UNIVERSITI TEKNOLOGI MARA

SYNTHESIS OF CHIRAL HYDROXYPROLINE-BASED ORGANOCATALYSTS AND THEIR APPLICATIONS IN ALDOL AND MICHAEL ADDITION REACTIONS

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ABSTRACT

Chiral compounds are common in nature and can have profoundly varied effects in chiral biological systems based on stereochemistry. Organic chemist creates chiral molecules utilizing enantiopure substance, reagent, and catalyst to produce a single enantiomer with ideal pharmacology, toxicity, pharmacokinetics, and metabolism properties. This leads to asymmetric reactions using more efficient organocatalysts to prevent waste, increase atom economy, save energy, and increase stereoselectivity. One interesting organocatalyst that is demanded is prolineamide-derived organocatalyst. The first aim of this study is to synthesize prolineamide-derived organocatalyst via 3-hydroxyproline precursor. A new synthetic strategy was developed starting with the Michael addition reaction of glycine ethyl ester, **79** with ethyl acrylate, **78**, to give the desired ethyl-3-[(2-ethoxy-2-oxoethyl)amino]propanoate, **80** with an overall yield of 62%. The next strategy was to protect the nitrogen atom with *tert*-butoxycarbonyl (BOC) using a simple method utilizing NaOH as the base, resulting in 81% yield. The *N*-BOC protected intermediate diester **81** formed underwent Dieckmann Cyclization to obtain 58% of cyclic compound *N*-BOC-3-ketoproline ethyl ester, **82.** The ester at the C-2 position and carbonyl ketone of the C-3 ring moiety were subsequently reduced using a combination of $NaBH_4$-$MgCl_2$ where 75.5% *cis* isomer, **83** was obtained. In the final step, the hydrolysis reaction takes place using lithium hydroxide in aqueous ethanol, furnishing 86.6% yield of inseparable mixtures of enantiomers, **84a** and **84b.** Without being discouraged by the outcome, we synthesize six new prolineamide-based organocatalysts (catalyst 1 to catalyst 6) by coupling *N*-BOC-*L*-proline and *N*-BOC-*trans*-4-*L*-hydroxyproline with different secondary amines. After optimizing the reaction conditions, the yield of organocatalysts obtained was up to 97% yield. The six organocatalysts were evaluated in Aldol and Michael addition reactions by screening the organocatalyst in the different solvents, different catalyst loading and different additives. The efficiency of the organocatalysts was described by taking into account the enantioselectivity (enantiomeric excess), diastereoselectivity (diastereomeric ratio) and the yield of the major products. In the aldol reaction, the model reaction chosen was between cyclohexanone and 4-nitrobenzaldehyde, whereas in the Michael addition reaction, the model reaction was between cyclohexanone and *trans*-β-nitrostyrene. In the aldol reaction, catalysts 1 and 2 show promising results in water, where catalyst 1 obtained 81% yield, 79% ee and 46:54 (anti: syn) diastereomeric ratio, whereas catalyst 2 produced 80% yield, 84% ee and 44:56 diastereomeric ratio (anti: syn) and 80% yield, respectively. Catalysts 3 to 6 afforded reasonable yields in aldol reactions. However, in the Michael addition reactions, only satisfactory results (30 - 41% yield) in water/EA were obtained for catalysts 1 and 2. Each catalyst demonstrates the ability to facilitate asymmetric aldol and Michael reactions with adequate yield, enantioselectivity, and diastereoselectivity. Structural conformations of all synthesized compounds were analyzed by mass spectroscopy (MS) and nuclear magnetic resonance spectroscopy (NMR) techniques. The enantiomeric access (ee) was analyzed by High-performance Liquid Chromatography (HPLC), and the diastereomeric ratio (dr) was performed using NMR.

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