

ORGANOCATALYSIS: KEY TRENDS IN GREEN SYNTHETIC CHEMISTRY,
CHALLENGES, SCOPE TOWARDS HETEROGENIZATION AND
IMPORTANCE FROM RESEARCH AND INDUSTRIAL POINT OF VIEW

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(A peer reviewed book)

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Dedicated to my Mother

Some holy text and people say, “Mother is the precious person in our lives, to the extent that even Heaven can be placed metaphorically under her feet.” I experience the same. Caring is one of the important aspects of love; it has the power of healing. I give many thanks to my Mother (Mrs. *Ahmedbee R. Shaikh*) for taking care of me. Author: Isak R. Shaikh

“Love begins by taking care of the closest ones - the ones at home.” – Mother Teresa

FOREWORD

This is the first time in my 27 year career that I have written a foreword and, I'm proud to say that this is one of the most in-depth, multi-dimensional review works of scientific literature and researches. I have spent a lot of time reading firstly the introductory-cum-tutorial part and analyzing how the author has approached the subject of catalysis, the classical classifications, examples, etc. This part, I am sure, will help undergraduates and post-graduates including early researchers learn the concept. In the later part, the author has elaborated on how the organocatalysis has revolutionized asymmetric synthesis and also on how the key trends in organocatalysis might influence the green chemistry research. His vision of greening chemical processes at industries is clearly understood from the book. I understand from the *biography of the primary author* that apart from being a chemistry researcher, Mr. Isak Rajjak Shaikh is actively engaged in science communication. I quote, "He ensures teaching and research through philosophical-transactions as the core values of his philanthropy." I had opportunities to interact with the primary author during my stay in South Korea and also here in the National Chemical Laboratory (NCL), India. I understand from his discussions with me that he (the author) has realized the commercial importance of catalysis and the diverse challenges the subject has stimulated over the recent times. Increasing activities of research on organocatalysis has brought deeper levels of understanding, and these have been confirmed by a continually growing amount of published material. The author is gifting such scientific literature, his research and perspectives - important academically and industrially, to the readers for free. I think you will find this quite informative and thought provoking!



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PREFACE

Chemistry lies at the very heart of everything within us and around us. Its knowledge and the chemical methods steadily increased over the centuries. In spite of the long history of the use of chemical methods, the *science* of catalysis was conceptualized one and half century ago. Right from the inception of the term catalysis, its knowledge and the chemical methods steadily increased over the years. There are two complementary principles at the core of chemistry: (i) the act of creation, combining, or synthesis, and (ii) the act of analysis, characterization, destruction or separation. These chemical techniques were continuously modified and refined and, as a result, catalysis became more manifold and powerful.

Friherre Jöns Jacob Berzelius coined the term “*catalysis*,” recognizing that a single concept could account for changes in compositions of numerous substances resulting from their mere contact with liquids, solids or “ferments”. Berzelius’ insight bears on phenomena that had earlier puzzled the al-chemists, (studying Alchemy; word origin:-Arabic:*al-kimia*; Greek:*chimia* is both a philosophy and a pseudoscientific practice with an aim of achieving ultimate wisdom as well as immortality), who also aware of the mysterious actions of these “ferments” and other substances (“contacts”), sought unsuccessfully for a philosopher’s stone to change base metals into gold. William Ostwald was the first to write down a definition of catalyst (year 1865): ‘A *catalyst is a substance that changes the rate of a chemical reaction without itself appearing in the products*’. Ostwald’s definition of catalysis rests on reaction kinetics and, indeed, at about the time he stated it, the beginnings of physical chemistry were emerging in the quantitative representation of thermodynamics and kinetics of chemical reactions.

Today, the growing need for the atom efficiency, energy efficiency and environmental concerns stemming from the increase in chemical products demand necessitate the development of the ‘sustainable or environmentally benign’ production methods. In this context, ‘green’ processes can be described as chemical conversions that consume a minimal amount of energy and produce the least waste. Catalysis is a key solution to this problem. Therefore, nowadays, almost 70% of all chemicals that are produced have been in contact with a catalyst somewhere in their synthesis process. This number stresses the importance of the role of catalysis in the chemical industry. Without a catalyst, processes are less selective and sometimes impossible to perform.

Catalysis at an interface (usually a solid surface) is called *heterogeneous catalysis*; it means that more than one phase is present in the reactor i.e. for example, a gas or liquid in contact with a solid. The *catalysts* and their applications are fascinating and significant concepts in science, and *catalyst* is one of the few words that have carried over broadly outside scientific language. A catalyst works by interacting with reactants, generating intermediates that react to give products. It affects the rate of approach to equilibrium of a reaction but not the position of the equilibrium. It also provides subtle control of chemical conversions; increasing the rate of a desired reaction pathway but not the rates of undesired side reactions (i.e. the selectivity of a chemical process). Heterogeneous catalysis is an applied science, which could help us shift towards sustainable chemical technology in order to overcome great scientific, economic, and technological challenges.

Asymmetric catalysis constitutes one of the most important subjects in synthetic organic chemistry. Asymmetric synthesis achieving atom economy is a challenge for organic synthesis and homogeneous catalysis using metal complexes leads the way. But the application of such methodologies in chemical industry is rather limited due to the high cost of chiral ligands and noble metals used in such transformations. Moreover, the pharmaceutical entities and food industry products do not tolerate a contamination, of even traces, of any such metals for that matter. Synthesis of chiral drugs has a major financial impact in pharmaceutical industries on a global scale. Different enantiomers or diastereomers of a molecule often have different biological activity. Most of the drugs might be soon sold as single enantiomers in the coming years. There is a huge demand for metal-free catalysts leading to 100% yield 100% ee of the desired product. The need from chemical industry, especially pharmaceutical, for reliable asymmetric transformations of molecular skeletons is higher than ever. Therefore, (asymmetric) organocatalysis is in a process of attaining maturity into a very powerful, practical and broadly applicable methodological approach in the catalytic asymmetric synthesis. The term “organocatalyst” is a concatenation of the words “organic” and “catalyst.” The organocatalyst could be achiral or chiral and could be composed of C, H, N, S and P. Organocatalysis has several advantages not only because of its synthetic range but also for the economic reasons. The absence of metal in organocatalyst brings an undeniable advantage considering both the principles of "green chemistry" and the economic point of view. Importantly, readers who have remarkably wide interdisciplinary interest will be motivated to investigate structure, stereochemistry, function and mechanisms involved in biomolecules or biologically active molecules for their catalytic activity in life processes.

This book purports to review the origin, key trends, challenges, examples, scope and importance of organocatalysis. As mentioned earlier, the definition of organocatalyst corresponds to a low molecular weight organic molecule which in sub-stoichiometric amounts catalyzes a chemical reaction. The use of the term *heterogenized organocatalyst* herein will be exclusively confined to a catalytic system containing an organic molecule immobilized onto some sort of support material and is responsible for accelerating a chemical reaction. Firstly, a brief description of the field is provided putting it in a green and sustainable perspective of chemistry. Next, research findings on the use of organocatalysts on various inorganic supports including nano(porous)materials, nanoparticles, silica, zeolite/zeolitic materials, etc. will be scrutinized. Then future scope, research directions, academic and industrial applications will be outlined. A succinct account will summarize some of the research and developments in the field of organocatalysis.

The general scope of the book is thus to bring many outstanding researches together and shows the vitality of the organocatalysis through several aspects and also to offer suggestions for new and innovative directions of research as well as scope for incorporating perspectives on teaching “organocatalysis” to chemistry graduate and post-graduates. I believe, in fact, that heterogeneous organocatalysis is not a mature field of research and that important breakthroughs can be derived through basic research, but that these advances will only come about through less conventional approaches in terms of both theory and applications.

In a religious book, it is written that God has created human being from sounding clay, and also that the clay (carbon) and water are the basic

components of life. Billions of years ago, the early Earth was unsuitable to host “*pre-biotic*” soup of carbon-based (organic) chemicals and also the *life as-we-know-it*. This is because it is impossible to explain how atoms first came together to make up the three crucial molecular components of living organisms: DNA, RNA, and proteins. Organocatalysis played a determinant role in the formation of pre-biotic key building blocks, such as sugars: researchers [S. Pizzarello and A. L. Weber *Science* 303 (2004) 1151] reported that L-isovaline, found in the Murchison meteorite, catalyzes the self-aldol reaction of glycolaldehyde in water, generating aldol products such as l-threose and d-erythrose. New research by Professor Steven Benner (Speaker at: Goldschmidt Conference 2013, Florence, Italy) suggests that life was transported to the planet earth on meteorites. This therefore leaves us with an evidence to believe that it is more likely that life came to Earth small-organic molecules and minerals on meteorite, rather than starting on this planet. I therefore believe that apart from the potential *green chemistry* (by now, we know what this means) applications of organocatalysts in industries, there is a lot of scope for research (i) in the field of organo catalysts for in understanding the pre-biotic chemistry, (ii) role of organic-inorganic hybrid materials in various bond formations, (iii) synthesis, structure, mechanism and applications of organic molecules useful in God’s chemistry, I mean, biological products and processes.

“ORGANOCATALYSIS: KEY TRENDS IN GREEN SYNTHETIC CHEMISTRY, CHALLENGES, SCOPE TOWARDS HETEROGENIZATION AND IMPORTANCE FROM RESEARCH AND INDUSTRIAL POINT OF VIEW” accounts the chemistry behind the “catalytic magic” of small organic molecules. Many topics in chemistry and catalysis are treated in this book, with relevant references giving the brief on research and development of the underlying science and relating it to catalytic

practice and industrial point of view. I believe that these approaches provide a collection that are of value to academic, research and industrial personnel. I welcome comments, criticism and additions on this draft and suggestions of topics for future volumes. I hope that your work will go beyond this book.

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Abstract:

This manuscript purports to review the origin, key trends, challenges, examples, scope and importance of organocatalysis. The definition of organocatalyst corresponds to a low molecular weight organic molecule which in sub-stoichiometric amounts catalyzes a chemical reaction. In this review, the use of the term *heterogenized organocatalyst* will be exclusively confined to a catalytic system containing an organic molecule immobilized onto some sort of support material and is responsible for accelerating a chemical reaction. Firstly, a brief description of the field is provided putting it in a green and sustainable perspective of chemistry. Next, research findings on the use of organocatalysts on various inorganic supports including nano(porous)materials, nanoparticles, silica, zeolite/zeolitic materials, etc. will be scrutinized. Then future scope, research directions, academic and industrial applications will be outlined. A succinct account will summarize some of the research and developments in the field of organocatalysis. This review tries to bring many outstanding researches together and shows the vitality of the organocatalysis through several aspects.

Keywords: catalysis; organocatalyst; heterogeneous organocatalysis

1. Introduction

In 1987, the United Nations Commission on Environment and Development (Brundtland Commission)¹ defined “sustainable development” as the development that meets the needs of the present without compromising the ability of future generations to meet their own needs. Two of the key aspects of sustainable development from an energy and chemical perspective are to develop more renewable forms of energy and to reduce pollution. Chemistry during the twentieth century changed the living standard of human beings. Among the greatest achievements of chemistry are petrochemical and pharmaceutical industries. But, these industries are often blamed for polluting environment. The challenge for the present-day chemical industry is to continue providing applications and socio-economic benefits in an environmentally friendly manner. Over the last few decades, green chemistry has been recognized as a culture and methodology for achieving sustainable development.² Green chemistry is chemistry able to promote innovative technologies that reduce or eliminate the use or generation of hazardous substances. P. C. Anastas defined the 12 principles of green chemistry (Figure 1).³ Catalysis (including enzyme catalysis, heterogeneous catalysis and organocatalysis, in particular) is identified to be at the heart of *greening of chemistry* ⁴ because this branch of science is found to reduce the environmental impact of chemical processes.⁵

2. Catalysis – a multidisciplinary area of chemistry

Catalyst is one of the few conceptual words that have carried over broadly outside scientific language. Catalysis is a significant multidisciplinary area of chemistry. The term “catalysis” was first introduced in 1836 by Berzelius who tried to explain special powers of some chemical substances capable of influencing various decomposition and chemical transformations. According to Ostwald (1895), “*a catalyst accelerates a chemical reaction without affecting the position of the equilibrium.*” A catalyst works by interacting with reactants, generating intermediates that react to give products. It affects the rate of approach to equilibrium of a reaction but not the position of the equilibrium (Figure 2). Most of the times, it also provides subtle control of chemical conversions; increasing the rate of a desired reaction pathway but not the rates of undesired side reactions (i.e. the selectivity of a chemical process).

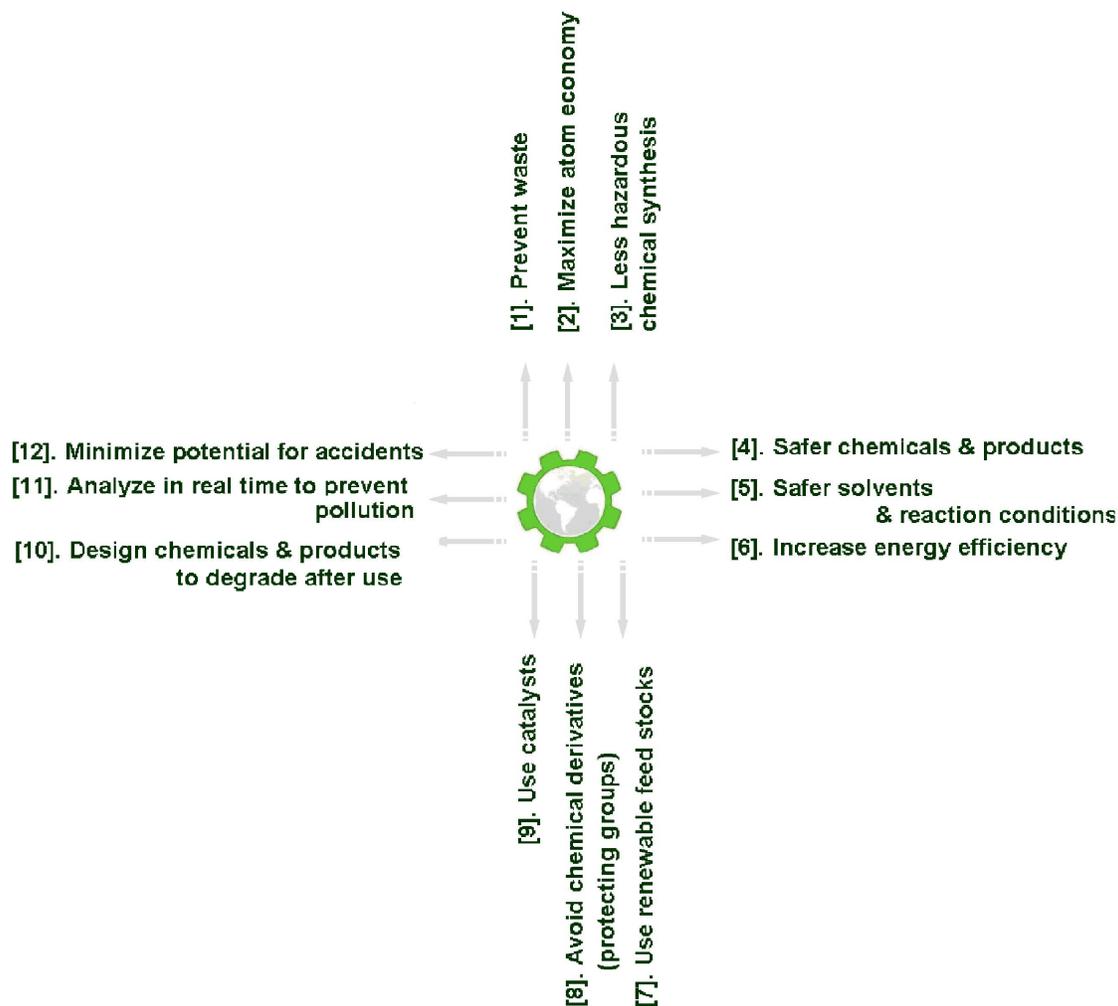


Figure 1. Inspired by *the 12 principles of green chemistry*; from *Green Chemistry: Theory and Practice*, Oxford University Press (1998) Authors: P. T. Anastas & J. C. Warner

Catalysts are usually classified according to structure, composition, area of application, or state of aggregation. According to the state of aggregation in which the catalysts act, there are two main groups: homogeneous catalysts and heterogeneous catalysts. Homogeneous catalysts are well-defined chemical compounds or coordination complexes, which, together with the

reactants, are molecularly dispersed in the reaction medium and carry out processes in a uniform gas or liquid phase. Heterogeneous catalysis takes place between different phases. Generally the catalyst is in solid state, and the reactants are gases or liquids. In between are the immobilized catalysts obtained by attaching homogeneous catalysts to solid. In supported catalysts the catalytically active substance is applied to a support material that has a large surface area and is usually porous. Arguments for and against shall always be made while discussing the merits and limitations of individual groups of catalysts for their respective applications in industries.

3. Application of Catalysis

Catalysis has played a pivotal role in the success of the chemistry industry in the twentieth century. More than 90% of chemical manufacturing processes in the world utilize catalysts.^{6,7} Historically, the first industrially applied catalytic process was for the hydrogenation of oils and fats to produce margarine using finely divided nickel as catalyst. Thus, heterogeneous catalysis was applied first industrially. The issue of metal leaching and the avoidance of trace catalyst residues are very important from environmental health point of view. All the basic raw materials or building blocks for chemicals are manufactured by very important set of heterogeneous catalytic reactions (Table 1).⁷ Although catalysts are not consumed by the reaction itself, they may be inhibited, deactivated or destroyed by secondary processes. The solid-state catalytic materials are the most important type of catalysts.

Implementation of “clean” and “green” chemical technology in industries may help address the problem of environmental degradation besides producing useful chemicals.⁸⁻¹¹ Some catalysts also present important technology in the

prevention of emissions; e.g.: catalytic converter for automobiles. Keeping in mind the fragile ecosystem and the importance of preserving the environment, the heterogeneous catalysts are tested in the pollution abatement¹²⁻¹³ and to remove aqueous organic wastes, volatile organic compound and vehicular primary emissions such as CO, unburned hydrocarbon, NOx and soot.

Table 1. List of some of the industrially applied reactions and catalysts

Reaction	Catalyst	Inventor (Year)
Sulphuric acid (lead – chamber process)	Nox	Clement, Desormes (1806)
Chlorine production by HCl oxidation	CuSO ₄	Deacon (1867)
Nitric acid by NH ₃ oxidation	Pt, Rh nets	Ostwald (1906)
Fat hardening	Ni	Normann (1907)
Ammonia synthesis (H ₂ + N ₂)	Fe	Mittach, Haber, Bosch (1908); Production 1913 BASF
Hydrogenation of coal to hydrocarbons	Fe, Mo, Sn	Bergius (1913); Pier (1927)
Methanol synthesis from Co/H ₂	Zno/Cr ₂ O ₃	Mittach (1923)
Hydrocarbons from CO/H ₂ (motor fuels)	Fe, Co, Ni	Fischer, Tropsch (1925)
Alkylation of olefins to gasoline	AlCl ₃	Pines (1932)
Cracking of hydrocarbons	Al ₂ O ₃ /SiO ₂	Houdry (1937)
Cracking in a fluidized bed	Aluminosilicates	Lewis, Gilliland (1939)

Ethylene polymerization at low pressure	Ti compounds	Ziegler, Natta (1954)
Hydrogenation, isomerization, hydroformylation	Rh-, Ru complexes	Wilkinson (1964)
Asymmetric hydrogenation	Rh/chiral phosphine	Knowles (1974)
Three-way catalyst	Pt, Rh/monolith	General Motors (1974)
Methanol conversion to hydrocarbons	Zeolites	Mobil Chemical Co. (1975)
Alpha-olefins from ethylene	Ni/chelate phosphine	Shell company (1977)
Sharpless (epi)oxidation	Ti/ROOH/Tartarate	May, Baker, Upjohn, ARCO (1981)
Selective oxidations with H ₂ O ₂	TS-1 (titanium silicate)	Enichem (1983)
Hydroformylation	Rh/phosphine	Rhone-Poulenc-Ruhrchemie (1984)
Polymerization of olefins	Zirconocene / MAO	Sinn, Kaminsky (1985)
Selective catalytic reduction (SCR)	V, W, Ti oxides/monolith	1986

Heterogeneous catalysis which takes place between different phases has now grown into an important branch of science.^{7-11,14} Exciting new opportunities are emerging in this field based on nanotechnology approaches. Hence, research efforts are being directed to develop chemistry of nanomaterials and their applications in catalysis for developing cost-effective, selective, energy sufficient, eco-friendly and environmentally benign synthetic processes for industries. Though this involves a great scientific, economic, and technological challenge, it is essential to a sustainable and healthy way of life.

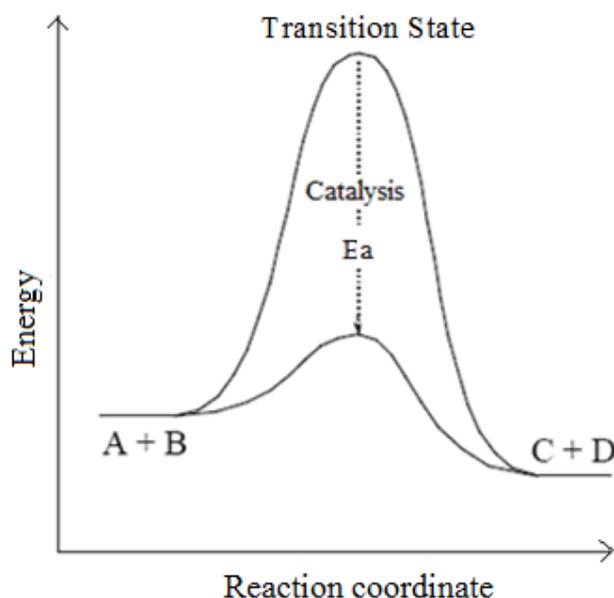


Figure 2. Schematic illustration of the effect of a catalyst on the transformation of A + B into C + D.

The petroleum, fine chemical and pharmaceutical industries mostly rely on catalysts to produce everything from natural gas/fuels to various commodities.¹⁴⁻¹⁵ There are a variety of new challenges in creating alternative fuels, reducing harmful by-products in manufacturing, cleaning up the environment and preventing future pollution, dealing with the causes of global warming, and creating safe chemicals and pharmaceuticals. Thus, catalysts are

needed to meet these challenges of health, safety and environmental, energy-related and economic issues, but their complexity and diversity demand an insight on the way catalysts are studied, designed and used. This could come into reality only through the application of an interdisciplinary approach involving new methods for synthesising and characterizing molecular and material systems. Research in heterogeneous catalysis demands the cooperation of scientists from analytical chemistry, solid-state chemistry, (nano)materials chemistry, physical chemistry, surface science, computational and theoretical chemistry, reaction kinetics & mechanisms, reaction engineering, etc. Opportunities to understand and predict how catalysts work at the atomic scale are now appearing, made possible by breakthroughs in the last decade in computation, measurement techniques, characterisation, spectroscopy, imaging and especially by new developments in surface-reactivity studies, model catalyst design, and evaluation.¹⁵⁻¹⁶ Surface science and spectroscopy has its prominent role in analysing surface reaction chemistry on the catalyst.¹⁷⁻¹⁸

Fermentation of sugar to ethanol and the conversion of ethanol to acetic acid catalyzed by enzymes was an example of catalysis in antiquity. Off late, enzymatic catalysis is considered as a separate branch of (biological) catalysis. It is the most recent branch widely included in many commercial applications.¹⁹⁻²⁰ Enzymes are also highly active under mild conditions such as temperature, pressure and pH, which make them easier to work with on a small scale; but are also more appealing on an industrial scale on a cost and efficiency basis. Another benefit is that reactions are preferentially carried out in aqueous media therefore providing a 'greener' route. Not to forget, the

development of water-based organic transformations is also an area of rapidly growing importance in chemistry.²¹⁻²²

The homogeneous catalysis prior to the recognition of the effects of heterogeneous catalysts started with the action of nitrous oxides in the lead chamber process. Although the fundamental processes for refining petroleum and its conversion to basic building blocks are based on heterogeneous catalysts, many important value-added products are manufactured by homogeneous catalytic processes (Table 2).¹¹ Homogeneous catalysts have been well researched, since their catalytic centers can be relatively easily defined and understood, but difficulties in separation and catalyst regeneration prevent their wider use.^{11, 23-27} The most widely used homogeneous catalysts are simple acids or bases which catalyze well known reactions such as ester and amide hydrolysis or esterification. The market share of homogeneous catalysts is estimated to be only ca. 10–15 %. Many of the benefits of homogeneous catalysts, especially high selectivity, arise from tailored made catalysts involving transition metals (or lanthanides) and appropriate ligands. Such catalysts are inexpensive enough that they can be neutralized, easily separated from organic materials and disposed of. This contributes to the huge quantity of aqueous salt waste generated by industry. Organometallic catalysts are currently widely used in industry, but the search for improved efficiencies, enantioselectivities, or recycling is still a matter of intense researches.²⁸⁻³² It is true that homogeneously catalyzed processes such as hydroformylation, carbonylation, oxidation, hydrogenation, metathesis, and hydrocyanation contribute with millions of tons to the bulk chemicals, but on the other hand the progress of homogeneous catalysis is also going on with fine chemicals.^{24, 32} In spirit of that, the beginning of this century saw the

renaissance of organocatalysis presenting an environmental advantage over metal-based catalysts for stereoselective or asymmetric synthetic methodologies. The absence of metal in organocatalyst brings an undeniable advantage considering the principles of "green chemistry" and the economic point of view (Table 3 & 4).

Table 2. Differences between homogeneous catalysts and heterogeneous catalysts

Homogeneous Catalysts	Heterogeneous Catalysts
same phase as reaction medium	Solid phase
difficult separation	easily separable
No recyclability	Recyclability and regeneration
often high rates of reaction	Low rates of reaction
No diffusion control	Diffusion control
Robust to poisoning	poisoning, de-activation
High selectivity	Low selectivity
short life	long catalytic life
Mild conditions	Energy-consuming process
Well understood mechanism	poor mechanistic understanding

Table 3. Comparison among Organometallic, Enzyme and Organocatalysts

Organometallic catalyst	Enzyme catalyst	Organocatalyst

wide substrate scope; high catalytic activity; involves tedious process; potential heavy metal pollution	limited substrate scope; high selectivity & catalytic activity; usually single enantiomer	robust; inexpensive; readily available; non-toxic; inert toward moisture and oxygen; method especially attractive for the preparation of compound that do not tolerate metal contamination (pharmaceuticals products)
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Table 4. Advantages and disadvantages of organocatalysts

Advantages	Disadvantages
Easy preparation or availability	high catalyst loading
Easy handling; inert towards moisture (water) and air(oxygen)	relatively pre-mature field
Easy scale-up	
no metal contamination	
easy screening	
useful in complex (steric) reactions	

Understanding catalytic systems involve study of structure, state and composition of catalysts and the phase in which they perform, And, for this,

one needs to understand chemistry of molecules and materials useful as catalysts and or catalyst carriers.

4. Materials for Catalysis

The diversity of research field connected to the chemistry of materials is significant for their applications in many areas including adsorption, catalysis, electrochemistry, surface science, etc. Nanoparticles,³³ metal oxide and mixed metal oxides³⁴⁻³⁷ prepared by simple methods are useful catalysts. Research involving metal-organic frameworks,³⁸⁻³⁹ mesoporous silica,⁴⁰⁻⁴² microporous or open-framework inorganic⁴³⁻⁴⁵ and or mesopore modified⁴⁶ materials have steadily increased following the widespread utility of aluminosilicate zeolites,⁴⁷⁻⁵⁰ titanosilicates⁵¹⁻⁵² and aluminium phosphates.⁵³⁻⁵⁴

In industries, research endeavours are mainly devoted towards the study and development of zeolites or zeolitic materials with several attractive features such as catalytic active site(s), large surface area, zeolitic pore walls, pore size control and so on. The synthesis and characterization of the crystalline aluminosilicate materials with tunable meso/microporosity and their strong acidity have potentially important technological implications for shape-selective catalytic reactions, ion exchange, and adsorption of organic compounds.⁵⁵⁻⁵⁷ The pore diameters can be finely chosen, tuned, and utilized for exhibiting shape-selective catalysis depending on the molecular shape/size of organic reactant and product. The widespread interest has been developed in the zeolitic science towards the development and discovery of zeolites with desired characteristics since conventional zeolites lack fine tuning of their properties to acid/base and redox or bifunctional or multifunctional properties. Organic functionalisation add new catalytic functions to zeolites.⁵⁸

Zeolites are microporous crystalline aluminosilicates with unique properties used for many processes. Zeolites possess acid sites that are associated with the tetrahedral aluminium atoms in their framework, and therefore, the amount of acidity depends on the aluminium content of the zeolite. Zeolite acid catalysts have wide application in industrial processes. The introduction of Y-zeolites to replace amorphous silica-aluminas in fluidized catalytic cracking (FCC) and in hydro-cracking processes in the early 1960's was a breakthrough application in acid catalysis. With the ever increasing research efforts in this area leading to discoveries of new structures and modification schemes by academic and industrial laboratories alike, the potential of solid acids has evolved tremendously. However, with the exception of the ZSM-5, Mordenite, and to some extent Beta zeolite, very few of these structures have been applied in industrial processes to any significant extent. Yet one can account for relatively few applications to the huge number of new materials introduced. Notable examples are the reported uses of SAPO's in lube dewaxing and in natural gas to olefin technologies, and MCM-22 in aromatics alkylation. The zeolite structures with large-pore/bimodal porosity and tunable acidity can be a remarkable benefit for catalytic processes in industries. Within industrial catalysis, there are constant innovation and changing approaches to provision of selective, economically viable and environmentally benign processes.

Recently, enormous growth in the chemical diversity of inorganic materials with transition-metal incorporation in new compositional domains has also been explored due to their potential application in adsorption and catalysis. Inorganic polymers, transition metal phosphates and metal-organic frameworks³⁸⁻³⁹ with novel catalytic, electronic, magnetic and unique structural

properties are particularly promising candidates.⁵⁹⁻⁶³ The mesoporous structure with strong acidity can be a remarkable benefit for catalytic reactions involving large organic molecules, in which diffusion constraints and/or adsorption of reactant molecules onto the strong acid sites are the main concern. A lot has been reported about the pathways to develop mesostructured silica.⁶⁴ In terms of surface functionalization, the performance of mesoporous silica has been polished by several methods such as metal incorporation,⁶⁵ metal deposition,⁶⁶ grafting by organic functional groups⁶⁷ and immobilizing metal complex.⁶⁸ New approaches to synthesis and characterization of bimodal i.e. micro-meso and or meso-macroporous (nano)materials might assist us in understanding the phenomena of diffusion, confinement effects, selectivity, etc..⁴⁶

5. Organocatalysis – a novel synthetic philosophy

The term “organocatalyst” is a concatenation of the words “organic” and “catalyst.” The definition corresponds to a low molecular weight organic molecule which in sub-stoichiometric amounts catalyzes a chemical reaction. The organocatalyst could be achiral or chiral and could be composed of C, H, N, S and P. Organocatalysis has several advantages not only because of its synthetic range but also for the economic reasons. The absence of metal in organocatalyst brings an undeniable advantage considering both the principles of "green chemistry" and the economic point of view (Figure 3).

Nowadays organocatalysis is one of the hot research topics in advanced organic chemistry. It is a novel synthetic philosophy and mostly an alternative to the prevalent transition metal catalysis. Organocatalysts are often based on non-toxic organic compounds originating from biological materials. Organocatalysts can be Lewis bases, Lewis acids, Brønsted bases and Brønsted

acids. Most of the organocatalysis reported so far are explained by Lewis base mechanism. The Lewis base mechanism can be simplified as:

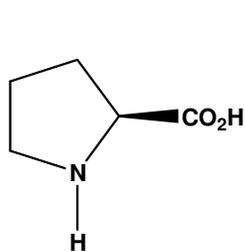
Step I: Lewis base, e.g. cinchona alkaloid, initiates catalysis *via* a nucleophilic addition to, or deprotonation of, the substrate

Step II: The chiral intermediate undergoes reaction

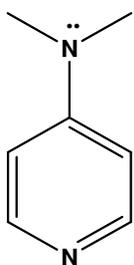
Step III: Separation of product(s) from the catalyst

Step IV: Regeneration of the catalyst and its availability for a new catalytic cycle.

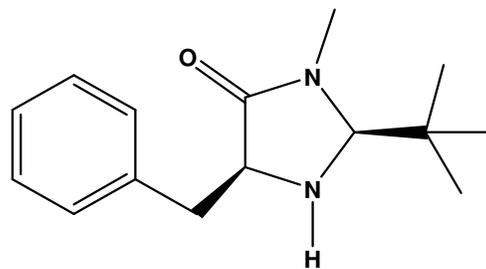
There are many organocatalytic reactions that need a second mechanism to explain the catalytic cycle involved. This is called bi-functional organocatalysis in which the organocatalyst possess not only a Lewis base (nitrogen or phosphorus atom) but also a Brønsted acidic site. There is a lot to be done in redox catalysis and in exploitation of the synergetic effect of different catalytic active sites within one organic compound or material.



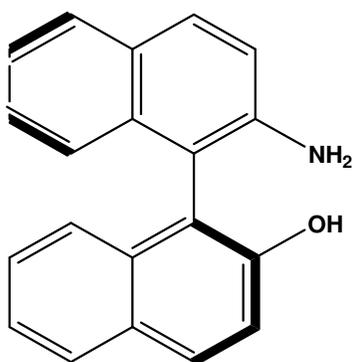
L-Proline



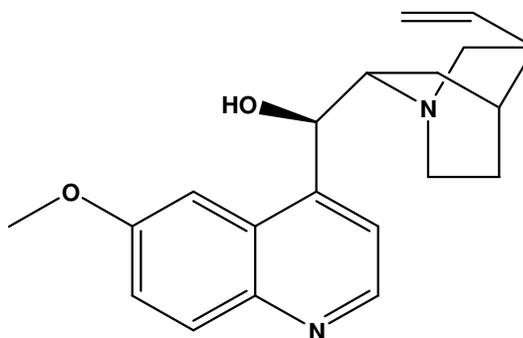
DMAP



MacMillan's catalyst



Nobin



Quinine

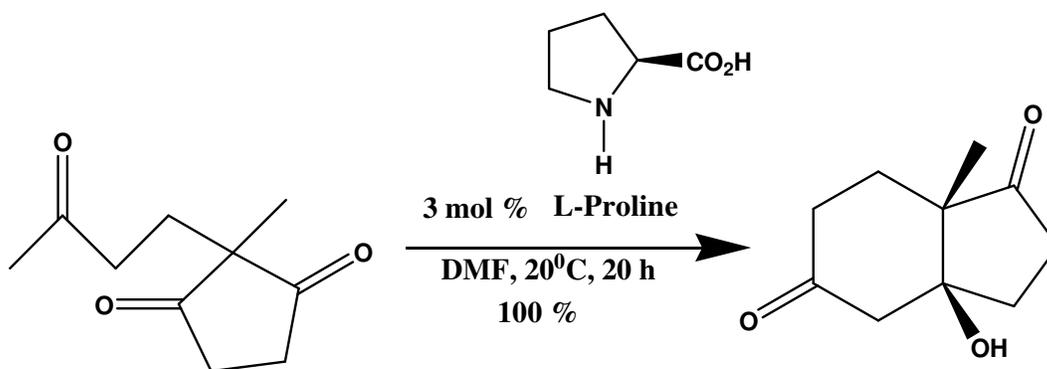
Figure 3. Few famous examples of organocatalysts: L-Proline, DMAP, Quinine, MacMillan's catalyst

Some advantages of organocatalysts include:

- (i). Reactions performed by organocatalysts have potential application in large scale production in industries.
- (ii) Scope: Organic reactions which are not in practice and not possible by other forms of catalysts e.g. asymmetric synthetic processes.
- (iii). Price / Availability: Low cost; Alkaloids, natural amino acids, L-proline, tartaric acid, etc. are easily available and are economically attractive.
- (iv). Recycling issues: Immobilization of the catalyst is the simplest way to recover it.
- (v). Some of the examples include bioderived and biodegradable organocatalysts.
- (vi). Organocatalysts work at mild reaction conditions.
- (vii). Sometimes the final products of reactions contain high levels of metal contamination derived from catalyst degradation phenomena, which pose a serious drawback if the metal is toxic for pharmaceutical and food industries. Absence of transition-metal brings organocatalysis at the heart of greening chemistry.

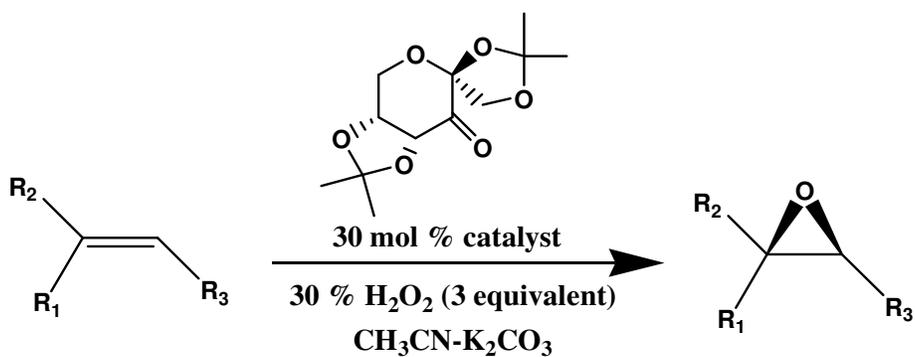
Organocatalysis can be categorized into our different types as:

Type-I: Activation of the reaction based on the nucleophilic/electrophilic properties of the catalyst



Scheme 1. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. ⁸²

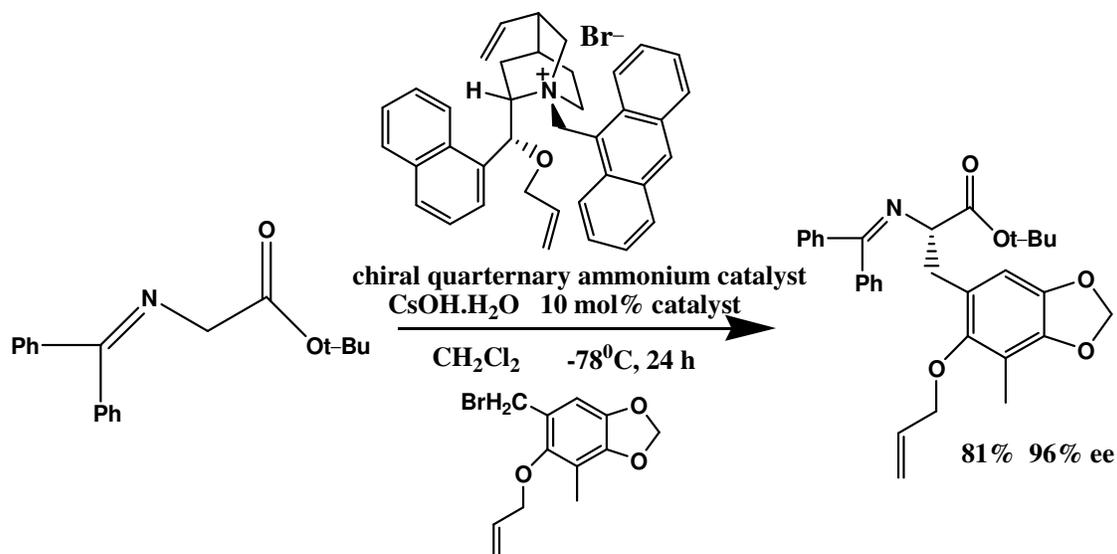
Type-II: Organic molecules forming reactive intermediates. The chiral catalyst is consumed in the reaction and requires regeneration in parallel catalytic cycle as it is reported in Scheme 2.



Scheme 2. Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807–8810. ^{245b}

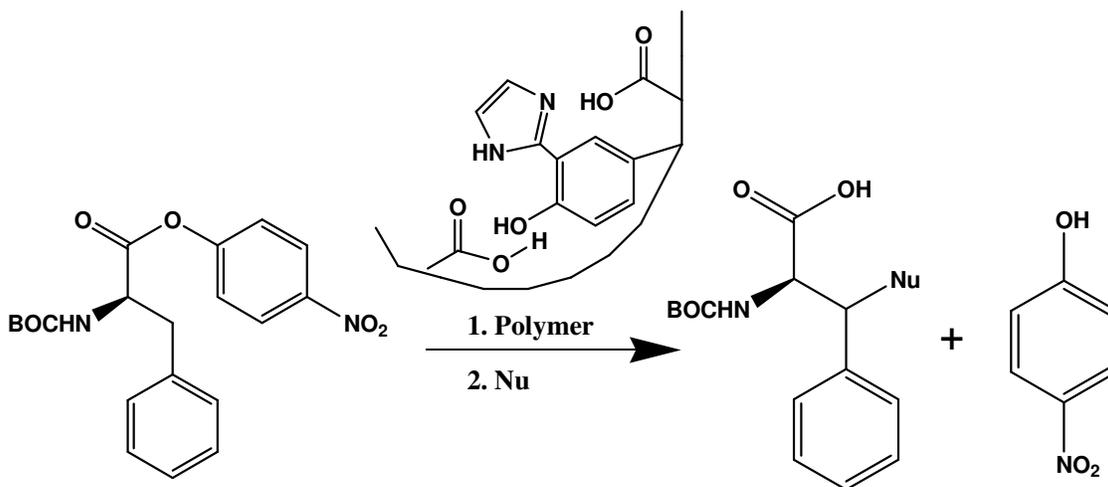
Type-III: Phase-transfer reactions. The chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and a second phase.

Catalytic Enantioselective Enolate Alkylation (Scheme 3) :



Scheme 3. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.²³⁴

Type-IV: Molecular-cavity-accelerated asymmetric transformations in which the catalyst may select between competing substrates, depending on size and structure criteria (Scheme 4).



Scheme 4. Sellergren, B.; Karmalkar, R. N.; Shea, K. J. *J. Org. Chem.* **2000**, *65*, 4009–4027.⁶⁹

6. Discovery and the history of organocatalysis

Liebig's synthesis of oxamide from dicyan and water is the first organocatalytic reaction reported.⁷⁰ Acetaldehyde was further identified to behave as the then-named "ferment," now called as enzyme. Dakin in 1909 demonstrated that in a Knoevenagel type condensation between aldehydes and carboxylic acids or esters with active methylene groups, the amine catalysts could be mediated by amino acids.⁷¹ Wolfgang Langenbeck is remembered for developing enamine-type reactions and the application of simple amino acids and small oligopeptides as catalysts.⁷² Natural products in particular strychnine, brucine and cinchona alkaloids and amino acids (including short oligopeptides) were among the first organic catalysts tested.⁷³⁻⁷⁴ Though the field of small-molecule catalysts seems very simple, there are evidences that prove their pivotal role in synthesis of building blocks for life. L-alanine and L-isovaline capable of catalyzing certain C-C bond formation reactions had been found on meteorites.⁷⁵

An asymmetric transformation with an organic molecule was published in 1912 by Bredig and Fiske.⁷⁶ Pracejus applied cinchona alkaloids in the asymmetric conversion of ketenes to (S)-methyl hydratropate.⁷⁷⁻⁷⁸ An initial research by Yamada S. & Otani G. was important, too.⁷⁹ The seventies brought another milestone, Hajos and Parrish reported a L-proline catalyzed Robinson annulation in excellent enantioselectivities.⁸⁰⁻⁸² Wiechert reported organocatalytic aldol reactions in good enantioselectivities.⁸³ To summarize, in 1970s, Hajos and Parrish and, independently, Eder, Sauer, and Wiechert published a series of papers and patents involving such organocatalytic transformations. The asymmetric synthesis of enediones - useful building blocks in natural product total syntheses, was achieved. (S)-proline induced the formation of (S)-enediones.

Two mechanisms [**Scheme 1**; Citation: *Theory of Asymmetric Organocatalysis of Aldol and Related Reactions: Rationalizations and Predictions*” Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H-Y; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 568-569] were proposed: (1) involving the formation of a carbinolamine intermediate, followed by the displacement of the proline moiety by nucleophilic attack of the enol from the side chain ketone. (2). Involving an enaminium intermediate acting as a nucleophile in the C-C bond formation with concomitant NH---O hydrogen transfer. Wynberg and coworkers firstly published various 1,2 and 1,4 additions catalyzed by cinchona bi-functional organocatalysis.⁸⁴⁻⁸⁶ All these research endeavours were not carefully looked into till List and Barbas reported in 2000 proline catalyzed aldol reaction in good enantiomeric excesses.⁸⁷⁻⁸⁸

Asymmetric catalysis constitutes one of the most important subjects in synthetic organic chemistry. Asymmetric synthesis achieving atom economy is a challenge for organic synthesis and homogeneous catalysis using metal complexes leads the way. But the application of such methodologies in chemical industry is rather limited due to the high cost of chiral ligands and noble metals used in such transformations. Moreover, the pharmaceutical entities and food industry products do not tolerate a contamination, of even traces, of any such metals for that matter. Synthesis of chiral drugs has a major financial impact in pharmaceutical industries on a global scale. Different enantiomers or diastereomers of a molecule often have different biological activity. Most of the drugs might be soon sold as single enantiomers in the coming years. There is a huge demand for organocatalysts leading to 100% yield 100% ee of the desired product. The need from chemical industry,

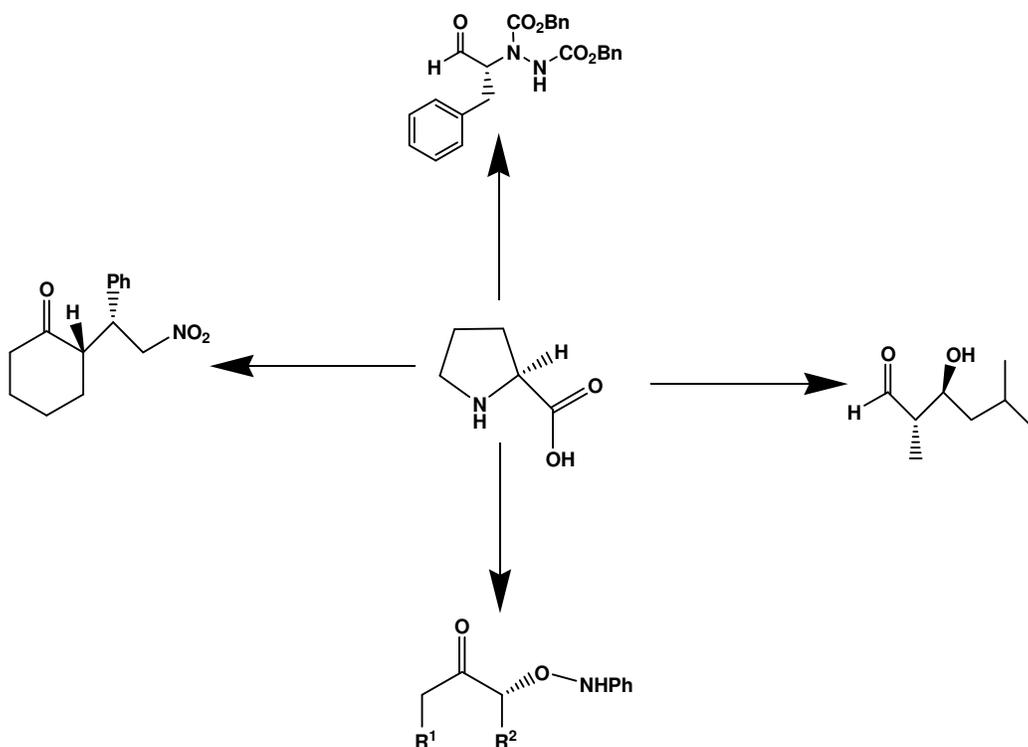
especially pharmaceutical, for reliable asymmetric transformations of molecular skeletons is higher than ever. Therefore, asymmetric organocatalysis is in a process of attaining maturity into a very powerful, practical and broadly applicable methodological approach in the catalytic asymmetric synthesis.

7. Some examples and developments in catalyst structural variants

Following are the famous examples of organocatalysts:

[I]. Proline and derivatives

The proline catalyzed Robinson annulation was one of the earliest examples of an enantioselective reaction using an organic catalyst.⁷⁹ This amino acid contains both a nucleophilic secondary amino group and a carboxylic acid moiety functioning as a Brønsted acid. The availability of proline in both enantiomeric forms brings advantages over enzymatic methods. Arguably, the first example of proline catalyzed asymmetric aldol reaction is reported by Hajos and Parrish.⁸⁰⁻⁸² The Wieland-Miescher ketone is a useful synthetic building block for which a classical asymmetric procedure using (S)-proline was published forty years ago.⁸³ It is quite significant that the first efficient organocatalyzed asymmetric reactions were described by Hajos & Parrish,⁸⁰⁻⁸¹ and by Eder, Sauer & Wiechert,⁸³ both teams from pharmaceutical companies (Hoffmann-la-Roche and Schering). The asymmetric synthesis of the Wieland-Miescher ketone is also based on proline and another early application was one of the transformations in the total synthesis of Erythromycin by Robert B. Woodward.⁸⁹ Proline is recognized as a versatile organocatalyst of these times (Scheme 5).



Scheme 5.

In fact, the renewal of proline-catalyzed transformations in early 2000 by D. W. C. MacMillan, Carlos F. Barbas III, and Benjamin List saw the renaissance of the concept and it was the starting point of the word 'Organocatalysis'. Professor MacMillan's group reported the first enantioselective organocatalytic Diels-Alder reaction.⁹⁰ Proline was identified as an effective organocatalyst for asymmetric aldol reaction.⁹¹ The catalytic asymmetric α -alkylation of aldehydes was reported by Benjamin List.⁹² This transformation had been accomplished with the help of covalently attached auxiliaries. α -Methyl L-proline exhibits higher enantioselectivities and improved reaction rates when compared to L-proline. In recent years, proline - especially L-proline, have been used to catalyse essential transformations used in the fine chemical and pharmaceutical industries, such as the direct asymmetric aldol reactions,⁹³⁻¹⁰¹ Diels-Alder reactions, Michael Reactions,¹⁰²⁻¹⁰⁹ Mannich reaction,¹¹⁰⁻¹¹⁶ Multi-

component reactions¹¹⁷⁻¹¹⁸ and α -Amination¹¹⁹ α -Aminoxylation¹²⁰⁻¹²² α -Oxyaldehyde dimerization,⁹⁴ α -functionalization of carbonyl compounds,¹²³ and α -alkylation of aldehydes.¹²⁴ Organocatalytic cyclopropanation reactions were typically performed using catalyst-bound ylides. However, MacMillan demonstrated that activation of olefin substrates using catalytic (*S*)-(-)-indoline-2-carboxylic acid is a viable route for the formation of highly enantioenriched cyclopropanes.¹²⁵

Prof. K. A. Jørgensen has made an important breakthrough in asymmetric synthesis by developing (*R*)- and (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether as excellent chiral organocatalysts in the direct organocatalytic α -functionalization of aldehydes. Diarylprolinol silylether reagents were found to catalyze C–C, C–N, C–O, C–S, and C–Hal bond forming reactions.¹²⁶⁻¹³² Enders' group developed proline-derived organocatalyst for a chemo-, diastereo-, and enantioselective three-component domino reaction to yield tetra-substituted cyclohexene carbaldehydes.¹³³ The four stereogenic centers are generated in three consecutive carbon–carbon bond formations, i.e., Michael/Michael/aldol condensation with high diastereo- and complete enantiocontrol. The synthesis of polyfunctional cyclohexene building blocks involving proline catalytic steps are reported in this domino reaction.

Though this segment of our book is dedicated to proline as an important class of organocatalysts, it would also be a good place to acknowledge the research contributions from Prof. D. W. C. MacMillan to the field of organocatalysis.^{90,93-}

94,97,121,125,134-143

Heterogenized proline:

An explosion of research articles in the area of homogeneous organocatalysis occurred within the last decade or so. In addition to the initial proline catalyzed reactions, the word 'Organocatalysis' covers nowadays many other well-known organocatalysts and organic reactions. Proline immobilized onto some sort of inorganic support paved the way towards heterogenization of other organocatalysts.¹⁴⁴⁻¹⁴⁶ A simple and efficient synthesis of polystyrene-supported proline and prolinamide is reported. Polystyrene-supported proline catalyzes the asymmetric aldol reaction between cyclohexanone and substituted benzaldehydes in water. High yields, diastereoselectivities and ee values have been observed. The versatility of this resin was also confirmed by selenenylation of aldehydes. Both proline and prolinamide resins gave high yields. Recycling studies showed that the proline resin performs as a better heterogeneous organocatalyst as compared to the prolinamide resin.¹⁴⁶ An aldol reaction catalyzed by proline functionalized silica gel was investigated in continuous-flow microreactors by reaction-progress kinetic analysis and nonlinear chromatography.¹⁴⁷

Though the research community advocates asymmetric synthesis for industrial application, organocatalysts have been seldom applied in industry, due to insufficient efficiency and the difficulties in catalyst separation and recycling.¹⁴⁸⁻¹⁵² The concept of heterogenizing organocatalyst on supports combines the advantages of both homogeneous organocatalysis and heterogeneous recycling. Though this might seem simple and present opportunities in industrial chemical processes, the research in heterogeneous organocatalysis demands a multidisciplinary approach by identifying catalytic activity upon bonding organocatalyst covalently to the support; understanding non-covalent interaction as structure-reactivity and conformation deciding

factor; taking into consideration the characteristic properties of the supports, confinement effects, if any, etc. Some recent examples will be described on the applications of supported proline as organocatalysts for their pre-industrialization study. The later half of this review, in general, irons out the detailed discussion on key trends with examples, scope, challenges and “green” applications of heterogeneous organocatalysts.

[II]. Other Amino Acids

Barbas and co-workers found the proteinogenic amino acid tryptophan (Figure 4) to be an excellent organocatalyst for the Mannich reaction of hydroxyacetone with a variety of imines performed in DMF leading the desired *anti* amino alcohols in excellent diastereoselectivities (up to >19:1) and enantioselectivities (90–98% ee).¹ Similarly, *t*-butyl protected threonine catalyzed the aldol reaction of hydroxyacetone and various aldehydes in NMP to give the corresponding *syn*-aldol adducts in high yields and good to excellent enantio- and diastereoselectivities.¹⁵³ Professors Marc Snapper and Amir Hoveyda reported¹⁵⁴ the development of an amino-acid based small molecule capable of promoting asymmetric monosilylation of *meso*-1,2-diols. Furthermore, the catalyst can be recycled with equal efficiency. Three-component reaction involving condensation of aldehyde, 1,3-carbonyl compound and (thio)urea is known as Biginelli reaction. Various organocatalysts such as tartaric acid, oxalic acid, citric acid, lactic acid, etc. were found effective in producing Biginelli products.¹⁵⁵⁻¹⁶³

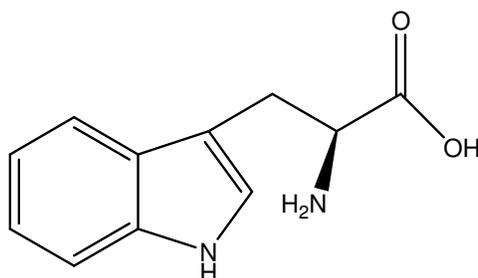


Figure 4. L-tryptophan

Because of the "privileged" green nature of this field, it has become an obligation for scientific community and academic institutions to be mindful and teach this branch of catalysis to students and also keep it as a driving force in the generation and dissemination of knowledge in pursuit of efficient synthetic methodologies and processes using organocatalysts. The synthesis of new chiral building blocks or complex molecular structures involving organocatalytic step(s) are being reported almost everyday in scientific literature. As it is not possible here to discuss all the catalysts individually in detail, the author decides to present salient developments in organocatalysis and allied research areas.

Synthesis of pro-chiral cyclohexanones by amine catalyzed self Diels–Alder reactions of α,β -unsaturated ketones in water brought coupled the concept of green chemistry with catalysis. Useful asymmetric heterodominant reactions for the highly diastereoselective synthesis of symmetrical and nonsymmetrical synthons of benzoannulated centropolyquinanes were reported.¹⁶⁴⁻¹⁶⁵

In recent years, trials are being made by using amino acids, especially L-proline, to catalyse essential transformations in the fine chemical and pharmaceutical industries. The interest in this field has thus increased spectacularly in the last few years. However, organocatalytic methods often require catalyst loadings as high as 30 mol% for the achievement of high conversions in reasonable reaction times.¹⁶⁶ Some critics suggest that low turnover numbers might limit the potential uses of organocatalysis for industrial applications. Process development and scale up are being tested for several organocatalytic

reactions confirming organocatalysis as a valuable tool for industrial-scale solutions. Scientists are reporting novel organocatalytic systems in various reputed international research journals and those catalysts exhibit various valuable functions derived from a variety of structural, ionic/electronic, chemical properties, etc. Broad variety of efficient syntheses will contribute to an increasing number of organocatalytic large-scale reactions in the future. The organocatalysts shall be used in various fields, especially in asymmetric organic synthesis.

[III]. Amine and Chiral Vicinal Diamines

Proline and pyrrolidine derivatives, commonly known as Hayashi– Jørgensen catalysts, in the form of ferrocenyl pyrrolidine is applied as organocatalyst wherein the ferrocene moiety controls the conformational space and a simple alkyl group effectively covers a face of the derived enamine (Figure 5).¹⁶⁷

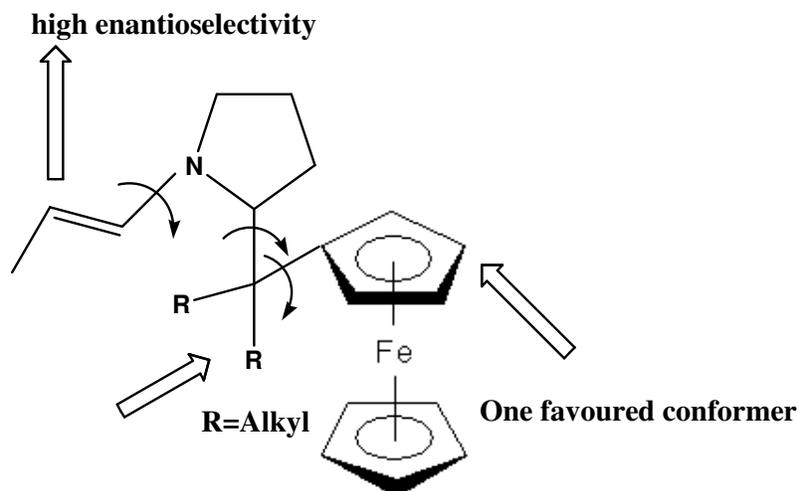


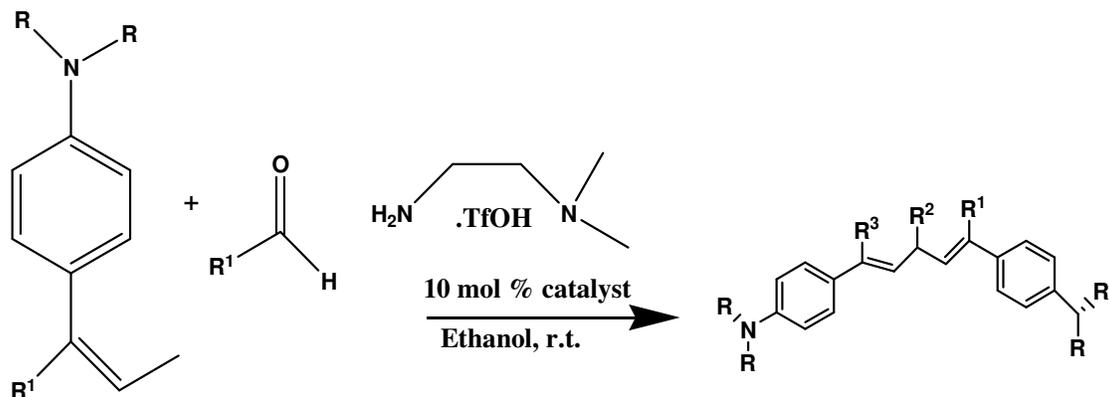
Figure 5.

Alexakis et al. reported chiral amines catalyzing asymmetric conjugate addition to nitroolefins and vinyl sulfones via enamine activation.¹⁶⁸

A bifunctional H-bond directing aminocatalytic system is found to achieve high stereo- and regiocontrol over dienamine mediated hetero-Diels-Alder reaction.¹⁶⁹

Though amine catalysis is a constructing a wide variety of chiral scaffolds in asymmetric synthesis, organocatalysis with amines for non-asymmetric transformations is also developing at very fast.¹⁷⁰⁻¹⁷¹ The [2+2] Cycloaddition of Enals with Nitroalkenes is catalyzed by a chiral secondary amine in the presence of an achiral thiourea for the enantio- and diastereo-selective synthesis of highly functionalized cyclobutanes. Mechanistically, two consecutive Michael reactions proceed through an unprecedented combination of an dienamine/iminium activation mode.¹⁷² The reaction engineering of dienamine catalysis for single-step syntheses of highly

functionalized molecules such as natural products or bioactive compounds is reviewed in literature.¹⁷³

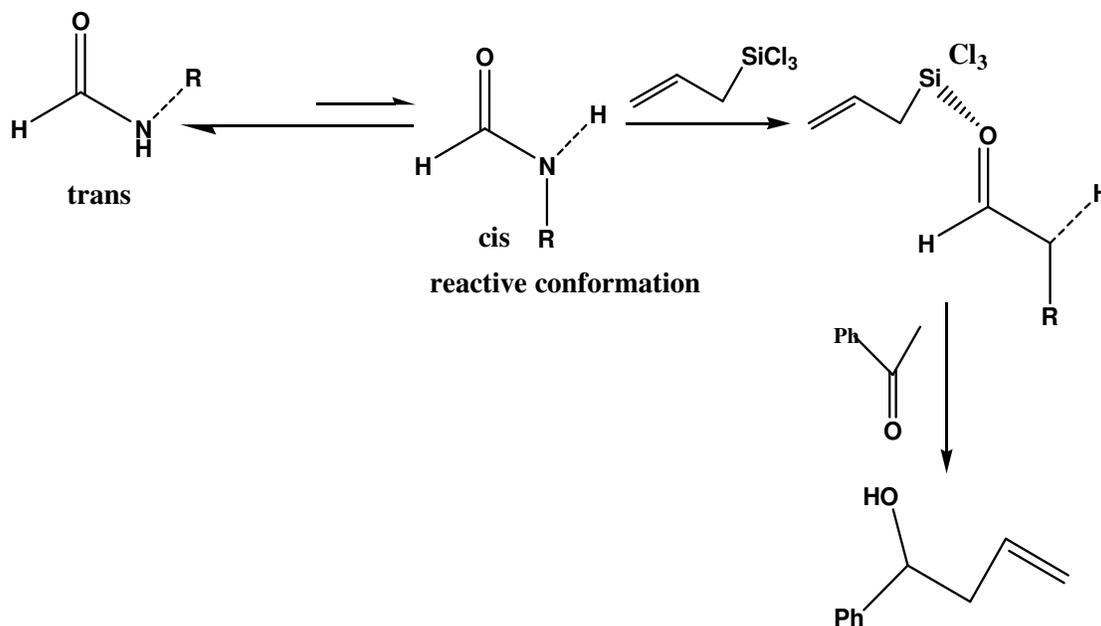


Scheme 6.

Jik Chin and co-workers have recently reported some preliminary theoretical and experimental studies for converting a parent diamine into other chiral vicinal diamines. These diamines can be handy as ligands for chiral catalysts or they can make chiral heterocyclic rings and beta-lactams.¹⁷⁴⁻¹⁷⁶ There are some C-C bond forming reactions catalyzed by such diamine organocatalysts (Scheme 6).¹⁷⁷

[IV]. Amides

Recently, the synthesis of multifunctional organocatalysts, easily obtained by the condensation of (*S*)-proline with 2-aminopyridine, 2,6-diaminopyridine, or 2-aminoimidazole is reported. These chiral prolinamides promoted the aldol condensation between cyclohexanone and different aromatic aldehydes (up to 98 % *ee*), and also catalysed Diels–Alder and Michael reactions.¹⁷⁸⁻¹⁷⁹



Scheme 07.

Rationally designed pyrazoleamides function as Michael donors in urea-catalyzed asymmetric Michael reactions with excellent chemical and optical yields.¹⁸⁰

A structure–activity relationship with regard to formamides as organocatalysts is explored. This study highlights that the *cis* conformation of secondary formamides is the reactive conformation in the allylation of aldehydes with allyltrichlorosilane (Scheme 7).¹⁸¹

[V]. Imidazolidinones

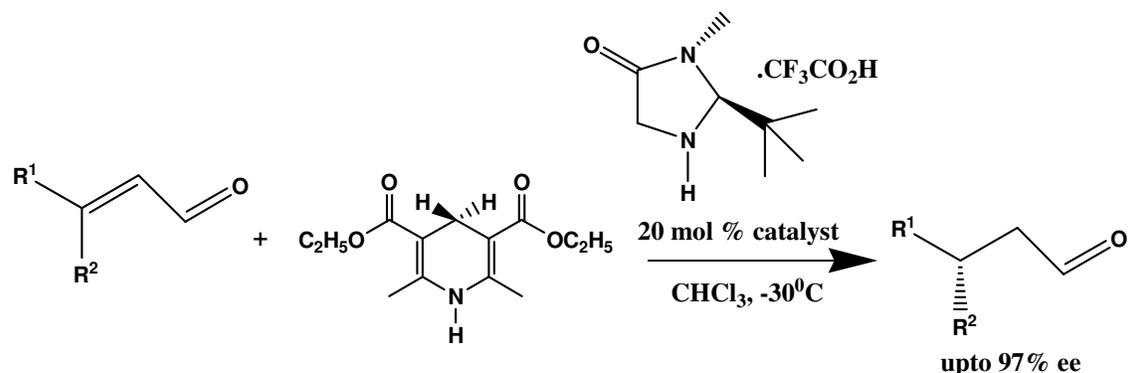
A certain class of imidazolidinone compounds (also called **MacMillan Imidazolidinone OrganoCatalysts™**) function as catalysts for many asymmetric organic transformations such as asymmetric Diels-Alder reactions. The original such compound was derived from the chiral biomolecule phenylalanine.¹⁸²⁻¹⁸³

The first highly enantioselective organocatalytic Diels–Alder reaction using a chiral OrganoCatalyst™ was reported in MacMillan’s pioneering work where

the activated iminium ion, formed through condensation of the imidazolidinone and an α,β -unsaturated aldehyde, reacted with various dienes to give [4+2] cycloadducts in excellent yields and enantioselectivities. MacMillan reported many other asymmetric reactions such as the 1,3-dipolar cycloadditions, Friedel–Crafts alkylations, α -chlorinations, α -fluorinations, and intramolecular Michael reactions using MacMillan's OrganoCatalysts^{90,143,184-187}

MacMillan also reported the combination of imidazolidinone OrganoCatalyst™ and Hantzsch ester to facilitate the first enantioselective organocatalytic hydride reduction of α,β -unsaturated aldehydes (Scheme 8).¹⁸⁸⁻¹⁸⁹ This imitated nature's stereoselective enzymatic transfer hydrogenation with NADH cofactor.

Non-covalent interaction is a structure-reactivity and conformation deciding factor which requires immediate attention for understanding organocatalysis.¹⁹⁰ Of special interest would be the identifying and understanding other non-covalent interactions such as charge-transfer,¹⁹¹ p-p stacking immobilization¹⁹² and adsorption or entrapment of organocatalysts in nanomaterials.¹⁹³



Scheme 8. Ouellet, S. G. et. al. *J. Am. Chem. Soc.* **2005**, *127*, 32.¹⁸⁸

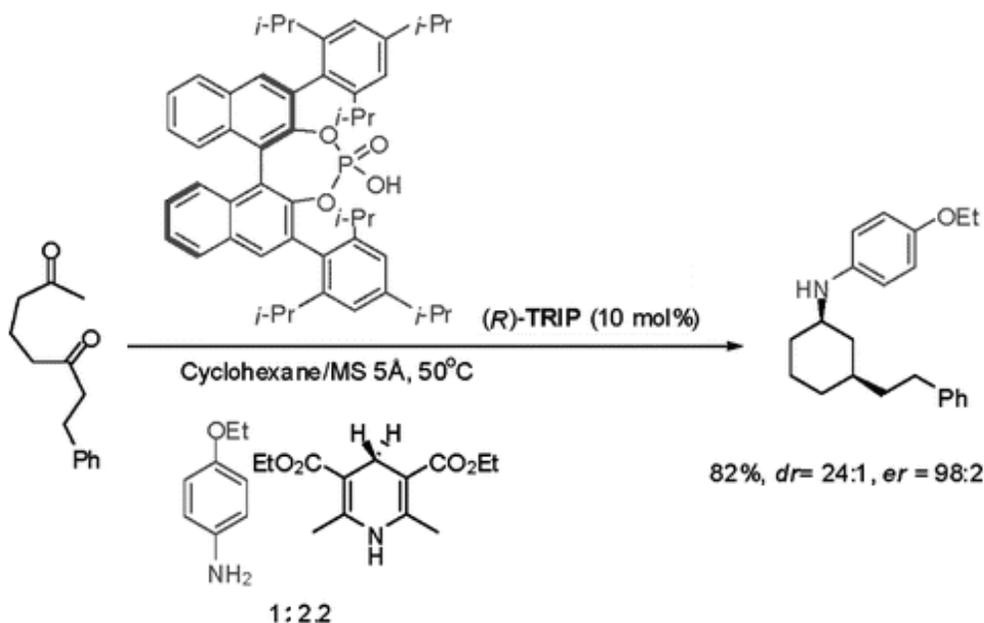
Homogeneous and Heterogenized MacMillan's OrganoCatalyst:

An asymmetric Diels-Alder reaction was catalyzed with high efficiency and recyclability by a soluble, "self-supported" chiral organosilica polymer with embedded imidazolidinone catalytic moieties.¹⁹⁴

[VI]. Chiral Phosphoric Acids

BINOL-derived phosphoric acids catalyze nucleophilic addition reactions to imine substrates. A direct Pictet-Spengler reaction was reported using a geminally disubstituted tryptamine organocatalyst to form isoquinolines in excellent yield and enantiomeric excess.¹⁹⁵ Phosphoric acid catalyzing the reduction of an imine with a Hantzsch ester in good enantiomeric excess was firstly reported by Rueping et al. Benjamin List reported an improvement to this methodology.¹⁹⁶⁻¹⁹⁷

MacMillan's research group reported a one-pot reductive amination of a range of methyl ketones and aryl amines.¹⁹⁸ Reductive amination of 2-butanone over silylated phosphoric acid MacMillan TiPSY catalyst was obtained with good enantiomeric excess.



Scheme 09. Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498.¹⁹⁹

Benjamin List published on the use of chiral Brønsted acid (R)-TRIP for highly enantioselective synthesis of pharmaceutically relevant 3-substituted cyclohexylamines from 2,6-diketones wherein the achiral amine substrate accelerates the cascade reaction before getting incorporated into the final product (Scheme 9).¹⁹⁹

J. C. Antilla reported VAPOL derived phosphoric acid catalyzed addition of sulfonamides to BOC-protected aryl imines and protected amins in excellent enantioselectivities.²⁰⁰

The (R)-TRIP catalyzed the aza-Diels-Alder reaction of aldimines with Danishefsky's diene to yield piperidinone derivatives with high enantioselectivity. Addition of acetic acid was found to improve both reactivity and enantioselectivity.²⁰¹ Six chemical bonds, five stereogenic centers, and three cycles were formed in one-pot four-component Ugi-Type reaction

catalyzed by a chiral BINOL derived phosphoric acid.²⁰² BINAP is the one of the early commercially applied ligand in industrial catalysis.²⁰³ A microporous recyclable heterogeneous catalyst, offering excellent enantioselectivity, was made from a 1,1'-binaphthalene-2,2'-diol (binol)-derived phosphoric acid chloride and was found as active as the corresponding homogeneous catalyst.²⁰⁴

[VII]. Chiral Diols

Rawal reported on use of TADDOLs (Figure 6) as Brønsted acid organocatalysts in highly stereoselective hetero-Diels–Alder reactions.²⁰⁵

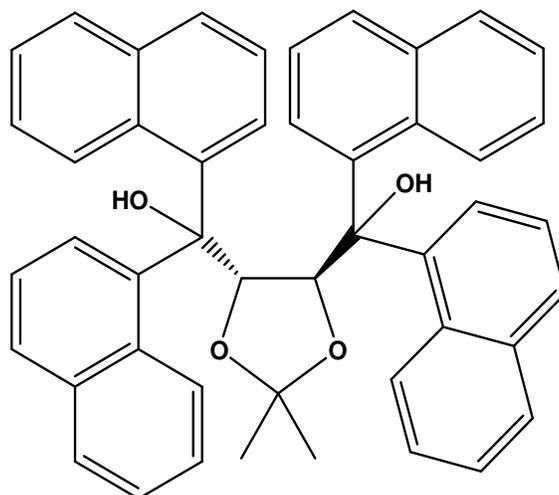


Figure 06.

The α -amination of carbonyl compounds has also been accomplished by using the 1-naphthyl TADDOL derivative as a Brønsted acid organocatalyst.²⁰⁶ Schaus reported asymmetric Morita–Baylis–Hillman reaction i.e. the addition of cyclohexenone to different aldehydes catalyzed by octahydro-BINOL-derived Brønsted acid.²⁰⁷

[VIII]. Jacobsen Thioureas

Prof. E. N. Jacobsen's research group identified chiral thioureas (Figure 7) as versatile and effective organocatalysts. 1 mol % of the thiourea was reported to have catalytic activity in the hydrocyanation (Strecker reaction) of both aldimines and ketoimines with very high enantioselectivities.²⁰⁸

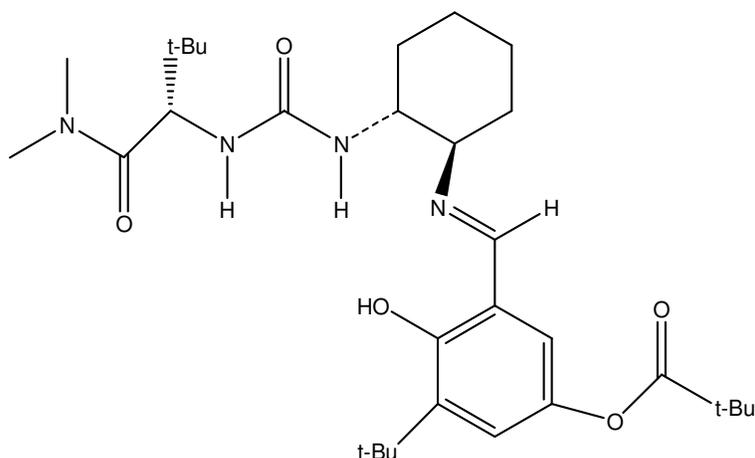
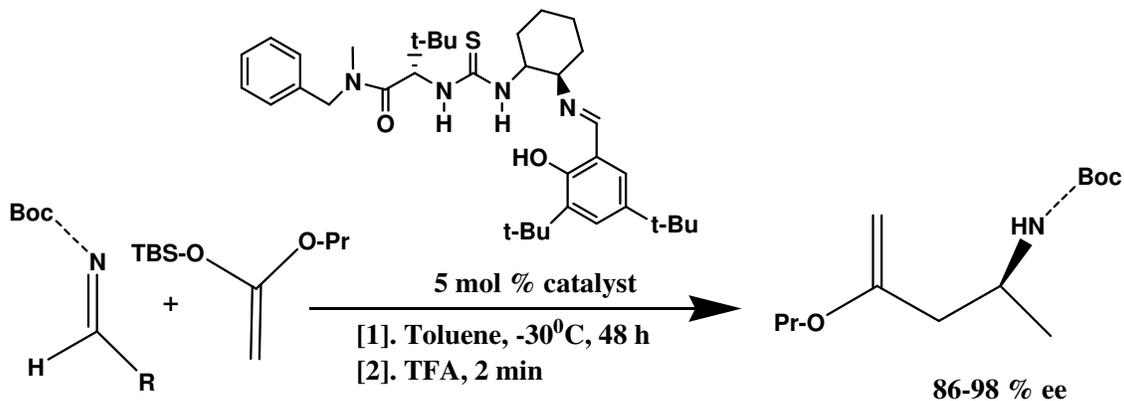


Figure 07.

Imine hydrophosphonylation, particularly effective with electron-withdrawing ester substituents on the phosphate, took place in the presence of 10 mol % of the catalyst.²⁰⁹ Mannich reactions of BOC-protected imines have also been reported (Scheme 10)²¹⁰ with excellent yields and enantioselectivities and shows heterocyclic substrate tolerance.



Scheme 10.

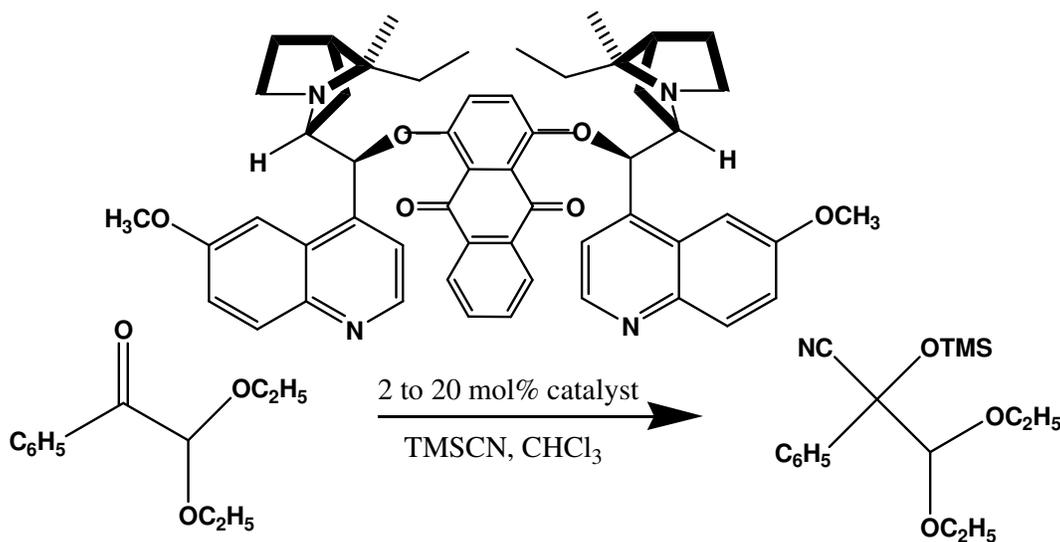
A variant of thiourea organocatalyst was found to catalyze the cyanosilylation of ketones and aldehydes in high yields and enantiomeric excesses.²¹¹ Thiourea organocatalyst was put to use in the acyl-Pictet–Spengler reaction to form tetrahydro- β -carbolines.²¹² The acyl-Mannich reaction, providing a route to enantioenriched heterocycles from aromatic starting materials and trichloroethyl chloroformate (TrocCl), is also catalyzed by the thiourea organocatalyst.²¹³ Bifunctional Thiourea-Base Catalyzed Double-Michael Addition of Benzofuran-2-ones to Dienones is reported for the synthesis of Optically Enriched Spirocyclic Benzofuran-2-ones.²¹⁴ In another interesting example, benzoylthiourea–pyrrolidine catalyst was synthesized and used in the asymmetric Michael addition of ketones to nitroalkenes.²¹⁵

Primary Amine-Thioureas were improvised to catalyze difficult Michael reactions synthesizing (*S*)-Baclofen, (*R*)-Baclofen and (*S*)-Phenibut.²¹⁶

[IX]. Cinchona Alkaloids

The cinchona alkaloids catalyze many useful processes with high enantioselectivities. Asymmetric phase-transfer catalysis (PTC) presents a “green” alternative to homogeneous synthetic organic chemistry methodologies. Cinchona alkaloids are synthetically modified for their usage in asymmetric PTC. *O*-alkyl *N*-arylmethyl derivatives of cinchona alkaloid led highly enantioselective alkylation of glycine imines to generate α -amino acid derivatives. And for the same reaction, dimeric cinchona alkaloid obtained 97–99% enantiomeric excess.²¹⁷⁻²¹⁸ Cinchona alkaloids deprotonate substrates with relatively acidic protons forming a contact ion pair between the resulting anion and protonated amine. This interaction generates a chiral pool around the anion and facilitates enantioselective reactions with electrophiles. The control

over the formation of quaternary asymmetric centers is essential to obtain high enantiomeric excesses. The α -functionalization of ketones (Scheme 11) by the addition of TMSCN to the corresponding cyanohydrin in excellent yield and enantiomeric excess is catalyzed by the (DHQD)₂AQN catalyst.²¹⁹



Scheme 11. Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900-9901.²¹⁹

Increasingly remote stereocenters are being targeted in asymmetric aminocatalysis. Organocatalytic allylic amination presents an alternative to the conventional palladium catalyzed methodology. Amination at the remote γ -position using (DHQ)₂PYR forms highly functionalized amine compounds.²²⁰

Jørgensen's group reported the first enantioselective conjugate addition of β -diketones to both aromatic and aliphatic alkynones using (DHQ)₂PHAL catalyst.²²¹ Cinchona-based primary amine catalysis is found to offer high efficiency and reliability in the asymmetric functionalization of carbonyl compounds.²²³⁻²²⁴ Organocatalysts derived from cinchona alkaloids function as Lewis base catalyst in the cyclizations of allenates with electron-deficient

olefins and imines and emerged as important synthetic tool in the preparation of biologically active and pharmaceutically interesting cyclic compounds, including natural products.²²⁵ Recently, cinchona thioureas have been reported for the first time as catalysts in the area of asymmetric oxidations.²²⁶ Cinchona and cinchonidine-derived catalysts performs asymmetric direct aldol reaction of pyruvic aldehyde dimethyl acetal with isatin derivatives.²²⁷ Likewise, there are various other examples reported where cinchona or its variants are used as organocatalysts for syntheses of various biologically important molecules.²²⁸⁻²³³

[X]. Maruoka Phase-Transfer Catalysts

The chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and a second phase. Example: Catalytic Enantioselective Enolate Alkylation ²³⁴ As we know that chiral quaternary ammonium catalysts can be useful in asymmetric synthesis. Maruoka reported C₂-symmetric ammonium salts catalyzing monoalkylation of glycine-derived Schiff bases with alkyl halides to synthesize α -alkyl- α -amino acids under remarkably low catalyst loadings.²³⁵⁻²³⁷

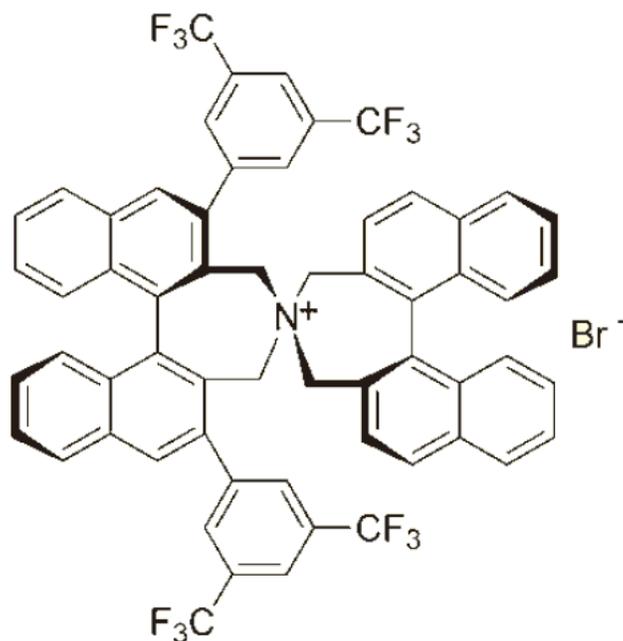


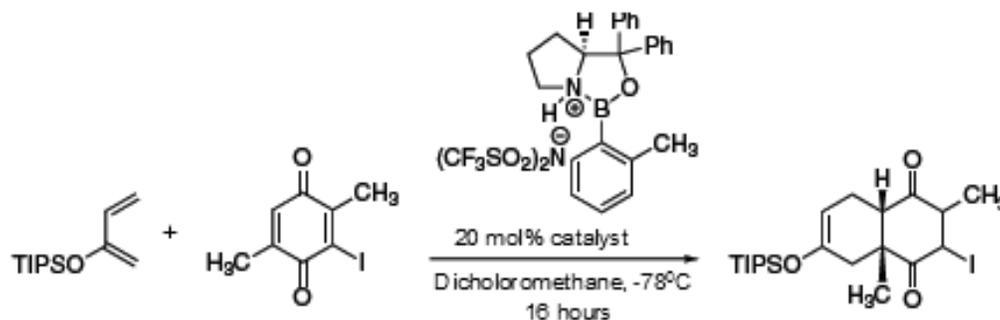
Figure 08. T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka: " Direct Asymmetric Aldol Reactions of Glycine Schiff Base with Aldehydes Catalyzed by Chiral Quaternary Ammonium Salts", *Angew. Chem. Int. Ed.*, **2002**, 41, 4542-4544.

Utilizing the solubility of aqueous quaternary ammonium salts into organic solvents, Prof. Maruoka developed spiro-type chiral ammonium salt with two binaphthyl rings as a novel chiral phase transfer catalyst. The (Figure 8) depicts the organocatalyst for direct asymmetric aldol reaction of β -hydroxy- α -amino acid derivative.

[XI]. Oxazaborolidines

Chiral oxazaborolidines (known as **CBS Oxazaborolidines** after **Corey**, **Bakshi**, and **Shibata**) catalyze the reduction of prochiral ketones, imines, and oximes to produce chiral alcohols, amines and amino alcohols, respectively, in high yields and excellent enantiomeric excesses. The chiral Lewis acid generated from *o*-

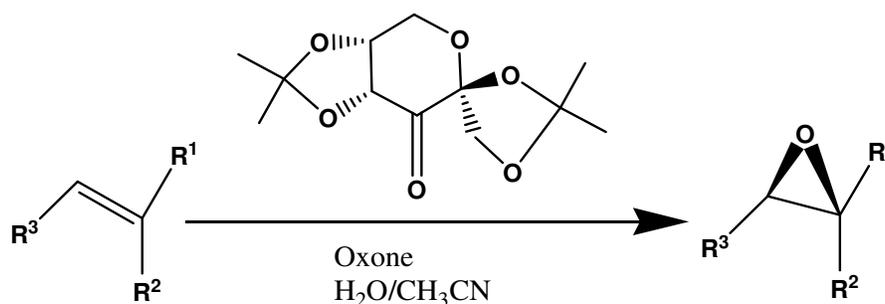
tolyl-CBS-oxazaborolidine after protonation with trifluoromethanesulfonimide is very useful in the enantioselective Diels–Alder reaction (Scheme 12).²³⁸⁻²⁴⁴



Scheme 12.²³⁸⁻²⁴⁴

[XII]. Shi Epoxidation Catalyst

Shi reported a fructose-derived ketone in efficient asymmetric epoxidation of trans-olefins (Scheme 13).^{245a} Shi Epoxidation Catalyst is able to epoxidize *trans* alkenes and certain *cis* alkenes with good to excellent yields and selectivities.²⁴⁶⁻²⁴⁷ Jørgensen's group reported an asymmetric organocatalytic epoxidation of alpha,beta-unsaturated aldehydes with environmentally friendly oxidant hydrogen peroxide.²⁴⁸



Scheme 13.

[XIII]. N-Heterocyclic Carbene (NHC) as Organocatalysts

(i). Rovis Catalyst

The conjugate addition of an aldehyde to an α,β -unsaturated compound (Stetter reaction) is a practical methodology for the construction of 1,4-dicarbonyl compounds bearing quaternary stereocenters. Triazolium salt in the presence of a base functions as an N-heterocyclic carbene organocatalyst (Figure 9) in highly enantioselective intra-molecular Stetter reactions.²⁴⁹⁻²⁵⁰

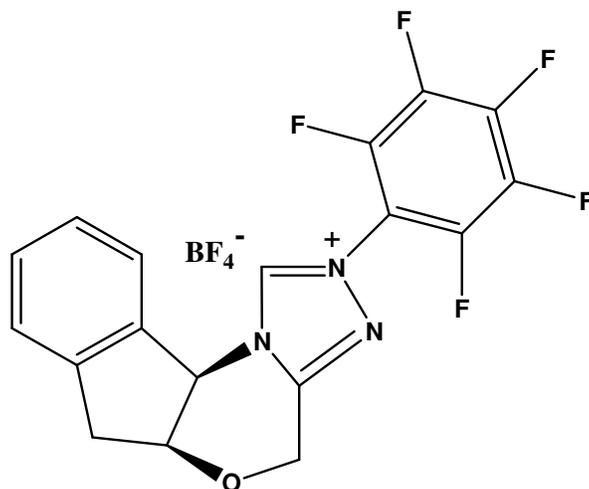


Figure 09.

(ii). Bode Catalyst

Bode's studies on NHCs (Figure 10) mainly involve catalytic generation of reactive species such as enolates, homoenolates and activated carboxylates. N-mesityl substituent on an imidazolium or triazolium NHC precursor generates highly enantioselective annulations from simple starting materials under mild reaction conditions.²⁵¹⁻²⁵² In an interesting example, the catalyst facilitates highly enantioselective cyclopentene-forming annulations of simple enals and activated enones.²⁵³ Redox esterifications and amidations of α -functionalized aldehydes using achiral catalyst are also reported.²⁵⁴ Uniting unique activation modes of N-heterocyclic carbene (NHC) catalysts with the concept of domino

asymmetric organocatalyzed sequential or domino transformations including C-C or C-N bond formation.²⁷⁰ Cyclopropenone-catalyzed conversion of aldoximes and primary amides into nitriles in a one-pot mild reaction widens the scope of the utilization of cyclopropenones in organic synthesis.²⁷¹ The first asymmetric organocatalytic synthesis by phosphine-catalyzed [3+2] cycloaddition of allenoates onto fullerene is reported to yield enantiomerically pure carbocyclic fullerene derivatives under mild conditions.²⁷² A new [3+2] cycloaddition/cycloreversion strategy for organo-catalytic and thermally allowed carbonyl–olefin metathesis is reported.²⁷³ Recently, a strong evidence for halogen-bond based organocatalysis is reported for the reaction of 1-chloroisochroman with ketene silyl acetals.²⁷⁴ Acid-catalyzed asymmetric acetalizations of aldehydes are also described.²⁷⁵ Beta – Isocupreidine catalyzed the enantioselective Morita–Baylis–Hillman reaction of maleimides with isatin derivatives to form 3-substituted 3-hydroxyoxindole derivatives.²⁷⁶⁻²⁷⁷

Recent advances in asymmetric catalysis resulted in utilizing the less discussed electrophilic properties of iminium type intermediates in complex annulations of indoles²⁷⁸⁻²⁷⁹ and also pyridines.²⁸⁰⁻²⁸¹ Shibatomi and Narayama discussed the catalytic enantioselective α -chlorination of carbonyl compounds and stereospecific substitution reactions of the resulting optically active alkyl chlorides.²⁸²

Though there is no relation between the development of two different fields of organocatalysis and gold catalysis, an interesting synthetic utility and merger of both catalytic systems in the same reaction flask is explored.²⁸³

Following are the synthetic methodologies reported on Mannich reactions using various organocatalytic systems.

Asymmetric three component Mannich reaction and anti-Mannich reactions were reported by organocatalysts.^{116,166} The title reaction provides facile access to enantioenriched 3,4-dihydroquinazolin-2(1*H*)-ones containing a quaternary stereogenic center in high yields with excellent enantioselectivities. Subsequent transformations lead to the convenient preparation of the anti-HIV drug DPC 083 and N-fused polycyclic compounds without loss of enantiomeric excess.²⁸⁴

An asymmetric catalytic, desulfonylative Mannich reaction of keto imines with aldehydes, as catalyzed by diarylprolinol silyl ether, was developed. It gave the Mannich product in good yield with excellent *anti* and enantioselectivity.²⁸⁵ New chiral bis(betaine)s, containing two catalytically active centers, have been designed and have proven to be promising organocatalysts for the direct Mannich-type reaction of azlactones with a broad spectrum of aliphatic imines.²⁸⁶ L. Hong and R. Wang reviewed advances in asymmetric organocatalytic Construction of 3,3'-Spirocyclic Oxindoles.²⁸⁷ And among the applications of organocatalysts in total synthesis and natural product synthesis include: enantioselective synthesis of *Amaryllidaceae* alkaloids (+)-Vittatine, (+)-*epi*-Vittatine, and (+)-Buphanisine.²⁸⁸⁻²⁸⁹

8. Heterogeneous Organocatalysis - new direction in research and development

Making of Heterogeneous Catalyst from Homogeneous Catalyst – the Concept and Methodologies

With the knowledge of *heterogeneous catalysis* and *chemistry of materials* at hand, several modified and different systems are made these days and are

tested for their catalytic applications in various organic transformations. Following are the most common and well-known methods for the heterogenization of homogeneous catalysts:

- impregnation
- occlusion in porous materials (ship-in-a-bottle)
- grafting or tethering (through covalent bond)

Impregnation is the immobilisation of catalytic element via electrostatic interactions with a solid support. One of the famous examples include: Rh-diphosphine cationic complexes impregnated on anionic resins via ion-pair formation.²⁹⁰ Similarly, organocatalysts supported on solid could be envisioned to yield a recyclable catalyst.

Heterogenisation via catalyst entrapment is a typical method that is applied to zeolite supports and termed as “ship-in-bottle” catalysis. A famous example includes in situ synthesis of the transition metal complex in support cages.²⁹¹⁻²⁹² The great practical advantages of “ship-in-bottle” single-site heterogeneous catalysts were well illustrated by Bäckvall’s research.²⁹³ Similar approach, retaining steric factors, could be applicable as another methodology for heterogenization of organocatalysts.

While in **grafting**, the catalytic active site is directly anchored on the support. This procedure is previously used for supporting organometallic complexes (Figure 11).²⁹⁴⁻²⁹⁸ The tethering technique involves a spacer that is introduced between the catalyst and the support. The characteristic chemical nature and the structure of the spacer should be chosen to avoid the steric hindrance, if

any. Though structurally different, catalytic activity can be expected to be similar to catalyst in homogeneous state.

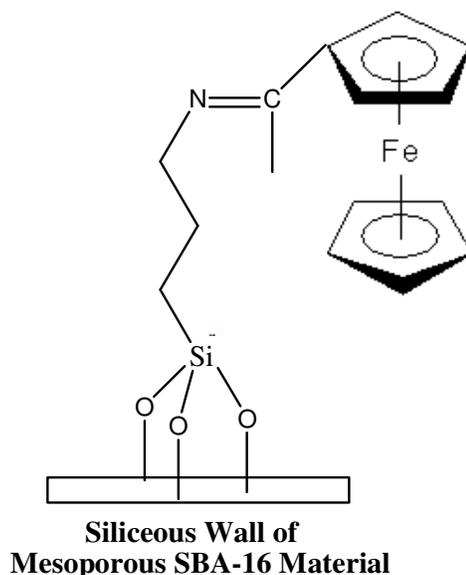


Figure 11.²⁹⁷

Catalyst immobilization has been widely explored with asymmetric transition metal catalysts and enzymes aiming to improve their applicability and practicability. Similarly, the immobilization strategy has also been frequently attempted for organocatalysis even before its renaissance. The preparation of supported or immobilized catalysts involve either organic polymers such as linear, non-cross-linked or cross-linked polymers as supports or porous inorganic solids such as alumina, silica, zirconia, clays, zeolites, MCM, SBA type mesoporous materials, etc. Many inorganic supports have robust composition and offer large surface areas due to the presence of internal pores. Different routes to immobilisation of (homogeneous) catalyst can alter the nature of the catalytic active site. When the anchoring of catalytic moieties on silica is concerned, the key aspect is the functionalisation of silanol groups on the surface. The pre-treatment temperature of the parent silica determines the

nature of the hydroxy groups (isolated, geminal, hydrogen bound), their location and reactivity. In nanostructured mesoporous silica of the MCM-41-type, the reactivity of the siloxanes is considered to be sufficient for covalent linking with a tether.²⁹⁹ Subsequent silylation with trimethylchlorosilane neutralizes residual hydroxyl groups and increases the hydrophobicity. Various aluminosilicates and mesoporous silicas could be envisioned as suitable hosts for and encapsulating and anchoring organocatalysts.

Organocatalysis has drawn a lot of interest in both academia and industry. The fact is that the asymmetric version of organocatalysis is the fastest growing field of synthetic organic chemistry. Few applications in industries include: (i). Epoxidation of Chalcones, and (ii) Alkylation of Cyclic Ketones. Along with a commentary on very recent research endeavors in organocatalysis, the scope of heterogeneous organocatalysis in asymmetric synthesis, other important organic reactions, green chemistry and scope for industrial applications are presented in this review.

Organic functionalization of nanostructured, nanoporous and other nanomaterials widens the range of their applications and allow for the manipulation of the surface properties that control the interaction with various organic and inorganic guest species and thereby adds new catalytic functions to the materials. One of the basic premises behind the preparation of these kinds of materials is aiming at the development of heterogeneous and supported catalysis for their practical purposes that would have distinct advantages over widely investigated homogeneous catalysts and organometallic compounds that are vulnerable to decomposition due to oxidation of the ligand bound to the metal center.

Using a rationale, similar to that reported earlier for the immobilisation of transition-metal amino acid complexes,³⁰⁰⁻³⁰³ amino acids with functional side chains that can react with tethering silanes such as lysine, arginine, glutamic acid, cysteine or amino acid derived organocatalysts could be covalently anchored to the inner walls of porous silica and other relevant inorganic structures. These materials have therefore been identified as promising supports for making organocatalysts heterogeneous for industrial significant reactions. This field is therefore well poised for their potential large scale applications in industry.

An organocatalyst attached to some sort of support/material is called as heterogenized organocatalyst for this bring-in the advantageous characteristics of a heterogenous catalyst. When used in heterogeneous system, one ensures no leaching of catalyst entity into the reaction medium and simple work-up or easy separation of catalyst from the products. Such catalyst can be reused. In order to obtain heterogeneous organocatalyst, many approaches have been explored, including impregnation to layered material,³⁰⁴ covalent grafting to solid support,³⁰⁵⁻³⁰⁶ electrostatic interaction between organocatalyst and the support,³⁰⁷ encapsulation to porous material³⁰³ and adsorptive method.³⁰⁸ Several solid supports have been introduced for heterogenizing of organocatalysts in terms of covalent grafting such as polymer matrix, zeolites, amorphous silica and mesoporous silica.³⁰⁹⁻³¹² Due to the strong covalent bond to silica surface, the covalently anchored organic moieties are supposed to be more resistant toward leaching during the catalytic reactions. Typically, the immobilization of organocatalysts has been achieved via covalent attachment onto solid supports such as polystyrene,³¹²⁻³¹⁶ poly(ethylene glycol),³¹⁷⁻³¹⁸

dendrimers,³¹⁹ etc. However, most of these supported organocatalysts demonstrated reduced activity and selectivity comparing with their small molecular parent catalysts. There has also been increasing examples of supported organocatalysts via non-covalent strategies starting to show their potentials in this field. There are major progresses regarding the development of non-covalently supported asymmetric organocatalysts, with a focus on the immobilization methods, their advantages, applications and limitations. Non-covalent immobilization includes minimal modification of the parent catalyst, facile catalyst linkage and combinatorial flexibility for the identifications of an optimal supported catalyst. Different modes of immobilization, such as acid–base, ion–pair, hydrophobic, biphasic as well as self-assembled gel-type, give different types of heterogeneous organocatalysts. The catalysts obtained by different methods have their advantages and disadvantages at the same time. There is a scope for developing new methodology for heterogenization of organocatalysts.

Immobilization is an effective methodology for heterogenizing an organic molecule onto inorganic material. The two principle mechanisms of organocatalysis is of both covalent and non-covalent nature which lead to (i) the formation of covalent adduct between catalyst and substrate, and (ii) the processes that rely on non-covalent interactions such as hydrogen bonding or within the catalytic cycle is the formation of ions pairs.³²⁰ Owing to the application of organocatalysis in industrial set-up, strategies for heterogenizing organocatalysts are being explored in fine chemical industries as well as pharmaceutical industries. Though the stability of an immobilised catalyst may vary in batch operation and continuous flow operation at higher reaction temperatures, such catalysts are expected to avail the advantages of

heterogeneous catalysis. Heterogeneous organocatalysis is well poised for its potential industrial applications in industry with sustainable and energy efficient approaches. In order to implement the concepts of green chemistry and engineering in the pharmaceutical industry, one must develop large scale organocatalytic reactions processes that involve:

- (i). Immobilization of Organocatalysts (for recycling purposes);
- (ii). No leaching problems due to covalent bonding with the support unlike metal complexes;
- (iii). Results superior to those obtained with free analogous; and
- (iv). solution-phase catalysis

The immobilisation of amino acid derived organocatalysts could be covalently anchored to the inner walls of porous silica and other relevant inorganic structures. These materials have shown promise as heterogeneous organocatalysts for industrial significant reactions, such as the Hajos–Parrish–Eder–Sauer–Wiechert reaction⁸³ and intramolecular [4+2] cycloadditions.³²¹ This approach has the potential to improve recoverability and recyclability, use far less mol% of catalyst and potentially give rise to significant improvements in activity and selectivity. Organocatalysts can be covalently anchored to mesoporous silica by building on current methodologies that are reported in the literature. Tethering is carried out through the side-chain or a functionalized side-chain of a derivatised amino acid, because the mechanism of catalysis relies on the amino and carboxylate groups to be free for substrate binding. Through spatial constraints, nature of the active site and a precise balance of substrate–catalyst–pore wall interactions, the stereoselectivity of the catalytic reaction could also be suitably enhanced. Judiciously controlling the orientation of the channels and the pore-diameter of the mesoporous

support could facilitate enhancements in the desired stereochemical outcome, as observed earlier with anchored transition-metal amino acid complexes. The range of substrates and scope of reactions that can be catalysed by heterogenised amino acids and their derivatives is ever expanding and immobilisation of these organic moieties could result in the design and development of more stable, highly active heterogeneous catalysts.³²²⁻³²⁴ The potential for expanding the scope and industrial applicability of heterogenised organocatalysts demands a greater understanding of the synergistic effects, between the support and the organocatalyst, say e.g. amino acid, at a molecular level, which could provide valuable insights on structure–property relationships and its mechanistic significance. The current organocatalysts development is more focused on solving practical asymmetric synthesis and processes.³²⁵ Following are some interesting examples reported in the field.

Copolymer-supported heterogeneous organocatalyst is prepared and applied for asymmetric aldol addition in aqueous medium.³²⁶ Aldol reaction between acetone and 4-nitrobenzaldehyde was catalyzed by covalently grafted lysine onto silica. The immobilisation technique was found to create well-defined and isolated catalytic sites offering improved activity and chemoselectivity when compared to the homogeneous system.³²⁴

Enantiomerically pure iminium cations supported on zeolite Y – a microporous material and on Al-MCM-41 a mesoporous material were found effective for the epoxidation of aryl alkenes by using peroxymonosulfate as the stoichiometric oxidant. The catalytic reaction gave high conversions and enantioselectivities. The catalysts can be simply recycled by filtration and their activity and selectivity are found much higher than the homogeneous

counterpart.³²⁸ Chiral organocatalyst team up with heterogeneous inorganic semiconductors form C-C bond through stereoselective photocatalysis.³²⁹ Direct stereoselective alpha-functionalization of aldehydes forming C-C, C-N, C-F, C-Br, and C-S bonds are reported over organocatalysts.³³⁰ Solvent-free non-covalent organocatalysis is reported on enantioselective addition of nitroalkanes to alkylideneindolenines.³³¹ DMAP-NCP, a new network nanoporous conjugated polymer containing 4-(*N,N*-dimethylamino)pyridine catalytic moieties, exhibits catalytic activity in the acylation of alcohols and phenols, even under neat and continuous-flow conditions for practical applications on a large scale.³³² An asymmetric Diels-Alder reaction was catalyzed with high efficiency and recyclability by a soluble, “self-supported” chiral organosilica polymer with embedded imidazolidinone catalytic moieties.³³³ The role of some ionic liquids as organocatalysts or co-catalysts requires further understanding and there is a scope for future research in conceptualization of this field, its applications and the context for heterogeneous organocatalysis (Figure 12).³³⁴⁻³³⁵

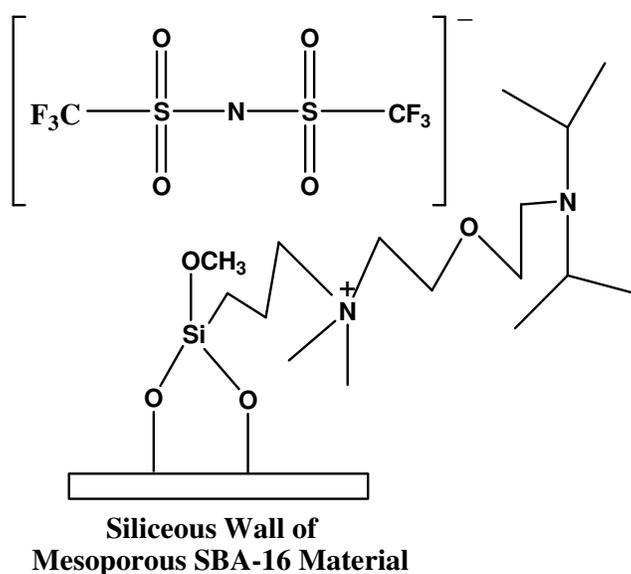


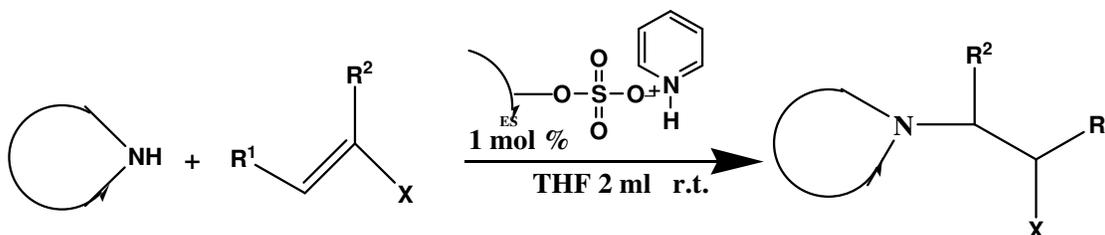
Figure 12.³³⁴

Heterogeneous Organocatalysts from Renewable Resources

Dennis Kühbeck et al. reported a critical assessment of the efficiency of a neutral pH chitosan biohydrogel beads as recyclable heterogeneous organocatalyst for a variety of C–C bond formation reactions (*i.e.* aldol reaction, Knoevenagel condensation, nitroaldol (Henry) reaction).³³⁶

Researchers Françoise Quignard (France) and Luca Bernardi (Italy) undertake development of new heterogeneous organocatalysts based on polysaccharides (chitosan, alginate or carrageenan). The polysaccharides are made available from renewable resources and exploited for their intrinsic catalytic activities. E.g., chitosan is known to bring basic functions while alginate and carrageenan are acidic polymers. The variety of functional groups provides polysaccharides with a surface reactivity especially appealing for specific catalysis processes.

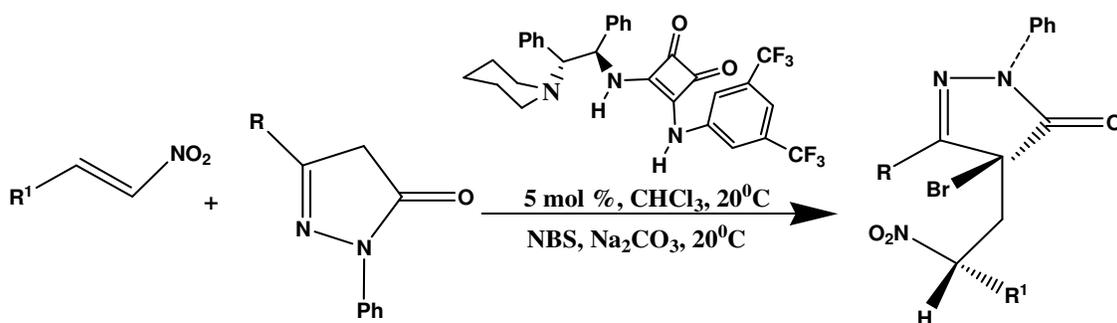
Sanny Verma et al. reported a cost effective, environmentally benign, easily accessible, biodegradable, recyclable and highly efficient pyridinium-based bifunctional organocatalyst (ES-SO₃⁻ C₅H₅NH⁺) grafted to the chemically modified expanded starch, a biomaterial, for the synthesis of β-amino carbonyls by aza-Michael reaction of amines to electron deficient alkenes under mild reaction conditions (Scheme 14).³³⁷



Scheme 14.

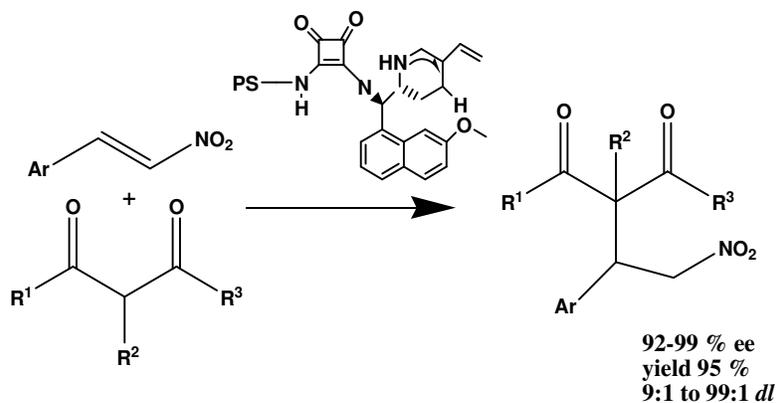
Heterogeneous organocatalysts for their use under continuous flow conditions

In the spirit of developing eco-friendly syntheses, researchers are interested in immobilization of various organocatalysts known to be efficient in aqueous media and in their use under continuous flow.³¹³



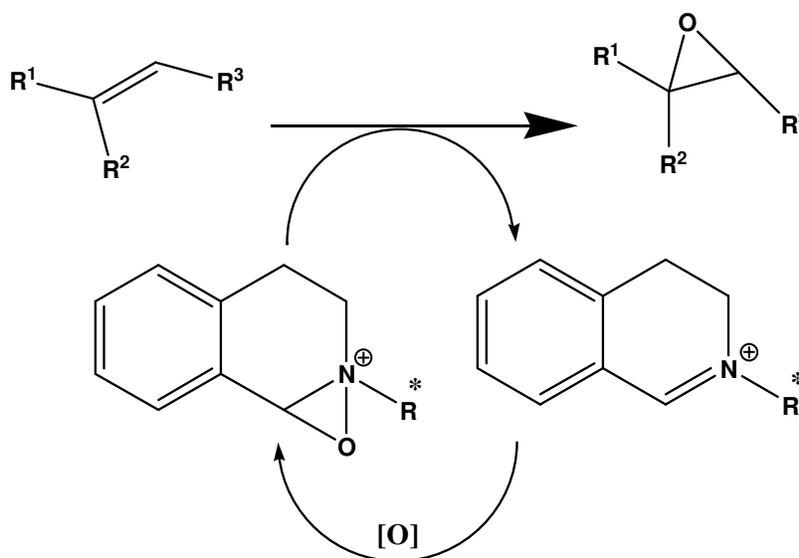
Scheme 15.

An interesting tether-free but immobilized bifunctional squaramide organocatalyst^{338(a)} has found potential application in batch and flow reactions (Scheme 15). A polystyrene-supported highly recyclable squaramide organocatalyst for the enantioselective Michael addition of 1,3 dicarbonyl compounds to β -nitrostyrenes has also found potential industrial utility.^{338(b)}

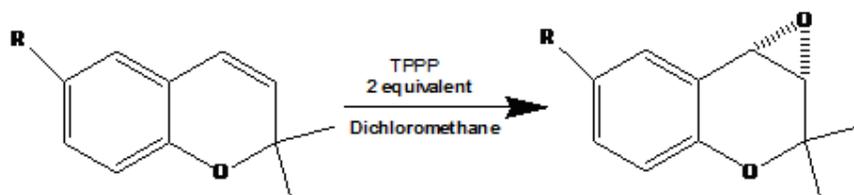


Scheme 16.

Because of their stability and recyclability, solid-supported organocatalysts (Scheme 16) are therefore particularly suitable for continuous flow systems,^{147, 339-340} which allow large-scale synthesis usually accompanied by higher turnover numbers. The miniaturised flow reactors allow improved control of mass and heat transfer and the inherently low reaction volume increases safety making them valuable tools for green chemistry. Reaction-progress kinetic analysis and nonlinear chromatography were applied to investigate a model aldol reaction performed in continuous-flow microreactors packed with proline-functionalized silica gel. The study facilitated by an online instrumental monitoring assessed optimal operation and feed variables.¹⁴⁷



Scheme 17. Mediation of alkene epoxidation by oxaziridinium cations³²⁸



Scheme 18. Epoxidation of chromenes by MCM catalyst³²⁸

Enantiomerically pure iminium cations, supported on microporous Zeolite Y and on mesoporous Al-MCM-41, are effective asymmetric catalysts for the epoxidation of a range of aryl alkenes, giving high conversions quickly and with enantioselectivities (Scheme 17 & 18).³²⁸

9. Pre-industrialization organocatalysis

In 2004, a special issue of the *Advanced Synthesis and Catalysis* research journal was dedicated to organocatalysis.^{341(a)} In year 2006, a special issue of the *Advanced Synthesis and Catalysis* research journal on *Multiphase Catalysis, Green Solvents and Immobilization* published Prof. Cozzi describing in detail the immobilization of organic catalysts.^{341(b)} Several synthetic strategies are developed for the polymeric immobilization of chiral organocatalysts.³⁴²⁻³⁴⁴ Lu and Toy reviewed organic polymer supports for synthesis and for reagent and catalyst immobilization.³⁴⁵ A lot has been done on supported proline and proline-derivates for their applications as heterogeneous organocatalysts.³⁴⁶ A heterogeneous catalyst (L-Pro LDHs) was developed using intercalation of L-proline in Mg–Al Layered Double Hydroxides (LDH). An investigation of the thermal stability and optical stability showed that the immobilization of the chiral catalytic centers in restricted galleries enhanced the enantiomeric stability against thermal treatment and light irradiation. Asymmetric aldol reaction of benzaldehyde and acetone was carried out using L-Pro LDHs as catalyst, resulting in a good yield (90%) and a high enantiomeric excess (94%). Heterogenized L-proline catalyzed the asymmetric aldol reaction using anionic clays as intercalated support.³⁴⁷

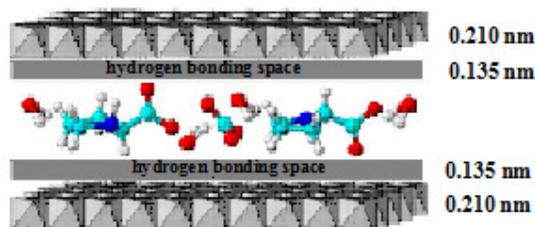


Figure 13. The schematic model of L-Pro LDHs (molar ratio of Mg/Al = 3:1, intercalated yield = 59 %).³⁴⁷

F. Calderon et al. researched³⁴⁸ the aldol reaction of hydroxyacetone with different aldehydes using immobilized proline on a mesoporous support, assisted by heat and microwaves. It was found that heterogenized L-proline on MCM-41 catalyzed aldol reactions in both hydrophilic and hydrophobic solvents, and provided stereoselectivities in some cases complementary to the homogeneous catalyst. The heterogeneous catalysts could be reused without significant loss of stereoselectivity. In a recent example, supramolecular assemblies of amphiphilic L-Proline regulated by compressed CO₂ as a recyclable organocatalyst for the asymmetric Aldol reaction.³⁴⁹ Noncovalently supported heterogeneous chiral amine is used as catalyst for asymmetric direct Aldol and Michael addition reactions.³⁵⁰ An amine grafted on amorphous silica performs as an effective organocatalyst for microwave-promoted Michael reaction of 1,3-dicarbonyl compounds in water.³⁵¹ Silica-immobilized N-hydroxyphthalimide was found to catalyze autoxidation.³⁵² Silica, identified as a useful support material for homogeneous catalysts, facilitates the catalyst recovery and reusability.³⁵³ A heterogeneous organocatalyst for cyanosilylation is also reported lately.³⁵⁴

There are some interesting patents in the literature on usage of some organocatalysts in innovative chemical technologies with some industrial application. There is no need for metal based catalysis thus making a contribution to green chemistry. In this context, simple organic acids have been used as catalyst for the modification of cellulose in water on multi-ton scale.³⁵⁵ In recent years, the emphasis has been on the variety of nano(porous)materials for that has found use in such catalytic systems: these includes nanoparticles, dendrimers, metal oxides, inorganic polymers, mesoporous materials such as MCM-n materials and SBA-n materials. In 2009, a patent related to the use magnetic nanomaterial-supported glutathione and cysteine organocatalysts as “green” nano-catalysts for various reactions such as Paal-Knorr reactions, aza-Michael addition and pyrazole synthesis, etc was filed and later granted in year 2012.³⁵⁶ Sulfonamide-based organocatalysts and method for their use is patented by inventors Rich Garrett Carter and Hua Yang. Proline sulfonamide organocatalysts performing various enantioselective or diastereoselective reactions such as the aldol reactions, conjugate additions, Michael additions, Robinson annulations, Mannich reactions, alpha.-aminoxylation, alpha.-hydroxyaminations, .alpha.-aminations and alkylation reactions, etc. Among the various methodologies claimed, a sulfonamide derived catalyst was used for the construction of allcarbon bicycles, such as [2.2.2]-bicycles.³⁵⁷

Organocatalysts are blamed for not being recoverable after a reaction. There are interesting reports that study homogeneous or heterogeneous nano-supports for easy recovery of the organocatalysts. Caminade et al identified perfectly defined hyperbranched polyphosphorhydrazone dendrimers, either

neat or attached to siliceous solid material, as nano-supports for easy recycling of organocatalysts.³⁵⁸⁻³⁶¹

10. Characterization tools and techniques

In order for us to research catalysis and relevant aspects, we may require spectroscopic techniques, magnetic measurements, transport and thermal measurements, scattering techniques, microscopic techniques, thin-film deposition techniques, etc. The catalytic systems, especially the heterogenized organocatalysts, prepared can be characterized by X-ray diffraction (XRD), nitrogen sorption, scanning electron microscopy (SEM), transmission electron microscopy (TEM), FT-IR, UV-Visible, Nuclear Magnetic Resonance (NMR), Raman, etc. In case of nanoporous materials, the pore diameters could be uniformly tailored. The NMR studies of organocatalysts in porous materials could also be of importance for understanding the structure and bonding within the organic and inorganic part of a catalytic system. There is always a scope for identifying and utilizing new characterisation techniques for studying catalytic systems and properties, especially the surface behaviour, hydrophilic/hydrophobicity, interactions, molecular sorptions, recognitions, etc. and many more.

11. Future Scope of heterogeneous organocatalysts

It is always a risk to predict what the future holds for any research area, but several aspects of modifications of existing catalysts and also heterogenisation of organocatalysts onto some sort of robust high surface area support including nanomaterials or nanoporous materials undoubtedly attract researchers' attention. Tremendous efforts should be directed towards the discovery and design of catalytic systems with better efficiency, new

reactivities and greater turnover numbers. Perhaps the most crucial area of research in the future will be the identification of important organic transformations at industries that are not available using other branches of catalysis. Given the huge growth and impact of organocatalysis in its present form, it will certainly be exciting to observe the development of the field upon heterogenization.

A variety of reactions such as reduction, oxidation, multicomponent, Mannich, alkylation, condensation, deprotection, cycloaddition, hydroxylation, dehydration, dehydrogenation, transesterification, reactions involving biomimetic oxygen-evolving catalysts and other important C–C bond forming reactions are well presented on the heterogenized organocatalysts under a variety of reaction conditions.

For any large-scale catalytic process, the most salient considerations are cost and safety and so critics' opinion on low turnover numbers limiting the potential usage might not discourage the industrial applications. Because organocatalysts are often cheaper than metal-based catalysts, they can be used in larger quantities than metal-based ones for the same price. Moreover, it is widely recognized in manufacturing that the removal of toxic catalyst related impurities from the waste stream can often have a larger financial impact than the turn over number of the catalyst. In the coming years, various approaches for immobilisation will be considered, with a focus on whether a novel methodology for the immobilisation of organocatalysts could be discovered. The benefits of heterogenisation will become apparent on evaluation of the catalytic potential. Apart from the nature of the support, the degree of catalyst loading and selection of reaction media or solvent tune the

catalytic behaviour. Alternatively, immobilized organocatalysts can be prepared that are linked to the solvents like ionic liquids that allow the catalytic entity be separate from the reaction medium by simple extraction or filtration. In another approach, the immobilized organocatalyst might permit us to perform the reactions in biphasic or different conditions. This catalytic system and reaction conditions could find industrial application. Scientific and technical tasks researchers can undertake are the immobilization of the organocatalyst on solvent and or onto the walls of a reactor. Future catalysts development should be more oriented toward real problems in synthetic processes. It would be also interesting to see (i) the explorations of non-covalent interactions and entrapment in nanosized materials in developing supported organocatalysts; (ii). Fine tuning of the screened catalysts and their thermal, mechanical and catalytic stability; (iii) Evaluation of catalyst deactivation and its rejuvenation mechanisms

12. Conclusions

The literature survey and ideas jotted above do not fully claim to conceptualize all the aspects of this new field of heterogeneous organocatalysis. The aim of this review is to illustrate the significance of a variety of organic molecules as catalysts employed for a wide variety of organic transformations. The most highlighted fact is that these organocatalysts represent an interesting scope for heterogenization. In the review of literature, the basic concept of organocatalyst, strategies for heterogenization, preparation methods and various applications of heterogeneous organocatalysts have been discussed. Like in other heterogeneous catalytic systems, the materials or supports could also play very important role in the total catalyst system used both as catalyst

and catalyst carriers. The emphasis has been on the variety of nano(porous)materials that has found or could find use in such catalytic systems: these includes nanoparticles, dendrimers, metal oxides, inorganic polymers, mesoporous materials such as MCM-n materials and SBA-n materials.³⁶²

In this book, the author focused on applications of organocatalysts in asymmetric synthesis, synthesis of fine chemicals and green chemistry. The preceding pages are an account of recent research and developments made in the use of organic molecules as catalysts. It is highlighted that organocatalysts are versatile which not only catalyse the most fundamental reactions in organic chemistry but also finds applications in processes of commercial importance in chemical industries. Several very useful applications of organocatalysts are in production of agro-chemicals, clean energy, drugs, polymers, and petrochemicals, etc. In view of the globally increasing interest towards energy efficient and environmentally friendly chemical technology for industries, research on the development of robust, recyclable, selective, metal-free, easy-to-scale up catalysts and their useful preparation methods are thus the need of the hour.

Great strides are still to be made in the synthesis and characterization of supported or immobilized organocatalysts in order to apply them as heterogeneous catalysts that emphasize applications in existing industrial processes. These catalysts are going to be modified in future and make their catalytic activities accessible in industrial set up for sustainable and environmentally benign technologies.

The author has also outlined recent progress in the use of heterogeneous organocatalysts by briefing on the recent publications in scientific publications. The year 2012 saw thematic series, dedicated to showcase the current state of the art of organocatalysis, published by the *Beilstein Journal of Organic Chemistry*. For those readers who are expecting an update on the recent trends in organocatalysis, the author lists herein³⁶³⁻³⁷¹ excellent reviews published in the year 2013 on some very very specialized topics of organocatalysis.

This book encloses 371 useful references for providing readers with a well described state-of-the-art. The studies to address the scope of this catalytic science are underway. The scientific discoveries and innovations involving organocatalysts are reported almost on a daily basis. Many researchers are joining this field, especially to understand the catalytic phenomena and develop heterogeneous catalysts for asymmetric synthetic methodologies for chemical industry. Let's catalyze the green chemistry revolution! As rightly said by Prof. Benjamin List, "*the research in organocatalysis constitutes the tip of the iceberg of a novel catalytic principle, of which the entire scope still remains to be fully uncovered.*"

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14. References

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