DEVELOPMENT OF COPPER APATITE CATALYST FOR C-C AND C-N BOND FORMATIONS

The thesis mainly deals with the development of copper-fluorapatite catalyst obtained by incorporating basic species F^- in apatite *in situ* by co-precipitation and subsequent exchange with Cu (II) and its performance for a variety of organic reactions particularly, C-C, C-N bond-formation reactions. Chapter I highlights the importance of heterogeneous catalysis and discuss various options for the synthesis of heterogeneous catalysts. An overview of copper mediated organic transformation is configured. The need and development of "cleaner" and "greener" alternative technologies using homogeneous and heterogeneous catalysts for the preparation of fine chemicals and pharmaceuticals is also described in this chapter. Chapter II mainly deals with the synthesis and characterization of fluorapatite- supported copper catalyst (CuFAP) and its catalytic activity was explored for *N*-arylation of nitrogen-containing heterocycles with aryl, heteroaryl and vinyl boronic acids. Chapter III deals with the *N*-arylation of heterocycles and amines with aryl and vinyl halides using copper-fluorapatite catalyst. Chapter IV presents the synthesis of homoallylalcohols and Stille cross coupling of aryl halides using copper-fluorapatite catalyst. Chapter V describes the synthesis of triazoles and synthesis of benzoxazoles using copper-fluorapatite catalyst.

Chapter-I: Introduction

This chapter describes the various catalysts / process options available for an industrial chemist to effect different organic transformations. It includes a brief introduction of homogeneous, heterogeneous catalysis and basic concepts commonly encountered in catalysis such as selectivity, turnover number, atom economy etc. This chapter also describes the structure, properties and applications of apatite, and its importance as a catalyst in organic reactions. Further the scope of copper as a catalyst is also presented in

this chapter**.** The need for the design and development of environmentally cleaner catalytic methodologies using supported copper catalysts is also presented in this chapter.

Chapter-II: Preparation and Characterization of Fluorapatie-Supported Copper Catalyst for *N*-Arylation of Heterocycles with Aryl, Heteroaryl and Vinyl Boronic Acids

This chapter is divided into two sections.

Section I: This section deals with the preparation and characterization of fluorapatite-supported copper catalyst

Section II: This section deals with the *N*-arylation of nitrogen-containing heterocycles with aryl, heteroaryl and vinyl boronic acids using copper-fluorapatite catalyst.

Section I: **Preparation and Characterization of Fluorapatie-Supported Copper Catalyst**

Solid-supported catalysts are complex assemblies. Their preparation is a challenging task. Minor changes of their preparation conditions can significantly influence the delicate balance of conflicting demands: high activity, high selectivity, and long lifetime.

The support usually has an impact on the activity of the catalytic system. Particle size, surface area, pore structure, and acid-base properties are important parameters of the support. Heterogeneous metal catalysis can offer significant benefits in achieving simple and clean organic syntheses because they have the following advantages: (i) they allow the use of non-polluting oxidants, (ii) they possess high catalytic activity and selectivity, (iii) they have high substrate tolerance, (iv) they allow a simple work-up procedure and easy recovery of the catalyst, and (v) they are recyclable.

Apatites attracted wide attention due to their versatile applications in the fields of bioceramics, chromatographic adsorbents and acid base catalysis. Calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], is not only a main constituent of phosphate rock, but also the main constituent of bones and teeth, which possess tunable acid-base properties, ion-exchange ability and adsorption capacity to manifest promising catalytic properties.

It has been well established that the Ca^{2+} sites of CaHAP can be replaced by divalent cations such as Sr^{2+}, Ba^{2+}, Pb^{2+}, Cd^{2+} etc. Kaneda and co workers demonstrated the utility of the CaHAP as a solid support for Ru and Pd to perform many organic transformations that include oxidation of alcohols, Heck reaction and Diels-Alder reactions.

Section I: *N*-Arylation of Nitrogen-Containing Heterocycles with Aryl, Heteroaryl and Vinyl Boronic Acids by using Copper-Fluorapatite Catalyst

Nitrogen containing heterocycles are found in numerous natural products and in many biologically active pharmaceuticals. *N*-arylimidazole derivatives have been reported to have biomedical applications, serving as cyclic AMP phosphodiesterase inhibitors, AMPA receptor antagonists, cardiotonic agents, thromboxane synthase inhibitors, and topical antiglaucoma agents. Furthermore recent high-resolution X-ray analyses have shown a N-(2-hydroxyphenyl) imidazole motif formed by histidine (His^{240}) and tyrosine (Tyr^{244}) residues through a C-N linkage, in the active site of cytochrome *c* oxidase (C*c*O)

Arylation of heterocyclic nitrogen is a long-standing problem, which is far from being satisfactorily solved. The most straightforward synthesis of *N*-arylimidazoles and other heterocycles involve the direct formation of the aryl-nitrogen bond. However, the standard practice for carrying out such reactions involves the nucleophilic aromatic substitution, and traditional Ullmann-type coupling of imidazoles with aryl halides as well

as the coupling of imidazoles with aryllead, arylbismuth, arylborane and arylsilane. These reactions suffer several limitations, such as harsh reaction conditions, high temperature, strong bases, and often the use of toxic polar solvents such as hexamethylphosphoramide (HMPA). These drawbacks commonly result in low functional group tolerance and low and/or irreproducible yields. Thus, the search for new arylation methods is an attractive for synthetic and mechanistic studies.

The present work in this chapter deals with room temperature and base free *N*-arylation of nitrogen-containing heterocycles with aryl, heteroaryl and vinyl boronic acids using copper-fluorapatite (CuFAP) (Scheme 1- 4).

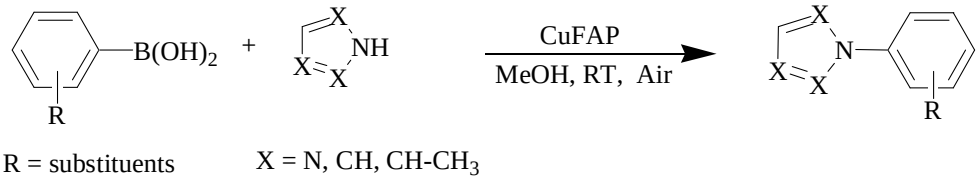
The noticeable merits of CuFAP catalyst *N*-arylation reactions are

(1) Base free *N*-arylation

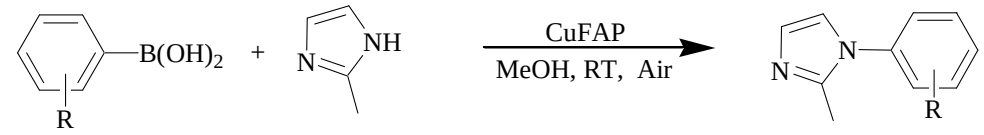
(2) The reaction is carried out at room temperature.

(3) The procedure works well with a variety of nitrogen containing heterocycles and structurally divergent organo boranes, affording good to excellent yields of the desired product.

(4) Reusability of the catalyst.

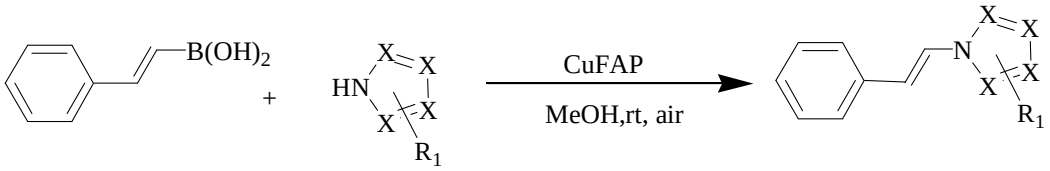


Scheme 1. *N*-Arylation of Pyrazoles with Aryl boronic Acids Catalyzed by CuFAP



R = substituents

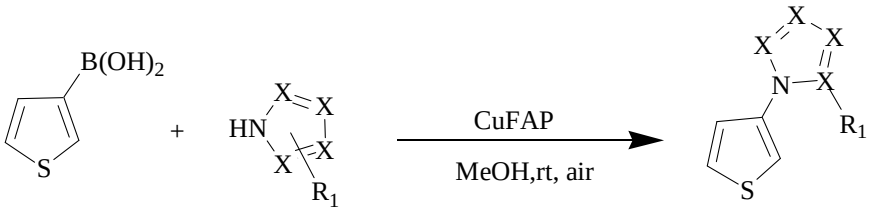
Scheme 2. *N*-Arylation of Imidazoles with Aryl boronic Acids Catalyzed by CuFAP



X= CH or N, CH-CH_3

R_1 = substituents or benzofused

Scheme 3. *N*-Arylation of Nitrogen Containing Heterocycles with Vinyl boronic acids by CuFAP



X= CH or N, CH-CH_3

R_1 = substituents or benzofused

Scheme 4. *N*-Arylation of nitrogen containing heterocycles with hetero aryl boronic Acids

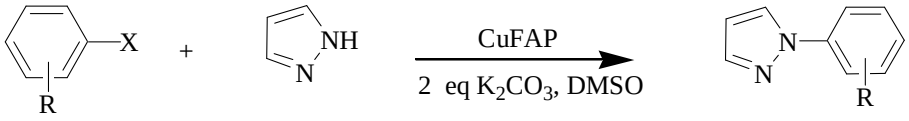
Chapter-III: *N*-Arylation of Nitrogen Heterocycles, Amines and Amides with Aryl and Vinyl Halides using Copper-Fluorapatite Catalyst

N-Aryl heterocycles are common motifs in pharmaceutical research and these can be prepared either by nucleophilic aromatic substitution or by Ullmann-type coupling. The former method requires substrates bearing electron withdrawing substitutents and the later coupling reaction requires use of stochiometric amount of copper with low to moderate

yields. During the past ten years, several reports describing copper mediated cross-coupling reactions and Ullmann condensations for the formation of aryl-heteroatom bonds in organic synthesis are reported. Unfortunately the scope of the Cu (II) catalyzed C-N bond coupling reactions is rather limited. Some methods require expensive ligands or additives to afford higher conversions.

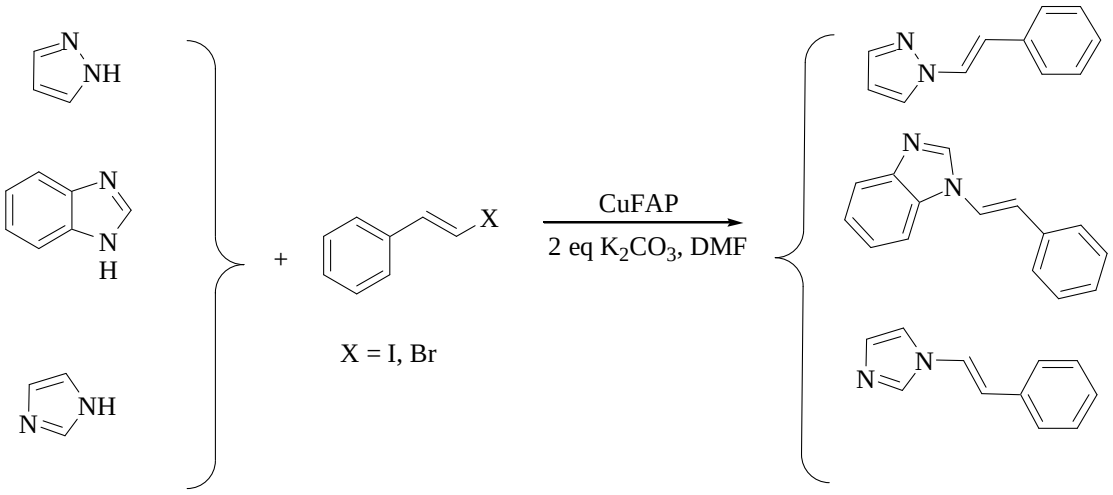
A mild and efficient method for *N*-arylation of nitrogen heterocycles with aryl and vinyl halides to afford *N*-aryl and vinyl heterocycles in excellent yields using copper fluorapatite catalyst without the use of any additive was developed (Schemes 5, 6 and 7). This present catalyst has the following advantages:

- High catalytic activity under very mild conditions.
- Use of inexpensive bases and no need of additives or ligands.
- Easy separation of the catalyst by simple filtration and reusability.



X= I, Br

Scheme 5. CuFAP catalyzed *N*-Arylation of Pyrazoles with Aryl halides

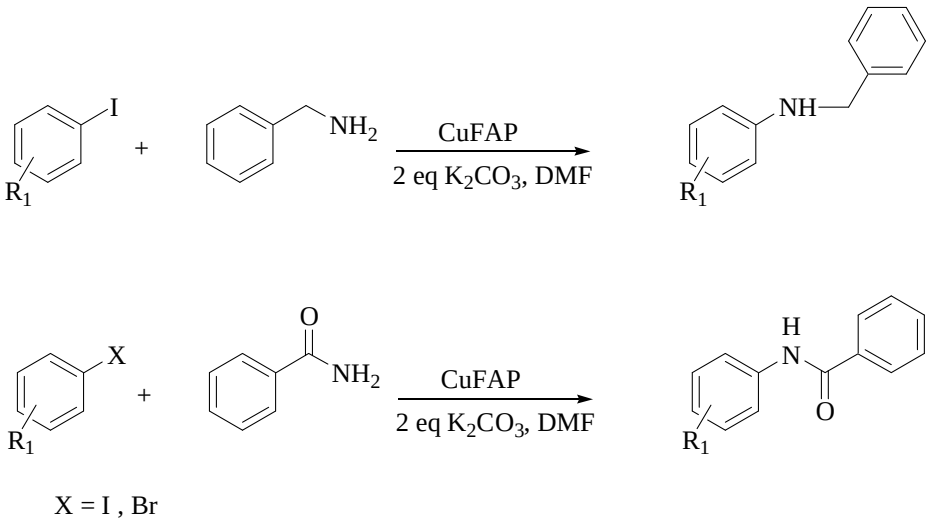


Scheme 6. CuFAP catalyzed *N*-Arylation of Azoles with Vinyl halides

The synthesis of functionalized aromatic and heteroaromatic amines, amides has attracted much interest due to their importance as building blocks for pharmaceuticals, polymers, or materials. Traditional copper catalyzed amination reactions were pioneered by Fritz.

Ullmann and Irma Goldberg in the early 1900's. These reactions typically involve the coupling of aromatic halides with amines for the synthesis of aryl amines, such as Ullmann coupling protocols which necessitate the use of high temperatures and often require the use of stoichiometric amounts of copper reagents, these protocols lead to problems of waste disposal and additionally they have been plagued by poor substrate scope. Consequently, transition metal assisted amination of haloarenes has been developed in the past few years as a most viable and direct method to the synthesis of a large variety of substituted amines.

The present chapter describes the preparation of *N*-arylamines via cross coupling of aryl halides with amines catalyzed by CuFAP.



Scheme 7. *N*-Arylation of amines and amides with aryl halides using Copper-Fluorapatite Catalyst.

Chapter-IV: Copper-Fluorapatite Catalyst for the Synthesis of Homoallyl Alcohols and Stille Cross Coupling of Aryl Halides

This chapter is divided into two sections.

Section I: This section deals with the synthesis of homoallyl alcohols with aromatic and aliphatic aldehydes by using copper-fluorapatite catalyst.

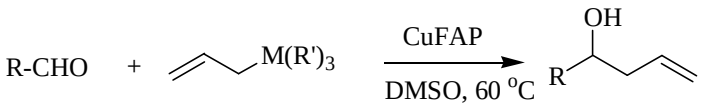
Section II: This section deals with the copper-fluorapatite catalyst for Stille cross coupling of aryl halides.

Section I: Synthesis of Homoallyl Alcohols with Aromatic and Aliphatic Aldehydes by using Copper-Fluorapatite Catalyst

Allylation of aldehydes by various allylic metals is an important synthetic transformation as the resultant homoallylic alcohols are versatile synthons in the preparation of materials, natural products, bioactive compounds and many complex

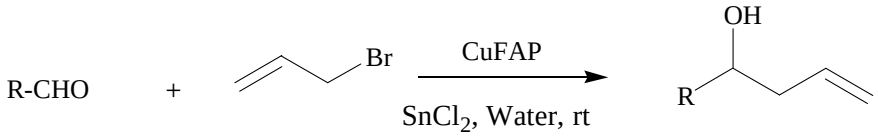
molecules. The general practice for preparation of homoallylic alcohols is carried out by nucleophilic addition of allylic metal reagent to carbonyl compounds. Previously numerous reports on such transformation was carried out using various Lewis acids, Bronsted acids, metal salts, β-cyclodextrin, organometallic reagents in organic media, aqueous media, ionic liquids and PEG. Barbier reaction is an alternative method for the synthesis of homoallylic alcohols, it is the reaction of a carbonyl compound and an organic halide in the presence of magnesium metal.

The present chapter addresses a convenient method involving the use of CuFAP catalyst for allylation of aldehydes with allyltributylstannane or allytrimethylsilane and Barbier type allylation of carbonyl compounds with allyl halides for synthesis of homoallylic alcohols. This catalyst offers several advantages including mild reaction conditions, shorter reaction time, and good yields of the products with low catalytic loading.



$M(R')_3 = SnBu_3$, $Si(CH_3)_3$

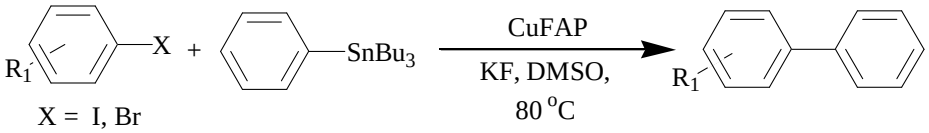
Scheme 8. Allylation of aldehydes with allyltributylstannane and allytrimethylsilane catalyzed by CuFAP



Scheme 9. Barbier type allylation of aldehydes catalyzed by CuFAP

Section II: Copper-Fluorapatite Catalyst for Stille Cross Coupling of Aryl Halides

Cross coupling of aryl halides or triflates with organostannane in the presence of palladium and base to synthesize biaryl compounds is known as Stille coupling reaction. Biaryl compounds are important intermediates for pharmaceuticals, herbicides, chiral ligands for catalysis and in material science. Much work in this area was carried out using homogeneous precious palladium catalysts, such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ or palladium(II) salts, along with phosphines, phosphates, carbenes or thioether ligands. The use of such electron-donating phosphine ligands is undesirable because of their toxicity, air as well as moisture-sensitivity. Moreover, phosphines and their palladium complexes are prone to decompose so that excesses of phosphine and palladium are required which increases the cost of the process. Despite the synthetic elegance and high turnover numbers, the non-reusability of the precious palladium precludes wide synthetic applications in the pharmaceutical industry. In view of the above, it is highly desirable to develop a ligand-free and alternative catalytic system which can perform the same job. The present work in this chapter deals with the synthesis of biaryl compounds via Stille cross-coupling of iodoarenes with phenyltributyl tin catalyzed by CuFAP (Scheme 10).



Scheme10. CuFAP catalyzed Stille cross-coupling of aryl halides with pheny tributyltin

Chapter V. Synthesis of Triazoles and Synthesis of benzoxazoles using Copper-Fluorapatite Catalyst.

This chapter is divided into two sections

Section I: This section deals with the Synthesis of 1, 2, 3-trizoles by using copper-fluorapatite catalyst

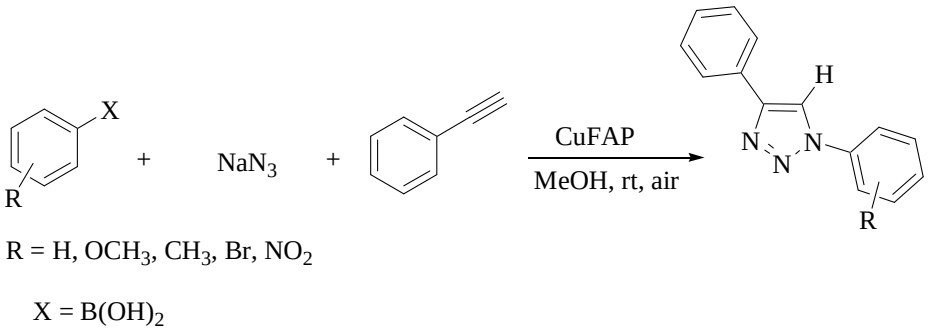
Section II: This section deals with the synthesis of benzoxazoles using copper-fluorapatite catalyst.

Section I: Synthesis of 1, 2,3-Triazoles by using Copper-Fluorapatite Catalyst

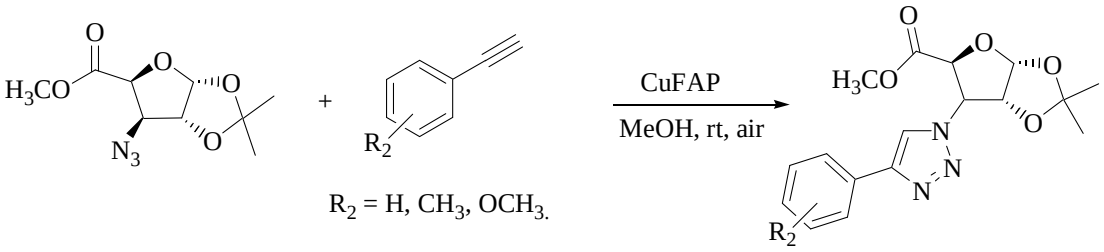
The synthesis of 1, 2, 3-triazoles and its derivatives has been intensively conducted because of their wide range of industrial applications in agrochemicals, corrosion inhibitors, dyes, optical brighteners, light stabilizers. Moreover 1, 2, 3-triazole derivatives show significant antibacterial, anti-HIV, anti-allergic, anti-inflammatory, mascarnic and anti-epileptic activities.

Most common method for the synthesis of 1,2,3-triazole derivatives is the 1,3-dipolar cycloaddition reactions between substituted acetylenes and an aryl or alkyl azide derivatives. Triazoles can also be prepared by the cycloaddition of azides with electron deficient alkenes, metal acetylides, alkynic Grignard reagents, phosphonium salts, and various substituted alkynes. Organic azides (trimethylsilyl, alkyl, allyl, aryl), metal azides, or hydrazoic acid are commonly used in the cycloaddition reactions with alkynes. This kind of methodology lacks regioselectivity. Homogeneous Cu(I) salts like CuI, CuCl have been employed with high regioselectivity but side products like diacetylenes, and the usage of nitrogen containing base does not support its use. Other methods requires the insitu generation of Cu(I) from the copper sulphate by addition of sodium ascorbate in *t*-BuOH/H_2O solvent system which makes the process more complex, therefore it is highly desirable to develop an efficient method to synthesize 1,2,3-triazoles.

The present work in this chapter addresses one pot synthesis of 1, 2, 3-triazoles by reacting alkyl or aryl halides or organoboranes with alkynes, and sodium azide using CuFAP catalyst.



Scheme11. CuFAP catalyzed Synthesis of Triazoles with Aryl, alkyl halides and Boronic acids

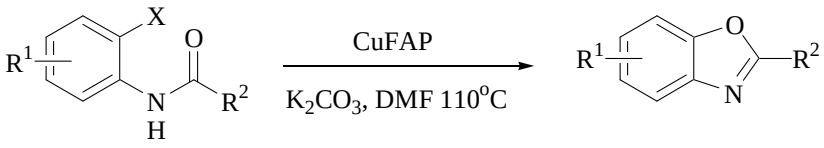


Scheme12. Synthesis of Triazoles via Sugar Azides

Section II: Synthesis of Benzoxazoles using Copper-Fluorapatite Catalyst

Benzoxazoles are important class of molecules and common heterocyclic scaffolds in biologically active and medicinally significant compounds. Benzoxazoles are found in a variety of natural products and are important targets in drug discovery. Previously benzoxazole ring system was synthesized by two ways taking aminophenols as starting material. The first method involves the coupling of the 2-aminophenols with carboxylic acid derivatives under strongly acidic conditions, such as boric acid or polyphosphoric acid, with high reaction temperatures or with microwave-assisted reaction conditions. The second method involves the uses of 2-aminophenols with an aldehyde via the oxidative

cyclization of imine intermediates. The development of alternative routes for the synthesis of benzoxazole ring is an important research area, because it would allow the use of milder reaction conditions, and it would overcome the requirement of using 2-aminophenols as precursors. In the present chapter we report an efficient and more sustainable protocol for intramolecular O-arylation of *o′*-haloanilides for synthesis of benzaoxazole core using heterogeneous copper-fluorapatite catalyst (Scheme 13).



Scheme 13. Synthesis of benzoxazoles using CuFAP