Harnessing the reactivity of alkenyl heteroarenes through copper catalysis and Lewis acids
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Chapter 1

Synthesis and Functionalization of Aromatic Heterocycles
1.1 Introduction

Heterocycles, both aliphatic and aromatic, are ubiquitous motives in nature, and they found application in several areas such as medicine, materials and dyes, and synthetic chemistry. Their immense importance is reflected by the massive presence of heterocyclic structures among the alkaloids. Alkaloids are well known for the many biological activities displayed by the members of this class of compounds. In the past, alkaloids were defined as nitrogen containing organic compound found in plants with strong bioactivity and basic character, while nowadays many molecules without basic properties are considered members of this family in virtue of their pronounced biological activity. The synthetic strategies to access chiral heterocyclic derivatives can be divided in two main classes: 1) cyclization reactions or 2) direct functionalization of a heterocyclic scaffold. In both approaches the chiral information can be introduced using an external source (i.e. catalyst, nucleophiles, electrophiles) or can be dictated by a chiral moiety already present in the substrates. Despite the first approach often relies on long multistep process, due to the major versatility it offers, it is the most commonly used one, while the second approach is an emerging field. Among the plethora of heterocyclic structures found in alkaloids and other biologically active compounds, only the heterocycles relevant for this thesis will be discussed in this chapter.

1.2 Pyridines

Being commonly found in bioactive compounds and functional materials, pyridines and their synthesis have always attracted the attention of organic chemists. This interest resulted in the appearance of a conspicuous amount of reports in literature on the topic. De novo construction of the pyridine ring, through both inter- and intramolecular processes, is one of the most exploited startegies, due to the high structural diversity that can be achieved. Forefather of this approach is the Hantzsch pyridine synthesis, a formal [2+2+1+1] multicomponent cyclization reaction between ammonia, formaldehyde and β-keto esters (Scheme 1).

The growing knowledge on transition metal catalysed processes contributed significantly in the development of new synthetic routes to access pyridine derivatives. In 1998, Roesch and Larock reported one of the first example of formal [4+2] cycloaddition reaction between halovinyl imines and internal alkynes promoted by catalytic amount of Pd. Several multi-substituted pyridines and other heterocycles could be synthesized using this protocol (Scheme 2a). The proposed mechanism starts with oxidative addition of the halovinyl imine 34 on Pd(0) species affording organopalladium compound 37. Insertion of the latter on the acetylene generates intermediate 38, that upon reaction with the imine moiety forms 7-member palladacycle 39. Finally, in the reductive elimination step final product 36 is obtained and the Pd(0) species is regenerated (Scheme 2b).
Scheme 2: Pd-catalysed synthesis of substituted pyridines via annulation reaction.

Besides Pd, formal [4+2] cycloaddition reactions for the construction of the pyridine ring have been achieved using many others transition metals such as Fe, Rh, Au, Ru and Cu. Copper catalysis itself has been used by Liu and Liebeskind in one of the few examples of C-N cross coupling/electrocyclization cascade sequence. Simple α,β-unsaturated ketoxime O-pentafluorobezoates 40, derived by condensation of α,β-unsaturated ketone with hydroxylamine followed by acylation with perfluorinated benzoyl chloride, undergoes N-imination in presence of Cu(II) salt and alkenyl boronic acid 41 (Scheme 3).

Scheme 3: Cu-catalysed C-N cross coupling/electrocyclization cascade sequence

The reaction is believed to be proceeding through formation of azatriene (E)-42 and azatriene (Z)-42 with the latter undergoing electrocyclization to afford a dihydropyridine intermediate that is oxidised to pyridine 43. This represents a straightforward way to access mono-, di-, and tri-substituted pyridine rings.

Cycloaddition reactions enabling the formation of pyridine derivatives are not limited to [4+2] strategies. Several [3+3] approaches have been reported as well as some [2+2+2] and [3+2+1] methodologies. In a recent example, Chiba and co-workers developed an elegant formal [3+3] annulation using vinyl azides and cyclopropanols accessing a wide range of di- and tri-substituted pyridines in overall good yields. In this process, a Mn(III) salt oxidises cyclopropanol 44 via single electron transfer, generating the oxo-radical 45 that evolves in carbo-radical species 46 (Scheme 4).

The newly formed radical undergoes conjugate addition to vinyl azide 47 affording iminyl radical 48 with consequent elimination of a molecule of N₂. Intermediate 48 reacts with the Mn(II) species in order to form the iminyl metal species 49 that upon direct addition to the carbonyl moiety affords oxanion 50. Hydrolysis of the latter restores the Mn(III) catalyst and releases disubstituted tetrahydropyridine 51. Dehydration and oxidation of 51 finally produce the desired product 52. Another interesting [3+3] cycloaddition procedure has been developed by Manning and Davies.²² Isoxazole 53 reacts with diazovinyl compound 54 in presence of Rh(II) catalyst to deliver multisubstituted pyridines 55 (Scheme 5).

Scheme 5: Rh-catalysed cycloaddition of isoxazoles and diazovinyl compounds.

The reaction is believed to proceed via formation of a Rh-carbene and its insertion into the N-O bond of isoxazole 53 results in the formation of intermediate 56, that upon heating and oxidation forms pyridine 55. Main limitation of the approach is the necessity of high
temperature to promote the release of N\textsubscript{2} from 54 and the presence of carbonyl moiety (ester or ketone) as R\textsuperscript{3}- substituent on the diazo compound.

Due to the sp\textsuperscript{2}-character of the carbons constituting the pyridine core, the synthesis of chiral pyridines requires the use of stoichiometric amount of chiral molecules that will be incorporated in the structure of the final product. To the best of our knowledge, only few examples have been reported of such transformation.\textsuperscript{23} A different approach for the synthesis of decorated pyridine rings is represented by the direct functionalization of the pyridine moiety itself through coupling reaction,\textsuperscript{24,25} α-metallation, or addition of strong nucleophiles to pyridinium analogues followed by oxidation.\textsuperscript{25} The latter is an established field with a plethora of highly yielding process covering a large spectrum of functionalities. Regioselectivity issues (1,2- vs 1,4-addition) can be circumvented by a careful choice of the nucleophile. As for common Michael acceptors, hard nucleophiles will be directed in 2-position, whereas soft nucleophiles will prefer the attack in 4-position (Scheme 6).

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\text{Scheme 6: Nucleophilic addition to pyridinium derivatives.}
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The lack of scientific reports in literature on the chiral version of such strategy is mainly due to the necessity of employing configurationally stable chiral nucleophiles. Synthesizing nucleophiles of this type is not always straightforward especially for small simple moieties. Moreover, use of stoichiometric amounts of chiral reagents to prepare the chiral nucleophile is often required, making this approach tedious and not practical. To achieve this goal, coupling chemistry could represent a more convenient approach.\textsuperscript{26} Aggarwal and co-workers recently developed a stereospecific coupling of boronic esters with activated pyridines (Scheme 7).\textsuperscript{7a}

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\text{Scheme 7: Stereospecific coupling of boronic esters to pyridines.}
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Secondary and tertiary enantioenriched boronic esters undergo transmetallation with ortho- and para-lithiated pyridines affording intermediate 59 shown in scheme 7 only for the para-lithiated substrate. Essential for the reaction to proceed, is the 2,2,2-trichloroethyl chloroformate (TrocCl) that at first promote the 1,2 migration of the alkyl group from the boron centre to the pyridine and later the hydrolysis/rearomatization process by increasing the electrophilicity of intermediates 60 and 61. NMR and React-IR studies confirmed the formation of all the postulated intermediates during the reaction, with the only exception of 60 due to an extremely fast reaction leading directly to compound 61 upon addition of TrocCl to the reaction mixture. The high yields and stereospecificities with which α-chiral pyridines can be accessed using this methodology partially compensate the necessity to use pre-formed chiral boronic esters.

In spite of their importance, enantioselective catalytic methods are still rare. Based on their previous studies on C-H bond addition of aromatic and heteroaromatic compounds to alkenes, Huo and co-workers explored the possibility to develop an asymmetric variant of this transformation (Scheme 8). Chiral half-sandwich Sc-complexes promoted the addition of 2-substituted pyridines to several terminal alkenes yielding chiral 2,6-disubstituted pyridines with excellent results.

![Scheme 8: Sc-catalysed addition of substituted pyridines to terminal alkenes.](image)

### 1.3 Benzoxazoles and Its Analogues

Benzoxazoles and analogue scaffolds, such as oxazoles, thiazoles, imidazoles and their benzo-fused counterparts, found extensive application in medicinal chemistry. Therefore, development of new synthetic methodologies for the preparation and modification of this class of compounds is a continuous challenge in organic chemistry. As for the other heterocycles already discussed in this chapter, also in this case, typical strategies for their construction rely on cyclization reactions or direct functionalization of the heterocycle scaffold. In this section the focus will be on benzo-fused five member rings, namely benzoxazole and benzothiazole.

Cyclization reactions occur between ortho-substituted aniline and either aldehydes or carboxylic acid derivatives. In the first case the reaction proceed via formation of imine intermediate 67, that in turn reacts with the nucleophilic substituent on the aniline moiety followed by oxidation/rearomatization process to afford final product 69 (Scheme 9).
Scheme 9: Intermolecular cyclization between ortho-substituted anilines and aldehydes.

An interesting variation on this methodology have been proposed by Punniyamurthy and co-workers. In place of ortho-substituted anilines, arylxoyamines were used, and condensation with arylaldehydes generates bisaryloxime ether $^{33}$ (Scheme 10). According to their mechanistic studies, compound 70 undergoes chelation with the copper salt, forming intermediate 71. The latter rearranges to intermediate 72, that upon intramolecular cyclization affords copper species 73. Finally, a reductive elimination step delivers 2-arylbenzoxazole 74.

Scheme 10: Synthesis of 2-arylbenzoxazoles through Cu(II) catalysed bisaryloxime ethers rearrangement.

When carboxylic acid derivatives are taken into account, the first step is the formation of intermediate amide 76 (Scheme 11). Based on the nature of the X-substituent on the ortho-position, two different route are possible. If X is a nucleophilic substituent, like alcohols, amines or thiols, then it will undergoes direct addition to the carbonyl moiety providing compound 77. Elimination of a molecule of water will lead to the formation of benzoxazole 69. The intramolecular cyclization requires harsh condition and/or the use of strong Lewis acids. When X- is a halogen, usually bromine, the final step towards product 69 is a cross-coupling reaction, most commonly catalysed by copper salts.

Scheme 11: Intermolecular cyclization between ortho-substituted anilines and carboxylic acid derivatives.
In general, it can be concluded that cyclization reactions for the synthesis of substituted benzoxazoles often require high temperature and catalytic amount of metal catalyst (i.e. Pd, Cu, Sn, Zr), even though few metal-free strategies that rely instead on the use of microwave irradiation have been reported.\textsuperscript{31m,36}

The continuous advances in transition metal catalysed chemistry and C-H activation, led to a flourishment of reports on the direct functionalization of heteroaromatic scaffolds.\textsuperscript{24b,32} These methodologies allow a straightforward and easy access to a broad spectrum of structures starting from simple reagents. Arylation of benzoxazoles and related structures have received significant attention due to wide application of 2-aryl azoles in pharma industry.\textsuperscript{37} Since the seminal work of Nakamura in the 80s,\textsuperscript{38} an increasing number of reports on arylation methodologies have appeared. The majority of them are based on a Pd(0)-Pd(II) catalytic system in combination with phosphine ligands.\textsuperscript{32,39} The general catalytic cycle derived from the studies of Miura and co-workers is depicted in scheme 12.\textsuperscript{40}

![Scheme 12: Catalytic cycle for Pd-catalysed arylation of azoles.](image)

A Pd(0) species undergoes oxidative addition to aryl halide 78 and the subsequent nucleophilic addition of 80 to the newly formed Pd(II) species 79, affords adduct 81. Deprotonation of the latter leads to re-aromatised azole ring 82, that upon reductive elimination releases product 83 closing the cycle. Alternatively, Rh and Cu catalysts have been employed successfully in this transformation.\textsuperscript{24b,32b,32c,41} Recently, Gao et al. reported a simple copper catalysed direct arylation of benzoxazoles (Scheme 13).\textsuperscript{31c}

![Scheme 13: Copper catalysed direct arylation of benzoxazoles.](image)
Cheap copper salts and triphenyl phosphine ligand promote the coupling of several aryl bromides affording the desired product in good to excellent yields. Moreover, other heteroaromatic scaffolds, such as pyridines and quinolines, can be coupled effectively.

In contrast, alkylation processes are less common, even rare when their asymmetric version is considered.\textsuperscript{31d,31m,31n,42} This is partially due to the tendency of metal-alkyl intermediates to undergo β-hydride elimination, consuming the alkylating agent in an unproductive way.\textsuperscript{43} Filloux et al. have recently disclosed a Rh(I)-catalysed asymmetric alkylation of benzoxazoles using bidentate phosphine ligand \textit{90} (Scheme 14).\textsuperscript{42b}

Scheme 14: Rh-catalysed asymmetric alkylation proposed by Filloux et al.

Moreover, they gained useful insight on the mechanism and on the origin of the enantioselectivity with a series of competition and deuterium labeling experiments. Based on the results obtained, the catalytic cycle depicted in scheme 15 is proposed. Rh-Complex \textit{91} mediates the \textit{C-H} activation of \textit{92} and generates the Rh-heteroaryl complex \textit{93}. Rh-enolate \textit{95} is formed upon migratory insertion on acrylate \textit{94}. β-hydride elimination process triggers isomerization to \textit{97} via Rh-η\textsuperscript{2} complex \textit{96}. Hydrolysis mediated by acetic acid restores catalytically active species \textit{91} and releases final product \textit{98}.

Scheme 15: Proposed catalytic cycle for the Rh-catalysed asymmetric alkylation of benzoxazoles.
The labeling experiments suggest that the enantiodetermining step is the migratory insertion. Subsequent stereospecific β-hydride elimination/hydorhodation leading to intermediate 97, prevents epimerization of the newly formed stereocentre.

1.4 Conclusion

Over the years, the extensive studies on the synthesis and functionalization of heterocyclic compounds led to the development of hundreds of reports, covering a significantly broad scope of catalytic systems, substrates and reaction partners. Despite this incredible production, effective asymmetric synthesis is still difficult to achieve. The continuous demand of new heteroaromatic structures with potential biological activity urges the scientific community to further improve the already existing methods and explore new ones. In the past decade, exploitation of heteroaromatic moiety as activating group, though a weak one, has arisen as new tool for synthetic chemists to install stereogenic centres in a remote position. Pioneering in this field has been the work of Lam and Lautens. In chapters 2 and 4 of this manuscript, the advances in the field and our contribution to it will be discussed in more details.

1.5 Outline of the Thesis

The aim of this thesis is the development of efficient methodologies for the modification of heterocyclic scaffolds in catalytic asymmetric fashion, using synthetic strategies involving metal catalysts. Moreover, for each transformation mechanistic studies have been conducted to gain a deeper understanding of the corresponding catalytic cycles.

In Chapter 2, the copper catalysed asymmetric conjugate addition of Grignard reagents to alkenyl heteroarenes is discussed. Main player of this chapter is boron based Lewis acid BF₃∙OEt₂, able to promote a process otherwise impossible. Linear Grignard reagents, as well as branched, functionalised and aromatic ones, can be added to a wide range of alkenyl aromatic heterocycles under cryogenic conditions. The desired addition products are obtained in high yields and excellent enantiomeric excesses. Interestingly, a side-reaction of this process made us realize that Lewis acids can be used, not only to activate electrophilic substrates, but also to gain control over the chemoselectivity of a given reaction.

The trapping process of the heteroaromatic enolate formed upon conjugate addition to alkenyl aromatic heterocycles using enoates is discussed in Chapter 3. The high chemoselectivity exhibited by the process has been studied by use of low temperature NMR spectroscopy.

Chapter 4 describes the development of a catalytic system for the conjugated addition of organometallic reagents to various alkenyl pyridine scaffolds. Combination of copper salts, diphosphine ligands and strong Lewis acid trimethylsilyl trifluorometanesulfonate (TMSOTf) enabled the conjugate addition of alkyl Grignard reagents to pyridine substrates usually considered poorly reactive. In presence of substrates bearing reactive functional groups, the process showed a remarkable functional group tolerance.

Finally, Chapter 5 presents the results of the mechanistic studies conducted on the catalytic system for the alkylation of alkenyl pyridines. Experimental studies revealed important insights on the role of the Lewis acid in the process as well as on the influence of the double bond geometry on the selectivity of the reaction. Additional information on the catalytic cycle have been acquired conducting low temperature NMR spectroscopy analysis of the reaction system.
1.6 Bibliography


