent dependency on enantiomeric control was observed with the best enantiomeric excesses (up to 91%) being obtained in the presence of water.

1. Introduction

The nitroaldol (Henry) reaction is a convenient method of C-C bond formation which affords useful products for organic synthesis.[1a-b] As a result, considerable research effort has been invested into finding suitable methods for carrying out this reaction in high yields and stereocontrol. Such methods include applications of organocatalysts,[2a-f] enzymes,[3a-b] and transition metal-chiral ligand complexes.[4a-b] In particular, Cu(II) complexes of a variety of bidentate[5a-d] and tridentate[6a-e] ligands have recently been utilised with good results. Using these catalysts, it is generally believed that the transition state consists of a square pyramidal copper (II) center that is coordinated by the chiral ligand, the substrate aldehyde and nitroalkane and in some cases a counteranion such as acetate and that it is the subsequent combination of the apically coordinated nitronate and equatorially bonded aldehyde that results in the formation of the desired B-nitroalcohols in good yields and with good stereocontrol.[7a-d] Further studies have indicated that the presence of bulky groups near to the metal center can also play an important role.[8a-c]

Encouraged by these results, a number of groups have prepared some elaborate chiral ligands containing substructures as diverse as sparteine,[9] paracyclophane,[10] binaphthylazepine[11] and cinchona alkaloids[12] and employed them with good results in the Henry reaction. As an extension of our own work on the application of Cu(II) complexes of chiral tricoordinate ONO Schiff base complexes for this purpose,[13] we recently reported that an aspartic acid derived Schiff base ligand (Figure 1) that contains an additional proximal hydroxy group afforded better enantioselectivities than related tridentate ligands.[14]

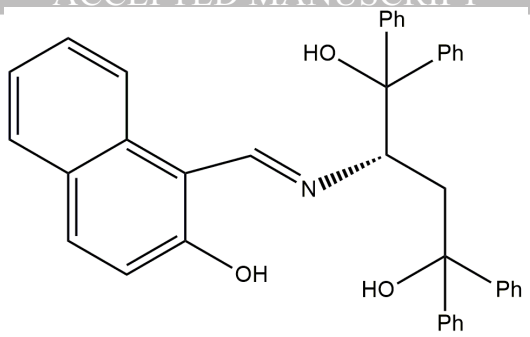
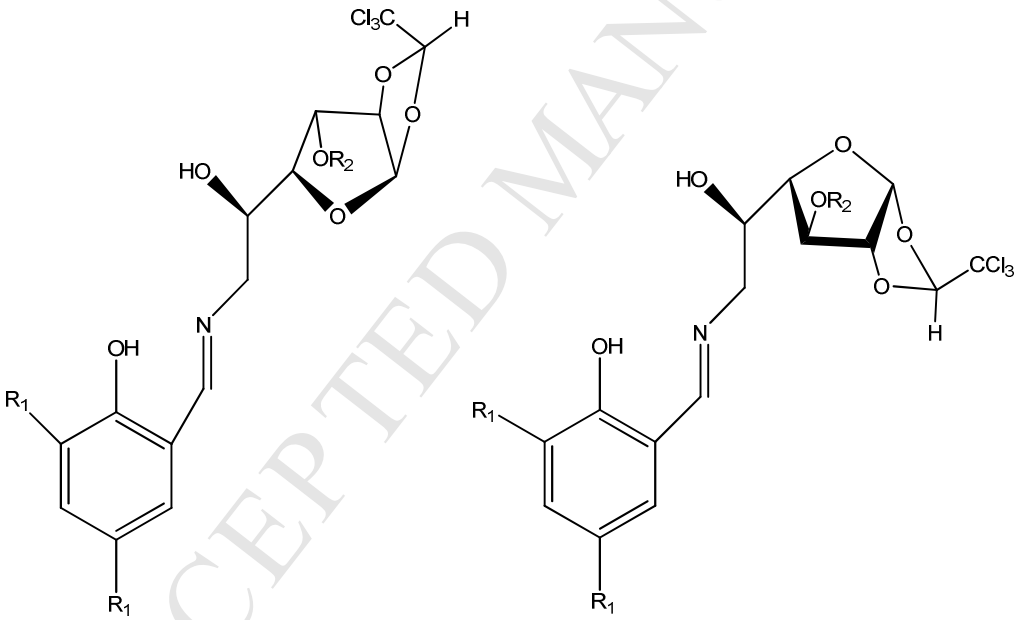


Figure 1. Structure of an aspartic acid derived Schiff base ligand.

As a further continuation, we decided to prepare Schiff base ligands (**3a-6a**, **3b-6b**) from aminochloralose derivatives of glucose (**3-4**) and galactose (**5-6**) (Figure 2.). Thus, it was anticipated that we could learn about the applicability of chloraloses in asymmetric synthesis and learn more about the effect of the proximal hydroxy groups (OR^2, R^2 = H) which are present in ligands **4** and **5**.



3a (R_1=H, R_2=CH_3)
3b (R_1= *t*Bu, R_2=CH_3)
4a (R_1=H, R_2=H)
4b (R_1= *t*Bu, R_2=H)

5a (R_1=H, R_2=H)
5b (R_1= *t*Bu, R_2=H)
6a (R_1=H, R_2=CH_3)
6b (R_1= *t*Bu, R_2=CH_3)

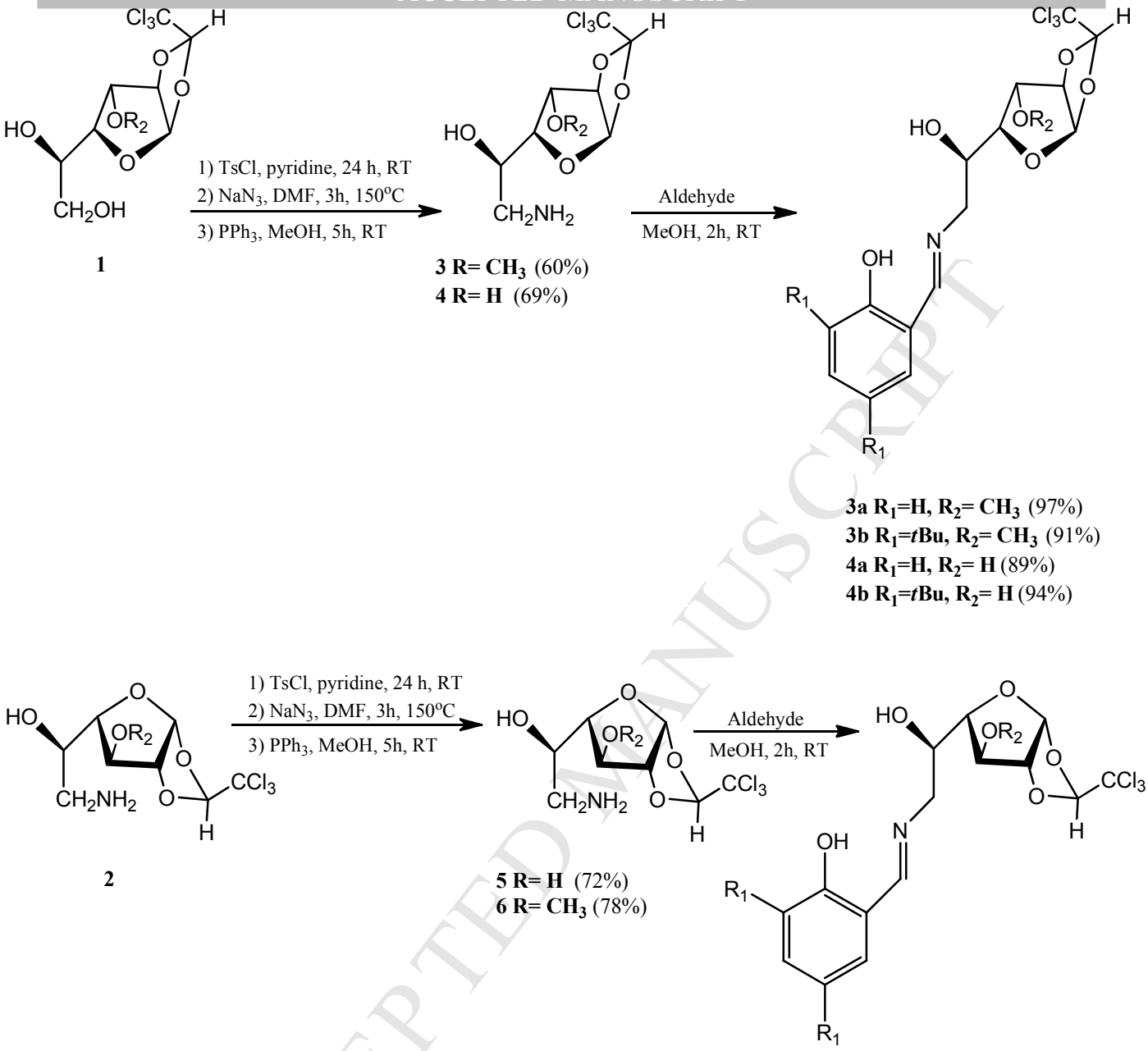
Figure 2. Structure of Schiff base ligands (**3a-6a**, **3b-6b**) from aminochloralose derivatives of glucose (**3-4**) and galactose (**5-6**).

Chloraloses have been known since 1889 when Heffter reported the preparation of α- and β-chloralose (or -glucochloralose), from the simple reaction of glucose and chloral.[15] Within a few years these stable compounds were shown to be of therapeutic use by Hanriot.[16a,b]

The first used preparative method has proven to be of wide scope and as a result, similar preparations of xylochloralose,[16b,17] arabinochloralose, [16b,18a-c] galactochloralose [16b,19] and mannochloralose [16b,20] have also been reported. To the present time, all of the known chloraloses contain the 1,2-*O*-trichloroethylidene group in the furanose form. Unlike most acetals, 1,2-*O*-trichloroethylidene acetals are very stable protecting groups under acidic conditions because of the inductive effect of the trichloromethyl group. They can also be stable under mildly basic conditions but in the presence of strong bases such as potassium tert-butoxide they are converted to the more reactive ketene acetals.[18a,20] The only reported method for the removal of this protecting group is a Raney Nickel procedure.[21] The most well-known chloralose, (R)-1,2-*O*-trichloroethylidene-α-D-glucofuranose (or α-chloralose), is a commercially available product and possesses anesthetic and hypnotic effects.[16a,22] It has been widely used as a rodenticide,[23] bird repellent, and veterinary drug.[22,24a,b] It was also used as an anaesthetic for humans in the twentieth century.[22] Many derivatives of chloraloses have been reported such as amines,[18b] lactones,[25] orthoesters,[18a,c,20] *O*-glycosides,[18c] dialdofuranoses,[20,26] uronic acids,[26] Wittig products,[27] oximes,[28] *spiro*endoperoxides,[29] thiosemicarbazones,[30] and oxetanes.[31]

2. Results and discussion

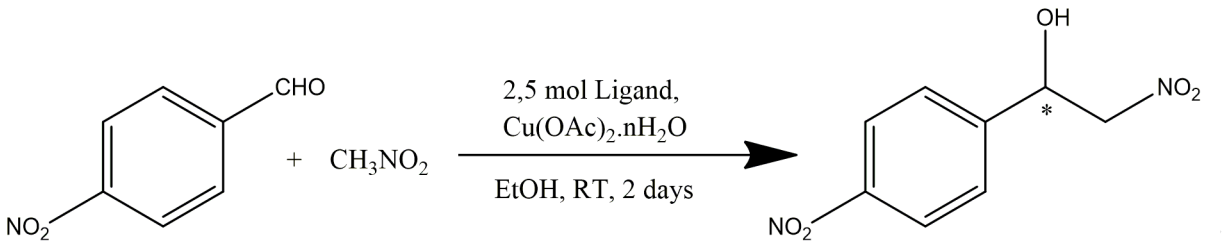
Our prepararative routes to the Schiff base ligands involved formation of aminochloraloses by selective tosylation of the appropriate chloralose followed by azidation and reduction reactions as can be seen in Scheme 1. Subsequent reaction with either salicylaldehyde or 3,5-ditbutylsalicylaldehyde afforded the desired Schiff base ligands.



Scheme 1. Syntheses of aminosugar derivatives (**3-6**) and Schiff base derivatives **(3a-6a, 3b-6b)**.

Once the ligands had been prepared, they were used as catalysts for the Henry reaction in ethanol solvent in the presence of $Cu(OAc)_2$ (Table 1).

Table 1. Optimization of catalytic ligands (**4a-5a**, **4b-5b**) effect on the asymmetric Henry reaction.



Entry	Ligand	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config[b]
1	**4a**	rt	2	34	1	*S*
2	**4b**	rt	2	80	4	*R*
3	**5a**	rt	2	65	1	*R*
4	**5b**	rt	2	92	41	*R*

[a] All reactions were performed with 0.5 mmol 4-Nitro-benzaldehyde, 2.5% mol ligand and $Cu(OAc)_2 .nH_2 O$, and 5 mmol nitromethane in 1 mL of EtOH at room temperature.

[b] Isolated yields by column chromatography using 5:1 hexane:ethyl acetate.

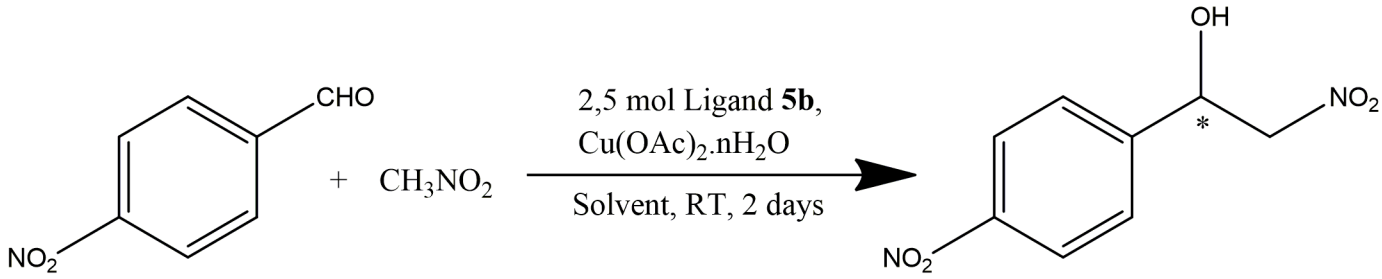
[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.[13]

Surprisingly, ligand **4** gave very disappointing results. For ligands **4a** and **4b**, molecular models had confirmed that the hydroxy group (OR_2, R_2 = H) is capable of acting as a fourth donor site, thus turning the tridentate ligand into a potential tetradentate ligand. From our results with aspartic acid, we had anticipated that this might lead to high enantioselectivity, but this was clearly not the case. In fact, the only ligand that gave a promising e.e. was ligand **5b**. As can be seen in Figure 2, for ligand **5b**, it is clearly not possible for the β-hydroxy group (OR_2, R_2 = H) to coordinate to the Cu^{2+} ion. This can be taken to indicate that for these examples, the presence of a beta hydroxy group which can potentially act as a fourth donor site is not an important requirement to obtain high enantiocontrol. It is also noteworthy that **5b** contains a tertiary butyl group *ortho* to the phenolic group. These observations suggest that it may be the overall steric nature of substituents that have an influence on the active site which may be important for high enantiomeric control.

It was subsequently decided to investigate the effect of the solvent on the reaction and the results of these experiments are given in Table 2.

Table 2. The solvent effect on the asymmetric Henry reaction between nitromethane and 4-nitrobenzaldehdye in the presence of 10% mol ligand **5b** and $Cu(OAc)_2 .nH_2O$.



Entry	Solvent	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config[d]
1	CH_2Cl_2	rt	2	72	12	*R*
2	IPA	rt	2	78	12	*R*
3	CH_3CN	rt	2	70	20	*R*
4	TBME	rt	2	53	8	*R*
5	EtOH	rt	2	92	41	*R*
6	MeOH	rt	2	80	58	*R*
7	MeOH/H_2O (10/1)	rt	2	72	30	*R*
8[e]	MeOH/H_2O (1/1)	rt	2	71	70	*R*
9	MeOH/H_2O (1/3)	rt	2	75	83	*R*
10	CH_3NO_2/H_2O (1/3)	rt	2	70	90	*R*
11[e,f]	EtOH/H_2O (1/3)	rt	2	78	80	*R*
12	IPA/H_2O (1/3)	rt	2	87	82	*R*
13	t-BuOH/H_2O (1/3)	rt	2	85	85	*R*

[a] Reactions were performed with 0.5 mmol 4-nitro-benzaldehyde, 10% mol ligand and $Cu(OAc)_2 .nH_2 O$, and 0.25 mL (5 mmol) nitromethane in 1 mL of solvent unless otherwise stated.

[b] Isolated yields by the column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.[13]

[e] 0.5 mL nitromethane used

[f] overall solvent composition = 0.25 mL MeOH : 0.75 mL H_2O : 0.5 mL nitromethane

As can be seen, the observed enantiomeric excess of the products showed a strong solvent dependency: The non-protic solvents dichloromethane, acetonitrile and ^{t}butyl methyl ether all gave disappointing results whereas mixed results were obtained for alcoholic solvents: Methanol afforded an enantiomeric excess (58%) significantly more promising than ethanol (40%) while isopropyl alcohol (12%) was as disappointing as the non-protic solvents. With these results in mind, it was decided to employ methanol/water mixtures as solvents for the reaction and some interesting results were obtained from these experiments. Thus, use of a 10/1 MeOH/H_2O mixture resulted in a quite dramatic decrease in e.e. to 30%. However, when a 1/1 mixture of MeOH/H_2O was employed, a biphasic system was obtained whereby the dark green coloured catalyst remained entirely in the lower organic (nitromethane) phase and in this experiment it was observed that the enantiomeric excess increased to 70%. Interestingly, addition of further water to the biphasic system resulted in a further increase and an optimum value of 83% was reached when the ratio of MeOH/H_2O was 1:3. Similar results were observed for mixtures of different alcohols and water. Finally, when water was added to the reaction mixture in the absence of an alcohol, the observed enantiomeric excess obtained from the biphasic system increased to 90%. Further experiments showed that decreasing the amount of nitromethane in the reaction in order to obtain a homogeneous solution failed to yield higher enantiomeric excesses.

Thus, it appears that for these reactions, the best results were obtained in nitromethane solution that was saturated with water, and this is most easily achieved in a biphasic system. This would appear to indicate that the presence of water has an effect on the transition state. This may be a direct effect such as coordination to the copper center or it could conceivably be a more subtle effect such as changing the most stable conformation of the galactochloralose moiety by rotation around the C4-C5 bond. Such solvent-dependent conformational changes are well-known in biological systems such as peptides and proteins[32] but have only rarely found applications in metal ion-catalysed asymmetric reactions.[33]

Our next stage in the investigation was to prepare the methoxy derivatives **3** and **6** to see what effect loss of the hydroxy function on the furanose ring would have. As can be seen in Table 3, the results obtained with the methoxy substituted ligands showed a similarity to their parent hydroxy compounds. This is consistent with our suggestion that in these cases, the steric nature of the substituents rather than the presence of an additional hydroxy group may be responsible for determining the degree of enantiocontrol.

Table-3 Effect of OMe group on the value of ee.

Ligand	Solvent	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config[d]
3a	EtOH	rt	2	50	10	*R*
	H_2O	rt	2	68	13	*S*
3 b	EtOH	rt	2	39	30	*R*
	H_2O	rt	2	74	24	*S*
6a	EtOH	rt	2	88	20	*R*
	H_2O	rt	2	92	45	*R*
6b	EtOH	rt	2	73	68	*R*
	H_2O	rt	2	67	66	*R*

[a] Reactions were performed with 0.5 mmol 4-nitro-benzaldehyde, 10% mol ligand and $Cu(OAc)_2 .nH_2 O$, and 5 mmol nitromethane in 1 mL of solvent.

[b] Isolated yields by the column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.[13]

Finally, we applied our method using catalyst **5b** to a variety of aromatic aldehydes at different temperatures. Moderate to good enantiomeric excesses were obtained in all cases, although in some cases, such as *ortho*-substituted aldehydes, the obtained yields at room temperature were dissapointing.

Table-4 Range of the aldehydes used in the Henry reactions in the presence of 10% mol ligand **5b** and $Cu(OAc)_2 .nH_2 O$.

Entry	Aldehyde	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config[d]
1	4-nitrobenzaldehyde	rt	2	70	90	*R*
2	4-nitrobenzaldehyde	5	3	67	89	*R*
3	2-nitrobenzaldehyde	rt	5	95	72	*R*
4	3-nitrobenzaldehyde	rt	5	90	91	*R*
5	2-chlorobenzaldehyde	rt	5	10	60	*R*
6	4-chlorobenzaldehyde	rt	5	12	40	*R*
7	p- anisalaldehyde	rt	5	10	70	*R*
8	p- anisalaldehyde	40	5	60	54	*R*
9	o- anisalaldehyde	40	5	55	60	*R*

[a] Reactions were performed with 0.5 mmol aldehyde, 10% mol ligand and $Cu(OAc)_2 .nH_2 O$, and 5 mmol nitromethane in 1 mL of H_2O.

[b] Isolated yields by the column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.[13]

3. Conclusions

Schiff base ligands containing chloralose substructures can be easily prepared from aminochloraloses and salicylaldehyde derivatives. Our results show that these ligands in the presence of metal ions show considerable promise as catalysts in asymmetric synthesis.

4. Experimental

All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian AS 400+ Mercury FT NMR spectrometer at ambient temperature. IR spectra were recorded on a Perkin Elmer 100 FTIR spectrometer. The enantiomeric excesses of the Henry reaction products were determined by HPLC using a chiralcel OD-H column. Optical rotations were determined using a Rudolph Research Analytical Autopol I automatic polarimeter.

4.1. General procedure for the preparation of 3-6

The synthesis of amino sugars and their derivatives is well documented in the literature. Additionally, Yenil has reported the synthesis of a family of chloraloses and their amino derivatives.[18b] We first aimed at a simple synthesis of the 6-amino derivatives of 1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (α-chloralose) **(1)** and 1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose **(2)**. Our preparative route involved first preparing the trichloroethylidene acetals of D-glucose[15] and D-galactose[19] according to the literature procedures. It is well-known that these monosaccharides react in their furanose forms with chloral to give trichloroethylidene acetals. 1,2-*O*-(*R*)-trichloro-ethylidene-α-D-glucofuranose is also known α-chloralose and is a commercially available compound. The target molecules were then synthesised from a simple sequence involving protection of primary hydroxyl groups,[34] nucleophilic substitution and reduction reactions.

First, a solution of chloralose derivative (0.1 mol) in pyridine (50 ml) was cooled in an ice bath and p-toluenesulfonyl chloride (0.12 mol) was added. The mixture was stirred for 24 h at room temperature. TLC (toluene–MeOH, 9:1) showed that a very small amount of starting sugar remained. The reaction mixture was

concentrated to half volume and poured into ice-water (600 mL). Then, it was extracted with CH_2Cl_2 (3 x300 mL). The organic phase was washed with water, dried over anhydrous Na_2SO_4, filtered, and then the solvent was removed. The monotosyl chloralose derivative was purified by column chromatography (toluene:MeOH, 100:1). Secondly, to a solution of monotosyl chloralose derivative (0,1 mol) in DMF (100 mL) NaN_3 (0.2 mol) was added. The mixture was heated with stirring in an oil bath at 150 °C for 3 h. TLC (toluene‑MeOH, 9:1) showed completion of the reaction. The reaction mixture was poured into ice-water (500 mL) and then, it was extracted with CH_2Cl_2 (3 x250 mL). The organic phase was washed with water and dried over anhydrous Na_2SO_4, filtered and then the solvent was removed. The product was crystallized from MeOH:H_2O to afford the pure monoazido chloralose derivative. Finally, to a solution of monoazido chloralose derivative (0.1 mol) in MeOH (100 mL) triphenylphosphine (0.15 mol) was added. The reaction mixture was stirred for 5 h at room temperature. TLC (toluene‑MeOH, 9:1) showed completion of reaction. The solvent was evaporated under reduced pressure and the syrupy product was purified by column chromatography eluting with toluene‑MeOH (100:1) to give the pure amino sugar derivative.

4.1.1. 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (3)

The title product was synthesized via 60% (1.2 g) yield. $[\alpha]_D^{20}$= -35.0, (c 0.4, MeOH); IR cm^{-1} (KBr); 3299 (-NH_2 and -OH), 1591 (N-H), 1100 (-OMe); ^{1}H NMR **(**DMSO-d_6, δ ppm): 6.00 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.42 (s, 1H, $HCCl_3$), 4.80 (d, 1H, H-2), 4.22 (dd, 1H, $J_{4,5}$=9.0 Hz , H-4), 3.85 (d, $J_{3,4}$=2.8 Hz, H-3), 3.64 (m, 1H, H-5), 3.36 (s, 3H, OCH_3), 3.30 (dd, 1H, H-6a), 3.29 (br s, 3H,-NH_2, -OH), 2.75 (dd, 1H, $J_{6a,6b}$=13 Hz, H-6b); ^{13}C NMR: 106.7, 107.7 (HC-CCl_3, C-1), 97.4 (HC-CCl_3), 83.7, 83.4, 82.4 (C-2, C-3, C-4), 64.3 (C-5), 58.1 (OCH_3), 43.3 (C-6). *m/z* calculated for $[M+1]^+$ $C_9H_{14}Cl_3NO_5$ 322.00, found 321.99.

4.1.2. 6-Amino-6-deoxy-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (4)

The title product was synthesized in 69% (0.7 g) yield. mp= 75-76 °C, $[\alpha]_D^{20}$= +12.0, (c 0.5, MeOH); IR cm^{-1} (KBr); 3372 (-NH_2 and -OH), 1598 (N-H); ^{1}H NMR **(**DMSO-d_6, δ ppm): 6.00 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.39 (s, 1H, $HCCl_3$), 4.59 (d, 1H, H-2), 4.18 (d, 1H, $J_{4,5}$=8.0 Hz , H-4), 4.11 (s, $J_{3,4}$=0 Hz, H-3), 3.61 (m, 1H, H-5), 3.59 (dd, 1H, H-6a), 2.70 (dd, 1H, $J_{6a,6b}$=12 Hz, H-6b); ^{13}C NMR: 106.3, 105.8 (HC-CCl_3, C-1), 97.7 (HC-CCl_3), 87.3, 83.7, 73.0 (C-2, C-3, C-4), 68.7 (C-5), 45.5 (C-6). *m/z* calculated for $[M+1]^+$ $C_8H_{12}Cl_3NO_5$ 309.98, found 309.98.

4.1.3. 6-Amino-6-deoxy-1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose (5)

The title product was synthesized via 72% (0.75 g) yield. . mp= 120-121 °C, $[\alpha]_D^{20}$= -14.0 (c 0.4, MeOH); IR cm^{-1} (KBr); 3444 (-NH_2 and -OH), 1574 (N-H); ^{1}H NMR **(**DMSO-d_6, δ ppm): 6.16 (d, 1H, $J_{1,2}$=4.0 Hz,

H-1), 5.72 (s, 1H, $HCCl_3$), 4.74 (d, 1H, H-2), 4.18 (d, 1H, $J_{3,4}$=2.8 Hz , H-3), 3.80 (br s, H-4), 3.43 (m, 1H, H-5), 3.20 (br s, 3H,-NH_2, -OH), 2.65 (dd, 1H, H-6a), 2.75 (dd, 1H, $J_{6a,6b}$=16 Hz, H-6b); 108.3, 106.7 (HC-CCl_3, C-1), 99.7 (HC-CCl_3), 89.9, 85.6, 75.2 (C-2, C-3, C-4), 71.1 (C-5), 46.2 (C-6). *m/z* calculated for $[M+1]^+$ $C_8H_{12}Cl_3NO_5$ 309.98, found 309.98.

4.1.4. 6-Amino-6-deoxy-3-*O*-methyl-1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose (6)

The title product was synthesized via 78% (0.8 g) yield. $[\alpha]_D^{25}$= -21.0, (c 1.0, MeOH); IR cm^{-1} (KBr); 3368 (-NH_2 and -OH), 1670 (N-H), 1100 (-OMe); ^{1}H NMR (DMSO-d_6, δ ppm): 6.14 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.75 (s, 1H, $HCCl_3$), 4.88 (d, 1H, H-2), 4.24 (br s, 1H, H-4), 3.93 (br s, H-3), 4.24 (br s, 3H,-NH_2, -OH), 3.89 (m, 1H, H-5), 3.57 (dd, 1H, H-6a), 3.31 (s, 3H, OCH_3), 2.75 (dd, 1H, $J_{6a,6b}$=12Hz, H-6b); ^{13}C NMR: 108.6, 107.0 (HC-CCl_3, C-1), 99.6 (HC-CCl_3), 87.5, 86.7, 85.1 (C-2, C-3, C-4), 70.9 (C-5), 57.3 (OCH_3), 44.5 (C-6). *m/z* calculated for $[M+1]^+$ $C_9H_{14}Cl_3NO_5$ 322.00, found 321.98.

4.2. General procedure for the preparation of the chiral Schiff bases

The solution of aldehyde (1 mmol) in MeOH was added dropwise into the solution of amino sugar derivative (1 mmol) in 5 mL of MeOH. The reaction mixture was stirred for 2h at room temperature. Evaporation of the solvent provided a residue, which was crystallized from CH_2Cl_2 :hexane to give yellow or orange crystals (52%-97%yields).

4.2.1. 6-deoxy-3-*O*-methyl-1,2-*O*-(*R*)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-glucofuranose (3a)

Yellow syrupy, 97% (280 mg) yield, , $[\alpha]_D^{19}$= +102.5 (c 0.4, CH_2Cl_2); IR (KBr), 3390, 3060, 2937, 2836, 1634, 1582, 1497, 1462, 1280, 1159, 757 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ ppm) 8.38 (s, 1H, -CH=N-), 7.70 (m, 1H), 7.60 (m, 1H), 7.28 (dd, J= 8 Hz, 1H), 6,88 (m, 1H), 6.10 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.28 (s, 1H, $HCCl_3$), 4.75 (d, 1H, H-2), 4.54 (dd, $J_{4,5}$=8.0 Hz, H-4), 4.38 (br s, 1H, -OH), 4.22 (m, 1H, H-5), 4.08 (d, 1H, $J_{3,4}$=3.6 Hz , H-3), 4.01 (dd, 1H, H-6b) 3.99 (br s, 1H, -OH), 3.68 (dd, 1H, $J_{6a,6b}$=12.6 Hz, H-6a), 3.46 (s, 3H, OCH_3); ^{13}C NMR: 167.6, 161.4, 133.0, 132.9, 131.6, 129.7, 118.6, 107.1, 105.9, 96.7, 83.7, 83.5, 81.8, 68.3, 62.3, 58.1.

Anal. Calcd for $C_{16}H_{40}Cl_3NO_6$: C, 45.02; H, 4.22; N, 3.28. Found: C, 45.64; H, 4.98; N, 3.11.

4.2.2. 6-deoxy-3-*O*-methyl-1,2-*O*-(*R*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-glucofuranose (3b)

Yellow crystals, 91% (300 mg) yield, mp=84-85 °C, $[\alpha]_D^{26}$= +6.0 (c 1.0, CH_2Cl_2); IR (KBr), 3412, 2937, 2872, 1634, 1470, 1442, 1362, 1251, 1161, 1103, 1060, 830, 805, 772 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm) 8.42 (s, 1H, -CH=N-), 7.39 (d, J=2.4 Hz, 1H), 7.09 (d, 1H), 6.12 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.31 (s, 1H, $HCCl_3$), 4.76 (d, 1H, H-2), 4.58 (dd,1H, $J_{4,5}$=8.8, H-4), 4.23 (br s, 2H, -OH), 4.12 (d, 1H, $J_{3,4}$=3.6 Hz , H-3), 3.93 (dd, 1H, $J_{5,6a}$=8 Hz, H-5), 3.75 (dd, 1H, $J_{6a,6b}$=12.4 Hz, H-6b), 3.49 (s, 3H, OCH_3), 3.47 (d, 1H, H-6a); ^{13}C NMR: 168.9, 157.9, 140.2, 136.7, 131.9, 127.2, 126.2, 117.7, 107.1, 105.9, 96.7, 83.7, 83.5, 81.6, 68.4, 62.5, 58.1, 35.0, 34.1, 31.5, 31.3, 29.4, 29.3.

Anal. Calcd for $C_{24}H_{12}Cl_3NO_6$: C, 52.89; H, 7.35; N, 2.57. Found: C, 53.48; H, 6.82; N, 2.45.

4.2.3. 6-deoxy-1,2-*O*-(*R*)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-glucofuranose (4a)

Yellow crystals, 89% (218 mg) yield, mp=90-91 °C, $[\alpha]_D^{19}$= +30.0 (c 0.4, CH_2Cl_2); IR (KBr), 3372, 2954, 1635, 1532, 1493, 1279, 1158, 1101, 1030, 828, 806, 758 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm) 8.22 (s, 1H, -CH=N-), 7.32 (m, 1H, Ar-H), 7.18 (dd, J=8.0 Hz, 6 Hz, 1H, Ar-H), 6.85 (d, J= 8 Hz, 1H, Ar-H), 6,77 (m, 1H, Ar-H), 6.10 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.26 (s, 1H, $HCCl_3$), 4.69 (d, 1H, H-2), 4.56 (d, 1H, $J_{3,4}$=3.6 Hz , H-3), 4.35 (d, $J_{3,4}$=2.8 Hz, H-4), 4.24 (m, 1H, H-5), 3.95 (dd, 1H, H-6b), 3.68 (dd, 1H, $J_{6a,6b}$=12.6 Hz, H-6a), 3.48 (s, 3H, OCH_3); ^{13}C NMR: 167.5, 165.8, 134.6, 132.4, 118.8, 117.8, 117.3, 107.1, 105.8, 96.8, 87.5, 82.1, 74.1, 68.4, 59.7.

Anal. Calcd for $C_{15}H_{16}Cl_3NO_6$: C, 43.64; H, 3.88; N, 3.39. Found: C, 43.84; H, 4.13; N, 3.74.

4.2.4. 6-deoxy-1,2-*O*-(*R*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-glucofuranose (4b)

Yellow crystals, 94 % (296 mg) yield, mp=55-58 °C, $[\alpha]_D^{19}$= +20.0 (c 0.4, CH_2Cl_2); IR (KBr), 3407, 2961, 1651, 1469, 1441, 1363, 1272, 1170, 1103, 1030, 828, 802, 771 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm) 8.43 (s, 1H, -CH=N-), 7.60 (d, J=2.4 Hz, 1H, Ar-H), 7.41 (d, 1H, Ar-H), 7.26 (d, 1H, Ar-H), 7.10 (d, 1H, Ar-H), 6.10 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.26 (s, 1H, $HCCl_3$), 4.71 (d, 1H, H-2), 4.60 (m, 1H, H-4), 4.57 (d,1H, $J_{3,4}$=4.0, H-3), 4.32 (dd, 1H, $J_{5,6a}$=8 Hz, H-5), 3.95 (dd, 1H, $J_{6a,6b}$=12.4 Hz, H-6b), 3.375 (dd, 1H, H-6a); ^{13}C NMR: 169.2, 159.1, 140.4, 136.9, 131.9, 127.6, 126.3, 120.0, 117.6, 107.1, 105.7, 96.7, 87.4, 81.4, 74.8, 69.6, 61.9, 35.0, 34.1, 31.5, 31.3, 29.4, 29.3.

Anal. Calcd for $C_{23}H_{38}Cl_3NO_6$: C, 52.02; H, 7.16; N, 2.63. Found: C, 51.86; H, 6.10; N, 2.60.

4.2.5. 6-deoxy-1,2-*O*-(*S*)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-galactofuranose (5a)

Yellow crystals, 81% (150 mg) yield, mp=128-129 °C, $[\alpha]_D^{19}$= -30.0 (c 0.1, MeOH); IR (KBr), 3460, 3060, 2940, 1635, 1580, 1493, 1460, 1280, 1152,1102, 808, 751 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm) 8.41 (s, 1H, -CH=N-), 7.57 (dd, J=3.20 Hz, 6 Hz,1H, Ar-H), 7.34 (m, 1H, Ar-H), 7.29 (m, 1H, Ar-H), 7.91 (m, 1H), 6.11 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.56 (s, 1H, $HCCl_3$), 4.95 (d, 1H, H-2), 4.51 (d, 1H, $J_{3,4}$=3.6 Hz , H-3), 3.15 (d, $J_{3,4}$=2.8 Hz, H-4), 3.93 (m, 1H, H-5), 3.84 (dd, 1H, H-6b), 3.75 (dd, 1H, $J_{6a,6b}$=12.6 Hz, H-6a), 2.41 (s, 2H, -OH); ^{13}C NMR: 167.6, 161.3, 133.0, 132.1, 119.1, 118.8, 117.0, 108.4, 106.8, 99.7, 90.0, 89.9, 75.2, 70.2, 62.3.

Anal. Calcd for $C_{15}H_{16}Cl_3NO_6$: C, 43.64; H, 3.88; N, 3.39. Found: C, 44.15; H, 3.95; N, 3.97.

4.2.6. 6-deoxy-1,2-*O*-(*S*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-galactofuranose (5b)

Yellow crystals, 89 % (210 mg) yield, mp=78-79 °C, $[\alpha]_D^{18}$= +2.5 (c 0.4, CH_2Cl_2);IR (KBr), 3412, 2961, 2872, 1630, 1470, 1442, 1362, 1260, 1161, 1103, 1060, 830, 805, 764 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm) 8.43 (s, 1H, -CH=N-), 7.39 (d, J=2.4 Hz, 1H), 7.09 (d, 1H), 6.30 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.70 (s, 1H, $HCCl_3$), 5.00 (d, 1H, H-2), 4.48 (s, 1H, H-3), 4.17 (dd,1H, $J_{4,5}$=6.8, H-4), 3.93 (dd, 1H, $J_{5,6a}$=5.6 Hz, H-5), 3.75 (dd, 1H, $J_{6a,6b}$=11.2 Hz, H-6b), 3.80 (dd, 1H, H-6a), 2.48 (s, 2H, -OH); ^{13}C NMR: 168.8, 158.0, 140.4, 136.8, 127.9, 127.5, 126.3, 117.7, 109.4,107.1, 99.3, 89.7, 89.5, 76.3, 70.2, 62.1, 35.0, 34.1, 31.5, 31.3, 29.4, 29.3.

Anal. Calcd for $C_{23}H_{38}Cl_3NO_6$: C, 52.02; H, 7.16; N, 2.63. Found: C, 52.10; H, 6.18; N, 2.73.

4.2.7. 6-deoxy-3-*O*-methyl-1,2-*O*-(*S*)-trichloroethylidene-6-[(2'-ylimino)methyl]phenol-α-D-galactofuranose (6a)

Yellow crystals, 89% (300 mg) yield, mp=119-120 °C, $[\alpha]_D^{19}$= -9.0 (c 0.4, CH_2Cl_2); IR (KBr), 3390, 3060, 2937, 2836, 1634, 1582, 1497, 1462, 1280, 1159, 757 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm) 8.39 (s, 1H, -CH=N-), 7.31 (dd, J=3.20 Hz, 6 Hz,1H), 7.31 (m, 1H), 6.96 (d, J= 6 Hz, 1H), 6,88 (m, 1H), 6.16 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.64 (s, 1H, $HCCl_3$), 4.93 (d, 1H, H-2), 4.18 (dd, $J_{4,5a}$=8 Hz, H-4), 3.99 (d, 1H, $J_{3,4}$=3.6 Hz , H-3), 3.95 (m, 1H, H-5), 3.78 (dd, 1H, H-6b), 3.73 (dd, 1H, $J_{6a,6b}$=12.6 Hz, H-6a), 3.40 (s, 3H, OCH_3); ^{13}C NMR: 167.6, 161.0, 132.7, 131.6, 118.7, 118.6,117.0, 109.4, 107.2, 99.3, 87.3, 86.7, 85.4, 70.6, 62.3, 57.7.

Anal. Calcd for $C_{16}H_{40}Cl_3NO_6$: C, 45.02; H, 4.22; N, 3.28. Found: C, 44.78; H, 4.93; N, 3.24.

4.2.8. 6-deoxy-3-*O*-methyl-1,2-*O*-(*S*)-trichloroethylidene-6-[2',4'-ter-butyl-(6'-ylimino)methyl]phenol-α-D-galactofuranose (6b)

Yellow crystals, 93% (700 mg) yield, mp=103-104 °C, $[\alpha]_D^{18}$= -22.5 (c 0.4, CH_2Cl_2); IR (KBr), 3412, 2959, 2872, 1631, 1470, 1442, 1362, 1275, 1161, 1101, 750 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm) 8.43 (s, 1H, -CH=N-), 7.40 (d, J=4 Hz, 1H), 7.12 (d, 1H), 6.26 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.73 (s, 1H, $HCCl_3$), 5.00 (d, 1H, H-2), 4.20 (dd,1H, $J_{4,5}$=8.0, H-4), 4.01 (d, 1H, $J_{3,4}$=3.6 Hz , H-3), 3.99 (dd, 1H, $J_{5,6a}$=4 Hz, H-5), 3.80 (dd, 1H, $J_{6a,6b}$=12.0 Hz, H-6b), 3.77 (d, 1H, H-6a), 3.49 (s, 3H, OCH_3); ^{13}C NMR: 168.8, 157.9, 140.3, 136.7, 131.9, 127.9, 127.3, 126.2, 117.7, 109.4, 107.2, 99.3, 87.5, 86.8, 85.5, 62.4, 57.7, 58.1, 35.0, 34.2, 34.1, 31.5, 31.3, 29.4, 29.3.

Anal. Calcd for $C_{24}H_{12}Cl_3NO_6$: C, 52.89; H, 7.35; N, 2.57. Found: C, 53.57; H, 6.82; N, 2.74.

4.3. General procedure for the asymmetric Henry Reaction

To a solution of ligand (0.01 mmol) and 1 mL of solvent at the given temperature was added $Cu(OAc)_2.nH_2O$ (0.01 mmol). The mixture was stirred for the given time. The aldehyde (0.1 mmol) and nitromethane (5 mmol) were added into the solution. The progress of the reaction was monitored by TLC. After completion, the solvent was evaporated and the residue was purified by column chromatography using hexane:ethyl acetate (5:1) to afford the desired Henry product. The enantiomeric excess values were determined by HPLC using a Chiralcel OD-H column.

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Highlights

- A series of chiral Schiff base ligands has been prepared using aminochloralose derivatives of glucose and galactose.
- The Schiff base ligands were used as catalysts for the asymmetric Henry reaction in the presence of Cu(II) ions.
- These ligands in the presence of metal ions show considerable promise as catalysts in asymmetric synthesis.