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Simple D-glucosamine-based phosphine-imine and phosphine-amine ligands in Pd-catalyzed asymmetric allylic alkylations

Katarzyna Glegoła [a], Sine A. Johannesen [b], Laura Thim [b], Catherine Goux-Henry [a], Troels Skrydstrup [b,*], Eric Framery [a,*]

[a] Université de Lyon, F-69622, Lyon, France, Université Lyon 1, Villeurbanne, CNRS, UMR5246, ICBMS Equipe Synthèse Asymétrique, France
[b] Center for Insoluble Protein Structures, Department of Chemistry and Interdisciplinary Nanoscience Center, University of Aarhus, Langelandsgade 140, 8000 Aarhus C, Denmark

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ABSTRACT

A new family of phosphine-imine and phosphine-amine ligands based on D-glucosamine were synthesized in order to probe previous asymmetric allylic alkylation results with those of disaccharide ligands of the same class. In most cases, good-to-excellent activities and enantioselectivities were observed with these ligands with ee's reaching up to 87% in the Pd-catalyzed allylic alkylation reaction of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate as the nucleophile.

Carbohydrates represent excellent tools as chiral auxiliaries, reagents, organocatalysts and ligands for asymmetric synthesis,[1] as they can be easily functionalized to provide efficient ligands, which are applicable in a large number of catalytic asymmetric reactions.[2] Derivatives of the most accessible NH_2-containing sugar, D-glucosamine, have been evaluated as chiral ligands in numerous transition metal-catalyzed asymmetric catalysis based on Mn,[3] Ni,[4] V,[5] Cu,[6] Zn,[7] and Pd. With the exception of the few examples studied in the Suzuki–Miyaura[8] and the Mizoroki–Heck[8a,9] reactions, the most studied Pd-catalyzed reactions, applying ligands derived from glucosamine, are the allylic substitution reactions, which represent powerful processes for the asymmetric construction of carbon-carbon and carbon-heteroatom bonds.[10]

The main results in the Pd-catalyzed asymmetric allylations with glucosamine-based ligands are those obtained from diphenylphosphinoaryloxazoline **1**,[11] phosphinite-oxazoline **2**,[12] phosphite-oxazoline **3**,[13] and the phosphite-phosphoramidite **4**[14] (Fig. 1). These ligands provide products of high enantioselectivities (up to 98%) in the allylic alkylation of 1,3-symmetrically disubstituted acetates. A conceptually simpler and more readily available ligand is represented by the phosphine-amide ligands **5** (Fig. 1), which was introduced by us in 2003.[15] Whereas high enantioselectivities can also be obtained with this ligand, they are nevertheless strongly dependent on the C1-alkoxy group and on the anomeric configuration. In order to further probe this class of ligands, these

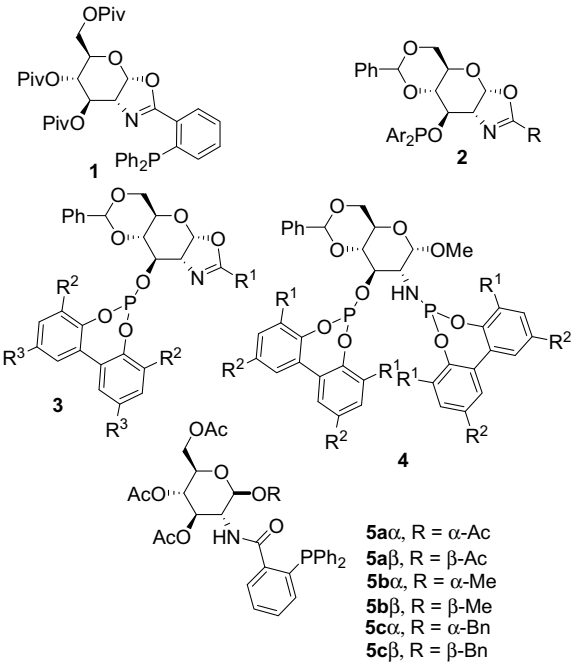

Figure 1. Ligands based on D-glucosamine used in allylic alkylation.

* Corresponding authors. Tel.: +45 894 239 32; fax: +45 861 961 99 (T.S); tel.: +33 472 446 263; fax: +33 472 448 160 (E.F).
E-mail addresses: ts@chem.au.dk (T. Skrydstrup), framery@univ-lyon1.fr (E. Framery).

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monosaccharide phosphines were extended to their disaccharide derivatives, as illustrated in Figure 2.[16,17] Of the three classes of disaccharide ligands prepared, the phosphine-imine derivatives **7** rather than the amide **6** or the amines **8** exhibited the highest ee's attaining 99% for the allylic alkylation of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with various nucleophiles. This came as a surprise as (1) phosphine imine ligands are generally not good ligands for these types of palladium-catalyzed reactions as examined with other NH_2-containing sugars[18] and (2) our previous study with ligand **5** showed that it was superior to its corresponding imine-phosphine and amine-phosphine. Suspecting that the role of the reducing sugar of these disaccharide ligands for the good enantioselectivities observed is simple sterical bulk, we have prepared a series of simpler ligands based on 2-amino-2-deoxyglucosides with varying degrees of sterical bulk at the anomeric center and have investigated their activities in asymmetric allylic alkylations of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The results of this study are communicated in this Letter.

The functionalization of the amino group on the D-glucosamine derivatives provided an easy access to various phosphine-imine ligands,[19] as well as to two phosphine-amine ligands[20] based on the carbohydrate moiety (Scheme 1). The condensation of 2-(diphenylphosphino)-benzaldehyde onto 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose **9a** or alkyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosides **9b–e** using $MgSO_4$ as the drying agent in toluene furnished the corresponding phosphine-imine derivatives **10** with yields in the range of 63–85%, except from benzyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside **9e** where a yield of 31% was obtained after purification. The reduction of the imino group of the derivatives **10a** and **10b**, using $NaBH_3CN$ in a mixture of acetic acid and methanol, provided the phosphine-amine ligands **11a** and **11b** in quantitative yield.

The starting materials **9** were easily generated from the commercially available D-glucosamine hydrochloride. 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose **9a** was obtained in three steps according to the literature procedure:[21] protection of the NH_2 group with *p*-anisaldehyde, acetylation of the OH group, removal of the *p*-methoxybenzylidene group with HCl, and a basic washing to give the free amino group. The other glycosides **9b–e** were prepared following the process described by Billing and Nilsson[22] in the case of the methyl glycoside **9b** from 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide

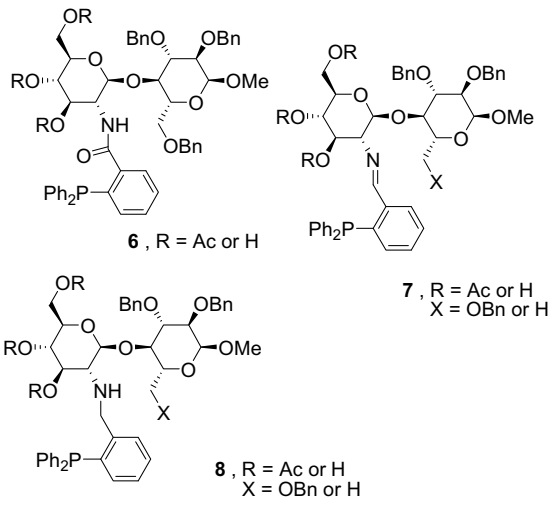
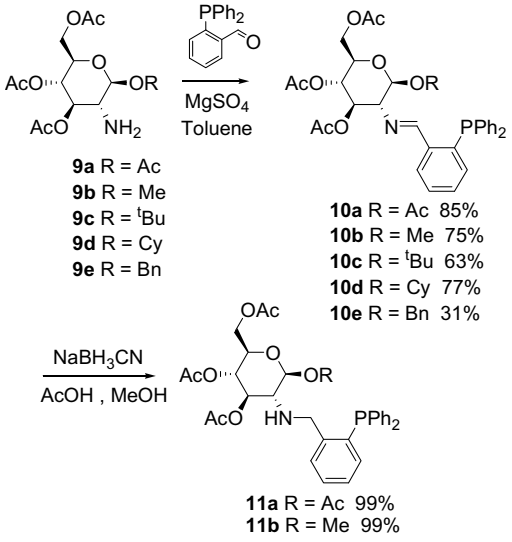


Figure 2. Ligands based on disaccharides with one D-glucosamine unit used in allylic alkylation.

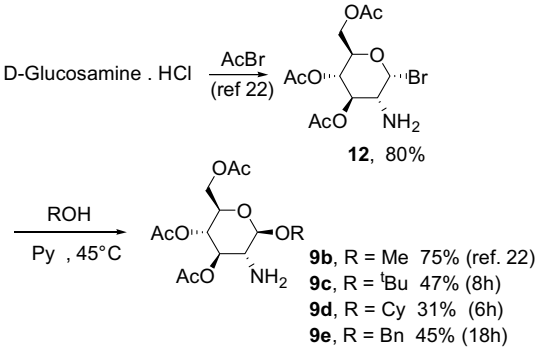


Scheme 1. Preparation of phosphine-imine and phosphine-amine ligands **10** and **11**.

12 (Scheme 2). The treatment of the D-glucosamine by a large excess of acetyl bromide gave the compound **12** in 80% yield. Then, the derivative **12** and pyridine (1.2 equiv) were dissolved in the corresponding alcohol (ROH) to give after a stirring at 45 °C for the desired time, the corresponding alkyl glycosides **9c–e** with yields in the range of 31–47%.

The phosphine-imine and phosphine-amine ligands **10** and **11** were examined in the palladium-catalyzed asymmetric allylic alkylation of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Table 1). The reactions were performed in THF (0.125 M) at 25 or 60 °C for 24 h, using 2 mol % of $[(\eta^3\text{-}C_3H_5)PdCl]_2$, 4 or 8 mol % of the sugar ligand, 3 equiv of dimethyl malonate, and a mixture of *N,O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv) and KOAc (2 mol %) as the base.[24] The results were compared to those obtained previously using the phosphine-amide, phosphine-imine, and phosphine-amine ligands **5–8**.

We first examined the results obtained using phosphine-imine derivatives **10a–e** as ligands. In the case of a Pd/L ratio of 1/1, after 24 h at 25 °C, the nature of the substituent at the β-anomeric position of the carbohydrate moiety of the ligand had no influence on the reactivity as complete conversion and high yield (97–99%) of the allylic product was obtained. On the other hand, this substituent greatly influenced the enantioselectivity with enantiomeric excesses produced in the range of 38–87% (Table 1, entries 1, 3, 5, 7 and 9). The use of ligands **10c** or **10e**, carrying a *t*-butoxy or benzyloxy group (Table 1, entries 5 and 9), afforded high ee's (87% or 82%,



Scheme 2. Preparation of alkyl glycosides **9b–e**.