Open-shell nitrene- and carbene-complexes of cobalt

Characterisation and reactivity

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Open-shell nitrene- and carbene-complexes of cobalt: characterisation and reactivity

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Monalisha Goswami
Geboren te Tirap, India
The research presented in this dissertation was performed at the Homogeneous, Supramolecular and Bio-inspired Catalysis group at the van ‘t Hoff Institute for Molecular Sciences of the University of Amsterdam. The work was financially supported by the Netherlands Organization for Scientific Research through an NWO-CW VICI Grant (project 016.122.613) to B. de Bruin.
Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

Marie Skłodowska-Curie

You cannot hope to build a better world without improving the individuals. To that end, each of us must work for his own improvement and, at the same time, share a general responsibility for all humanity, our particular duty being to aid those to whom we think we can be most useful.

Marie Skłodowska-Curie
The cover, designed by the author is her impression (acrylic on paper) of the colourful molecules, called porphyrins; a macrocycle that has been profusely used in this thesis as a ligand. Their presence can give colours to the wings of certain butterflies and their lack is what strips the green to give way to the autumn colours, let's say, in the Norwegian woods.
~ For my parents Nivedita and Ashok and my sister Manisha ~
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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 enables mankind to perform these processes under mild(er) conditions,\(^1\) 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,\(^2\) 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,\(^3\) and similarly catalysts on the interface of traditional homogeneous and heterogeneous catalysis also exist (e.g. immobilized molecular catalysts).\(^4\) 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. In the coordination sphere of a metal, radicals this might be true, in the coordination sphere of a metal. 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 Cu\textsuperscript{II}-tyrosyl radical unit to perform two-electron redox chemistry. GOase couples the reduction of O\textsubscript{2} to H\textsubscript{2}O\textsubscript{2} 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 $\sim 1.59 \times 10^4 \text{M}^{-1}\text{s}^{-1}$. Oxidation of the active site by molecular oxygen produces a Cu$^{II}$-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$^{I}$↔Cu$^{II}$ 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](image)

*Scheme 1*. The mechanism of oxidation by the GOase enzyme. Two one-electron-redox cycles, Cu$^{I}$↔Cu$^{II}$ and 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. 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 \( \text{K}^+\text{O}^+\text{Bu}^- \) 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 \( (\text{SQ}^-) \) 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.
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 $[\text{A}]^+$. 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 H$_2$ adduct $[\text{A}.\text{H}_2]^+$ that undergoes deprotonation by a base. Further oxidation and deprotonation provides an effective route for the oxidation of H$_2$. In the overall process, the electrons of H$_2$ 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, \([(Me_3tpa)Ir^{II}(ethene)]^{2+}\) in Scheme 5 (Me_3tpa= 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 sitecis to the ethene ligand is sterically shielded by the three Me fragments of the Me_3tpa 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 diazo acetate (EDA) the three-carbon bridged dinuclear species 6 is formed.\(^{17}\)

Scheme 5. The open-shell iridium complex 1, \([(Me_3tpa)Ir^{II}(ethene)]^{2+}\) (Me_3tpa= 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 tetradeinate macrocyclic nitrogen ligands that form air-stable complexes with Co\(^{II}\) 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 prophyrinato 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.

![Diagram](image.png)

**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. The simplest version, the cobalt tetr phenyl 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). 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}

Scheme 6. The modular approach towards the synthesis of D\textsubscript{2}-symmetric porphyrins starting from a tetrabrominated synthon as reported by Zhang and co-workers.

![Scheme 6](image)

\textbf{Figure 2.} A D\textsubscript{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.

\textit{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
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. 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. 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.

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.
[CoII(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 II and/or III.

**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 III. According to these calculations, the ‘bridging carbene’ complex II is a metal-centred radical, with its unpaired electron residing mainly in the cobalt 3d_2 orbital, in good agreement with the measured EPR parameters. The spin distribution in the ‘terminal carbene’ III complex is strikingly different. The unpaired electron resides mainly on the ‘carbene’ carbon (methyl 2-yldeneacetate) moiety, and is slightly delocalized over the neighbouring cobalt and oxygen atoms. This electronic structure agrees well with the EPR spectrum of III, which is indicative of an ‘organic radical’. Hence, the ‘terminal carbene’ species 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.

**Figure 4.** Individual components I, II, and III contributing to the EPR spectrum shown in Figure 3. I is the [Co(ChenPhyrin)(EDA)] adduct, II is the ‘bridging carbene’ species [CoII(ChenPhyrin)(CHCOOEt)], and III is the terminal carbene radical species [CoII(ChenPhyrin)(CHCOOEt)].
The interaction with the singlet :CHCOOMe moiety pushes the energy of the cobalt $d_{z^2}$ orbital above the energy of the antibonding molecular orbital (MO). This MO is constructed from the carbon $p_y$ orbital and cobalt $d_{yz}$ orbital. This raising of energy of the $d_{z^2}$ 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 $[\text{Co}^{II}(\text{por})]$ 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.\textsuperscript{22} Formation of C can be accelerated by stabilization of C and TS1 via hydrogen bonding that is accessible in case of $[\text{Co}^{II}(\text{ChenPhyrin})]$. Calculated barriers for $[\text{Co}^{II}(\text{por})]$-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 $[\text{Co}^{II}(\text{por})]$-based systems in the cyclopropanation of electron-deficient olefins.
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 [Co^II(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 [Co^II(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.\(^{30}\) 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.\(^ {31}\)

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\textsuperscript{32} or haloamine-Ts\textsuperscript{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\textsuperscript{34} and Ru\textsuperscript{35} noble metals. Amongst the first row transition metals, there have been reports of Mn\textsuperscript{36}, Cu\textsuperscript{37} and Fe\textsuperscript{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.\textsuperscript{39} In the pursuit of finding more nitrene transfer reagents with easily removable groups on the nitrogen atom, trichloroethoxysulfonyl azide (TcesN\textsubscript{3}) was found to be effective.\textsuperscript{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.\textsuperscript{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,\textsuperscript{42} and lead to an increased catalyst efficiency and lifetime. Enantioselective aziridination of alkenes were reported a few years ago using chiral [\textbf{Co}\textsuperscript{II}(\textbf{ChenPhyrin})] with TcesN\textsubscript{3}, and enantioselectivity of 99% could be obtained.\textsuperscript{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).\textsuperscript{42} Species D’ easily 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\textsuperscript{II}(porAmide)) over the non-functionalized system [Co\textsuperscript{II}(por)].\textsuperscript{42a}
Scheme 10. a) DFT calculated mechanism of cobalt(II) porphyrin mediated benzylic C–H amination of ethylbenzene by $N_2C(O)OMe$. b) cobalt(II) porphyrin mediated aziridination of styrene with $PhSO_2N_3$.

Selected examples of reactions where these nitrene-radicals are active intermediates are schematically represented in Figure 6. Until recently, aziridination was the only intermolecular 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 iminoiodane 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 heterocyles 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) 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 carbene moiety, namely the difluorocarbene (CF$_2$). While carbene transfer via a metal complex is quite well-explored, transfer of CF$_2$ via a metal complex remains a long-standing challenge. The special electronic properties of the CF$_2$-carbene typically causes the metal-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 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).


Chapter 2

Characterisation of porphyrin-cobalt(III)-‘nitrene radical’ species relevant in catalytic nitrene-transfer reactions

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Introduction

Ligand-centred radical complexes play a pivotal role in a number of bio- and ‘bio-inspired’ catalytic transformations, providing a powerful tool to control the reactivity and selectivity of the catalyst.\(^1\) Such species are well-studied and characterized for transition metal complexes containing typical polydentate redox non-innocent ligands, such as semi quinone-type radical ligands\(^2\) and their nitrogen analogs,\(^2,3\) reduced bipyridine and terpyridine ligands,\(^4\) \(\alpha\)-iminopyridine ligands\(^5\) and pyridine-2,6-diimine ligands.\(^6\) More recently, considerable efforts have been made to understand the (electronic) structure and reactivity of monodentate redox non-innocent substrate-type ligands, such as carbenes,\(^7\) which play a key role in catalytic carbene transfer reactions.\(^8\) So far, only a few examples have been reported in which complexes bearing monodentate nitrogen-based radicaloid ligands were experimentally detected. Thus, well-studied complexes with redox active aminyl ligand radicals are limited to only a few well-characterized examples,\(^9\) and related complexes bearing redox non-innocent nitrene ligands are even scarcer.

‘Catalytic functionalization’ of C–H bonds is a holy grail in chemistry as it is an atom-, time-, and cost-efficient alternative to traditional hydrocarbon functionalization.\(^10\) In this context C–H insertion of carbenoid and nitrenoid species has emerged as a promising protocol.\(^11\) The insertion of metal carbenoids into C–H bonds is now a well-established transformation, and many transition metal catalysts that can catalyse such reactions have been disclosed in the past decade.\(^11,12\) In addition to catalytic cyclopropanation and C–H insertion, metal catalysed carbene transfer has also made it possible to perform insertions into X–H bonds (X = O, N, S, Si), and to convert alkynes to cyclopropenes (including some cycloaddition reactions).\(^11\) Given the ubiquity of nitrogen atoms in biologically active compounds,\(^13\) nitrene transfer reactions also have important applications in making molecules of interest. Cobalt(II) porphyrins have emerged as successful catalysts for nitrene transfer reactions. Its superiority lies not only in the performance but also in the fact that organic azides can be employed as nitrene sources. Till the early 2000s, it was quite common to use iminoiodanes\(^14\) or haloamine-T\(^15\) compounds as nitrene sources. These are, however, not the most benign nitrene sources as they lead to the formation of undesirable side products like phenyl iodide and other halogen containing compounds.

The mechanistic aspects of two nitrene transfer reactions catalysed by cobalt porphyrins have been elucidated by our group previously (Scheme 1).\(^9,16\) The mechanism of C–H bond amination of ethyl benzene, toluene, and 1,2,3,4-tetrahydronaphthalene (tetralin) using a series of different organic azides (\(\text{N}_3\text{C(O)OMe, N}_3\text{SO}_2\text{Ph, N}_3\text{C(O)Ph and N}_3\text{P(O)(OMe)}_2\)) as nitrene sources was studied using Density Functional Theory (DFT) and Electron Paramagnetic Resonance (EPR) spectroscopy (Scheme 1a).\(^16\) The mechanism of cobalt(II) porphyrin-mediated aziridination of styrene with PhSO\(_2\)N\(_3\) was also studied (Scheme 1b). For both amination and aziridination reactions, the DFT calculations revealed a stepwise radical process involving coordination of the azide to the cobalt(II) centre, followed by release of dinitrogen to produce an unusual ‘nitrene radical’ intermediate C (Scheme 1). In addition, experimental EPR spectroscopic studies, combined with DFT calculated EPR properties being in good agreement with the experimental data, revealed the formation of a (por)Co\(^{\text{II}}\)–N\(_3\) ‘nitrene radical’ adduct C from the catalyst in the presence of an excess of the azide in benzene. Formation of a nitrene moiety at cobalt(II) effectively leads to electron transfer from the metal to the nitrene, thus reflecting the redox non-innocence of the nitrene ligand. The spin density of this intermediate resides almost entirely on the nitrogen atom of the nitrene moiety. A simplified molecular orbital picture showing
the frontier π-interactions and explaining the unusual electronic structure of this intermediate is depicted in Scheme 2.

Scheme 1. a) DFT calculated mechanism of cobalt(II) porphyrin mediated benzylic C–H amination of ethylbenzene by N$_3$C(O)OMe.

b) Cobalt(II) porphyrin mediated aziridination of styrene with PhSO$_2$N$_3$. For both amination and aziridination reactions, the DFT calculations revealed a stepwise radical process involving coordination of the azide to the cobalt(II) center, followed by release of dinitrogen to produce an unusual ‘nitrene radical’ intermediate C.

Scheme 2. Redox non-innocent behaviour of nitrene ligands coordinated to open-shell [Co$^{II}$(por)] species (A), a simplified bonding scheme explaining this behaviour (B), and alternative bonding scheme involving a triplet nitrene (C).

A thorough understanding of these key intermediates is essential to make advances in using these catalytic systems, to unleash their full potential in terms of activity and selectivity. Given the importance of these radicaloid nitrene species in metal-catalysed nitrene transfer and C–H functionalization reactions, we gathered more experimental evidences for the formation of the previously reported mono-nitrene radical complexes upon reaction of cobalt(II)-porphyrins with nitrene transfer reagents.$^{9,16}$ Furthermore, we here reveal the first example of a bis-nitrene species of 1$^{P1}$ upon reacting the stronger oxidizing nitrene transfer agent N-nosyl iminoidane 4$_{Ns}$ with 1$^{P1}$ (see Figure 1 and Figure 2). This bis-nitrene species has a markedly different electronic structure than the
previously detected mono-nitrene species, and also differs from the electronic structure of the previously reported diamagnetic \textit{bis-imido} Ru$^{VI}$-porphyrin species (por)Ru$^{VI}$[ (=NR’’)]. The work described herein further bears some similarity with the \textit{mono-} and \textit{bis-nitrene} species of non-heme iron complexes disclosed by Che and coworkers, but again the electronic structures reported herein are entirely different.

**Results and discussion**

At the start of this project, the DFT calculations and existing X-band EPR data strongly indicated the formation of substrate-centred (por)Co$^{III}$–N$\equiv$R’’ ‘nitrene radicals’, which are proposed to be key intermediates in the mechanisms of the catalytic C–H amination and alkene aziridination reactions mediated by [Co$^{II}$ (por)] catalysts and employing organic azides as nitrene sources. These ‘nitrene radicals’ had thus far only been detected by means of X-band EPR spectroscopy. Here we disclose their detection and characterization with a variety of spectroscopic and mass spectrometric techniques.

**Figure 1.** Different [Co$^{II}$ (Por)] used to experimentally detect cobalt(III)-nitrene radicals in this study. 1$^{P1}$ is the commercially available [Co$^{II}$ (TPP)] and 1$^{P2}$ is a chiral $D_2$-symmetric porphyrin with a chiral pocket.

**Figure 2.** Various nitrene transfer reagents commonly employed in nitrene-transfer reactions. The organic azides like Nosyl azide, Troc azide etc are more desirable than the iminoiodanes like or the Haloamine-T.
To study the key nitrene intermediates in nitrene transfer reactions mediated by \([\text{Co}^\text{II}(\text{Por})]\), we chose to react a few of the commonly used nitrene sources with two different types of \([\text{Co}^\text{II}(\text{Por})]\): The tetraphenyl-substituted porphyrin 1\(^\text{P1}\) and the bulkier (and chiral) H-bond donor appended porphyrin 1\(^\text{P2}\) (see Figure 1). Complex 1\(^\text{P2}\) serves as a model system for all reported cases where Co\(^\text{II}\) porphyrins with H-bonding moieties were proven to give superior catalytic results and where H-bonds stabilise the formed nitrene intermediates.\(^\text{16}\) In total, four different nitrene sources were employed. As mentioned before, these sources are known in literature to be active in different nitrene transfer reactions like aziridination and amination. Three of these were organic azides 2\(^\text{Ns}\), 2\(^\text{Ts}\) and 2\(^\text{troc}\) (see Figure 2): Nosyl Azide (2\(^\text{Ns}\); \(\text{NsN}_3\); \(\text{Ns} = \text{nosyl} = \text{p-NO}_2\text{-PhSO}_2\text{–}\)), Tosyl Azide (2\(^\text{Ts}\); \(\text{TsN}_3\); \(\text{Ts} = \text{tosyl} = \text{p-MePhSO}_2\text{–}\)) and Troc Azide (2\(^\text{troc}\); \(\text{TrocN}_3\); troc = 2,2,2-Trichlorethoxycarbonyl = \(\text{CCl}_3\text{CH}_2\text{O(CO)}\text{–}\)). The fourth nitrene transfer reagent investigated was the stronger oxidizing \(\text{N-Nosyl Iminoiodane} (\text{PhI}=\text{NNs}) 4\(^\text{Ns}\). To perform the EPR, UHR-ESI, UV-Vis and XAS studies, the following method was used: To a solution of the catalyst in benzene-\(\text{d}_6\) we added a 100-fold excess of the nitrene precursor. The catalyst concentrations of these solutions were typically 2.5 mM. The solvent used was benzene-\(\text{d}_6\) in all cases and this was chosen to avoid any cases of C–H insertions as is known for these systems in toluene, cyclohexane and other related solvents. Unless mentioned otherwise, deuterated benzene was chosen as the solvent to further slow-down any C–H activation of the benzene ring itself.

**EPR spectroscopy of the mono-nitrene species 3\(^\text{P1}\)\(_\text{Ns}\)**

Upon reaction of 1\(^\text{P1}\) with a 100-fold excess of 2\(^\text{Ns}\), and 1\(^\text{P2}\) with a 100-fold excess of either 2\(^\text{Ts}\) or 2\(^\text{troc}\) (Scheme 3), clear gradual changes in the X-band EPR spectra occurred that point to the formation of mono-nitrene radical species, revealing the redox non-innocence of the nitrene moiety. The disappearance of signals characteristic for the \([\text{Co}^\text{II}(\text{Por})]\) is associated with appearance of signals corresponding to mono-nitrene species of the type 3\(^\text{P1}\)\(_\text{Ns}\). An example of such a spectrum is shown in Figure 3 (left). The room temperature (r.t.) EPR measurement of the same samples gave spectra characteristic for ligand radical species and the simulated spectra fit best to a mono-nitrene species of the type 3\(^\text{P1}\)\(_\text{Ns}\).

**Scheme 3.** Scheme depicting different combinations of \([\text{Co}^\text{II}(\text{Por})]\) and organic azides used to study the formation of mono-nitrene species. To a solution of the catalyst in benzene-\(\text{d}_6\) we added a 100-fold excess of the nitrene precursor. The catalyst concentrations of these solutions were typically 2.5 mM.
Figure 3. (Left) Disappearance of signals of $1^{P2}$ with simultaneous appearance of new signals characteristic for $3^{P2}_{troc}$. (Right) Davies ENDOR spectrum of $3^{P1}_{Ns}$. Experimental conditions: 40 K, RF-pulse 20 µs, Inversion pulse 40 ns. Pink line represents spectral simulation according to the parameters extracted from the HFEPR spectrum (depicted on the left). Due to relaxation effects, the broad wing around 30-35 MHz is suppressed in the experiment.

The X-band EPR spectrum recorded from a reaction mixture of $1^{P1}$ and $2_{Ns}$ in frozen benzene-$d_6$/o-terphenyl solution at 50 K was quite isotropic, but the $g$-anisotropy is clearly resolved in high frequency (244 GHz) EPR measurements (Figure 4, right). The experimental $g$-anisotropy is very small, and smaller than calculated with DFT (Table 1). This may be caused by a small mismatch between the calculated and experimental geometries, as the calculated $g$-tensor is sensitive to the orientation of the -SO$_2$Ar fragment of the nitrene radical moiety with (e.g., optimization with and without dispersion corrections). It should be noted at this point that complexes of type $3^{P1}_{Ns}$ need not be 5-coordinate. Coordination of an additional ligand to the cobalt(III) center is perhaps even likely (vide infra), and this will also have some influence on the (calculated) $g$-tensor and hyperfine coupling parameters of the mono-nitrene complex, albeit very small (see Table 1 for a comparison of the experimental EPR parameters and the DFT calculated values of 5-coordinate $3^{P1}_{Ns}$ and its 6-coordinate NsNH$^-$ and OH$^-$ adducts).

Additionally, a quite anisotropic cobalt hyperfine interaction (HFI) tensor was revealed by Q-band Davies ENDOR measurements. The Q-band Davies ENDOR experiment (Figure 3, right) revealed broad features spanning 1-60 MHz. Apart from the characteristic proton signals centered around 52 MHz, strong lines are observed around 22 and 12 MHz. The position of these features is consistent with the $^{59}$Co hyperfine parameters estimated from the high field EPR spectrum (Figure 3), which are summarized in Table 1. Low frequency contributions (<8 MHz) are attributed to the porphyrin nitrogen atoms. The corresponding DFT calculated values match the experimental ones quite well (Table 1), albeit that the calculated anisotropy of the cobalt hyperfine tensor is a bit larger than in the experimental spectrum. Unfortunately, the anisotropic nitrene nitrogen hyperfine couplings were not resolved for technical reasons.
Interestingly, the mono-nitrene species \( \text{3} \) did not form instantaneously upon mixing the azides and the \([\text{Co}^{III}\text{por}]\) catalysts at r.t. For example, only 10% of the mono-nitrene species \( \text{3}^{\text{P2}}\text{troc} \) was formed upon mixing \( \text{1}^{\text{P2}} \) and azide \( \text{2}\text{troc} \) at r.t. after 15 minutes. These conversions were determined by comparison of the spin concentrations (double integration) with a sample of TEMPO of the same concentration. It should be mentioned that the relaxation times of TEMPO and the mono-nitrene species \( \text{3} \) are likely markedly different, and hence the spin integrations gave only a rough qualitative comparison of the spin concentrations. However, upon heating the samples, higher intensities were observed immediately; and on letting them heat overnight at 45 °C, the maximum intensities for all of these species were observed. The resulting solutions still contained the (excess) organic azide (as revealed by analysis of crystals recovered upon evaporation of the solvent) and were still catalytically active in aziridination of styrene (as confirmed by \(^1\text{H} \) NMR and GC-MS analysis of the crude reaction mixture).

**Figure 4.** Left: Experimental and simulated (Table 1) X-band EPR spectra of nitrene radical ligand complex \( \text{3}^{\text{P1}}\text{Ns} \) in solution at r.t. Isotropic spectrum in solution recorded at r.t.\(^{42} \) (Freq. = 9.38056 GHz; Mod. Amp. = 1 G; MW power = 0.2 mW). Right: Experimental and simulated (Table 1) high field EPR spectra of nitrene radical ligand complex \( \text{3}^{\text{P2}}\text{Ns} \) obtained by mixing \( \text{1}^{\text{P2}} \) and \( \text{2}\text{Ns} \) in frozen solution (Freq. = 243.76176 GHz, Mod. Amp. = 1 mT, power = 1 mW, 50 K).

**Figure 5.** EPR spectra of \( \text{3}^{\text{P2}}\text{troc} \) (r.t.; benzene-\( \text{d}_6 \)) showing increasing intensities over time on heating at 45 °C , only 10% of the mono-nitrene species \( \text{3}^{\text{P2}}\text{troc} \) was formed upon mixing \( \text{1}^{\text{P2}} \) and azide \( \text{2}\text{troc} \) at r.t. after 15 minutes. These conversions were determined by comparison of the spin concentrations (double integration) with a sample of TEMPO of the same concentration.
Among the series of complexes and nitrene precursors studied, the maximum intensities were obtained for the combination of \(1^{P2}\) and \(2_{\text{trans}}\) (see Figure 5). This can be explained on the basis of better stabilization of the formed ‘nitrene radical’ intermediate by H-bonding between the amide arms of the porphyrin backbone in \(1^{P2}\) and the nitrene transfer agent \(2_{\text{trans}}\). The concentration of this species was found to be ~80% referenced against a sample of TEMPO with the same concentration as the cobalt precursor.

**EPR spectroscopy of the bis-nitrene species \(5^{P1}_{Ns}\)**

In contrast to the use of organic azides that produced *mono*-nitrene species of the type \(3^{P1}_{Ns}\) upon reaction with the cobalt(II) porphyrin complexes, reaction of an excess of \(N\)-nosyl iminoidane \(4_{Ns}\) with \(1^{P1}\) at room temperature in benzene-\(d_6\) yielded an entirely different species (Scheme 4), as revealed by X-band EPR spectroscopy in solution at r.t. A completely different isotropic spectrum was obtained with \(4_{Ns}\) (Figure 6, left) than that with nosyl azide \(2_{Ns}\) or tosyl azide \(2_{T}\) (Figure 4, left). The multiline

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**Table 1. EPR parameters of nitrene radical complex \(3^{P1}_{Ns}\) in frozen solution at 50 K and in isotropic solution at r.t.**

<table>
<thead>
<tr>
<th></th>
<th>50 K</th>
<th>298 K</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(g_{11})</td>
<td>(g_{22})</td>
</tr>
<tr>
<td>Exp</td>
<td>2.0087</td>
<td>2.0049</td>
</tr>
<tr>
<td>DFT a</td>
<td>2.0490</td>
<td>2.0154</td>
</tr>
<tr>
<td>5-coord</td>
<td>2.0287 (^e)</td>
<td>2.0029 (^e)</td>
</tr>
<tr>
<td>NsNH f</td>
<td>2.0311</td>
<td>2.0052</td>
</tr>
<tr>
<td>OH (^g)</td>
<td>2.0387</td>
<td>2.0116</td>
</tr>
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\(A^{Co}_{\text{av}}\) \(A^{Co}_{\text{av}}\) \(A^{Co}_{\text{av}}\) \(A^{Co}_{\text{av}}\) \(A^{Co}_{\text{av}}\)

|         | \(A^{Co}_{12}\) b) | \(A^{Co}_{22}\) b) | \(A^{Co}_{33}\) b) | \(A^{Co}_{av}\) b) | \(A^{Co}_{iso}\) b) |
|         | 50 \(^c\)        | 50 \(^c\)        | 20 \(^c\)    | 7 \(^c\)    | 25         |
| DFT c   | -98             | 65              | 13           | 7           | 7          |
| 5-coord | -18 \(^e\)     | -89 \(^e\)     | 15 \(^e\)    | -42 \(^e\)  | -31 \(^e\) |
| NsNH f  | -59             | 30              | 11           | -6          | 6          |
| OH \(^h\) | -62            | 50              | 67           | 18          | 18         |

\(A^{N}\) \(A^{N}_{11}\) b) \(A^{N}_{22}\) b) \(A^{N}_{33}\) b) \(A^{N}_{av}\) b) \(A^{N}_{iso}\) b)

|         | \(A^{N}_{11}\) d) | \(A^{N}_{22}\) d) | \(A^{N}_{33}\) d) | \(A^{N}_{av}\) d) | \(A^{N}_{iso}\) d) |
|         | n.r. \(^d\)      | n.r. \(^d\)      | n.r. \(^d\)    | n.r. \(^d\)    | 10         |
| DFT d   | -20             | -14             | 81           | 15          | 16         |
| 5-coord | -23 \(^e\)     | -14 \(^e\)     | 84 \(^e\)    | 16 \(^e\)   | 16 \(^e\)  |
| NsNH f  | -11             | -9              | 87           | 22          | 22         |
| OH \(^g\) | -13            | -10             | 84           | 20          | 20         |

Geometry of \(3^{P1}_{Ns}\) optimized with Turbomole (full atom model, BP86, def2-TZVP) employing Grimme’s D3-dispersion corrections (disp3); EPR parameters calculated with ORCA, (b3-lyp/def2-TZVP); MHz; \(^c\) Data from Q-band Davies ENDOR measurements; \(^d\) Not resolved; \(^e\) Geometry of \(3^{P1}_{Ns}\) (full atom model) optimized with Turbomole at the b3-lyp, def2-TZVP level without dispersion corrections to match the solution data. \(^f\) Optimized geometry of 6-coordinate NsNH' amido adduct of \(3^{P1}_{Ns}\) (full atom model, BP86, def2-TZVP) employing Grimme’s D3-dispersion corrections (disp3). \(^g\) Optimized geometry of 6-coordinate OH' hydroxido adduct of \(3^{P1}_{Ns}\) (full atom model, BP86, def2-TZVP) employing Grimme’s D3-dispersion corrections (disp3).
spectrum revealed an isotropic g-value close to $g_e$ (2.003) with well-resolved hyperfine interactions with the two equivalent N-nitrene atoms ($A_{\text{N-nitrene}}^{\text{iso}} = 10.0$ MHz) and the four equivalent N-porphyrin atoms ($A_{\text{N-porphyrin}}^{\text{iso}} = 3.5$ MHz), again indicating formation of a ‘ligand radical’ complex. The isotropic cobalt HFI in $5^1\text{P}_1\text{Ns}$ ($A_{\text{Co}}^{\text{iso}} = 2.0$ MHz) was very small, even smaller than in the mono-nitrene case (25 MHz). The spectrum could be satisfactorily simulated based on the DFT-calculated EPR parameters (Figure 6 and Table 2).

To prove that the largest detected nitrogen hyperfine couplings stem from the two equivalent nitrene moieties, we further prepared the $^{15}$N-labeled iminoiodane $^{15}$N-4Ns (PhI=^{15}NNs) and recorded the r.t. EPR spectrum of $^{(15)}\text{N}_2\cdot5^1\text{P}_1\text{Ns}$ generated in a mixture of $1^1\text{P}_1$ and $^{15}$N-4Ns. This led to clear differences in the hyperfine coupling pattern compared to the non-labelled analogue $5^1\text{P}_1\text{Ns}$ (Figure 6, top).

**Scheme 4.** Reaction of [Co$^{II}$Por]$^{1^1\text{P}_1}$ and nitrene transfer reagent 4Ns to give bis-nitrene species $5^1\text{P}_1\text{Ns}$. Please note that the formation of a one-electron oxidized porphyrin ligand is indicated with a positive charge on the porphyrin ring, using the ‘$\pi$-cation radical’ convention commonly used in Cytochrome P450 chemistry, but this is in fact a mono-anionic por$^{-}$ligand.

**Figure 6.** (left) Overlay of the isotropic X-band EPR spectra of unlabeled $5^1\text{P}_1\text{Ns}$ (red) and labeled $^{(15)}\text{N}_2\cdot5^1\text{P}_1\text{Ns}$ (blue). (right) Experimental and simulated isotropic EPR spectra of species $^{(15)}\text{N}_2\cdot5^1\text{P}_1\text{Ns}$ in benzene-$d_6$. Freq = 9.38126 GHz, mod. ampl. = 1 G, microwave power = 0.2 mW, $T = 298$ K.
Table 2. Experimental (298 K) \textsuperscript{a)} and DFT \textsuperscript{b)} calculated EPR parameters of $5^{\text{Ns}}_{P1}$ and \((^{15}\text{N})_{2}-5^{\text{Ns}}_{P1}$

<table>
<thead>
<tr>
<th>Equiv. Nuclei</th>
<th>Exp \textsuperscript{a)}</th>
<th>DFT \textsuperscript{b)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{\text{iso}}$</td>
<td>2.003</td>
<td>2.008</td>
</tr>
<tr>
<td>$A^{\text{Co,iso}}_{\text{iso}} \textsuperscript{c)}$</td>
<td>1 (I = 7/2)</td>
<td>−2.0</td>
</tr>
<tr>
<td>$A^{\text{N-nitrene,iso}}_{\text{iso}}^{14}\text{N} \textsuperscript{c)}$</td>
<td>2 (I = 1)</td>
<td>10.0</td>
</tr>
<tr>
<td>$A^{\text{N-nitrene,iso}}_{\text{iso}}^{15}\text{N} \textsuperscript{c)}$</td>
<td>2 (I = ½)</td>
<td>14.0</td>
</tr>
<tr>
<td>$A^{\text{N-por,iso}}_{\text{iso}} \textsuperscript{c)}$</td>
<td>4 (I = 1)</td>
<td>3.5</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} Derived from spectral simulations shown in Figure 5; \textsuperscript{b)} Geometry optimized with Turbomole (b3-lyp/def2-TZVP) using a simplified model of $5^{\text{Ns}}_{P1}$ without porphyrin Ph substituents without dispersion corrections to match the r.t. solution EPR data; EPR parameters calculated with ORCA (b3-lyp/def2-TZVP); \textsuperscript{c)} MHz; \textsuperscript{d)} Average of two $A^{\text{N-nitrene}}$ hyperfines; \textsuperscript{e)} Average of four $A^{\text{N-por}}$ hyperfines.

EPR simulation using an expected 1.4 times larger $A^{\text{N-nitrene,iso}}_{\text{iso}}^{15}\text{N}$ (I = ½) hyperfine coupling (14 MHz) compared to the unlabeled $^{14}\text{N}$-$A^{\text{N-nitrene,iso}}_{\text{iso}}$ constant of 10 MHz (I = 1) in $5^{\text{Ns}}_{P1}$ and otherwise identical spectral parameters provided an excellent fit of the experimental spectrum (Figure 6, bottom; Table 2). Hence, the largest detected nitrogen hyperfine couplings indeed stem from the two equivalent nitrene moieties.

In case of the bis-nitrene species $5^{\text{Ns}}_{P1}$ the intensity of the signal was not as strong as the mono-nitrene species, for example, $3^{\text{Ns}}_{P1}$. On heating the sample shortly, the intensity increased only very slightly and was at least 10 times lower than that of the mono-nitrene species (spin counting amounts to ~8%, using a reference sample containing TEMPO at the same concentration as $1^{\text{Ns}}$). The poor solubility of the N-nosyl iminoiodane substrate in benzene-d$_6$ could well be a reason for the low intensities obtained for species $5^{\text{Ns}}_{P1}$. It is also worth mentioning that the experimentally detected signal of species $5^{\text{Ns}}_{P1}$ stems from a (net) doublet spin state (S = ½), leading to the characteristic EPR data shown in Figure 6 and Table 2, but in DFT (b3-lyp) the doublet (S = ½) and quartet (S = 3/2; $\Delta G = +0.2$ kcal mol$^{-1}$) spin states of $5^{\text{Ns}}_{P1}$ are predicted to be of nearly equal energy.\textsuperscript{19} As only the doublet state is detectable with EPR at r.t. in solution, the potential existence of a (slow) thermal equilibrium between the two spin states might also explain the relatively low EPR intensity of the signal, which stems from the S = ½ state of bis-nitrene species only. Furthermore, it is worth mentioning that the bis-nitrene species are intrinsically more reactive. In contrast to the mono-nitrene species $3^{\text{Ns}}_{P1}$, which increased in time upon heating the solution to 45 °C, species $5^{\text{Ns}}_{P1}$ decomposed at this temperature, causing the EPR signal of the bis-nitrene species to disappear completely overnight (i.e. in absence of other substrates). Catalyst decomposition may be less important in the presence of suitable substrates, as heating the solution in the presence of styrene did reveal the expected aziridination activity (as confirmed by $^1$H NMR and GC-MS analysis of the crude reaction mixture).
Steric and electronic influence of the catalyst on formation of the nitrene intermediates

The steric and electronic influence of the catalyst on the species obtained, even when using the more oxidizing \( N \)-nosyl iminoiodane \( 4_{Ns} \), is quite dramatic. For example, on using the bulkier porphyrin complex \( 1^{P2} \) in combination with the oxidizing \( N \)-nosyl iminoiodane \( 4_{Ns} \), the bis-nitrene species was detected only in minor amounts. Instead, a major EPR signal corresponding to the mono-nitrene species was detected (Figure 7). Thus, it may be concluded that the bulky side groups on the porphyrin backbone of \( 1^{P2} \) make it difficult for the second molecule of \( N \)-nosyl iminoiodane \( 4_{Ns} \) to react.

In contrast to the decomposition observed for species \( 5^{P1}_{Ns} \) that was obtained from a mixture of \( 1^{P1} \) and an excess of \( 4_{Ns} \), mono-nitrene species \( 3^{P2}_{Ns} \) obtained from a mixture of \( 1^{P2} \) and excess \( 4_{Ns} \) proved to be much more stable. On heating the latter sample to 45 °C, the signal intensity decreased, with the complete disappearance of the initially detected small amount of bis-nitrene species \( 5^{P2}_{Ns} \). In contrast, a significant amount of mono-nitrene species \( 5^{P2}_{Ns} \) remained present in solution, even after heating for a period of 18 h (Figure 7). These results clearly show that the bis-nitrene species \( 5 \) are more reactive than the mono-nitrene species \( 3 \), and that complex \( 1^{P2} \) is more stable than complex \( 1^{P1} \) when combined with \( N \)-nosyl iminoiodane \( 4_{Ns} \). The latter can perhaps be attributed to stabilizing H-bonding interactions between the nitrene radical moiety and the H-bond donating amido functionalities incorporated in the porphyrin backbone of \( 1^{P2} \). At the same time, it also suggests that \( N \)-nosyl iminoiodane \( 4_{Ns} \) is not a very benign nitrene transfer reagent for these reactions as it seems to undergo subsequent side reactions with the catalyst (especially for the less bulky ones and in the absence of another substrate).

UHR-ESI-MS spectrometry

To further corroborate the above observations in the EPR measurements, the reactions were also investigated with mass spectrometry. We investigated the formation of both the mono- and the bis-nitrene species. High resolution ESI-MS mass spectrometry proved to be a suitable method to detect the formation of both mono and bis-nitrene species. However, since these species are neutral (or perhaps anionic, vide infra), only signals resulting from protonation, (one-electron) oxidation and formation of Na⁺ adducts can be expected in positive mode UHR-ESI-MS.
A reaction mixture of $1^\text{P1}$ with nosyl azide $2_{\text{Ns}}$ in C$_6$D$_6$/MeCN produced clear ESI-MS signals around m/z 872 characteristic for formation of the mono-nitrene species $3^\text{P1}_{\text{Ns}}$ (Scheme 3). The isotope distribution pattern and exact masses determined by ESI-MS match the theoretical values ($\Delta$ m/z < 0.004 Da) for the species in its protonated form $[3^\text{P1}_{\text{Ns}}+H]^+$ (Figure 8). The relatively low intensity of the detected nitrene radical species derived from reaction of complex $1^\text{P1}$ with azide $2_{\text{Ns}}$ is likely a result of incomplete conversion to $3^\text{P1}_{\text{Ns}}$, as the measurements were performed within 30 minutes of sample preparation.

At the same time, subsequent reactions with the co-solvent acetonitrile cannot be neglected. While $3^\text{P1}_{\text{Ns}}$ is detected as a 5-coordinate species in its protonated form with ESI-MS, this does not exclude $3^\text{P1}_{\text{Ns}}$ from being 6-coordinate as the 6th ligand might easily dissociate in the ionization chamber of the ESI-MS spectrometer. We were not able to detect $3^\text{P1}_{\text{Ns}}$ in negative mode ESI-MS measurements (cold-spray ionization). However, interestingly, in the positive mode ESI-MS measurements (cold-spray ionization), a Na$^+$ adduct of NO$_2$PhSO$_2$NHD was detected from a mixture of $1^\text{P1}$ and $2_{\text{Ns}}$. Note that formation of NO$_2$PhSO$_2$ND$^-$ radicals, detected with EPR, has been reported earlier. On this basis, the most likely candidates for the sixth ligand coordinated to the mono-nitrene species are either the NO$_2$PhSO$_2$NDH amine ligand or the NO$_2$PhSO$_2$ND$^-$ amido ligand (in both cases detected as the Na$^+$ adduct of the amine in the ESI-MS measurements, in the first case directly and in the second case after hydrogen atom transfer (HAT)).

ESI-MS spectra recorded from a mixture of $1^\text{P1}$ and N-nosyl iminiodane $4_{\text{Ns}}$ revealed signals pointing to the presence of bis-nitrene species $5^\text{P1}_{\text{Ns}}$ (Scheme 4). This species was observed as the protonated form of its hydrogen atom abstraction (HAA) reaction product ($[5^\text{P1}_{\text{Ns}}+H^+ + H^+]$), thus pointing to rapid HAA from the co-solvent MeCN. Substantially weaker signals corresponding to the mono-nitrene species $3^\text{P1}_{\text{Ns}}$ were still detected ($[3^\text{P1}_{\text{Ns}} + H]^+$), which likely resulted from incomplete conversion of $1^\text{P1}$ to $5^\text{P1}_{\text{Ns}}$ and/or fragmentation of $5^\text{P1}_{\text{Ns}}$ to $3^\text{P1}_{\text{Ns}}$ in the ionization chamber of the ESI-MS spectrometer.

**Electronic structures and UV-Vis spectra of mono- and bis-nitrene species**

To gain additional insight into the electronic structures of the generated nitrene species, we performed DFT geometry optimizations at the b3-lyp/def2-TZVP level using simplified models of $3^\text{P0}_{\text{Ns}}$ and $5^\text{P0}_{\text{Ns}}$ without meso-phenyl substituents on the porphyrin ring $\text{P}^0$ (Figure 9). According to these calculations, mono-nitrene species $3^\text{P0}_{\text{Ns}}$ formed from $1^\text{P0}$ and $2_{\text{Ns}}$ is best described as a Co$^{\text{III}}$ species with one 1e reduced nitrene moiety and a normal, non-oxidized (por$^{2-}$) porphyrin ligand. Note again the experimental complex $3^\text{P0}_{\text{Ns}}$ need not be 5-coordinate. Coordination of an additional ligand to the
cobalt(III) center cannot be excluded and even seems likely \((\text{vide infra})\). However, note that all 6-coordinate analogs of \(3^{\text{P0}\text{Ns}}\) considered computationally have almost identical spin density distributions as the one shown for 5-coordinate mono-nitrene complex \(3^{\text{P0}\text{Ns}}\) in Figure 9. In these calculations full atom models were optimized at the BP86/def2-TZVP/disp3 level (Turbomole), followed by single point calculations at the b3-lyp/def2-TZVP level (ORCA), considering several different (neutral and anionic) ligands bound \text{trans} to the nitrene radical moiety.

\textbf{Figure 9.} Spin density plots (b3-lyp/def2-TZVP) of mono-nitrene species \(3^{\text{P0}\text{Ns}}\) (top) and bis-nitrene species \(5^{\text{P0}\text{Ns}}\) (bottom).

The mono-nitrene species \(3^{\text{P1}\text{Ns}}\) formed from \(1^{\text{P1}}\) and \(2^\text{N}\) is best described as a Co\textsuperscript{III} species with one 1e reduced nitrene moiety and a normal, non-oxidized (por\textsuperscript{2−}) porphyrin ligand. The bis-nitrene species \(5^{\text{P0}\text{Ns}}\), on the other hand, is a triple-radical containing two 1e-reduced nitrene moieties and a 1e-oxidized porphyrin ring (from por\textsuperscript{2−} to the por\textsuperscript{−} radical monoanion). As is clear from the positive and negative spin density distribution, two of the three unpaired electrons in \(5^{\text{P0}\text{Ns}}\) are antiferromagnetically coupled, thus effectively leading to a (net) doublet state \((S_{\text{total}} = \frac{1}{2})\). Both \(3^{\text{P1}\text{Ns}}\) and \(5^{\text{P0}\text{Ns}}\) were found to contain a low-spin \(d^6\) \((S_{\text{Co}} = 0)\) Co\textsuperscript{III} center.

The bis-nitrene species \(5^{\text{P0}\text{Ns}}\), on the other hand, is a triple-radical containing two 1e-reduced nitrene moieties and a 1e-oxidized porphyrin ring (from por\textsuperscript{2−} to the por\textsuperscript{−} radical monoanion). As is clear from the positive and negative spin density distribution (Figure 8, right), two of the three unpaired electrons in \(5^{\text{P0}\text{Ns}}\) are antiferromagnetically coupled, thus effectively leading to a (net) doublet state \((S_{\text{total}} = \frac{1}{2})\). Both \(3^{\text{P1}\text{Ns}}\) and \(5^{\text{P0}\text{Ns}}\) were found to contain a low-spin \(d^6\) \((S_{\text{Co}} = 0)\) Co\textsuperscript{III} center. Hence, formation of \(5\) involves one-electron oxidation of Co\textsuperscript{II} to Co\textsuperscript{III} upon formation of the first nitrene-radical \(3\) and a second intramolecular electron transfer from the porphyrin ring to the second nitrene moiety in the second step.

The DFT calculated electronic structures are qualitatively in agreement with UV-Vis measurements, revealing the presence of a non-oxidized porphyrin ring in \(3^{\text{P1}\text{Ns}}\) and a ‘porphyrin radical’ ligand in \(5^{\text{P1}\text{Ns}}\) (Figures 9 and 10). Metal- (not porphyrin-) centered oxidation of \([\text{Co}^\text{II}(\text{por})]\) is known to produce characteristic red-shifts of both the Soret- and Q-bands.\(^{20}\) The same is also true for binding donor ligands, such as pyridine or bipyridyl ligands, to the central metal ion of \([\text{Co}^\text{II}(\text{por})]\).\(^{21}\) Such shifts were indeed observed upon measuring UV-Vis spectra of a mixture of \(1^{\text{P1}}\) and \(2^\text{N}\) immediately upon mixing.
In Figure 10, the UV-Vis spectrum of a mixture of $\text{1}^{\text{P1}}$ and $\text{2}_\text{N}$ was followed in time (after 40 minutes of sample preparation). In these spectra, the observed shifts in the Q- and Soret-bands are due to formation of a simple azide adduct (mostly likely a mono-azide adduct). Indeed, measuring EPR spectra of these same mixtures (again 40 minutes after mixing the reagents) without any additional heating revealed extremely weak EPR signals in the region around $g = 2.0$, corresponding to formation of only a tiny amount of ‘nitrene-radical’ species $\text{3}^{\text{P1}}_\text{N}$.

Figure 10. UV-Vis spectra of a mixture of $\text{1}^{\text{P1}}$ and $\text{2}_\text{N}$ followed in time (after 40 minutes of sample preparation). Clear shifts in both the Q- and Soret-bands were observed corresponding to azide ligation to the cobalt(II) center. The observed shifts in the Q- and Soret-bands are due to formation of a simple azide adduct (mostly likely a mono-azide adduct).

Figure 11. UV-Vis spectral changes upon reaction of (top) complex $\text{1}^{\text{P2}}$ with azide $\text{2}_\text{troc}$ to give mono-nitrene species $\text{3}^{\text{P2}}_\text{troc}$ formed after heating the solution overnight. The shift in the Soret and the Q-band is indicative of oxidation of the metal from cobalt(II) to cobalt(III) and (or) ligation to the sixth coordination site, leaving the porphyrin ligand intact without oxidation upon formation of mono-nitrene radical species $\text{3}^{\text{P2}}_\text{troc}$.

Bottom spectra belong to reaction of complex $\text{1}^{\text{P1}}$ with iminoiodane $\text{4}_\text{N}$ to give bis-nitrene species $\text{5}^{\text{P1}}_\text{N}$ within 1 hour. The species exhibited characteristic, strongly red-shifted bands at 863 and 977 nm. Similar spectral changes have been reported for Co(III) complexes with a 1e-oxidized octaethylporphyrin ligand.
On measuring the UV-Vis spectra of these same solutions after heating them overnight at 45 °C (i.e. solutions that gave strong EPR signals characteristic for $3^{P1}_N$s) clearly revealed the presence of a new species in the UV-Vis spectra (Figure 11, top), concomitant with much higher EPR intensities corresponding to ‘nitrone radical’ species $3^{P1}_N$s. Illustrative spectra comparing $1^{P2}$ and species $3^{P2}_{troc}$ formed upon heating a solution of complex $1^{P2}$ in the presence of an excess of $2_{troc}$ are shown in Figure 11.

Reaction of complex $1^{P2}$ with azide $2_{troc}$ resulted in red-shifts of the Soret band at 438 nm and shifting of the Q-band to 648 nm. In addition, a new peak at ~753 nm was also observed (Figure 11, top). The shift in the Soret and the Q-band is indicative of oxidation of the metal from cobalt(II) to cobalt(III) and (or) ligation to the sixth coordination site, leaving the porphyrin ligand intact without oxidation upon formation of mono-nitrone radical species $3^{P2}_{troc}$. The additional band at ~753 nm is likely a charge-transfer band (e.g. a MLCT or LMCT band involving the nitrone radical and the cobalt(III) centre).

Formation of porphyrin-based ligand radicals is known to cause drastic changes in the UV-Vis spectrum with appearance of red-shifted bands, disappearance of the Q-band and obvious shape-changes of the Soret band compared to unmodified (i.e. non-reduced/non-oxidized) dianionic porphyrinato ligands (por$^{2-}$).$^{22}$ This is what was observed upon formation of bis-nitrone species $5^{P1}_N$s in the reaction of complex $1^{P1}$ with $N$-nosyl iminoiodane $4_{Ns}$ (Figure 11, bottom). As mentioned before, when using iminoiodane $4_{Ns}$, formation of the bis-nitrone species is comparatively faster than formation of the mono-nitrone when using azide $2_{Ns}$. Accordingly, in the case on measuring the UV-Vis spectra of a mixture of $1^{P1}$ and $4_{Ns}$, the disappearance of the Q- and Soret-bands was observed within an hour of making these samples (Figure 11, bottom). As shown in Figure 11, the species exhibited characteristic, strongly red-shifted bands at 863 and 977 nm. Similar spectral changes have been reported for Co$^{III}$ complexes with a 1e-oxidized octaethylporphyrin ligand.$^{23}$ Hence, we assign these spectral changes to formation of the bis-nitrone species $5^{P1}_Ns$. This is also in correspondence with the EPR measurements. Both the EPR and UV-Vis signals characteristic for the nitrone radical species $5^{P1}_Ns$ were completely lost upon heating the mixture overnight at 45° C.

In accordance with the EPR spectroscopic studies, once again the mono-nitrone species $3^{P2}_{troc}$ was found to be more stable than bis-nitrone species $5^{P1}_Ns$. UV-Vis spectroscopy clearly indicated that solutions of $3^{P2}_{troc}$ obtained from complex $1^{P2}$ and $4_{troc}$ remained stable for even two days while a significant amount of decomposition already occurred for $5^{P1}_Ns$ obtained from complex $1^{P1}$ and $4_{Ns}$ within two hours. This points to a higher intrinsic reactivity of bis-nitrone species $5^{P1}_Ns$ compared to mono-nitrone species $3^{P1}_Ns$. Indeed, DFT calculations (using $3'$ and $5'$, which are simplified models of $3^{P1}_Ns$ and $5^{P1}_Ns$ without phenyl substituents on the porphyrin ring and having a N-SO$_2$Ph base nitrone instead of N-Ns) predict a ca. 1.3 kcal mol$^{-1}$ lower activation energy for HAA from ethyl benzene for $5'$ ($\Delta G^f = +30.4$ kcal mol$^{-1}$) than for $3'$ ($\Delta G^f = +31.7$ kcal mol$^{-1}$).

Note that the exact geometry of the mono-nitrone species, however, remains uncertain. It could either be 5-coordinate or 6-coordinate and none of the spectroscopic techniques undertaken so far are informative in this regard. So we take up X-Ray Absorption Spectroscopy (XAS) on these nitrone radical intermediates and some other cobalt porphyrin complexes that serve as reference compounds. This will be the topic of discussion for the next chapter.
Summary and conclusions

In this work, we have demonstrated that activation of both organic azides and iminoiodanes by cobalt(II) porphyrin complexes leads to formation of ‘cobalt(III)-nitrene radical’ complexes. Both species bear substantial spin density at the ‘nitrene-moiety’ and are key intermediates in cobalt-catalysed nitrene transfer reactions. Notably, for the less bulky porphyrin complexes, the obtained species are markedly different. While organic azides generate predominantly mono-nitrene species, hypervalent iodine reagents such as iminoiodanes produce bis-nitrene species such as 5P1Ns. The stronger oxidising nature of the nitrene precursor 4Ns is considered important to generate such species. The bis-nitrene species 5P1Ns has a markedly different electronic structure from the mono-nitrene species 3P1Ns, 3P2Ts, and 3P2troc, and also differs markedly from the electronic structure of the previously reported diamagnetic bis-imido RuIV-porphyrin species (por)RuIV((=NR’’)).

Depending on the nature of the nitrene precursor, the intermediates can be a result of a single oxidation of the catalyst at the metal centre or a double oxidation where the second oxidation step occurs at the porphyrin ring. In addition, the bis-nitrene species 5P1Ns, though formed faster, lives shorter and is more reactive than the mono-nitrene species 3P1Ns. Degradation of bis-nitrene species 5P1Ns occurs within hours after initial formation while decomposition of mono-nitrene species 3P1Ns is much slower. In addition, the studies described here clearly demonstrate the better performance of specially tailored [CoII(Por)] like complex 1P2, which not only give to higher conversions to the nitrene-radical species, but also help in preserving them for longer periods by the stabilizing effects of H-bonding between the catalyst amide arms and the nitrene moiety. The steric influence of the bulk in complex 1P2 also has an implication on the type of intermediates formed, as was shown for the reactions of 1P1 and 1P2 with N-nosyl iminoiodane 4Ns. We will find out more about the spectroscopic oxidation state of the metal and the exact coordination mode of the mono-nitrene species in the next chapter.

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References and notes


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Chapter 3

Geometry and spectroscopic metal oxidation state of mono- and bis-nitrene radical complexes based on the cobalt-porphyrin platform; An X-ray Absorption Spectroscopy (XAS) study.*

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Introduction

In the previous chapter the electronic structure of the porphyrin-Cobalt(III)-‘nitrene radical’ was fully described. They are the reactive intermediates in the various nitrene transfer reactions catalysed by cobalt(II) porphyrins. By combining different nitrene transfer reagents together with cobalt(II) porphyrins and probing the thus obtained reaction mixtures with different spectroscopic techniques (EPR, UV-vis and UHR-ESI-MS), we could confirm the formation of porphyrin-cobalt(III)-‘nitrene radicals’. Depending on the type of the nitrene transfer reagent, two different types of nitrene radical species were observed. For the milder reagents like organic azides mono-nitrene species were formed with a single nitrene radical attached to the central cobalt atom of the cobalt porphyrin. On the other hand upon using more oxidising nitrene transfer reagents like the N-nosyl iminoiodane (PhI=NNs) bis-nitrene species with two nitrene radicals attached to cobalt were formed. The first nitrene radical is formed due to formal oxidation of cobalt from +II to +III. Conversion of the mono-nitrene species to the bis-nitrene species is associated with a second oxidation step. This second oxidation takes place on the porphyrin ligand leading to a porphyrin cation radical. The species on the whole, thus, has three unpaired electrons of which two are anti-ferromagnetically coupled. As a result, just as the mono-nitrene system the bis-nitrene also was a spin=1/2 system. All the spectroscopic techniques used thus far helped us describe the electronic structures of these intermediates in great detail, but did not give us any information about their geometry, nor any direct spectroscopic evidence for the cobalt(III) oxidation state of the metal in these complexes. X-ray absorption spectroscopy (XAS) studies can be used to gain this information. A further question one might ask is, whether or not the mono-nitrene complex has an additional ligand Y (in case of the mono-nitrene) and if so, what is the nature of that ligand. While the coordination geometry of the bis-nitrene species 5\text{P1}\text{Ns} is expected to be octahedral (6-coordinate), the geometry of the mono-nitrene species 3\text{P1}\text{Ns} is less clear. In the absence of X-ray structures of these intermediates, these questions are not easily answered. To shine more light on this matter, the coordination geometry of the intermediates was probed by the aid of X-ray Absorption Spectroscopy (XAS). Detailed analysis of the features in the X-ray absorption near edge structure (XANES) and the extended X-ray absorption fine structure (EXAFS) could help us pin-point the coordination mode of these two types of nitrene-radical species.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Left: The mono-nitrene species of the type 3\text{P1}\text{Ns} obtained from 1\text{P1} and organic azide 2\text{Ns}. Right: The six-coordinate bis-nitrene species 5\text{P1}\text{Ns} obtained from 1\text{P1} and N-nosyl-iminoiodane 4\text{Ns}.}
\end{figure}
Results and discussion

For the XAS studies, samples were prepared in Mössbauer/XAS cups made from Delrin® and the window side was sealed with Kapton® tape. All probes were made in benzene solution with a concentration of 10 mM and immediately frozen and stored at 77 K when the desired intermediate was formed in maximum yield, following reaction kinetics previously investigated by UV/vis and EPR spectroscopy. The temperature was kept below the melting point during storage and transfer. A He Displex cryostat was used for temperature control during the measurement, with typical sample temperatures of ~20 K. Data were collected as fluorescence spectra using a 31 element solid-state Ge detector (Canberra), over an energy range of 7508 – 8328 eV (k ~ 12 Å⁻¹). Each scan required approximately 40 minutes. A Co foil spectrum was collected simultaneously using a PMT for energy calibration; the first inflection point of the metal foil reference was set to 7709 eV.

The thus obtained XANES of species $3P1$$_{Ns}$ and $5P1$$_{Ns}$ (Figure 1) are shown in Figure 2. Electronically the XANES was in excellent agreement with the electronic structures proposed thus far using other complimentary spectroscopic techniques (EPR, UV-vis and UHR-ESI-MS spectroscopy) as described in Chapter 2. The XANES part of the XAS spectra showed pre-edge signals corresponding to cobalt(III) species for both mono- and bis-nitrene species. This is in line with other experimental data (see Chapter 2 of this thesis). The starting [Co$^{II}$TPP] complex $1P1$ exhibited an edge inflection energy of ca. 7720.7 eV. A shoulder feature along the rising edge at 7715.4 eV corresponds to a 1s to 4p + LMCT shakedown transition, in accord with the observed 4-coordinate square planar structure of this complex. This transition is strongest in 4-coordinate square planar Co complexes, but is also observed in 5-coordinate square pyramidal geometries (it is not present in either $T_4$ or $O_6$ geometries). Finally, a broad 1s to 3d pre–edge peak was observed at 7708.9 eV, with preliminary peak fitting analysis indicating a peak area of approximately 8.1 units. The energies of the edge and 1s→3d pre-edge transitions are in accord with the reported values for other cobalt(II) complexes.¹

![Graph](image)

**Figure 2.** K-pre edge XAS data of $1P1$ ([Co$^{II}$TPP], green), $3P1$$_{Ns}$ (mono-nitrene, blue) and $5P1$$_{Ns}$ (bis-nitrene, red).
The XANES of $5^{\text{P1}}_{\text{Ns}}$ showed a +1.9 eV blue-shift of the edge inflection energy to 7722.56 eV, relative to complex $1^{\text{P1}}_{\text{Ns}}$, supporting metal-centred oxidation from cobalt(II) to cobalt(III). The 1s→3d pre-edge transition was also blue-shifted by ~1.0 eV to 7710.2 eV and the pre-edge increased in intensity (peak-area of 12.0 units). Most notably, $5^{\text{P1}}_{\text{Ns}}$ lacks the diagnostic 1s→4p (+ LMCT shakedown) transition shoulder on the rising edge, providing strong evidence for a 6-coordinate O$_h$ cobalt site. Finally, the XANES data on $3^{\text{P1}}_{\text{Ns}}$ revealed the existence of edge and 1s→3d pre-edge transitions at nearly identical positions (7722.8 and 7710.2 eV, respectively) relative to $5^{\text{P1}}_{\text{Ns}}$. Again no clear 1s to 4p + LMCT shakedown transition seems to be visible, suggesting that also $3^{\text{P1}}_{\text{Ns}}$ is 6-coordinate. However, this transition could also be hidden underneath the rising edge and as such we cannot fully exclude this species being 5-coordinate. Comparison of experimental and TD-DFT calculated (Orca) K-edge XAS data of of 5-coordinate mono-nitrene $3^{\text{P1}}_{\text{Ns}}$ and 6-coordinate bis-nitrene $5^{\text{P1}}_{\text{Ns}}$ showed this discrepancy in the K-edge XAS data. The mono-nitrene species is predicted to have a higher intensity band at 7712 eV, which is missing in the experimental spectrum of the mono-nitrene species.

![Figure 3. Comparison of experimental data (solid lines) and TD-DFT calculated (Orca) K-edge XAS data (dotted lines) of 5-coordinate mono-nitrene $3^{\text{P1}}_{\text{Ns}}$ (blue) and 6-coordinate bis-nitrene $5^{\text{P1}}_{\text{Ns}}$ (red).](image)

Consequently, this initially led us to believe that a sixth ligand binds to the mono-nitrene species, trans to the nitrene radical moiety. This ligand was so far not detected using EPR, UV-vis and UHR-ESI-MS. As such we wondered if a 6$^\text{th}$ ligand is really bound to $3^{\text{P1}}_{\text{Ns}}$ or not, and if so what is the nature of this ligand. In an attempt to gain more information about this assumed 6$^\text{th}$ ligand, we decided to take up more DFT calculations to simulate the XANES part of the XAS spectra. Initially, we considered coordination of a neutral unreacted nosyl azide ligand under the conditions of the EXAFS measurements. However, DFT geometry optimizations and calculation of the Co K-edge features of the optimized structures with DFT methods revealed that such nosyl azide species have too long Co–N distances to explain the experimental XAS data. The same holds for the aqua adduct of $3^{\text{P1}}_{\text{Ns}}$. The Ns-NH$_2$ amine and ammonia (NH$_3$) adducts of $3^{\text{P1}}_{\text{Ns}}$ have shorter Co–N bond distances, which substantially decreases the calculated intensity of the pre-edge transitions in the Co K-edge region.
Figure 4. TD-DFT calculated (Orca) K-edge XAS data comparing five-coordinate mono-nitrene 3^{P1}_{Ns} with six-coordinate bis-nitrene 5^{P1}_{Ns} and some six-coordinate adducts of mono-nitrene 3^{P1}_{Ns} based on possible neutral ligands NsNs, H_2O, NsNH_2 and NH_3.
The best agreement between the calculated and experimental pre-edge intensities seems, however, to be obtained for anionic ligand adducts of mono-nitrene $3^{P_1}N$s. The optimized geometries of $N$sNH$^{-}$, NH$_2^{-}$ and OH$^{-}$ adducts of $3^{P_1}N$s species have comparable Co–N and Co–X distances for the nitrene radical ligand and the 6$^\text{th}$ ligand L$_2$ (Figure 2), respectively. Hence, similar pre-edge intensities are also computed as obtained for bis-nitrene species $5^{P_1}N$s. Considering the detection of the Na$^{+}$ adduct of NO$_2$PhSO$_2$NHD as mentioned earlier in the ESI-MS studies in combination with the abovementioned calculated pre-edge intensities, the $N$sNH$^{-}$ amido ligand is a likely candidate occupying the sixth coordination site of the mono-nitrene species. Notably, the DFT calculated geometrical parameters for $3^{P_1}N$s ($N$sNH$^{-}$) is in reasonable agreement with the EXAFS data (see additional information Table 3). This would mean, however, that $3^{P_1}N$s is anionic (perhaps containing an $N$sNH$_3^{+}$ counter ion). Formation of such a charged species in benzene is unexpected, and as such we cannot exclude the 6$^\text{th}$ ligand being the neutral $N$sNH$_2$ amine donor (despite a better agreement between the calculated and experimental XAS pre-edge intensities for the $N$sNH$^{-}$ amido ligand). It is further worth mentioning that
this sixth ligand L₂ does not prevent conversion of mono-nitrene species 3²⁺ₙs to bis-nitrene species 5²⁺ₙs upon treatment with the strongly oxidizing N-nosyl iminoiodane 4ₙs. On adding an excess of 4ₙs to a solution of previously formed mono-nitrene species 3²⁺ₙs, clear EPR signals corresponding to bis-nitrene species 5²⁺ₙs appeared, once again displaying the strongly oxidizing nature of N-nosyl iminoiodane. Apparently, the ligand L₂ can be replaced or converted to a nosyl nitrene radical moiety upon reaction of mono-nitrene 3²⁺ₙs with iminoiodane 4ₙs. At this point, purely looking at the intensity of the DFT simulated XANES spectra of various contenders as an anionic ligand seemed to be a more plausible candidate for the 6th ligand. These were ligands like NH₂⁻, OH⁻ or the NsNH⁻. Because, we detected the mass of the corresponding amine for the azide during all mass measurements, we initially proposed this sixth ligand to be the anionic ligand NsNH⁻. However, considering the ionic nature of such species, formation of which we considered rather unlikely in the apolar solvent benzene used in both these experiments and in catalysis, we started to reconsider our initial interpretations.

Hence, as a follow-up of these studies we decided to perform XAS on two other very related and well-defined neutral cobalt(III) complexes. These were [CoII₃(TPP)(Cl)] and [CoII₃(TPP)(CF₃)]. From the crystal structure ([CoII₃(TPP)(CF₃)])³ and X-ray powder diffraction studies ([CoII₃(TPP)(Cl)]) (see Figure 14, additional information) we could confirm the geometry of these two complexes. Both of these complexes are five-coordinate with no axial ligand occupying the 6th position. Thus, pre-edge X-ray absorption features (XANES) of these complexes would give us a more realistic picture of how much the intensities of these transitions are affected by the geometry of the complexes. Based on the conclusions we drew from the observations with the nitrene radical species, these two new five-coordinate species should display distinct Co K-edge features. The corresponding experimental spectra are shown in Figure 6.

Once again, the two complexes were ascertained to be cobalt(III) complexes, but with different pre-edge intensities with respect to each other. The [CoII₃(TPP)(CF₃)] showed a higher intensity of the diagnostic pre-edge feature compared to the coordinative identical [CoII₃(TPP)(Cl)] complex. More interestingly, the definite five-coordinate [CoII₃(TPP)(Cl)] actually displays a weak pre-edge intensity, of almost comparable low intensity as that of the previously measured mono-nitrene species (which was so far considered to be six-coordinate). Apparently, π-donor ligands like Cl⁻ (and nitrene/imido ligands) lower the intensity, even for 5-coordinate species. σ-donating ligands like CF₃ give rise to higher pre-edge intensities. This prompted us to also calculate these intensities using ORCA as we did for the various mono-nitrene complexes. The results are shown in Figure 7.
Figure 6. Experimental XANES spectra of the five-coordinate $\text{[Co}^{\text{III}}(\text{TPP})(\text{Cl})]\text{]}$ and $\text{[Co}^{\text{III}}(\text{TPP})(\text{CF}_3)\text{]}$ complexes overlaid also with the experimental spectra of the mono-nitrene species $3_{\pi^*}\text{Ns}$.

Figure 7. TD-DFT calculated (Orca) K-edge XANES data comparing the five-coordinate mono-nitrene species $3_{\pi^*}\text{Ns}$. $\text{[Co}^{\text{III}}(\text{TPP})(\text{Cl})]\text{]}$ and $\text{[Co}^{\text{III}}(\text{TPP})(\text{CF}_3)\text{]}$ and some of their adducts with neutral ligands.
Figure 8. Some six-coordinate adducts of [CoIII(TPP)(Cl)] and [CoIII(TPP)(CF₃)] based on a plausible neutral ligand like H₂O.

Analysis of the transitions that give rise to the observed bands showed that in the [CoIII(TPP)(Cl)] complex, the pre-edge is the lowest energy transition at ~7694 eV. This arises from a core-to-valence d-shell transition (transition to dₓ²₋ᵧ², with some mixing with the pₓ orbital). The second band at ~7704 eV has contributions from transitions between the core 1s orbitals to the π* orbitals of the porphyrin ring. The metal valence d-orbitals and the 4p-orbitals seem to play a minor role in all of these transitions. This could well be caused by lowering the symmetry on going from 4- to 5-coordination, leading to stronger mixing of the p/d-orbitals with the porphyrin π* orbitals. As mentioned above, this second band could well be hidden underneath the rising edge in the experimental spectra (both for the 5- and 6-coordinate complexes). Thus, unlike the [CoII(TPP)] complex, for the [CoIII(TPP)(Cl)] complex the pre-edge does not seem to be a pure 1s to 4p + LMCT shakedown transition. So while for the 4-coordinated [CoII(TPP)] the band at ~7702 eV has a major contribution from a "1s to 4p" transition, the band at ~7702 eV is in fact constructed from a collection of transitions, some of them being a transition from the core 1s orbital to a porphyrin ring π* orbital, with minor involvement of metal d- or p-orbitals.

The very weak pre-edge band at ~7694 eV computed for [CoII(TPP)] is again dominated by 1s-to-metal-d-orbital transitions, but it now involves the dₓ²₋ᵧ² orbital instead of the dₓ² orbital. This is in line with the fact that the only completely empty d-orbital in this complex is the dₓ²₋ᵧ² orbital. The p-d mixing in the dₓ²₋ᵧ² orbital can be expected to be small in the square planar [CoII(TPP)]. Such mixing becomes much stronger for the dₓ²-orbital of 5-coordinate complexes like [CoIII(TPP)(Cl)] and [CoIII(TPP)(CF₃)]. Hence, this leads to an increase in the pre-edge intensity. For the 6-coordinate complex this intensity drops as compared to a 5-coordinate complex, but not so much as in the case of with an empty dₓ²-orbital. In this case the empty dₓ² involved must always be quite strongly mixed with the 4pₓ (and the 4s) orbital (to even allow the binding of a 5th or 6th donor to the axial position). So the intensity remains relatively strong compared to the 4-coordinate cobalt(II) complex [CoII(TPP)]. Additionally, the drop in intensity of the second band for the 5-coordinate complexes can also be reasoned based on the fact that on going from 4-coordination to 5-coordination, due to a change in symmetry, the 1s-to-4p transition is mostly removed but transitions from the core 1s orbitals to the π* orbitals of the porphyrin ring still remain.
On comparing the experimental pre-edge (~7694 eV) intensities of the 5-coordinate chlorido complex [CoIII(TPP)(Cl)] with that of the mono-nitrene species 3P1_Ns, one could perhaps conclude that the latter is also 5-coordinate. However, the DFT computed pre-edge intensities of [CoIII(TPP)(Cl)] and 3P1_Ns do not match up, with [CoIII(TPP)(Cl)] having a much lower intensity than the 5-coordinate 3P1_Ns (factor 3 roughly). The computed intensity of 6-coordinate 3P1_Ns with a neutral NH2Ns amine donor at the 6th coordination site, however, closely matches that of [CoIII(TPP)(Cl)]. Based on this DFT comparison, and experimental detection of NH2Ns in the catalytic reaction mixtures, we are tempted to conclude that 3P1_Ns is indeed a 6-coordinate species, but with a neutral NH2Ns donor coordinated rather to cobalt(III) than an anionic NsNH− ligand.

Summary and conclusions
Based on the XAS data on the cobalt(III) complexes [CoIII(TPP)(Cl)] and [CoIII(TPP)(CF3)] presented in this chapter it can be concluded that the relative intensities of the XANES features cannot always be straightforwardly correlated to the coordination numbers around the metal centre. The use of XANES as a diagnostic tool to distinguish reliably between 5- and 6-coordinate [CoIII(Por)] species is complicated by several contributing factors. Pre-edge intensities are influenced by π- donation and higher energy transitions (in all cases) between 7713-7720 eV are not purely 1s to 4p + LMCT shakedown transitions, but largely 1s to porphyrin π* transitions for many of the [CoIII(Por)] species. Furthermore, these transitions can be hidden underneath the rising edge. While for the mono-nitrene species the absence of a shakedown transition and the weak pre-edge intensity initially led us to believe that an anionic donor binds to the 6th coordination site of 3P1_Ns , it is now safe to conclude that this is not the case. This is also in line with the experimental observations from catalysis, where reactions are performed in apolar solvents and the use of additives does not have a dramatic effect in nitrene-transfer reactions catalysed by cobalt(II) porphyrins. The sixth ligand in the mono-nitrene species is therefore most likely a neutral amine donor (derived from the azide), rather than an anionic (amido) ligand.

Supporting information, experimental and computational details
- EXAFS analysis of [CoI(TPP)] 1P1, mono-nitrene 3P1_Ns, bis-nitrene 5P1_Ns, [CoII(TPP)(Cl)] and [CoII(TPP)(CF3)]

Extended X-ray absorption fine structure (EXAFS) analysis revealed further structural details (Figure 10, Figure 9, Table 1, Table 3, Table 4, Table 2). For complex 5P1_Ns, the first coordination sphere could be satisfactorily fitted by considering six N/O scatterers at a distance of 1.92 Å (Table 1). Although the additional outer-shell features could be satisfactorily accounted for by considering single scattering paths involving 8 carbons at 2.94 Å, 12 carbons at 3.35 Å, and 4 oxygen donors at 3.57 Å distance from cobalt, the fit could be significantly improved by introducing multiple-scattering pathways. The best fit for 5P1_Ns is represented by fit 12 in Table 2 and Figure 9B. It is important to note that efforts were also made to include the effect of the sulfur scatterers originating from the two –NNS units. However, all fits (fits 9-11 in Table 1) including any kind of S-shell showed negative Debye-Waller factors in the fit parameters; and hence they were not considered in the fitting procedure.

Interestingly, consistent with the XANES data, our attempts to do a set of fits for a back transformation range limited to the first shell (r = 0.8 – 2.1 Å) for 3P1_Ns also pointed to a 6-coordinate geometry (fits 1-3; Table 2). This was thus far not identified based on the other spectroscopic techniques. The best fit to the data of the mono-nitrene species requires six N/O scatterers at ~1.95 Å distance from the
cobalt(III) centre, which is slightly longer (although almost identical within the error of measurements) than the Co–N distance of 1.92 Å obtained from the EXAFS data of bis-nitrene species $^{5}$P$_{1}^{-}$.  

![Figure 9](image9.png)  

**Figure 9.** Overlaid Fourier transform EXAFS spectra for $^{1}$P$_{1}$, $^{3}$P$_{1}^{-}$.Ns and $^{5}$P$_{1}^{-}$.Ns. All spectra are weighted by $k^3$.

**Table 1.** Summary of comparison of the EXAFS determined metrical parameters (for the first three shells) of $^{3}$P$_{1}^{-}$.Ns and $^{5}$P$_{1}^{-}$.Ns with that of the DFT calculated values for $^{3}$P$_{1}^{-}$.Ns(Ns-NH$^-$), $^{3}$P$_{1}^{-}$.Ns(Ns-NH$_2$) and $^{3}$P$_{1}^{-}$.Ns.

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![Figure 10](image10.png)  

**Figure 10.** A) XANES of [Co$^II$(TPP)] (red), $^{3}$P$_{1}^{-}$.Ns (green) and $^{5}$P$_{1}^{-}$.Ns (blue). Spectra are referenced to the first inflection point of a cobalt reference foil set to 7709.0 eV. B) Fourier transform EXAFS spectra of $^{5}$P$_{1}^{-}$.Ns (dotted line) and the best fit (red line); the inset shows the EXAFS data on a wave vector scale weighted by $k^3$ with respective representation. C) Fourier transform EXAFS spectra of $^{3}$P$_{1}^{-}$.Ns (dotted line) and the best fit (red line); the inset shows the EXAFS data on a wave vector scale weighted by $k^3$ with respective representation.
Table 2. Summary of the EXAFS fitting for [Co$^n$(TPP)] $1^p$. The best fit for the date (fit 9) is represented in bold. $r$ is in units of Å; $\sigma^2$ is in units of $10^{-3}$ Å$^2$; $\Delta E_0$ is in units of eV; R-factor represents the GOF. Fourier transform range: $k$ 1.5-5.0 Å$^{-1}$. The fit was optimized in $R$ space with a $k$-weight of 3. The fitting range is 0.8-4.0 Å for fits 1-4 and 0.8-5.0 for fits 5-11.

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* multiscattering (2 legs) with a degeneracy of 2 for the shown paths and untreated $\sigma^2$ values.
' smaller fitting range

Table 3: Summary of EXAFS fitting for $5^p_{Ns}$. Bold line represents the best fit for the system (fit 12). $r$ is in units of Å; $\sigma^2$ is in units of $10^{-3}$ Å$^2$; $\Delta E_0$ is in units of eV; R-factor represents the GOF. Fourier transform range: $k$ 1.5-5.0 Å$^{-1}$. The fit was optimized in $R$ space with a $k$-weight of 3. The fitting range is 0.8-2.1 Å for fits 1-2 and 0.8-4.8 for fits 3-11.

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* multiscattering (2 legs) with a degeneracy of 2 for the shown paths and untreated $\sigma^2$ values.
Table 4. Summary of EXAFS fitting for 3P. Bold line represents the best fit for the system (fit 10). \( r \) is in units of Å; \( \sigma^2 \) is in units of \( 10^{-3} \) Å; \( \Delta E_0 \) is in units of eV; R-factor represents the GOF. Fourier transform range: \( k 1.5-5.0 \) Å\(^{-1}\). The fit was optimized in R space with a \( k \)-weight of 3. The fitting range is 0.8-2.1 for fits 1-3 and 1.2-5.0 for fits 4-11.

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<th>Co···C/N</th>
<th>Co···D/N</th>
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* multiscattering (2 legs) with a degeneracy of 2 for the shown paths and untreated \( \sigma^2 \) values.

\( ^{1} \) smaller fitting range

Figure 11. \( k^3 \)-weighted FT of the Co K edge EXAFS data and best fit of [Co\(^{III}\)(TPP)(CF\(_3\))] (not phase corrected). Fitting was optimized for all \( k \)-weights (1-3). The inset shows the data and best fit in \( k \)-space, and presented in \( k \) space with a weighting of 3.
Figure 12. Molecular structure of $[\text{Co}^{III}(\text{TPP}) ]$, with atomic labels.

Table 5. Summary table of the EXAFS fitting parameters for $[\text{Co}^{III}(\text{TPP})(\text{CF}_3)]$. Fitting parameters; $S_0^2=0.81$ (as determined by a Co foil standard), $\Delta E_0 = +1.27$. Fitting range; $3 < k < 14$, $1 < R < 4.9$. The final R-factor was 0.031. Single scattering paths are shown in bold.

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<th>Scattering path (path indicator, see Figure 12)</th>
<th>N</th>
<th>$\sigma^2 (\text{Å}^2)$</th>
<th>$\Delta R (\text{Å})$</th>
<th>$R_{\text{eff}} (\text{Å})$</th>
<th>$R_{\text{fitted}} (\text{Å})$</th>
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<td>0.0020</td>
<td>-0.006</td>
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**Figure 13.** $k^3$-weighted FT of the Co K edge EXAFS data and best fit of $[\text{Co}^{III}(\text{TPP})(\text{Cl})]$ (not phase corrected). Fitting was optimized for all $k$-weights (1-3). The inset shows the data and best fit in $k$-space, and presented in $k$ space with a weighting of 3.

**Table 6.** Summary table of the EXAFS fitting parameters for $[\text{Co}^{III}(\text{TPP})(\text{Cl})]$. Fitting parameters; $S_0^2=0.81$ (as determined by a Co foil standard), $\Delta E_0 = -0.16$. Fitting range; $3 < k < 14$, $1 < R < 4.9$. The final R-factor was 0.022. Single scattering paths are shown in bold.

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<td>4.897</td>
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</table>
- Powder XRD data of $[\text{Co}^{III}(\text{TPP})(\text{Cl})]$ sample used for XAS experiments

![Figure 14. Powder XRD obtained for the sample of $[\text{Co}^{III}(\text{TPP})(\text{Cl})]$ used for the XAS measurements.](image)

- Experimental and computational details

For samples $1P1$, $3P1N$, and $5P1N$, XAS measurements were performed on NSLS X3B, which is equipped with a sagitally focusing Si(111) double-crystal monochromator and a post-monochromator Ni-coated harmonic rejection mirror. Note that while the Ni mirror was in the beampath during data collection, metallic Ni contamination is not significant based on measurement of an experimental blank spectrum. Hence Cobalt EXAFS could only be collected up to the Nickel K-edge energy. The samples were prepared in Mössbauer/XAS cups made from Delrin® and the window side was sealed with Kapton tape. All probes were made in benzene solution with a concentration of 10 mM and immediately frozen and stored at 77 K when the desired intermediate was formed in maximum yield, following reaction kinetics previously investigated by UV/vis and EPR spectroscopy. The temperature was kept below the melting point for storage period and transfer. A He Displex cryostat was used for temperature control during the measurement, with typical sample temperatures of ~20K. Data were collected as fluorescence spectra using a 31 element solid-state Ge detector (Canberra), over an energy range of 7508 – 8328 eV (k ~ 12 Å⁻¹). Each scan required approximately 40 minutes. A Co foil spectrum was collected simultaneously using a PMT for energy calibration; the first inflection point of the metal foil reference was set to 7709 eV.

For the two subsequent complexes, $[\text{Co}^{III}(\text{TPP})(\text{Cl})]$ and $[\text{Co}^{III}(\text{TPP})(\text{CF}_3)]$, XAS measurements were performed at B18 (Diamond Light Source, beamtime SP15305-1), using a Si(111) crystal monochromator with Pt harmonic rejection mirrors. Samples were in powder form and sealed between two pieces of 13 micron Kapton® foil, and measured at room temperature as fluorescence spectra using a 36 element solid state Ge detector. Spectra was collected up to $k=14$ Å⁻¹, and averaged over at least 20 scans, with a total time per sample of 40 minutes. All spectra were referenced to a Co foil (EXAFS Materials), with the first peak in the first derivative set to 7709 eV.
Data averaging and processing (including background subtraction etc) was carried out using Athena from the ifeffit/Demeter package. Reference spectra for individual scans were carefully aligned to ensure that the energy scale was identical for all spectra. Sets of scans at each spot were examined for photoreduction effects. No evidence for photo reduction was observed based upon edge energies or spectral changes although slight burn marks were visible after the measurement.

EXAFS analysis and fitting was performed with Artemis from the ifeffit package and FEFF. The fitting process is summarized in tables for each sample showing the major fitting parameters. The goodness of the fit (GOF) is represented by the R-factor (value from ifeffit package) which is defined by 

\[ R = \frac{\sum [\chi_{\text{dat}}(R_i) - \chi_{\text{th}}(R_i)]^2}{\chi_{\text{dat}}(R)^2}. \]

Geometry optimizations were carried out with the Turbomole program package\textsuperscript{6} coupled to the PQS Baker optimizer\textsuperscript{7} via the BOpt package\textsuperscript{8} at the DFT level using the b3-lyp functional\textsuperscript{9} and def(2)-TZVP basis set\textsuperscript{10} for the geometry optimizations of all stationary points. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by numerically calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated.

XAS Co K–edge absorption parameters of complex \(5P_{1Ns}\), five coordinate \(3P_{1Ns}\) and several ligand adducts of \(3P_{1Ns}\) were calculated with ORCA\textsuperscript{11} using geometries obtained from Turbomole optimizations [BP86/def2-TZVP\textsuperscript{9} using Grimme’s dispersion corrections disp3\textsuperscript{12}]. XAS parameters were calculated with ORCA TD-DFT calculations\textsuperscript{13} at both the BP86/def2-TZVP and the b3-lyp/def2-TZVP level employing COSMO dielectric corrections.

Acknowledgements

We thank Dr. Erik R. Farquhar (NLS, Brookhaven) for help with XAS data collection. Dr. David J Martin and Dr. Moniek Tromp are thanked for help with XAS data collection and data interpretation of compounds \([\text{Co}^{II}(TPP)\text{CF}_3]\) and \([\text{Co}^{II}(TPP)\text{Cl}]\).
References and notes


(2) However, the absence of the 1S to 4p+LMCT shakedown transition could also be because it is hidden underneath the rising edge, and also the weak intensity of the pre-edge transitions could have a different reason than formation of 6-coordinate species.

(3) Goswami, M.; de Bruin, B.; Dzik, I. W.; Chem. Commun. 2017, 53, 4382-4385. Also see chapter 7 of this thesis.


(5) (a) EXAFS analysis of \(1^1P_1\), \(3^1P_1\), and \(5^3P_1\) were performed by K. Ray and co-workers and S. De Beer and co-workers. (b) EXAFS analysis of \([Co^{III}(TPP)(Cl)]\) and \([Co^{II}(TPP)(CF_3)]\) were performed by D. J. Martin and M. Tromp.


Chapter 4

Porphyrin-Co(III)-‘nitrene radical’ catalysed synthesis of phenoxazinone and o-amino-azobenzenes

Parts of this chapter have been published and are reproduced from:
Goswami, M.; Rebreyend, C.; de Bruin, B. Molecules, 2016, 21, 242.
Introduction

In the previous two chapters, we have discussed the electronic and geometric structures of nitrene-radical intermediates that are formed as a result of azide activation by cobalt(II)-porphyrins. In chapter 1 we also summarised the catalytic transformations that these systems can perform (Figure 12, chapter 1).¹ For the porphyrin-Cob(III)-nitrene radicals the reactivities were limited to intramolecular C-H insertions and aziridination reactions. For the carbene radicals, however, the current scope of reactions is much broader. Intermolecular reactions with alkynes can not only give cyclopropenes but also lead to ring compounds (see example C and E in Figure 11, chapter 1).² For cobalt(III)-nitrene radicals, addition to triple bonds (alkynes, for example) are currently not reported. This limitation in reactivity of the nitrene radicals might in part be because of the high-energy azirines that are formed as products.³ The 1H-azirines (C–C double bond) very easily undergo rearrangements to form the more stable 2H-azirines (Figure 1). 2H-azirines are the same three membered N-heterocyles but with an N–C double bond. The 2H-azirines also undergo follow-up reactions with electrophiles and nucleophiles alike.³ This is in marked contrast with the corresponding three-membered cyclopropenes which are relatively more stable (possibly due to lower ring-strain compared to azirines).

![Figure 1. The three-membered N-heterocycles called azirines. They undergo rearrangements of the double bond and can undergo ring-opening reactions with nucleophiles or electrophiles.](image)

For the porphyrin-cobalt(III)carbene radicals, intermolecular reactions with reaction partners like acetylenes to give ring-compounds have been successful (Figure 11, chapter 1). An elegant example is that of the catalytic synthesis of 2H-Chromenes which was reported by de Bruin and co-workers in 2014.⁴ This reaction proceeds via the attack of the carbene-radical intermediate B on the alkyne functionality of phenyl acetylene. The transformation and mechanism is outlined in Scheme 1.

![Scheme 1. DFT calculated mechanism of Co(II) porphyrin catalysed synthesis of 2H-Chromenes.](image)
DFT studies on the mechanism of this system reveal the formation of the salicyl–vinyl radical intermediate C by the [Co\textsuperscript{II}(Por)] metalloradical. Unexpectedly, subsequent hydrogen atom transfer (HAT) from the hydroxyl moiety to the vinyl radical (intermediate C) leads to formation of an α-quinone methide intermediate D. This intermediate dissociates from the metal centre to undergo an endocyclic, sigmatropic ring-closing to give the 2H-chromene (Scheme 1). This was confirmed by EPR experiments and radical poisoning experiments using the 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) free radical.

This reaction inspired us to extend the chemistry to related ring-closing reactions, but this time using a nitrene precursor instead of a carbene precursor. We hypothesized that a similar substrate containing an azide functionality could also be activated by cobalt(II) porphyrins leading to N-containing heterocycles. N-containing heterocycles are interesting synthetic targets, given their ubiquity in natural products. The thus formed heterocycles in this case are called benzoxazines. They are used in polymers, resins, and as cross-linking agents due to their favourable thermal and chemical resistance and electrical properties. Many variants are also pharmaceutically active compounds. On the other hand, as these nitrene radicals are not reported in reactions with alkynes they are also mechanistically very interesting cases to study. Experimentally, however, these reactions take a different course and new pathways are discovered. The results of these investigations are disclosed in this chapter.

**Results and Discussion**

As an initial test reaction, α-azido phenol 1 was reacted with [Co\textsuperscript{II}(TPP)] (Figure 2) in the presence of phenyl acetylene with the expected formation of benzoxazine 2 as the product (Scheme 2). However, on analysing the crude reaction mixture the expected product 2 was not detected. Instead, new \textsuperscript{1}H-NMR peaks were observed, and the azide was fully consumed. The major product was separated from the reaction mixture by column chromatography, and proved to be the phenoxazinone 3 (Scheme 2).

![Figure 2](image-url)

_Figure 2. The two different [Co\textsuperscript{II}(Por)] complexes used as catalysts in this study._

![Scheme 2](image-url)

_Scheme 2. Formation of phenoxazinone 3 from α-azido phenol 1 catalysed by [Co\textsuperscript{II}(TPP)]._
compound 4 (Scheme 3). Attack of the imine N atom of 4 at the para position (w.r.t to the carbonyl group) of another molecule of 4, followed by 1,5- sigmatropic migration of an H atom, subsequent deprotonation and oxidation would lead to formation of the phenoxazine product 3. Such a pathway using ortho-amino phenol (OAP) has also been reported before using manganese porphyrins that use H$_2$O$_2$ as the external oxidant. In our case, the deprotonation and oxidation steps probably took place in air during column chromatography.

Scheme 3. Proposed mechanism for formation of 3 from 1 mediated by [Co$^{II}$TPP]]

Compound 3 has anti-inflammatory and immunomodulatory properties and is, therefore, valuable for its medicinal properties. As mentioned before, other reported methods involving metalloporphyrin catalysed synthesis of 3 from OAP make use of more powerful oxidants like hydrogen peroxide, and are believed to be formed via different mechanisms. To see if formation of 3 could be avoided by using an excess of the alkyne, the reaction was also performed in neat alkyne. However, also in this case almost exclusive formation of compound 3 was observed. In addition to that, simple aziridinations of alkenes like cyclohexene and styrene were also attempted using o-azido phenol 1, which in all cases led to formation of only one identifiable and major product: phenoxazinone 3 (Table 1).
Table 1. Reaction of o-hydroxy phenyl azide 1 with different substrates under reaction conditions a and b.*

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<th>Substrate</th>
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<th>Obtained product</th>
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<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
</tr>
</tbody>
</table>

*Reaction conditions: a) 0.5 mmol of azide 1, 1 mmol of substrate, 5 mol% [Co^II(TPP)] (w.r.t. azide), 4 mL toluene, 50 °C, 18h.  
b) 0.6 mmol of azide 1, 15 mL of substrate, 5 mol% [Co^II(TPP)], 50 °C, 18h. No nitrene transfer to the solvent (toluene) was observed in any case under the applied reaction conditions.

To be able to trap the proposed reactive intermediate 4 with a different substrate we decided to protect the phenyl ring on the 5-position, so that coupling of two iminoquinones to give products like 3 is prevented. As such, 2-azido-5-nitrophenol 5 was synthesized. As a test reaction, we tried to trap the corresponding o-quinone monoamine intermediate with 1-butoxyethene in an Inverse Electron Demand Diels Alder (IEDDA) reaction (Scheme 4). For this transformation, however, no fruitful results were obtained when using [Co^II(TPP)] as the catalyst. The crude reaction mixtures showed formation of a mixture of products containing a lot of azide starting material. This is most likely due to the inherent inability of [Co^II(TPP)] to activate the azide under the applied reaction conditions. However, on switching to [Co^II(TPPF_20)] (Figure 2), the desired transformation could be achieved and product 6 was obtained in 80% isolated yield. Non-catalytic trapping of o-quinone monoimines has been reported earlier, but the method uses stoichiometric amounts of halogen containing oxidants, which is avoided in the reaction depicted in Scheme 4.

![Scheme 4. Trapping of the o-quinone monoimine in an IEDDA reaction.](image10)

Substrate 5 was also tested in reactions with other potential reaction partners, in which we expected to be able to trap the iminoquinone intermediate with different C=C and C=C bonds. With phenyl acetylene, no reaction involving the C=C bond was observed. Other alkenes also proved unreactive in this process. Apparently, only electron rich alkenes like 1-butoxyethene are suitable reaction partners in this process.
Table 2. Reaction of azide 5 with different substrates

<table>
<thead>
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<th>Entry</th>
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<th>Obtained Product</th>
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<tr>
<td>1a,b</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Expected Product 1" /></td>
<td><img src="image3" alt="Obtained Product 1" /> (-10 %)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Substrate 2" /></td>
<td><img src="image5" alt="Expected Product 2" /></td>
<td>......</td>
</tr>
<tr>
<td>3</td>
<td><img src="image6" alt="Substrate 3" /></td>
<td><img src="image7" alt="Expected Product 3" /></td>
<td><img src="image8" alt="Obtained Product 3" /> (80 %)</td>
</tr>
</tbody>
</table>

*Reaction conditions: a) 0.5 mmol of azide 1, 1 mmol of substrate, 5 mol% [Co(II)(TPP)] (w.r.t. azide), 4 mL toluene, 50 °C, 18 h. b) 0.6 mmol of azide 1, 15 mL of substrate, 5 mol% [Co(TPP)20], 50°C, 18 h. No nitrene transfer to the solvent (toluene) was observed in any case under the applied reaction conditions.

To investigate the generality of the observed HAT reactivity, we decided to explore the reactivity of aryl azide 7, containing an NH₂ substituent in the ortho-position instead of an OH substituent. The o-amino phenylazide 7 was synthesized and tested under the same reaction conditions, using [Co(II)(TPP)] as the catalyst (Scheme 5). In contrast to our expectations, however, azobenzene 8 was obtained as the major product. This observation intrigued us, as formation of azo compounds as products in reaction of azides with [Co(III)(Por)] catalysed processes has been reported only once before, and only as a minor side product.7

Scheme 5. Reaction of o-amino phenylazide 7 with [Co(III)(TPP)].

Two mechanistic proposals for formation of azo compounds in [Co(III)(Por)] catalysed reactions have been suggested: (I) Attack of the azide starting compound on the nitrene intermediate, producing azobenzene with simultaneous N₂-loss, and (II) dinuclear N-N coupling involving two nitrene complexes (Scheme 6). However, formation of amines from the azides via the nitrene (radical) intermediates has also been reported, likely involving HAT from the reaction medium (solvent) to the cobalt(III) nitrene radical intermediate. The latter process, actually, also provides an alternative (and perhaps more likely) pathway for formation of azo compounds (see below).
It is not so clear how the reaction conditions influence the formation of azobenzenes. One suggested possibility was that in the presence of a large excess of another reaction partner, the concentration of the nitrene intermediate cannot build-up in a sufficient manner to allow formation of azo compounds via dinuclear N-N coupling. To check this hypothesis, we repeated the reaction of azide 7 in the presence of a large excess of phenyl acetylene or styrene in refluxing toluene. However, once again the azo compound 8 was obtained as the major product. This led us to believe that there is something unique about the NH₂ substituent in azide 7 that relates to formation of only the azo compound. We speculate that this relates to rapid formation of o-phenylene diimine (OPDI) undergoing further reactions to form 8.

**Scheme 6. Possible side reactions in [Co(II)(Por)] catalysed reactions with organic azides.**

**Scheme 7. Plausible mechanism for the formation of azobenzene from the reaction of azide 7 catalysed by [Co(II)(TPP)].**
The formation of azobenzene 8 from ortho-amino phenyl azides via the proposed phenylene diimine intermediate 9 can be reasoned in the mechanism depicted in Scheme 7. On formation of the OPDI the N atom of one of the imine moieties does a nucleophilic attack on an imine nitrogen atom of another OPDI molecule. Rearrangement of a proton then leads to the formation of the azobenzene 8 as depicted in the Scheme 7.

It is worth mentioning that this reaction of ortho-amino substituted phenyl azides to give the corresponding azobenzene compounds as the major product is one of the few catalytic examples reported so far to synthesize azo compounds in high yields. Currently, only a few examples of catalytic synthesis of azobenzenes via azides are reported. These are summarized in Scheme 8. The iron based example of Groysman and co-workers is limited in the sense that only azides with bulky substituents like mesityl groups result in formation of azo compounds. With trifluoromethyl and methyl substituents dimers of the metal complex are obtained. The other example from Cundari and co-workers involves a nickel complex, but this system produces only stoichiometric amounts of azo compounds. An example involving a ruthenium metallo-radical system reported by Peters and co-workers proceeds via a free nitrene intermediate and works catalytically only for aryl azides with electron rich substituents like OMe and OEt. The other example by Cundari and co-workers involves a nickel complex, but this system produces only stoichiometric amounts of azo compounds.

Therefore, we decided to extend this reactivity of [Co II(TPP)]  for the synthesis of other substituted o-amino azobenzenes. The reason for this is two-fold. Firstly, this catalytic method allows for a mild chemical method to synthesise azobenzenes from azides that is tolerant to primary amines to access azobenzenes via azides. The sole by-product in this key step is dinitrogen. The only other way to synthesise azobenzenes from organic azides is by thermolysis which is a very unselective reaction in general and the explosive nature of the azides is often problematic in such high temperature reactions. Secondly, as ortho substituents are known to have dramatic effects in the photochemical properties of azobenzenes the functional group tolerance of the cobalt-catalysed method here gives access to a series of o-amino-substituted azobenzenes which have thus far received limited attention with regard to their photophysical properties or as switchable molecules in general. Furthermore, the primary amine substituent can provide an easy handle for further functionalisation. This presents new possibilities for the use of azobenzenes in a variety of applications including optical switches. Overall this method allows for synthesis of new azobenzenes starting from commercially available anilines in good to excellent isolated yields.

Azide 10 (2-azido-6-(tert-butyl)aniline) was synthesised according to the method described by Jiao and co-workers. In a first test reaction, 10 (0.3 mmol) and [Co II(TPP)] (5 mol%) were dissolved in freshly
distilled toluene, and the reaction mixture was heated at 90 °C for 18 hours (Scheme 9). During this time the reaction proceeded cleanly to give the corresponding azobenzene in near quantitative yield. The product was isolated by running a preparatory thin layer chromatography (prep-TLC) in pure dichloromethane (DCM). The isolated compound is a deep-red coloured solid and it could be crystallised to confirm the formation of the azobenzene product.

Scheme 9. [CoII(TPP)] catalysed reaction of 2-azido-6-(tert-butyl)aniline to give the corresponding trans-azobenzene product. (below) Crystal structure of the thus formed azobenzene.

With these results in hand we set out to optimise this reaction further. Unfortunately, lowering the catalyst loading and/or temperature was detrimental to the reaction. These results are summarised in Table 3. The reaction temperature plays a very important role in this reaction, as does the catalyst loading. Thus, while with 1 mol% catalyst loading in toluene at 90 °C the reaction proceeded, but the yields dropped (Entry 4). Lower temperatures didn’t lead to any azobenzene formation in benzene or in THF (Entry 2 and 5). Also, with no catalyst present the azide was unreactive and could be fully recovered from the reaction (Entry 6).

Table 3. Optimisation of [CoII(TPP)] catalysed synthesis of azobenzene from azide 10 as a test substrate.*

<table>
<thead>
<tr>
<th>ENTRY</th>
<th>SOLVENT</th>
<th>TEMPERATURE (°C)</th>
<th>CATALYST LOADING</th>
<th>YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>90</td>
<td>5 mol%</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>Benzene</td>
<td>60</td>
<td>5 mol%</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>60</td>
<td>5 mol%</td>
<td>----</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>90</td>
<td>1 mol%</td>
<td>60 %</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>60</td>
<td>5 mol%</td>
<td>----</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>90</td>
<td>No catalyst</td>
<td>----</td>
</tr>
</tbody>
</table>

* All reactions were carried out with 0.3 mmol of azide, [CoII(TPP)] in 4mL of Toluene. The reaction mixtures were bubbled with dinitrogen for 15 minutes prior to thermostating at mentioned temperature for 18h.

Thus with the optimised reaction conditions we proceeded towards synthesising various other substituted o-azidoanilines. These results are summarised in Table 4. The reaction proved to be quite versatile, and a variety of new substituted azobenzenes could be synthesised using the cobalt(II)-metalloradical catalysed azide-coupling methodology. Substrates with electron-donating substituents like in 10, 11, and 12 performed better in this reaction than those with electron-withdrawing groups.

For example, the phenyl substitution in 13 gave 60% of the product while bromine substitution in 14 gave a 48% yield. Also with the substrate containing CF₃ substituent 15 or fluorine substituent 16 the
reaction did not proceed at all. In these cases the unreacted azide was recovered pointing at the inherent inability of $[\text{Co}^{II}(\text{TPP})]$ to activate these azides in these reaction conditions.

**Table 4.** Substrate screening for $[\text{Co}^{II}(\text{TPP})]$ catalysed synthesis of azobenzenes from $\alpha$-amine substituted azides.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td>E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td>J</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All reactions were carried out with 0.3 mmol of azide, $[\text{Co}^{II}(\text{TPP})]$ (5 mol%) in 4mL of Toluene. The reaction mixtures were bubbled with dinitrogen for 15 minutes prior to thermostatting at mentioned temperature for 18h. Isolated yields are reported.

**Electronic properties of the synthesised $\alpha$-amino-substituted-azobenzenes**

UV-vis spectra of these compounds reveal that all synthesised products show a red shift of the $\pi-\pi^*$ and $n-\pi^*$ transitions compared to the parent azobenzene compound. Three such UV-vis spectra with electronically different substituents are shown in Figure 3 (left). The $\pi-\pi^*$ transitions are shifted to wavelengths above 450 nm and $\pi-\pi^*$ transitions between 300-350 nm are almost of equal intensity as the $n-\pi^*$ transitions. For azobenzenes with electron-donating substituents the $\pi-\pi^*$ transition is more red-shifted than of those with electron-withdrawing substituents (Figure 3, left). Time-dependent DFT (TD DFT) calculation also reasonably reproduced these experimentally observed transitions and relative intensities. For example, for the bromo-substituted compound P14 the $\pi-\pi^*$ transition value matched almost exactly ($\lambda= 323$ nm) while the $n-\pi^*$ transition was more red shifted in reality than predicted by TD DFT calculations ($\lambda= 430$ nm (TD DFT) and 463 nm (experimental)).
Figure 3. UV-vis spectra of o-amino azobenzenes P11 (R= i-Pr), P13 (R= Ph) and P14 (R= Br) with varying electronic substituents in solvent acetonitrile (left). TD-DFT calculated (blue) and experimental UV-vis spectra (red) of compound P14 (right).

H-bonding between the H atom of the NH$_2$ and the N atom of the azo group was also evident from the crystal structure of compound P10. The NH···N=N hydrogen bond was found to be 2.219 Å. Such H-bonding interactions are known to hinder the isomerisation pathway between the trans- and the cis-isomers of amino-azobenzenes (Figure 4). Also in 2-hydroxy-azobenzenes, intramolecular H-bonding between the azo-nitrogen atom and the hydroxyl group is reported to lock the molecule in the trans confirmation. The 2-hydroxyazobenzenes provide a versatile platform for the design of reversible photoacids to generate significant pH pulses and oscillations with monochromatic light. Similar behaviour can therefore be expected for the ortho-amino-azobenzenes reported here, but is beyond the scope of this current study.

Figure 4. The NH···N=N hydrogen bonds in P10 as revealed by X-ray diffraction studies.

DFT studies of the mechanism

To investigate the reaction barriers for the assumed facile HAT process from the ortho substituent (OH or NH$_2$) to the nitrene moiety, we investigated this process with DFT for both the OH and the NH$_2$ substituents.

Starting from the cobalt(III)-nitrene radical species the intramolecular HAT reaction of the cobalt(III)-nitrene radical of the azide 5 was found to proceed via a 6-membered transition state, further stabilized by a hydrogen bonding interaction between the transferred hydrogen atom and a pyrrole
nitr**ogen atom of the porphyrin (Figure 5). The barrier is very low (+1.0 kcal mol$^{-1}$), thus explaining the experimental observations. Overall, the HAT process is exergonic by $-10.8$ kcal mol$^{-1}$.

![Figure 5](image)

**Figure 5.** The DFT calculated barrier for HAT from the ortho hydroxyl group to the nitrene moiety. $\Delta G^{\circ}_{298 K}$ in kcal mol$^{-1}$, calculated at the BP86, def2-TZVP level with dispersion corrections.

We further evaluated the changes in spin density distribution (see Figure 6 and Table 5) during the HAT process (see also Figure 5). The spin density distribution of the transition state is very similar to that in the initial cobalt(III)-nitrene radical, but after the HAT barrier and transfer of the hydrogen atom from the $-\text{OH}$ group, most of the spin density moves back to cobalt (Figure 6 and Table 5). Simultaneously, the bond length of the Co-N bond elongates from 1.818 Å in the nitrene radical to 1.923 Å in the imide as depicted in Table 4.

![Figure 6](image)

**Figure 6.** Changes in the spin density distribution during the HAT process shown in Figure 5.
Table 5. Changes of the N, O and Co atom spin populations during the HAT shown in Figure 5

<table>
<thead>
<tr>
<th>Atom</th>
<th>2A</th>
<th>2B</th>
<th>2C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co</td>
<td>11.1%</td>
<td>8.5%</td>
<td>60.6%</td>
</tr>
<tr>
<td>N</td>
<td>39.6%</td>
<td>33.5%</td>
<td>16.1%</td>
</tr>
<tr>
<td>O</td>
<td>5.3%</td>
<td>10.0%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

Table 6. Relevant bond length (Å) changes during the HAT shown in Figure 5

<table>
<thead>
<tr>
<th>Structure</th>
<th>Co-N</th>
<th>N-C</th>
<th>C-C</th>
<th>C-O</th>
<th>N-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A</td>
<td>1.81769</td>
<td>1.32018</td>
<td>1.47138</td>
<td>1.34208</td>
<td>1.86203</td>
</tr>
<tr>
<td>2B</td>
<td>1.81731</td>
<td>1.31667</td>
<td>1.48868</td>
<td>1.30627</td>
<td>1.33591</td>
</tr>
<tr>
<td>2C</td>
<td>1.92289</td>
<td>1.32157</td>
<td>1.50424</td>
<td>1.24441</td>
<td>1.03461</td>
</tr>
</tbody>
</table>

The almost barrierless abstraction of a neighbouring hydrogen atom by the otherwise highly reactive cobalt(III)-nitrene radical thus prevents any intermolecular coupling reactions of the nitrene moiety with exogenous substrates. A similar process was also calculated for the NH$_2$ substituted azide, and once again the barrier for intramolecular HAT between the NH$_2$ group and the nitrene moiety was found to be low (see Figure 7). The free energy required to reach the transition state is only +9.1 kcal mol$^{-1}$ implying that this intramolecular process is fast, even at room temperature. The overall transformation is exergonic by $-3.1$ kcal mol$^{-1}$.

Figure 7. The DFT calculated barrier for HAT from the ortho amino group to the nitrene moiety. $\Delta G^{\circ}_{298K}$ in kcal mol$^{-1}$, calculated at the BP86, def2-TZVP level with dispersion corrections.

The computed changes in the spin density distributions are once again in line with the HAT process, and similar to those computed for HAT from the OH substituent. During the HAT process the spin population shifts from the nitrene radical in 3A to cobalt in 3C, and after the HAT process the spin
density is mostly concentrated at the cobalt atom. The bond distance analysis of the relevant bonds are shown in Table 8. Here once again, the Co-N bond in the final structure elongates from 1.8521 Å in the TS 3B to 1.9604 Å in the final structure 3C. Interestingly, the adduct remains coordinated to the cobalt complex, as is evident from the bond distances.

![Figure 8](image1.png)

*Figure 8. Changes in spin density distribution for HAT depicted in Figure 7.*

<table>
<thead>
<tr>
<th>Atom</th>
<th>3A</th>
<th>3B</th>
<th>3C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co</td>
<td>8%</td>
<td>11%</td>
<td>63%</td>
</tr>
<tr>
<td>N</td>
<td>36%</td>
<td>24%</td>
<td>10%</td>
</tr>
<tr>
<td>O</td>
<td>10%</td>
<td>20%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*Table 7. Changes of the N, O and Co atom spin populations during the HAT shown in Figure 7.*

<table>
<thead>
<tr>
<th>Structure</th>
<th>Co-N</th>
<th>N-C</th>
<th>C-C</th>
<th>C-N</th>
<th>N-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A</td>
<td>1.8411</td>
<td>1.3161</td>
<td>1.4835</td>
<td>1.3576</td>
<td>2.1848</td>
</tr>
<tr>
<td>3B</td>
<td>1.8521</td>
<td>1.3126</td>
<td>1.5060</td>
<td>1.3262</td>
<td>1.3213</td>
</tr>
<tr>
<td>3C</td>
<td>1.9604</td>
<td>1.3152</td>
<td>1.5022</td>
<td>1.4378</td>
<td>1.0340</td>
</tr>
</tbody>
</table>

*Table 8. Relevant bond length (Å) changes during the HAT process shown in Figure 7.*

While the barrier for the HAT process depicted in Figure 5 is low, it is not barrierless. Hence, to exclude the possibility of intermolecular coupling of the nitrone radical to phenyl acetylene (see Scheme 2b) being in competition with the intramolecular HAT process (Figure 7), we decided to make a direct computational comparison of the two processes. Attack of the porphyrin cobalt(III)-nitrone radical on the alkyne to form the γ-radical species C’ (see also Scheme 2b) was computed at the same DFT level (see Figure 9). The latter process is exergonic (−10.8 kcal mol⁻¹), but has a computed barrier of +13.4 kcal mol⁻¹. This barrier is almost 4 kcal mol⁻¹ higher than the barrier for intramolecular HAT (see Figure 7), and hence this process cannot efficiently compete with the intramolecular HAT reaction. Formation of the OPDI intermediate by HAT is expected under all reaction conditions.
Figure 9. DFT computed reaction barrier for attack of the cobalt(III) nitrene radical on phenyl acetylene leading to formation of a γ-alkyl radical intermediate. $\Delta G^\circ_{298K}$ in kcal mol$^{-1}$ computed at the BP86, def2-TZVP level with dispersion corrections.

The spin density distribution changes were once again calculated for the structures 4A, 4B and 4C. Interestingly, in contrast to the structures shown in Figures 6 and 8, the spin density in structure 4C is strongly delocalized over the carbon atoms of the γ-alkyl radical and the adjacent phenyl ring, with barely any spin density at the cobalt atom (see Figure 10).

Figure 10. Changes in spin density distributions during the HAT depicted in Figure 9.

Summary and conclusions

While trying to evaluate the effectiveness of ortho-substituted phenyl azides (OH/NH$_2$ substitution) in ring-closing reactions catalysed by [Co$^0$(Por)], we discovered that the hydrogen atom of the ortho-substituent is readily abstracted by the nitrene radical intermediate. This leads to formation of reactive intermediates like $\alpha$-quinone monoimines (OQMI; for OH) and $\alpha$-phenylenediimines (OPDI; for NH$_2$). These reactive compounds rapidly undergo follow-up reactions, thus preventing any direct (radical-type) coupling reactions of the nitrene radical intermediate with C=C or C≡C bonds of other substrates to give ring-compounds. The $\alpha$-quinone monoimines (Y = OH) easily dimerize and produce
phenoxizinone 3 under aerobic conditions. In the presence of 1-butoxyethene the α-quinone monoimine can also be trapped in an IEDDA reaction, producing benzoxazine 6. Formation of orthophenylenediimine (OPDI) from ortho-NH₂-phenylazide is also associated with H atom abstraction of the Co(III) nitrene radical from the NH₂ substituent in the ortho position. As a result, azo compound 8 is obtained. Attempts to react ortho substituted azides with other reaction partners by altering the reaction conditions were not successful. DFT computations are in agreement with the experiments; HAT from the ortho-YH substituent (Y = O or NH) to the nitrene moiety has a (very) low barrier in both cases. These transformations are summarised in Figure 11.

![Figure 11. Transformations observed in this study.](image)

On one hand, the observed facile HAT from the ortho-substituent (OH or NH₂) to the nitrene moiety prevents the initially anticipated radical-type coupling of the cobalt(III) nitrene radical intermediate to C=C and C≡C bonds of other substrates. On the other hand, it does provide a mild route to prepare highly reactive α-iminoquinonoids and α-phenylenediimines which can be employed in several follow up reactions. Having said that, the possibility of further reactivity of these intermediates occurring in the coordination sphere of the catalyst cannot yet be ruled out and might even be plausible based on the bond distance data that we obtained from the DFT optimized structures of these compounds after HAT. The other way in which this transformation is unique is that this is the only chemical pathway towards substituted α-amino-azobenzenes directly from azides. The cobalt(II) porphyrins catalysed pathway is, therefore, a functional group tolerant system to synthesise azobenzenes from azides which in turn are prepared in one step from commercially available amines. The synthesised azobenzenes are bathochromically shifted compared to the unsubstituted azobenzenes. Based on the crystal structure, the ortho-amine substituent is seen to participate in H-bonding interactions with the azo N atom. This can be expected to have consequences on the trans-cis isomerisation of these compounds but is currently beyond the scope of this study. At the same time, the amine functionality in these compounds can also act as a point of functionalisation for future applications.

Supporting information experimental and computational details

**General information**

All manipulations were performed under N₂ atmosphere by standard Schlenk techniques or in a glovebox. Methanol and acetonitrile were distilled under nitrogen from CaH₂. THF, toluene and pentane were distilled under nitrogen from Na wire.

All NMR spectra for these experiments were recorded at 293 K.
\(^1\)H NMR: A Bruker Avance 400 (400 MHz) or Mercury 300 (300 MHz) machine was used. These spectra were referenced internally to residual solvent resonance of CDCl\(_3\) (\(\delta = 7.26\) ppm) or DMSO-d\(_6\) (\(\delta = 2.50\)).

\(^{13}\)C\(^{1}(\text{H})\) NMR: A Bruker Avance 400 (101 MHz) or Bruker Avance 500 (126 MHz) machine was used. These spectra were referenced internally to residual solvent resonance of CDCl\(_3\) (\(\delta = 77.2\) ppm) or DMSO-d\(_6\) (\(\delta = 39.5\)).

**Synthetic details**

Details of the newly synthesized compounds and catalytic reactions are listed

- **Synthesis of compound 5**

  2-amino-5-nitrophenol (72.4 mmol) was added to aqueous HCl (6 M, 100 mL) at 0 °C in a three neck round bottom flask. To the latter a solution of NaNO\(_2\) (96.5 mmol) in 20 mL water was added dropwise. After stirring this mixture for 5 minutes NaN\(_3\) (96.5 mmol) that was predissolved in 60 mL of water was added dropwise and stirred for 45 minutes. The precipitate was extracted with chloroform and then washed with water. The organic layer was dried over MgSO\(_4\). On evaporation of the solvent a dark pink solid was obtained. This was purified further by flash chromatography over silica (EtOAc:Hex = 1:1) to give a dark pink solid in 80% yield.

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta 7.87\) (dd, \(J = 8.7, 2.5\) Hz, 1H), 7.80 (d, \(J = 2.5\) Hz, 1H), 7.19 (d, \(J = 8.7\) Hz, 1H), 5.65 (s, 1H).

\(^{13}\)C NMR (75 MHz, Chloroform-d) \(\delta 147.46, 145.53, 133.08, 118.25, 116.92, 111.66\)

- **Synthesis of [Co\(^{II}\)(TPP\(_{20}\))]**

  Per-fluorinated tetraphenylporphyrin TPPH\(_{20}\)F\(_{20}\) (0.5 mmol, 480 mg) was refluxed in acetic acid (300 mL) with an excess of CoCl\(_2\).6H\(_2\)O (2.6 mmol, 620 mg) and sodium acetate (15 mmol, 1.24 g) for one hour. The mixture was allowed to cool down and the solvent was evaporated until most solids precipitated out. The red solids thus obtained were washed with water, aqueous sodium bicarbonate and finally with a minimum amount of cold methanol. The solid was then dried in-vacuo to give [Co(TPP\(_{20}\))] (90% yield). UV-vis spectrum (THF), \(\lambda_{max}/nm: 408, 520, 558\).

- **Catalytic reaction of compound 1 to give product 3**

  In a flame dried Schlenk flask loaded with a stirrer 1 mmol of 1 was added followed by 0.05 mmol of [Co\(^{II}\)(TPP)]. The Schlenk flask was then evacuated and refilled with nitrogen (three times). Subsequently 4 mL of dry chlorobenzene was added, and the flask was thermostatted at 50 °C for 18 h. After evaporating the solvent the mixture was directly loaded on a silica gel column. The product was eluted with Hex:EtOAc (1:1) to give product 3 in 80% isolated yield.

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta 7.79 – 7.72\) (m, 1H), 7.45 (ddd, \(J = 8.3, 6.9, 1.6\) Hz, 1H), 7.42 – 7.32 (m, 2H), 6.48 (s, 1H), 6.42 (s, 1H), 5.11 (s, 2H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 180.00, 149.72, 142.25, 133.23, 129.59, 128.29, 125.05, 115.56, 114.24, 103.61\).

For the other reactions of compound 1 with other substrates, the same stoichiometry was used (also see the footnote in Table 1).

- **Catalytic reaction of compound 5 to give product 6**

  In a flame dried Schlenk flask loaded with a stirrer 1 mmol of 5 was added followed by 0.05 mmol of [Co\(^{II}\)(TPP\(_{20}\))]. The Schlenk flask was then evacuated and refilled with nitrogen (three times). Subsequently 4 mL of chlorobenzene was added, and the reaction was thermostatted at 50 °C for 18 h.
After evaporating the solvent, the mixture was directly loaded on a silica gel column. The product was eluted with Hex:EtOAc (1:1) to give product 6 in 80% yield.

\[ \text{H NMR (300 MHz, Chloroform-}d) \delta 7.82 - 7.65 (m, 2H), 6.53 (d, J = 8.7 Hz, 1H), 5.27 (t, J = 2.4 Hz, 1H), 4.57 (s, 1H), 3.85 (dt, J = 9.7, 6.7 Hz, 1H), 3.62 (dt, J = 9.7, 6.6 Hz, 1H), 3.58 - 3.46 (m, 1H), 3.51 - 3.38 (m, 1H), 1.54 (dq, J = 8.6, 6.8 Hz, 2H), 1.29 (dt, J = 14.9, 7.4 Hz, 3H), 0.86 (t, J = 7.4 Hz, 4H). \]

\[ \text{C NMR (75 MHz, CDCl}_3) \delta 140.14, 139.16, 138.81, 119.53, 113.78, 112.78, 93.85, 68.60, 44.42, 31.54, 19.25, 13.86. \]

For the other reactions of compound 5 with other substrates, the same stoichiometry was used (also see footnote in Table 2).

- **Catalytic reaction of 7 to give compound 8**

In a flame dried Schlenk flask loaded with a stirrer compound 7 (67 mg, 0.5 mmol) and [Co\textsuperscript{II}(TPP)] (17 mg, 0.025 mmol) was added and the flask was evacuated and backfilled with dinitrogen (three times). Subsequently 4 mL of PhCl was added, and the reaction mixture was thermostatted at 50 °C for 18 h. The reaction mixture was then subjected to preparative TLC (DCM as eluent) and a bright orange band was obtained which was analyzed and found to be compound 8.

\[ \text{H NMR (400 MHz, Chloroform-}d) \delta 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.23 – 7.06 (m, 1H), 6.93 – 6.63 (m, 2H), 5.48 (s, 2H). \]

\[ \text{C NMR (126 MHz, CDCl}_3) \delta 143.11, 137.73, 131.37, 124.29, 117.66, 117.04. \]

**Synthesis of the azides**

**Caution:** All azides were synthesized in 1 mmol scale reactions in separate Schlenk tubes. After the reactions were complete, they were combined together before work-up and column separation.

Compound 10 was synthesized according to the reported procedure of Jiao\textsuperscript{12} and the spectral data matched with those reported.

**Compound 11 (2-azido-6-iso-propylaniline)**

1 mmol of isopropylaniline was added to a flame dried Schlenk tube that contained 0.1 mmol CuBr. Then trimethyl silyl azide (2 mmol) was added followed by addition of 4 mL of freshly distilled acetonitrile. Finally 2 mmol of tetrabutyl hydroperoxide (TBHP) (5.0-6.0 M in decane) was added and the reaction was thermostatted at 30 °C for 6h. After this 15 mL of ethyl acetate was added the reaction mixture concentrated on a rotary evaporator. This was then directly loaded on to a silica column and eluted with pet ether: ethylacetate (60:1).

\[ \text{H NMR (400 MHz, Chloroform-}d) \delta 7.04 – 6.87 (m, 2H), 6.81 (t, J = 7.8 Hz, 1H), 3.84 (s, 3H), 2.98 – 2.66 (m, 1H), 1.25 (d, J = 6.8 Hz, 6H). \]

\[ \text{C NMR (75 MHz, CDCl}_3) \delta 135.71, 134.34, 125.79, 122.40, 119.26, 116.19, 28.42, 22.69. \]

**Compound 12 (2-azido-6-methylaniline)**

1 mmol of o-toluidine was added to a flame dried Schlenk that contained 0.10 mmol of CuBr. Then trimethyl silyl azide (2 mmol) was added followed by addition of 4mL of freshly distilled acetonitrile. Finally 2 mmol of TBHP (5.0-6.0 M in decane) was added and the reaction thermostatted at 30 °C for 6h. After this 15mL of ethyl acetate was added the reaction mixture concentrated on a rotary evaporator. This was then directly loaded on to a silica column and eluted with pet ether: ethylacetate (60:1).
H NMR (300 MHz, Chloroform-d) δ 6.94 (d, J = 7.9, 1H), 6.87 (d, J = 7.4 Hz, 1H), 6.73 (t, J = 7.7 Hz, 1H), 3.77 (s, 2H), 2.17 (s, 3H).

13C NMR (75 MHz, CDCl3) δ 136.31, 126.74, 124.83, 123.46, 118.36, 115.96, 17.35.

Compound 13 (3-azido-[1,1'-biphenyl]-2-amine)
2-Phenylaniline (1 mmol) was added to a flame dried Schlenk tube that contained 0.10 mmol of CuBr. Then TMSN3 (2 mmol) was added followed by addition of 4 mL of freshly distilled acetonitrile. Finally 2 mmol of TBHP (5.0-6.0 M in decane) was added and the reaction was heated at 30°C for 6 hours. Then 15 mL of ethyl acetate was added, reaction mixture evaporated. It was then directly loaded on silica (Petroleum ether: ethylacetate (60:10)) to give the desired product in 60% isolated yield. Analytical data matched literature.\(^\text{12}\)

\(^{1}\)H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.34 (m, 5H), 7.05 (dd, J = 7.8, 1.5 Hz, 1H), 6.94 (dd, J = 7.6, 1.5 Hz, 1H), 6.85 (t, J = 7.7 Hz, 1H), 3.94 (s, 2H).

\(^{13}\)C NMR (101 MHz, Chloroform-d) δ 136.51, 128.72, 125.97, 118.89, 117.31, 109.55.

HRMS calcd. 211.96976 for C6H5BrN4 found 211.96964.

\(9\)-\((E)\)-2,2'-\((diazene-1,2-diyl)dianiline\)
Using the general procedure (Prep-TLC using pure DCM), 80% isolated yield. Analytical data matched literature.\(^\text{14}\)

\(^{1}\)H NMR (400 MHz, Chloroform-d) δ 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.23 – 7.06 (m, 1H), 6.93 – 6.63 (m, 2H), 5.48 (s, 2H).

\(^{13}\)C NMR (126 MHz, CDCl3) δ 143.11, 137.73, 131.37, 124.29, 117.66, 117.04.
**P10- (E)-6,6''-(diazene-1,2-diyl)bis(2-(tert-butyl)aniline)**

Using the general procedure (Prep-TLC using DCM), 98% isolated yield.

$^1$H NMR (300 MHz, Chloroform-$d$) $\delta$ 7.50 (dd, $J = 8.1$, 1.4 Hz, 1H), 7.40 – 7.24 (d, 7.8 1H), 6.70 (t, $J = 7.9$ Hz, 1H), 1.49 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 145.00, 140.29, 135.73, 129.74, 117.76, 115.97, 35.10, 30.25.

HRMS calcd 324.23140 for C$_{20}$H$_{28}$N$_4$ found: 324.23120.

**P11- (E)-6,6''-(diazene-1,2-diyl)bis(2-isopropylaniline)**

Using the general procedure (Prep-TLC using DCM), 98% isolated yield.

$^1$H NMR (300 MHz, Chloroform-$d$) $\delta$ 7.52 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.19 (dd, $J = 7.8$, 1.4 Hz, 1H), 6.77 (t, $J = 7.8$ Hz, 1H), 5.24 (s, 2H), 3.10 – 2.83 (m, 1H), 1.32 (d, $J = 6.8$ Hz, 6H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.53, 138.65, 134.21, 117.61, 117.30, 27.67, 22.34.

HRMS calcd. 296.20005 for C$_{18}$H$_{24}$N$_4$, found 296.20050

**P13- (E)-3,3''-(diazene-1,2-diyl)bis([(1,1'-biphenyl)-2-amine])**

Using the general procedure (Prep-TLC using DCM: hexane= 1:1), 60% isolated yield.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.70 (dd, $J = 8.1$, 1.6 Hz, 1H), 7.60 – 7.48 (m, 5H), 7.19 (dd, $J = 7.2$, 1.6 Hz, 1H), 6.86 (t, $J = 7.7$ Hz, 1H), 5.55 (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 143.00, 141.4, 135.73, 130.64, 115.72, 114.87.

HRMS calcd. 364.16880 for C$_{24}$H$_{20}$N$_4$ found 364.16870

**P14- (E)-6,6''-(diazene-1,2-diyl)bis(2-bromoaniline)**

Using the general procedure (Prep-TLC using DCM: hexane= 1:1), 48% isolated yield.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.64 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.48 (dd, $J = 7.8$, 1.5 Hz, 1H), 6.70 (t, $J = 7.9$ Hz, 1H), 6.09 (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 141.75, 138.80, 138.09, 132.64, 129.45, 129.35, 129.17, 129.11, 127.72, 121.42, 117.32.

HRMS calcd. 367.92722 for C$_{12}$H$_{10}$Br$_2$N$_4$ found 367.92762

**Computational details**

Geometry optimizations were carried out with the Turbomole program package$^{15}$ coupled to the PQS Baker optimizer$^{16}$ via the BOpt package$^{17}$ at the DFT level using the b3-lyp functional$^{18}$ and def(2)-TZVP basis set$^{19}$ for the geometry optimizations of all stationary points. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by numerically calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated.
Table 7. SCF energies, enthalpies and free energies of the compounds involved in the HAT step described in Figure 3 in the main text in Hartree (BP86, def2-TZVP, disp3).

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Table 8. SCF energies, enthalpies and free energies of the compounds involved in the HAT step described in Figure 5 in the main text in Hartree (BP86, def2-TZVP, disp3).

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Table 9. SCF energies, enthalpies and free energies of the compounds involved in the HAT step described in Figure 7 in the main text in Hartree (BP86, def2-TZVP, disp3).

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Acknowledgements

We thank Dr. W.I Dzik (HIMS, UvA) for assistance with X-ray Diffraction studies and Ed Zuidinga (HIMS, UvA) for mass measurements.
References


(16) (a) PQS version 2.4, 2001, Parallel Quantum Solutions, Fayetteville, Arkansas, USA (the Baker optimizer is available separately from PQS upon request); (b) Baker, J. J. Comput. Chem. 1986, 7, 385.


Chapter 5

Synthesis, characterisation and application of anionic \([\text{Co}^{II}(\text{Cor})]\)^− corrole complexes in ring-closing C–H amination of an aliphatic azide.*

*We thank Paul Geuijen for his valuable contributions to this chapter.
Introduction

N-containing ring-compounds are one of the most commonly found heterocycles in natural products and pharmaceuticals. Synthesising such heterocycles via direct C–H amination, i.e. C–H activation combined with a C–N bond forming ring-closing step, is time and atom-efficient and hence an attractive way to make such compounds. One such strategy of doing so is via reactive metallo-nitrene intermediates. In this method a metal catalyst activates a nitrene precursor which leads to the formation of a metallo-nitrene intermediate. Depending on its reactivity, this metallo-nitrene intermediate can insert into challenging bonds, such as thermodynamically and kinetically stable C–H bonds. Organic azides are particularly attractive nitrene precursors in this perspective, as they are easy to synthesise and generate only N₂ as a waste product in the amination step. However, only a handful of examples exist where intramolecular C–H amination reactions using organic azides to form N-heterocyclic compounds have been reported. A particular system that has shown successful activity in this type of reactivity is the [Co¹(Por)] catalyst, capable of a variety of nitrene transfer reactions from azides. In addition to the classical inter- and intramolecular aziridination reactions, also intramolecular benzylic/allylic/benzallylic C–H amination reactions have been reported. Mechanistic studies using DFT reveals a step-wise mechanism involving an experimentally well-characterised CoIII-nitrene radical intermediate. DFT calculations further suggest that the rate determining step of these catalytic reactions is the activation of the azide at the metal centre, which has a substantial barrier. Consequently, in many of these reactions high temperatures are required. This is most evident in reactions involving unactivated alkyl azides (azide moiety positioned directly next to a CH₂ group), which require heating to ~100 °C to activate the azide using [Co¹(Por)] catalysts. Notably, in the azide activation step the metal centre undergoes an oxidation from cobalt(II) to cobalt(III). As such, we expected that application of ligands imposing a high electron density at cobalt could be beneficial, lowering the barrier of the rate limiting step, thus leading to faster catalytic reactions. Some earlier studies seem to confirm this hypothesis in an indirect manner, but the beneficial effect of electron-donating ligands on the rate of these reactions is evident from recent studies performed in our group. In a direct comparative study, the electron-rich [Co⁶(TMP)] was shown to outperform [Co⁶(TPP)] in the intramolecular C–H amination of aliphatic azides (Scheme 1). As such, we hypothesised that a ligand scaffold that retains the square planar geometry of a porphyrin but is more electron-rich could well be beneficial for the activation of aliphatic azides.

Scheme 1. [Co¹(Por)]-catalysed intramolecular C–H amination of aliphatic azides.

Hence, we turned our attention to the corrole macrocycle. Corroles are tetrapyrrolic molecules, maintaining the skeletal structure of corrin. The difference with porphyrins is that in corroles one of the methine bridges (which links the pyrrole units together) has been replaced with a direct pyrrole–pyrrole bond (Figure 1). Thus, corroles have a trianionic charge when bound to transition metals and there is one less position for a meso-substituent. As a consequence, corroles have a slightly smaller metal-binding pocket, allowing for a ‘tighter grip’ on the metal. In addition, there is one less carbon in...
the aromatic ring of corroles, which next to the trianionic charge of a corrole ligand further increases the electron density of corrole complexes relative to porphyrin complexes. As a result, corroles are expected to stabilize transition metals in higher oxidation states, even better so than porphyrins. Hence, this feature is expected to have a positive influence on the azide activation step, which occurs at the metal ion of the catalyst, with cobalt undergoing one-electron oxidation. Even though corrole complexes of cobalt have been extensively studied in oxidation and reduction reactions, mono-anionic cobalt(III)-corrole complexes have so far never been employed as metalloradical catalysts for nitrene- or carbene-insertion into C–H bonds. This provides an opportunity to study the metalloradical reactivity of mono-anionic \[\text{[Co}^{\text{III}}\text{(Cor)]}^-\] complexes in mediating catalytic radical-type reactions in general, which go beyond the one particular nitrene-transfer reaction described in this chapter.

\[\text{Figure 1. Various tetradentate macrocycles. From left to right: Chlorin - Porphyrin - Corrole - Corrin.}\]

### Results and discussion

To test the feasibility of corroles as ligands in cobalt-catalysed nitrene transfer reactions, we set out to synthesise three corrole ligands with electronically different substituents. These are depicted in Figure 2.

\[\text{Figure 2. Three [Co}^{\text{III}}\text{(Cor)] with varying substituents applied in the ring-closing C–H amination of alkyl azides.}\]

In their mono-reduced (mono-anionic) cobalt(III) form, all of these complexes should be much more electron rich than the corresponding cobalt(III) porphyrin complexes. Additionally, the electronic properties within the series of corrole complexes differs. The dibromo-substituted \[\text{[Co}^{\text{III}}\text{(Br}_2\text{Cor)](PPh}_3\text{)}\] should contain the least electron-rich corrole, the mesityl-substituted \[\text{[Co}^{\text{III}}\text{(Mes}_2\text{Cor)](PPh}_3\text{)}\] should contain the most electron-rich corrole, and the (unsubstituted) \[\text{[Co}^{\text{III}}\text{(Ph}_2\text{Cor)](PPh}_3\text{)}\] should have electronic properties in-between those of \[\text{[Co}^{\text{III}}\text{(Br}_2\text{Cor)](PPh}_3\text{)}\] and \[\text{[Co}^{\text{III}}\text{(Mes}_2\text{Cor)](PPh}_3\text{)}\]. Reduction of these complexes using a suitable chemical reductant should produce the corresponding mono-anionic metalloradical \[\text{[Co}^{\text{II}}\text{(Cor)]}^-\] complexes. For this purpose, in
order to find the right reducing agent, we first studied the electro-chemical properties of the 
$[\text{Co}^{\text{III}}(\text{Cor})(P\text{Ph}_3)]$ complexes.

**Synthesis of the $[\text{Co}^{\text{III}}(\text{Cor})(P\text{Ph}_3)]$ complexes**

The three corroles were synthesised via the dipyrromethane route, following the procedures reported 
by Gryko and co-workers$^{11}$ (with some modifications). This is schematically represented in Scheme 2. 
Details of the synthetic procedures are described in the experimental section.

![Scheme 2. Generalised scheme for the synthesis of the corrole complexes $[\text{Co}^{\text{III}}(\text{Br}_2\text{Cor})(P\text{Ph}_3)]$, $[\text{Co}^{\text{III}}\text{Ph}_2(\text{Cor})(P\text{Ph}_3)]$ and $[\text{Co}^{\text{III}}\text{Mes}_2(\text{Cor})(P\text{Ph}_3)]$.](image)

While the crystal structure of $[\text{Co}^{\text{III}}(\text{Ph}_2\text{Cor})(P\text{Ph}_3)]$ is reported, the X-ray structural data of 
$[\text{Co}^{\text{III}}(\text{Br}_2\text{Cor})(P\text{Ph}_3)]$ and $[\text{Co}^{\text{III}}(\text{Mes}_2\text{Cor})(P\text{Ph}_3)]$ were previously unknown. We were able to grow 
crystals of these complexes. The molecular structure of $[\text{Co}^{\text{III}}(\text{Br}_2\text{Cor})(P\text{Ph}_3)]$ and some relevant bond 
distances derived from these measurements are shown in Figure 3. As is evident from the structure, 
the Co–N(corrole) bonds are significantly shorter than the Co–N(porphyrin) bonds (1.867 and 1.880 
in $[\text{Co}^{\text{III}}(\text{Br}_2\text{Cor})(P\text{Ph}_3)]$ compared to 1.949 in $[\text{Co}^{\text{II}}(\text{TPP})]$).$^{12}$ This is to be expected, both based on the 
trianionic charge and the smaller ring size of the corrole macrocycle. For the $[\text{Co}^{\text{III}}(\text{Mes}_2\text{Cor})(P\text{Ph}_3)]$ 
complex the atom connectivity could be determined, confirming the structure of the formed complex. 
However, unfortunately the X-ray data were of insufficient quality to derive reliable information about 
the bond lengths of this complex. This structure is shown in the supporting information.
Redox chemistry of the [CoIII(Cor)(PPh3)] complexes

Cyclic voltammetry (CV) experiments were used to study the redox behaviour of the three above described [CoIII(Cor)(PPh3)] complexes. For the application of these complexes as catalysts in nitrene transfer reactions we were particularly interested in the first reduction- and corresponding re-oxidation waves of these complexes. The first (chemically irreversible) reduction peak potential is important to choose a suitable chemical reductant, reducing the parent [CoIII(Cor)(PPh3)] complexes to corresponding mono-anionic complexes without over-reduction. The corresponding re-oxidation peak potential gives direct information about the reductive power of the mono-anionic [Co^(I)(Cor)]⁻ complexes.

The [Co^(II)(Cor)(PPh3)] complexes show the expected redox behaviour, similar to that observed previously for related complexes. The first one-electron reduction process is electrochemically irreversible for all these complexes, at least at the applied scan rate of 100 mV/s of the CV measurements (Figure 4 A, B and C). The first reduction wave is coupled to an anodically shifted re-oxidation wave for all complexes, in an overall chemically reversible electrochemical-chemical-electrochemical-chemical (ECEC) process (Figure 4D). A second reduction peak at more negative potentials is also observed for all these complexes, which is fully reversible in all cases (see Figure 9, supporting information). In accordance with the electronic nature of the substituents, the peak potential of the first reduction process shifts to more negative potentials upon increasing the electron-donating properties of the substituents. This is summarised in Figure 4D ([Co^(III)(Mes₂Cor)(PPh3)] < [Co^(III)(Ph₂Cor)(PPh3)] < [Co^(III)(Br₂Cor)(PPh3)]). Based on these peak potentials, either cobaltocene (CoCp₂: E₁/₂ ~ −1.3 V vs Fc/Fc⁺) or decamethylcobaltocene (CoCp*₂: E₁/₂ ~ −1.9 V vs Fc/Fc⁺) can be used as a suitable reductant for these complexes.

The ECEC sequence of events, explaining the observed behaviour of the first reduction process with an anodically shifted re-oxidation wave, is schematically represented in Figure 4D. One-electron reduction of the parent [Co^(III)(Cor)(PPh3)] complex at the metal centre leads to the formation of an anionic [Co^(I)(Cor)(PPh3)]⁻ complex, followed by PPh₃ dissociation producing [Co^(I)(Cor)]⁻. Oxidation of [Co^(I)(Cor)]⁻ to [Co^(III)(Cor)] occurs at a higher redox potential than
reduction of $[\text{Co}^{III}(\text{Cor})(\text{PPh}_3)]$ to $[\text{Co}^{III}(\text{Cor})(\text{PPh}_3)]^-$, and is followed by re-coordination of PPh$_3$ to regenerate the parent $[\text{Co}^{III}(\text{Cor})(\text{PPh}_3)]$ complex.

**Figure 4.** (A) CV of $[\text{Co}^{III}(\text{Br}_2\text{Cor})(\text{PPh}_3)]$, (B) CV of $[\text{Co}^{III}(\text{Ph}_2\text{Cor})(\text{PPh}_3)]$, (C) CV of $[\text{Co}^{III}(\text{Mes}_2\text{Cor})(\text{PPh}_3)]$ in THF referenced against Fc/Fc$^+$ (using Fc* (bis(pentamethylcyclopentadienyl)iron) as internal standard). (D) Schematic representation of different species that are proposed to be present during the reduction and re-oxidation events during the CV scan. (E) Peak currents for the first reduction and the corresponding re-oxidation wave of the three complexes referenced against the Fc/Fc$^+$ couple (using Fc* as internal standard).

EPR spectroscopic and UV-Vis spectro-electrochemical measurements (SEC) were performed to confirm the ECEC mechanism shown in Figure 4D. The SEC measurements were performed by coupling coulometric CV experiments to UV-vis measurements in an optically transparent thin layer electrochemical (OTTLE) cell. These experiments also allowed us to determine if any decomposition
occurs on the couloumetric timescale or if any long-lived intermediates are formed during the reduction/re-oxidation events. Upon one-electron reduction, in all cases the absorbance of the soret bands undergo a bathochromic shift with the absorbance at ~380 nm decreasing in intensity with a new absorbance arising around at ~420 nm. In addition, the absorbance of the Q bands between 550 and 700 nm show an increase in intensity, probably due to a decreased difference in energy between the π-π* orbitals of the reduced complex. The rather small red-shifts observed are strongly suggestive of PPh₃ dissociation upon reduction. A representative example of the spectral changes observed upon reduction of [CoIII(Ph₂Cor)(PPh₃)] is shown in Figure 5. For similar spectra of the two other complexes, see Figure 10 (supporting information). When the complexes are allowed to re-oxidise (at the anodically shifted redox potential), the original [CoIII(Ph₂Cor)(PPh₃)] complex is cleanly regenerated from the [CoII(Ph₂Cor)]⁻ complex, as evidenced by the UV-vis measurements. Multiple and quite sharp isosbestic points are indicative of clean interconversion of the reduced and oxidized species, without going through long-lived intermediates.

![Figure 5. UV-vis spectra obtained in the spectro-electrochemical experiments of [CoIII(Ph₂Cor)(PPh₃)].](image)

Having ascertained the reduction peak potentials of these complexes, as well as clean conversion to the reduced species, we also performed X-band electron paramagnetic resonance (EPR) studies on these complexes. Using a chemical reductant (bis(cyclopentadienyl)cobalt(II) (CoCp₂) for [CoIII(Br₂Cor)(PPh₃)] and [CoIII(Ph₂Cor)(PPh₃)] and bis(pentamethycyclopentadienyl)cobalt(II) (CoCp*₂) for [CoIII(Mes₂Cor)(PPh₃)]), all of these complexes could be reduced to give EPR spectra (anisotropic spectra, measured at 20 K in a MeTHF glass) characteristic for formation of cobalt(II) metalloradicals. The EPR spectra of the [CoIII(Mes₂Cor)]⁻ complex is shown in Figure 6. For EPR spectra of the other complexes, see Figure 11 (supporting information). The EPR spectrum shown in figure 6 reveals clear cobalt hyperfine couplings along the two higher g-values (g₁₁ = 3.56, A_{Co1} = 740 MHz; g₂₂ = 2.22, A_{Co2} = 260 MHz) and a sharper featureless line at the lowest g-value (g₃₃ = 1.85). No (resolved) phosphorus hyperfine couplings are visible along any of these directions in the anisotropic spectrum, in agreement with PPh₃ dissociation upon one-electron reduction of [CoIII(Mes₂Cor)(PPh₃)].

DFT optimisation of the anionic [CoII(Cor)]⁻ complex clearly showed that the singly occupied molecular orbital (SOMO) is the dₓ orbital, thereby leading to different spin-orbit interactions than in the related [CoII(Por)] complexes. This is in agreement with the EPR spectra being distinctly different from those of the porphyrin complexes.
Application of anionic $[\text{Co}^{\text{II}}(\text{Cor})]^{-}$ complexes in ring-closing C-H amination of (4-azidobutyl)benzene

With access to the three mono-anionic $[\text{Co}^{\text{II}}(\text{Cor})]^{-}$ complexes, we decided to test the activity and selectivity of these complexes in the direct ring-closing reaction of (4-azidobutyl)benzene to give the heterocyclic pyrrolidine product. This is a reaction that was reported to proceed with $[\text{Co}^{\text{II}}(\text{TMP})]$, selectively producing the Boc-protected pyrrolidine product. The high barrier and slow reactions associated with the cobalt-porphyrin catalysed process prompted us to test the more electron-rich mono-anionic cobalt(II)-corrole complexes as catalysts for this reaction. We argued that a more facile electron transfer from cobalt(II) to the nitrene-moiety generated at cobalt upon N$_2$-loss from the coordinated aliphatic azide in the transition state for nitrene-radical formation (see Chapter 2) might lead to a lower barrier of the rate limiting azide activation step.

Using the same reaction conditions as reported for the $[\text{Co}^{\text{II}}(\text{TMP})]$ system we performed this reaction with the $[\text{Co}^{\text{II}}(\text{Cor})]^{-}$ complexes described above. These were generated from the corresponding $[\text{Co}^{\text{III}}(\text{Cor})(\text{PPh}_3)]$ complexes by one-electron reduction with a suitable cobaltocene reducing agent prior to catalysis. We followed the appearance of the product and disappearance of the azide substrate in time, using NMR integrations against an internal standard. The results are summarised in Figure 7.
As is evident from these reaction profiles (Figure 7), in each case the substrate azide was fully consumed and pyrrolidine product was formed (Table 1, entry 1-3). In absence of the reductant no reaction took place. This proves that it is only the reduced complex that is able to activate the azide in this reaction and not the parent complex itself (Table 1, entry 5). Also, in the absence of the Boc₂O no reaction took place. The same was observed in the cobalt-porphyrin catalysed reactions, which was ascribed to product inhibition due to binding of the pyrrolidine product to cobalt(II) in absence of Boc₂O, while the Boc-protected pyrrolidine does not inhibit the reaction. Product inhibition in absence of Boc₂O, therefore, also seems to be an issue in the cobalt(II)-corrole catalysed reactions (Table 1, entry 4). For all three catalysts, the reaction has an initiation time of about 2 hours before the azide starts to get consumed (Figure 7). This initiation time can be attributed to the poor solubility of the charged [Co^{II}(Cor)]⁻(cobaltocenium⁺) complexes in toluene-d₈ solvent used in these reactions. Upon reduction of the neutral [Co^{III}(Cor)(PPh₃)] complexes to the anionic [Co^{II}(Cor)]⁻ complexes the solubility decreases drastically. This is also visually observable from the NMR tubes in which the reactions are conducted, revealing almost quantitative precipitation of the [Co^{II}(Cor)]⁻(cobaltocenium⁺) salts (Figure 13D, supporting information). After heating to 100 °C for about two hours, the complex (or a part of it) slowly gets solubilised, so it can take part in the reaction. This process is likely assisted by a slow reaction between the azide and the precipitated [Co^{III}(Cor)]⁻(cobaltocenium⁺) salts. Once the reaction starts, all azide is consumed within about six hours in each case. This is a remarkable improvement in reaction time (about 2.5 folds) as compared to the benchmark [Co^{II}(TMP)] system, which takes about 16 hours before all the azide is consumed. This proves that the more electron-rich mono-anionic [Co^{II}(Cor)]⁻ complexes are indeed faster catalysts than the corresponding neutral porphyrin complexes [Co^{II}(Por)].
As far as the relative performances of the three \([\text{Co}^\text{II}(\text{Cor})]^-\) catalysts are concerned, the \([\text{Co}^\text{II}(\text{Ph}_2\text{Cor})]^-\) catalyst consistently proved to give the highest yields of the desired pyrrolidine product. The \([\text{Co}^\text{II}(\text{Br}_2\text{Cor})]^-\) catalyst gave lower yields, and the lowest yields were obtained with the \([\text{Co}^\text{II}(\text{Mes}_2\text{Cor})]^-\) catalyst. This behaviour is counterintuitive, as we expected best reaction results for the more electron-rich \([\text{Co}^\text{II}(\text{Mes}_2\text{Cor})]^-\) catalyst and the poorest for the least-electron rich \([\text{Co}^\text{II}(\text{Br}_2\text{Cor})]^-\) catalyst. However, it should be noted that these yields do no correlate directly to the

Notably, even though all azide substrate is consumed, the yield of the pyrrolidine product is not proportional to the consumption of the azide (based on \(^1\text{H} N\text{MR}\)). The highest yield of the pyrrolidine product (78%) was found when using the \([\text{Co}^\text{II}(\text{Ph}_2\text{Cor})]^-\) catalyst. This means that apart from the pyrrolidine product, other side products are produced as well. This must be a complex mixture of several (non-characterised) side-products, which only give rise to small, poorly recognisable peaks in the crude \(^1\text{H} N\text{MR}\) spectra of these reaction mixtures. So, while the activity of the system is increased, its selectivity is somewhat compromised. Formation of the linear \(N\)-Boc protected amine product (\(\text{Ph(CH}_2)_3\text{NHBoc}\); Scheme 3) provides only a partial explanation for the unaccounted mass-balance. While \(\text{Ph(CH}_2)_3\text{NHBoc}\) is a known by-product in related reactions,\(^4\) it is only formed in minor amounts in the reactions studied here (see Table 1). A Staudinger reaction between \(\text{PP}_3\) liberated from the catalyst (producing the iminophosphorane) can account for a maximum loss of 5 mol% of the starting material (Scheme 4, supporting information). Hence, other (poorly defined) side products must be formed in these reactions.

![Figure 7. Reaction profiles for the ring-closing C–H amination shown in Scheme 3. Top left: \([\text{Co}^\text{II}(\text{Br}_2\text{Cor})]^-\); top right: \([\text{Co}^\text{II}(\text{Ph}_2\text{Cor})]^-\) and bottom left: \([\text{Co}^\text{II}(\text{Mes}_2\text{Cor})]^-\). Bottom right: overlay of the pyrrolidine product formation (red: \([\text{Co}^\text{II}(\text{Br}_2\text{Cor})]^-\); blue: \([\text{Co}^\text{II}(\text{Ph}_2\text{Cor})]^-\); black: \([\text{Co}^\text{II}(\text{Mes}_2\text{Cor})]^-\)).](image-url)
relative activities, as the rates (max. slopes in Figure 7, bottom right [Co\(^{II}\)(Br\(_2\)Cor)]\(^{-}\) > [Co\(^{II}\)(Ph\(_2\)Cor)]\(^{-}\) > Co\(^{II}\)(Mes\(_2\)Cor)]\(^{-}\) not only do not differ much, but these values are also likely to be influenced by the (slow) rate of solubilisation of the salts. It is further of importance to note that the [Co\(^{II}\)(Mes\(_2\)Cor)]\(^{-}\) and [Co\(^{II}\)(Br\(_2\)Cor)]\(^{-}\) catalysts are more sterically hindered around cobalt when compared to [Co\(^{II}\)(Ph\(_2\)Cor)]\(^{-}\) catalyst. As such, favourable electronic effects of electron-donating side-groups at the corrole ring of these catalysts could be (partly) counterbalanced by unfavourable steric interactions.

Table 1. Performance of different [Co\(^{II}\)(Cor)]\(^{-}\) catalysts in the intramolecular ring closing C-H amination of (4-azidobutyl)benzene to give the corresponding Boc-protected pyrrolidine.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Remarks</th>
<th>Pyrrolidine({\dagger})</th>
<th>Linear product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Co(^{II})(Br(_2)Cor)](^{-})</td>
<td>Toluene</td>
<td></td>
<td>73%</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>[Co(^{II})(Ph(_2)Cor)](^{-})</td>
<td>Toluene</td>
<td></td>
<td>78%</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>[Co(^{II})(Mes(_2)Cor)](^{-})</td>
<td>Toluene</td>
<td></td>
<td>64%</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>Any [Co(^{II})(Cor)](^{-})</td>
<td>Toluene</td>
<td>No Boc(_2)O</td>
<td>Not observed</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>Any [Co(^{II})(Cor)](^{-})</td>
<td>Toluene</td>
<td>No reductant</td>
<td>Not observed</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>Any [Co(^{II})(Cor)](^{-})</td>
<td>THF</td>
<td></td>
<td>Not observed</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>[Co(^{II})Ph(_2)(Cor)](^{-})</td>
<td>Acetonitrile/Toluene</td>
<td></td>
<td>43%</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>[Co(^{II})Ph(_2)(Cor)](^{-})</td>
<td>DCM/Toluene</td>
<td></td>
<td>31%</td>
<td>15%</td>
</tr>
<tr>
<td>9</td>
<td>[Co(^{II})Ph(_2)(Cor)](^{-})</td>
<td>THF/Toluene</td>
<td></td>
<td>11%</td>
<td>---</td>
</tr>
<tr>
<td>10</td>
<td>[Co(^{II})Ph(_2)(Cor)](^{-})</td>
<td>Toluene</td>
<td>NBu(_4)PF(_6) added</td>
<td>29%</td>
<td>---</td>
</tr>
</tbody>
</table>

* Reactions were performed in 0.3 mmol scale in dry toluene at 100°C with 5 mol% precatalyst, 5 mol% reducing agent, and 1.1 eq di-tert-butyldicarbonate (Boc\(_2\)O) for 16h. \({\dagger}\)H-NMR yields are reported using mesitylene as an internal standard.

Next we tried to increase the efficiency of this reaction by attempting to increase the solubility of the in-situ reduced catalyst. In order to see if the solubility of the reduced catalyst could be increased by changing the polarity of the reaction mixture, we tried a few other solvents in this reaction. These results are summarised in Table 1 (entry 6-10). Unfortunately, when changing the solvent to more polar solvents like tetrahydrofuran (THF), no formation of product was observed, and upon using solvent mixtures like acetonitrile/toluene, DCM/toluene or THF/toluene the yield of the pyrrolidine product dropped drastically. In the DCM/toluene mixture 15% of the unwanted linear product was also observed. Also with N-butyl ammonium phosphate as a phase transfer catalyst (PTC) the yield of the pyrrolidine dropped to 29%. Hence it seems these reactions only work well in apolar aromatic solvents like toluene and benzene, at least for the [Co\(^{II}\)(Cor)]\(^{-}\) catalysts studied here.

DFT calculated mechanism

Next, to confirm if indeed the azide activation step had a lower barrier for the [Co\(^{II}\)(Cor)]\(^{-}\) systems, we computed the energy changes of this step computationally, using DFT methods. The computations were performed at the BP86 and def2-TZVP level using the non-functionalised [Co\(^{II}\)(Cor)]\(^{-}\) system. The choice for this computational method is based on previous realistic mechanistic pathways calculated by us on such systems.\(^{7-9}\) We further incorporated Grimme’s dispersion corrections (DFT-D3) for these systems. For the substrate, we included a full model for the azide substrate (4-azidobutyl)benzene. The energies are depicted in Figure 8 (left). Indeed the transition state barrier (TS_N\(_2\)-loss) for this step
is dramatically lower than that of the previously reported neutral \([\text{Co}^{ii}(\text{Por})]\) complexes reported by us earlier \(^9\) \(\Delta G^\ddagger = +13.9 \text{ kcal mol}^{-1}\) for \([\text{Co}^{ii}(\text{Cor})]^-\) versus \(\Delta G^\ddagger = +21.3 \text{ kcal mol}^{-1}\) for \([\text{Co}^{ii}(\text{Por})])\).\(^9\) Thus, the hypothesis that an anionic electron-rich complex should be more efficient at azide activation compared to the neutral porphyrin complexes indeed holds true. Yet, unfortunately, the temperature needed for this reaction couldn’t be lowered by replacing the neutral \([\text{Co}^{ii}(\text{Por})]\) complexes by any of the \([\text{Co}^{ii}(\text{Cor})]^-\) complexes investigated here. This we attribute to the low solubility of the ionic \([\text{Co}^{ii}(\text{Cor})]^-\) (cobaltocenium\(^+\)) salts, which immediately precipitate from toluene solutions upon reduction of the neutral complex at room temperature and only slowly re-solubilise under the catalytic reaction conditions in the presence of azide substrate at 100 °C. Thus, synthesis of a \([\text{Co}^{ii}(\text{Cor})]^-\) complex with higher solubility in such apolar solvents (benzene or toluene) or performing ion exchange to increase solubility may well be a promising strategy to lower the temperatures for such C–H amination reactions proceeding via azide activation.

Next, we also calculated the spin-density of the corrole-based cobalt(III)-nitrene complexes. Despite the fact that the spin density of the parent complexes resides in a different d-orbital (d\(_{xy}\)) when compared to the corresponding \([\text{Co}^{ii}(\text{Por})]\) complexes (d\(_z^2\)), the nitrene moiety also shows maximum spin-density at the nitrene nitrogen atom for the corrole complexes. Thus, it can be expected that mechanistically the reactions with the \([\text{Co}^{ii}(\text{Cor})]^-\) complexes proceed via similar cobalt(III)-nitrene radical intermediates as previously reported for the \([\text{Co}^{ii}(\text{Por})]\) complexes.\(^7,9\)

**Figure 8.** (A) DFT-D3 calculated (Turbomole BP86, def2-TZVP) free energies \((\Delta G_{298K}^\ddagger \text{ in kcal mol}^{-1})\) for the key step of azide activation by the \([\text{Co}^{ii}(\text{Cor})]^-\) complex. (B) Spin density plot of the thus formed nitrene radical intermediate B showing maximum spin density at the nitrene nitrogen.

**Summary and Conclusion**

For nitrene transfer reactions from azides catalysed by \([\text{Co}^{ii}(\text{Por})]\) catalysts, azide activation on the catalyst is known to be the rate limiting step. In this step the cobalt centre undergoes an oxidation from cobalt(II) to cobalt(III). Therefore, we hypothesised that the use of a ligand that retains the planar geometry of the porphyrin ligand but is more electron-rich could be beneficial for such reactions. Corroles are porphyrin-like ligands with a smaller pocket and a higher electron-density overall. Therefore, we synthesised three corrole complexes of cobalt \([[\text{Co}^{iii}(\text{Cor})]\text{[(PPh}_3\text{)]}]\) with electronically different substituents. As a benchmark reaction we chose the intramolecular ring-closing C–H amination reaction of (4-azidobutyl)benzene (in presence of Boc\(_2\)O) to give the saturated N-heterocycle tert-butyl-2-phenylpyrrolidine-1-carboxylate. This reaction is known to proceed with excellent yields
using the \([\text{Co}^\text{II}(\text{TMP})]\) catalyst, but requires a long reaction time of about 16h. The synthesised \([\text{Co}^\text{II}(\text{Cor})(\text{PPh}_3)]\) complexes investigated in this study could be chemically reduced to generate the corresponding mono-anionic \([\text{Co}^\text{II}(\text{Cor})]^\text{−}\) complexes, which are catalytically active in the same ring-closing C−H amination reaction. These reduced species were characterised by CV, EPR and UV-vis spectro-electrochemistry. Upon reduction, all synthesised \([\text{Co}^\text{II}(\text{Cor})(\text{PPh}_3)]\) complexes proved not only active in the ring-closing C−H amination reaction of (4-azidobutyl)benzene, but also to be much faster (more than 2.5 times) than the reported \([\text{Co}^\text{II}(\text{TMP})]\) catalyst in the same reaction. We also performed computational studies to confirm that the improved rates are due to lower barriers of the rate limiting azide activation step. Indeed, DFT calculations reveal a much lower transition state barrier for this step for the mono-anionic \([\text{Co}^\text{II}(\text{Cor})]^\text{−}\) complexes than for the neutral \([\text{Co}^\text{II}(\text{Por})]\) complexes. Despite a different starting electronic structure, the thus produced nitrene species are best described as nitrene-radical intermediates, with most of their spin density located at the nitrene nitrogen atom, similar to the nitrene-radical intermediates reported for the neutral \([\text{Co}^\text{II}(\text{Por})]\) systems.

In conclusion, we have demonstrated for the first time in an unequivocal manner that anionic \([\text{Co}^\text{II}(\text{Cor})]^\text{−}\) complexes are effective metalloradical catalysts. Moreover, we demonstrated that increased electron-density of the corrole cobalt(II) complexes compared to porphyrin cobalt(II) complexes has a positive impact on the rate of the ring-closing reactions of aliphatic azides to give pyrroldine N-heterocycles. Although the reaction temperatures couldn’t be lowered, the reaction times were significantly decreased. In the catalysts tested in this study the reactions were about 2.5 faster than the corresponding \([\text{Co}^\text{II}(\text{Por})]\) catalysts. The selectivity was, however, somewhat compromised. In future studies solubility issues will need to be tackled. With more soluble \([\text{Co}^\text{II}(\text{Cor})]^\text{−}\) catalysts in hand, several other metalloradical transformations (carbene and nitrene transfer reactions) may become feasible, and this should definitely be explored in the near future.

Supporting information, experimental and computational details

General information

All manipulations were performed under an N\(_2\) atmosphere using standard Schlenk techniques or in a glovebox unless otherwise mentioned. Acetonitrile and DCM were distilled under nitrogen from CaH\(_2\). THF and toluene were distilled under nitrogen from Na wire. CoCp\(_2\) and CoCp*\(_2\), were purchased from commercial sources and stored in the glove-box. Mesitylene or trimethoxy benzene was used as internal standard was purchased from Sigma-Aldrich. Mesitylene was degassed prior to use and stored under molecular sieves.

\(^1\text{H}\) NMR: All \(^1\text{H}\) NMR spectra were recorded on a Bruker Avance 400 (400 MHz) or Mercury 300 (300 MHz), referenced internally to residual solvent resonance of CDCl\(_3\) (δ = 7.26 ppm).

\(^{13}\text{C}\) (\(^1\text{H}\)) NMR: All \(^{13}\text{C}\) NMR spectra were recorded on a Bruker Avance 400 (101 MHz), or Mercury 300 (75 MHz), referenced internally to residual solvent resonance of CDCl\(_3\) (δ = 77.2 ppm). Abbreviations used are: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad.

High Resolution Mass spectra were measured on an AccuTOF LC, JMS-T100LP Mass spectrometer (JEOL, Japan). FD/FI probe (FD/FI) is equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 μm. Current rate 51.2 mA/min over 1.2 min FI Emitter, Carbotec or Linden (Germany), FI 10 μm.
Flashing current 40 mA on every spectra of 30 ms. Typical measurement conditions are: Counter electrode –10kV, Ion source 37V.

- (4-azidobutyl)benzene was synthesised according to procedure described in literature.4

- **Synthesis of [Co^III(Br_2Cor)(PPh_3)]**

The corrole was made using the general dipyrrromethane condensation method of Gryko et al. 11

2,6-dibromophenyl dipyrrromethane (1 mmol) was dissolved with benzaldehyde (0.5 mmol) in 100 mL methanol. To this 50 mL H_2O and 5 mL concentrated (37%) HCl were added. The mixture was allowed to stir for 2 hours. The bilane intermediate was extracted with chloroform and washed with water. The organic layer was dried with Na_2SO_4, filtered and concentrated. The concentrate was diluted to a volume of 250 mL chloroform, after which p-chloranil (1.5 mmol) was added allowed to stand overnight without stirring. The mixture was then condensed and flushed though a plug of silica with dichloromethane. This gave a purple solution which was concentrated to give a purple solid which is the 5,15-bis(2,6-dibromophenyl)-10-phenylcorrole. ^1^H NMR (400 MHz, CDCl_3) δ 8.99 (d, J = 4.2 Hz, 2H), 8.59 (d, J = 4.7 Hz, 2H), 8.51 (d, J = 4.7 Hz, 2H), 8.40 (d, J = 4.2 Hz, 2H), 8.21 – 8.16 (m, 2H), 8.00 (d, J = 8.1 Hz, 4H), 7.72 (dd, J = 5.0, 1.7 Hz, 3H), 7.49 (t, J = 8.1 Hz, 2H).

5,15-bis(2,6-dibromophenyl)-10-phenylcorrole (0.1 mmol) was then refluxed for 1 hour in MeOH (60 ml) together with cobalt acetate tetrahydrate (0.2 mmol) and triphenyl phosphine (0.2 mmol). After which the solution is condensed and flushed through a silica plug with dichloromethane as eluent, collecting the deep red fractions which to give the desired cobalt(III) corrole complex. Slow evaporation from DCM yielded deep red crystals.

^1^H NMR (300 MHz, CDCl_3) δ 8.37 (t, J = 5.1 Hz, 4H), 8.27 (d, J = 6.5 Hz, 1H), 8.10 (d, J = 4.8 Hz, 2H), 8.01 (t, J = 7.9 Hz, 1H), 7.80 (dd, J = 7.6, 2.7 Hz, 7H), 7.73 (d, J = 4.9 Hz, 3H), 7.33 (dd, J = 16.3, 8.2 Hz, 3H), 7.00 (t, J = 7.5 Hz, 3H), 6.69 (td, J = 7.7, 2.3 Hz, 6H), 5.17 – 5.05 (m, 6H).

^13^C NMR (126 MHz, CDCl_3) δ 146.14, 145.61 (d, J = 3.3 Hz), 144.39 (d, J = 2.3 Hz), 143.28, 142.82, 135.88 (d, J = 3.2 Hz), 134.59, 131.00, 130.29, 130.21, 129.24 (d, J = 2.7 Hz), 127.58, 127.46 – 127.27 (m), 127.22, 126.94, 126.58, 126.45 (d, J = 2.3 Hz), 125.93, 124.68 (d, J = 2.3 Hz), 122.75, 122.09 (d, J = 4.5 Hz), 120.74 (d, J = 2.6 Hz).

HRMS (FD); m/z: Calcd. For ([M]^+) C_{55}H_{34}Br_{14}CoN_{4}P= 1160.4280, found= 1159.7722 Dalton ([M]^+),
Calcd. For (M -PPh_3)^+C_{37}H_{19}Br_{14}CoN_4 = 898.1362 Dalton, found= 897.7435 Dalton

- **Synthesis of [Co^III(Ph_2Cor)(PPh_3)]**

Freshly alumina filtered pyrrole (10 mmol) and benzaldehyde (5 mmol) were dissolved in 200 ml MeOH. To this 200 mL H_2O and 5 mL concentrated (37%) HCl were added, after which the reaction mixture was allowed to stir for 3 hours at room temperature. The bilane intermediate was extracted
The free base 5,10,15-triphenylcorrole (0.3 mmol) was refluxed for 1 hour in MeOH (180 ml) together with cobalt acetate tetrahydrate (0.6 mmol) and triphenyl phosphine (0.6 mmol) for 1 hour in dark conditions. After which the solution was condensed and flushed through a silica plug with dichloromethane as eluent, collecting the deep red fraction with the desired cobalt(III) corrole complex (91 mg, 36%).

$^{1}H$ NMR (300 MHz, CDCl$_3$) δ 8.60 (d, $J = 4.4$ Hz, 2H), 8.33 (d, $J = 4.8$ Hz, 2H), 8.09 (d, $J = 4.8$ Hz, 3H), 8.03 (d, $J = 4.6$ Hz, 2H), 7.98 (s, 1H), 7.68 – 7.52 (m, 11H), 7.36 (d, $J = 7.4$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 3H), 6.76 – 6.64 (m, 6H), 4.72 (dd, $J = 10.7$, 8.1 Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 146.27, 145.57, 145.01, 141.88, 136.42, 132.12 (d, $J = 9.6$ Hz), 131.94, 131.74 (d, $J = 9.2$ Hz), 131.55, 130.92, 130.74, 129.85, 129.30, 128.55, 127.63, 127.36, 127.11 (d, $J = 6.2$ Hz), 127.00, 125.39, 124.11, 123.05, 118.58.

HRMS (FD); m/z: Calcd. for ([M]+), C$_{55}$H$_{38}$CoN$_{4}$= 844.8440 Dalton, found= 844.2140 Dalton

Calcd. For (M -PPh$_3$)$_{+}$C$_{37}$H$_{23}$CoN$_{4}$= 582.5522 Dalton, found= 582.1199 Dalton

- **Synthesis of [Co$^{III}$][Mes$_2$Cor](PPh$_3$)**

The corrole was made using the hindered dipyromethane condensation method of Gryko et al.$^{11}$ 5-(mesityl)dipyromethane (2 mmol) was dissolved with 2,4,6-trimethoxybenzaldehyde (1 mmol) in 200 mL methanol, after which 100 ml H$_2$O and 10 ml concentrated (37%) HCl were added to the reaction mixture. The mixture was allowed to stir for 2 hours. The bilane intermediate was extracted with chloroform and washed with water. The organic layer was dried with either Na$_2$SO$_4$ or MgSO$_4$ and filtered. The tetrapyrrole/bilane solution was from here on kept under dark conditions and diluted to a volume of 500 mL chloroform. While kept in dark conditions p-chloranil (3 mmol) was added and the bilane was allowed to oxidize overnight with stirring. The mixture was then condensed and flushed through a silica plug with dichloromethane, collecting the purple solution, giving near pure corrole (115 mg, 16%). The $^1$H NMR spectra were in accordance with those reported in literature.$^{19}$
5,15-dimesyl-10-(2,4,6-trimethoxyphenyl)corrole (0.1 mmol) was refluxed for 1 hour in MeOH (60 ml) together with cobalt acetate tetrahydrate (2 eq) and triphenyl phosphine (2 eq) for 1 hour in dark conditions. After cooling down the solution is condensed and flushed through a silica plug with DCM as eluent, collecting the deep red fraction which contains the desired cobalt(III) corrole complex. Crystallization via slow evaporation in DCM resulted in crystals.

**NMR:** when measured in pyridine the NMR spectrum matches literature, which does not show the PPh₃.

$$\text{^1H NMR (300 MHz, CDCl}_3 \delta 8.19 \ (d, J = 4.6 \text{ Hz, 2H}), 8.05 \ (d, J = 4.4 \text{ Hz, 2H}), 7.91 \ (d, J = 4.7 \text{ Hz, 2H}), 7.64 \ (d, J = 4.4 \text{ Hz, 2H}), 7.03 \ (d, J = 11.4 \text{ Hz, 4H}), 6.94 \ (d, J = 8.0 \text{ Hz, 3H}), 6.64 \ (d, J = 7.9 \text{ Hz, 7H}), 6.54 \ (d, J = 2.2 \text{ Hz, 1H}), 6.45 \ (d, J = 2.2 \text{ Hz, 1H}), 5.23 \ (t, J = 9.4 \text{ Hz, 6H}), 4.09 \ (s, 3H), 3.66 \ (s, 3H), 3.17 \ (s, 3H), 2.50 \ (s, 6H), 1.74 \ (s, 6H).}$$

$$\text{^13C NMR (126 MHz, CDCl}_3 \delta 161.55, 159.62, 158.89, 147.52, 145.99, 137.99, 136.77, 136.54, 136.27, 131.68 (d, J = 9.8 \text{ Hz}), 128.88, 128.12, 127.81, 127.47, 127.19 (d, J = 9.9 \text{ Hz}), 124.32, 123.00, 122.29, 119.23, 116.01, 114.20, 91.15, 90.89, 56.33, 55.71, 55.40, 29.86, 21.47, 20.42, 19.94.}$$

**HRMS (FD); m/z:** Calcd. For ([M]+) C₆₄H₅₆CoN₄O₃P= 1018.3422 Dalton, found= 1018.3451 Dalton

Calcd. For (M -PPh₃)+ C₆₄H₄₁CoN₄O₃= 756.2511 Dalton, found= 756.2512 Dalton

- **X-ray single crystal determination**

$$\text{[Co^{III}(Br₂Cor)[PPh₃]] C}_{55}\text{H}_{34}\text{Br}_2\text{CoN}_4\text{P Fw = 1160.36, purple-black rough fragment, 0.25 x 0.14 x 0.05 mm, orthorhombic, Pnma (no. 62), a = 16.5436(17), b = 19.975(2), c = 13.5943(15) Å, β = γ = α = 90 °, V = 4492.4(8) Å³, Z = 4, D_x = 1.716 g cm}^{-3}, \bar{\rho} = 4.020 \text{ mm}^{-1}. \text{ In total, 22100 reflections were measured on a Bruker D8 Quest Eco diffractometer, equipped with a TRIUMPH monochromator and a CMOS PHOTON 50 detector ( \bar{\rho} = 0.71073 Å) up to a resolution of (sin(\bar{\rho}/λ)} = 0.84 Å}^{-1} \text{ at a temperature of 150(2) K. The intensity data were integrated with the Bruker APEX2 software.}$$

Absorption correction and scaling was performed with SADABS. Absorption correction and scaling was performed with SADABS. absorption correction and scaling was performed with SADABS. Absorption correction and scaling was performed with SADABS. In total, 4069 reflections were unique (R_int = 0.110), of which 2829 were observed (I > 20σ(I)). The structure was solved with direct methods using the program SHELXS-97 and refined with SHELXL-2013 against F² for all reflections. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were introduced in calculated positions and refined with a riding model. R₁/wR₂ ([I > 20σ(I)]): 0.0581/0.1682. S = 1.025. Residual electron density between -1.174 and 0.677 e Å⁻³. Geometry calculations and checking for higher symmetry was performed with the PLATON program.
\[ \text{[Co}^{\text{III}}(\text{Mes}_2\text{Cor})(\text{PPh}_3)] \] unfortunately the crystal diffracted poorly. But the connectivity between the atoms could be clearly seen to ascertain the structure.

- **CV measurements**

Cyclic voltammograms were recorded using a Metrohm Autolab AUT85221 potentiostat in conjunction with Nova 1.8.17 at a scan rate of 0.1 V/s. The electrodes used were a glassy-carbon working electrode, a platinum counter electrode and a silver reference electrode. A solution of 0.3 M \( \text{n-Bu}_4\text{NPF}_6 \) in dry THF was used as the electrolyte, and potentials were referenced to \( \text{FeCp}_2 \) by using \( \text{FeCp}_2^* \) (\( E^{0\,1/2} = -0.45 \text{ vs } \text{FeCp}_2 \text{ in THF} \)) as an internal reference.

CV measurements of the three \([\text{Co}^{\text{III}}(\text{Cor})(\text{PPh}_3)]\) complexes showing the two reduction waves:

![CV plots with both reduction peaks for [CoIII(Br2Cor)(PPh3)] (left), CoIII(Ph2Cor)(PPh3)] (centre) and [CoIII(Mes2Cor)(PPh3)] (right) referenced to FeCp2 by using FeCp2* (E01/2 = -0.45 vs FeCp2 in THF)14 as an internal standard.](image)

- **UV-vis spectro-electrochemical measurements**

UV-Vis spectro-electrochemistry was performed by using an Autolab95 pgstat10 and a Hewlett Packard 8453 spectrometer. Absorbance spectra were recorded with UV-visible chemstation B.05.02. A solution of 0.3 M \( \text{n-Bu}_4\text{NPF}_6 \) in dry THF was used as the electrolyte. The concentration of the corrole complexes was roughly \( 5 \times 10^{-4} \text{ M} \). The scan speed used was 0.02 V/s. SpectraGryph 1.0.6 was used for processing the spectra.

An initial UV/VIS spectrum was recorded before applying any voltage in order to record the spectrum of the neutral compound in THF itself. Following this, the CV was started with further UV/VIS measurements taken every 0.1 V or until the spectrum started showing significant changes in which case spectra were taken every 0.05 V. This continued until either \(-1.0 \text{ V} \) was reached or the spectrum no longer showed any changes when the applied potential was increased. For the back oxidation a
similar strategy was followed. By initially taking spectra every 0.1 V until changes in the spectra started to show, after which new spectra were recorded every 0.05 V until 0 V was reached again.

- **UV-vis spectra** of the $[\text{Co}^\text{III}(\text{Br}_2\text{Cor})(\text{PPh}_3)]^-$ and $[\text{Co}^\text{II}(\text{Br}_2\text{Cor})]^{-}$ species (left) and the $[\text{Co}^\text{III}(\text{Mes}_2\text{Cor})(\text{PPh}_3)]$ and $[\text{Co}^\text{II}(\text{Mes}_2\text{Cor})]^{-}$ species (right) obtained in an OTTLE-cell.

**Figure 10.** UV-vis spectra of the $[\text{Co}^\text{III}(\text{Br}_2\text{Cor})(\text{PPh}_3)]$ and $[\text{Co}^\text{II}(\text{Br}_2\text{Cor})]^{-}$ species (left) and the $[\text{Co}^\text{III}(\text{Mes}_2\text{Cor})(\text{PPh}_3)]$ and $[\text{Co}^\text{II}(\text{Mes}_2\text{Cor})]^{-}$ species (right) obtained in an OTTLE-cell.

- **EPR studies**

Inside a glove box, 0.005 mmol of the cobalt corrole complex and 0.75 eq cobaltocene or decamethylcobaltocene (for $[\text{Co}^\text{II}(\text{Mes}_2\text{Cor})(\text{PPh}_3)]$) were dissolved in dry 1.5 ml methyl-THF and 0.5 ml DMSO after which 0.2 mL of this solution was transferred into an EPR tube. The sample was then measured at 20K. After the initial measurements, the tubes were opened and the contents exposed to air for ~2 minutes after which the tubes were closed and the samples measured again at 20K.
- EPR spectra of the anionic [Co(\(\text{Br}_2\text{Cor}\))]** and [Co(\(\text{Ph}_2\text{Cor}\))]** complexes.

**Figure 11.** EPR spectra (20K) of the anionic [Co(\(\text{Br}_2\text{Cor}\))]** complex (top left, with and without exposure to air) and the anionic [Co(\(\text{Ph}_2\text{Cor}\))]** complex (top right, with and without exposure to air). Bottom left EPR spectra (20K) of [Co(\(\text{Mes}_2\text{Cor}\))]**.

**Figure 12.** EPR of spectrum cobaltocene only in methyl-THF measured at 20K.

**Scheme 4.** Possible pathway of azide degradation via formation of an iminophosphorane on reaction with PPh\(_3\).
• **General procedure for the catalytic reactions.**

Reactions were performed in 0.3 mmol scale. To a flame dried and nitrogen filled Schlenk tube were added catalyst 5 mol%, 1 eq (4-azidobutyl)benzene, 1.1 eq di-tert-butylidicarbonate (Boc₂O) and 5 mol% reductant (cobaltocene) in dry toluene (5.0 ml). The mixture was then stirred for 16 hours at 100°C. After drying either mesitylene or 1,3,5-trimethoxybenzene was then added to use as external standard to determine the yield via NMR. 6.1 ppm or 6.8 ppm were used as reference for 1,3,5-trimethoxybenzene or mesitylene respectively. Product peaks at 5.4-7.5 ppm in CDCl₃ were to determine yield of the product.

NMR scale reactions were performed using the same method but in 0.06 mmol scale and in toluene-d₈. Product appearance was monitored by integrating the peaks at 5.4-7.5 ppm and azide consumption was monitored via the decreasing peaks at 3.34 and 2.74 ppm.

![Figure 13. Stacked ¹H NMR spectra of reaction progress in time of (4-azidobutyl)benzene with (a) [Co²⁺(Br₂Cor)PPh₃], (b) [Co²⁺(Ph₂Cor)PPh₃] and (c) [Co²⁺(Mes₂Cor)PPh₃]. Product appearance was monitored by emerging peaks at 5.4-7.5 ppm and azide consumption was monitored via the disappearing peaks at 3.34 and 2.74 ppm (d) The reaction mixture before (left) and after (right) heating. Precipitation of the reduced catalyst was observed before heating the reaction mixture.](image)

**DFT Studies**

Geometry optimizations were carried out with the Turbomole program package²³ coupled to the PQS Baker optimizer²⁴ via the BOpt package.²⁵ We used unrestricted ri-DFT-D3 calculations at the BP86 level,²⁶ in combination with the def2-TZVP basis set,²⁷ and a small (m4) grid size. Grimme’s dispersion
corrections\textsuperscript{28} (version 3, disp3, ‘zero damping’) were used to include Van der Waals interactions. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterised by calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The nature of the transition states was confirmed by following the intrinsic reaction coordinate.

Table 2. Energies of optimised geometries shown in Figure 8.

<table>
<thead>
<tr>
<th></th>
<th>Total Energy (SCF) Hartree</th>
<th>Total free energy (G)</th>
<th>H_correction</th>
<th>H (SCF+H_correction)</th>
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</thead>
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<tr>
<td>Corrole</td>
<td>-2333.32575</td>
<td>-2333.12186</td>
<td>0.26428</td>
<td>-2333.06147</td>
</tr>
<tr>
<td>A Corrole Azide adduct</td>
<td>-2886.70483</td>
<td>-2886.30796</td>
<td>0.49200</td>
<td>-2886.21283</td>
</tr>
<tr>
<td>TS_N2 loss</td>
<td>-2886.68121</td>
<td>-2886.28582</td>
<td>0.48866</td>
<td>-2886.19255</td>
</tr>
<tr>
<td>B nitrene</td>
<td>-2777.13107</td>
<td>-2776.74058</td>
<td>0.47918</td>
<td>-2776.65189</td>
</tr>
<tr>
<td>N2</td>
<td>-109.58</td>
<td>-109.593</td>
<td>0.00543</td>
<td>-109.57457</td>
</tr>
<tr>
<td>B+N2</td>
<td>-2886.71107</td>
<td>-2886.33358</td>
<td>0.48461</td>
<td>-2886.22646</td>
</tr>
</tbody>
</table>

Acknowledgements
We thank Dr. W.I. Dzik (HIMS, UvA) for the X-Ray diffraction studies and Ed Zuidinga (HIMS, UvA) for mass measurements.
References and notes


(13) All redox potentials are reported against the ferrocene/ferrocenium (Fc/Fc+) redox couple. Decamethylferrocene was used as an internal standard (E = 0.427 V vs. Fc/Fc+ in THF).


(17) In these spectra, contamination by an asymptotic signal was observed which increased in intensity on exposure to air. This signal probably arises from oxygen binding to the reduced species as is reported also for other related complexes.


(20) Bruker, APEX2 software, Madison, WI, USA, 2014.


(23) TURBOMOLE Version 6.5 (TURBOMOLE GmbH, Karlsruhe, Germany, 2013).

(24) (a) PQS version 2.4, 2001, Parallel Quantum Solutions, Fayetteville, Arkansas, USA (the Baker optimizer is available separately from PQS upon request); b) Baker, J. J. Comput. Chem.; 1986, 7, 385.


Chapter 6

Cobalt(II) porphyrin catalysed synthesis of indolines via a 1,5-H atom transfer pathway.*

*We thank Alexander Karns (UC Irvine) for his valuable contribution to this chapter (concepts and experiments).
Introduction

Direct C-H activation is a highly desirable way to functionalise molecules. In this context, metal-catalysed carbene and nitrene transfer reactions provide unique possibilities. In these transformations metal catalysts that can activate carbene or nitrene precursors are employed, typically leading to the formation of metal-carbenedoids or -nitrenoids species. Depending on the reactivity of the thus formed metal-carbenedoids and -nitrenoids, they can add to a variety of saturated (C-H bonds) or unsaturated bonds (alkenes and alkynes, for example). Transition-metal-catalysed carbene insertion into a saturated X-H (X= C, Si, O, N etc.) bond is an appealing methodology for construction of carbon-carbon or carbon-heteroatom bonds. Many of these methods find application in natural product synthesis and pharmaceuticals. Metal-catalysed carbene insertion into C-H bonds has proven to be an effective strategy for stereo- and enantioselective synthesis of five- and four-membered heterocycles. Significant advances in this area have been made with the Rh-/Ru-catalysed decomposition of diazo esters, reactions which are postulated to proceed via reactive metal-carbene intermediates. A special type of reactivity involving related carbene transfer pathways is displayed by cobalt. In its +2 oxidation state porphyrin complexes of cobalt exist as stable metalloradicals with well-defined open-shell doublet d^{7}-electronic configuration. These [Co^{I}(Por)] complexes have been successfully employed in carbene transfer reactions with unique activities. For example, cyclopropanation reactions mediated by [Co^{II}(Por)] catalysts have been proven to be very effective and selective for conversion of electron-deficient olefins. Their activities are not only limited to cyclopropanation/cyclopropanation but they have recently also been applied in a variety of other ring-closing reactions to form heterocycles. Mechanistically, these reactions proceed via radical mechanisms involving Co^{II}−carbene radical intermediates, which can be viewed as one-electron reduced Fischer-type carbene complexes (Figure 1). Consequently, the substrate acquires radical-character at the carbene-carbon, enabling controlled radical type reactivity in the coordination sphere of the metal. These carbene-radical intermediates also have a reduced tendency to undergo undesirable carbene dimerization reactions that are typical of free carbenes. The other added advantage of the [Co^{II}(Por)] systems is that N-tosylhydrazones can be directly used as carbene precursors in combination with a suitable base. This obliterates the need to isolate the toxic and potentially explosive diazo compounds, unlike many Rh and Ru catalysts used in carbene transfer reactions.

**Figure 1.** Formation of Co^{II}−carbene radicals (one-electron reduced Fischer-type carbenes) upon reaction of carbene precursors with planar, low spin cobalt(II) complexes.

Despite distinct advantages and unique reactivities of the [Co^{II}(Por)] catalysts in carbene transfer reactions, so far they haven’t been employed in the construction of N-containing heterocycles via the Co^{II}−carbene radical intermediates. Given the ubiquity of nitrogen atoms in biologically active compounds it is desirable to find ways in which N-containing heterocycles can be formed by such [Co^{II}(Por)] addition or insertion reactions of carbenes. We were particularly interested in the synthesis of indolines. The indoline heterocycle is one of the most commonly observed among natural product and pharmaceutical scaffolds. Consequently indole and indoline synthesis is an important field of
A variety of strategies using metal-catalysed reactions have been reported (Figure 2). For example, Ru catalyst in ring-closing olefin metathesis (RCM)/elimination sequence or an RCM/tautomerization sequence of functionalized pyrrole precursors, [RuCl₂(CO)₃]₂/dppp for the intramolecular oxidative amination of various aminoalkenes in presence of K₂CO₃ and allyl acetate to give the corresponding cyclic imines and indoles. Inter and intra-molecular cross-couplings with Pd, Cu, and Rh(III)- and Rh(II)- catalysed reactions, and many related synthetic protocols have also been developed. Carbene precursors have also previously been used in the synthesis of indolines with precious metals. Che and co-workers discovered the propensity of in-situ generated ruthenium carbenoids to undergo 1,2-insertion, a fundamental reaction of metal carbenes, to form indolines. Additionally, the Che group has also disclosed a method for indoline synthesis from nitrene precursors, involving a 1,5-hydrogen atom abstraction and subsequent formation of the key C-N bond using an iron catalyst. These strategies are summarised in Figure 2.

**Figure 2.** (Top) General strategies towards synthesis of the indoline heterocycle. (Bottom) Carbene and nitrene insertion pathways towards synthesis of indolines reported by Che and co-workers.
synthesis, the susceptibility of free radicals to undergo 1,5-HAT is often an unwanted pathway. Herein, we turn the 1,5-HAT reactivity Co(III)-carbene radical intermediate to our advantage. The general concept of the approach used in this work is shown in Scheme 1 (right).

Scheme 1. (left) Radical reactivity from carbene precursors and application in formal 1,2-addition. (right) Envisioned Co\textsuperscript{III}-carbene radical catalysed synthesis of indolines via 1,5 HAT.

Results and discussion

The substrates required for the envisioned cobalt-catalysed radical type C-C bond ring-closing reaction shown in Scheme 1 (right) were synthesised using the generalised synthetic scheme shown in Scheme 2.

Scheme 2. General strategy for synthesis of diazo-precursors employed in the [Co\textsuperscript{II}(TPP)]-catalysed ring-closing reaction to give indolines.

Starting from the commercially available (2-aminophenyl)methanol reagents A we first protected the amino functionality with Boc-anhydride (di-tert-butyl dicarbonate) to give B. Oxidation of the Boc-protected anilines B using MnO\textsubscript{2} gave the corresponding aldehydes C. This was followed by benzylation of the protected amines to give D. Refluxing D with tosyl-hydrazide then produces the
desired substrates S with the N-tosylhydrazone functionality. Substrate S can be treated with base to produce the corresponding diazo functionality in-situ. The final step in the sequence is the cobalt-catalysed ring-closing step; the focus of the work described in this chapter.

The cobalt-catalysed radical type ring-closing reaction was then tested with substrate S1 (R= Ph, R’= H) using LiO’Bu (1.7 equiv.) as base, benzene as solvent and 5 mol% catalyst loading at 60 °C. We were pleased to see that under these reaction conditions the reaction proceeded cleanly to give the 5-membered indoline P1 within 18 hours. We also tested the ring-closing of substrate S1 with some other cobalt(II) catalysts that are known to be active in carbene insertion reactions. The results are summarised in Table 1.

Table 1. Screening of various cobalt(II) catalysts for the ring-closing reaction to give indolines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Co(^{II})(TPP)] (5 mol%)</td>
<td>LiO’Bu (1.7 equiv.)</td>
<td>C(_6)H(_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td>(none)</td>
<td>LiO’Bu (1.7 equiv.)</td>
<td>C(_6)H(_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>CoCl(_2) (25 mol%)</td>
<td>LiO’Bu (1.7 equiv.)</td>
<td>C(_6)H(_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>[Co(^{II})(MeTAA)] (5 mol%)</td>
<td>LiO’Bu (1.7 equiv.)</td>
<td>C(_6)H(_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>83%</td>
</tr>
<tr>
<td>5</td>
<td>[Co(^{II})(salen)] (5 mol%)</td>
<td>LiO’Bu (1.7 equiv.)</td>
<td>C(_6)H(_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>76%</td>
</tr>
</tbody>
</table>

The [Co\(^{II}\)(TPP)], [Co\(^{II}\)(MeTAA)] and [Co\(^{II}\)(Salophen)] complexes used as catalysts in this reaction are shown in Figure 3. [Co\(^{II}\)(TPP)], [Co\(^{II}\)(MeTAA)] and [Co\(^{II}\)(Salophen)] were all active in this reaction, while CoCl\(_2\) showed no reactivity. This shows that the ligand plays a significant role in the activity of this class of catalysts. For reasons of superior activity, availability and ease of handling, we chose to perform further optimisations with the air- and moisture stable complex [Co\(^{II}\)(TPP)].

![Figure 3. [Co\(^{II}\)(TPP)], [Co\(^{II}\)(Salophen)] and [Co\(^{II}\)(MeTAA)] catalyst applied in the ring closing reaction shown in Table 1.](image-url)
Table 2. Evaluation of different base equiv. for the \([\text{Co}^{II}(\text{TPP})]\)-catalysed ring-closing reaction to give indolines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([\text{Co}^{II}(\text{TPP})]) (5 mol%)</td>
<td>LiO(^{t})Bu (1.2 equiv.)</td>
<td>(\text{C}_6\text{H}_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>([\text{Co}^{II}(\text{TPP})]) (5 mol%)</td>
<td>LiO(^{t})Bu (3 equiv.)</td>
<td>(\text{C}_6\text{H}_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>([\text{Co}^{II}(\text{TPP})]) (5 mol%)</td>
<td>LiO(^{t})Bu (1.7 equiv.)</td>
<td>(\text{C}_6\text{H}_6)</td>
<td>60 °C</td>
<td>6 h</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>([\text{Co}^{II}(\text{TPP})]) (1 mol%)</td>
<td>LiO(^{t})Bu (1.7 equiv.)</td>
<td>(\text{C}_6\text{H}_6)</td>
<td>60 °C</td>
<td>18 h</td>
<td>98%</td>
</tr>
</tbody>
</table>

Next, we investigated the effect of different base equivalents in this reaction (Table 2). 1.7 equiv. of base was found to be optimal amount for this reaction. While lower equivalents (entry 1) didn’t lead to full conversion, higher equivalents (entry 2) gave other unidentified products. Thus, using \([\text{Co}^{II}(\text{TPP})]\) (5 mol\%) as the catalyst, 1.7 equiv. of LiO\(^{t}\)Bu as the base, and benzene as the solvent, 95% of the product could be obtained in 6 hours reaction time. Finally, we could lower the catalyst loading to 1 mol\% by increasing the reaction time, so to obtain excellent yields of the indoline product P1 (98%). Screening of different solvents (with \([\text{Co}^{II}(\text{Salen})]\) as the catalyst) showed that the reaction proceeded in good to moderate yields in apolar solvents like toluene and cyclohexane. Lower yields were obtained in more polar solvents like THF. The best solvent was benzene where the indoline product was formed selectively with no other side products. These results are summarised in Table 5 (see additional information).

Thus, with the optimised reaction conditions in hand we moved on to synthesise substrates with varying substituents, both at the aromatic ring, as well as substituents on the N-atom (Table 3). In all cases where an activated C-H bond was present next to the N-atom, the reaction proceeded smoothly. The electron-donating or withdrawing nature of the substituent on the benzyl ring on the N-atom didn’t affect the reaction much. To our delight, even furanyl (entry 6, Table 3) and o-pyridine substituents (entry 5, Table 3) are tolerated in the reaction.

Less activated C-H bonds proved unsuitable for the radical-type ring closing reaction. With a methyl or ethyl substitution on the N-atom ring-closure did not occur (entry 7 and 8, Table 3). The only identified products in these cases were results of unwanted carbene dimerisation. This shows that C-H activation in this system is possible only for activated C-H with a (radical) stabilising group connected to the activated position. Different substituents on the aromatic ring were also tested and these reactions also gave moderate to excellent yields. When an electron-withdrawing CF\(_3\) group was present close to the \textit{in-situ} formed diazo functionality (entry 11), the yield dropped to 68%.
Table 3. Substrate scope for the [Co\(^{II}\)(TPP)]-catalysed ring-closing reaction to give indolines (substituents on N-atom and phenyl ring).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>S1</td>
<td>P1</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>R= Ph</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R'= H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>S2</td>
<td>P2</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>R= -(p-O\text{Me})-Ph</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R'= H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>S3</td>
<td>P3</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>R= -(p-CF(_3))-Ph</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R'= H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>S4</td>
<td>P4</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>R= -(o-Me)-Ph</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R'= H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>S5</td>
<td>P5</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>R= Pyridyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R'= H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>S6</td>
<td>P6</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>R= Furany</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R'= H</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enantioselective synthesis of indolines via cobalt(II)-metalloradical catalysis

Next we explored a few chiral catalysts for the enantioselective indoline synthesis. Because the reaction also proceeded with [Co\(^{II}\)(Salophen)] we chose two chiral salophens and two chiral [Co\(^{II}\)(Por)] complexes to perform the reaction enantioselectively. These catalysts are shown in Figure 4. Unfortunately, very high enantioselectivities could not be achieved in this reaction using these catalysts. The best outcome from each catalyst is summarised in Table 4. While enantioselectivities were higher at room temperature, the yields dropped drastically below 60°C. At best an ee of 25% could be achieved at RT on using [Co\(^{II}\)(Salophen)] 1, but the yield for this reaction was only 11%.
Table 4. Summary of results of enantioselective synthesis of indolines using some chiral catalysts (Figure 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Co(^{II})(Salophen)] 1</td>
<td>C(_6)H(_6)</td>
<td>rt</td>
<td>11%</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>[Co(^{II})(Salophen)] 2</td>
<td>C(_6)H(_6)</td>
<td>60 °C</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>3</td>
<td>[Co(^{II})(Por)] 3</td>
<td>C(_6)H(_6)</td>
<td>rt</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>[Co(^{II})(Por)] 4</td>
<td>C(_6)H(_6)</td>
<td>rt</td>
<td>27%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Figure 4. Different chiral [Co\(^{II}\)(Salophen)] and [Co\(^{II}\)(porphyrin)] complexes used in the enantioselective synthesis of indolines.

DFT mechanistic studies

Next, to shed some light on the mechanism, we explored this reaction computationally using DFT methods. In line with the similar systems that have been previously studied extensively, we considered a radical-type pathway involving activation of the in-situ formed diazo compound by the [Co\(^{II}\)(Por)] catalyst. The computations were performed at the BP86 and def2-TZVP level using the non-functionalised [Co\(^{II}\)(Por)] system. The choice for this computational method is based on previous realistic mechanistic pathways calculated by us on such systems. We further incorporated Grimme’s dispersion corrections (DFT-D3) for these systems. For the substrate, we included a full model for the diazo compound formed from substrate S1. Based on the energies obtained from these calculations we propose the mechanistic cycle depicted in Figure 5. Coordination of the diazo substrate on the catalyst to form a substrate-bound adduct B is exergonic by -5.0 kcal mol\(^{-1}\). From this adduct B, elimination of dinitrogen via TS1 (barrier: \(\Delta G^\ddagger = +8.6\) kcal mol\(^{-1}\)) leads to the formation of a carbene-radical intermediate C (\(\Delta G^* = -13.8\) kcal mol\(^{-1}\)). From this intermediate C the key step of HAT proceeds readily via a low barrier TS2 (barrier: \(\Delta G^\ddagger = +2.9\) kcal mol\(^{-1}\)) to give intermediate D (\(\Delta G^* = -21.5\) kcal mol\(^{-1}\)).
mol$^{-1}$). Ring-closing by radical rebound and homolysis of the Co-carbene bond proceeds through a slightly higher barrier TS3 ($\Delta G^\ddagger = +11.5$ kcal mol$^{-1}$).

![Diagram](image)

**Figure 5.** (A) DFT-D3 calculated (Turbomole BP86, def2-TZVP) free energies ($\Delta G_{298K}^\ddagger$ in kcal mol$^{-1}$) for the proposed reaction pathway. Energies of all intermediates are reported with respect to species A as the reference point (barriers for the transition states are reported in brackets). (B) Spin density plot of intermediate C showing maximum spin density at the carbene carbon. (C) Spin density plot of intermediate D after the 1,5-HAT step showing maximum spin density on the benzylic carbon and some delocalisation over the adjacent phenyl ring.

The computed barriers of all steps of the catalytic cycle depicted in Figure 5 are surprisingly low. This suggests that formation of the diazo compound from the tosyl hydrazone precursors, which requires heating, is the actual rate limiting step of the reaction. Once the diazo compound is generated, the next highest barrier in the catalytic reaction is the ring-closing step from species D to liberate the product and regenerate catalyst A. This is in agreement with the experimental observations, with chiral catalysts giving some chirality transfer in the ring-closing step. Release of product and regeneration of free catalyst is overall exergonic by -30.0 kcal mol$^{-1}$. Also, we calculated the spin densities on the intermediates C and D (Figure 5 B and C). Maximum spin-density in intermediate C is indeed located on the “carbene carbon” with some further delocalisation in the neighbouring phenyl ring (Figure 5B). The unpaired electron of the intermediate D formed after the HAT is delocalised on the benzylic carbon with considerable delocalisation also on the adjacent phenyl ring (Figure 5C).

In an attempt to prove the involvement of radical intermediates (as shown in Figure 5), we performed some radical trapping experiments using up to 10 equivalents of the radical scavenger TEMPO (TEMPO= 2,2,6,6-tetramethylpiperidinoxyl). However, in all the attempts to scavenge species C or D, the indoline product was still the major product. This is in agreement with the very low barriers of all
reaction steps shown in Figure 5, suggesting that the ring-closing steps are too fast to trap these intermediates. Kinetically, the intramolecular reaction seems to outcompete the inter-molecular radical trapping by TEMPO free radical, at least with the concentrations used in these experiments.

Summary and Conclusions
In this work we report a novel route for the synthesis of several substituted indolines which are substructures of a variety of natural products and pharmaceutically relevant compounds. It proceeds efficiently via a [Co\(^{II}\)(Por)]-catalysed pathway via activation of an in-situ formed diazo compound. The key-step in this reaction is a 1,5 HAT reaction, which is usually considered to be an undesirable pathway in organic free-radical chemistry. In this reaction, however, it is a desirable step, making catalytic synthesis of indolines possible. To the best of our knowledge, this is the first example of the synthesis of N-heterocycles via a cobalt(III)-carbene radical mediated C-H activation/rebound mechanism. The reaction uses commercially available starting materials and is thus a practical method to synthesise substituted indolines. Tosyl-hydrazone substrates can be used as precursors for the diazo functionality which can be generated in-situ in these reactions, thus precluding the need to isolate them. The metallo-radical catalysed indoline synthesis in this work represents an example of a net, formal (intramolecular) carbene insertion reaction into a benzylic C-H bond, but proceeds via a radical mechanism and displays highly controlled reactivity of the key Co\(^{III}\)-carbene radical intermediates involved.

Supporting information, experimental and computational details

1. General
All manipulations were performed under a nitrogen atmosphere using standard Schlenk techniques. All solvents used for catalysis were dried over and distilled from sodium (toluene, tetrahydrofuran (THF)) or CaH\(_2\) (dichloromethane (DCM), hexane, methanol).

All NMR spectra were recorded at 293 K.

\(^1\)H NMR: All \(^1\)H NMR spectra were measured on a Bruker Avance 400 (400 MHz) or Mercury 300 (300 MHz), referenced internally to residual solvent resonance of CDCl\(_3\) (\(\delta = 7.26\) ppm), or dmso-d\(_6\) (\(\delta = 2.5\) ppm)

\(^{13}\)C\(^{1}\)H NMR: Bruker Avance 400 (101 MHz) or Bruker Avance 500 (126 MHz), referenced internally to residual solvent resonance of CDCl\(_3\) (\(\delta = 77.2\) ppm) or dmso-d\(_6\) (\(\delta = 39.52\))

Individual peaks are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hz.

High Resolution Mass spectra were measured on an AccuTOF LC, JMS-T100LP Mass spectrometer (JEOL, Japan). FD/FI probe (FD/FI) is equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 \(\mu\)m. Current rate 51.2 mA/min over 1.2 min FI Emitter, Carbotec or Linden (Germany), FI 10 \(\mu\)m. Flashing current 40 mA on every spectra of 30 ms. Typical measurement conditions are: Counter electrode –10kV, ion source 37V.

2. Chemicals used
All chemicals were purchased from commercial sources unless otherwise mentioned. Solvents for all catalytic reactions were freshly distilled from sodium (toluene) and for acetonitrile or over calcium
hydride (acetonitrile). Reactions were performed using standard Schlenk techniques under an atmosphere of dinitrogen. [Co(HMeTAA)]\textsuperscript{5b}, [Co(HSalophen)]\textsuperscript{17}, chiral catalysts [Co(HSalophen)]\textsuperscript{2}\textsuperscript{18}, [Co(Por)]\textsuperscript{3}\textsuperscript{19} and [Co(Por)]\textsuperscript{4}\textsuperscript{20} were synthesised according to literature methods.

3. Synthesis of N-substituted substrates

Substrates S1-S8 compounds were synthesised starting from t-butyl(2-formyl phenyl)carbamate using the following generalised procedure. 1 mmol of t-butyl(2-formyl phenyl)carbamate, 1.3 mmol of RCH\textsubscript{2}Br (BnBr for S1, 2-methyl benzyl bromide for S2, 1-(bromomethyl)-4-methoxybenzene for S3, 4-trifluoro benzylbromide for S4, MeI for S5, ethyl iodide for S6, Bromomethyl pyridine.HBr for S7, Bromomethyl furan for S8) was dissolved in 1.5 mL DMF. This mixture was cooled to 0 °C. To this was added dropwise over 5 min a solution of 1 mmol of NaH in 670 μL of DMF. This reaction mixture was allowed to stir for 20h after which 5 mL of saturated NH\textsubscript{4}Cl solution was added slowly. The mixture was extracted three times with EtOAc. The organic layer was dried over MgSO\textsubscript{4}, filtered and concentrated to give the N-Boc-substituted aldehydes. These N-Boc-substituted aldehydes were reacted with tosyl hydrazide using the procedure described in literature to give the final compound.\textsuperscript{5b}

4. Synthesis of Substituted Anilines
Synthesis of substrate **S9**:

6.6 mmol of the carboxylic 2-amino-6-methylbenzoic acid was dissolved in 14 mL of THF in a round bottom flask. The reaction mixture was cooled to 0 °C and 16 mmol of LiAlH₄ was added. Subsequently, additional 14 mL of THF was added and the reaction was let to stir for 6 hours, allowing it to warm to rt during this time. The reaction mixture was filtered through a plug of celite and concentrated to give the corresponding benzyl alcohol. Without further purification, 1.1 equiv. of Boc₂O was added in THF (13 mL) and refluxed for 16 hours. The reaction mixture was then concentrated to give a brown oil. This brown oil was directly refluxed with 10 equiv. of MnO₂ in DCM for 16 h. The crude reaction mixture was filtered through celite and the filtrate was concentrated. It was then chromatographed on silica (0-5% EtOAc/Hex) to give the corresponding aldehyde. The aldehyde was then benzylated according to procedure described in 5.

**Synthesis of substrate S10:**

1 g (~8 mmol) of 4-trifluoromethyl aniline was dissolved in 4 mL of THF. To this was added 1.9 g (~8.8 mmol) of Boc₂O. The mixture was refluxed for two days after which it was evaporated to dryness, taken up in EtOAc followed by washing with 1M HCl and H₂O. Concentrating the organic layer gave a white solid which was washed with hexanes to give a white solid. This white solid was dissolved in 14 mL of dry THF followed and cooled to -78 °C. To this was added 8 mL tBuLi (1.7 M solution in pentane) followed by 2.9 mL of DMF. After the addition the mixture was stirred at -20 °C for 1 h and then at RT for two hours. The reaction was quenched by slowly adding ~100 mL of 5% HCl solution followed by 200 mL of Et₂O. The ether layer was washed with water and then concentrated to give a yellow solid which was the aldehyde. The aldehyde was then benzylated according to procedure described in 5.

**Synthesis of substrate S11:**

To a round bottom flask was sequentially added the aldehyde (1.00 g, 5.52 mmol, 1 equiv.), absolute ethanol (16.5 mL), iron powder (1.23 g, 22.1 mmol, 4 equiv.) and 0.1M HCl (2.8 mL, 0.28 mmol, 0.05 equiv.). The reaction mixture was heated to 65 °C for 2 hours, followed by heating at 75 °C for 2 hours. Following complete reduction, the reaction mixture was cooled to room temperature, quenched with saturated aqueous NaHCO₃ (10 mL), and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated to a brown oil.
The crude product mixture was immediately dissolved in dry THF (5.5 mL), and Boc₂O (2.5 mL, 11.0 mmol, 2 equiv.) was added in one portion. The reaction mixture was heated at 50 °C for 24 hours, at which point thin-layer chromatography indicated low conversion. An additional 2 mL of Boc₂O was added, and the reaction mixture was heated to reflux for 72 hours. Upon completion, the reaction mixture was concentrated and immediately purified by silica gel chromatography. The aldehyde was then benzylated according to procedure described in 5.

5. General Procedure for the Synthesis of Hydrazone Precursors from the corresponding aldehydes (S9-11)

![Chemical structure](image)

To a flame-dried Schlenk vial was added sodium hydride (217 mg, 5.42 mmol, 60% w/w dispersion in mineral oil, 1.2 equiv.). The vial was evacuated and filled with nitrogen three times, and DMF (3.3 mL) was added. The suspension was cooled to 0 °C, and a solution of the aldehyde (1.00 g, 4.52 mmol, 1 equiv.) and benzyl bromide (805 µL, 6.78 mmol, 1.2 equiv.) in DMF (7.5 mL) was added dropwise over 10 minutes. Following addition, the reaction mixture was removed from the water bath and stirred overnight. Upon completion, the reaction mixture was diluted with ethyl acetate (20 mL) and saturated aqueous ammonium chloride (10 mL) was added dropwise. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated to a yellow oil.

The yellow oil was immediately dissolved in dry methanol (9 mL), and tosyl hydrazide (926 mg, 4.97 mmol, 1.1 equiv.) was added. The reaction mixture was capped and stirred vigorously overnight. Upon completion, the reaction mixture was filtered, and the precipitate was washed sequentially with methanol and hexanes, and dried under a stream of air to afford the product as a white solid.

6. General Procedure for Cobalt-Catalyzed Indoline Formation

![Chemical structure](image)

To a flame dried Schlenk tube 0.3 mmol of the substrate was added followed by the catalyst (1 mol %). The Schlenk tube was evacuated and back-filled with nitrogen three times. Then inside a glove box 1.6 equiv of LiOtBu was added to this schlenk flask. The solids were dissolved in 6 mL of benzene and set to react at 60°C for 18 h. After that the reaction mixture was opened to air and 6mL of water was added. The organic layer was separated and the water layer was extracted 3 times with hexane (3 X 6mL). The organic portions were collected, dried over MgSO₄, concentrated and chromatographed on silica.
Table 5. Screening of different solvents for the ring-closing reaction to give indolines.

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₆</td>
<td>60 °C</td>
<td>18 h</td>
<td>76%</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>60 °C</td>
<td>18 h</td>
<td>16%</td>
</tr>
<tr>
<td>3</td>
<td>PhCl</td>
<td>60 °C</td>
<td>18 h</td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>60 °C</td>
<td>18 h</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>Cyclohexane</td>
<td>60 °C</td>
<td>18h</td>
<td>77%</td>
</tr>
</tbody>
</table>

7. Analytical data

Substrate S1

![Substrate S1 Diagram]

¹H NMR (500 MHz, Chloroform-d) δ 11.56 (s, 1H), 7.86 – 7.69 (m, 3H), 7.60 (d, J = 7.8 Hz, 1H), 7.40 (s, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.30 – 7.18 (m, 4H), 7.10 (dd, J = 19.2, 7.7 Hz, 3H), 4.72 (d, J = 15.4 Hz, 2H), 2.35 (s, 3H), 1.12 (s, 6H).

¹³C NMR (126 MHz, Chloroform-d) δ 153.99, 143.54, 143.48, 140.67, 137.39, 136.35, 131.25, 130.49, 129.85, 128.46, 127.47, 127.46, 127.30, 125.46, 80.04, 52.92, 27.90, 21.15.

HRMS (FD): Calculated for - 479.1879[M+], found- 479. 1875 Dalton

Substrate S2

![Substrate S2 Diagram]
$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.57 (s, 1H), 7.85 – 7.67 (m, 3H), 7.58 (d, $J$ = 7.7 Hz, 1H), 7.39 (s, 2H), 7.38 – 7.19 (m, 2H), 7.06 (s, 2H), 7.06 – 6.92 (m, 2H), 4.92 – 4.40 (m, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 1.18 (d, $J$ = 44.7 Hz, 7H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 153.96, 143.71, 143.47, 136.50, 135.23, 130.56, 130.39, 127.46, 125.99, 28.07, 21.32, 19.01.

HRMS (FD): Calculated $C_{27}H_{31}N_3O_4S_1$ [M+] 493.2035, found - 493.2038 Dalton

**Substrate S3**

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.55 (s, 1H), 7.87 – 7.64 (m, 3H), 7.60 (d, $J$ = 7.9 Hz, 1H), 7.38 (d, $J$ = 7.9 Hz, 2H), 7.30 (d, $J$ = 7.7 Hz, 1H), 7.23 (d, $J$ = 7.8 Hz, 1H), 7.13 – 6.97 (m, 3H), 6.77 (d, $J$ = 8.1 Hz, 2H), 4.64 (bs, 2H), 3.69 (s, 3H), 2.34 (s, 3H), 1.11 (s, 6H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 158.42, 153.79, 143.39, 140.52, 136.19, 131.12, 130.31, 129.69, 129.13, 127.74, 127.13, 125.28, 113.66, 79.79, 54.94, 52.12, 27.76, 20.99.

HRMS (FD): Calculated for $C_{27}H_{31}N_3O_5$ [M+] 509.1984, found - 509.1994 Dalton

**Substrate S4**

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.58 (d, $J$ = 2.6 Hz, 1H), 7.81 (d, $J$ = 2.4 Hz, 1H), 7.78 – 7.68 (m, 2H), 7.62 (t, $J$ = 8.1 Hz, 3H), 7.47 – 7.30 (m, 5H), 7.27 (d, $J$ = 7.7 Hz, 1H), 7.12 (d, $J$ = 7.8 Hz, 1H), 5.05 – 4.60 (m, 2H), 2.34 (d, $J$ = 2.5 Hz, 3H), 1.52 – 0.98 (m, 11H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 143.42, 143.15, 142.21, 140.45, 136.15, 130.89, 130.51, 129.68, 128.80, 128.08, 127.66, 127.36, 127.12, 126.00, 125.20, 122.40, 80.22, 27.72, 20.97.

$^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ -60.87.

HRMS (FD): Calculated for $C_{27}H_{28}F_3N_3O_5$ [M+] 547.1753, found - 547.1755 Dalton

**Substrate S5**

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.58 (s, 1H), 7.81 (s, 1H), 7.58 (s, 1H), 7.39 (s, 2H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.06 – 6.92 (m, 2H), 4.92 – 4.40 (m, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 1.18 (d, $J$ = 44.7 Hz, 7H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 153.96, 143.71, 143.47, 136.50, 135.23, 130.56, 130.39, 127.46, 125.99, 28.07, 21.32, 19.01.

HRMS (FD): Calculated $C_{27}H_{31}N_3O_4S_1$ [M+] 493.2035, found - 493.2038 Dalton
**Substrate S6**

\[
\begin{align*}
\text{H NMR} (300 \text{ MHz, DMSO-}d_6) \delta & \ 11.52 \ (d, J = 4.2 \text{ Hz, 1H}), \ 7.87 \ (d, J = 4.4 \text{ Hz, 1H}), \ 7.83 - 7.61 \ (m, 3H), \\
& \ 7.40 \ (d, J = 7.7 \text{ Hz, 3H}), \ 7.36 - 7.12 \ (m, 2H), \ 3.19 - 2.93 \ (m, 3H), \ 2.36 \ (d, J = 4.5 \text{ Hz, 3H}), \ 1.11 \ (s, 7H).
\end{align*}
\]

HRMS (FD): Calculated for C\(_{20}\)H\(_{25}\)N\(_3\)O\(_4\)S [M+] 403.1566, found - 403.1566 Dalton

**Substrate S7**

\[
\begin{align*}
\text{H NMR} (400 \text{ MHz, DMSO-}d_6) \delta & \ 11.55 \ (s, 1H), \ 7.89 \ (s, 1H), \ 7.74 \ (d, J = 8.1 \text{ Hz, 2H}), \ 7.69 \ (dd, J = 7.8, \\
& \ 1.6 \text{ Hz, 1H}), \ 7.40 \ (d, J = 8.1 \text{ Hz, 3H}), \ 7.30 \ (t, J = 7.6 \text{ Hz, 1H}), \ 7.20 \ (dd, J = 7.9, 1.2 \text{ Hz, 1H}), \ 2.35 \ (s, 3H), \\
& \ 1.09 \ (s, 7H), 0.93 \ (t, J = 7.1 \text{ Hz, 4H}).
\end{align*}
\]

HRMS (FD): Calculated for C\(_{21}\)H\(_{27}\)N\(_3\)O\(_4\)S [M+] 417.1722, found - 417.1752 Dalton

**Substrate S8**

\[
\begin{align*}
\text{H NMR} (300 \text{ MHz, DMSO-}d_6) \delta & \ 11.56 \ (s, 1H), \ 7.72 \ (d, J = 7.5 \text{ Hz, 3H}), \ 7.62 \ (d, J = 7.5 \text{ Hz, 1H}), \ 7.47 - \\
& \ 7.42 \ (m, 1H), \ 7.38 \ (d, J = 8.2 \text{ Hz, 2H}), \ 7.33 \ (d, J = 7.3 \text{ Hz, 0H}), \ 7.26 \ (d, J = 7.6 \text{ Hz, 1H}), \ 7.07 \ (d, J = 7.8 \\
& \ 6.17 \ (d, J = 49.5 \text{ Hz, 2H}), \ 4.69 \ (s, 2H), \ 2.34 \ (s, 3H), \ 1.09 \ (s, 7H).
\end{align*}
\]

HRMS (FD): Calculated for C\(_{25}\)H\(_{27}\)N\(_3\)O\(_5\)S [M+] 480.1831, found - 481.1853 Dalton
Substrate S9

![Structural formula of S9](image)

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.55 (s, 1H), 7.94 (s, 1H), 7.73 (d, $J = 8.2$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 7.33 – 7.18 (m, 3H), 7.18 – 7.02 (m, 3H), 6.78 (d, $J = 7.7$ Hz, 1H), 4.80 (d, $J = 15.3$ Hz, 1H), 4.24 (s, 1H), 2.33 (s, 4H), 2.22 (s, 4H), 1.16 (s, 9H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 153.90, 144.85, 143.39, 141.60, 137.51, 136.15, 129.99, 129.62, 129.45, 128.27, 127.32, 127.21, 79.70, 52.87, 27.80, 21.70, 20.97.

HRMS (FD) - Calculated for C$_{27}$H$_{31}$N$_3$O$_4$S $[M+]$ 493.2035, found- 493.2059 Dalton

Substrate S10

![Structural formula of S10](image)

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.81 (s, 1H), 9.58 (s, 1H), 7.79 (d, $J = 9.4$ Hz, 2H), 7.71 (dd, $J = 7.7$, 5.7 Hz, 3H), 7.64 (d, $J = 8.2$ Hz, 1H), 7.43 – 7.33 (m, 5H), 7.27 – 7.16 (m, 3H), 7.16 – 7.09 (m, 2H), 4.72 (s, 1H), 2.39 (s, 2H), 2.34 (s, 3H), 1.12 (s, 8H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 153.25, 143.64, 143.44, 141.70, 136.87, 136.02, 135.48, 132.31, 129.77, 129.44, 128.43, 128.19, 127.81, 127.50, 127.10, 126.83, 125.48, 121.88, 121.69, 80.62, 48.62, 27.64, 21.05, 20.98.

$^{19}$F NMR (282 MHz, DMSO-$d_6$) $\delta$ -61.26.

HRMS (FD) - Calculated for C$_{27}$H$_{28}$F$_3$N$_3$O$_5$S $[M+]$ 547.1753, found- 547.1753 Dalton

Substrate S11

![Structural formula of S11](image)

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.55 (s, 1H), 7.72 (t, $J = 4.1$ Hz, 3H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.20 (dd, $J = 10.0$, 6.7 Hz, 2H), 7.17 – 7.08 (m, 2H), 7.05 (d, $J = 2.9$ Hz, 1H), 6.96 (d, $J = 8.7$ Hz, 1H), 4.79 – 4.40 (m, 2H), 3.72 (s, 3H), 2.35 (s, 3H), 1.13 (s, 11H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 157.52, 154.20, 143.50, 143.20, 137.33, 136.12, 133.71, 132.04, 129.73, 129.04, 128.35, 127.34, 127.22, 116.18, 109.19, 79.74, 55.26, 53.00, 27.82, 21.03.

HRMS (FD) - Calculated for C$_{27}$H$_{31}$N$_3$O$_5$S- 509.1984[M+], found- 509.1990 Dalton
Analytical data of synthesised indolines

**Product P1**

![Structure of P1]

$^1$H NMR (300 MHz, Chloroform-d) δ 7.91 (s, 1H), 7.34 – 7.17 (m, 6H), 7.12 (d, J = 7.4 Hz, 1H), 6.98 (td, J = 7.4, 1.0 Hz, 1H), 5.37 (d, J = 10.6 Hz, 1H), 3.68 (dd, J = 16.3, 10.6 Hz, 1H), 2.97 (dd, J = 16.3, 3.5 Hz, 1H), 1.30 (d, J = 16.2 Hz, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ = 28.1, 37.8, 62.6, 80.7, 114.6, 122.5, 124.8, 125.2, 127.1, 127.6, 128.5, 129.1, 143.3, 144.7, 152.3.

HRMS (FD): calculated for C$_{19}$H$_{21}$NO$_2$ [M+1] 295.1572, found 295.1565 Dalton

**Product P2**

![Structure of P2]

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.89 (br, 1H), 7.20 (dd, J = 7.5, 7.5 Hz, 1H), 7.11 – 7.09 (m, 3H), 6.96 (dd, J = 7.5, 7.0 Hz, 1H), 6.80 – 6.77 (m, 2H), 5.30 (br, 1H), 3.76 (s, 3H), 3.63 (dd, J = 16.0, 11.0 Hz, 1H), 2.93 (dd, J = 16.0, 3.0 Hz, 1H), 1.34 (br, 9H). Matched literature.$^{21}$

**Product P3**

![Structure of P3]

$^1$H NMR (400 MHz, Chloroform-d) δ 7.95 (bs, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.33 (s, 1H), 7.31 – 7.23 (m, 2H), 7.13 (d, J = 7.4 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 5.61 – 5.27 (m, 1H), 3.71 (dd, J = 16.3, 10.7 Hz, 1H), 2.93 (dd, J = 16.3, 3.5 Hz, 1H), 1.57 – 1.02 (m, 9H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 152.04, 129.53, 129.21, 127.75, 125.50, 125.37, 124.80, 122.78, 122.67, 114.66, 99.86, 62.03, 37.47, 28.06, 0.94. $^{19}$F NMR (282 MHz, Chloroform-d) δ -62.39.

HRMS FD Calculated for C$_{20}$H$_{20}$F$_3$NO$_2$ [M+] 363.1446, found 363.1450 Dalton

**Product P4**

![Structure of P4]

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.98 (br, 1H), 7.23 (m, 1H), 7.14 – 7.01 (m, 5H), 6.96 (dd, J = 7.5, 7.0 Hz, 1H), 5.57 (br, 1H), 3.68 (dd, J = 16.0, 11.0 Hz, 1H), 2.82 (app. d, J = 16.0 Hz, 1H), 2.38 (s, 3H), 1.23 (br, 9H). Matched literature.$^{21}$

**Product P5**

![Structure of P5]
$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.65 – 8.26 (m, 1H), 7.96 (s, 1H), 7.59 (td, $J$ = 7.7, 1.6 Hz, 1H), 7.23 (dd, $J$ = 15.9, 8.1 Hz, 1H), 7.12 (dt, $J$ = 13.6, 6.9 Hz, 3H), 6.96 (t, $J$ = 7.4 Hz, 1H), 5.52 (d, $J$ = 10.6 Hz, 1H), 3.71 (dd, $J$ = 16.4, 10.8 Hz, 1H), 3.08 (dd, $J$ = 16.2, 3.7 Hz, 1H), 1.30 (s, 9H).

$^{13}$C NMR (75 MHz, Chloroform-$d$) $\delta$ 149.42, 136.84, 127.74, 124.96, 122.87, 122.16, 119.20, 114.90, 28.28.

HRMS (FD): Calculated for $C_{20}H_{23}NO_2$ [M+] 309.1729, found 309.1740 Dalton

**Product P6**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.81 (br, 1H), 7.27 (s, 1H), 7.19 (dd, $J$ = 6.5, 6.5 Hz, 1H), 7.15 (d, $J$ = 6.0 Hz, 1H), 6.96 (dd, $J$ = 6.5, 6.5 Hz, 1H), 6.26 (m, 1H), 6.12 (s, 1H), 5.47 (br, 1H), 3.52 (dd, $J$ = 13.5, 9.0 Hz, 1H), 3.15 (dd, $J$ = 13.5, 2.5 Hz, 1H), 1.47 (br, 9H). Matched literature$^{21}$

**Product P9**

$^1$H NMR (300 MHz, Chloroform-$d$) $\delta$ 7.85 (s, 1H), 7.36 – 7.23 (m, 3H), 7.19 (d, $J$ = 7.5 Hz, 2H), 6.87 – 6.53 (m, 2H), 5.36 (s, 1H), 3.78 (s, 3H), 3.66 (dd, $J$ = 16.4, 10.5 Hz, 1H), 2.93 (dd, $J$ = 16.3, 3.4 Hz, 1H), 1.29 (s, 9H).

$^{13}$C NMR (75 MHz, Chloroform-$d$) $\delta$ 155.70, 152.35, 128.52, 127.15, 125.31, 112.14, 111.21, 77.49, 77.07, 76.65, 55.68, 37.92, 28.21.

HRMS (FD): Calculated for $C_{20}H_{23}NO_3$ [M+] 325.1678 Dalton, found 325.1788 Dalton

**Product P10**

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.79 (s, 1H), 7.32 – 7.25 (m, 3H), 7.22 (d, $J$ = 8.8, 7.1 Hz, 2H), 7.16 (d, $J$ = 7.8 Hz, 1H), 6.82 (d, $J$ = 7.5 Hz, 1H), 5.39 (s, 1H), 3.56 (dd, $J$ = 16.3, 10.7 Hz, 1H), 2.89 (dd, $J$ = 16.4, 3.6 Hz, 1H), 2.18 (s, 3H), 1.48 – 1.19 (m, 9H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 152.32, 144.93, 142.75, 134.05, 130.24, 128.44, 127.70, 127.00, 125.14, 123.59, 112.02, 77.28, 76.96, 76.64, 62.47, 36.75, 29.63, 28.07, 18.49.

HRMS (FD): Calculated for $C_{20}H_{23}NO_2$ [M+] 309.1729, found 309.1679 Dalton
Product P11

\[
\begin{array}{c}
\text{Product P11} \\
\text{\includegraphics[width=0.5\textwidth]{product_p11.png}}
\end{array}
\]

\(^1\)H NMR (300 MHz, Chloroform-\(d\)) \(\delta\) 7.97 (s, 1H), 7.55 – 7.47 (m, 1H), 7.36 (s, 1H), 7.33 – 7.23 (m, 3H), 7.16 (dd, \(J = 7.7, 1.8\) Hz, 2H), 5.41 (dd, \(J = 10.8, 3.5\) Hz, 1H), 3.70 (dd, \(J = 16.6, 10.7\) Hz, 1H), 3.01 (dd, \(J = 16.6, 3.6\) Hz, 1H), 1.29 (d, \(J = 17.4\) Hz, 9H).

\(^1^3\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 151.99, 143.86, 128.55, 127.36, 125.73, 125.37, 125.33, 125.30, 125.26, 125.05, 124.62, 124.30, 123.97, 123.03, 121.71, 121.67, 120.34, 114.10, 77.23, 76.91, 76.60, 62.97, 37.32, 29.60, 29.27, 27.93, 22.60. \(^1^9\)F NMR (282 MHz, Chloroform-\(d\)) \(\delta\) -61.42.

HRMS (FD) Calculated for \(\text{C}_{20}\text{H}_{20}\text{F}_{3}\text{NO}_{2}\) [M+] 363.1446, found 363.1765 Dalton

8. Computational details

Geometry optimizations were carried out with the Turbomole program package4 coupled to the PQS Baker optimizer22 via the BOpt package.23 We used unrestricted ri-DFT-D3 calculations at the BP86 level,24 in combination with the def2-TZVP basis set,25 and a small (m4) grid size. Grimme’s dispersion corrections26 (version 3, disp3, ‘zero damping’) were used to include Van der Waals interactions. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The nature of the transition states was confirmed by following the intrinsic reaction coordinate.

\[\text{Figure 6. Energy Diagram for the computed mechanism for catalytic indoline synthesis using [Co}^{\text{III}}\text{Por]}\] DFT-D3 calculated (Turbomole BP86, def2-TZVP) free energies (\(\Delta G^{298K}_f\) in kcal mol\(^{-1}\)) are reported for each step.
Table 6. Energies of optimised geometries shown in Figure 6

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<th>Ring-closing for indolines BP86-def2TZVP_disp3</th>
<th>Total Energy (SCF) Hartree</th>
<th>Total free energy (G) Hartree</th>
<th>H_correction Hartree</th>
<th>H (SCF+H_correction) Hartree</th>
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<td>-1051.46963</td>
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<tr>
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<td>-109.593</td>
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<td>-109.57457</td>
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<tr>
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</table>

Acknowledgements

Ed Zuidinga (HIMS, UvA) and Dorette Tromp (HIMS, UvA) are thanked for mass measurements.
References and notes


7. Aziridine (three membered N-heterocycles) synthesis via nitrene transfers have been reported using cobalt(II) porphyrins. See chapter 1 of this thesis and references therein.


(22) (a) PQS version 2.4, 2001, Parallel Quantum Solutions, Fayetteville, Arkansas, USA (the Baker optimizer is available separately from PQS upon request); b) Baker, J. J. Comput. Chem.; 1986, 7, 385.


Chapter 7

*Difluorocarbene (CF₂) transfer from a cobalt complex to an electron-deficient alkene.*

*convenient source of CF₂, earth-abundant metal*

Parts of this chapter have been published and are reproduced here from:

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Introduction
The presence of a fluorine atom in organic compounds is known to alter their reactivity and physical properties. The high electronegativity of fluorine, its moderately small size and its three non-bonding electron pairs makes the match between the 2s orbitals of fluorine and the 2p orbitals of carbon unique. The C-F bonds are polarised and are stronger than other C-X bonds. Secondly, because of its high electronegativity fluorine also prefers to bind to carbon orbitals with higher p character, thus leading to smaller bond angles. For example, the F-C-F angle is 108.3°, which is significantly smaller than the H-C-H bond angle of 113.7° in CH₂F₂. These effects are even more pronounced in the three membered rings of cyclopropanes, which are considerably strained. Fluorine substitution in a cyclopropane ring has effect on its geometry, causes further destabilization and thereby makes the ring more reactive. These effects can be understood by considering the effects of the fluorine substitution on the hybridization of the carbon atom. Because of its high electronegativity, it is beneficial for fluorine to form bonds with carbon orbitals with enhanced p-character. In cyclopropanes this is already the case in the strained C-C bonds. When additionally a hydrogen atom is replaced by a fluorine atom, the C-C bond further lose p-character, which destabilizes the ring. Fluorinated-cyclopropanes thus exhibit novel reactivity, interesting regiochemistry and accelerated rates in reactions. Additionally, fluorine substituents typically also enhances the biological activity of cyclopropane-containing compounds, and in some cases the potency of known biologically active molecules.

Thus far, the synthesis of difluorocyclopropanes has been reported using various CF₂ generating reagents. In particular, the use of trimethylsilyltrimethyl silane (TMSCF₃ also known as the Ruppert-Prakash reagent) that was reported in 2011 is an attractive way to generate CF₂, as it circumvents the disadvantages of other synthetic routes such as harsh reaction conditions, high toxicity, lack of commercially available reagents and low yields; for example, in methods that involve the use of sodium chlorodifluoroacetate (or sodium bromodifluoroacetate), PhHgCF₂ and Me₃SnCF₂ (Seyferth reagents), FSO₂CF₂CO₂SiMe₃ (TFDA), and Zn/CF₂Br₂. It is also important to note that the synthesis of some of these reagents requires the use of ozone-depleting CBrClF₂.

The method described by Olah et al., that uses TMSCF₃, allows low to room temperature generation of the CF₂ carbene which then inserts into alkenes to form the gem-difluorinated cyclopropanes (Scheme 1). The initiator used to trigger the release of CF₂ from the CF₃⁻ anion is tetrabutylammonium fluoride (TBAF). On increasing the temperatures to 65°C and using NaI as the initiator this system can also cyclopropanate some more challenging alkenes (i.e. somewhat more electron-deficient ones). The mechanism by which NaI plays a role of the initiator is outlined in Scheme 2. Moreover, alkynes can be cyclofluoropropenated if temperatures are increased to 110°C, using THF as the solvent.

![Scheme 1](image)

Scheme 1. Gem-difluorocyclopropanation of alkenes using TMSCF₃ and NaI as initiator.
Scheme 2. Mechanism of activation of TMSCF₂ by NaI in gem-difluorocyclopropanation of alkenes.

This method was, however, not reported to be successful for the very electron deficient alkenes like acrylates. Same is the case for the PPh₃/CF₂Br₂ system that is reported to also function at room temperature. To the best of our knowledge the only systems that are known to be able to fluorocyclopropanate acrylates are the ones that employ sodium chlorodifluoroacetate (or sodium bromodifluoroacetate), TFDA or MDFA. The reaction conditions for these are, however, quite harsh and in some cases require a reaction time of days. It is therefore desirable to develop a protocol that can perform the addition of the CF₂ carbene to electron-deficient alkenes like acrylates.

We therefore set out to develop a metal catalysed protocol for CF₂ transfer to electron-deficient alkenes. Compared to other metallocarbenes, the chemistry of metallo-difluorocarbenes is thus far rather underdeveloped. Only a handful of well-defined metal difluorocarbenes are reported, and an example of Fe and Ir based complexes is depicted in Scheme 3. Recently, the group of Baker disclosed some electron rich cobalt(I) and nickel(0) difluorocarbene complexes containing a nucleophilic M=CF₂ moiety (Scheme 4). These species undergo cycloaddition reactions with tetrafluoroethylene (C₂F₄) or difluorocarbene producing perfluorinated metallocyclobutanes and metallacyclobutanes, respectively. A related electrophilic cobalt(III) complex mediated the insertion of difluorocarbene into a Co-perfluoroalkyl bond. However, the stability of the thus formed perfluoroalkyl metal complexes prohibited further reactivity.

Scheme 3. Generation of difluorocarbene complexes of Fe and Ir that are generated from the corresponding CF₃ complexes. In case of the Fe complex this is done by reaction with a Lewis acid and in case of Ir the complex is reduced using KC₈.
Thus, to the best of our knowledge, no examples of catalytic CF$_2$ transfer to electron deficient alkenes have been reported, likely due to the electrophilic nature of the difluorocarbene moiety. We envisioned that by employing a transition metal centre that can render the difluorocarbene moiety more nucleophilic, the transfer of CF$_2$ to an electron deficient olefin would be facilitated (Scheme 5). Reaching this goal could enable catalytic gem-difluorocyclopropanation of electron deficient double bonds. Cobalt(II) porphyrin complexes are efficient catalysts for cyclopropanation of electron deficient alkenes using (stabilized) diazo esters as carbene precursors. This contrasts with the Fischer-type reactivity of the majority of cyclopropanation catalysts, which have a general preference for electron rich alkenes. The observed ‘umpolung’ of the reactivity of the cobalt-carbenoid species as compared to other metallo-carbenes is caused by the transfer a discrete unpaired electron to the coordinated (Fischer-type) carbene ligand. This renders the carbene moiety more nucleophilic and weakens the metal-carbon bond. We hypothesized that this feature might also promote the formation of difluorocyclopropanes from related cobalt difluorocarbenoid intermediates. In this perspective the use of trimethyl(trifluoromethyl)silane (Me$_3$SiCF$_3$) as the difluorocarbene source is attractive, as it can operate at mild temperatures.

Scheme 4. (top) A trifluoromethyl cobalt complex that upon reduction gives the corresponding difluorocarbene complex. (Bottom) A difluorocarbene complex of cobalt that upon reaction with excess tetrafluoroethylene gives a perfluoroalkylated metallacycle.

Thus, to the best of our knowledge, no examples of catalytic CF$_2$ transfer to electron deficient alkenes have been reported, likely due to the electrophilic nature of the difluorocarbene moiety. We envisioned that by employing a transition metal centre that can render the difluorocarbene moiety more nucleophilic, the transfer of CF$_2$ to an electron deficient olefin would be facilitated (Scheme 5). Reaching this goal could enable catalytic gem-difluorocyclopropanation of electron deficient double bonds. Cobalt(II) porphyrin complexes are efficient catalysts for cyclopropanation of electron deficient alkenes using (stabilized) diazo esters as carbene precursors. This contrasts with the Fischer-type reactivity of the majority of cyclopropanation catalysts, which have a general preference for electron rich alkenes. The observed ‘umpolung’ of the reactivity of the cobalt-carbenoid species as compared to other metallo-carbenes is caused by the transfer a discrete unpaired electron to the coordinated (Fischer-type) carbene ligand. This renders the carbene moiety more nucleophilic and weakens the metal-carbon bond. We hypothesized that this feature might also promote the formation of difluorocyclopropanes from related cobalt difluorocarbenoid intermediates. In this perspective the use of trimethyl(trifluoromethyl)silane (Me$_3$SiCF$_3$) as the difluorocarbene source is attractive, as it can operate at mild temperatures.

Scheme 5. The hypothesised route towards gem-difluorocyclopropanated products from electron deficient via trifluoromethyl complexes.
Results and discussion

To evaluate the feasibility of difluorocarbene transfer from cobalt to an olefin we first decided to investigate whether a difluorocarbene cobalt(II) complex can be formed by one-electron reduction of the novel trifluoromethyl cobalt(III) complex [Co\textsuperscript{III}(TPP)(CF\textsubscript{3})] (TPP = meso-tetraphenyl-porphyrinato). Formation of a cobalt difluorocarbene complex by reduction and subsequent dissociation of fluoride from a cobalt trifluoromethyl complex has been reported by Baker and co-workers.\textsuperscript{13a} Thus, we anticipated that the release of F\textsuperscript{−} from the anionic [Co\textsuperscript{II}(TPP)(CF\textsubscript{3})]\textsuperscript{−} complex could lead to formation of a [Co(TPP)(CF\textsubscript{3})] species, potentially capable of CF\textsubscript{2} transfer to acrylates under mild reaction conditions.

The trifluoromethyl cobalt(III) porphyrin complex [Co\textsuperscript{III}(TPP)(CF\textsubscript{3})] required for these studies was obtained in 80% yield (see ESI for characterisation) by reacting [Co\textsuperscript{III}(TPP)(Cl)] with Me\textsubscript{3}SiCF\textsubscript{3} and CsF as an initiator (Scheme 6).

\textbf{Scheme 6.} Synthesis of [Co\textsuperscript{III}(TPP)(CF\textsubscript{3})] from the corresponding [Co\textsuperscript{III}(TPP)(Cl)] complex.

To evaluate the potential of [Co\textsuperscript{III}(TPP)(CF\textsubscript{3})] to form a difluorocarbene complex we investigated its electrochemistry under reductive conditions. The cyclic voltammogram (CV) of complex [Co\textsuperscript{III}(TPP)(CF\textsubscript{3})] in THF reveals a reversible reduction wave at -1.71 V, followed by an irreversible one with the peak wave at -2.13 V vs Fc/Fc\textsuperscript{+} (Figure 1). The first wave can be attributed to the one-electron reduction of the [Co\textsuperscript{III}(TPP)(CF\textsubscript{3})] to form the anionic complex [Co\textsuperscript{II}(TPP)(CF\textsubscript{3})]\textsuperscript{−}. The subsequent irreversible reduction leads to clean formation of [Co(TPP)]\textsuperscript{−} as evidenced by an independent measurement of an original [Co\textsuperscript{III}(TPP)] sample (Figure 2). These results show that one-electron reduction of [Co\textsuperscript{III}(TPP)(CF\textsubscript{3})] leads to formation of the anionic complex [Co\textsuperscript{II}(TPP)(CF\textsubscript{3})]\textsuperscript{−}, which is stable on the CV timescale (scan rate 100 mV/sec). The second reduction step leads to rapid (net) loss of the CF\textsubscript{3}\textsuperscript{−} anion from the cobalt centre.
Knowing that $[\text{Co}^{\text{III}}(\text{TPP})(\text{CF}_3)]^-$ can be selectively accessed using reductants with a reduction potential in the $-1.8$–$2.0$ V range (vs Fc/Fc$^+$), we next investigated its propensity to generate a metallo-difluorocarbene species on an extended timescale and at elevated temperatures. Interestingly, the intended reduction of $[\text{Co}^{\text{III}}(\text{TPP})(\text{CF}_3)]$ with one equivalent of decamethylcobaltocene (CoCp*$_2$, $E^0 = -1.91$ vs Fc/Fc$^+$) in the presence of n-butyl acrylate at 65°C indeed led to the formation of the desired gem-difluorocyclopropanated acrylate in 12% yield as determined by $^{19}$F NMR (Scheme 7 and Figure 3). Additionally, C$_2$F$_4$ was formed as a side product. In the absence of CoCp*$_2$, no reaction took place.

**Scheme 7.** Reaction of $[\text{Co}^{\text{III}}(\text{TPP})(\text{CF}_3)]$ with n-butyl acrylate upon one-electron reduction.

---

**Figure 1.** Subsequent electrochemical waves during reduction $[\text{Co}^{\text{III}}(\text{TPP})(\text{CF}_3)]$. The waves of the $[\text{Co}(\text{TPP})]$ product formed as a result of the second reduction event are marked with an asterisk (*).

**Figure 2.** Overlay of cyclic voltammograms of $[\text{Co}^{\text{III}}(\text{TPP})(\text{CF}_3)]$ (red) and $[\text{Co}(\text{TPP})]$ (blue) in the presence of decamethylferrocene (marked with a hash #).
Figure 3. $^{19}$F NMR spectrum of a reaction mixture of gem-difluorocyclopropanation of n-butyl acrylate with [Co$^{III}$(TPP)(CF$_3$)] and CoCp*. The inset shows the zoom for the signals that belong to the products.

The formation of the desired difluorocyclopropane suggests that upon reduction of [Co$^{III}$(TPP)(CF$_3$)] a cobalt-difluorocarbene complex is formed, which is apparently nucleophilic enough to facilitate CF$_2$ transfer to the electrophilic C=C bond of the acrylate.

The feasibility of the stoichiometric reaction shown in Scheme 7 triggered us to evaluate whether catalytic CF$_2$ transfer from Me$_3$SiCF$_3$ to n-butyl acrylate is possible when directly using a divalent cobalt(II) porphyrin catalyst in the presence of NaI as the activator. Indeed, with 5 mol% of [Co$^{II}$(TPP)] in THF catalytic formation (TON = 2.4) of the desired gem-difluorocyclopropanated acrylate was observed (Table 1, entry 1), albeit in low yield (12%). Besides the desired cyclopropane, the only other $^{19}$F-NMR detected fluorine containing side product was C$_2$F$_4$, presumably formed by free carbene dimerization. Control experiments show that in the absence of cobalt (Table 1, entry 2) no gem-difluorocyclopropane product was formed, which makes it unlikely that the cyclopropanation proceeds via free CF$_2$ or the free CF$_3^-$ anion. Additionally, we also tested other sources of CF$_2$ in this reaction but to no avail.
Table 1. Catalyst screening for CF₂ transfer from Me₃SiCF₃ to n-butyl acrylate

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<th>#</th>
<th>Catalyst</th>
<th>Solvent</th>
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<td>0%</td>
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<td>3</td>
<td>[Co²⁺(acac)₂]</td>
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<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>[Co²⁺(TPPF₂₀)]</td>
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Reaction conditions: 0.5 mmol of n-butyl acrylate; 2 mL of solvent; 5 mol% catalyst and 4 equivalents of TMSCF₃ with respect to n-butyl acrylate using ¹⁹F NMR spectroscopy and fluorobenzene as an internal standard. b Turnover numbers. c A second batch of 4 equivalents of Me₃SiCF₃ was added after 4 hours.

The low turnover numbers obtained using [Co(TPP)] as the catalyst suggests that the catalyst quickly deactivates under the applied reaction conditions. Hence, in an attempt to increase the TONs we explored a few additional catalysts (Table 1). The complexes [Co²⁺(acac)₂] and [Co²⁺(salophen)] proved inactive (entries 3-4), but the perfluorinated porphyrin complex [Co(TPPF₂₀)] (TPPF₂₀ = meso-tetra(pentafluorophenyl)-porphyrinato) indeed proved to be a somewhat more robust catalyst (entry 5) than [Co(TPP)], producing the desired gem-difluorocyclopropanated acrylate in 24% yield (TON = 4.8). Changing the initiator, solvent and the amount of Me₃SiCF₃ did not improve the yield of the difluorinated cyclopropane. However, when an additional batch of 4 equivalents of Me₃SiCF₃ was added after 4 hours (Table 1, entry 6), the yield increased to 40% (TON = 8). Any further addition of Me₃SiCF₃ did not lead to an increased yield.

The reactions reported in Table 1 serve as a proof-of-principle, clearly showing the feasibility of cobalt-catalysed CF₂ transfer from Me₃SiCF₃ to electron-deficient alkenes. However, the currently applied catalysts do not seem to be robust enough to obtain the cyclopropane product in high yields exceeding 40%. Hence, additional catalyst screening is clearly a subject of follow-up research.

Due to the redox non-innocent behaviour of carbenes,¹⁷ the electronic structure of oxidation state +II group 9 transition metal carbene complexes is best described as metal(III) ‘carbene radical’ species in which the unpaired electron resides mainly in the p-orbital of the carbene moiety (the SOMO being the metal d - carbene p antibonding π* molecular orbital, which is strongly polarized to carbon). This phenomenon has been reported for various transition metal carbene complexes, and can lead to unique reactivity of the carbene moiety.¹⁷⁻¹⁸ A similar behaviour has been reported for group 9 nitrene complexes.¹⁹ However, as pointed out by Woodcock and co-workers, cobalt porphyrinato difluorocarbene complexes actually might not behave as so-called ‘carbene radicals’.²⁰ According to their NBO analysis (DFT, M06-L functional) the spin density is mainly located on the metal (71%) rather than on the carbon atom (28%) and thus Co(por)CF₂ should have a substantial Fischer-type carbene character. Hence, unlike all other reported carbene adducts of cobalt(II) porphyrins,¹⁷⁻¹⁸,²⁰ the CF₂ adduct might not behave as a genuine ‘carbene radical’. Thus, we wondered if the CF₂ carbene adduct reacts with alkenes via a stepwise (typical for ‘carbene radicals’) or a concerted (typical for Fischer carbenes) mechanism. Therefore we performed additional DFT calculations to shed light on the
mechanistic details concerning the observed CF₂ transfer reactions from the [Co(por)(CF₂)] complex to the electron deficient acrylate.

**Scheme 8. Spin density plot and resonance structures of [Co(por)(CF₂)].**

In agreement with the results reported by Woodcock,¹⁰ the DFT (BP86, def2-TZVP) calculated NBO spin populations of [Co(por)(CF₂)], which is a simplified model of the experimental porphyrin complexes without meso-substituents, are 65% for cobalt and only 23% for the carbene carbon atom (Scheme 8).

**Figure 4. DFT calculated pathway for difluorocyclopropanation of methyl acrylate by a cobalt(II) porphyrinato complex (red) and metal-free CF₂ insertion on the left (blue).**

However, despite the dominant metalloradical character of the [Co(por)(CF₂)] species, the computed carbene transfer to methylacrylate proceeds via a stepwise radical process, just like for other cobalt(II) porphyrin catalysed carbene and nitrene transfer reactions (Figure 4, right). All attempts to find the transition state for a concerted addition of acrylate failed and converged to the stepwise pathway. Addition of the difluorocarbene species A to the olefin proceeds via a relatively low energy transition state (TS₁, ΔG°²⁹⁸K = +14.4 kcal mol⁻¹), generating the [Co(por)(CF₂-CH₂-CH•COOMe)] species B, which has its unpaired electron primarily localized at the γ-carbon of the ‘alkyl’ moiety. Hence, despite its significant Fischer-type character in the ground state, the reactivity of [Co(por)(CF₂)] follows the characteristics of a ‘carbene radical’ species. The transition state TS₂ for ring closure leading to formation of the cyclopropane product involves simultaneous C–C bond formation and homolytic cleavage of the Co–C bond. The barrier for this process is higher (ΔG°²⁹⁸K = +20.7 kcal mol⁻¹) and seems to be the rate limiting step of the overall reaction.
We also investigated an alternative pathway in which the difluorocarbene generated on the cobalt centre dissociates to react with the acrylate outside the metal coordination sphere. The release of free difluorocarbene from cobalt is energetically uphill ($\Delta G^{\circ}_{298K} = +16.3$ kcal mol$^{-1}$) and the reverse reaction is barrierless (Figure 4, left). This energy is comparable to the energy barrier for coupling of the cobaltocarbene with methyl acrylate. Formation of free CF$_2$ in this manner could be responsible for the observed formation of C$_2$F$_4$ as a side product in the reaction. However, free CF$_2$ carbene formation is unlikely associated with formation of the cyclopropane product, as the addition of free difluorocarbene to methyl acrylate has a much higher barrier ($\Delta G^{\ddagger}_{298K} = 28.0$ kcal mol$^{-1}$) than those associated with the metal-mediated pathway (TS1 and TS2 in Figure 4). Lewis-acid activation of the acrylate also seems unlikely, as in a separate control experiment with [Zn(TPP)] only traces (<1%) of the gem-difluorocyclopropane product was formed.

**Scheme 9. Proposed catalytic cycle for the difluorocyclopropanation of n-butyl acrylate catalysed by a cobalt(II) porphyrinato complex.**

Based on the above considerations we propose a mechanism in which the CF$_3^-$ anion (generated by the reaction of Me$_3$SiCF$_3$ and NaI) coordinates to [Co(PPP)] to form the anionic complex [Co(PPP)(CF$_3$)]$^-$, which produces the neutral carbene adduct [Co(PPP)(CF$_2$)] upon loss of a fluoride anion (Scheme 9). The cobalt difluorocarbene complex subsequently undergoes a stepwise radical-type addition to the acrylate double bond, forming an alkylcobalt(III) intermediate with the unpaired electron residing at the γ-carbon atom of the alkyl chain. Subsequent (and likely rate limiting) ring closure with concerted Co-C bond cleavage furnishes the difluorocyclopropane and regenerates the [Co(PPP)] catalyst.

**Summary and conclusions**

In conclusion, cobalt(II)-porphyrinato complexes catalyse difluorocarbene transfer from the trifluoromethyl anion to n-butyl acrylate forming a gem-difluorocyclopropane. The reactions reported here serve as a proof-of-principle, clearly showing the feasibility of cobalt-catalysed CF$_2$ transfer from Me$_3$SiCF$_3$ to electron-deficient alkenes. The data further show that the current cobalt(II) porphyrin catalysts quickly deactivate under the applied reaction conditions (maximum TON = 8), thus suggesting that future investigations aimed at the development of efficient protocols for catalytic CF$_2$
transfer reactions using Me₃SiCF₃ as the carbene source should focus on using catalysts that are more stable in the presence of the reactive, free CF₂ and CF₃⁻ intermediates generated under the applied reaction conditions.

Experimental and computational details

General information

All manipulations were performed under an N₂ atmosphere by standard Schlenk techniques or in a glovebox. Methanol and acetonitrile were distilled under nitrogen from CaH₂. THF, toluene and pentane were distilled under nitrogen from Na wire. The n-butyl acrylate substrate was passed through a plug of basic alumina, deoxygenated by bubbling dinitrogen for at least an hour and stored at 4°C in a Schlenk flask. [Co(TPP)] was purchased from STREM and used without further purification. [Co(TPPF₂₀)], [Co(TPP)Cl] and Co(salophen) (N,N'-bis(3,5-di-tert-butylsalicylidine)-1,2-benzenediamine(-2H))cobalt(II)) and PPh₃BrCF₂ were synthesised according to published procedures. [Co(acac)₂], TMSCF₃, TBAT (Tetrabutylammonium difluorotriphenylsilicate), LiI, SCDA (Sodium chlorodifluoroacetate), MDFA (Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate), K₂CO₃. K₂CO₃ Tetrabutyl ammonium bromide, CoCp*₂Bis(pentamethylcyclopentadienyl)cobalt(II) and TMSCF₃Br was purchased from commercial sources and used without further purification. NaI was dried at 100 °C in a vacuum oven overnight prior to use. Fluorobenzene was purchased from Sigma-Aldrich, degassed prior to use and stored with molecular sieves.

All NMR spectra were recorded at room temperature.

¹H NMR: Bruker Avance 400 (400 MHz) or Mercury 300 (300 MHz) machine was used and spectra were referenced internally to residual solvent resonance of CDCl₃ (δ = 7.26 ppm).

¹³C {¹H} NMR: Bruker Avance 400 (101 MHz), or Mercury 300 (75 MHz) machine were used and spectra were referenced internally to residual solvent resonance of CDCl₃ (δ = 77.2 ppm) or THF-d₈ (67.21, 25.31).

Abbreviations used are: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad.

High Resolution Mass spectra were measured on an AccuTOF LC, JMS-T100LP Mass spectrometer (JEOL, Japan). FD/FI probe (FD/FI) is equipped with FD Emitter, Carbotec or Linden (Germany), FD 10 μm. Current rate 51.2 mA/min over 1.2 min FI Emitter, Carbotec or Linden (Germany), FI 10 μm. Flashing current 40 mA on every spectra of 30 ms. Typical measurement conditions are: Counter electrode ̶ 10kV, Ion source 37V.

Synthesis of compounds

• Synthesis of [CoIII(TPP)(CF₃)]

113 mg of [Co(TPP)Cl] (0.16 mmol) and 1.5 mg of CsF (0.01 mmol) were dissolved in 3 mL of THF in a flame-dried Schlenk tube at room temperature. Subsequently 48 μL of TMSCF₃ (0.32 mmol) was added dropwise with a microsyringe. Subsequently, the reaction mixture was allowed to stir overnight. Evaporation of solvent led to formation of a red solid which was washed successively with water (5 mL) and pentane (5 mL) and dried in vacuo. Yield: 94 mg (80 %).

¹H NMR (300 MHz, Chloroform-δ) δ 8.96 (s, 8H, belonging to pyrrolic protons from the porphyrin ring), 8.13 (s, br, 8H, α-protons from the phenyl rings in the porphyrin ring), 7.75 (m, br, 12H, m-and p-protons of the phenyl rings)). ¹⁹F NMR (CDCl₃) −19.08 ppm. ¹³C NMR (75 MHz, THF-d₈) δ 142.64, 140.30, 131.90, 130.43, 125.68, 124.67, 118.38. (The CF₃ carbon was not detectible). UV-vis (MeOH), λmax/nm:
411, 540. **HRMS (FD):** calculated for C_{45}H_{28}CoF_{3}N_{4} (m/z) = 740.1598 (Da/e), found (m/z) 740.1624 (Da/e).**Elemental analysis**- No reliable CHNF analysis could be obtained even after multiple trials due to incomplete combustion (which is more commonly observed for F-containing compounds).

- **Gem-difluorocyclopropanation of n-butyl acrylate with [Co^{III}(TPP)(CF_{3})]**

Inside a glove-box, 37 mg (0.05 mmol) of [Co^{III}(TPP)(CF_{3})] and 8 μL (0.05 mmol) of n-butyl acrylate were dissolved in a Schlenk tube in 2 mL THF. Then 16.5 mg (0.05 mmol) of CoCp^{*} and 9.4 μL of fluorobenzene (0.1 mmol) were added. The Schlenk tube was then taken out of the glovebox and heated at 65 °C for 6 hours. An aliquot of the reaction mixture was dissolved in CDCl_{3}, filtered through a Teflon syringe filter and conversion to the product was determined using $^{19}$F NMR.

- **General procedure for catalytic gem-difluorocyclopropanation of n-butyl acrylate with TMSCF_{3} and optimisation studies**

0.025 mmol of the catalyst and 15 mg (0.1 mmol) of NaI was added to a flame dried Schlenk tube equipped with a stirring bar. Then 4 mL of THF was added followed by 72 μL (0.5 mmol) of n-butyl acrylate and 94 μL (1 mmol) of fluorobenzene internal standard. Finally 300 μL (~2 mmol) of TMSCF_{3} was added. The reaction mixture was then heated to a given temperature. At the end of the reaction an aliquot of the reaction mixture was dissolved in CDCl_{3} and the yield was determined by integration of the $^{19}$F NMR signals of butyl 2,2-difluorocyclopropane-1-carboxylate and fluorobenzene. Analytical data matched those reported in literature.\(^{25}\)

Different CF_{2} precursors were also tested in this reaction. The results of these reactions are summarised in the following table.

<table>
<thead>
<tr>
<th>catalyst</th>
<th>CF_{2} source</th>
<th>Initiator or another reagent</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Co(TPP)] and [Co(TPPF_{20})]</td>
<td>PPh_{3}CF_{2}Br</td>
<td>none</td>
<td>80 °C</td>
<td>0%</td>
</tr>
<tr>
<td>[Co(TPP)] and [Co(TPPF_{20})]</td>
<td>MDFA</td>
<td>KI, TMSCI</td>
<td>60 °C</td>
<td>0%</td>
</tr>
<tr>
<td>[Co(TPP)] and [Co(TPPF_{20})]</td>
<td>SCDA</td>
<td>K_{2}CO_{3} in DMF</td>
<td>60 °C</td>
<td>0%</td>
</tr>
<tr>
<td>[Co(TPP)] and [Co(TPPF_{20})]</td>
<td>TMSCF_{2}Br</td>
<td>Tetrabutyl ammonium bromide</td>
<td>60 °C</td>
<td>0%</td>
</tr>
</tbody>
</table>

- **CV studies**

0.01 mmol (7.4 mg) of [Co^{III}(TPP)(CF_{3})] and 50 mg of tetrabutylammonium hexafluorophosphate (NBu_{4}PF_{6}) were dissolved in 4 mL of THF. The solution was placed in a gastight single-compartment three-electrode cell equipped with a glassy carbon working electrode, coiled platinum wire auxiliary, and silver wire pseudoreference electrodes. All redox potentials are reported against the ferrocene/ferrocenium (Fc/Fc') redox couple. Decamethylferrocene was used as an internal standard (E = 0.427 V vs. Fc/Fc').\(^{26}\)

- **EPR studies**

In order to trap any reactive intermediates formed during the reaction of [Co^{III}(TPP)(CF_{3})] with CoCp^{*} we attempted the following reaction:
Inside a glove box, 1.7 mg (0.005 mmol) of CoCp*₂ was dissolved in 2 mL of 2-MeTHF. This solution was added to 3.7 mg (0.005 mmol) of [Co^{III}(TPP)(CF₃)] in a Schlenk tube. The Schlenk tube was sealed and taken out of the glove-box. To this, 7 μL of BF₃·Et₂O was added at −78°C under an N₂ atmosphere and allowed to stir for 10 minutes. The Schlenk tube was then reintroduced to the glove-box and 0.2 mL was transferred to an EPR tube. This sample was then measured at 20K. The corresponding spectrum is reported in Figure 5.

![Figure 5. EPR spectrum (20 K) of a mixture of [Co^{III}(TPP)(CF₃)], CoCp*₂ and BF₃·Et₂O in 2-MeTHF](image)

Consequently we also measured the EPR spectrum of the parent [Co^{II}(TPP)] complex in 2-MeTHF. This gave the same spectrum as observed previously on adding BF₃·Et₂O to the reduced [Co^{III}(TPP)(CF₃)] complex. This means that no intermediates were observed under these reaction conditions and the reduced complex underwent follow-up reactions to give the [Co^{II}(TPP)]. Adding acrylate to this reaction mixture did not lead to a different EPR spectrum.

An EPR spectrum was also measured directly after adding the CoCp*₂ (1.7 mg, 0.005 mmol) reductant to the [Co^{III}(TPP)(CF₃)] (3.7 mg, 0.005 mmol) complex in 2 mL THF. This time a distinctly different spectrum was obtained pointing to the formation of the anionic, paramagnetic [Co^{II}(TPP)(CF₃)]⁻ complex (Figure 6). Addition of acrylate to this mixture led to rapid loss of intensity of the signal, and apparently any other intermediates involved in the difluorocyclopropanation reaction of the n-butyl acrylate are too short-lived to detect with EPR spectroscopy.
Figure 6. (red) EPR spectrum of [Co^{II}(TPP)] complex in 2-MeTHF (20K). (blue) EPR spectrum of reduced [Co^{III}(TPP)CF_{3}] complex under the same conditions.

Computational details

Geometry optimizations were carried out using the TURBOMOLE 6.5 program package coupled with the PQS Baker optimizer via the BOpt package using the BP86 functional, def2-TZVP basis set and the resolution-of-identity method. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by numerical calculation of the Hessian matrix. Zero point energy and gas phase thermal corrections (enthalpy and entropy, 298K, 1 bar) were calculated. Estimated condensed phase (1 L mol^{-1}) free energies were obtained from these data by neglecting the enthalpy RT term and subsequent correction of the condensed phase (CP) reference volume \([S_{CP} = S_{GP} + R \ln(1/24.5)]\) for all steps involving a change in the number of species.

Figure 7. Two possible pathways for cyclopropanation of methyl acrylate mediated by [Co(por)(CF_{3})]. Free energies in kcal mol^{-1}. Selected bond distances (Å) are presented as well.
Table 2. Absolute calculated SCF energies ($E_{\text{SCF}}$), zero point corrections (ZPE), thermal corrections (ZPE+RT+TRV), entropy contribution (TS), zero point energies ($E_{\text{ZPE}}$), enthalpies (H) and free energies ($G^{298}$).

<table>
<thead>
<tr>
<th></th>
<th>$E_{\text{SCF}}$ /hartree</th>
<th>ZPE /hartree</th>
<th>ZPE+RT+TRV /hartree</th>
<th>TS /hartree</th>
<th>$E_{\text{ZPE}}$ /hartree</th>
<th>H /hartree</th>
<th>$G^{298}$ /hartree</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF$_2$</td>
<td>-237.8190788</td>
<td>0.00651</td>
<td>0.01048</td>
<td>0.0274</td>
<td>-237.813</td>
<td>-237.809</td>
<td>-237.836</td>
</tr>
<tr>
<td>Methylacrylate (MA)</td>
<td>-306.6104266</td>
<td>0.0921</td>
<td>0.09983</td>
<td>0.03833</td>
<td>-306.518</td>
<td>-306.511</td>
<td>-306.549</td>
</tr>
<tr>
<td>TS3</td>
<td>-544.4259534</td>
<td>0.10064</td>
<td>0.1116</td>
<td>0.04788</td>
<td>-544.325</td>
<td>-544.314</td>
<td>-544.362</td>
</tr>
<tr>
<td>Cyclopropane</td>
<td>-544.5041566</td>
<td>0.10485</td>
<td>0.11487</td>
<td>0.04479</td>
<td>-544.399</td>
<td>-544.389</td>
<td>-544.434</td>
</tr>
<tr>
<td>Co(por)</td>
<td>-2371.924224</td>
<td>0.26691</td>
<td>0.28559</td>
<td>0.06188</td>
<td>-2371.66</td>
<td>-2371.64</td>
<td>-2371.7</td>
</tr>
<tr>
<td>Co(por)CF$_2$</td>
<td>-2609.78417</td>
<td>0.27591</td>
<td>0.29839</td>
<td>0.07267</td>
<td>-2609.51</td>
<td>-2609.49</td>
<td>-2609.56</td>
</tr>
<tr>
<td>TS1</td>
<td>-2916.388542</td>
<td>0.36903</td>
<td>0.39901</td>
<td>0.09089</td>
<td>-2916.02</td>
<td>-2915.99</td>
<td>-2916.08</td>
</tr>
<tr>
<td>B</td>
<td>-2916.41412</td>
<td>0.37122</td>
<td>0.40082</td>
<td>0.08919</td>
<td>-2916.04</td>
<td>-2916.01</td>
<td>-2916.1</td>
</tr>
<tr>
<td>TS2</td>
<td>-2916.379734</td>
<td>0.3703</td>
<td>0.40021</td>
<td>0.09097</td>
<td>-2916.01</td>
<td>-2915.98</td>
<td>-2916.07</td>
</tr>
</tbody>
</table>
Table 3. Relative calculated SCF energies ($\Delta E_{SCF}$), zero point energies ($\Delta E_{ZPE}$), enthalpies ($\Delta H$) entropy contributions ($T_S$), and free energies in gas ($\Delta G^{298}$) and solution phase ($\Delta G_{sol}^{298}$).

<table>
<thead>
<tr>
<th></th>
<th>$\Delta E_{SCF}$</th>
<th>$\Delta E_{ZPE}$</th>
<th>$\Delta H$</th>
<th>$T_S$</th>
<th>$\Delta G^{298}$</th>
<th>$\Delta G_{sol}^{298}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Co(por)CF$_2$]+ MA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TS3 + [Co(por)]</td>
<td>27.87356</td>
<td>27.5849</td>
<td>27.22722</td>
<td>-0.04788</td>
<td>28.01205</td>
<td>28.01205</td>
</tr>
<tr>
<td>B</td>
<td>-12.251</td>
<td>-10.2367</td>
<td>-10.6195</td>
<td>13.68802</td>
<td>3.068524</td>
<td>0.582524</td>
</tr>
</tbody>
</table>

Figure 8. Calculated structure of [Co(por)CF$_2$], and of the stationary points along the stepwise addition of methyl acrylate to Co(Por)CF$_2$: TS1; intermediate B; and TS2.
Single crystal X-ray diffraction studies

Despite numerous attempts of crystallization of [Co\textsuperscript{II}(TPP)(CF\textsubscript{3})] using various solvent combinations, the obtained crystals were always diffracted very poorly or were of bad quality. The best data could be obtained from the material obtained by slow evaporation of a chloroform solution of [Co\textsuperscript{II}(TPP)(CF\textsubscript{3})] in dark. This resulted in formation of clustered crystals of [Co\textsuperscript{II}(TPP)(CF\textsubscript{3})] chloroform solvate which despite twinning and overall poor data quality, have shown the expected connectivity between atoms.

Data was collected on a Bruker D8 Quest Eco diffractometer, equipped with a TRIUMPH monochromator and a CMOS PHOTON 50 detector, using Mo-K\textsubscript{α} radiation (\(\lambda = 0.71073\) Å). Data collection was conducted at 150(2) K. The intensity data were integrated with the Bruker APEX2 software.\textsuperscript{33} Absorption correction and scaling was performed with SADABS.\textsuperscript{34} The structures were solved with SHELXS-97.\textsuperscript{35} Least-squares refinement was performed with SHELXL-2013\textsuperscript{35} against \(F^2\) of all reflections. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were located at calculated positions using a riding model.

Apparent crystal data: \(C_{45}H_{28}CoF_3N_4\cdot CHCl_3\) \(F_w = 860.01\), red rough fragment, 0.32 x 0.21 x 0.20 mm, monoclinic, \(P\ 2_1/n\) (no. 14), \(a = 13.4359(9)\), \(b = 18.2392(13)\), \(c = 15.6674(11)\) Å, \(\beta = 90.312(4)\), \(V = 3839.4(5)\AA^3\), \(Z = 4\), \(R1/wR2: 0.1221/0.3091\). \(S = 2.081\).

\begin{figure}[h]
  \centering
  \includegraphics[width=0.5\textwidth]{image.png}
  \caption{Connectivity of [Co\textsuperscript{II}(TPP)(CF\textsubscript{3})] as determined by single crystal X-ray diffraction. The CHCl\textsubscript{3} solvate molecule is shown.}
\end{figure}

Acknowledgements

Ed Zuidinga (HIMS, UvA) is thanked for mass measurements.
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Summary

Nitrene- and carbene-complexes of cobalt(II) porphyrins that are best described as porphyrin cobalt(III)-nitrene and carbene-radicals, respectively, are the key players in this thesis. Discrete spin transfer from the cobalt(II) metalloradical to the nitrene and carbene moiety induces interesting reactivity in these systems; especially for application in catalytic systems. Starting from rigorous characterisation to application in catalysis, this thesis shows that in the coordination sphere of metals, radicals are tamed and their reactivities can be attuned for applications in challenging and new chemical transformations.

CHAPTER 1 gives an overview of the metalloradical chemistry of cobalt, and the bio-inspired tools used in open-shell organometallic chemistry to get control over radical-type reactions in the coordination sphere of transition metals. Radicals are generally considered too reactive to be selective. While this might be true for free radicals, for radicals in the coordination sphere of a metal complex this is certainly not the case. For example, in the active site of 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. Such 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 perform most commercially relevant chemical processes using base metals. Base metals, however, typically show one-electron reactivity and thus easily take part in radical-type reactions, just as in nature. 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 opens new ways towards chemical transformations which are otherwise difficult or even impossible to perform using traditional methods.

Metal complexes with an unpaired electron in their d-orbitals (metalloradicals) can take part in one-electron reactions. One strategy of exploiting them is by using the redox non-innocence of substrates. Electrophilic substrates like electron-deficient carbenes and nitrenes are well suited for this. One such catalyst that has been particularly successful in this strategy are the cobalt(II) porphyrins. Application of cobalt(II) porphyrins in carbene and nitrene transfer reactions goes beyond classical carbene and nitrene reactivity (cyclopropanations and aziridinations). While the mechanisms and intermediates for carbene transfer reactions catalysed by [Co^II(Por)] catalysts have been studied in detail, limited experimental evidence exists that supports the DFT calculated mechanisms and intermediates in nitrene transfer reactions catalysed by [Co^II(Por)] catalysts. The detailed characterisation and understanding of these systems is inevitable in enriching the synthetic applicability of these systems.

CHAPTER 2 describes the rigorous characterisation of the porphyrin cobalt(III)-nitrene radical species using a variety of spectroscopic and spectrometric techniques. To fully characterise the Co^III-‘nitrene radical’ species that are proposed as intermediates in nitrene transfer reactions mediated by cobalt(II)
porphyrins, different combinations of cobalt(II) complexes of porphyrins and nitrene transfer reagents were combined and the generated species were studied using EPR, UV-Vis, IR, VCD, UHR-ESI-MS and XANES/XAFS measurements. Reactions of cobalt(III) porphyrins **1** (P1 = meso-tetraphenylporphyrin (TPP)) and **1** (P2 = 3,5-DiBu-ChenPorphyrin) with organic azides 2 (NsN3), 2 (TsN3) and 2 (trocN3) led to the formation of mono-nitrene species **3**, **3**, and **3**, respectively, which are best described as [Co(II)(por)(NR’’)] ‘nitrene radicals’ (imidyl radicals) resulting from single electron transfer from the cobalt(II) porphyrin to the ‘nitrene’ moiety (Ns: R’’ = S(O2)pC6H12NO2; Ts: R’’ = S(O)C6H12CCl3). Remarkably, the reaction of **1** with N-nosyl iminoiodane (Phl=NNs) 4 led to the formation of a bis-nitrene species **5**. This species is best described as a triple-radical complex [[(por’’)Co(III)(NR’’’’)]2] containing three ligand-centred unpaired electrons: two nitrene radicals (NR’’’’) and one oxidized porphyrin radical (por’’’). Thus, the formation of the second nitrene radical involves another intramolecular one-electron transfer to the ‘nitrene’ moiety, but now from the porphyrin ring instead of the metal centre. Interestingly, this bis-nitrene species is observed only on reacting 4 with **1**. Reaction of the more bulky **1** with 4 results again in formation of mainly mono-nitrene species **3**, according to EPR and ESI-MS spectroscopic studies. Additionally, conversion of mono-nitrene species **3** into bis-nitrene species **5** upon reaction with 4 was demonstrated. Solutions containing **3** and **5** proved to be still active in catalytic aziridination of styrene, consistent with their proposed key-involvement in nitrene-transfer reactions mediated by cobalt(II) porphyrins.

![Figure 1](#)

**Figure 1.** Left: The mono-nitrene species of the type **3** obtained from **1** and organic azide 2. Right: The six-coordinate bis-nitrene species **5** obtained from **1** and N-nosyl-iminoiodane 4.

**Chapter 3** describes 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). All the spectroscopic techniques used thus far in chapter 2 helped us describe the electronic structures of these intermediates in great detail, but did not give us any information about their geometry, nor any direct spectroscopic evidence for the cobalt(III) oxidation state of the metal. X-ray absorption spectroscopy (XAS) studies can be used to gain this information. A further question that rises is, whether or not the mono-nitrene complex **3** has an additional ligand Y and if so, what is the nature of that ligand. To shine more light on this matter, theses intermediates was probed by the aid of XAS. EXAFS analysis of the spectra led to the confirmation that both mono- and bis-nitrene species contain a cobalt(III) centre. More interestingly, they are also both six-coordinate, meaning that there is indeed a sixth ligand Y present in case of the mono-nitrene **3**, which was so far not detected. This led us to perform some TD-DFT calculations of K-edge XAS to find a reasonable fit (plausible neutral or anionic...
ligands) based on the relative intensity of the rising edge of the XANES experimental spectra. At this stage, calculated spectra suggested that anionic ligands show similar intensities as that of the experimental spectrum for the mono-nitrene species.

Subsequently, we decided to perform XAS measurements of two other five-coordinate porphyrin complexes containing a cobalt(III) metal centre, whose coordination geometries were ascertained via X-ray diffraction. These were \([\text{Co}^{III}(\text{TPP})(\text{Cl})]\) and \([\text{Co}^{III}(\text{TPP})(\text{CF}_3)]\). The XAS data of these five-coordinate complexes also showed similar intensities of the rising edge in the XANES region as those of the mono-nitrene species. Supporting TD-DFT calculations were performed, and carefully analysed.

Based on the combination of experimental and theoretical XAS data of the Co\textsuperscript{II}–nitrene radical intermediates (3\textsuperscript{P}_1NS and 5\textsuperscript{P}_1NS) and the cobalt(III) complexes \([\text{Co}^{III}(\text{TPP})(\text{Cl})]\) and \([\text{Co}^{III}(\text{TPP})(\text{CF}_3)]\) we could conclude that the relative intensities of the XANES features cannot always be straightforwardly correlated to the coordination numbers around the metal centre. The use of XANES as a diagnostic
tool to distinguish reliably between 5- and 6-coordinate [Co\(^{III}\)(Por)] species is complicated by several contributing factors. Pre-edge intensities are influenced by π- donation and higher energy transitions (in all cases) between 7713-7720 eV are not purely 1s to 4p + LMCT shakedown transitions, but largely 1s to porphyrin π* transitions for many of the [Co\(^{III}\)(Por)] species. Furthermore, these transitions can be hidden underneath the rising edge. While for the mono-nitrene species the absence of a shakedown transition and the weak pre-edge intensity (experimental and DFT calculated) initially led us to believe that an anionic donor binds to the 6th coordination site of 3\(^{P3}\)N\(_5\), it is now safe to conclude that this is actually not the case. This is also in line with the experimental observations from catalysis, where reactions are performed in apolar solvents and the use of additives does not have a dramatic effect in nitrene-transfer reactions catalysed by cobalt(II) porphyrins. The sixth ligand in the mono-nitrene species is therefore most likely a neutral amine donor (derived from the azide), rather than an anionic (amido) ligand.

**Chapter 4** describes 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. We initiated these investigations in an attempt to broaden the scope of using nitrene-radicals in organic synthesis. For the porphyrin-Co(III)-nitrene radicals the reactivities were thus far limited to intramolecular C–H insertions and aziridination reactions, while for the carbene radicals the current scope of reactions is currently much broader. Therefore, we wanted to use organic azides with other reaction partners like alkynes so that they could take part in ring-closing reactions to give N-heterocycles. While trying to evaluate the effectiveness of ortho-substituted phenyl azides (OH/NH\(_2\) substitution) in ring-closing reactions with phenyl acetylene catalysed by [Co\(^{II}\)(Por)], we discovered that the hydrogen atom of the ortho-substituent is readily abstracted by the nitrene radical intermediate. This leads to formation of reactive intermediates like o-quinone monoimines (OQMI; for OH) and o-phenylinendiimines (OPDI; for NH\(_2\)). These reactive compounds rapidly undergo follow-up reactions, thus preventing any direct (radical-type) coupling reactions of the nitrene radical intermediate with C=C or C≡C bonds of other substrates to give ring-compounds. The o-quinone monoimines (Y = OH) easily dimerize and produce phenoxizinones under aerobic conditions (Figure 4). In the presence of 1-butoxyethene the o-quinone monoimine can also be trapped in an inverse electron demand Diels Alder (IEDDA) reaction, producing benzoazines (Figure 4). Formation of orthophenylinendiimine (OPDI) from ortho-NH\(_2\)-phenylazide is also associated with H atom abstraction of the cobalt(III) nitrene radical from the NH\(_2\) substituent in the ortho position. As a result, azobenzenes are obtained (Figure 4). Attempts to react ortho substituted azides with other reaction partners by altering the reaction conditions were not successful. DFT computations are in agreement with the experiments; HAT from the ortho-YH substituent (Y= O or NH) to the nitrene moiety has a (very) low barrier in both cases.
The transformation of the o-NH₂-phenyl azides is unique in the sense that it is the only chemical pathway towards substituted o-amino-azobenzenes directly from azides. The cobalt(III) porphyrin catalysed pathway is a functional group tolerant system to synthesise azobenzenes from azides which in turn are prepared in one step from commercially available amines. The synthesised azobenzenes are bathochromically shifted compared to the unsubstituted azobenzenes. Based on the crystal structure, the ortho-amine substituent was found to participate in H-bonding interaction with the azo N-atom. This can be expected to have consequences on the trans-cis isomerisation of these compounds, worthy of future investigations (the aspect is beyond the scope of the studies described in this thesis). At the same time, the amine functionality in these compounds can also be used for further functionalisation of the azobenzenes in future studies.

**Figure 4.** Transformations observed in reaction of o-substituted (OH or NH₂) phenyl azides with [Co\(^{II}\)(Por)] catalysts.

**CHAPTER 5** describes our efforts to use a different ligand system in a nitrene-transfer reaction; Corroles instead of porphyrins. For nitrene transfer reactions from azides catalysed by [Co\(^{II}\)(Por)] catalysts, azide activation on the catalyst is known to be the rate limiting step. In this step the cobalt centre undergoes an oxidation from cobalt(II) to cobalt(III). Therefore, we hypothesised that the use of a ligand that retains the planar geometry of the porphyrin ligand but is more electron-rich could be beneficial to lower the barrier of this rate-limiting azide activation step. Corroles are porphyrin-like ligands with a smaller pocket and a higher electron-density overall. Therefore, we synthesised three corrole complexes of cobalt ([Co\(^{III}\)(Cor)(PPh\(_3\))] with electronically different substituents. As a benchmark reaction we chose the intramolecular ring-closing C–H amination reaction of (4-azidobutyl)benzene (in presence of Boc\(_2\)O) to give the saturated N-heterocycle tert-butyl-2-phenylpyrrolidine-1-carboxylate (Scheme 1). This reaction is known to proceed with excellent yields using [Co\(^{II}\)(Por)] catalysts (in particular [Co\(^{II}\)(TMP)]), but requires a long reaction time of about 16h. The synthesised [Co\(^{III}\)(Cor)(PPh\(_3\))] complexes investigated in this study could be chemically reduced to generate the corresponding mono-anionic [Co\(^{III}\)(Cor)]\(^−\) complexes, which are catalytically active in the same ring-closing C–H amination reaction. These reduced species were characterised by CV, EPR and UV-vis spectro-electrochemistry. Upon reduction, all synthesised [Co\(^{III}\)(Cor)(PPh\(_3\))] complexes proved not only to be active in the ring-closing C–H amination reaction of (4-azidobutyl)benzene, but also to be much faster (more than 2.5 times) than the reported [Co\(^{II}\)(TMP)] catalyst in the same reaction. We
also performed computational studies to confirm that the improved rates are due to lower barriers of the rate limiting azide activation step (Figure 5). Indeed, DFT calculations reveal a much lower transition state barrier for the mono-anionic \([\text{Co}^\text{II}(\text{Cor})]^-\) complexes than for the neutral \([\text{Co}^\text{II}(\text{Por})]\) complexes. Despite a different starting electronic structure of the catalyst, the thus produced nitrene species are best described as nitrene-radical intermediates, with most of their spin density located at the nitrene nitrogen atom, similar to the nitrene-radical intermediates reported for the neutral \([\text{Co}^\text{II}(\text{Por})]\) systems.

\[
\text{Scheme 1. Application of } [\text{Co}^{\text{II}}(\text{Cor})(\text{PPh}_3)] \text{ pre-catalysts in the ring-closing amination reaction of (4-azidobutyl)benzene.}
\]

\[
\begin{align*}
&\text{[Co}^{\text{III}}(\text{Cor})(\text{PPh}_3)] (5 \text{ mol\%}) \\
&\text{reductant (5 mol\%)} \\
&\text{Toluene, 100 °C, 16h}
\end{align*}
\]

\[
\begin{align*}
&\text{Boc}_2\text{O} \\
&\text{BocN} \\
&\text{+} \\
&\text{NHBoC}
\end{align*}
\]

\[
\text{Figure 5. (left) DFT-D3 calculated (TurboMoloe BP86, def2-TZVP) free energies (\Delta G_{298K} \text{ in kcal mol}^{-1}) for the key step of azide activation by the } [\text{Co}^{\text{III}}(\text{Cor})]^-\text{ complex. (right) Spin density plot of the thus formed nitrene radical intermediate B showing maximum spin density at the nitrene nitrogen.}
\]

\text{CHAPTER 6 describes a novel route developed for the synthesis of several substituted indolines, which are substructures of a variety of natural products and pharmaceutically relevant compounds (Scheme 2). It proceeds efficiently via a } [\text{Co}^\text{II}(\text{Por})]\text{-catalysed pathway via activation of an in-situ formed diazo compound. The key-step in this reaction is a 1,5 HAT reaction, which is usually considered to be an undesirable pathway in organic free-radical chemistry (Scheme 2). In this reaction, however, it is a desirable step, making catalytic synthesis of indolines possible.
Scheme 2. General strategy for synthesis of diazo-precursors employed in the \([\text{Co}^{II}(\text{TPP})]\)-catalysed ring-closing reaction to give indolines.

To the best of our knowledge, this is the first example of the synthesis of \(N\)-heterocycles via a cobalt(III)-carbene radical mediated C–H activation/rebound mechanism. DFT calculations show that the reaction proceeds via unusually low barriers and the spin density in intermediates C and D are delocalised in the organic fragments (Figure 6). The metallo-radical catalysed indoline synthesis in this work represents an example of a net, formal (intramolecular) carbene insertion reaction into a benzylic C–H bond, but proceeds via a radical mechanism and displays highly controlled reactivity of the key Co\(^{III}\)-carbene radical intermediates involved.

Figure 6. (A) DFT-D3 calculated (Turbomole BP86, def2-TZVP) free energies (\(\Delta G_{298K}^\circ\) in kcal mol\(^{-1}\)) for the proposed reaction pathway. Energies of all intermediates are reported with respect to species A as the reference point (barriers for the transition states are reported in brackets). (B) Spin density plot of intermediate C showing maximum spin density at the carbene carbon. (C) Spin density plot of intermediate D after the 1,5-HAT step showing maximum spin density on the benzylic carbon and some delocalisation over the adjacent phenyl ring.
CHAPTER 7 describes our efforts to enable CF₂-carbene transfer reactions with cobalt(II)-porphyrin catalysts. While carbene transfer from diazo precursors via a metal complex is more or less well explored, transfer of difluorocarbene (CF₂) via a metal complex remains a long-standing challenge. The special electronic properties of the CF₂ carbene causes the metal-CF₂ bond to be typically 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 CF₂ carbene moiety to an organic substrate. To evaluate the feasibility of difluorocarbene transfer from cobalt to an olefin we first decided to investigate whether a difluorocarbene cobalt(II) complex can be formed by one-electron reduction of the novel trifluoromethyl cobalt(III) complex [Co³⁺(TPP)(CF₃)]. Based on precedents in literature, we anticipated that the release of F⁻ from the anionic [Co²⁺(TPP)(CF₃)]⁻ complex could lead to formation of a [Co(TPP)(CF₂)] species, potentially capable of CF₂ transfer to acrylates under mild reaction conditions. This was indeed successful in a stoichiometric reaction shown in Scheme 3 (but with low yields). A catalytic version of the same transformation using a [Co³⁺(TPP₁₂₀)] complex gave a turnover number of 8 towards the gem-difluorocyclopropanated product.

Scheme 3. Reaction of [Co³⁺(TPP)(CF₃)] with n-butyl acrylate upon one-electron reduction.

In agreement with the results reported by Woodcock and co-workers the DFT (BP86, def2-TZVP) calculated NBO spin populations of [Co(por)(CF₂)], which is a simplified model of the experimental porphyrin complexes without meso-substituents, are 65% for cobalt and only 23% for the carbene carbon atom. However, despite the dominant metalloradical character of the [Co(por)(CF₂)] species, the computed carbene transfer to methylacrylate proceeds via a stepwise radical process, just like for other cobalt(II) porphyrin catalysed carbene and nitrene transfer reactions as shown in Figure 7.

The low TON of 8 in this system suggests that future investigations aimed at the development of this protocol using Me₃SiCF₃ as the carbene source should focus on using catalysts that are more stable in the presence of the reactive, free CF₂ and CF₃⁻ intermediates generated under the applied reaction conditions.
Combined, the work described in this thesis shows enzyme-like controlled radical-type reactions with metallo-radical complexes of cobalt(II) provide interesting, new synthetic routes to useful organic products. Formation of nitrene-radical and carbene-radical species upon activation of nitrene and carbene precursors with these catalysis, respectively, leads to fascinating follow-up reactivity involving controlled radical-type reaction steps, made possible by the intrinsic one-electron reactivity of cobalt. The reactivity can be controlled by changing the ligands, and the reactions lead to interesting products such as phenoxazines, benzoxazines, azobenzenes, indolines and difluorocyclopropanes. Future studies in the field of cobalt(II) metalloradical catalysis are expected to uncover many more exciting and novel reactions proceeding via one-electron pathways. This will not only be of synthetic use, but also provides an inspiration for additional fundamental research in molecular catalysis, stimulating additional mechanistic studies and encouraging many thought-provoking synthetic shortcut explorations.
Samenvatting


In HOOFDSTUK 1 wordt een overzicht gegeven van de metallo-radicaalchemie van kobalt en de biogeïnspireerde instrumenten (strategien? Of methoden?) die gebruikt worden in ‘open-shell’ organometalchemie om controle te krijgen over radicaalreacties in de coördinatieschil van overgangsmetalen. Van radicalen wordt vaak aangenomen dat ze te reactief zijn om selectief te kunnen reageren. Hoewel dit waarschijnlijk waar is voor vrije radicalen, is dit voor radicalen in de coördinatieschil van metalcomplexen zeker niet het geval. Bijvoorbeeld, in het actieve centrum van het enzym ?GOase vinden selectieve één-elektron-reacties plaats rondom het centrale koperatoom. In het actieve centrum neemt niet alleen het koperatoom maar ook een aminozuurfragment rondom het metaalcentrum deel aan overall gecombineerde twee-elektron redoxreacties. De vinden echter plaats in stapsgewijze één-elektron processen, waarbij een radicalair aminozuurfragment gevormd wordt. Dit ‘ligand radicaal’ is direct betrokken in een cooperatief C-H activeringsprocess, waarbij in samenwerking met het koper(II) ion een alcohol selectief geoxideerd wordt tot een aldehyde. Scheikundigen zijn geïnspireerd geraakt door dit soort biochemische strategieën en proberen radicaalreacties te sturen met eenvoudige synthetische moleculaire katalysatoren door gebruik te maken van vergelijkbare instrumenten zoals die gebruikt worden in de natuur maar zonder de complexiteit van een enzym. Dit soort op de biologie geïnspireerde strategieën waren initiële gedreven door wetenschappelijke nieuwsgierigheid, maar in het licht van duurzaamheidsproblematiek en materiaalschaarste is dit een dringende behoefte geworden. Er is een overvloed aan eerste-rij overgangsmetalen en de prijzen van deze metalen zijn relatief laag, in tegenstelling tot de hoge prijs van schaarse edelmetalen. Met dit in het achterhoofd is het wenselijk om nieuwe kataysatoren te ontwikkelen voor commercieel relevante chemische processen op basis van eerste-rij overgangsmetalen. Dergelijke metalen vertonen vaak één-elektron reactiviteit en nemen dus gemakkelijk deel in radicaalreacties, net zoals in de natuur. Daarom is het belangrijk om radicaalreacties in de coördinatieschil van overgangsmetalen beter te begrijpen en de controlemechanismen toe te passen in nieuwe duurzame benaderingen. Gecontroleerde radicaalreacties in de coördinatieschil van eerste-rij overgangsmetaalkatalysatoren maken tevens de weg vrij om nieuwe chemische transformaties te ontwikkelen die moeilijk of zelfs onmogelijk uit te voeren zijn via traditionele methodes.

Metaalcomplexen met een ongepaard elektron in hun d-orbitalen (metallo-radicalen hebben precies één ongepaard electron in de d-schil) kunnen gemakkelijk deelnemen aan één-elektron reacties. Een mogelijke strategie om hiervan te profiteren is door gebruik te maken van redox-actieve (‘noninnocent’) substraten. Elektrofiele substraten zoals elektron-arme carbenen en nitreen zijn hiervoor zeer geschikt. Kobalt(II) porfyriene katalysatoren zijn bijzonder succesvol in het genereren
van zogenoemde carbeen- of nitreenradicalen. De toepassing van kobalt(II) porfyrines in carbeen en nitreen-gebaseerde additie- en insertiereacties gaan de klassieke carbeen- en nitreenreactiviteit voorbij (cyclopropanaties en aziridinaties). Van carbeenoverdrachtsreacties gekatalyseerd door $[\text{Co}^0(\text{Por})]$ zijn de mechanismen en intermediairen in detail bestudeerd, maar er bestond voorafgaand aan het onderzoek beschreven in dit proefschrift nog maar weinig experimenteel bewijs ter ondersteuning van vergelijkbare, op DFT berekeningen gebaseerde radicaalmechanismen voor nitreenoverdrachtsreacties gekatalyseerd door $[\text{Co}^0(\text{Por})]$. Van deze systemen is een gedetailleerde karakterisering en meer begrip nodig om de synthetische toepassingen van deze systemen te verrijken en optimaliseren.

In **Hoofdstuk 2** wordt de grondige karakterisering van porfyrine kobalt(III) nitreenradicaal verbindingen beschreven. Hiervoor is gebruik gemaakt van diverse spectroscoïpische en spectrometrische technieken. $\text{Co}^{III}$-nitreen radicaalverbindingen zijn eerder gepostuleerd als belangrijke reactieve intermediairen, die een sleutelrol spelen in nitreenoverdrachtsreacties gekatalyseerd door kobalt(II) porfyrines. Om deze verbindingen volledig te karakteriseren zijn verschillende combinaties gebruikt van kobalt(II) porfyrine complexen en nitreen-precursors. De aldus gevormde nitreenradicaalverbindingen zijn bestudeerd met EPR, UV-Vis, IR, VCD, UHR-ESI-MS en XANES/XAFS metingen. De reacties van kobalt(II) porfyrines $1^{P1}$ (P1 = meso-tetraphenylporfyrine (TPP)) en $1^{P2}$ (P2 = 3,5-Di$'$/Bu-CH$_2$Ph) met organische aziden $2_{Ns}$ (NsN$_3$), $2_{Ts}$ (TsN$_3$) en $2_{troc}$ (trocN$_3$) heeft geleid tot de vorming van de mono-nitreen verbinding $3^{P1}_{Ns}$, $3^{P2}_{Ns}$ en $3^{P2}_{troc}$ (Figuur 1). Deze verbindingen kunnen het best beschreven worden als $[\text{Co}^{III} (\text{por}) (\text{NR}''^{+})]$ ‘nitreenradicaal’ (imidyl radicalen) en zijn het gevolg van de overdracht van één elektron van het kobalt(III) porfyrine naar de ‘nitreen’ groep tijdens de activering van het azide substraat aan kobalt (Ns: $R'' = \text{SO}_2-p$-$\text{C}_6\text{H}_4\text{NO}_3$; Ts: $R'' = \text{SO}_2 \text{C}_6\text{H}_4\text{Cl}$; troc: $R'' = \text{C}(\text{O})\text{OCH}_2\text{CCl}_3$). Opmerkelijk is dat de reactie van $1^{P1}$ met N-nosyl iminioiodaan (Phl=NNs) $4_{Ns}$ leidt tot de vorming van een bis-nitreen verbinding $5^{P1}_{Ns}$ (Figuur 1). Deze verbinding kan het best worden beschreven als een drievoudig radicaal complex $[(\text{por}^{+})\text{Co}^{III} (\text{NR}''^{+})]$, met drie ligand-gecentreerde ongepaarde elektronen: twee nitreen radicalen (NR''$^{+}$) en één geoxideerd porfyrine radicaal (por$^{+}$). De vorming van het tweede nitreenradicaal is alleen mogelijk door een intramoleculaire overdracht van een ongepaard elektron naar het tweede ‘nitreen’ ligand. Dit elektron komt echter niet zoals tijdens de vorming van het eerste nitreenradicaal van cobalt, maar ditmaal uit de porfyrine ring in plaats van het metaalcentrum. Interessant genoeg worden deze bis-nitreenradicaalverbindingen alleen waargenomen wanneer N-nosyl iminioiodaan $4_{Ns}$ met $1^{P1}$ reageert.

**Figuur 1.** Links: De mono-nitreenverbinding van het type $3^{P1}_{Ns}$ die verkregen wordt door de reactie van $1^{P2}$ met het organische azide $2_{Ns}$. Rechts: De zesvoudig gecoördineerde bis-nitreen verbinding $5^{P1}_{Ns}$ die verkregen wordt door de reactie van $1^{P1}$ met N-nosyl-iminioiodaan $4_{Ns}$.
Volgens EPR en ESI-MS spectroscopische studies resulteert de reactie van het sterisch gehinderde cobalt(II) porfyrinecomplex $1^{P1}$ met $4_{Ns}$ voornamelijk in de vorming van mono-nitreen verbinding $3^{P1}_{Ns}$. Verder is aangetoond dat mono-nitreen verbinding $3^{P1}_{Ns}$ wordt omgezet in bis-nitreen verbinding $5^{P1}_{Ns}$ waarneer het reageert met $4_{Ns}$. Oplossingen die $3^{P1}_{Ns}$ en $5^{P1}_{Ns}$ verbindingen bevatten zijn actief in de katalytische aziridinering van styreen. Dit is in overeenstemming met hun gepostuleerde sleutelrol in nitreenoverdrachtsreacties gekatalyseerd door kobalt (II) porfyrine complexen.

In HOOFDSTUK 3 worden inspanningen beschreven om de geometrie en de spectroscopische oxidatietoestand van de nitreen-radicaal verbindingen vast te stellen met behulp van X-ray Absorptie Spectroscopie (XAS). Alle spectroscopische technieken die tot dusver gebruikt zijn in hoofdstuk 2 hebben geholpen om de elektronische structuur van deze intermediairen tot in detail te bestuderen, maar hebben weinig informatie verschaft over de coordinatiegeometrie van deze verbindingen. Ook was er nog geen direct spectroscopisch bewijs voor de gepostuleerde kobalt(III) oxidatietoestand van het centrale metaalcenter. Studies met behulp van X-ray Absorptie Spectroscopie (XAS) kunnen worden gebruikt om deze informatie te verkrijgen. De studies in dit hoofdstuk zijn ook gebruikt om de vraag te beantwoorden of het mono-nitreen complex $3^{P1}_{Ns}$ wel of niet een extra Y ligand bevat, en zo ja dan wel de aard van dit ligand. Om deze vragen te kunnen beantwoorden zijn de nitreenradicaal intermediairen zoals beschreven in hoofdstuk 2 onderzocht met behulp van XAS. Uit gedetailleerde analyse van de XAS spectra kan geconcludeerd worden dat zowel de mono- als de bis-nitreen verbindingen een kobalt(III) centrum bevatten. Interessant genoeg laten de XAS metingen ook zien dat beide verbindingen zesvoudig gecoördineerd zijn, wat betekent dat er inderdaad een zesde Y ligand aanwezig moet zijn in het geval van mono-nitreen $3^{P1}_{Ns}$. Dit was tot dan toe helemaal niet duidelijk geworden op basis van de metingen zoals beschreven in hoofdstuk 2.

Om meer duidelijkheid te krijgen over de aard van het ligand Y zijn ondersteunende TD-DFT berekeningen van de K-edge XAS spectra uitgevoerd om een redelijke fit te verkrijgen van de berekende relatieve intensiteit van de rising edge in vergelijking met de experimenteel verkregen XANES spectra (Figuur 2). Daarbij zijn diverse mogelijk neutrale en anionische liganden Y onderzocht. De berekende XANES spectra van complexen met een anionische ligand Y gaven op het eerste oog de beste overeenkomst met de experimentele spectra van de mono-nitreen verbindingen. In dit stadium van het onderzoek leek het dus logisch te concluderen dat het gedetecteerde ligand Y wellicht anionisch zou kunnen zijn.

**Figuur 2.** (links) K-pre edge XAS data van $1^{P1}$ ([Co$^3$(TPP)], groen), $3^{P1}_{Ns}$ (mono-nitreen, blauw) en $5^{P1}_{Ns}$ (bis-nitreen, rood). (midden) TD-DFT berekende (Orca) K-edge XAS data waar vijfzijdig gecoördineerd mono-nitreen $3^{P1}_{Ns}$ en zesvoudig gecoördineerd bis-nitreen $5^{P1}_{Ns}$ wordt vergeleken met verschillende zesvoudig gecoördineerde adducten van mono-nitreen $3^{P1}_{Ns}$ gebaseerd op mogelijke
neutrale liganden $\text{NsN}_3$, $\text{H}_2\text{O}$, $\text{NsNH}_2$, en $\text{NH}_3$. (rechts) TD-DFT berekende (Orca) $K$-edge XAS data waarbij vijfvdig gecoördineerd mono-nitreen $3\pi^*_\text{Ns}$ en zesvdig gecoördineerd bis-nitreen $5\pi^*_\text{Ns}$ worden vergeleken met verschillende zesvdig gecoördineerde adducten van mono-nitreen $3\pi^*_\text{Ns}$ gebaseerd op mogelijke anionische liganden $\text{Ns}^-$, $\text{OH}^-$, $\text{Ns(NH)}^-$, en $\text{NH}_3^-$. Echter, dit zou betekenen dat de gevormde mono-nitreenverbindingen zouden zijn, gebaseerd op negatief geladen mono-nitreen cobalt(III) complexen. Zoutvorming in een oplosmiddel als benzeen of toluue lijkt niet logisch, en daarom is besloten om XAS metingen uit te voeren aan twee goed gedefinieerde vijfvdig gecoördineerde porfyrine complexen met een kobalt(III) metaalcentrum. Dit zijn de complexen [Co$^{\text{III}}$(TPP)(Cl)] en [Co$^{\text{III}}$(TPP)(CF$_3$)], waarvan eerste de coördinatiegeometrie werd bevestigd met X-ray diffractiometeringen. Opmerkelijk genoeg laten de XAS data van deze onomstotelijk vijfvdig-gecoördineerde complexen vergelijkbare intensiteiten van de rising edge in het XANES gebied zien als de mono-nitreen verbindingen. TD-DFT berekeningen die zijn uitgevoerd en zorgvuldig geanalyseerd ondersteunen dit (Figuur 3).

Figuur 3. (links) Experimentele XANES spectra van vijfvdig gecoördineerd [Co$^{\text{III}}$(TPP)(Cl)] en [Co$^{\text{III}}$(TPP)(CF$_3$)] complexen vergeleken met de experimentele spectra van mono-nitreen verbinding $3\pi^*_\text{Ns}$ (rechts) TD-DFT berekende (Orca) $K$-edge XANES data waar de vijfvdig gecoördineerde mono-nitreen verbinding $3\pi^*_\text{Ns}$ [Co$^{\text{III}}$(TPP)(Cl)] en [Co$^{\text{III}}$(TPP)(CF$_3$)] worden vergeleken, inclusief enkele zesvdig gecoördineerde verbindingen met neutrale liganden als zesde ligand.

Uit de combinatie van experimentele en theoretische XAS data van de Co$^{\text{III}}$-nitreen radicaal intermediaren ($3\pi^*_\text{Ns}$ en $5\pi^*_\text{Ns}$) en de kobalt(III) complexen [Co$^{\text{III}}$(TPP)(Cl)] en [Co$^{\text{III}}$(TPP)(CF$_3$)] kan geconcludeerd worden dat de relatieve intensiteit van de XANES kenmerken niet altijd eenvoudig kan worden gecorrelear bij de coördinatiegetallen rondom het metaalcentrum. Het gebruik van XANES als diagnostisch hulpmiddel om op een betrouwbare manier vijf- en zesvdig gecoördineerde [Co$^{\text{III}}$(Por)] verbindingen van elkaar te onderscheiden wordt gecompliceerd door een aantal factoren. De pre-edge intensiteiten worden voor veel [Co$^{\text{III}}$(Por)] verbindingen beïnvloed door $\pi$-donatie en hogere energie overgangen (in alle gevallen) tussen 7713-7720 eV zijn niet uitsluitend 1s naar 4p + LMCT shakedown overgangen, maar voornamelijk 1s naar porfyrine $\pi^*$ overgangen. Ook kunnen deze overgangen verborgen zijn onder de rising edge. De afwezigheid van een shakedown overgang en de zwakke pre-edge intensiteit (experimenteel bepaald en berekend met DFT) voor de mono-nitreen verbindingen, liet ons in eerste instantie denken dat een anionische donor bindt aan de zesde coördinatie plaats van $3\pi^*_\text{Ns}$ maar op basis van de additionele metingen
aan \([\text{Co}^{III}(\text{TPP})(\text{Cl})]\) en \([\text{Co}^{III}(\text{TPP})(\text{CF}_3)]\) kunnen we nu veilig concluderen dat dit waarschijnlijk niet het geval is. De data wijzen wel op de aanwezigheid van een zesde ligand gebonden aan de mononitreen verbindingen, maar dit is hoogstwaarschijnlijk een neutrale amine donor (afgeleid van het azide) in plaats van een anionisch (amido) ligand. De aanwezigheid van zo’n zesde ligand is in overeenstemming met de experimentele waarnemingen dat het gebruik van additieven geen significant effect heeft op de nitreenovergangs reacties uitgevoerd in apolare oplosmiddelen en gekatalyseerd door kobalt(II) porfyine complexen.

In Hoofdstuk 4 worden inspanningen beschreven om nitreen-radicaal intermediairen te laten reageren met alkyne. Bij deze pogingen kwamen onverwachte reacties aan het licht, waarbij een waterstofatoom wordt overgedragen van een amine- of hydroxy-groep naar het nitreenradicaal, en waarbij toelaat andere reactieve intermediairen gevormd worden. Dit onderzoek is gestart als poging om de scope van nitreenradicaalen in organische synthese te vergroten. Vergeleken met de uitgebreide reactiviteit van carbeenradicaal is de scope van porfyine-kobalt(III)-nitreenradicaalen tot dusver beperkt gebleven tot intramoleculaire C-H insertie en aziridine-reacties. Om de scope van deze deeltjes te verbreden zijn pogingen ondernomen om organische aziden te gebruiken in combinatie met andere reagentia, zoals alkyne, om zo nieuwe ringsluitingsreacties tot N-heterocyclische verbindingen te ontwikkelen. Echter, bij pogingen om ortho-gesubsitueerde fenyllaziden (OH/NH\(_2\) substitutie) te gebruiken in dergelijke \([\text{Co}^{II}(\text{Por})]\)-gekatalyseerde ringsluitingsreacties met fenylacetylen werd waargenomen dat het waterstofatoom van de ortho-substituent erg gemakkelijk wordt overgedragen aan het nitreenradicaal. Dit leidt tot de vorming van onverwachte reactieve intermediairen zoals o-quinone monoamines (OQMI; voor OH) en o-fenylineendiimines (OPDI; voor NH\(_2\)). Deze reactieve verbindingen ondergaan snelle voltreacties, waardoor een directe (radicaal-type) koppelingsreactie van het nitreenradicaal met een C=C of C≡C binding van een ander substraat effectief wordt voorkomen en de gewenste N-heterocyclische ringverbindingen niet worden gevormd. In plaats daarvan dimeriseren de o-quinone monoamines (Y = OH) eenvoudig onder zuurstofvrije condities, om zo fenoxazinen te vormen (Figuur 4). In de aanwezigheid van 1-butoxyetheen kan o-quinone monoamine echter wel gevangen worden in een ‘reversed electron-demanding Diels Alder’ (IEDDA) reactie, waarbij benzoazelines worden gevormd (Figuur 4). De vorming van orthofenyleenendimine (OPDI) vanuit ortho-NH\(_2\)-fynlazide is ook geassocieerd met de overdracht van een waterstofatoom, in dit geval van de NH\(_2\) substituut naar het kobalt(III)-nitreenradicaal. Dit resulteert opmerkelijk genoeg in de vorming van azobenzene als product (Figuur 4). Pogingen om ortho-gesubsitueerde azides te laten reageren met andere reactiepartners door de reactiecondities aan te passen waren niet succesvol. In alle gevallen werden azobenzene gevormd. DFT-berekeningen zijn in overeenstemming met deze experimenten; HAT (hydrogen atom transfer) van de ortho-YH substituenten (Y = O of NH) naar de nitreen groep heeft in beide gevallen een (erg) lage energie barrière.
Figuur 4. De geobserveerde transformaties in reacties van o-gesubstitueerde (OH of NH₂) fenylazides met [Co⁴(Por)] katalysatoren.

De omzetting van o-NH₂-fenyl azides verloopt via? een uniek reactiepad, waarbij interessante gesubstitueerde o-amino-azobenzen gevormd worden direct vanuit azides gekatalyseerd door kobalt(II) porfyriën. Het is een uniek éénstapsprocess om op een milde manier azobenzen te synthetiseren uit azides, die op hun beurt weer in één stap gemaakt kunnen worden uit commercieel verkrijgbare amines. Het reactieprotocol is vrij tolerant ten opzichte van verschillende functionele groepen. De gesynthetiseerde azobenzenen zijn bathochromisch verschoven in het UV-vis spectrum ten opzichte van de ongesubstitueerde azobenzenen. De kristalstructuur van één van deze verbindingen is indicatief voor een waterstofbrug tussen de azo-groep en de ortho-amine substituenten. Dit heeft waarschijnlijk consequenties voor de snelheid en evenwichtsligging van de fotochemische trans-cis isomerisatie van deze verbindingen. Dit aspect lijkt interessant voor vervolgonderzoek, maar valt buiten het onderzoek beschreven in dit proefschrift. In vervolgstudies kan de amine groep in deze verbindingen ook gebruikt worden om azabenzenen verder te functionaliseren.

In HOOFDSTUK 5 worden inspanningenwederom niet mijn keuze maar persoonlijk beschreven om een ander ligand systeem te gebruiken in een nitreense-verdrachtsreactie, namelijk corrolen in plaats van porfyriën. Het is bekend dat voor nitreense-verdrachtsreacties die gekatalyseerd worden door [Co⁴(Por)] vanuit azides, de activering van het azide door de katalysator de snelheidsbepalende stap is. In deze stap wordt het kobalt centrum geoxideerd van kobalt(II) naar kobalt(III). Het lijkt daarom aannemelijk te veronderstellen dat kobalt(II) complexen met een elektronrijker ligand, maar waarbij de planaire geometrie van het complex behouden blijft, bevorderlijk zou kunnen zijn om de energiebarrière van de snelheidsbepalende stap te verlagen. Corrolen zijn porfyriën-achtige liganden met een kleinere pocket en hebben over het algemeen een hogere elektrondichtheid. Om deze reden hebben we drie corrole-complexen van kobalt gésynthetiseerd ([Co⁴(Cor)(PPh₃)]) met elektronisch verschillende substituenten. De intramoleculaire ringsluitings C-H amineringsreactie van (4-azidobutyl)benzeen (in de aanwezigheid van Boc₂O) om een verzadigd N-heterocyclisch tert-butyl-2-fenylpyrroldine-1-carboxylaat (Schema 1) te maken, diende hiervoor als maatstaf. Van deze reacție is bekend dat hoge opbrengsten kunnen worden behaald wanneer [Co⁴(Por)] katalysatoren (met name [Co⁴(TMP)]) worden gebruikt maar dat hiervoor een lange reactietijd van ongeveer 16
uur nodig is. De gesynthetiseerde [Co<sup>III</sup>(Cor)(PPh<sub>3</sub>)] complexen die onderzocht zijn in deze studie konden chemisch worden gereduceerd om zo de mono-anionische [Co<sup>II</sup>(Cor)]<sup>-</sup> complexen te genereren die katalytisch actief zijn in dezelfde ringsluitings C-H amineringseactie. Deze gereduceerde verbindingen zijn gekarakteriseerd doormiddel van CV, EPR en UV-vis spectro-elektrochemie. Alle gesynthetiseerde [Co<sup>III</sup>(Cor)(PPh<sub>3</sub>)] complexen lieten nadat ze gereduceerd waren zien dat ze niet alleen actief waren in de ringsluiting C-H amineringseactie van (4-azidobutyl)benzeen, maar ook dat ze veel sneller zijn (meer dan 2.5 keer) dan de gerapporteerde [Co<sup>II</sup>(TMP)] katalysator voor dezelfde reactie. Hiervoor hebben we ook computationele studies uitgevoerd om te bevestigen dat de verbeterde snelheden het gevolg zijn van lagere barrières voor de snelheidsbepalende azide activeringsstap (Figuur 5). DFT berekeningen laten inderdaad een veel lagere overgangstoestand barrière zien voor de mono-anionische [Co<sup>II</sup>(Cor)]<sup>-</sup> complexen dan voor de neutrale [Co<sup>II</sup>(Por)] complexen. Ondanks dat de elektronische beginstructuur van de katalysator verschillend is, worden de geproduceerde nitreenverbindingen het best beschreven als nitreen-radiaal intermediairen, met het meeste van hun spin dichtheid gelokaliseerd op het stikstof atoom van het nitreer, vergelijkbaar met de nitreen-radiaal intermediairen gerapporteerd voor de neutrale [Co<sup>II</sup>(Por)] systemen.

**Schema 1.** De toepassing van [Co<sup>III</sup>(Cor)(PPh<sub>3</sub>)] pre-katalysatoren in de ringsluitings amineringseactie van (4-azidobutyl)benzeen.

![Schema 1](image1)

**Figuur 5.** (links) DFT-D3 berekende (TurboMole BP86, def2-TZVP) vrije energieën (ΔG<sub>298K</sub> in kcal mol<sup>-1</sup>) voor de essentiële stap van de azide activering door het [Co<sup>II</sup>(Cor)]<sup>-</sup> complex. (rechts) Spindichtheidssplot van het gevormde nitreenradiaal intermediair B waaruit blijkt dat het grootste deel van de spindichtheid zich op het stikstof atoom van het nitreenligand bevindt.

In **HOOFDSTUK 6** wordt een nieuwe route beschreven die ontwikkeld is voor de synthese van een aantal gesubstitueerde indolines. Dit zijn substructuren van een variëteit aan natuurlijke producten en farmaceutisch relevante verbindingen (Schema 2). De route verloopt efficient via een reactiepad
dat gekatalyseerd wordt door \([\text{Co}^\text{III}(\text{Por})]\) via activering van een in-situ gevormde diazo-verbinding. In deze reactie is de 1,5-HAT reactie de essentiële stap, terwijl zo’n reactie normaal gesproken vaak beschouwd wordt als een ongewenst reactiepad in andere organische reacties die verlopen via vrije-radicalen (Schema 2). In deze reactie is het juist een gewenste stap, die de katalytische synthese van indolines mogelijk maakt.

![Schema 2. Algemene strategie voor de synthese van diazo-precursors die gebruikt worden in de \([\text{Co}^\text{III}(\text{TPP})]\) gekatalyseerde ringsluitingsreactie voor de vorming van indolines.](image)

Dit zijn de eerste voorbeelden van metallo-radicaal gekatalyseerde vorming van \(N\)-heterocyclische verbindingen die verlopen via een radicaal-type C-H-activering gevolgd door een ‘radical rebound’ stap en waarbij kobalt(III)-carbeen radicalen een cruciale rol spelen. DFT-berekeningen laten zien dat de reactiestappen ongebruikelijk lage barrières hebben en dat de spindichtheid in de intermediairen C en D voornamelijk op hun organische fragmenten is gedelokaliseerd (Figuur 6). De metallo-radicaal-gekatalyseerde indoline synthese is een voorbeeld van een (intramoleculaire) carbeen insertie reactie in een benzylische C-H binding die verloopt via een gecontroleerd radicaal mechanisme. De hoge mate van controle over de radicaal-type intermediairen is mogelijk omdat de Co\(^{III}\)-carbeen-radicaal intermediairen dichtbij het metaalcentrum gevormd worden.
Figuur 6. (A) DFT-D3 berekende (Turbomole BP86, def2-TZVP) vrije energiën ($\Delta G_{298}^{\circ}$ in kcal mol$^{-1}$) voor het voorgestelde reactiepad. De energiën van alle intermediairen zijn gerapporteerd ten opzichte van verbinding A als referentiepunt (barrières voor de overgangstoestanden zijn gerapporteerd tussen haakjes). (B) Spindichtheidsplot van intermediair C die een maximale spindichtheid laat zien op het koolstof atoom van het carbeen. (C) Spindichtheidsplot van intermediair D na de 1,5-HAT stap die een maximale spindichtheid laat zien op het benzylische koolstof met enige delokalisatie over de aangrenzende fenylling.

In HOOFDSTUK 7 worden inspanningen still studies dan? beschreven om CF$_2$-carbeenoverdrachtsreacties met kobalt(II) porfyris katalysatoren mogelijk te maken. Hoewel de overdracht van carbenen vanuit diazoverbindingen via een metaalcomplex uitgebreid onderzocht is, blijft de overdracht van difluorocarbeen (CF$_2$) via een metaalcomplex een grote uitdaging. De speciale elektronische eigenschappen van het CF$_2$ carbeen zorgt er namelijk voor dat de metaal-CF$_2$ binding meestal te sterk is voor carbeenoverdracht naar (andere) substraten. Echter, kobalt(III)-carbeenradicalen (zoals die beschreven in hoofdstuk 6) hebben een totaal andere elektronische structuur, orbitaal eigenschappen en reactiviteit dan traditionele (Fischer-type) carbeencomplexen. Ook zijn de Co–C bindingen intrinsiek veel zwakker omdat het ongepaarde electron zich in een Co–C antibonding $\pi$-binding bevindt. Met die inzichten in het achterhoofd is in dit project geprobeerd om effectief gebruik te maken van verzwakte Co–CF$_2$ bindingen van vergelijkbare reactieve CF$_2$-gebaseerde cobalt-carbeen intermediairen om CF$_2$-overdracht van kobalt naar organische substraten mogelijk te maken. Om dit concept te evalueren is eerst onderzocht of een difluorocarbeen kobalt(II) complex gevormd kan worden door een één-elektron-reductie van een nieuw trifluormethyl kobalt(III) complex [Co$^{\text{III}}$(TPP)(CF$_3$)]. Gebaseerd op voorbeelden uit de literatuur werd verwacht dat het vrijmaken van F$^-$ uit het resulterende anionische [Co$^{\text{III}}$(TPP)(CF$_3$)]$^-$ complex zou kunnen leiden tot de vorming van een [Co(TPP)(CF$_3$)] CF$_2$-carbeencomplex, vanaf waarvan mogelijk een CF$_2$-carbeen overgedragen kan worden naar een acrylaat substraat onder milde reactiecondities. Dit bleek
inderdaad mogelijk. Stoichiometrische CF₂-overdracht van [CoIII(TPP)(CF₃)] naar n-butylacrylaat bleek succesvol in aanwezigheid van een geschikte reductor (Schema 3). Deze reactie had echter wel een vrij lage opbrengst. Een katalytische versie van dezelfde transformatie, gebruik makend van een wat stabielere [CoII(TPP)F₂O] complex, gaf een maximaal turnovergetal (TON) van 8 naar het gewenste gem-difluorocyclopropaan product.

![Schema 3](image)

**Schema 3.** Reactie van [CoIII(TPP)(CF₃)] met n-butylacrylaat tijdens een één-elektron reductie.

De DFT (BP86, def2-TZVP) berekende NBO spinpopulaties van [Co(por)(CF₂)] (versimpeld model van de experimentele porfyrine complexen zonder meso-substituenten) zijn 65% voor kobalt en slechts 23% voor het koolstof atoom van het carbeen. Dit is in overeenstemming met de resultaten die gerapporteerd zijn door Woodcock en collega’s, en suggereert dat deze CF₂-complexen (in tegenstelling tot de carbeenradicaal complexen zoals beschreven in hoofdstuk 6) slechts een beperkt ‘carbeenradicaal karakter’ hebben. Ondanks het dominante metalloradicaalkarakter verloopt de berekende carbeenoverdracht van [Co(por)(CF₂)] naar methylacrylaat volgens een stapsgewijs radicaalproces, net zoals voor andere kobalt(II)-porfyrine-gekatalyseerde carbeen- en nitreenoverdrachtsreacties (zie Figuur 7). De lage maximale TON van 8 voor dit systeem suggereert dat toekomstig onderzoek zich zou moeten richten op de ontwikkeling van stabielere katalysatoren, die minder snel ontleden in de aanwezigheid van de reactive (vrije) CF₂ en CF₃⁻ deeltjes gevormd onder de experimentele reactiecondities waarbij Me₃SiCF₃ gebruikt wordt als bron voor CF₂⁻ carbenen.

![Figuur 7](image)

**Figuur 7.** Het voorgestelde mechanisme (gebaseerd op DFT-berekeningen) voor difluorocyclopropaanering van methylacrylaat door een kobalt(II) porfyrinato complex.
List of Publications

1. *Characterisation of porphyrin-cobalt(III)-’nitrene radical’ species relevant in catalytic nitrene-transfer reactions:*

2. *EPR Spectroscopy as a Tool in Homogeneous Catalysis Research:*


4. *Metal-catalysed azidation of organic molecules:*

5. *Difluorocarbene transfer from a cobalt complex to an electron-deficient alkene:*

6. *Cobalt(II) porphyrin catalysed synthesis of indolines via a 1,5-H atom transfer pathway:*
   Karns, A. S.; Goswami, M.; de Bruin, B.; *manuscript in preparation*

7. *Synthesis, characterisation and application of anionic [Co\textsuperscript{II}(Cor)]\textsuperscript{−} corrole complexes in ring-closing C–H amination of an aliphatic azide:*
   Goswami, M.; Geuijen, P.; de Bruin, B.; *manuscript in preparation*
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