Heterocycles are cyclic rings of atoms that contain at least one heteroatom such as N, O, S, P, Mg, Fe and Se in the parent scaffold. In general, it is the heteroatom that imparts distinctive and prominent features to the heterocycle [1]. It is interesting to note that nearly 50% of known organic compounds and 90% of active pharmaceuticals constitute heterocyclic moieties [2]. This emphasizes the significance of heterocycles in modern drug design.

Among all the known heterocyclic ring systems, nitrogen heterocycles are most abundant due to its wider presence in a large number of natural products and bioactive molecules [3]. They are also prevalent among fungicides, herbicides and other application-oriented molecules [4]. In particular, ring systems like pyrrole, imidazoles, pyrimidine, quinoline, tetrazoles and their benzo-fused analogues are associated with a wide range of biological activities. Recent analysis of database reveals that about 60% of the Food and Drug Administration (FDA) approved pharmaceuticals are nitrogen-based heterocycles [5]. Considering the large presence of nitrogen and sulphur-containing moieties in biologically active compounds, the integration of *N*- and *S*-arylation reactions in pharmaceuticals are increasing faster [6]. The copper catalysed C–N and C–S bond formation has emerged as extremely useful owing to its wider presence in pharmaceuticals, agrochemicals, natural products, organic materials and catalysts [7]. The utility and versatility of such transformation has led to increasing development of efficient and reliable protocols. Knowing the tremendous advantages of copper due to its inexpensive and less toxic behaviour, Cu catalysed C–N and C–S bond formation has caught the attention of various researchers [8]. The most influential C–N and C–S bond forming strategies available to a synthetic chemist are the Buchwald-Hartwig reaction, the Ullmann-Goldberg, the Chan-Lam cross-coupling and recently explored amination of alcohols [9,10].

On the other hand, the applicability of palladium catalysed C-O and C-C bond formation has seen a huge impact in the areas of natural product synthesis, modern drug design and industrial applications. However, palladium deposited on a support provides significant advantages over traditional ones in cross-coupling chemistry. Almost after 60 years of its discovery, cross coupling reactions stand among the most studied reactions in organic chemistry [11,12].

Objectives

The objectives of this thesis are:

i) Taking into consideration the importance of heterocycles from pharmaceuticals to agrochemicals, here, we envisioned to incorporate and design heterocyclic moieties into our work. Given the broad synthetic utility of nitrogen heterocycles and C–N bond, the development of a safer and synthetically useful methodology is always beneficial.

ii) The challenges of discovering and understanding new heterocyclic systems and their properties continue to stimulate research. We envisage the design of Lewis acid catalysed alkylation of heterocyclic thiones with alcohols as alkylating partner owing to the cheap and relatively abundant alcohol source in this thesis.

iii) Developing sustainable methodologies for Ullmann cross-coupling reaction between heterocyclic thiols and alkyl halides is advantageous to reduce the hazardous impact on the environment. Heterocyclic thiols containing C–S bond exhibit diverse biological and pharmacological activities. Considering the importance of C–S bond and heterocyclic moieties, Ullmann coupling is the most sought after process to synthesize C–S bond. In this context, we envisioned to explore the methodologies under copper catalysis.

iv) In the context of green chemistry, design of metal nanoparticles immobilized on bio-based derived support has been growing tremendously due to its economical and sustainable approach. Designing a sustainable palladium based heterogeneous catalytic system for C–O and C–C bond formation helps to achieve the principles of green chemistry that encourage the "use of renewable feedstocks" to reduce or minimise the hazardous impact on the environment. In the current thesis, the above mentioned points will be taken into consideration on top priority while carrying out the cross-coupling reactions.

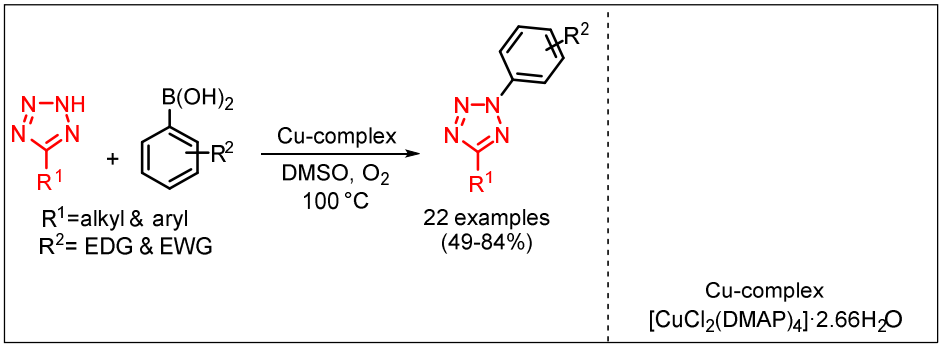
The Thesis

The thesis entitled, "**Exploration of Synthetic Methodologies for Carbon-Carbon and Carbon-Heteroatom (N, O, S) Bond Formation Reaction Catalysed by Cu & Pd**"

comprises of a total of six chapters. Chapter 1 covers the introduction. Chapters 2, 3 and 4 discuss the development of Cu–catalyzed methodologies for C–N cross-coupling, amination of alcohols and C–S cross-coupling while the subsequent chapter (Chapter 5) discusses C–O and C–C cross coupling chemistry using a Pd-based heterogeneous catalyst. Chapter 6, the last chapter of the thesis deals with conclusion and future scopes. Each work is systematically organized and discussed in the thesis.

Chapter 1: Chapter 1 is the introductory chapter detailing a general overview on heterocycles with a discussion on its importance and applications. The research objectives of the thesis are outlined in the beginning of this report.

Chapter 2: This chapter discusses a simple copper mediated protocol for the synthesis of 2,5-disubstituted tetrazoles with less toxic phenylboronic acids (Scheme **1**)**.** Exhibiting a wide substrate scope, various *o*-, *m*- and *p*-substituted phenylboronic acids reacted with tetrazoles under the optimized reaction condition to give regioselective 2,5-disubstituted tetrazoles in moderate to high yield (49-84%).



***Highlights of the Work*:**

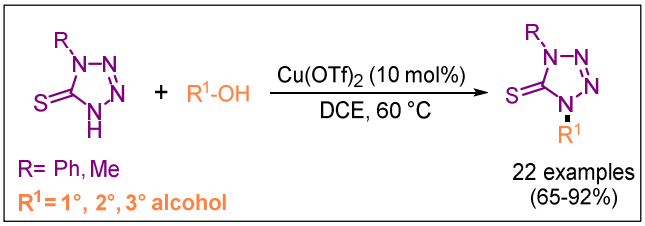
- Operationally simple
- Wide substrate scope and tolerance
- Regioselective
- Economical

Scheme **1**: Schematic representation of regioselective N^2-arylation of tetrazoles using arylboronic acids

In this reaction protocol, the developed catalyst is cheap, easy to prepare and has emerged as a promising mode to achieve regioselective N^2-arylation. Formation of the copper complex was confirmed with single crystal XRD. A controlled experiment was done to confirm the crucial role of O_2 as an ancillary oxidant and $[CuCl_2(DMAP)_4]\cdot 2.66H_2O$ as catalyst in this transformation. Nevertheless, an extensive

literature survey on tetrazoles, Chan-Lam cross coupling are discussed in the beginning of this chapter.

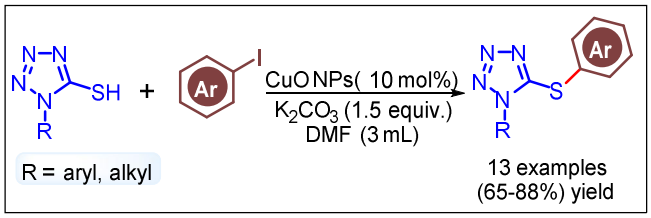
Chapter 3: This chapter explores $Cu(OTf)_2$ as Lewis acid catalyst for chemoselective amination of alcohols using heterocyclic thiones. The reaction occurred preferably at the nitrogen centre over the sulphur atom leading to chemoselective C-N bond formation (Scheme **2**). The reaction proceeded well without the usage of additives and showed good tolerance towards a variety of alcohols and thiotetrazole derivatives. This chapter also discusses the mechanistic study for this reaction to gain insight into the novel transformation. Using the developed protocol gram scale synthesis was also done. Over 22 examples have been synthesized using this protocol and all yielded good to excellent results. However, chapter 2 begins with a detail outline on the introduction of thiotetrazoles, amination of alcohols and other information relevant to our work.



Scheme **2**: Schematic representation of amination of alcohols using heterocyclic thiones

Chapter 4: This chapter discusses a cost-effective approach for *S*-arylation of heterocyclic thiols using copper oxide nanoparticles (CuO NPs) (Scheme **3**). The characteristic features of this method included the use of a ligand-free catalytic system, simple reaction procedure, shorter reaction time, wide substrate scope and high yields of the product. The developed protocol clearly demonstrated remarkable tolerance of CuO NPs towards a variety of functional groups. Heterogeneity of the catalyst was tested which reveals that the catalyst was recycled with a moderate change in reactivity over three consecutive cycles. A plausible reaction mechanism has been proposed for this reaction system. The protocol offers substantial benefits in achieving C–S arylation in presence of CuO NPs without the use of any ligands. An introduction to organosulfur

compounds, Ullmann coupling and several copper based C–S cross coupling reactions are discussed in detail in the beginning of this chapter.

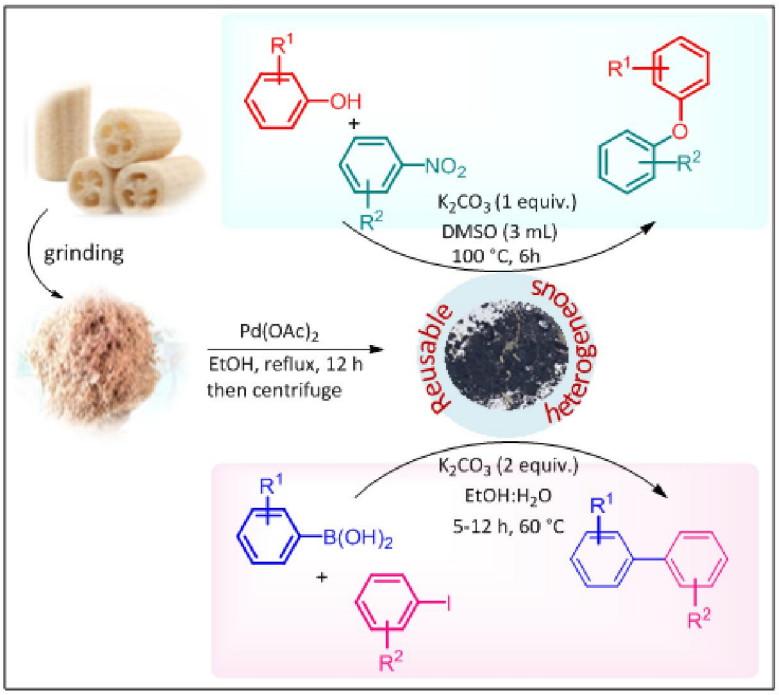


Highlights of the Work:

- Chemoselective product
- Catalyst reusability
- Economical
- Ligand free approach
- Moderate to high product yield

Scheme**3**: Schematic representation of *S*- arylation of thiotetrazoles using aryl iodides

Chapter 5: This chapter discusses the design of a heterogeneous catalyst (Pd NPs@LS) and its employment in the synthesis of C-O and C-C bond formation (Scheme **4**). The bio-based support used; Luffa sponge extracted from the waste feedstock of Luffa guard is a cheap, biodegradable, abundant and renewable source with netting-like three-dimensional porous structure. The developed catalyst, Pd NPs@LS was characterized by FT-IR, PXRD, SEM-EDX, TEM, XPS, and ICP-OES analyses. Using this developed catalyst, a wide range of substrates is studied for both C-O and C-C coupling reaction. Plausible mechanism has been proposed for both these coupling reactions involving organometallic pathway. Discussion detailing cross-coupling reactions, heterogeneous catalyst, denitrative ether reaction, Suzuki-Miyaura cross-coupling reaction was jotted down at the beginning of this chapter.



Highlights of the Work:

- Easy preparation of catalyst
- Both C-O and C-C reactions are studied
- Moderate to good yields are obtained
- Catalyst can be recycled up to third catalytic cycles
- Sustainable process

Scheme **4**: Schematic representation of C-O and C-C bond formation using Pd NPs@LS

Chapter 6: This chapter presents a summary of the significant findings of all the above works. This chapter also provides a future prospect to extend and improve the current works.

Bibliography

[1] Amin, A., Qadir, T., Sharma, P. K., Jeelani, I., and Abe, H. A Review on The Medicinal And Industrial Applications of *N*-Containing Heterocycles. *The Open Medicinal Chemistry Journal*, 16(1), 2022.

[2] Kerru, N., Gummidi, L., Maddila, S., Gangu, K. K., and Jonnalagadda, S. B. A review on recent advances in nitrogen-containing molecules and their biological applications. *Molecules*, 25(8):1909, 2020.

[3] Chernyshov, V. V., Popadyuk, I. I., Yarovaya, O. I., and Salakhutdinov, N. F. Nitrogen-containing heterocyclic compounds obtained from monoterpenes or their derivatives: synthesis and properties. *Topics in Current Chemistry*, 380(5):42, 2022.

[4] Heravi, M. M. and Zadsirjan, V. Prescribed drugs containing nitrogen heterocycles: an overview. *RSC Advances*, 10(72):44247-44311, 2020.

[5] Vitaku, E., Smith, D. T., and Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. *Journal of Medicinal Chemistry*, 57(24):10257-10274, 2014.

[6] Vantourout, J. C., Miras, H. N., Isidro-Llobet, A., Sproules, S., and Watson, A. J. Spectroscopic studies of the Chan–Lam amination: A mechanism-inspired solution to boronic ester reactivity. *Journal of the American Chemical Society*, 139(13):4769-4779, 2017.

[7] Yang, K., Qiu, Y., Li, Z., Wang, Z., and Jiang, S. Ligands for copper-catalyzed C–N bond forming reactions with 1 mol% CuBr as catalyst. *The Journal of Organic Chemistry*, 76(9):3151-3159, 2011.

[8] Biffis, A., Centomo, P., Del Zotto, A., and Zecca, M. Pd metal catalysts for cross-couplings and related reactions in the 21st century: a critical review. *Chemical Reviews*, 118(4):2249-2295, 2018.

[9] Ruiz-Castillo, P. and Buchwald, S. L. Applications of palladium-catalyzed C–N cross-coupling reactions. *Chemical Reviews*, 116(19):12564-12649, 2016.

[10] Pérez Sestelo, J. and Sarandeses, L. A. *Molecules,* 25(19):4500, 2020.

[11] Johansson Seechurn, C. C., Kitching, M. O., Colacot, T. J., and Snieckus, V. Palladium-catalyzed cross-coupling: a historical contextual perspective to the

2010 Nobel Prize. *Angewandte Chemie International Edition*, 51(21):5062-5085, 2012.

[12] D'Alterio, M. C., Casals-Cruañas, È., Tzouras, N. V., Talarico, G., Nolan, S. P., and Poater, A. Frontispiece: Mechanistic Aspects of the Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction. *Chemistry–A European Journal*, 27(54), 2021.

[13] Panova, Y. S., Kashin, A. S., Vorobev, M. G., Degtyareva, E. S., and Ananikov, V. P. Nature of the copper-oxide-mediated C–S cross-coupling reaction: leaching of catalytically active species from the metal oxide surface. *ACS Catalysis*, 6(6):3637-3643, 2016.

List of Publications

1. **Kataky, S.**, Sarma, B., and Thakur, A. J. Preparation of 2, 5-Disubstituted Tetrazoles using a Copper-Catalysed Regioselective Direct Coupling of Tetrazoles with Free NH Groups and Boronic Acid Derivatives. *ChemistrySelect*, *8*(42), e202301843, 2023.

2. **Kataky, S.**, Boruah, P., and Thakur, A. J. Lewis Acid Catalysed Chemoselective Amination of Alcohols Using Heterocyclic Thiones: An Avenue to Thiotetrazole Derivatives. *European Journal of Organic Chemistry*, e202300515, 2023.

3. Bhuyan, P., Bhorali, P., **Kataky, S.**, Bharali, S. J., Guha, A. K., and Saikia, L. $ZnCl_2$catalyzed cascade conjugative alkynylation/6-endo-dig cyclisation of N,N-dimethyl barbituric acid derived alkenes under ultrasonic irradiation: An improved, base & column-free access to pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones. *Sustainable Chemistry and Pharmacy*, 30:100852, 2022.

4. Ligand free CuO nanoparticles catalysed *S*-arylation of heterocyclic thiols using aryl halides. Authored by **Sudhamoyee Kataky**, Sultana Parveen Ahmed, Ankita Rakshit and Prof. Ashim Jyoti Thakur (*under communication*).

5. Pd nanoparticles supported on luffa sponge as a heterogenous catalyst for C-O and C-C coupling reaction: From waste to use. Authored by **Sudhamoyee**

Kataky, Bhavna Choudhury, Gayatri Neog, Manash R. Das and Prof. Ashim Jyoti Thakur (*under communication*).

Conference attended

1. National Seminar On “Research at The Interface Of Chemical, Biological And Material Sciences” organised by Department of Chemical Sciences in collaboration with Students’ Science Council, Tezpur University, March 10, 2023.

2. International Conference On "Interface of Chemistry, Material Chemistry and Pharmaceutical Sciences” organised by Department of Chemistry, Royal School of Pharmacy, Royal Global university and Department of Chemistry, Cotton University, November 10, 2023.

Keywords

- Active pharmaceutical ingredients
- Boronic acids
- 4-(Dimethylamino)pyridine
- Regioselective
- Tetrazoles
- Alcohols
- Amination
- Chemoselective
- Copper triflate
- Thiotetrazoles
- Copper oxide
- Nanoparticles
- Chemoselectivity
- Ullmann reaction
- Recyclability
- Cross-coupling
- Palladium
- Denitrative
- Suzuki–Miyaura Coupling