Application of asymmetric aqueous aldol reaction using water-compatible organocatalysts: Stereoselective synthesis of carbohydrates and spiroacetals.

Abstract

The proline catalyzes cross aldol reaction is one of the easiest procedures for the controlled introduction of a carbon-carbon bond, possesses hydroxyl groups as substituents, from a carbonyl compound. This reaction has found significant use in the carbohydrate synthesis as a convenient route to uloses. Suitable protected aldoses are readily convertible by the aldol reaction into the corresponding uloses.

A disadvantage of this and related methods is that they do not allow stereoselective aldol reaction in water. Since proline and the analogues have shown decreased selectivities in water, the conventional methods, using either hydrophilic or hydrophobic substrates, require using an organic solvent for stereoselective aldol reactions. In the midst of wide-ranging research on the role of organocatalysts in asymmetric aldol reactions, and the attendant focus on design of such catalysts, the important role of which in water is overlooked in the tedious ‘hydrophobic active pocket’ theory. This persistence is spread in some ‘organocatalytic chemists’, albeit mechanistic pathway of the aldol reaction essentially requires participation of water molecules as Janda described.

This limited solvent compatibility of the proline catalyzed asymmetric aldol reaction is one of the reasons that much effort has been put into developing other asymmetric organocatalysts, especially, development of the asymmetric catalysts catalyzing asymmetric aldol reaction in an aqueous media has focused on. In this context, prolinamido-glycoside catalyzed aldol reaction has been of particular value. With a view to achieving stereoselective cross aldol reaction in an aqueous medium, 1 and 2 were prepared. This thesis comprises stereoselective synthesis of carbohydrates by aldol reaction using the prolinamido-glycosides, namely, methyl 2-((1-prolyl)-amido-α-D-glucopyranoside 1 and methyl 2-((D-prolyl)-amido-α-D-glucopyranoside 2, catalysts that have been exploited for the aldol reaction in water (Fig. 1). Because of the fixed hydroxys of the sugar ring, such hydroxyl groups are capable of interacting with aldehyde acceptors in the transition state, they would be expected acting as water compatible organocatalysts. In previous studies, attempts to elucidating the stereochemical pathways of asymmetric aldol reaction in aqueous media using amino acyl sugar derivatives have demonstrated, and 1 and 2 offer useful potential as catalysts for aqueous aldol reaction.

![Fig. 1 Prolinamido-glycoside catalysts](image_url)
1. Aqueous aldol reaction of aldoses under prolinamido-glycoside catalyzed conditions (Scheme 1)

Scheme 1. Prolinamido-glycoside catalyzed aldol reaction

In aqueous media, they exhibited catalyzing the formation of aldol products with stereocontrol, and the observed stereoselectivity in their aldol reaction on ketones, using 1 or 2, was in general accordance with the empirical Felkin-Anh theory, especially if the conformational disposition of the chiral aldehydes had presented a favorable conformation by avoiding eclipsing bulky substituent along the C-1–C-2 bond, in which l-prolinamido-glycoside 1 selectively catalyzed re-facial attack, it has shown increased selectivity in the reactions with (2S)-aldehydes which possess a less hindered re-face, and d-prolinamido-glycoside 2 selectively catalyzed si-facial attack and prefers (2R)-aldehyde favor si-facial selective aldol reaction. The stereochemistry of these aldol reactions has been investigated in terms of the influence of conformational effects, and the results demonstrate that the configurations of the catalysts and the conformations of substrates are a determining factor in the stereochemical outcome of the reaction.

2. Tandem aldol-aldol reaction by the prolinamide catalysts (Scheme 2).
3. Stereospecific spiroacetalization of uloses

As an acidic treatment of the tandem aldol-aldol products, described in chapter 3, gave the corresponding spiroacetals (Scheme 3), found in the skeleton of many biologically active natural products.

Scheme 3. Stereospecific spiroacetalization of uloses.

In common with higher carbon polyhydroxyketones, the tandem aldol-aldol adducts, e.g., the 5-nonulose utilizes two of its hydroxyls to act as nucleophiles in intramolecular acetalization, via the hemiacetal which allows β-equatorial, γ-axial-diol or β-axial, γ-equatorial-diol but not diaxial-diol on a pyranose chair conformation. This ring structure originates from the open chain keto form by reversible reaction between the ketone function at C-5 and the hydroxyl at C-1 or C-9 (Fig. 2).

![Diagram showing stereochemistry of spiroacetals](image)

Fig. 2. Stereochemistry of the spiroacetalizations

Configurational studies on spiroacetals through X-ray crystallography, it revealed that an avoidance of a 1,3-diaxial interaction is a determining factor of orientations of the hydroxyls on the pyranose ring, in which β-equatorial, γ-axial form is more favored than β-axial, γ-equatorial form (Fig. 2).