Thesis Title- Organocatalytic Asymmetric Vinylogous C-C Bond Formation and Stereoselective [3+3] Cycloaddition Reaction with 3–Alkylidene–2–Oxindoles

Name- Manish Kumar Jaiswal

Entry Number- 2015CYZ8058

ABSTRACT

The thesis entitled "**Organocatalytic Asymmetric Vinylogous C-C Bond Formation and Stereoselective [3+3] Cycloaddition Reaction with 3–Alkylidene–2–Oxindoles"** deals with the evolution of stereoselective reactions for the synthesis of functionalized oxindole scaffolds. Different stereoisomers of a molecule are responsible for many important properties like the biological activity, effect on taste, odour and pharmaceutical activity. Therefore, it is crucial to selectively synthesize the desired enantiomers and diastereomers through smart synthetic design and conscious choice of catalysts and reaction conditions**.** We have developed organocatalytic highly diastereoselective and enantioselective methods for C-C bond forming reactions leading to functionally rich moieties of oxindole core.

This thesis has been divided into four chapters. In the **first chapter**, significance of chirality with various interesting examples has been explained. Synthetic routes to diastereomerically and/or enantiomerically pure compounds has been explained. The chapter has an introduction to asymmetric catalysis and detailed description of organocatalysis. Also highlighted are the various modes of organocatalysis such as covalent and non-covalent catalysis. Additionally, asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea has been described. Then, a brief introduction to the principle of vinylogy with example of 3-alkylidene-oxindole as a vinylogous nucleophile in asymmetric vinylogous aldol reaction, asymmetric vinylogous Michael reaction and cycloaddition strategy for synthesis of spirocyclohexene-oxindole has been described.

Chapter 2 describes an organocatalytic highly enantioselective vinylogous Aldol reaction of 3-alkylidene oxindole with α-ketophosphonates. Biological importance of oxindole scaffolds and α-Hydroxy phosphonic acid and their derivatives in particular quaternary α-hydroxy phosphonates has been described. The chapter also describes synthetic routes to asymmetric aldol reaction and vinylogous aldol reactions, along with discussion on asymmetric organocatalyzed vinylogous aldol reaction. In this chapter, the development of a cinchona alkaloid derivative, and a chiral organic catalyst system that effectively promotes the asymmetric vinylogous aldol reactions yielding, chiral δ-quaternary α-hydroxyphosphonato-3-alkylidene-2-oxindole and their derivatives is described. The scaffolds developed are unique as they are hybrid of oxindole and hydroxy-phosphonate moieties. Since, both type of scaffold has their own biological and pharmaceutical importance and they are the building blocks for the synthesis of biologically active compounds.

Chapter 3, deals with the synthesis of chiral γ -substituted 3-alkylidene oxindoles through enantioselective vinylogous Michael addition reaction of 3-alkylidene oxindole to β, γ – unsaturated α-ketoesters in presence of bifunctional amine-thiourea catalyst. Various nucleophiles that have been used for asymmetric Michael addition on β,γ–unsaturated α-ketoesters are also described. The lack of methodologies for asymmetric vinylogous Michael addition with biologically active vinylogous nucleophile such as 3-alkylidene-2-oxindoles is also highlighted. Among cyclic and acyclic vinylogous nucleophiles, particularly 3-alkylidene-2-oxindoles have shown great potential as nucleophiles for providing a functionalized indole or oxindole containing backbones. In this chapter, we have demonstrated the reaction can create highly functionalized vinylic scaffolds in regio- and stereoselective manner. Synthetic utility of the developed Michael adducts is exemplified by common synthetic transformations.

In **chapter 4**, formal [3+3] annulation of 3-alkylidene-2-oxindole with β,γ–unsaturated α–keto esters have been described for the diastereoselective synthesis of spirocyclohexene-oxindole. Numerous bioactive alkaloid natural products and pharmaceutically important compounds containing spirocyclohexene(-ane) oxindole core with a quaternary stereo center at the C3 position is shown. Also described the synthetic route for synthesis of cyclohexene-oxindole. This chapter discloses a novel route for the construction of these scaffolds in high yields and excellent selectivity through [3+3] cycloaddition reaction with DABCO as an organocatalyst. We have reported a preliminary bioactivity studies of these compounds that suggests its strong anti-cancer property.