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New ureas containing glycosyl and diphenylphosphinyl scaffolds: synthesis and the first attempts to use them in asymmetric synthesis

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ABSTRACT

Chiral ureas containing glycosyl and diphenylphosphinyl scaffolds were found to be an effective organocatalyst. They were synthesised in high yields by a one-pot tandem Staudinger/aza-Wittig coupling reaction. The first attempts of using them in asymmetric synthesis are presented. Yields of the Morita–Baylis–Hillman reaction were moderate with an enantiomeric excess of up to 80%.

1. Introduction

Saccharides, as naturally occurring compounds with defined stereogenic centre, are useful building blocks for many interesting structures.[1] Carbohydrates, which are inexpensive and readily available natural materials, have only recently also been employed as chiral backbones of organocatalysts. Examples of effective catalysts with a thiourea bridge which are often combined with saccharides, can be found in the literature.[2,9] Much less examples of application of urea saccharide organocatalyst in asymmetric synthesis can be found in the chemical reports.[3] Another significant feature of saccharides is their hydrophilicity which enables to perform enantioselective syntheses in aqueous media.

A wide range of saccharide combinations with chiral phosphines that incorporate a urea bridge are presented in this paper which describe the derivatives able to act both as organocatalysts or chiral ligands in metal complexes. Derivative **L1** is an effective chiral ligand in the stereoselective synthesis of vinyl-tetrahydrofurans.[4] The positive results of this reaction encouraged us to obtain a larger group of this type of compounds and to study them also as organocatalysts. The saccharide derivatives that include a chiral phosphine moiety were tested as organocatalysts in the Morita–Baylis–Hillman and aza-Henry reaction. There are known examples of effective thiourea sugar derivatives acting as organocatalysts in such type of reactions,[1c,d,2f,11d] but there are no reports describing the use of saccharides urea derivatives.

Enantioselective synthesis remains a challenge in organic chemistry due to the great importance of single stereoisomers in biological processes and also in many industrial sectors such as pharmaceutical and food chemistry. The activity of such optically pure compounds strongly depends on their absolute configuration. Chemical yields and stereoselectivity of the asymmetric reaction are related with the choice of the appropriate chiral ligand/catalyst in such transformation. Organophosphane derivatives constitute an important class of compounds used as chiral catalysts in asymmetric synthesis.[5,6]

Enantioselective reactions with organocatalysts have come into prominence.[7] The chiral organic molecules constituting sometimes various complex structures, can interact in the transition state with substrates resulting in asymmetric induction leading to the desired products in an enantioselective process. Nevertheless, it is very important to exclude even trace amounts of metal deriving from organocatalysts before the application of desired chiral products in the industry (especially pharmaceutical one).

The Morita–Baylis–Hillman (MBH) reaction is used in the C—C bond formation[8–10] and is known as a powerful tool for the construction of densely functionalised alcohols. It is well established that the MBH reaction efficiently converts simple starting materials into highly functionalised products which are versatile synthetic intermediates in organic synthesis. The asymmetric version of this reaction has attracted much attention in recent years.

The aza-Henry reaction is a highly valuable C—C bond forming process. The resulting nitroamine adduct can be either reduced producing 1,2 diamines or oxidised affording α-amino acids. They have remarkable structural units, which we can find in biologically

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active compounds or natural products. These moieties can be used as valuable building block, chiral auxiliaries and metal ligands.[11]

2. Results and discussion

2.1. Synthesis of organocatalysts

The synthetic route for the preparation of the chiral, sterically congested, bifunctional urea–phosphine organocatalysts is straightforward (Scheme 1). Bifunctional ureas **L1**–**6** were synthesised in high yields by coupling of the corresponding azido-cellobiose **1**[12a] with chiral amines **2**–**6** and achiral amine **7** in the presence of PPh_3 and CO_2.[13] All the amine derivatives are commercial products.

The highest yield, 99%, was obtained for ligand **L1** while the lowest yield of 66% was achieved for ligand **L2** with unit proline **3**. The simple and efficient synthesis of urea derivatives which is carried out under mild conditions, could be an attractive method for the preparation of this type of sugar organocatalysts.

Next the aza-Wittig reaction of other mono- and disaccharides was investigated (Scheme 2).

Organocatalyst **L7** was obtained in a high 99% yield from azido-glucose **8**[12b] and the aminocyclohexane **2**. The yields of ligands **L8**–**12** from azido-lactose **9**[12a] and azido-melibiose**10**[12a] were also satisfactory (60–98%).

The spectroscopic data of organocatalysts **L1**–**12** (IR, NMR and elemental analysis) are in full accordance with the proposed structures.

2.2. Application of the organocatalysts L1–12 in asymmetric synthesis

2.2.1. Morita–Baylis–Hillman reaction

Initially, we chose the reaction of ethyl acrylate with *p*-nitrobenzaldehyde as a model transformation in which organocatalysts **L1**–**12** were evaluated. The reaction was performed for 48 h in THF using 10 mol % of the organocatalysts. The results are summarised in Table 1.

The best result was obtained in the presence of **L11** as the organocatalyst at room temperature (Table 1, entry 5). Under the same conditions **L12** gave a product with a lower yield and a slightly lower enantioselectivity (Table 1, entry 6). Only a trace quantity of the product was observed in the presence of **L3**, **L5** and **L8**. The lowest enantioselectivity was observed for **L6** and **L9** bearing an achiral amine moiety (Table 1, entries 2 and 4). Ligands bearing tertiary nitrogen atom (**L2**, **L4** and **L10**) in the urea subunit were completely nonreactive. Table 1 reveals that the stereogenic centre which is located on the amine moiety exerts a crucial influence on both the stereochemistry and yield of the reaction. These results also showed that the distance between the phosphine (base) and the urea bridge had an effect on both the enantioselectivity and yield. In the nonpolar solvent such as toluene using the best disaccharide organocatalysts **L1**, **L11** and **L12** only traces of product MBH reaction, was observed.

Proposed transition state of this asymmetric MBH reaction is illustrated in Figure 1.

The urea hydrogens form a hydrogen-bond with the aldehyde carbonyl group, and the alkoxy enolate was formed via phosphinoyl attack on an activated carbonyl group from *si*-face and give *R*-product.

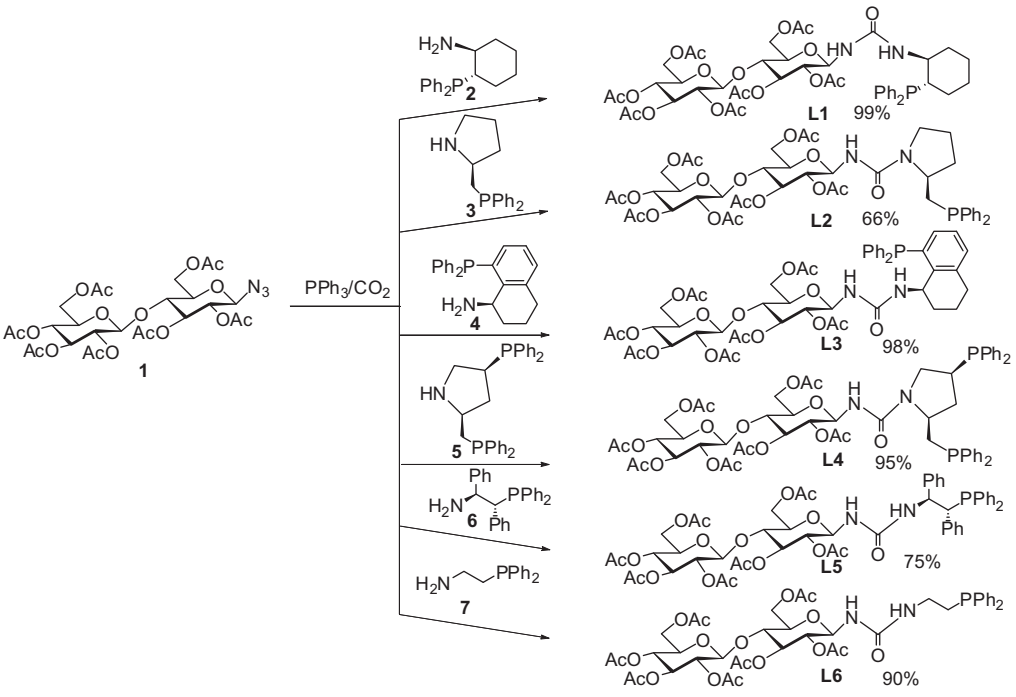
2.2.2. Aza-Henry reaction

The best disaccharide organocatalysts **L1**, **L11** and **L12** were also tested in the aza-Henry reaction. The results are collected in Table 2.

In presence of the derivative **L1** and **L12** products of aza-Henry reaction were synthesised with high yield but with low enantioselectivity. Organocatalyst **L11** was much less efficient.

3. Conclusions

In conclusion, we have prepared a new chiral bifunctional phosphinoureas derived from saccharides and in high yields using simple procedure. Organocatalysts **L11** and **L12** were efficient for the asymmetric Morita–Baylis–Hillman reaction of an acrylate



Scheme 1.