Abstract: This introductory chapter reviews the development made in the chemistry of transition metal catalyzed oxidative transformation reactions.
1.1. General Introduction

Chemical reactions involving the transformation of one organic molecule to another is one of the most challenging approaches to attain significant advancements in pharmaceuticals, agrochemicals and technology lead society. The formation of intermediates or transition state is an essential component in all these reactions, and so understanding the relationship between activation of molecules along with the driving force involved is essential to design a novel synthetic strategies.

During the last quarter of the 20th century, the transition metal-based catalysis has achieved tremendous growth and became a competent tool in many significant synthetic organic transformations reactions. Traditionally transition metals were effective only under high loading and inert condition, but now, they plays significant role in the development of novel methodology under catalytic amount for extensive use in the synthesis of natural products, active pharmaceutical ingredients (API) etc.

The basic principle of all metal catalysts is that they lower the energy barrier between reactants and products by offering an alternative reaction path. A catalyst decreases the activation energy of a reaction ($\Delta G\neq$ is lowered), thereby increasing the rate of the reaction, but has no effect on the chemical equilibrium of the reaction (does not alter Gibbs energy, $\Delta G$ of a reaction). The action of a catalyst can be very specific which, under ideal conditions, results in selective formation of the desired product and avoids side reactions. Further advantages include reduced time, low temperature, mild condition and high tolerance to organic functionalities during the process, which results in an overall progress toward environmental sustainability.
Among various metal catalysts, which were developed for different organic transformations, the use of palladium, copper, iron, manganese, samarium, titanium and silver have received maximum attention. Although, numerous transition metal catalyzed organic reactions are available for the synthesis of varied range of organic molecules, the use of oxidative transformation including cross-coupling reactions have received maximum considerations.

These reactions are operated under mild reaction conditions and provides simple mode for selective functionalization of complex organic molecules. Oxidative approach involving noble metal catalyst generally proceeds under low loading, open-air and aqueous medium, whereas conventional reagent-based reactions proceed under less desirable high loading conditions. Moreover, the selectivity with these metal catalysts can be adjusted by varying the electronic environment around metal using different ligands and additives. This property simplifies the transformation of sensitive and chiral substrates without decomposition or racemization.

The renaissance in the chemistry of oxidative transformation has come after the introduction and easy accessibility of different varieties and wide range of organometallic reagents, which have pacified the catalytic chemistry of transition metal to a more advance level. Organometallic reagents are important synthons in numerous organic transformations owing to their structural diversity and low-toxicity. They also offer frequent applications in various non-identical reactions. For example, the easily accessible and air stable organoboron reagents are widely recognized substrate in Suzuki coupling, hydroxylation, coupling carbonylation, etherification etc. Grignard reagents, the organic magnesium halide reagent, are well recognized
substrate in Kumada coupling and the preparation of alcohols, alkanes, ketones etc. In recent years, arylboronic acids have been emerged as a potential synthons for wide range of organic synthesis.\textsuperscript{1} The chemical stability of arylboronic acids in water and alcohols makes them highly attractive. Organoborons are efficient precursors in many sustainable organic reactions, as they can be used easily in the presence of water without taking special precautions. Arylboronic acids are structurally diverse, stable, easily accessible and environmentally benign with the ability to undergo rapid transmetalation with many metal catalysts. These characteristics have made boronic acid the most versatile species for frequent use in a variety of reactions.

Overall, with the advancement of transition-metal based catalysis and organometallic reagents numerous notable methods involving oxidative transformations have been reported, amongst which are \textit{ipso}-hydroxylation of arylboronic acid to phenols, oxidation of alcohols to carbonyl compounds, carbon-carbon and carbon-heteroatom cross-coupling reactions (Suzuki-Miyaura and Ullmann-type) are prominent. The present thesis deals with the study and development of some novel approach in the field of these oxidative transformations strategies; such as the catalyst preparation, optimization of safer and environmentally benign solvent system, and recyclable catalyst system. Herein, we present a small description on these oxidative transformation reactions, which plays significant role in various synthetic organic chemistry.

1.2. Alcohol oxidation

The oxidation of alcohols gives corresponding aldehydes or ketones which are ubiquitous structural motifs found across various natural, pharmaceuticals and
agrochemicals products. Conventional methods employ oxidants based on metals, such as copper, manganese and chromium, which performs efficiently only under high loading, generating huge amount of side-product.

These drawbacks are now removed and numerous novel methods are available for the efficient conversion of alcohols using catalytic amount of Pt, Pd, Fe, Mo, Ru, vanadium polyoxometalates, Mn, Os, etc., under O₂ or H₂O₂ or TBHP as oxidizing agent. Although, these homogeneous methods are very effective, they often suffer from the drawbacks like hard-to-separate catalysts, low recyclability and selectivity. Therefore, the developments of catalytic system with the merit of high effectiveness with easy recovery, reuse and selectivity have always attracted chemists.

Solid supported transition metal catalysts have found immense interest in recent years due to their easy recovery and efficient reusability. Easy recovery also allows minimum contamination of metal into the desired products. Thus, efforts are being made to transform active homogeneous catalytic structure into effective heterogeneous system by adopting various immobilization strategies. This includes the utilization of solid supports viz. clay, silica, polymer, and zeolite, etc. Among these the modified montmorillonite clays are chiefly considered as they are environmentally benign, cheap, easily available and robust supporting/stabilizing material for the immobilization of metal nanoparticles. Montmorillonite clays are abundant and collected from the natural deposits of western India. They are purified and activated using inorganic acids under controlled conditions to generate a matrix having high surface area and micro- and mesopores with diameter in the range 0.1 to
10 nm. These nano size pores act as a “Host” for the preparation of the Pd(0)- or Ag(0)-nanoparticles and controls the growth of the particles up to a desired size range.

1.3. Synthesis of phenols

For many years phenols and its derivatives are considered as vital precursors in numerous organic synthesis, and are key component in many natural products such as amino acids, flavonoids, alkaloids, hormones etc.\(^\text{16}\) However, the isolation of phenols from natural source is often very tedious process and the final yields are usually poor. So there is a strong need to develop synthetic protocols that meet the large demand of these vital ingredients. Industrially, cumene process is one of the most widely employed method for the preparation of phenols, which employs the Friedel-Crafts alkylation of benzene followed by oxidation.\(^\text{17}\) However, the use high loading of corrosive AlCl\(_3\) generates isomeric mixtures which are hard-to-separate and restricts regioselectivity. Another method utilizes benzene sulphonate salt.\(^\text{18}\) Acidification of the corresponding salt produces corresponding phenols. This method also suffers the drawback of limited selectivity and harsh reaction conditions limiting widespread applications.

Arylboronic acids are trivalent boron containing compounds bearing one aryl and two hydroxyl groups. The transformation of arylboronic acid to phenols is typically accomplished through transition metal-catalyzed hydroxylation or oxidative hydroxylation, which continues to remain an area of active investigation. The use of molecular oxygen, hydrogen peroxide or TBHP is highly favourable, since they are inexpensive and produces water as the sole by-product.
1.4. Suzuki-Miyaura cross-coupling reaction

Transition metal catalyzed cross-coupling reactions to form C-C, C-O, C-N and C-S bonds are among the most powerful transformations in organic synthesis.\textsuperscript{19} The cross-coupling strategies can be applied for the synthesis of complex organic frameworks that serve as the building block materials for the synthesis of wide range of vital compounds, such as pharmaceuticals, fine chemicals, agrochemicals, natural products and smart engineering materials such as conducting polymers, molecular wires etc.\textsuperscript{20}

In the past few decades, there has been remarkable progress in the cross coupling reactions of unsaturated electrophiles containing alkenyl, aryl, allyl groups with the organometallic reagents containing various nucleophiles such as B, Mg, Li, Sn, Al, Zn etc. The general catalytic cycle involves an oxidative addition of the organic electrophile to a coordinatively unsaturated metal complex, followed by transmetallation from the nucleophile to the intermediate species formed in the first step. Reductive elimination affords the coupling products with regeneration of the catalyst. Thus, in recent years a number of methodologies have been developed by using various transition metals such as cobalt, nickel, iron, palladium and copper etc for this purpose.\textsuperscript{21}

Among this plethora of cross-coupling reactions, our interest is mainly based on Pd-catalyzed carbon-carbon and carbon-oxygen cross-coupling reactions. The Suzuki-Miyaura cross-coupling reaction between an organic (pseudo) halide and an organoboron represents the most attractive approach for the synthesis of complex and functionalized biaryl derivatives with widespread applications in various fields of molecular development.\textsuperscript{22} This is due to the mild reaction conditions and the broad
functional group tolerance of this transformation. Furthermore, the organoborons reagents are easily accessible and exhibits high air- and moisture-stability. In addition, boron compounds are less-toxic and generate easily removable by-products.

The development of novel catalytic systems, which can promote Suzuki-Miyaura reactions in water with improved yield and simple reaction protocol, is another interesting topic to investigate. To deal with this, the industrial determination to use heterogeneous catalysis appears well suited, as the metal immobilized on solid supports remains insoluble in water and can be separated by simple filtration with minimum contamination on products and wastes. Moreover, the approach to recycle the isolated catalyst retaining their activity and efficiency is another goal to pursue.

1.5. Diaryl ether synthesis

Another transition-metal catalyzed cross-coupling reaction is the synthesis of diaryl ether via the connection of electrophilic and nucleophilic fragments. Many of these transformations utilizes aryl halides, arylboronic acids or arenes as coupling partners. Prior to late 1990s, aryl iodide and bromides were the most used electrophiles, owing to their relatively high reactivity. However, their synthesis involves multiple-steps, harsh reaction conditions and generates toxic halogenated waste product. In cross-coupling reactions the by-products generated from their coupling often hampers the isolation and purification of the desired products due to similar chromatography mobility. Therefore, the hunt for an efficient alternative to aryl halide is getting underway.

In 2011, Wu and co-workers have reported a simple etherification method using activated nitroarenes and arylboronic acids in presence of rhodium(I) complex
to prepare unsymmetrical diaryl ethers.\textsuperscript{28} This serendipitous finding has opened the door for the introduction of nitroarenes as alternative electrophile in $\text{C}_{\text{aryl}}$-$\text{O}$ cross-coupling chemistry. The $\text{S}_\text{N} \text{Ar}$ (etherification) reaction using activated nitroarenes containing ortho- or para-electron withdrawing group in the presence of strong nucleophiles is known to chemists since many years. However, the method develop by the group of Wu is unique in terms of mild transition metal-based catalytic conditions, simple carbonate base and high selectivity.

The development of efficient and less expensive methods is an ongoing challenge in the synthesis of organic compounds. The use of inexpensive phenols as an alternative to arylboronic acid makes them attractive starting materials for the preparation of diaryl ethers. In fact phenols are less expensive than the corresponding arylboronic acids and are therefore desirable alternatives. The ready availability, pronounced stability under a variety of reaction conditions, and ease of preparation of these phenolic substrates makes these coupling protocols highly attractive from the synthetic point of view.

1.6. References


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