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Influence on the enantioselectivity in allylic alkylation of the anomeric position of the phosphine-amide ligands derived from D-glucosamine

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Abstract—The synthesis of a new series of chiral phosphine amides derived from D-glucosamine is described. The palladium-catalyzed asymmetric allylic alkylations of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate using these ligands have been investigated. The results obtained and the NMR studies of free ligands and of their Pd-complexes obtained from dimer $[(\eta^3\text{-}C_3H_5)PdCl]_2$ revealed the mode of complexation and the influence of the configuration and of the nature of the substituent at the anomeric position on the enantioselectivity of the studied asymmetric allylic alkylation reactions.

1. Introduction

Palladium-catalyzed allylic substitutions have been developed as fundamentally important cross-coupling reactions.[1] Since the first example by Trost and Strege in 1977,[2] many asymmetric catalytic systems have been described. The best ones are Trost's *P,P* ligand[3] and Pfaltz's *P,N* ligand[4] with enantioselectivities up to 95% being obtained using these ligands.

During the last 10 years, carbohydrates have appeared as good sources of chiral ligands for asymmetric catalysis. Indeed, these chiral natural derivatives can be easily functionalized, and can be used as precursors of ligands used in a large number of catalytic asymmetric reactions.[5] These ligands have been mainly synthesized from carbohydrates including xylose, glucose, galactose, mannitol, and trehalose backbones. Few examples of ligands derived from D-glucosamine are described in the literature. In addition to Mn-catalyzed epoxidation of styrene,[6] Ni-catalyzed hydrovinylation of styrene,[7] V-catalyzed oxidation of thioanisole,[8] and Zn-catalyzed alkynylation of aldehydes,[9] the D-glucosamine has been used as precursor of ligands in Pd-catalyzed Suzuki–Miyaura,[10] Heck,[10a,11] and allylic substitution reactions. In the last Pd-catalyzed reaction, four types of ligands derived from D-glucosamine have been described: diphenylphosphinoaryloxazoline **1**,[12] phosphinite-oxazoline **2**,[13] phosphite-oxazoline **3**[14] and phosphine-amide **4**,[15] and **5**[16] ligands (Fig. 1).

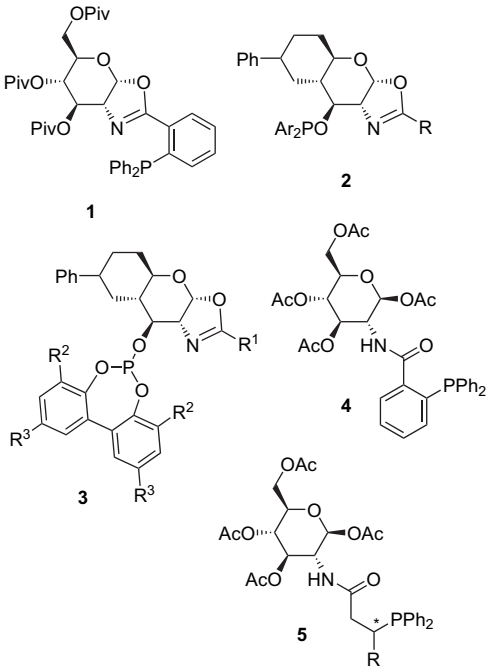

Figure 1. Ligands based on D-glucosamine used in allylic alkylation.

Keywords: D-Glucosamine; Phosphine amides; Allylic alkylation; NMR studies.
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The *P,N* ligands based on oxazoline **1**–**3**[12–14] gave enantioselectivities up to 98% in the allylic alkylation of 1,3-symmetrically disubstituted acetates. In 2003, we have reported the potential of the phosphine-amide ligands **4** derived from D-glucosamine.[15] With the phosphine-amide ligand **4**, enantioselectivities up to 97% have been obtained in the allylic alkylation of 1,3-diphenylprop-2-enyl acetate with various nucleophiles. We have shown that the enantioselectivity was higher with a ligand/palladium ratio of 1/1 than 2/1, corresponding probably to two different types of chelation: *P,O*-chelation versus *P,P*-coordination, respectively.[15] This difference in enantioselectivity could be explained by a more rigid *P,O*-chelated complex. We have also shown that the influence of the carbohydrate moiety on the enantioselectivity seemed to be the most important factor in this asymmetric reaction.[16]

In this context, we decided to prepare new phosphine-amide ligands derived from D-glucosamine by modification of the configuration and the nature of the substituent at the anomeric position. In this paper, we report the synthesis of these new phosphine-amide ligands **6**–**8** (Fig. 2), and compare the results obtained in the palladium-catalyzed asymmetric allylic alkylation of racemic 1,3-diphenylprop-2-enyl acetate with dimethyl malonate, using the catalysts prepared from ligand **4** and also ligands **6**–**8**.

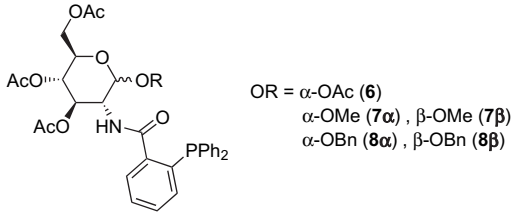


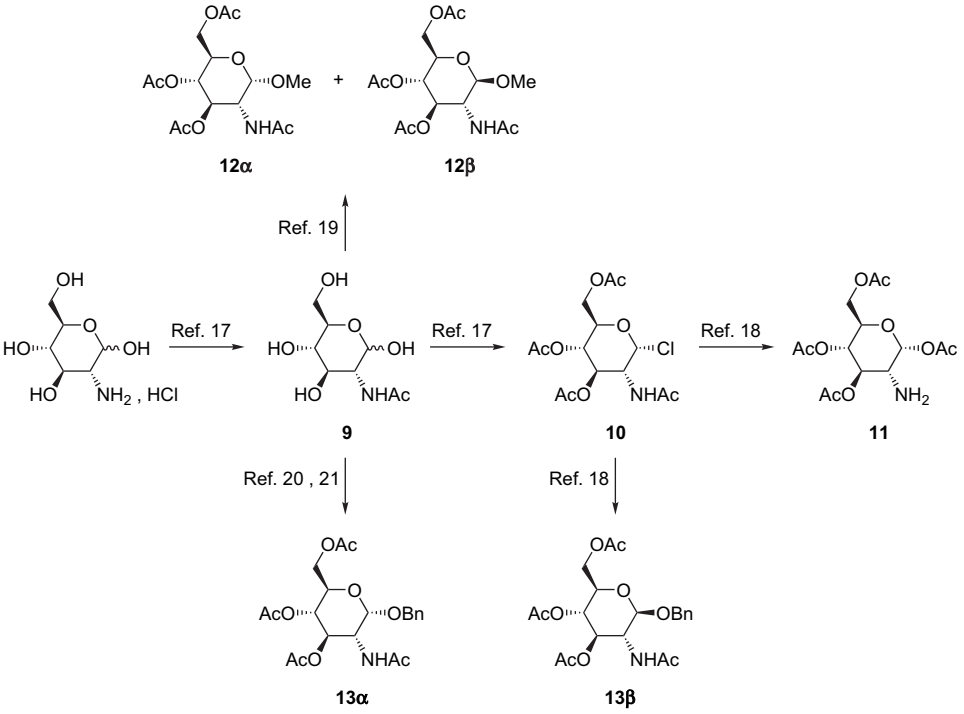
Figure 2. New phosphine-amide ligands **6**–**8** derived from D-glucosamine.

2. Results and discussion

2.1. Synthesis of ligands

Ligands **6**–**8** were prepared from commercial D-glucosamine hydrochloride (Schemes 1 and 2). According to the literature, the amino group of D-glucosamine hydrochloride was selectivity protected giving acetamide **9**. Then the peracetylation of the hydroxyl functions followed by the replacement of the acetyl group at the anomeric position by a chlorine afforded 3,4,6-tri-*O*-acetyl-2-acetylamino-2-deoxy-α-D-glucopyranosyl chloride **10**.[17] Treatment of derivative **10** with water in the presence of benzyltriethylammonium chloride in nitromethane led to the stereospecific formation of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl hydrochloride **11** as described by Pertel et al.[18]

The anomeric mixture of *N*-acetyl-D-glucosamine **9** was treated with 5% sulfuric acid/methanol to give, after acetylation of the remaining three hydroxyl functions, an anomeric mixture of methyl 3,4,6-tri-*O*-acetyl-2-acetylamino-2-deoxy-D-glucopyranoside **12** in an α/β ratio of 1.5 to 1, as reported by Oshima et al.[19] The two anomers **12α** and **12β** were separated on silica gel. The same procedure, but using benzyl alcohol instead of methanol, gave benzyl 3,4,6-tri-*O*-acetyl-2-acetylamino-2-deoxy-α-D-glucopyranoside **13α** in 52% yield after purification by column chromatography, as reported by Shulman and Khorlin,[20] or by Paul et al.[21] The anomer **13β** was obtained using the 1,2-*trans*-glycosaminide synthesis described by Pertel et al.[18] In the presence of benzyl alcohol and benzyltriethylammonium chloride, an



Scheme 1.