

Short Communication

Synthesis of novel carbohydrate-based chiral *P, N* ligands and their applications in Cu-catalyzed enantioselective 1, 4-conjugate additionsHaijun Xia ^a, Hua Yan ^b, Chao Shen ^a, Fangyi Shen ^a, Pengfei Zhang ^{a,*}^a College of Material Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, China^b School of Pharmaceutical and Chemical Engineering, Taizhou University, Linhai 317000, Zhejiang Province, China

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ABSTRACT

A new type of phosphate-pyridine (*P, N*) ligand derived from D-glucosamine and BINOL was synthesized and successfully applied in Cu-catalyzed enantioselective conjugate addition of diethylzinc to chalcones for the first time, high yields and enantioselectivities were obtained when the ligand **10a** which contains (*S*)-BINOL was used. The results also showed that the configuration of BINOL at the ligand backbone had remarkable effects on the activities and enantioselectivities.

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1. Introduction

Asymmetric conjugate additions of carbon nucleophiles to acceptor-activated double bonds represent an attractive tool for the stereoselective formation of C–C bonds [1–4]. In this regard, copper-mediated conjugate additions of diorganozinc reagents to α, β -unsaturated ketones have attracted particular synthetic interest and have dominated the field since their discovery in the 1990s [5–9]. And lots of chiral heterobidentate ligands which when equipped with a weak or a strong heteroatom pair such as *P, N*, *P, O*, *P, P*, or *N, N* also have been successfully prepared and applied in asymmetric reaction [10]. Such ligands also have been proven to be effective for obtaining high enantioselectivities through electronic and steric differentiations. In these ligands, the *P, N* ligands have been widely used for catalytic application and a great advance has been made in the past decades in achieving high enantioselectivities [11–13]. So more and more structure based on the biphenyl systems [14,15], binaphthyl-type ligands [16–19], Trost modular [20–22] and paracyclophanes [23,24] novel ligands were synthesized and applied. However, to the best of our knowledge, there are only a few reports on the study of chiral *P, N* ligands derivative from carbohydrates for asymmetric catalysis [25,26].

As we all know, carbohydrates have been widely used as cheap original material or chiral auxiliaries in organic synthesis. In recent years, some carbohydrate-based *P, N* ligands have been reported, for instance, Kunz et al. reported some carbohydrate-based ligands for the Pd-catalyzed asymmetric allylic substitution [27]. Woodward and

co-workers showed that a series of phosphinoamide-phosphinoester ligands which derived from amino-sugar were highly effective for achieving high enantioselectivities in asymmetric copper 1,4-addition reactions [28]. Recently, our group has described the synthesis of carbohydrate-based iminophosphinite ligands and their successful applications in Pd-catalyzed asymmetric allylic alkylations [29] (Fig. 1).

On the basis of our experience at studying carbohydrate and inspired by these successful carbohydrate-based ligands designed, we have designed and developed a new type of phosphate-pyridine (*P, N*) ligands **10a** and **10b** by tethering a pyridine amido component and a phosphate component to a *N*-acetylglucosamine. The new type of carbohydrate-based ligand was successfully employed in Cu-catalyzed conjugate addition of diethylzinc to chalcones and achieved moderate enantioselectivities. In addition, the novel ligands with carbohydrate chirality provide a more effective asymmetric environment for the enantioselective discrimination on a prochiral substrate, electronic and steric properties, so it could be finely tuned and future research is being carried out.

2. Experimental

2.1. General

All syntheses were performed using standard Schlenk techniques under a nitrogen atmosphere. All solvents were dried before using accord to standard procedures and stored under nitrogen. Column chromatography was performed on silica gel grade 60 (230–400 mesh). Analytical TLC: Silica Gel 60, F254 plates from Merck, which were visualized by UV and phosphomolybdic acid staining. Optical rotation values were measured on a PerkinElmer P241 polarimeter.

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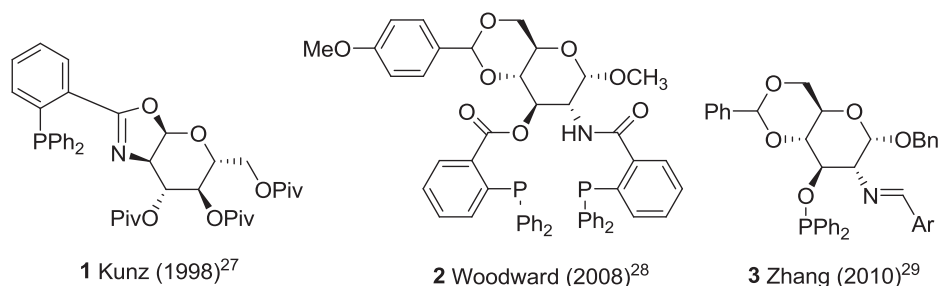


Fig. 1. Development of carbohydrate-based ligands in asymmetric catalytic reactions.

Enantiomeric excesses (% ee) were determined by HPLC (Agilent 1100 series) analysis using Chiralpak AD-H column and GC equipped with a Chiraldex A-TA column (50 m × 0.25 mm I.D.). The ¹H, ¹³C, and ³¹P NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer; chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks (¹H NMR and ¹³C NMR) or to an 85% H₃PO₄ in D₂O externally (³¹P NMR). Elemental analyses were performed on Carlo-Erba 1106. Compounds 2-aminoglucose **6** and Feringa's phosphorus-amidite (**8**, **9**) were prepared by previously described methods [30,31].

2.2. General procedure for asymmetric 1, 4-conjugate addition: preparation of catalyst

Ligand **10a** or **10b** (77.6 mg, 0.1 mmol), copper salt (0.1 mmol), and 10 mL of toluene were added to a 50 mL air-free Schlenk flask under a nitrogen atmosphere. After 30 min of stirring at room temperature, the solvent was stripped off in vacuo, 6 mL of CH₂Cl₂ was added to the flask, and the catalyst solution was used for the 1,4-conjugate addition reactions.

2.3. General procedure for asymmetric 1,4-conjugate addition

Chalcone substrate (0.5 mmol) and 3.0 mL of the above prepared catalyst solution were added to a flame-dried Schlenk tube under a nitrogen atmosphere. After the solvent has been stripped off, 4 mL of toluene was added. The slurry was stirred at room temperature for 10 min and then cooled to the desired temperature. After the slurry has been stirred for 15 min, 0.75 mL of Et₂Zn (1.0 M in toluene, 1.5 mol equiv) was added slowly. The resulting mixture was stirred at that temperature for 12 h and 4 mL of 5% hydrochloric acid was added to quench the reaction. The mixture was allowed to warm to room temperature, and then 15 mL of diethyl ether was added. The organic layer was washed with 5 mL of saturated NaHCO₃ and 5 mL of brine and then dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel and eluted with EtOAc/petroleum ether (1/40–1/20) to afford the addition product. The ee values of the addition products were determined by chiral HPLC (Chiralcel AD-H column, hexane/2-propanol = 99:1, 1.0 mL/min). The configuration of 1,4-conjugate addition product from these reactions was proven to be (*S*) by comparing the specific rotation with the literature values [32,33].

3. Results and discussion

3.1. Synthesis of carbohydrate-based phosphate-pyridine (*P,N*) ligands

The synthesis of chiral ligands **10a** and **10b** were initiated from inexpensive *N*-acetylglucosamine using a standard procedure. As shown in Scheme 1, C-1 is selectively benzylated at the α-position, then positions C-4 and C-6 are protected with a benzylidene ring and the protection at C-2 can be removed easily. Amidation of 2-

aminoglucose **6** with 1.0 equiv of 2-picolinic acid in the presence of 1.0 equiv 1,1'-carbonyldiimidazole (CDI) as the condensation reagent proceeded smoothly to afford the amide **7** through column chromatography in 85% yield. The (*S*)-Feringa's phosphorus-amidite ligand **8** was obtained in 90% yield and the (*R*)-Feringa's phosphorus-amidite ligand **9** was obtained in 92% yield refer to the literature. Then the optically pure phosphite-pyridine ligands **10a** and **10b** were respectively provided through refluxing the mixture of the amide **7** with **8** or **9** in toluene under nitrogen atmosphere in 78% and 52% yield respectively. The obtained ligands **10a** and **10b** are quite stable in the solid state and their ³¹P NMR, ¹H NMR, and ¹³C NMR spectral data are in good agreement with the suggested structures.

3.2. Cu-catalyzed enantioselective 1,4-conjugate additions

We initially tested the addition of Et₂Zn to chalcone in the presence of several copper salts and ligands **10a** and **10b** in toluene at room temperature. All the results are summarized in Table 1. Variety of copper (I) and (II) salts (i.e., CuBr, CuCl, CuF₂, Cu(OTf)₂, Cu(OAc)₂·2H₂O, [Cu(CH₃CN)₄]BF₄ and Cu(CF₃SO₃)₂·C₆H₆) were screened in this study. The first promising results were achieved with Cu(OAc)₂·2H₂O, which gave 82% yield and 70% ee in the addition of Et₂Zn to the model substrate chalcone at room temperature (entry 5, Table 1).

Some other copper salts such as Cu(OTf)₂ and [Cu(CH₃CN)₄]BF₄ showed almost the same results about 60% ee (entries 4 and 6, Table 1). The copper (II) salts gave good ee than copper (I) salts in generally (entries 4–7 vs 1–3, Table 1). On the basis of these results, we employed Cu(OAc)₂·2H₂O in the following studies, and some other choices may also be effective. Then different temperatures from –10 °C to –40 °C were also screened (entries 8–10, Table 1). Lowering the reaction temperature to –10 °C improves the enantioselectivity of the conjugate addition (entry 5 versus entry 8), without altering the reaction rate. A decrease in the reaction temperature from –10 °C to –40 °C did not give a favorable ee except the drop of yields (entries 9 and 10, Table 1). Replacing ligand **10a** with its diastereomer **10b** led to the addition products in poor yields and with low enantioselectivities (entry 8 versus entry 12), the results indicated that yields and enantioselectivities are affected by the configuration at the biaryl phosphite moieties. Both ligands afforded the same configuration in the end product, namely the (*S*)-enantiomer [34].

We next studied with the best ligand **10a**, the effect of several reaction parameters, such as solvent (i.e., THF, Et₂O, CH₂Cl₂, and ClCH₂CH₂Cl) copper-to-ligand ratio and Et₂Zn-to-substrate ratio. The results summarized in Table 2 showed that pure PhMe is advantageous over THF, Et₂O, CH₂Cl₂, ClCH₂CH₂Cl and mixed solvents for achieving high enantioselectivity (entries 1–6, Table 2). No improvement in enantioselectivity was observed with a ratio of Cu(OAc)₂·2H₂O/L **10a** ranging from 1/1 to 1/1.5 and 1/2 (entries 6–8, Table 2) and 1.5 equiv diethylzinc is better than 1.0 equiv for getting high ee (entry 6 versus entry 9, Table 2).

With the optimized reaction conditions in hand (PhMe as solvent, Cu(OAc)₂·2H₂O as copper salt, Cu(OAc)₂·2H₂O/ligand = 1:1,

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