Introduction
Chirality is a key factor in the efficacy of many drugs and agrochemicals.\textsuperscript{1} Natural predisposition for shape and handedness in molecular binding by receptors, pumps, and enzymes has been recognized as essential principle for effective drug design.\textsuperscript{2} Increasing importance of chiral species in biological and pharmaceutical chemistry has resulted in a great surge of interest in:

i. Environment friendly and economically feasible methods for synthesis and

ii. Development of accurate and convenient methods for measuring enantiomeric purity and absolute configuration of chiral compounds.

This thesis describes the results of our efforts in targeting these two important issues. The thesis, for convenience, has been divided into two parts. Part I, new biocatalyst for nitrile hydrolysis, deals with biocatalytic approach to nitrile hydrolysis. Biological catalysts have emerged as one of the leading technologies in the area of green chemistry.\textsuperscript{3} Biocatalysis reinforces and widens the options available to process research and development chemists in their quest for cost-competitive processes to manufacture key intermediates along with reducing the environmental impact.\textsuperscript{4} Both the increased focus on the synthetic power of nature by chemists, and the increased mechanistic and structural interest of biologists and biochemists, will surely increase the importance of bioconversions in years to come.

Commercial success of hydrolytic enzymes\textsuperscript{5, 6} in past two decades resulted in intensive search for the next generation hydrolytic biocatalysts especially for nitrile hydrolysis, as illustrated by the growing number of articles dealing with development and application of nitrile hydrolyzing biocatalysts.\textsuperscript{7-11} Nitriles are versatile intermediates in organic synthesis, because they can be transformed to amines, amides, carboxylic acids, carbonyl and other compounds. Due to the favourable economics of their preparation, nitriles are attractive starting points in fine chemical manufacturing. Biocatalyzed hydrolysis of nitriles provides a greener alternative to the chemical methods that employ strong acids and bases as catalysts, which are often incompatible with sensitive structures of pharmaceutically relevant compounds and fine chemicals. An additional advantage over chemical hydrolysis is in terms of high regio- and enantioselectivity. Nitrile-hydrolysis is due to the activity of one of two enzyme systems, nitrilase or nitrile hydratase (NHase) plus amidase.
Although few commercial processes that utilize nitrilase and nitrile hydratase exist but so far, the popularity of biocatalytic routes compared to chemical routes has remained rather low. Lack of availability of stable strains or enzymes ready for use for a new product has been a major issue, which has prevented widespread use of the biocatalysts in process chemistry. Wide application of biocatalysts requires that they are robust, commercially available and specific, yet sufficiently general to be applicable to most classes of compound. The objective of this part of study was to isolate and characterize a new microbial biocatalyst for nitrile hydrolysis.

Part II, novel chiral solvating agents for NMR enantiodiscrimination of cyanohydrins, deals with development of accurate and convenient methods of measuring enantiomeric purity and absolute configuration of cyanohydrins. The most common methods employed in the literature have been optical rotation and chiral HPLC. NMR is a useful and convenient technique to complement or provide an alternative to optical rotation and chiral HPLC for evaluation of enantiomeric purity.\textsuperscript{12,13}

Chiral cyanohydrins are of synthetic interest as they can be transformed into a number of key functional groups including \(\alpha\)-hydroxy acids, \(\alpha\)-hydroxyketones, \(\beta\)-hydroxy amines, \(\alpha\)-amino nitriles, \(\alpha\)-hydroxyesters or \(\beta\)-amino alcohols, among others under conditions that conserve high optical purity. Enantiomerically enriched cyanohydrins have emerged as versatile synthons and many high yielding chiral catalysts and enzymes have been described for asymmetric synthesis of cyanohydrins.\textsuperscript{14,15} Therefore, a facile, accurate and convenient method is required for determining their enantiomeric purity and assigning absolute configurations.

Although there were few examples of use of chiral derivatizing agents and solvating agents for determination of enantiomeric excess of cyanohydrins, there was no thorough study available for enantiodiscrimination of cyanohydrins; that can be used for assigning absolute configuration until 2006 when Louzao \textit{et al.} established first derivative based method.\textsuperscript{16} In this report, rigorous validation on MPA esters of aldocyanohydrins was done for determining absolute configuration. The method suffers from typical drawbacks of a derivatization method, viz., chances of resolution and racemization during derivatization and difficulties in recovering cyanohydrin after the analysis. Also, the ketocyanohydrins were not studied in this report.
The NMR method developed by us for determination of e.e. and absolute configuration of cyanohydrins (i) does not require any derivatization and (ii) it is applicable to both aldo and ketocyanohydrins. At the time, we started our work; no NMR based method was available for ketocyanohydrins. However, a method appeared from Louzao et al. in 2009\(^{17}\) almost in parallel with publication of our results.\(^{18}\) Moreover, the method of Louzao et al. again required a derivatization step.

Part I and II are further divided into two chapters each. In each part, Chapter 1 is a mini-review and Chapter 2 describes the results and discussion.

References


