1
Introduction

1.1 Motivation

For an effective and sustainable organic synthesis, catalysis is crucial. Nested between catalysis and supramolecular chemistry, supramolecular catalysis is now a recognized discipline. It is one of the fields of chemistry that is expanding the fastest and has had a significant impact on the creation of many cutting-edge ideas. Excellent instances of selective and effective catalytic transformations carried out by enzymes, metabolons, organelles, and even cells may be found in nature. Historically supramolecular architectures found inspiration from nature especially the examples of biological species such as the DNA double helix and the structures of proteins. (Shakhnovich et al., 1996, Klug, 1983) The supramolecular organization is essential in each of these cases. Nature is the maestro of self-assembly as it creatively utilizes a variety of weak forces and non-covalent interactions and by this fact, nature has been a huge source of inspiration for researchers working on supramolecular catalysis and supramolecular chemistry in general is therefore not surprising.

1.2 Supramolecular chemistry

Supramolecular chemistry, as defined by Lehn in the 1970s is "***chemistry beyond the molecule***"(Lehn, 1979) Supramolecular chemistry is a novel area of study that has emerged quickly from pure synthetic chemistry. Its novelty has encouraged interdisciplinary collaboration between physical, organic, inorganic, and biochemistry as well as with other branches of chemistry. Supramolecular chemistry primarily studies the weaker intermolecular interactions that led to several components associating and self-organize to form larger aggregates, it primarily studies the covalent bonding of atoms as shown in **figure 1.1** (Seel and Vögtle, 1992). The selective binding of alkali metal cations by crown ethers and cryptands, which are macrocyclic and macropolycyclic ligands found in nature and synthetically, marked the beginning of the supramolecular field. As a result, molecular recognition a new field of study emerged and became supramolecular chemistry(Lehn, 1993). Molecular recognition necessitates the storing and retrieval of molecular structure information at both the molecular and supramolecular levels. Numerous receptor molecule types, including calixarenes, cyclophanes, cryptophanes, spherands, cavitands, and crown ethers, have already been studied. A further important area of research lies in the development concerned with the design of supramolecular devices built on photoactive, electroactive, or ionoactive components, that operate with photons, electrons, and ions, respectively. Thus, it is possible to envision a wide range of photonic devices. Electrons and ions can pass through membranes due to molecular wires, ion carriers, and channels. These functional entities are gateways into the fields of molecular photonics, electronics, and ionics. They can be applied to molecular and supramolecular materials that can be used for storage and processing and the transfer of materials, signals, and information at levels(Böhmer, 1995). (Homden and Redshaw, 2008)

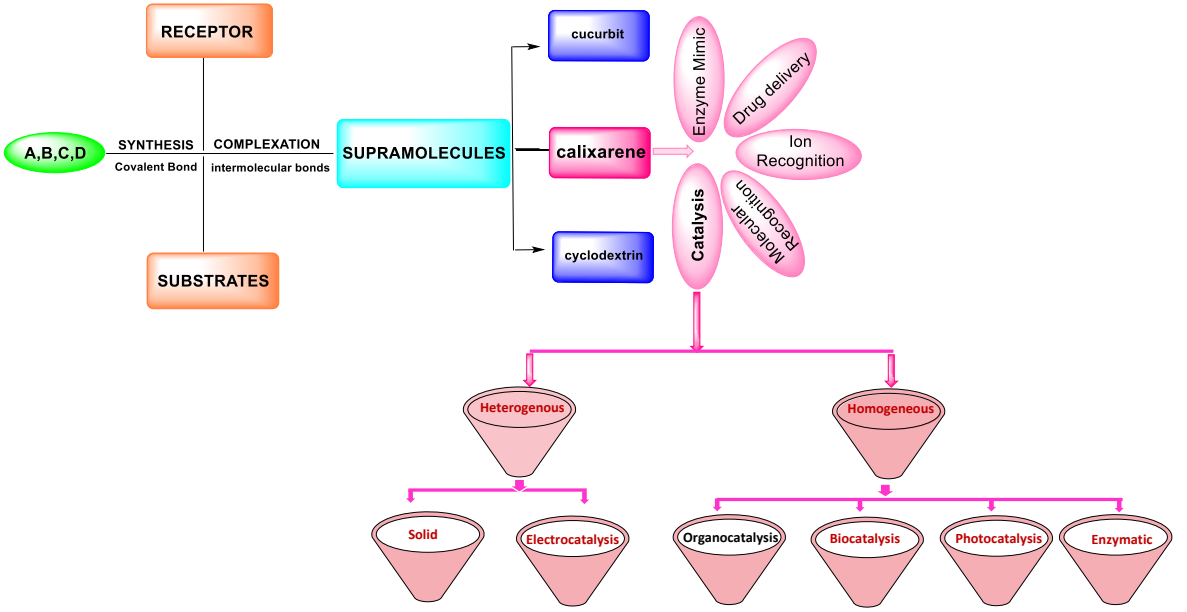


Figure 1.1 From molecular to supramolecular chemistry

The latest advances relate to the application of molecular information and recognition to regulate the evolution of supramolecular species during their construction from their constituent parts. Therefore, self-organization exists beyond the preorganization utilized in the synthesis of molecular receptors. It entails designing systems that, under specific circumstances, can self-assemble from their constituent parts to spontaneously produce well-defined supramolecular structures. (Rebek, 2000) The primary goal of supramolecular chemists is to create molecular structures that mirror the intricate functions of natural substances to achieve enantioselectivity in reactants and products via supramolecular chemistry and a variety of methodologies are being discovered. Catalysis involves the entire arsenal of supramolecular forces whether it is homogeneous, heterogeneous, or biocatalysts. In supramolecular chemistry, supramolecular forces bring together parts of the attaching molecule. Supramolecular interactions that play a role in catalysis are hydrogen bonding, π–π stacking, hydrophobic interactions, anion–π interactions, cation–π interactions, Lewis-acid metal–ligand interactions, ion–dipole interactions, cation–anion attractions, Dewar–Chatt–Duncanson metal–ligand interactions, van der Waals interactions, and charge–transfer interactions. (**Figure 1.2**). This thesis deals with the three main areas of supramolecular catalysis: the construction of catalysts via supramolecular interactions, substrate-catalyst interactions via supramolecular and non-covalent forces, and catalytic reactions. We will also consider ionic interactions, hydrogen bonding, and pi-pi interactions that are often involved in asymmetric transformations.

In the last decades, supramolecular catalysis has been in focus as it can bridge the gap between supramolecular chemistry and asymmetric catalysis. The combination of the supramolecular catalysts with a chiral moiety leads to multifunctional asymmetric catalytic systems. In this context, calix[n]arenes a renowned class of macrocyclic compounds that are being used for the design of molecular receptors, organocatalysts, and phase transfer catalysts due to their particular three-dimensional shape and ease of functionalization.

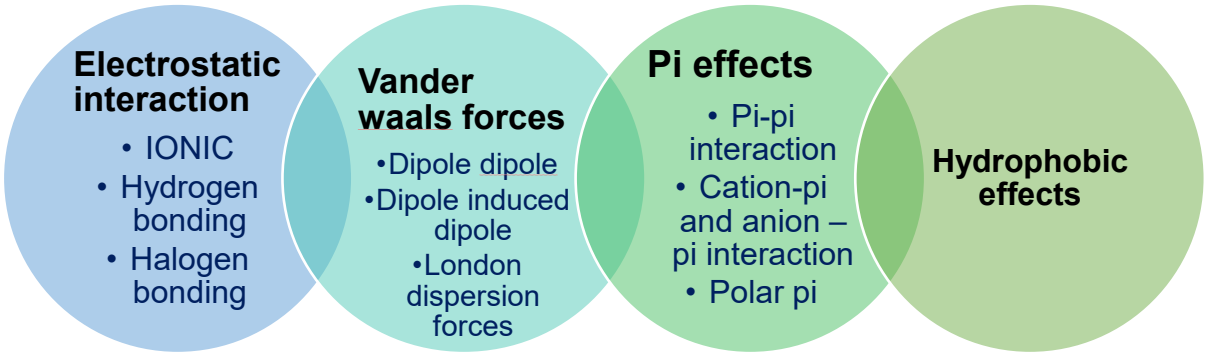


Figure 1.2 Non covalent interactions

1.3 History of Calix[4]arenes

Calixarenes are macrocyclic compounds and in 1941, Zinke discovered it while looking for a more straightforward phenol-formaldehyde condensation product. The phenol-formaldehyde chemistry was pioneered by Adolph Von Baeyer, he discovered a cement-like substance in 1872 though he was unable to obtain the pure substance yet he gave some structural insights. Further, Leo Hendrik Baekeland established that by using a controlled amount of base a polymer material Bakelite was achieved by condensation of phenol and aldehyde. L Lederer and O Manasse studied the based-induced reaction of formaldehyde with phenol and succeeded in isolating o-hydroxy-methyl phenol and p-hydroxy-methyl phenol as well defined-crystalline solids. In 1970 Gutsche and coworkers first coined the term "calixarene". The word calixarene is derived from the Latin word for chalice or cuplike and arene indicates the presence of the aryl rings. They developed a simple and reproducible procedure for synthesis of calix[4]arene (**figure1.3**) in good yields (Gutsche and Muthukrishnan, 1978; Gutsche *et al.*,1986) The calix[4]arenes offer a flexible framework for creating many structures with potentially valuable host-guest features as compared to naturally existing host molecules such as cyclodextrins. This family of compounds is a competitive candidate for research on the interactions involved in catalysis as well as valuable receptors due to their accessibility and selective functionalization on calix rims. Calixarene's molecular structure can be harnessed as a flexible molecular platform for the dynamic configuration of one or more structural units that can act as recognition and /or catalytic sites.(Atwood, 2017) . It can be used in asymmetric recognition as it can be modified to form chiral receptors and catalysts, Also the presence of a cavity and the unique property of host-guest binding capability makes them available for catalysis. Cram and co-workers initiated the use of macrocycles as phase transfer catalysts. They can be easily transformed into a variety of derivatives with different functional groups including ketone, amine, ester, amide, alcohol, ether, carboxylic acid, crown ether, and others. These molecules' propensities for catalysis are influenced by the calix[n]arenes ring size, the types of groups attached, the number of donor atoms, and the macrocyclic conformation.

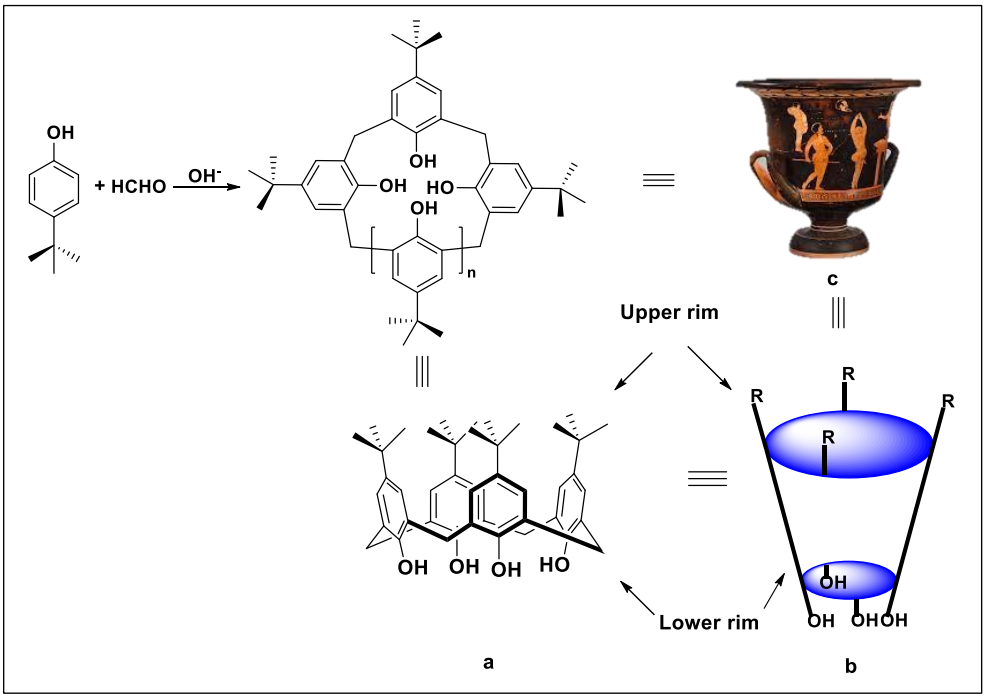


Figure 1.3 Cyclic condensation of *p-tert* butyl phenol with formaldehyde resulting in the formation of calixarenes. The 3D representation of calix[4]arenes with an indication of the nomenclatures used to identify the two rims, (b) the CPK model, and (c) the Greek vase that inspired their name.

1.4 Conformations of Calix[4]arene

Calix[4]arene can exist in four different conformations depending upon the substituent present at the lower rim as well as at the upper rim. Conformations can differ for the orientation of each aryl group, which can project upward (u) or downward (d) with respect to an average plane defined by the methylene bridge carbon atoms. These conformations have been named by Gutsche as a cone (u,u,u,u), partial cone (u,u,u,d), 1,3-alternate (u,d,u,d), and 1,2-alternate (u,u,d,d), At room temperature, all four isomers are found in equilibrium and theses isomers can be easily identified through their ^{1}H and ^{13}C NMR spectra**. (figure 1.4)**(Gutsche, 1983). Cone conformation is favored in solution because of strong intramolecular hydrogen bonding present between the presence of four OH groups present at the lower rim.

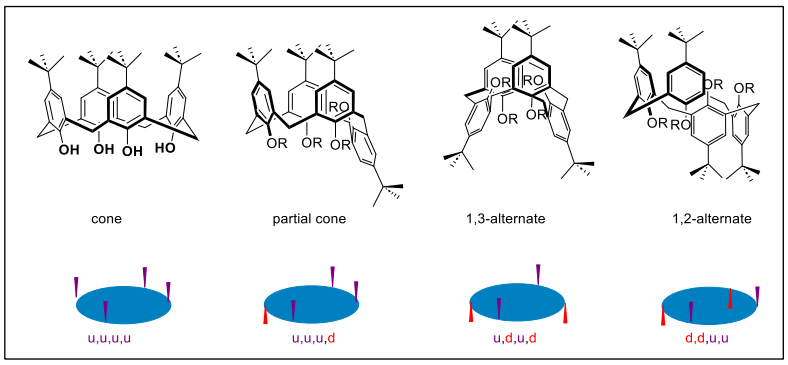


Figure 1.4 The four conformation of calix[4]arene and their symbolic representations

1.5 Chirality in Calix[4]arene

Calixarenes can be made chiral either by adding the chiral substituents to the lower or upper rim or by synthesizing inherently chiral derivatives that take advantage of the molecule's non-

planarity (**Figure 1.5)** In general, more challenging synthesis techniques and a difficult resolution are observed for inherent chiral calixarenes whereas attaching the chiral moieties to either on upper or lower rim is beneficial because enantiomerically pure derivatives can be obtained relatively easily. Therefore, chiral calix[4]arene derivatives not only supply a controlled means for studying the fundamentals of non-covalent interactions, but also provide new directions for expanding upon novel enantioselective sensors, asymmetric catalysts,(Gaeta et al., 2005, Marson et al., 2007) selectors, and other molecular devices. (Kim et al., 2004). Calix[4]arene is currently stimulating the study of catalysis, which operates by harnessing the various intramolecular interactions resulting in the emergence of calix[4]arene-based asymmetric catalysis.

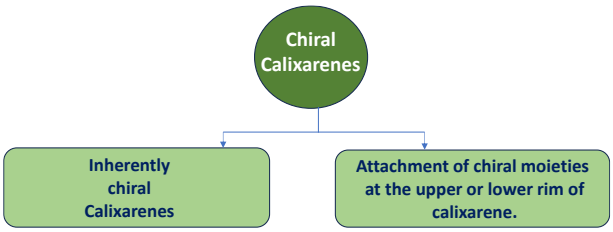


Figure 1.5 Pathways for the formation of chiral calixarenes

1.6 Asymmetric catalysis

Chiral calixarenes have attracted much attention because of their potential as enantioselective artificial receptors and asymmetric catalysts. The use of chiral supramolecular catalysts with multiple functional groups is less explored. Here selective functionalisation is crucial. Highly reliable and only chiral catalysts can be employed in such situations. Asymmetric catalysis is a challenging but exciting area of endeavor ability to control the generation of nearly identical chemical compounds and has captured the imagination of many outstanding researchers(Walsh and Kozlowski, 2009) Asymmetric catalysis the field essentially didn't exist too long ago. For instance, Sorensen and Nicolaou in the late 1990s precisely stated the definition of asymmetric catalysis in their outstanding book ''Classics in Total Synthesis'' stating that "*In a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral*." An intrinsic part of asymmetric synthesis is asymmetric catalysis which is dedicated to the synthesis and use of enantioriched catalysts to convert prochiral and racemic substances into chiral building which are valuable for synthesis. This perspective has now changed and it is now evident that modern asymmetric catalysis is built on three rather than two pillars, namely biocatalysis, metal catalysis, and organocatalysis. Organocatalysis is a form of catalysis, whereby the rate of a chemical reaction is increased by an organic molecule referred to as an "organocatalyst" consisting of carbon, hydrogen, sulfur, and other nonmetal elements. The two primary roles of the organocatalysts are to either activate the nucleophile or the electrophile (or both in the case of bifunctional catalysis) or to produce an asymmetric environment that determines the chirality. Organocatalysts can be categorized as covalent or non-covalent catalysts based on how they interact with the substrate or on their mode of action. Covalent catalysis increases the interaction between the substrate and the reagent and when the catalyst and the substrate interact non-covalently, Hydrogen bonds, and ionic interactions (e.g., chiral bases such as cinchona alkaloids and phase-transfer catalysts) are used to activate the substrate. Organocatalytic procedures are particularly appealing for the synthesis of molecules that do not tolerate metal contamination, such as active medicinal compounds. (Alemán and Cabrera, 2013) Calix[4]arene have been explored as an organocatalyst for various organic transformation

Phase transfer catalysis (PTC) has been introduced to perform the reaction for more than 5 decades. The term "Phase-Transfer Catalysis" (PTC) was first introduced by Starks in 1971 to define and explain the required presence of tetraalkylammonium or phosphonium salts (in the

form Q^+X^-) for promoting reactions between reagents located in immiscible phases (Starks, 1971) Depending on the chirality of the quaternary ammonium cation Q^+, PTC can be divided into symmetric and asymmetric catalysts. Significantly, PTC can swap out pricey solvents and hazardous bases that are under anhydrous conditions for inexpensive aqueous bases with eco-friendly and easily recyclable solvents. Phase-transfer catalysis (PTC) has been recognized as a dynamically developing field of organic chemistry as it enhances the rate of reaction between the substrates which are present in different phases. The primary and simple method for the production of enantiopure materials is often reaction systems catalyzed by a single catalyst. Many organocatalytic processes are well understood from their fundamental activation modes. Experimentally and theoretically, reaction routes from precursors to intermediates have been identified, enabling logical predictability for the completion of organocatalysis. The use of appropriate and compatible catalysts is essential for easy preparation, modification, and alteration of the catalyst backbone.

1.7 Objectives Of Thesis

1. To develop a series of homogeneous catalysts that possess specific features such as low cost, high activity and selectivity, recyclable, and their application in several important asymmetric catalytic reactions.
2. Preparation of highly optically pure compounds using designed new asymmetric catalytic processes.
3. Understanding chirality transfer and plausible reaction path.

1.8 Organisation Of Thesis

Chapter 1: Introduction
This chapter explores the motivation of this study. It explains the history of calixarenes and its applications in various fields
Chapter 2: Literature Review
This Chapter covers the literature survey of calix[4]arene based on various applications and the asymmetric reactions catalysed by calixarene catalysts
Chapter 3: Catalyst synthesis and characterisation
This chapter deals with the synthesis scheme of calix[4]arene appended phase transfer catalysts and organocatalysts.
Chapter 4: Asymmetric Michael Addition
This chapter addresses the application of prepared homogenous catalysts based on cinchona. Cinchona-based catalyst is used for asymmetric Michael addition of acetylacetone to nitroolefins also the mechanistic aspect is explained via DFT.
Chapter 5: Asymmetric alkylation reaction
This chapter deals with Cinchona-functionalized crown ether-strapped calix[4]arenes as PTCs for asymmetric α-alkylation of glycine imines to α-alkylated glycinates.
Chapter 6: Asymmetric Henry reaction
This chapter deals with a highly selective α- methylbenzylamine functionalized crown-ether-appended calix[4]arene derived phase transfer catalyst for asymmetric nitroaldol reaction to provide the desired nitroaldol adducts also the mechanistic aspect is discussed.
Chapter 7: Asymmetric Strecker reaction
This chapter deals with a highly selective camphor sulfonyl functionalized crown-ether-tethered Calix[4] arene-derived organocatalyst for asymmetric Strecker reaction to provide the desired cyano adducts in high yields and enantioselectivities. Furthermore, two step synthesis of the antiplatelet drug S-Clopidogrel exemplifies the potential of this method for the preparation of commercial compounds
Chapter 8: Summary and Future Directions
This chapter concludes the work of the thesis.

The important research articles, reviews, book chapters that are being used as references are listed in the reference section.