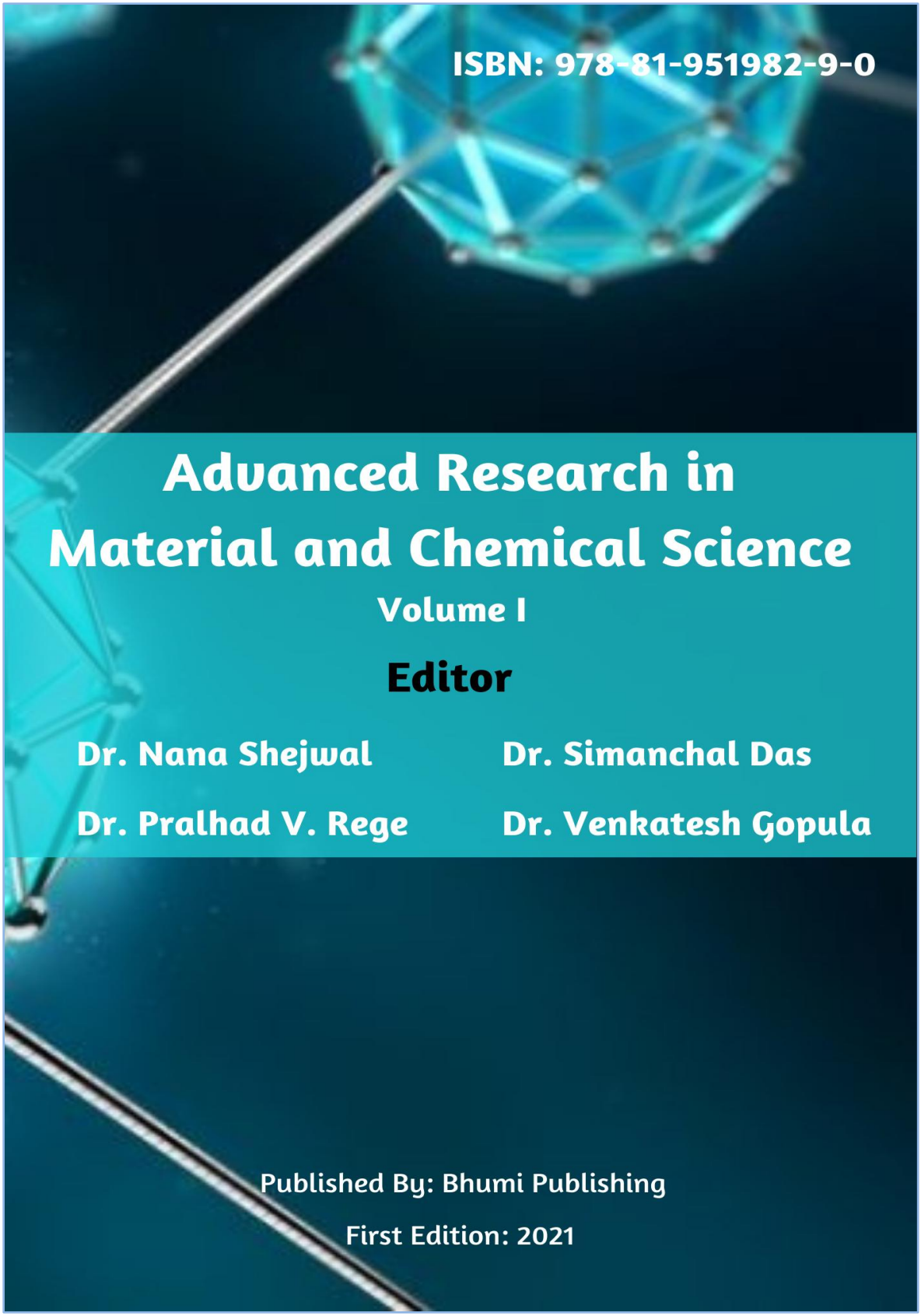

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Editor

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CONTENTS

ORGANOCATALYSIS: AN IMPORTANT STRATEGIC TOOL FOR TOTAL SYNTHESES

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Introduction:

Organocatalysis refers to a form of catalysis, whereby the rate of a chemical reaction is increased by an organic catalyst referred to as an "organocatalyst" consisting of carbon, hydrogen, sulfur and other nonmetal elements found in organic compounds. Over the last decade, catalysis of reactions by simple metal-free organic molecules (organocatalysis) has become an important area of research. Although organocatalysis frequently require a high catalyst loading and long reaction times, compare with catalysts made of metal complexes, organocatalysts show many extraordinary advantages including their lack of sensitivity to moisture and oxygen, their ease of preparation, low toxicity and less expensive.[1] All of these advantages are attractive towards the synthesis of pharmaceutical intermediates. Basically, organocatalysts can be divided into four types based on their modes of activation: Lewis bases, Lewis acids, Bronsted bases, and Bronsted acids. Since the rediscovery of organocatalysis at the dawn of the new millennium an exponential number of papers on this subject appeared over the years.[2] It generated several excellent reviews and books where various aspects of this field have been dissected.[3,4] Pavel Kocovsky pointed out that while the words ‘‘asymmetric’’ and ‘‘organocatalysis’’ were closely connected in the minds of the many scientists working in this field, chiral compounds are not the only important ones which can be easily prepared employing this methodology.[5] The well-known attractive aspects of organocatalysis such as environmentally friendly conditions (no need for anhydrous conditions or of transition metals)[3] without any doubt apply also to transformations affording achiral molecules as products.

This field is still in its early years, researchers are now starting to ‘‘think organocatalytic’’ when applying disconnecting strategies to total syntheses. Some non-asymmetric organocatalytic reactions are so surprising that they could not have been foreseen at the beginning of their relevant project. In several cases the achiral products are the undesired side

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products in an asymmetric transformation. As it has happened several times before, coincidence brought a significant advance in science.[6]

Types of organocatalysts:

Broadly speaking the organocatalysts can be classified into four main categories, (**Figure-1.1**) they are

1. Lewis Base catalyst,
2. Lewis Acid catalyst,
3. Bronsted Base catalyst and
4. Bronsted Acid catalyst

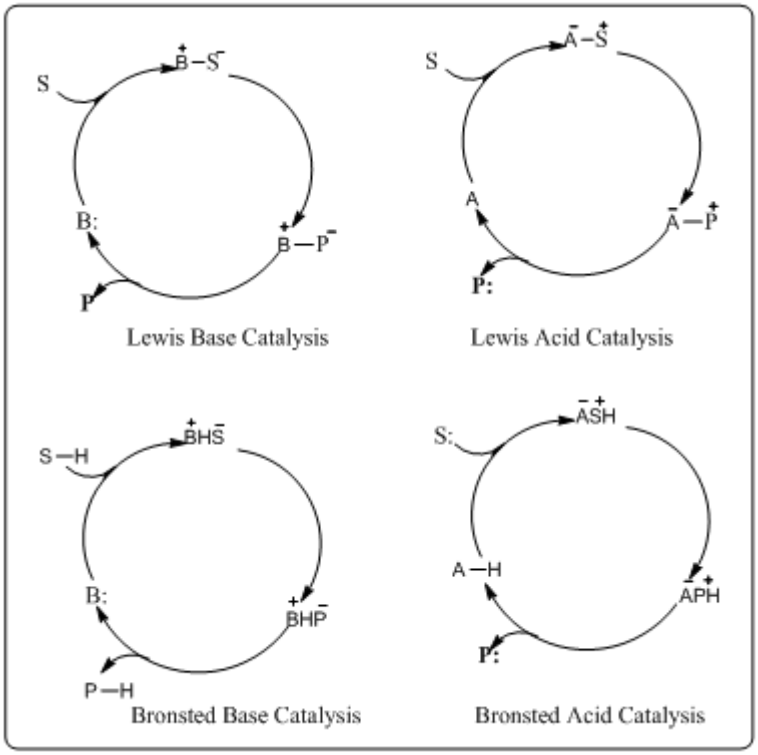


Figure 1.1: Types of organocatalysts

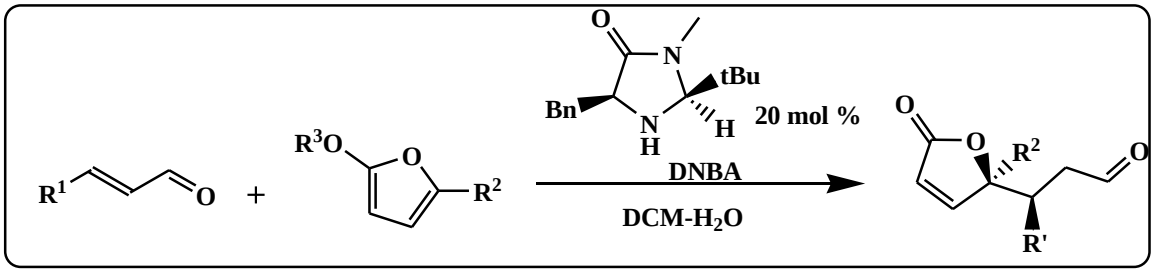
Lewis Basic Organocatalysts and Organocatalysis:

Various bases have been reported in the literature as an efficient organocatalysts. These include the iminium ion, phosphine, cyclic amino acids such as proline etc. The important examples of Lewis base organocatalysis have been discussed below.

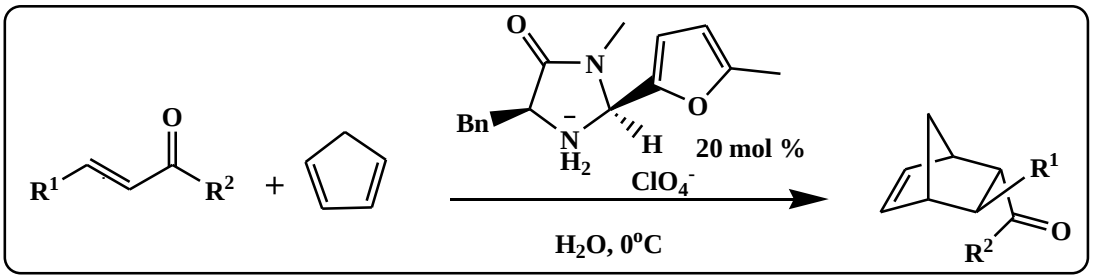
a) Diels-Alder Reaction:

Group of MacMillan reported first enantioselective organocatalytic Mukaiyama-Michael reaction leading to the direct access to enantioenriched γ-butenolide architecture via the 1,4

addition of substituted furan to α,β-unsaturated enals catalysed by imidazolidinone catalyst[7] (iminium ion), **scheme-1.1**. In Diels-Alder reactions, α,β-unsaturated carbonyl compounds as diene and 1,4-cyclopentadiene as dienophiles had also been reported by analogous catalyst[8] but with 5-methylfuryl substituent instead of *t*-butyl group, (**scheme-1.2**)



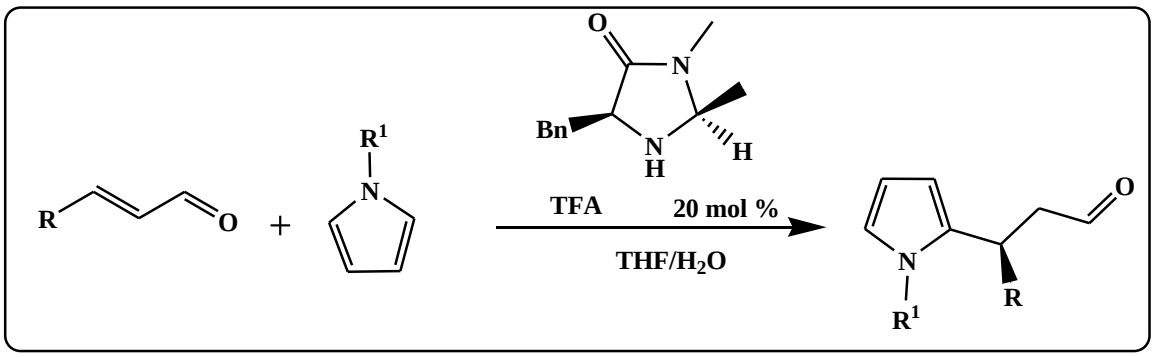
Scheme-1.1



Scheme-1.2

b) Friedel-Craft Alkylation of Pyrrole

To further demonstrate the potential of iminium-catalysis strategy, the group of MacMillan reported an asymmetric Friedel-Craft alkylation of pyrrole and indole, a variant that is currently unavailable using acid or metal catalysis. The reaction is common as it has wide scope with substituents on both, aldehydes as well as pyrrole[9] such as alkyl, alkoxy, benzyloxy and ester were well tolerated along with good to excellent yields and enantioselectivity, (**scheme-1.3**)



Scheme-1.3

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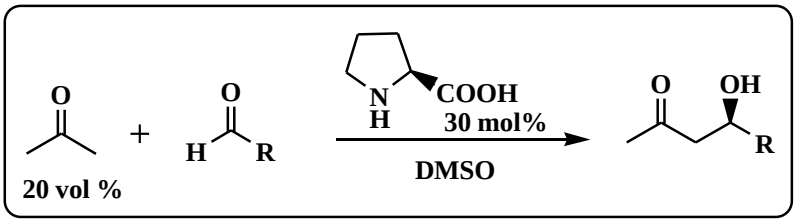
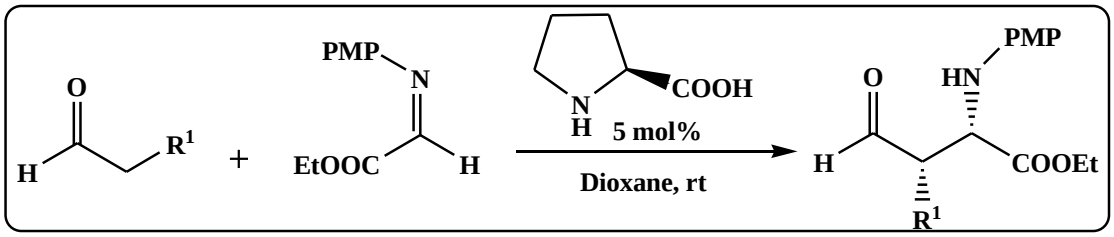
c) Aldol Reaction (Ketone-Aldehyde aldol)

Aldol condensation constitutes one of the key organic reactions leading to highly versatile β-hydroxy aldehyde or ketone building blocks. One of the versatile utilities of organocatalysis is the aldol condensation reaction. List *et. al.*[10] reported the L-proline catalysed asymmetric aldol condensation of enolisable ketone and aldehydes, (**scheme–1.4**). In addition the organocatalysis has been successfully achieved for Mannich reaction[11] using similar types of catalyst, (**scheme – 1.5**).



Scheme- 1.4



Scheme-1.5

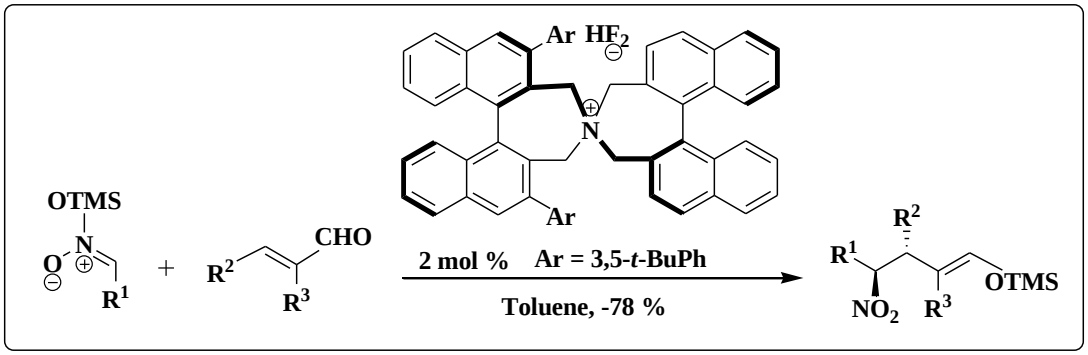
Lewis Acidic Organocatalysts and Organocatalysis:

An additional useful category of organocatalysis is Lewis acid organocatalysis, several efficient Lewis acid types of organocatalysts have been emerged recently. These include the phosphorous, nitrogen and boron based catalysts.

Some selected examples of Lewis acid organocatalysis are discussed below

a) Michael addition

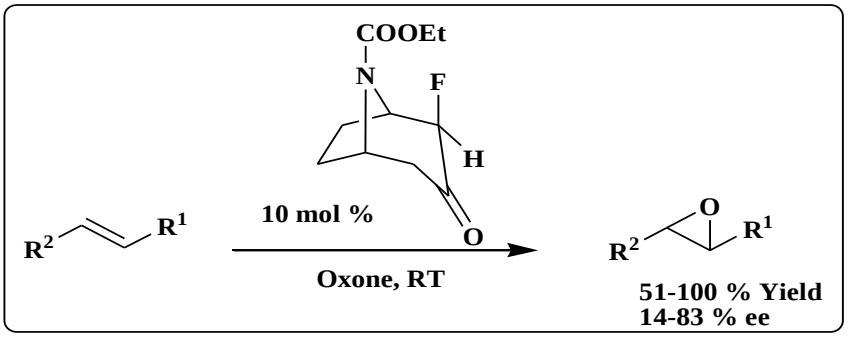
Maruoka *et al.*[12] reported the Chiral ammonium bifluorides as extremely efficient organocatalyst for highly enantioselective Michael addition of silyl nitronates to α, *β*-unsaturated aldehydes. This protocol provided the access to optically active *γ*-nitro aldehydes and their enol silyl ethers in high to excellent yields, (**scheme-1.6**).



Scheme-1.6

b) Epoxidation

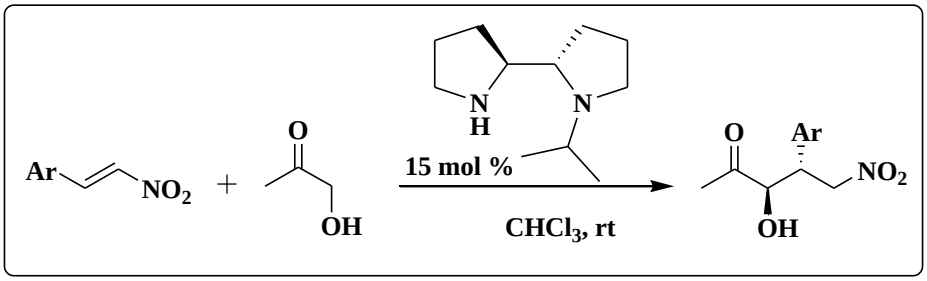
Lewis acidic catalyst such as cyclic amino ester α-fluoro-*N*-carbethoxytropinone[13] has been reported for the epoxidation of alkenes. The reaction proceeded efficiently and to afford wide variety of oxiranes in good to excellent yields and reasonably high enantiomeric excess, (**scheme-1.7**).



Scheme-1.7

c) *Insitu* Enamine: Michael Addition (Addition to nitroalkenes)

The direct Michael addition of α-hydroxyketones to β-arylnitroolefins catalysed by *N*-*iPr*-2,2'-bipyrrolidine is reported by the Alexakis group[14], (**scheme-1.8**). In this tertiary nitrogen of the catalyst leads to the formation of enamine intermediate that tells the diasteroselectivity and very high ee's.



Scheme- 1.8

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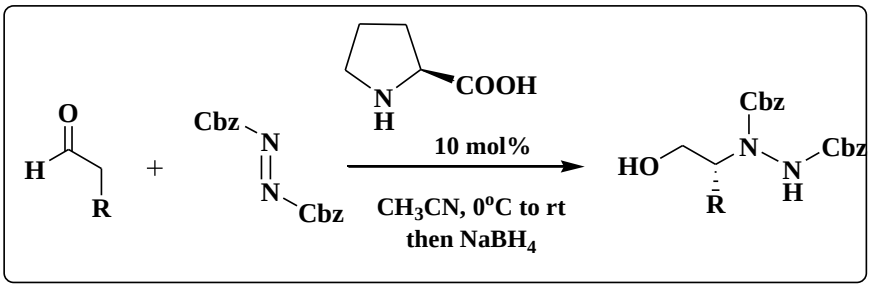
d) *Insitu* Enamine: Oxidations (α- Amination)

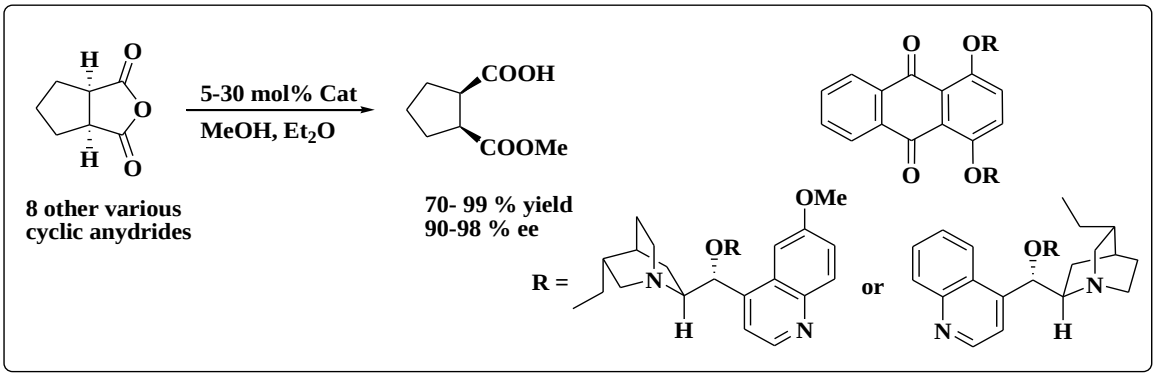
The β-amino alcohols are considered to be highly versatile building blocks in organic synthesis. The organocatalysed stereoselective process for β-amino alcohol have been recently developed by group of List[15] in which the addition of enolisable aldehyde to Cbz protected carbodiimide using S-proline followed by reduction affored the β-amino alcohol in excellent yield and distereoselectivity, (**scheme -1.9**).



Scheme- 1.9

Bronsted Basic Organocatalysis:

As compared to Bronsted acidic catalysis the information on the Bronsted basic organocatalysis are relatively scares. In 2000, the group of Deng[16] reported the cinchona alkaloid catalysed enantioselective opening of readily accessible prochiral cyclic anhydrides. The chiral hemiester with one or multiple stereogenic centres and two distinct functionalities were readily obtained in high to excellent yields and enantiomeric excess. (**Scheme-1.10)**.



Scheme-1.10

Bronsted Acidic Organocatalysis:

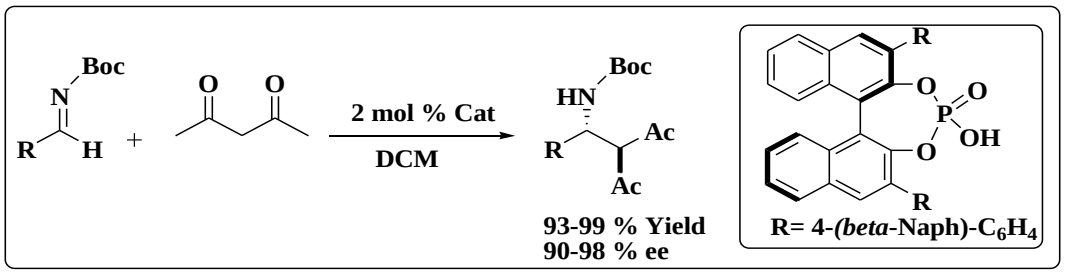
Recently, Jacobsen *et al.* have developed highly enantioselective Strecker reactions[17] and Mannich reactions[18] catalyzed by peptide-based thiourea derivatives as chiral Brønsted acids. The Bronsted acid organoctalysis has been recently extensively studied and well documented in

the literature. A plothera of Bronsted acid based on phosphorus and boron in particular, chiral catalyst have been synthesized in their pioneer work by group of List.

The various Bronsted acid catalysed reactions have been reviewed below

a) Addition of active methylene compound to imine

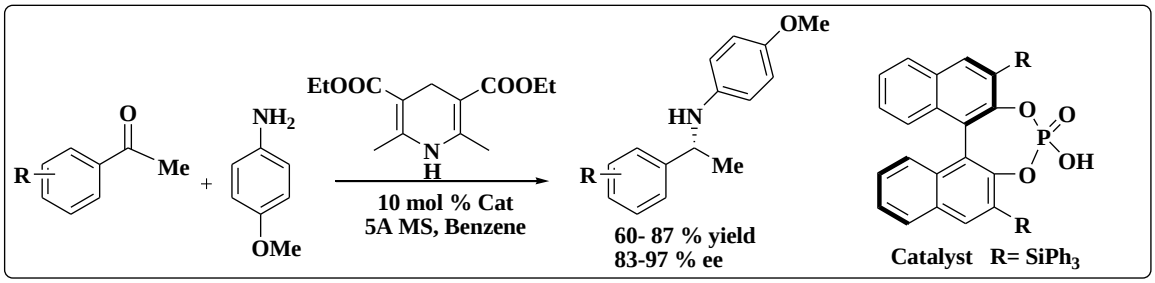
In 2004, Terada. *et al.*[19] reported the binol phosphoric acid derivatives which serve as highly effective catalyst for the direct addition of acetyl acetone to *N*-Boc-protected arylimines to construct the *β*-aminoketones in excellent yields and enantioselective under extremely mild conditions, (**scheme-1.11).**



Scheme-1.11

b) Reductive amination of aldehydes and ketones

In 2006, MacMillan *et al.*[20] first of all developed the enantioselective organocatalytic reduction amination of aldehydes and ketones in the presence of Hantsch ester mediated by binol based phosphoric acid catalyst in good to high yield. The method was found to be highly stereoselective as it provided the corresponding 2^0 amine in high to excellent enantiomeric excess, (**scheme-1.12**).



Scheme-1.12

c) Micheal Addition

In 2003, Takemoto *et al.*[21] reported the thiourea derivative catalyst as a bifunctional organocatalyst which promoted the Micheal reaction of malonates to various nitroolefins to gave nitro malonates derivatives in good to high yields and excellent enantioselectivitiy, **(scheme-1.13).**

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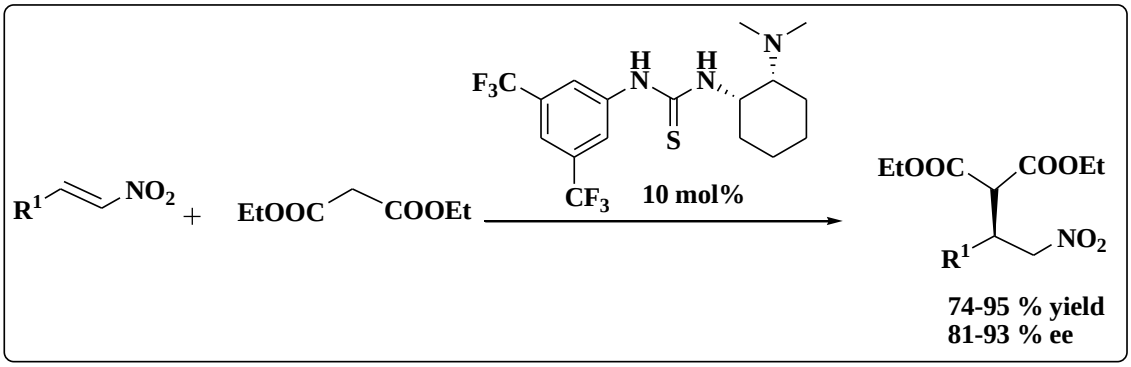
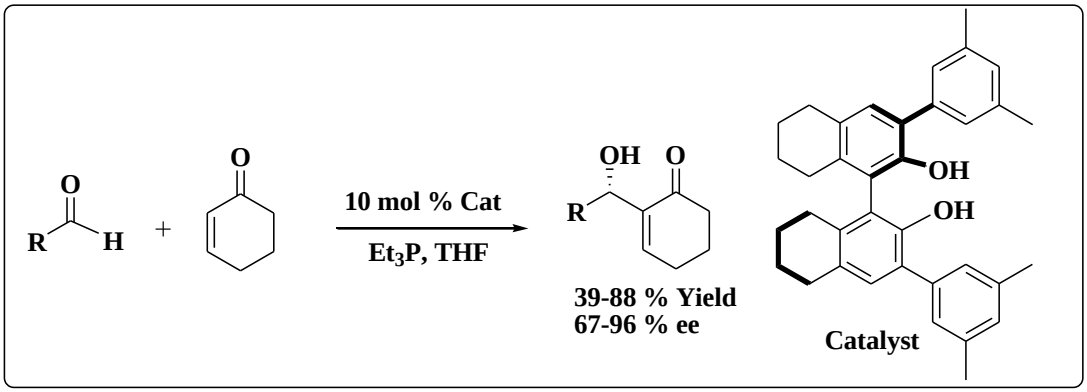


Scheme-1.13

d) Morita-Baylis-Hillman

Schaus *et al.*[22] in 2003, developed a highly enantioselective asymmetric Morita-Baylis-Hillman reaction involving the addition of cyclohexenone to aldehydes catalysed by a chiral BINOL derived Bronsted acid and yields were obtained in good to excellent with excellent enantiomeric excess, (**scheme-1.14).**



Scheme-1.14

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