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Synthesis of novel Schiff base ligands from gluco- and galactochloraloses for the Cu(II) catalyzed asymmetric Henry reaction

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

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

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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.

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1. Introduction

The nitroaldol (Henry) reaction is a convenient method of C–C bond formation, which affords useful products for organic synthesis.[1] 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,[2] enzymes,[3] and transition metal-chiral ligand complexes.[4] In particular, Cu(II) complexes of a variety of bidentate[5] and tridentate[6] ligands have recently been utilized 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.[7] Further studies have indicated that the presence of bulky groups near to the metal center can also play an important role.[5b,8]

Encouraged by these results, a number of groups have prepared some elaborate chiral ligands containing substructures as diverse as sparteine,[9] paracyclophane,[10] binaphthylazepine[8a] and cinchona alkaloids[11] 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,[12] we recently reported that an aspartic acid derived Schiff base ligand (Fig. 1) that contains an additional proximal hydroxy group afforded better enantioselectivities than related tridentate ligands.[13]

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**) (Fig. 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**.

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.[14] Within a few years these stable compounds were shown to be of therapeutic use by Hanriot.[15]

The first used preparative method has proven to be of wide scope and as a result, similar preparations of xylochloralose,[15b,16] arabinochloralose,[15b,17] galactochloralose[15b,18] and mannochloralose[15b,19] 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

* Corresponding authors. Tel.: +90 2323115451; fax: +90 2323888264.
E-mail addresses: yesim.salman@ege.edu.tr (Y. Salman), stephen.thomas.astley@ege.edu.tr (S.T. Astley).

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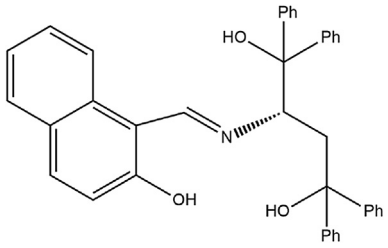


Fig. 1. Structure of an aspartic acid derived Schiff base ligand.

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.[17a,19] The only reported method for the removal of this protecting group is a Raney Nickel procedure.[20] 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.[15a,21] It has been widely used as a rodenticide,[22] bird repellent, and veterinary drug.[21,23] It was also used as an anesthetic for humans in the twentieth century.[21] Many derivatives of chloraloses have been reported such as amines,[17b] lactones,[24] orthoesters,[17a,b,19] *O*-glycosides,[17c] dialdofuranoses,[19,25] uronic acids,[25] Wittig products,[26] oximes,[27] *spiro*endoperoxides,[28] thiosemicarbazones,[29] and oxetanes.[30]

2. Results and discussion

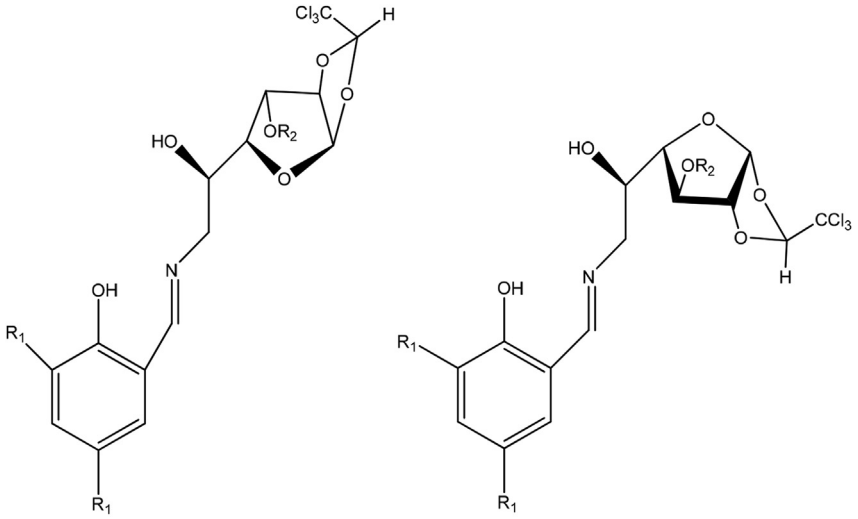
Our preparative routes to the Schiff base ligands involved formation of aminochloraloses by selective tosylation of the appropriate chloralose followed by azidation and reduction reactions as can be seen in Scheme 1. Subsequent reaction with either salicylaldehyde or 3,5-ditbutylsalicylaldehyde afforded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

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).

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 Fig. 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.

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 colored 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



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)

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

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