Chapter-V

Conclusion and Future Direction

5.1 General Conclusions

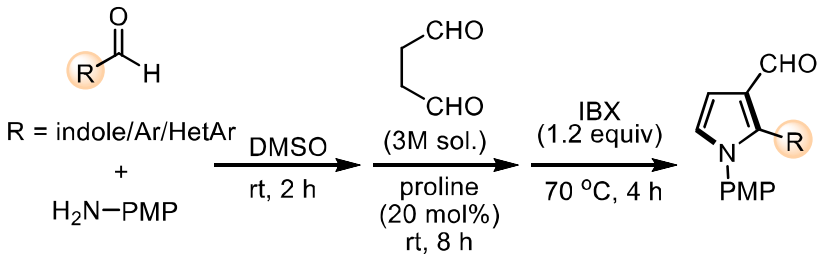
In recent years, the demand for straightforward organic synthetic methodology, which is capable of accessing the potent complex organic structures in a minimum number of synthetic steps from readily available precursors, is on peak among the synthetic chemists. In this context, multi-bond forming protocols such as cascade/domino-sequences, one-pot sequential tandem reactions, and one-pot multicomponent reactions (MCR) have emerged as a new tool in this direction. The ready availability, low toxicity of catalysts, and operational simplicity associated with organocatalysis make it essential strategic methods to assemble useful complex molecules. Amino acids, such as proline or its derivatives used as a catalyst in amine-catalyzed reactions, have presently acquired enormous attention in organic synthesis. The current thesis entitled "**Catalytic Approaches Towards the Synthesis of Indole based Heterocycles**" is mainly focused on the combination of indole-based heterocycles via aminocatalytic direct Mannich reaction-cyclization cascade sequence. These methods involve proline-catalyzed direct Mannich reaction-cyclization series between succinaldehyde/glutaraldehyde, and various indole-imines, followed by oxidative-aromatization/reductive-amination as overall [3+2]/[4+2] annulation to furnish five-membered pyrroles, and six-membered indole-based piperidines. These annulation methods provide direct and rapid access to Ar/Het/indole tagged pyrrole-3-carboxaldehyde, and indole-tethered piperidines in good to high yields. Besides, this thesis also includes the Cu-catalyzed oxidative dearomatization of several 2-phenylindoles to access dimerized products as well as indole addition products in one-pot at room temperature. The main advantage of the present research work is to overcome the multistep synthesis by developing a one-pot strategy by using simple, cheap and readily available precursors. In the new synthetic area, organocatalysis is turned into most productive resources for the construction of heterocyclic moieties and small molecular natural products (SMNPs), through C-C, C-N, C-O, C-S C-X, and C-P bond formation, without necessity requirement of prior activation of substrates. The cost-effective, time and atom-economical ways of formal cycloaddition reactions using organocatalysis have become the remarkable approaches to access heterocyclic compounds.

5.2 Specific Conclusions

The thesis entitled "**Catalytic Approaches Towards the Synthesis of Indole based Heterocycles**" is divided into four chapters. A brief discussed of these chapters is mentioned below.

The first chapter of the thesis describes a brief overview of organocatalysis, its scope in terms of reaction, mode of activation, and superiorities over other catalytic strategies. In particular, amine-catalysis, covalent way of activation of carbonyls, have been discussed briefly. The development of proline catalyzed direct Mannich reaction, and utilization in the synthesis of synthetic drugs, complex scaffolds, and mimicking the natural products have been discussed. A brief discussion on five and six-membered nitrogen-containing heterocycles and it's biological as well as artificial importance. Besides, a detailed report on the utilization of liner dialdehydes such as; succinaldehyde and glutaraldehyde for the synthesis of five and six-membered nitrogen heterocycles via aminocatalytic cascade transformations has been presented. In the end, this chapter also describes the overall research work carried out during the Ph.D. tenure.

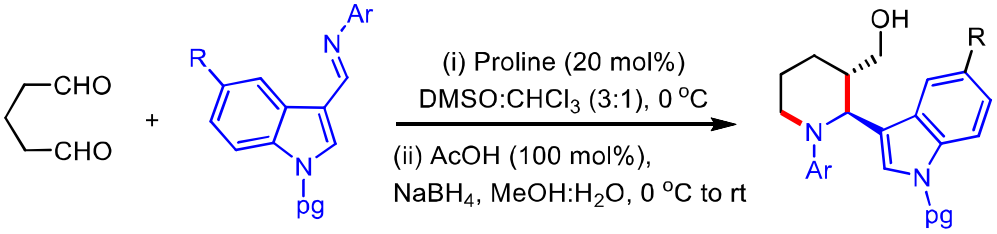
The second Chapter describes the multicomponent synthesis of 2,3-disubstituted pyrrole-3-carboxaldehydes in one-pot from succinaldehyde, Ar/HetAr/indole-aldehydes, p-anisidine, 4-chloroaniline, *o*-hydroxyaniline. This overall [3+2] annulation between in situ generated imines and succinaldehyde proceeded through direct Mannich reaction followed by IBX-mediated oxidative aromatization under mild conditions. A series of 2-aryl/hetAr/indolyl-pyrrole-3-carboxaldehyde compounds have been prepared in good to high yields. The developed method has been further explored in the synthesis of a few hybrid-heterocyclic compounds such as pyrrolo-acrylates, pyrrolo-phenanthridines, pyrrolo-oxadiazoles, and pyrrolo-quinolines.



Scheme 5.1 Three-component one-pot synthesis of pyrrole-3-carboxaldehydes

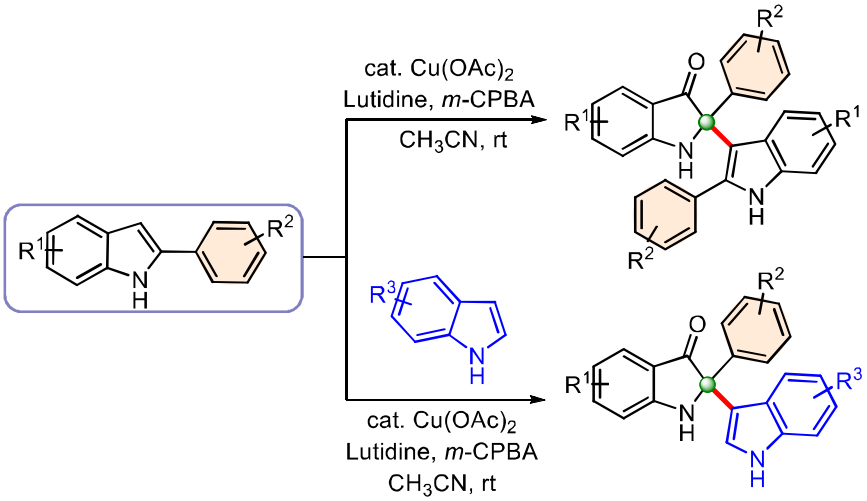
The third chapter revealed the integration of novel chiral indolyl-3-piperidines. This involves aminocatalytic [4+2] annulation between glutaraldehyde and indolyl-imines to access indolyl-3-piperidines asymmetrically. This one-pot protocol requires a proline-catalyzed direct Mannich

reaction between glutaraldehyde and indolyl-imines, followed by $NaBH_4$-mediated reductive-cyclization in good yields with high stereoselectivity (up to >25:1 dr, up to >99:1 er). A series of such indolyl-3-piperidines have been prepared. Apart from the synthetic utilities, these indolyl-piperidines were also tested against HIV-1-RT inhibitory activity using ELISA based assay exhibited satisfactory activity. Interestingly, some of the synthesized compounds show significant anti-HIV activities wr.t. the marketed drug EFAVIRENZ.



Scheme 5.2 Amine-catalyzed asymmetric synthesis of indolyl-3-piperidines

Chapter fourth describes an oxidative dearomatization of 2-arylindoles that lead the formation of 2,2-disubstituted indolin-3-ones decorated with quaternary stereocenters at the C-2 position. This chemo- and regioselective methodology underwent through *in situ* generated intermediated 2-phenyl-3*H*-indol-3-one, at which self-addition of 2-arylindoles or cross-addition of indole was carried out in the same pot to furnish, 2-disubstituted indolin-3-ones, respectively. The practical utility of the products was shown by performing the gram-scale reaction.



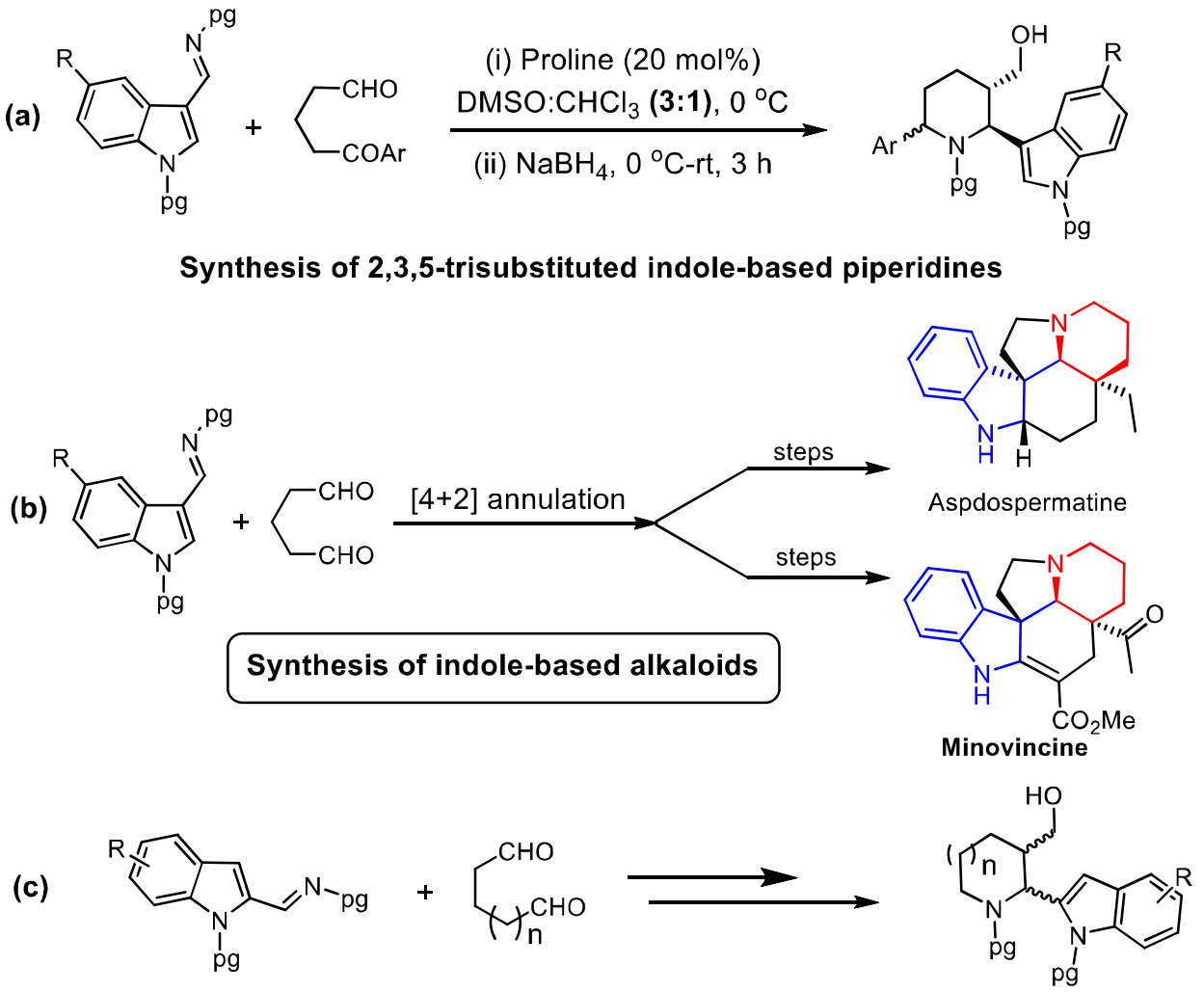
Scheme 5.3 Synthetic approaches from 2-aryl indoles to access 2,2-disubstituted indolin-3-ones

Additionally, ^{1}H, ^{13}C-NMR, HRMS mass spectroscopic data, optical rotation using polarimeter, and single X-ray diffraction techniques were used to identify all compounds synthesized in this

thesis. These synthetic strategies have the potential for the synthesis of novel bioactive compounds and natural products.

5.3 Future Scope of the Research Work

The C-C and C-N bond-forming reactions using organocatalysis, a mode of catalysis where pre-functionalization of substrates is not required, undoubtedly present a valuable tool to construct diverse molecular scaffolds and related hybrid frameworks that have broad applications in chemical and biological fields. Multi-bond forming approaches such as multi-component reactions, tandem reactions, cascade, and one-pot domino sequences are highly desirable for the synthesis of complex molecules. Besides, fused heterocyclic units are present as basic core structures in several critical natural products, alkaloids, and pharmacologically active drugs. Therefore, there is a need for organocatalytic approaches to synthesize such molecules by potentially alternative methods to avoid traditional multi-steps synthesis. The main focus of the thesis is to develop new catalytic processes for the synthesis of nitrogen-containing I, in particular, indole-based heterocycles. In this context, multicomponent access indole-derived pyrrole, indolyl-3-piperidines, and Cu-catalyzed combination of bis-indolin-3-ones bearing a C2-quaternary center have been developed. These developed one-pot approaches are quite suitable to access biologically relevant compounds or libraries of new heterocycles for biological screenings and alkaloids in time as well as with high atom economy. Therefore, these methods can be further utilized to access indole-based bioactive scaffolds in a non-asymmetric and asymmetric fashion, which are having remarkable practical utility in drug design and discovery. In the future scope of the developed protocol, we can extend these methods for the synthesis of 2,3,5-trisubstituted indole-based piperidines (Scheme 5.1a), by using 1,4-keto-aldehyde in place of glutaraldehyde. Besides, the developed [4+2] annulation process has enormous opportunities to access indole-based alkaloids (Scheme 5.1b). The synthetic methodology of indole-3-piperidine provides the idea to tether the nitrogen heterocycle at C-2 of indole by incorporating imine at the C2-position of indole and a similar way to access C2-substituted indolyl-piperidines asymmetrically.



Scheme 5.1 Presenting the utilities of thesis works for future scope

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