Chapter 1: General Introduction

Oxidation

Oxidation is a process by which an element undergoes net loss of electrons, hydrogen or gain of oxygen. In other words, oxidation is the conversion of a functional group in a molecule from one category to its higher oxidized form. Most of the naturally occurring processes are either oxidation or reduction or combination of both i.e. redox reaction. The oxidation and reduction process occur simultaneously and dependently.

1.1. Classification of Oxidation

Generally, the oxidation can be broadly categorized into

1. Stoichiometric oxidation
2. Catalytic oxidation

1.1.1. Stoichiometric Oxidation

Stoichiometric oxidations usually employs stoichiometric amount of metal oxidants like Cr, Mn, Os, Ce and others for carrying out the oxidation. Traditional stoichiometric oxidants such as dichromate, chromate, permanganate, manganese dioxide, osmium tetroxide, lead tetraacetate etc. still play an important role in industrial processes such as cumene process, kraft bleaching, conversion of acrolein to acrylic acid, photo processing and treatment of pharmaceutical wastewaters etc.

Classically, reactants and oxidants are used in stoichiometric amount to carry out the reaction. Most of the stoichiometric oxidants are toxic and excess usage of these oxidants lead to the release of large amount of inorganic effluents along with the target products, thus accounting for pollution and environmental degradation. This major drawback of conventional stoichiometric oxidations can be avoided by the development
of environmentally friendly catalytic oxidative methods. Thus it has become a necessity to develop catalytic oxidations from the environmental and green chemistry point of view.

1.2.2. Catalytic Oxidation

In search of an ideal synthetic process, to reduce energy consumption, protect the environment and to conserve natural resources are some of the challenges faced by synthetic organic chemists. A process which is more economical, energy-saving, environmentally benign and sustainable way to give products in high yield and high selectivity is challenging. These demands can be fulfilled by catalytic processes, where a metal or organic compound called catalyst was used in sub-stoichiometric amount to carry out the reaction. Catalysis lies as the heart of modern synthetic chemistry since 90% of all commercial chemicals are produced by methods that involve at least one catalytic step.

In catalytic oxidation, the stoichiometric oxidants employed are molecular oxygen, hydrogen peroxide, alkyl hydroperoxide, persulfate, percarbonate, hypochlorite, and hypochlorates. Their main advantage over stoichiometric oxidation is that catalytic oxidation do not release excess metal ion as a side product in the course of the reaction. Moreover, such methods would obey 4 of the 12 guiding principles of green chemistry proposed by Anastas and Warner. In recent years, the term “green chemistry” has become increasingly important, with the objective to create new products, industrial and laboratory processes, and services that achieve social and economic progress without environmental impairment. A clean synthetic technology should proceed with a high atom economy and the overall synthesis must be accomplished with a low $E$-factor, thereby minimizing the cost of waste disposal. The
ideal system for “green” oxidation is the use of molecular oxygen as the primary oxidant together with recyclable catalysts in nontoxic solvents or supercritical CO₂.¹²

Among the commercially available oxidants, molecular oxygen, hydrogen peroxide, and alkyl hydroperoxides can be regarded as the best oxidants compatible with current environmental concerns. Alkyl hydroperoxides, which can be regarded as an ‘activated’ form of hydrogen peroxide, are used as complementary to oxygen (O₂) and hydrogen peroxide (H₂O₂).

This catalytic oxidation can be further divided into

a. Transition metal-catalyzed oxidation

b. Organocatalyzed oxidation

1.2.2.1. Transition Metal-Catalyzed Oxidation

Transition metal-catalyzed oxidation has evolved as one of the most useful and powerful tools in organic synthesis.¹³ Metal-catalyzed oxidations have also been developed for selective oxidations that can be carried out in laboratory scale. This catalysis usually involves soluble transition metal salt such as acetates or naphthenates of Co, Mn, Fe, Cu, Pd, Rh and metal oxides. Furthermore, catalysis requires recycling of the metal species between several oxidation states by one equivalent changes.

1.2.2.2. Organocatalyzed Oxidation

In organic chemistry, the term organocatalysis refers to a form of catalysis, where the rate of a chemical reaction is increased by an organic molecule referred to as an "organocatalyst" consisting of carbon, hydrogen, sulfur and other non-metal elements.¹⁴ Organocatalysts can be classified as the following:
Biomolecules: Biomolecules are employed as the catalyst. e.g. proline 1.1, phenylalanine 1.2, secondary amine 1.3, cinchona alkaloids 1.4, certain oligopeptides 1.5 (Figure 1.1).

Figure 1.1. Biomolecules as organocatalyst

Hydrogen bonding organocatalysts: TADDOLs 1.6, BINOL 1.7, derivatives of BINOL such as NOBIN 1.8 and organocatalysts based on thioureas 1.9 (Figure 1.2).
➢ N-heterocyclic carbenes (NHCs): Several classes of NHCs like imidazolium carbenes 1.10, imidazolinium carbenes 1.11, triazolium carbenes 1.12, thiazolium carbenes 1.13 etc (Figure 1.3).

Figure 1.2. Hydrogen bonding organocatalysts

Figure 1.3. Representative types of N-heterocyclic carbenes used as organocatalyst
The main advantages of organocatalysis are:

- Simple organic molecule can be used as catalyst for the organic reactions
- Can promote various organic transformations through unique activation modes
- The process does not need metals for catalysis, thus making significant contribution to green chemistry
- When the organocatalyst is chiral, an avenue is opened for asymmetric catalysis

1.2. N-Heterocyclic Carbenes (NHCs)

Carbenes are those compounds possessing a neutral divalent carbon atom and six electrons in its valence shell and are usually short-lived.\(^{15}\) Their incomplete octet shell and coordinative unsaturation render highly unstable and more reactive intermediates in organic transformations. They were broadly classified into singlet carbenes (which are either nucleophilic or electrophilic in nature) and triplet carbenes (which are radical in nature). When the strong \(\pi\)-donor substituents are present in the neighboring atoms of the carbene carbon, electrophilicity of the carbene carbon decreases thereby increasing its nucleophilicity and are hence called as nucleophilic heterocyclic carbene (NHC). So, broadly NHCs are defined as heterocyclic species containing a carbene carbon flanked between two heteroatoms, among them at least one heteroatom should be nitrogen.\(^{16}\) Generally, NHCs feature bulky substituents on heteroatom adjacent to the carbene carbon, which helps to stabilize kinetically by sterically disfavoring dimerization to the corresponding olefin. Further electronic stabilization was given by neighboring heteroatoms.\(^{16c}\)

In the last two decades, there was tremendous development in the field of N-heterocyclic carbene chemistry and their application in catalysis.\(^{17-19}\) Their use as organocatalysts works as a powerful tool due to their lower toxicity and atom economy in contrast to the traditional metal-catalyzed synthesis.\(^{20}\) In account with ‘Green
Chemistry’ point of view, organocatalysis minimizes the release of metal waste to the environment.\textsuperscript{21} The NHC field had sluggish growth in the early stages. In 1943, Ukai \textit{et. al} observed that coenzyme thiamine (Vitamin B1) \textbf{1.14} can catalyze the benzoin reaction.\textsuperscript{22a} In 1970, Stetter \textit{et. al.} used thiazolium salts as organocatalyst to catalyze the benzoin reaction.\textsuperscript{22b} Then, Bertrand group isolated first stable phosphinocarbene \textbf{1.15}\textsuperscript{22c,f} in 1988 and in 1991, first stable crystalline NHC \textbf{1.16} was isolated by Arduengo \textit{et. al} (Figure 1.4).\textsuperscript{22g}

\begin{center}
\includegraphics[width=\textwidth]{figure1.4.png}
\end{center}

\textbf{Figure 1.4.} Earlier known N-heterocyclic carbenes

Due to the excellent $\sigma$–electron donor properties, NHC has found enormous practical significance in most important catalytic transformations in the chemical industry.\textsuperscript{17,18} The capacity of NHCs to act as either versatile ligands in transition metal catalysis or solely as organocatalyst has made them a powerful and valuable tool in catalysis and opened up a wide research area for the synthetic organic chemists to explore.

\subsection*{1.2.1. N-Heterocyclic Carbone (NHC) as Organocatalyst}

NHCs in organocatalysis are typically employed to render aldehydes nucleophilic, thereby reversing their typical reactivity referred to as umpolung
reactivity. Benzoin and Stetter reactions catalyzed by NHC are the examples for this reactivity in which nucleophilic aldehyde 1.17 or more commonly called as acyl anion equivalent 1.19 was used to form new C–C bonds (Scheme 1.1). Both the reactions were extended for the asymmetric version by using enantio-enriched thiazolium and triazolium salts as precatalysts.

Scheme 1.1. Schematic representation of Benzoin and Stetter reactions

1.2.2. Benzoin Reaction via NHC-catalysis

First Benzoin reaction was reported in 1832 by Liebig and Wöhler where cyanide ion catalyzes the formation of α-hydroxy ketones via the formation of new C–C bond between two aldehydes. After 40 long years, Ukai and co-workers reported thiazolium salts as organocatalyst for the Benzoin reaction. Later Breslow proposed a plausible mechanism for the same which involves acylazolium intermediate commonly known as Breslow intermediate. In 1966, Sheehan reported the use of chiral thiazolium salts for the asymmetric synthesis of chiral benzoin product from benzaldehyde in 22% ee. Scheme 1.2 depicts the details of various imidazolium
catalysts used in asymmetric versions for both intermolecular and intramolecular Benzoin reaction.\textsuperscript{23e-i}

\textbf{Scheme 1.2.} Asymmetric Benzoin reaction catalyzed by N-heterocyclic carbenes

1.2.3. NHC as Organocatalyst for Stetter Reaction\textsuperscript{24}

In 1970’s Stetter carried out the synthesis of 1,4-dicarbonyl compounds from the intermolecular addition of aldehydes to Michael acceptors catalyzed by cyanide which is an extension of Benzoin reaction.\textsuperscript{24a} Later, the same group found that thiazolium salts can also catalyze the same reaction.\textsuperscript{22b} Mechanism was analogous to the Benzoin reaction which involves Breslow intermediate. In 1996, Enders reported first asymmetric example of intermolecular Stetter reaction using thiazolium salt.\textsuperscript{24b} Scheme 1.3 shows some of the chiral NHC catalysts used in asymmetric Stetter reaction. This strategy was extended for the total synthesis of bioactive molecules.\textsuperscript{25}
Scheme 1.3. Asymmetric Stetter reaction catalyzed by chiral NHCs

In both Benzoin and Stetter reaction, reversal of polarity in aldehydes was observed \( i.e \) electron acceptor carbon atom on the substrate was converted into electron donor. NHC 1.37 can react with aldehyde 1.38 to give nucleophilic acyl anion 1.40, electrophilic acyl azoliums 1.41, nucleophilic enol 1.42 or homoenolates 1.43 via Breslow intermediate 1.39 (Scheme 1.4). Growing research in NHC-catalyzed reactions leads to the discovery of other modes of activation sites. Even NHCs are known to act as Brønsted base or it undergoes conjugate addition to \( \alpha,\beta \)-unsaturated ketones.\(^{26}\)

Scheme 1.4. Reactive intermediates in NHC catalysis involving aldehydes
1.2.4. NHC-Catalyzed Oxidative Reactions

NHC precatalyst 1.46 on treatment with base generates free carbene 1.48 which on reaction with aldehydes or activated aldehydes like α-functionalized aldehydes, α-halo aldehydes, epoxy aldehydes, aziridinyl aldehydes, α,β-unsaturated aldehydes 1.44 etc to generate acyl azolium intermediates 1.50. The mechanism for the formation of acyl azolium from aldehydes is shown in Scheme 1.5. These catalytically generated acyl azolium intermediates react with nucleophiles such as alcohols,27a-d thiols,27e carbon dioxide,27f amines27g and azides (1.45)27h to form esters, thioesters, carboxylic acids, amides and carbomyl azides (1.47) respectively.

Scheme 1.5. Mechanism of NHC redox catalysis involving aldehydes
1.2.5. **NHC-Catalyzed Oxidative Cyclization**

Sarkar and Studer observed a Michael addition of $\alpha,\beta$-unsaturated aldehydes $1.69$ to form dihydropyranones $1.71$ via NHC-catalysis (Scheme 1.6). $28a$ This consecutive umpolung methodology uses triazolium NHC as catalyst $1.68$ (2 mol%), quinones as oxidant and the products were obtained in good to excellent yields. In this methodology reactivity of enals were reversed from typical electrophilic to nucleophilic at $\beta$-position. Enantioselective synthesis of dihydropyranone derivatives were also been explained by Xiao, $28b$ You $28c$ and co-workers. Bode and co-workers synthesized dihydropyridinones from enamines and enals. $28e,f$

![Scheme 1.6. Triazolium-catalyzed synthesis of dihydropyranones](image)

In 2014, Park and co-workers developed a triazolium carbene $1.72$-catalyzed domino oxidation/*oxa*-Michael addition reaction for the synthesis of 3-substituted phthalides $1.74$ (Scheme 1.7). $28g$ This strategy has broad substrate scope and tolerates a wide range of functional groups and involves oxidation-cyclization sequence.
1.2.6. Role of NHC as Brønsted Base

In addition to the umpolung reactivity by NHCs, they can also act as a Brønsted base. In 2012, Scheidt and co-workers developed an intermolecular conjugate addition of alcohols 1.77 to α,β-unsaturated compounds 1.76 to give β-alkoxy or aryloxy ketones 1.78 catalyzed by carbene generated from imidazolium salt 1.75. (Scheme 1.8). This is the earliest report on the role of NHC as a Brønsted base where it forms a complex with alcohol, eventually activating it and thus facilitating the conjugate addition reaction with enone.

In 2011, Zhang and Kang observed the role of NHC as Brønsted base for aza-Michael addition of amines (Scheme 1.9). Various aromatic and aliphatic amines 1.81 reacted with α,β-unsaturated ketones 1.80 in the presence of imidazolium carbene

**Scheme 1.7.** Triazolium-catalyzed synthesis of phthalides

**Scheme 1.8.** Imidazolium carbene as Brønsted base for conjugate addition
catalyst 1.79 to form β-amino ketones 1.82 in good to excellent yields. Carbene generated from imidazolium salt reacts with amine to generate NHC-amine complex which further reacts with enone, thus facilitating the 1,4-addition of amine to enone to give the desired β-amino ketones.

Scheme 1.9. Imidazolium carbene as Brønsted base for aza-Michael addition

In 2012, Lupton and Candish developed NHC cascade catalysis for the synthesis of dihydropyranones 1.85 from cyclopropyl enol esters 1.84 (Scheme 1.10).29c In this methodology, the author observed that carbene derived from imidazolium salt 1.83 can act as dual catalyst and it was successfully applied to this transformation which requires both Brønsted and Lewis base activation. Mechanistic studies reveal that this transformation undergoes via electrocyclic cyclopropane rearrangement and an anionic oxy Claisen-rearrangement.
Scheme 1.10. Imidazolium carbene as Brønsted base rearrangement of cyclopropyl enol esters to dihydropyranones

In 2012, Cheng and Fan observed two different transformations of isocromene derivatives catalyzed by NHC as Brønsted base (Scheme 1.11). In this methodology imidazolium catalyst 1.86 and triazolium catalyst 1.87 were used for converting isocromene ketones 1.88 derivatives to 1-arylnaphthalenes 1.89 and α,β-unsaturated ketones 1.90 in high yields. Both conversions were achieved by the deprotonation of α-proton of the ketone by NHC catalyst thus acting as Brønsted base.

Scheme 1.11. NHC-catalyzed transformation of isocromenes

As explained in this chapter, the use of NHC as organocatalyst was found to be an active and attractive field of research in organic chemistry. This proves to be an alternative strategy in the present scenario as usage of metals can be avoided. These
catalysts can be used for the construction of new C–C or C–hetero atom bonds with high efficiency as they have various mode of activation. Thus, in the present thesis, the use of NHC as organocatalyst for various oxidative processes for the synthesis of different biologically relevant compounds is envisioned.

1.4 Objectives

In this context, the use of NHC as an organocatalyst for oxidative transformations can be considered as a promising alternative strategy for existing methods which employs toxic, expensive metals and reagents. Thus the proposed specific objectives of the thesis are given below:

1. Development of N-heterocyclic carbene (NHC) as organocatalyst for the synthesis of amides from simple aldehydes and primary and secondary amines via oxidation using N-bromosuccinimide (NBS) as the oxidant at ambient temperature.

![Reaction Scheme](image)

2. NHC-catalyzed oxidative C–H bond oxidation of alkylarenes and N-benzylamines using tert-butyl hydroperoxide (TBHP) as an oxidant to their corresponding carbonyl compounds was established. The developed methodology was extended for the synthesis of 3H-quinazolin-4-ones.
3. NHC-catalyzed synthesis of biologically active β-amino ketones from unfunctionalized ketones and 2-aminopyridines was performed. This metal-free strategy promises to be an alternative approach for the Mannich reaction for the preparation of β-amino ketones. The scope of the reaction includes heterocyclic ketone, 2-acetylnaphthalene, sterically hindered 2-substituted acetophenone and various substituted 2-aminopyridines.

4. NHC-catalyzed synthesis of substituted imidazoles from commercially available starting materials such as aryl methyl ketones and benzylamines using TBHP as oxidant under solvent-free condition was accomplished. The scope of the substrates comprises substituted acetophenones including 2-acetonaphthone, 2-acetylthiophene and benzylamines.
1.5 References


