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Short Communication

Synthesis of novel carbohydrate-based chiral *P, N* ligands and their applications in Cu-catalyzed enantioselective 1, 4-conjugate additions

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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.

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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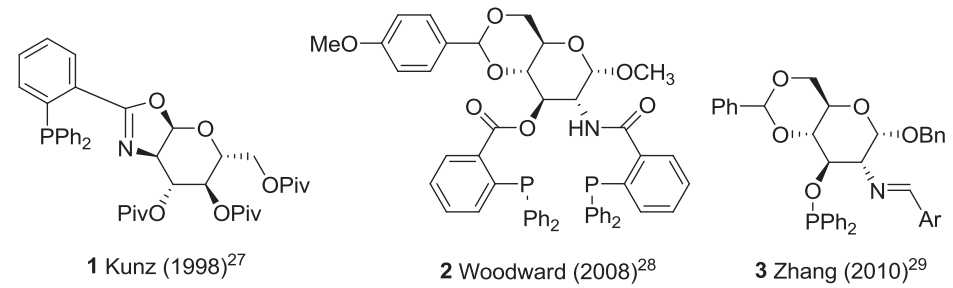


1 Kunz (1998)[27] **2** Woodward (2008)[28] **3** Zhang (2010)[29]

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 ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer; chemical shifts (d) are given in ppm and are referenced to residual solvent peaks (^{1}H NMR and ^{13}C NMR) or to an 85% H_3PO_4 in D_2O externally (^{31}P 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 CH_2Cl_2 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 Et_2Zn (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 $NaHCO_3$ and 5 mL of brine and then dried over anhydrous Na_2SO_4. 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 though 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 ^{31}P NMR, ^{1}H NMR, and ^{13}C NMR spectral data are in good agreement with the suggested structures.

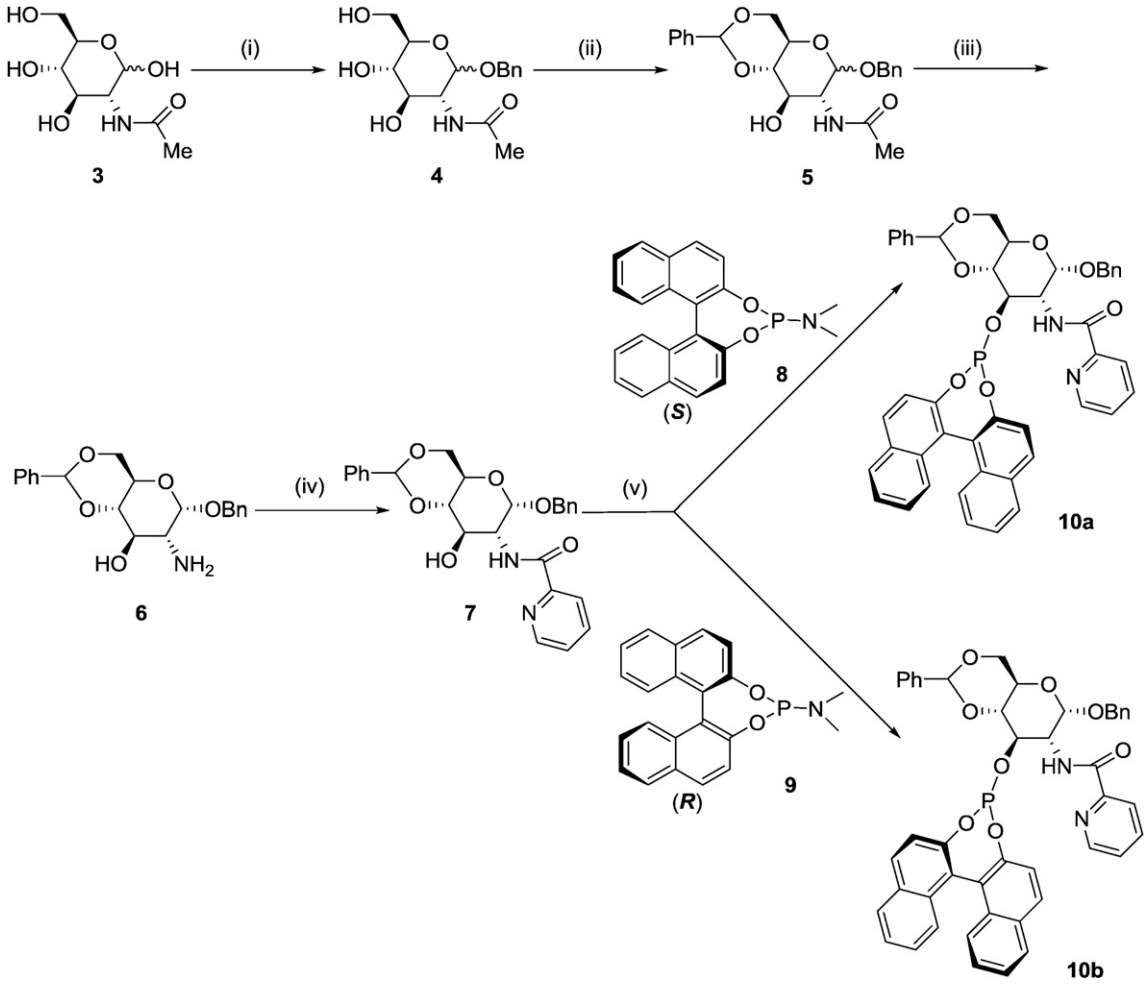
3.2. Cu-catalyzed enantioselective 1,4-conjugate additions

We initially tested the addition of Et_2Zn 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, CuF_2, $Cu(OTf)_2$, $Cu(OAc)_2\cdot 2H_2O$, $[Cu(CH_3CN)_4]BF_4$ and $Cu(CF_3SO_3)_2\cdot C_6H_6$) were screened in this study. The first promising results were achieved with $Cu(OAc)_2\cdot 2H_2O$, which gave 82% yield and 70% ee in the addition of Et_2Zn to the model substrate chalcone at room temperature (entry 5, Table 1).

Some other copper salts such as $Cu(OTf)_2$ and $[Cu(CH_3CN)_4]BF_4$ 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 $Cu(OAc)_2\cdot 2H_2O$ 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, Et_2O, CH_2Cl_2, and $ClCH_2CH_2Cl$) copper-to-ligand ratio and Et_2Zn-to-substrate ratio. The results summarized in Table 2 showed that pure PhMe is advantageous over THF, Et_2O, CH_2Cl_2, $ClCH_2CH_2Cl$ and mixed solvents for achieving high enantioselectivity(entries 1–6, Table 2). No improvement in enantioselectivity was observed with a ratio of $Cu(OAc)_2\cdot 2H_2O$/**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, $Cu(OAc)_2\cdot 2H_2O$ as copper salt, $Cu(OAc)_2\cdot 2H_2O$/ligand = 1:1,



Scheme 1. Synthesis of ligands 10a and 10b derived from *N*-acetylglucosamine. Reagents and conditions: (i) BnOH, H^+; (ii) PhCHO, $ZnCl_2$; (iii) KOH, EtOH; (iv) 2-picolinic acid, CDI, CH_2Cl_2; (v) PhMe, reflux.

Et_2Zn/chalcone = 1.5:1, and completing the reaction at −10 °C), we used ligand **10a** for Cu-catalyzed enantioselective conjugate addition of diethylzinc to various substituted chalcones (Table 3). The reactions were carried out at −10 °C in pure toluene with 1.5 equiv of diethylzinc as the nucleophilic reagent. From the results we found that there was no electronic effect for 4-substituted chalcones, the reason is that all of the 4-substituted chalcones gave almost enantioselectivities (entries 2–5, Table 3). Trans-4-phenyl-3-buten-2-one was also used as the substrate for the conjugate additions (entry 6, Table 3), but the reaction is not working. Next, the 1,4-additions of $ZnEt_2$ to 2-cyclohexenone were examined. However, poor enantioselectivities were observed (entries 1 and 2, Table 4).

Table 1
Optimizations of copper salts[a].

Entry	Ligand	Cu salts	*T* (°C)	*t* (h)	Yield[b] (%)	ee[c] (%) (config.)[d]
1	**10a**	CuBr	rt	12	82	41 (*S*)
2	**10a**	CuCl	rt	12	90	40 (*S*)
3	**10a**	CuF_2	rt	24	30	42 (*S*)
4	**10a**	$Cu(OTf)_2$	rt	12	83	63 (*S*)
5	**10a**	$Cu(OAc)_2{\cdot}2H_2O$	rt	12	82	70 (*S*)
6	**10a**	$[Cu(CH_3CN)_4]BF_4$	rt	24	43	60 (*S*)
7	**10a**	$Cu(CF_3SO_3)_2{\cdot}C_6H_6$	rt	12	73	55 (*S*)
8	**10a**	$Cu(OAc)_2{\cdot}2H_2O$	−10	12	81	78 (*S*)
9	**10a**	$Cu(OAc)_2{\cdot}2H_2O$	−25	48	56	76 (*S*)
10	**10a**	$Cu(OAc)_2{\cdot}2H_2O$	−40	48	16	79 (*S*)
11	**10b**	$Cu(OTf)_2$	−10	24	68	31 (*S*)
12	**10b**	$Cu(OAc)_2{\cdot}2H_2O$	−10	12	77	43 (*S*)

[a] Reaction was carried out under nitrogen in 3 ml of toluene, 0.5 mmol of chalcone, 0.75 mmol of Et_2Zn, 0.05 mmol of $Cu(OAc)_2{\cdot}2H_2O$, 0.05 mmol of Ligand **10a-b**.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column (eluent: hexane/2-propanol = 99:1, 1.0 ml/min).
[d] The absolute configuration was determined by comparison of the specific rotation with that of the literature [33,34].

Table 2
Optimizations of the solvent, Cu salts/ **L10a** and Et_2Zn/chalcone ratio of the reaction[a].

Entry	Solvent	Cu salts **L10a**	Et_2Zn/ chalcone	Yield[b] (%)	ee[c] (%) (config.)[d]
1	THF	1/1	1.5/1	87	34 (*S*)
2	Et_2O	1/1	1.5/1	49	28 (*S*)
3	CH_2Cl_2	1/1	1.5/1	67	33 (*S*)
4	toluene/CH_2Cl_2 (1/1)	1/1	1.5/1	70	53 (*S*)
5	$ClCH_2CH_2Cl$	1/1	1.5/1	44	17 (*S*)
6	toluene	1/1	1.5/1	81	78 (*S*)
7	toluene	1/1.5	1.5/1	86	70 (*S*)
8	toluene	½	1.5/1	59	71 (*S*)
9	toluene	1/1	1/1	77	46 (*S*)

[a] Reaction was carried out under nitrogen for 12 h in 3 ml of solvent, 0.5 mmol of chalcone, 0.05 mmol of $Cu(OAc)_2{\cdot}2H_2O$, 0.05 mmol of Ligand **10a**.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column (eluent: hexane/2-propanol = 99:1, 1.0 ml/min).
[d] The absolute configuration was determined by comparison of the specific rotation with that of the literature [33,34].

Table 3
Enantioselective 1,4-conjugate addition of Et_2Zn to acyclic enones[a].

Entry	Ligand	R^1	R^2	Yield[b] (%)	ee[c] (%) (config.)[d]
1	**10a**	Ph	Ph	81	78 (*S*)
2	**10a**	4-Cl-C_6H_4	Ph	52	74 (*S*)
3	**10a**	4-Me-C_6H_4	Ph	60	73 (*S*)
4	**10a**	4-MeO-C_6H_4	Ph	43	73 (*S*)
5	**10a**	4-O_2N-C_6H_4	Ph	30	46 (*S*)
6	**10a**	Ph	Me	Trace	N.D.[e]
7	**10a**	Ph	4-Me-C_6H_4	27	48 (*S*)

[a] Reaction was carried out under nitrogen at −10 °C for 12 h in 3 ml of toluene, 0.5 mmol of substrate, 0.75 mmol of Et_2Zn, 0.05 mmol of $Cu(OAc)_2\cdot 2H_2O$, 0.05 mmol of Ligand **10a**.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column (eluent: hexane/2-propanol = 99:1, 1.0 ml/min).
[d] The absolute configuration was determined by comparison of the specific rotation with that of the literature [33,34].
[e] N.D. means not determined.

Table 4
Enantioselective 1,4-conjugate addition of Et_2Zn to 2-cyclohexenone[a].

Entry	Ligand	Yield[b] (%)	ee (%)[c]	Config[d]
1	**10a**	51	22	(*S*)
2	**10b**	47	17	(*S*)

[a] Reaction was carried out under nitrogen at −10 °C for 12 h in 3 ml of toluene, 0.5 mmol of substrate, 0.75 mmol of Et_2Zn, 0.05 mmol of $Cu(OAc)_2\cdot 2H_2O$, 0.05 mmol of Ligand **10a-b**.
[b] Isolated yield.
[c] Determined by GC equipped with a Chiraldex A-TA column (50 m × 0.25 mm I.D.).
[d] The absolute configuration was determined by comparison with an authentic sample.

4. Conclusion

In summary, we have described a new type of carbohydrate-based phosphate-pyridine ligands **10a** and **10b** which have been successfully applied in Cu-catalyzed conjugate addition of Et_2Zn to chalcones. The advantage of these phosphate-pyridine ligands is that they can be easily prepared in a few steps from commercial *N*-acetylglucosamine, an inexpensive natural chiral feedstock, and electronic and steric properties could be finely tuned. Our investigations will be focused on the applications of these new *P, N* ligands **10a** and **10b** in other asymmetric catalytic reactions, as well as studying the mechanism. Further screening of these new chiral ligands with respect to other enones currently in progress and will be reported in due course.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.09.021.

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