

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 NaBH₄-MgCl₂ 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 excess (ee) was analyzed by High-performance Liquid Chromatography (HPLC), and the diastereomeric ratio (dr) was performed using NMR.

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TABLE OF CONTENTS

	Page
CONFIRMATION BY PANEL OF EXAMINERS	ii
AUTHOR'S DECLARATION	iii
ABSTRACT	iv
ACKNOWLEDGEMENT	v
TABLE OF CONTENTS	vi
LIST OF TABLES	x
LIST OF FIGURES	xii
LIST OF SCHEMES	xiv
LIST OF ABBREVIATIONS	xvii
CHAPTER 1 INTRODUCTION	1
1.1 The Importance of Chirality	1
1.2 Catalyst in Asymmetric Reactions	2
1.2.1 Enzyme or Biocatalysis	2
1.2.2 Metal or Organometallic Catalysis	4
1.2.3 Organocatalysis	5
1.3 Proline as Organocatalysts	11
1.4 Problem Statement	14
1.5 Objectives	15
1.6 Significance of Study	15
1.7 Synthesis Outline	16
1.7.1 Objective 1	16
1.7.2 Objective 2	17
1.7.3 Objective 3	18
1.7.4 Objective 4	18

CHAPTER 2 LITERATURE REVIEW	19
2.1 Proline Derivatives	19
2.1.1 Synthesis of 3-Hydroxyproline	21
2.1.2 Synthesis of 4-Hydroxyproline	24
2.2 Proline Catalysed Aldol Reactions	27
2.2.1 Mechanism of Proline Catalysed Aldol Reaction	28
2.2.2 Enantioselective Organocatalytic Aldol Reactions	29
2.3 Enantioselective Organocatalytic Michael Addition Reactions	42
2.3.1 Iminium Catalysis of Michael Addition Reactions	45
2.3.2 Possible Iminium Mechanism of Proline-catalysed Michael Reactions	46
2.3.3 Possible Enamine Mechanism of Proline-catalysed Michael Reactions	47
2.3.4 Pyrrolidines Organocatalysts in Michael Addition Reactions	48
2.3.5 Prolineamide Derivatives Organocatalysts in Asymmetric Michael Addition Reaction	51
CHAPTER 3 RESEARCH METHODOLOGY	54
3.1 General Experimental Procedures	54
3.1.1 Purification of Reagents, Compounds and Solvents	54
3.1.2 Preparation of Glassware	54
3.1.3 Infrared Spectra (IR)	55
3.1.4 Nuclear Magnetic Resonance (NMR)	55
3.1.5 High-Performance Liquid Chromatography (HPLC)	55
3.1.6 Gas-Chromatography Mass Spectroscopy (GCMS)	56
3.2 Individual Experimental Procedures	56
3.2.1 Synthesis of 3-Hydroxyproline	56
3.2.2 Synthesis of Organocatalyst	62
3.2.3 General Procedure for the Enantioselective Aldol Reaction	63
3.2.4 General Procedure for the Enantioselective Michael Addition	64
3.2.5 Experimental Data	65