Chapter 1

Introduction

*Substrate non-innocence and open-shell organometallic reactivity*
A general introduction to catalysis

The efficient synthesis of chemicals that are of use to mankind lies at the heart of chemical research. While many of these chemicals are manufactured in bulk because of their higher demand, many others are manufactured in relatively smaller scales and have more specific use. Bulk chemicals are often starting points for further chemical transformations to produce molecules with special functionalities. Catalysis, in general, helps enable mankind to perform these processes under mild(er) conditions, and in more sustainable, atom-efficient manners. Catalysis typically leads to more selective reactions, thus reducing high costs and energy demands associated with (large scale) separation techniques. Additionally, catalysts enable reactions between reagents under reaction conditions where otherwise no reaction takes place at all. This is because a catalyst paves way for alternative reaction pathways or shortcuts that are otherwise not accessible.

Research in the field of catalysis plays a key role in sustaining life on earth as we know today and in addressing environmental challenges that arise from our current fossil-based economy. Not only that, it also finds an important place in enabling our society to transit from the current fossil-based economy to one that is based on renewables. In the ideal situation, all future chemical processes will start from raw materials that are derived from abundant renewable sources, which are selectively converted in energy-efficient catalytic processes to products of interest, producing very little or no waste. The catalyst used in these processes should also be non-toxic, cheap, abundant and recyclable. As such, catalysis will always continue to play a pivotal role in society.

Three broad classes of catalysts can be distinguished: Homogeneous molecular catalysts, heterogeneous catalytic materials and enzymes (bio-catalysis). Of course hybrid systems that make use of both biological entities and non-natural molecular transition metal complexes have also been developed, and similarly catalysts on the interface of traditional homogeneous and heterogeneous catalysis also exist (e.g. immobilized molecular catalysts). The research described in this thesis focusses on molecular homogeneous catalysis, but takes inspiration from enzymatic processes to develop new catalysts and (perhaps most importantly) to uncover new reactions and reaction mechanisms.

In homogeneous catalysis, reactions are typically mediated by molecular complexes. The metal centres of these complexes are typically surrounded by ligands that interact with the metal. These ligands can be just simple spectators, while in many other cases they are capable of undergoing cooperative electronic transformations thus assisting bond-making and breaking processes. Molecular catalysts can usually be studied in great detail, with the aid of various spectroscopic techniques. In addition to the parent catalysts, intermediates can often be probed as well, thus giving valuable information on the modus operandi of the system. This is important because it helps us to improve on existing systems and offers windows of opportunities to perform other transformations.
Bio-inspired Catalysis

Like molecular catalysts, enzymes also use transition metals as catalytic centres. However, there are some distinct differences between manmade homogeneous catalysts (till date) and enzymes. In an enzyme, a complex network of protein residues surrounding the active site provides a special, often cooperative shell around the metal centre. This so-called second coordination sphere leads to all that is so special about enzymes. For example, it causes higher reactivities by cooperative substrate activation. The protein matrix shell also provides a protective ‘cage’ around the active site, preventing several deactivation pathways by site isolation. By taking advantage of hydrophobic and hydrophilic pockets the second coordination sphere also forces substrates to drift towards the active site and products away from it. Additionally, the second coordination sphere also ensures that only some geometries are allowed in the enzyme pocket containing the metal centre, leading to selectivity in the reactions. Needless to mention, enzymes are structurally complex and are a result of millions of years of evolution. Bio-inspired catalysis is a research field that focusses on molecular catalysis, but takes inspiration from nature to introduce similar features as used by enzymes to induce faster reactions, a higher degree of selectivity, and higher turn-over numbers. Typically, this requires making effective use of second coordination sphere effects. One approach to mimic enzyme-like second coordination sphere effects is to build supramolecular cages around a molecular catalyst. By taking advantage of supramolecular interactions between certain sites in the molecular containers and metal/ligands in the catalysts it is possible to encapsulate the catalyst inside a confined space so that effects like site isolation, substrate selectivity and protection of metal centres are also achieved in systems that are simpler than natural enzymes. Other approaches involve introduction of H-bonding or Lewis acidic/basic moieties connected (covalently or non-covalently) to the ligand, so to mimic and exploit second coordination sphere effects in catalysis.

Apart from the structural differences, the other difference between enzymes and manmade catalysts that truly stands out is the type of metal in play. Enzymes mostly incorporate earth-abundant metals in their active sites, while many manmade catalysts are based on non-abundant noble metals. This has consequences in the mechanisms that are responsible for successful reactions. While late transition metals mostly take part in processes that involve two-electron changes, first-row transition metals frequently show one-electron reactivity. This means that often radicals are involved as intermediates in reactions using base-metal catalysts (such as enzymes). Radicals are typically considered to be too reactive to be selective. While for free radicals this might be true, in the coordination sphere of a transition metal radical-type reactions can actually proceed very selectively. This is clearly the case for enzymes where open-shell intermediates are encountered in very selective and efficient reactions, leading to high chemo-, regio-, diastereo- and enantioselectivities. While the radical character allows for difficult bond-breaking/forming processes, the second-coordination sphere of the metallo-enzyme environment enables a high selectivity. To understand this in a context, let us take the classical example of the enzyme Galactose Oxidase (GOase). GOase is a well-studied member of the family of radical copper oxidases that use a novel Cu²⁺-tyrosyl radical unit to perform two-electron redox chemistry. GOase couples the reduction of O₂ to H₂O₂ with the oxidation of primary alcohols to aldehydes. As shown by X-ray crystallography, the so-called ‘inactive’ form of GOase features an unusual tyrosinate ligand (at amino acid 272 of the enzyme (Y272)) covalently linked to a cysteine (C228). In the ‘active’ form of the enzyme, this ligand exists as a one-electron oxidised tyrosyl radical that is stabilised by a nearby tryptophan (W290).
The mechanism of oxidation by GOase displays excellent features of radical control in the coordination sphere of transition metals (Scheme 1). It is chemo-selective for primary alcohols with rate constants of \(~1.59 \times 10^4\ M^{-1}\ s^{-1}\). Oxidation of the active site by molecular oxygen produces a Cu\textsuperscript{II}-coordinated tyrosinyl radical as well as a hydroperoxo ligand. In the next step the hydroperoxo ligand deprotonates the alcohol and forms the alcoholate ligand, thus, producing free hydrogen peroxide. The tyrosinyl radical ligand then abstracts a hydrogen atom from the \(\alpha\)-CH bond of the alcoholate ligand to produce the aldehyde. This coupling of the one-electron redox cycles, Cu\textsuperscript{I}↔Cu\textsuperscript{II} and tyrosine↔tyrosinyl•, to effect the overall two-electron catalytic half-reaction illustrates very well the metal and ligand synergism. From the point of view of an organometallic chemist this enzyme shows us a trick worthy of investigation. That is, how to use abundant base metals that typically undergo one-electron processes in transformations that require two-electron catalytic cycles. Metal-ligand cooperativity is therefore key in these transformations, as is the redox activity (or 'redox non-innocence') of the ligand in these processes. This example of the GOase enzyme is one of the many ways in which ligands can orchestrate, and in fact take active part in catalytic reaction steps.

**Scheme 1.** The mechanism of oxidation by the GOase enzyme. Two one-electron-redox cycles, Cu\textsuperscript{I}↔Cu\textsuperscript{II} tyrosine↔tyrosinyl• are coupled to result in an overall two-electron selective oxidation of a primary alcohol to an aldehyde.

**Cooperativity via redox non-innocent ligands**

**Ligands involved in substrate activation**

Inspired by the high activity and selectivity of enzymes, enormous efforts have been made to introduce enzyme-like features to molecular catalysts. In particular redox-active (redox non-innocent) ligands and substrates have gained a lot of recent attention in this perspective.\textsuperscript{11} For example, in 2007 Grützmacher and co-workers reported a catalytic alcohol oxidation reaction based on iridium. The
Ligands around the iridium were aminyl radical ligands (Scheme 2). Deprotonation of the parent complex A with KO\text{\textbf{\textit{t}}}Bu leads to the anionic intermediate B. This undergoes one-electron oxidation by benzoquinone (BQ) forming the radical intermediate C. Intermediate C reacts with the alcoholate intermediate D in a very similar way as the intermediate in the GOase cycle (Scheme 1). The dibenzotropylamino substituent plays the same role as a tyrosine moiety in GOase in that it enables facile hydrogen atom transfer (HAT) from the alcoholate substrate to the nitrogen-centred ligand. Oxidation of E by semiquinonate (SQ\textsuperscript{−}) produces the aldehyde and regenerates the catalyst. This seminal example elegantly shows that similar features as those used by natural enzymes can be introduced in molecular catalysts to gain control over radical-type reaction pathways.

Scheme 2. An iridium complex that performs alcohol oxidation using a cooperative redox-active ligand.

**Ligands as electron reservoirs**

An elegant way of avoiding ‘unfavourable’ oxidation states of metals in a reaction is to use redox-active ligands surrounding the metal that function as electron reservoirs. A curious example arises from the work of van der Vlugt et al. where a Pd complex takes part in single-electron transfer (SET) steps, while most Pd complexes typically take part in two-electron processes. The ligand used is a redox-active tridentate NNO ligand. The accessible oxidation states of the ligated palladium(II) complex is depicted in Scheme 3. One-electron reduction of the parent complex A leads to formation of a diamagnetic amidophenolato complex that is capable of activating an aliphatic azide. This is believed to proceed via a redox-noninnocent pathway wherein the redox-active ligand facilitates intramolecular **ligand-to-substrate** single electron transfer to generate a nitrene-substrate radical bound to palladium.
Scheme 3. Ligand to substrate electron-transfer cooperativity used in the activation of an azide to form a nitrene radical moiety.

Ligands that alter Lewis acidity/basicity of the metal

The reduction/oxidation of a redox-active ligand can heavily alter the Lewis acidity/basicity of the metal centre. This in turn modifies the substrate affinity of the metal catalyst. At the same time the energy profiles of the follow up steps in the reaction mechanism are also altered. An example of an iridium complex where ligand oxidation leads to increased Lewis acidity of the metal is shown in Scheme 4. Complex A is oxidized by silver tetrafluoroborate forming the cationic version of the complex [A]^+. This cationic complex contains a one-electron oxidized ligand-radical which makes the cationic complex a stronger Lewis acid than its neutral form A. In contrast to the neutral complex, the oxidised form of the complex is reactive enough to form a H₂ adduct [A.H₂]^+ that undergoes deprotonation by a base. Further oxidation and deprotonation provides an effective route for the oxidation of H₂. In the overall process, the electrons of H₂ thus reduce the oxidized form of the ligand back to its neutral form, and hence the redox-active ligand is not only used to increase the Lewis acidity of the metal, but also acts as an electron reservoir.

Scheme 4. An iridium complex where ligand oxidation leads to increased Lewis acidity of the metal.
Redox non-innocence of substrate ligands

A relatively under-explored, yet interesting way to use the cooperativity of redox active moiety is found in reactions in which a substrate bound to a transition metal acts as a redox-active ligand. This is beneficial because it leads to open-shell intermediates which are often highly reactive and show different reactivities when compared to the analogous closed-shell intermediates. For metal complexes that are paramagnetic the location of the unpaired electron is often not obvious. In some cases this might actually rest on a non-innocent substrate ligand; a consequence of discrete spin-transfer to the substrate. There are many examples of stoichiometric reactions where an open-shell metal complex is able to transfer its spin density to a non-innocent substrate. Some of these examples are shortly discussed here, once again taking an iridium complex as the example. Catalytic applications of redox-active substrates, in the context of cobalt metalloradical catalysis, are described in the sections following this iridium example.

The open-shell iridium complex 1, [(Me₃tpa)Ir(II)(ethene)]²⁺ in Scheme 5 (Me₃tpa= N,N,N-tris(6-methyl-2-pyridylmethyl)amine), displays both metalloradical and ligand-radical behaviour. The redox-active ligand is the alkene in this case.¹⁵ The vacant site cis to the ethene ligand is sterically shielded by the three Me fragments of the Me₃tpa ligand, and is not accessible by larger molecules. Acetonitrile, however, is small enough to bind to this site, and MeCN binding to the iridium(II) centre triggers radical reactivity at the ethene ligand.¹⁶ The otherwise stable metalloradical therefore gives rise to β-ethyl radical 2. Ethene dissociation from 2 leads to iridium(II) complex species 3, which couples with another molecule 2 to form the ethylene-bridged bis-iridium(III) species 4. Interestingly, if the reaction is performed in the presence of ethyl diazoacetate (EDA) the three-carbon bridged dinuclear species 6 is formed.¹⁷

Scheme 5. The open-shell iridium complex 1 [(Me₃tpa)Ir(II)(ethene)]²⁺ (Me₃tpa= N,N,N-tris(6-methyl-2-pyridylmethyl)amine). This complex displays both metalloradical and ligand-radical behaviour.

The latter reaction is believed to proceed via coupling of β-ethyl radical 2 with carbene radical species 5, formed by metalloradical activation of EDA by iridium(II) complex 3 (Scheme 5). This reaction provided an initial hint to formation of carbene-radicals in the coordination sphere of group 9 metalloradicals in our group.¹⁸ While these initial reactions were only stoichiometric, they did tell us a lot about their intrinsic underlying radical-type reactivity. The involvement of a carbenoid radical (5) to give complex 6 is of particular relevance for the development of new C–C bond-forming reactions. In fact, in the years that followed, porphyrin complexes of the group 9 metal cobalt have been
established as metalloradical catalysts that performs a myriad of catalytic reactions proceeding via carbene and nitrene radicals. An overview of their reactivity is provided in the following sections.

Cobalt(II) porphyrins as metalloradical catalysts

Porphyrins are tetradentate macrocyclic nitrogen ligands that form air-stable complexes with Co(Il) precursors. The resultant cobalt(II) porphyrin complexes are paramagnetic with \((d_{xy})^2(d_{xz,yz})^4(d_{z^2})^1\) electronic configuration stemming from the strong ligand field of the porphyrinato ligand. These complexes are essentially low spin well-defined metalloradicals. Additionally, the porphyrinato ligand is planar leaving two axial trans-sites free for coordination and subsequent reactivity. The lack of any cis-coordination site available for reactivity also means that formation of unwanted side-products formed by cis-coupling processes are generally avoided. At the same time the electronics and steric of metalloporphyrins can be tuned by varying the substituents on the peripheral positions.

\[
[\text{Co}^{II}(\text{TPP})] \text{ when } R= \text{ Ph}
\]

**Figure 1. The commercially available cobalt(II) porphyrin, \([\text{Co}^{II}(\text{TPP})]\) and its electronic configuration. The strong field character of the planar porphyrin ligand causes pairing of all electrons leading to a low-spin complex. The \(d_{z^2}\) orbital is singly occupied giving rise to a metalloradical.**

There, however, exists synthetic challenges to make these substituted porphyrins and the most common procedures are at best only low yielding.\(^1\) The simplest version, the cobalt tetraphenyl porphyrin (\([\text{Co}^{II}(\text{TPP})]\)) is commercially available though, and this makes this compound attractive as a catalyst. In this regard, a big step was made in 2005 when the group of Zhang disclosed a modular way to synthesise a variety of \(D_2\)-symmetric (chiral) porphyrins starting from a tetrabrominated synthon (Scheme 6).\(^2\) Performing quadruple coupling reactions on these tetrabrominated backbones gives access to well-decorated porphyrin ligands with hydrogen bonding (H-bonding) chiral substituents. These bromoporphyrin synthons can be prepared in multigram scale and stored for a long time. Next, by changing the aldehyde a range of different substituents (R) can be introduced at the alternating meso-positions. These can be introduce by quadruple Pd-catalysed amidation reactions, using a variety of commercially available (chiral) amides. These are high-yielding reactions and functional group tolerant. The structures of these \(D_2\)-symmetric (chiral) porphyrins reveal a lot about their potential as a metalloradical catalyst. The cross-coupling reaction installs the chiral amides in the meso-aryl positions such that they are directed towards the centre of the porphyrin. The almost perpendicular arrangement of all the meso-phenyl rings creates a chiral pocket around the metal centre. The trans positioning of the amido groups causes rigidity pushing the ortho-chiral R groups even closer towards the reaction centre. In addition, the N-H moiety in the amido units are positioned...
close enough to the metal centre to take part in H-bonding interactions with substrates that coordinate to the metal centre. These H-bonding interactions were expected to result in faster reactions, and facilitate chirality transfer.\textsuperscript{21}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme6.png}
\caption{Scheme 6. The modular approach towards the synthesis of \(D_2\)-symmetric porphyrins starting from a tetrabrominated synthon as reported by Zhang and co-workers.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{covalent.png}
\caption{A \(D_2\)-symmetric chiral cobalt(II) porphyrin developed by Zhang and co-workers. The trans positioning of the amido groups leads to rigidity, pushing the ortho-chiral \(R\) groups close to the reaction centre. Additionally, the \(N\)-H moieties of the amido units are positioned close enough to the metal centre to take part in H-bonding interactions with substrates that coordinate to the metal centre.}
\end{figure}

\textbf{Cobalt(II) porphyrins in carbene- and nitrene-transfer reactions}

For cobalt(II) porphyrins the earliest reactivity in carbene transfer was reported by Cenini and co-workers,\textsuperscript{22} and a little later by Zhang and co-workers in the cyclopropanation reactions of styrene.\textsuperscript{23} The reaction was not novel in itself because other metalloporphyrins of Fe,\textsuperscript{24} Ru\textsuperscript{25} and Rh\textsuperscript{26} could also catalyse this reaction. However, it was the selectivity of the reaction towards the cyclopropane product that was remarkable in the cobalt(II)-catalysed systems. In a cyclopropanation reaction involving a carbene, a common unwanted side product is the olefinic dimerization product of the
carbene. While for other metal porphyrins (Fe, Ru, Rh) the dimerization product of EDA varies between 20-40%, for the cobalt(II) porphyrin catalysts this was only (less than) ~1%. The substrate scope for this reaction was based on substituted styrenes as the alkene and the functional group tolerance was remarkable. Moderate enantioselectivities for cyclopropanation of styrene with EDA was also reported.

Scheme 7. The cyclopropanation of alkenes with EDA catalysed by [CoII(TPP)]. The reaction is more selective for the trans isomer of the cyclopropane. The dimerisation product of the carbene substrate is formed in negligible amounts.

With the advent of the bromoporphyrin synthons excellent enantioselectivities for this transformation could also be achieved.27 The catalyst in this case was the one depicted in Figure 2. In addition to that, the iron version of the same ligand performed very poorly in the same transformation, thus, underpinning the unique properties of the cobalt(II) porphyrin metalloradical catalyst.

Subsequently, the group of Zhang also reported the successful cyclopropanation of electron-deficient alkenes like acrylates and cyanoalkenes.28 While a number of catalytic systems worked exceptionally well with styrene derivatives and some electron-rich olefins, asymmetric cyclopropanation of electron-deficient olefins containing electron-withdrawing groups such as unsaturated carbonyl compounds and nitriles had previously proven to be a challenging problem. This can be understood by taking the electrophilic nature of the typical Fischer-type metal-carbene intermediates in the catalytic cycles of the other catalysts into account. Clearly, the metal carbene intermediate in case of cobalt(II) porphyrins has different electronics to benefit from in the cyclopropanation of electron-deficient alkenes. This was investigated in detail in our group in previous studies.29 The nature of the metal-carbene intermediate in case of cobalt(II) porphyrins was probed using EPR and ESI-MS techniques. The findings were further corroborated using DFT calculations.

The electronic structure of the elusive carbene adducts was investigated by our group for the reaction of the porphyrin complexes [CoII(TPP)] and [CoII(ChenPhyrin)] (Figure 3) with EDA by EPR spectroscopy. Solutions of [CoII(TPP)] became EPR silent upon addition of four equivalents of EDA with respect to the catalyst. A carbene-like [Co(TPP)(CHCOOEt)]+ species was, however, clearly observed in the ESI-MS spectrum of the same sample. In contrast, for [CoII(ChenPhyrin)] addition of EDA did not lead to EPR silence, but instead quite a complex EPR spectrum in toluene at 40 K was obtained (Figure 3) indicating the presence of three distinct paramagnetic cobalt species. Simulations revealed that the total signal stemmed from contributions from species I, II, and III in a ratio of 5:1:0.8 (Figure 4). Species I could be attributed to the EDA adduct [CoII(ChenPhyrin)(EDA)], with EDA coordinated to cobalt either via its carbon, carbonyl or dinitrogen moiety. The signals of species II could be assigned to the ‘bridging carbene’ species [CoII(ChenPhyrin)(CHCOOEt)]. The most interesting species, however, was species III, which could be assigned to an ‘organic radical’ revealing resolved hyperfine couplings with both cobalt and a proton. This species was therefore assigned to the ‘terminal carbene’ species
[Co\textsuperscript{II}](ChenPhyrin)(CHCOOEt)]. This was the first direct experimental evidence for a carbon-centred radical that was still in the coordination sphere of cobalt. ESI-MS measurements confirmed the presence of species \textbf{II} and/or \textbf{III}.

\textbf{Figure 3.} EPR spectra of [Co(ChenPhyrin)] with and without EDA. The spectrum in blue shows the signal belonging to the catalyst only. On adding EDA this spectrum evolves almost immediately to the spectrum in red. The measurements were performed in frozen toluene at 40 K.

DFT calculated electronic structures also fit the description of species \textbf{III}. According to these calculations, the ‘bridging carbene’ complex \textbf{II} is a metal-centred radical, with its unpaired electron residing mainly in the cobalt 3d\textsuperscript{z2} orbital, in good agreement with the measured EPR parameters. The spin distribution in the ‘terminal carbene’ \textbf{III} complex is strikingly different. The unpaired electron resides mainly on the ‘carbene’ carbon (methyl 2-ylideneacetate) moiety, and is slightly delocalized over the neighbouring cobalt and oxygen atoms. This electronic structure agrees well with the EPR spectrum of \textbf{III}, which is indicative of an ‘organic radical’. Hence, the ‘terminal carbenes’ are best described as carbon centred radicals (or ‘carbene radicals’) rather than true transition metal Fischer-type carbene moieties. This is what gives the nucleophilic character to this carbene species, making it capable of performing cyclopropanation on electron-deficient alkenes and effectively preventing carbene-dimerisation side-reactions. The orbital picture of this carbene radical intermediate is depicted in Figure 5.

\textbf{Figure 4.} Individual components \textbf{I}, \textbf{II}, and \textbf{III} contributing to the EPR spectrum shown in Figure 3. \textbf{I} is the [Co\textsuperscript{II}(ChenPhyrin)(EDA)] adduct, \textbf{II} is the ‘bridging carbene’ species [Co\textsuperscript{II}(ChenPhyrin)(CHCOOEt)], and \textbf{III} is the terminal carbene radical species [Co\textsuperscript{II}(ChenPhyrin)(CHCOOEt)].
The interaction with the singlet \( ^1\text{CHCOOMe} \) moiety pushes the energy of the cobalt \( d^2 \) orbital above the energy of the antibonding MO constructed from the carbon \( p_y \) orbital and cobalt \( d_{yz} \) orbital. This raising of energy of the \( d^2 \) orbital results in the intramolecular electron transfer from cobalt to the carbene moiety (Figure 5, A and B). Half filling of the Co-C \( \pi^* \) antibonding orbital consequently reduces the metal-carbon bond order. Hence, the ‘carbene’ species loses its typical Fischer-type character and becomes more nucleophilic. The open-shell radical character clearly places unpaired spin density on the ‘carbene’ carbon, making it distinctly different from closed-shell Fischer- and/or Schrock-carbenes.

The reactivity of the cobalt(III)-carbene radical is in line with its electronic structure. The reaction proceeds via a stepwise radical addition-substitution pathway, in which the redox non-innocent behaviour of the terminal carbene ligand in intermediate C plays a key role. The [Co\(^{II}\)(por)] catalyst A reacts with the diazoester compound to form a transient adduct B, which loses dinitrogen in a rate-limiting step (TS1) to form the ‘terminal carbene’ intermediate C. This proceeds via radical addition of the ‘carbene radical’ C to the double bond of the olefin to form a \( \gamma \)-alkyl radical intermediate D. The intermediates D then readily collapses in almost barrierless ring-closure reaction (TS3) to form the cyclopropane. Addition of the ‘terminal carbene’ C to the olefin (TS2) proceeds with a comparable barrier as its formation (TS1), thus explaining the previously reported first-order kinetics in both substrates and the catalyst.\(^{22}\) Formation of C can be accelerated by stabilization of C and TS1 via hydrogen bonding that is accessible in case of [Co\(^{II}\)(ChenPhyrin)]. Calculated barriers for [Co\(^{II}\)(por)]-mediated carbene dimerization are higher than the highest barriers for the olefin cyclopropanation. This provides an explanation to the suppression of carbene-dimerization under catalytic conditions. The proposed radical-type mechanism therefore explains the excellent performance of [Co\(^{II}\)(por)]-based systems in the cyclopropanation of electron-deficient olefins.

**Figure 5.** The orbital picture of this carbene radical intermediate. The interaction with the singlet :CHCOOMe moiety pushes the energy of the cobalt \( d^2 \) orbital above the energy of the antibonding MO constructed from the carbon \( p_y \) orbital and cobalt \( d_{yz} \) orbital, thus resulting in intramolecular electron transfer from cobalt to the carbene moiety (Figure A and B).
Scheme 8. The DFT calculated pathway for the Cobalt(II) Porphyrin mediated cyclopropanation of alkenes. Activation of the diazo compound at the catalyst is the rate determining step.

The [Co⁰(Por)] catalysed cyclopropanation reaction is therefore an example of redox-active reactivity of a substrate ligand playing a key-role in the catalytic cycle. Using the [Co⁰(Por)] platform, this concept has so far been extended and applied to the synthesis of a variety of organic molecules, in most cases with excellent diastereo- and enantioselectivities when applicable. For carbenes, addition to triple bonds in alkynes leading to the formation of cyclopropenes has also been reported to be very successful. In the last five years several ring-closing reactions have been reported using these versatile catalysts. Both inter- and intramolecular reactions are possible and some of these are summarised in Scheme 9.

Scheme 9. Selected examples of various carbene-transfer reactions catalysed by cobalt(II) porphyrins. Apart from insertions to alkenes, alkynes the cobalt(III)carbene radical intermediates can also perform C–H functionalization at benzylic/benzallylic position.
Like carbenes, nitrenes are also useful hypovalent moieties of synthetic interest. However, nitrene-transfer chemistry, although equally interesting, has thus far proved to be less rich in scope. This is partly because of the fact that unlike the carbenes, nitrenes only have one substituent. This makes tuning of the electronic properties of the metallo-nitrene intermediates limited, at least in comparison to carbene-transfer chemistry. Until the early 2000s, it was quite common to use iminoiodanes$^{32}$ or haloamine-Ts$^{33}$ compounds as nitrene sources. These are, however, not the most benign nitrene precursors as they lead to the formation of undesirable (waste-producing) side-products like phenyl iodide and other halogen containing compounds. With the efforts of various groups, organic azides were quite recently discovered to be interesting and potentially greener resources to generate nitrenes, as the only by-product formed during the generation of nitrenes from azides is dinitrogen.

Several catalysts have been developed for nitrene-transfer reactions, and the most successful ones are still based on non-abundant Rh$^{34}$ and Ru$^{35}$ noble metals. Amongst the first row transition metals, there have been reports of Mn,$^{36}$ Cu,$^{37}$ and Fe$^{38}$ catalysed systems as well. A variety of nitrene-transfer reagents have also been employed in combination with differently meso-substituted cobalt(II) porphyrin catalysts. For example, with the use of reagents like diphenyl phosphoryl azide (DPPA), it is possible to further modify the substituent, as the nitrogen-phosphorous bond in the product aziridine is readily hydrolyzed.$^{39}$ In the pursuit of finding more nitrene transfer reagents with easily removable groups on the nitrogen atom, trichloroethoxysulfonyl azide (TcesN$_3$) was found to be effective.$^{40}$ Apart from the nitrene precursors itself, specially tailored cobalt porphyrins (Figure 2), for example with H-bonding functionalities, have further enhanced the applicability of these systems.$^{41}$ Simple organic azides like tosyl azide can also be used as a viable nitrene precursors. H-bonding interactions between the nitrene moiety and the arms of the catalyst facilitate nitrenoid formation,$^{42}$ and lead to an increased catalyst efficiency and lifetime. Enantioselective aziridination of alkenes were reported a few years ago using chiral [Co$^{n}$((ChenPhyrin))] with TcesN$_3$, and enantioselectivity of 99% could be obtained.$^{40}$

'Nitrene transfer' to styrene also proceeds in a stepwise manner via radical addition of the 'nitrene radical' C to the C=C double bond of styrene to form γ-alkyl radical intermediates (Scheme 10).$^{42}$ Species D readily collapses in an almost barrierless ring closure reaction to form the aziridine, thereby regenerating the cobalt(II) porphyrin catalyst. Additionally, the computed free energy profile well explained the superior performance of the reported catalyst with H-bonding amide arms (Co$^{n}$((porAmide)) over the non-functionalized system [Co$^{n}$((por))].$^{42a}$
Scheme 10. a) DFT calculated mechanism of cobalt(II) porphyrin mediated benzylic C–H amination of ethylbenzene by N3C(O)OMe. b) cobalt(II) porphyrin mediated aziridination of styrene with PhSO2N3.

Selected examples of reactions where these nitrene-radicals are active intermediates are schematically represented in Figure 6. Until recently, aziridination was the only inter-molecular reaction reported for cobalt(II)-porphyrin-catalysed nitrene-transfer reactions. Most benzylic/allylic/benzallylic C–H amination reactions are intramolecular reactions.

Figure 6. Schematic representation of various intramolecular nitrene-transfer reactions catalysed by cobalt(II)-porphyrin catalysts. Until recently, aziridination was the only reported intermolecular cobalt(II) porphyrin catalysed nitrene-transfer reaction.
Aim and outline of the thesis

Having described the bio-inspired tools that can be used in open-shell organometallic chemistry it is clear that controlled radical-type reactions in the coordination sphere of transition metals is possible. For example, in the active site of the enzyme GOase, selective one-electron reactions take place in the active site around a central copper atom. In the active site, not only the copper atom but also the amino acid residues around the metal centre take part in step-wise one-electron processes in an overall combined two-electron reaction. Such strategies in biological systems inspire chemists to control radical-type reactions with simpler synthetic molecular catalysts, using similar tools as used by nature but without the full complexity of an enzyme. These bio-inspired strategies transit from the realms of pure scientific curiosity to a dire need in the light of sustainability. Keeping in mind the abundance and relative low-prices of first-row transition metals it is highly desirable to be able to uncover new types of reactivities using base metals. Therefore, understanding such radical-type reactions, and applying them towards new sustainable approaches is important. At the same time controlled radical-type reactions in the coordination sphere of base-metal catalysts open new ways towards chemical transformations which are otherwise difficult or even impossible to perform using traditional methods.

The substrate non-innocence of carbenes and nitrenes using the cobalt(II) platform has proven to be particularly successful. While the mechanistic proposals based on DFT are attractive, so far limited experimental evidence has been gathered to prove the existence of the porphyrin-cobalt(III)-nitrene-radical intermediates. The detailed characterisation and understanding of these species is inevitable in enriching the synthetic applicability of these systems. The first part of this thesis describes the characterisation and synthetic application of such nitrene-radical moieties. In the second half of the thesis we describe new carbene-transfer reactions that proceed via the porphyrin-cobalt(III)-carbene-radical intermediates.

In Chapter 2 we describe the rigorous characterisation of the porphyrin cobalt(III)-nitrene radical species using a variety of spectroscopic and spectrometric techniques. The identity of this intermediate is unequivocally established. Additionally, a bis-nitrene intermediate that is formed on using N-Nosyl iminiodane as the nitrene precursor is also identified and characterised.

In Chapter 3 we describe our efforts to ascertain the geometry and the spectroscopic oxidation state of the nitrene-radical species with the aid of X-ray Absorption Spectroscopy (XAS). Comparison of the X-ray absorption near edge spectrum (XANES) with other cobalt(III) porphyrin compounds gave us new information about the effect of ligands on the XANES features.

In Chapter 4 we describe our efforts to react nitrene-radical intermediates with alkynes. However, in contrast to our expectations, unexpected H-atom abstraction reactions were encountered, which led to formation of other reactive intermediates. One such intermediate is the o-phenylene diimine, which dimerised in-situ to give azobenzenes. Most reported syntheses of azobenzenes involve harsh reaction conditions that are not functional group tolerant. Therefore, we investigated the substrate scope of this reaction. The electronic properties of some of the synthesised azobenzenes were also investigated.
In Chapter 5 we describe our efforts to use a different ligand system; corroles instead of porphyrins. This was done in an attempt to increase efficacy of cobalt(II) metalloradicals in nitrene-transfer reactions. Corroles are trianionic and thus \([\text{Co}^{II}(\text{Cor})]\)\(^{-}\) complexes are anionic. We tested our hypothesis that a more electron-rich cobalt centre should lead to lower barriers for the rate-limiting azide activation step. We chose a challenging ring-closing reaction of an aliphatic azide to give the pyrrolidine heterocycle as the benchmark. Synthesis, characterisation and catalytic application of the \([\text{Co}^{II}(\text{Cor})]\)\(^{-}\) species is described in this chapter, including computational studies of the electronic structure of the key nitrene-radical intermediate and the transition state concerning formation of these species.

In Chapter 6, we report a metalloradical approach for the synthesis of five-membered \(N\)-containing heterocycles called indolines. These reactions proceed via cobalt(III)-carbene radicals formed at a cobalt(II)-porphyrin catalyst. Using a tosylhydrazone substrate in the presence of a base, we generated diazo compounds (carbene precursors) \textit{in-situ}. In a ring-closing sequence that proceeds via an unique 1,5 H-atom abstraction (HAT) we were able to synthesise indolines in excellent isolated yields. The mechanism of this reaction was also investigated computationally, using DFT methods.

In Chapter 7 we remain interested in the cobalt(II)-porphyrin metalloradical, but we turn our attention to a special \textit{carbene} moiety, namely the \textit{difluorocarbene} (\(\text{CF}_2\)). While carbene transfer via a metal complex is quite well-explored, transfer of \(\text{CF}_2\) via a metal complex remains a long-standing challenge. The special electronic properties of the \(\text{CF}_2\)-carbene typically causes the metal-\(\text{CF}_2\) bond to be too strong. Learning from the electronic and orbital properties of the cobalt(III)-carbene radical we sought to make use of the weak Co–C bond of these species as a tool to transfer a cobalt-bound \(\text{CF}_2\) moiety to an organic substrate. This was successfully achieved, and the results are described in Chapter 7.
References and notes

(1) It is important to realise that (exothermic) reactions that work at ambient conditions are not always desirable on industrial scale because cooling is an energy intensive process as well.


(21) This was indeed the case as was revealed by the enhancement in reactivities studied by means of DFT calculations; see reference (29) and 42(a).


