Manipulating radicals
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Citation for published version (APA):

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Controlled Radical-Type Catalytic Reactions via Transition Metal Bound ‘Substrate-Radicals’

1. Introduction – Base metals and non-innocent ligands

Organic compounds are the building blocks without which life could not exist. We can find them in our own bodies, as well as in all naturally occurring and manmade products we use. Modern lifestyle requires synthesis and production of many chemical compounds at massive scales, such as fuels, plastics, drugs, insecticides, cosmetics, perfumes or food additives. More of these chemicals, and new ones, will need to be produced to sustain our current living standards in a changing world with a rapidly increasing human population. For example, the development of new antibiotics is a crucial case to avoid issues with bacterial resistance to existing drugs. To address such matters in a sustainable manner, new, safe and selective synthetic protocols are required. **Synthetic chemistry** has evolved as an important scientific discipline over the past hundred years, both enabling large-scale production of existing matter as well as the creation of new compounds and materials. As such, synthetic chemistry has brought tremendous prospect to humanity. Nowadays almost any conceivable molecule imagined by man can be produced in the laboratory, given enough resources and time. However, that does not mean an efficient and sustainable route would be achieved. Many organic reactions still rely on stoichiometric transformations and elaborate protecting group strategies in complex, multistep procedures that require several work-up steps, making the whole synthetic protocol atom and energy inefficient, producing waste and increasing costs. More research in the field of catalytic organic synthesis is needed to develop more cost-effective, efficient and sustainable synthetic procedures.

One strategy that addresses current limitations is **transition metal catalysis**. The development of efficient and selective transition metal catalysts is an important goal of modern research in chemistry. Our society needs new catalysts to become more sustainable, and a desire for selectivity and efficiency in the preparation of medicines and materials has boosted our interest in developing new methods based on homogeneous catalysis, in particular on the development of new ligands which can be fine-tuned to specific needs. The properties of a metal complex as a whole are the result of the interaction between the metal centre and its surrounding ligands. In traditional approaches, the steric and electronic properties of the spectator ligand are used to control the performance of the catalyst, but most of the reactivity takes place at the metal. Recent new approaches deviate from this concept, and make use of ligands that play a more prominent role in the elementary bond activation steps in a catalytic cycle.\(^1,2\) The central idea is that the metal and the ligand can act in a synergistic manner to facilitate a chemical process. In this light, complexes based on
so-called ‘non-innocent’ ligands offer interesting prospects and have attracted quite some attention.\textsuperscript{3, 4, 5, 6, 7}

The term ‘non-innocent’ is broadly used and diverse authors give different interpretations to the term. The term was originally introduced by Jørgensen\textsuperscript{8} to indicate that assigning metal oxidation states can be ambiguous when complexes contain redox-active ligands. As such, ligands that get reduced or oxidized in a redox process of a transition metal complex are often referred to as ‘redox non-innocent’.\textsuperscript{9, 10} With modern spectroscopic techniques, combined with computational studies, assigning metal and ligand oxidations states has become less ambiguous, and hence many authors started to use the term ‘redox-active ligands’ instead. Gradually, many authors also started to use the term ‘non-innocent’ for ligands that are more than just an ancillary ligand, frequently involving ligands that have reactive moieties that can act in cooperative (catalytic) chemical transformations, act as temporary electron reservoirs or respond to external triggers to modify the properties or reactivity of a complex. A common objective of many of these investigations is to achieve better control over the catalytic reactivity of first-row transition metal complexes, with the ultimate goal to replace the scarce, expensive noble metals currently used in a variety of catalytic processes by cheap and abundant first-row transition metals.

Noble metals are frequently utilised in catalytic synthetic methodologies and many industrial processes.\textsuperscript{11} Their catalytic reactivity is most frequently based on their well-established ‘two-electron reactivity’, involving typical elementary steps such as reductive elimination and oxidative addition. These elementary steps easily occur for late (mostly 2\textsuperscript{nd} and 3\textsuperscript{rd} row) transition metals having two stable oxidation states differing by two electrons. However, most noble metals are scarce and therefore expensive (and sometimes toxic\textsuperscript{12}). Therefore it is necessary to develop catalysts based on cheaper, abundant and benign metals to arrive at cost-effective alternatives. This is not an easy task, as base metals (Fe, Co, Cu, Ni etc.) often favour one-electron redox processes, and typical elementary steps commonly observed in noble metal catalysis are only scarcely observed for base metals. As such, the unique properties of non-innocent ligands are advantageous to gain better control over the reactivity of base metals. In some cases, this leads to reactivity comparable to that of noble metal complexes (but more cost effective and benign), while in other cases the combination of a base metal with a ‘non-innocent’ ligand can actually give access to unique new types of reactivity.

Material scarcity and environmental issues put an increasing demand on the development of new, cheap and selective catalysts for sustainable synthesis in a
variety of processes. As such, replacing noble metals by cheaper base metals in homogeneous catalysis is tremendously desirable. ‘Non-innocent’ ligands offer several opportunities to achieve this goal. At its core, homogeneous catalysis is based on the properties of a metal complex and its surrounding ligands. Therefore, choosing the right combination of the metal and its surrounding ligands is key to the development of new catalysts. The use of ‘non-innocent’ ligands goes beyond that of classical ancillary ligands, and a ‘non-innocent’ ligand is typically directly involved in one of the key elementary steps of a catalytic reaction. In a broad description, ‘non-innocent’ ligands act synergistically with the metal to enhance the selectivity and activity of the catalyst. Active participation of a redox active ligand during a catalytic cycle following an open-shell radical-type pathway is represented schematically in Scheme 1. Roughly two different concepts have been explored in this field. In the first concept, electron-transfer between the metal and a substrate-based ligand leads to formation of substrate-centered radicals which directly participate in radical coupling reactions. In the second concept spectator redox-active ligands are used as electron reservoirs, facilitating different oxidation state changes than normally expected (e.g. two-electron oxidative addition/reductive elimination steps for first-row transition metals or radical-type one-electron processes for diamagnetic complexes). New reaction pathways are enabled by using the concept of redox non-innocence, which most typically involve controlling radicals and selectively yielding target products, thus taking advantage of the one-electron reactivity of the first row transition metals.

Scheme 1. Schematic representation of two main concepts explored in the use of redox active ligands/substrates in catalysis research.
2. Controlling Radicals

Generally, radicals are intrinsically reactive species, and are associated with fast uncontrolled and unselective transformations either useful for the synthetic chemist, such as free radical polymerizations, auto-oxidations and radical halogenations, or unwanted processes mainly in biochemistry that lead to DNA damage, ageing and cell death. Many scientists believed that radicals are too reactive to be selective, and thus radical chemistry has been regarded as a niche, or a form of exotic chemistry. As a result, research into this field has somehow been neglected in many areas of synthetic chemistry. However, nowadays the idea that radicals cannot be controlled due to their high activity is known to be a misconception. Selectivity is a matter of relative rates, not absolute rates. Therefore, it is certainly possible to control radical reactions despite their high reactivity. It is true that free radicals behave unpredictable, accessing multiple reaction pathways that present similar energy barriers leading to mixtures of products. However, one strategy to control the reaction pathway involves bringing the radical in or close to the coordination sphere of a transition metal complex, thereby controlling its reactivity.

An important source of inspiration for the synthetic chemist working in the area of first-row transition metal catalysis is the high activity and selectivity of transformations mediated by metalloenzymes. In fact, one can identify several natural catalysts in the form of metalloenzymes that take advantage of all characteristics presented above for sustainable radical-type synthesis: The use of first-row transition metals, “non-innocent” ligands and one-electron reactivity in the form of radical control. Despite their radical-type reactivity, the enzymes are highly active and selective for some of the most complex biochemical transformations, of key importance for life. Detailed analyses of biological systems revealed interesting characteristics that can be used in a bio-inspired approach by the synthetic chemist. Firstly, metalloenzymes contain exclusively earth abundant metals, mostly first-row transition metals and with no known examples of enzymes using non-abundant noble metals. Secondly, substrate radicals are generated in a catalytic manner, are bound to the metal and are generated in low concentrations, thus limiting competing side-reactions. Thirdly, the active site of the enzyme, the place where the radical is bound to the metal centre, is isolated from the reaction medium by a large and bulky protein shell, thus creating a hydrophobic pocket that limits even more unwanted reactions such as radical couplings and disproportionations. Fourthly, the protein matrix surrounding the active centre stabilizes the intermediates and transition states by using secondary coordination sphere effects such as hydrogen bonding. These interactions also organize the substrates and direct them such that only the
desired reaction coordinate is followed. In spite of the radical nature of the catalysed processes, high chemo-, regio- and enantio- selectivity is achieved by these metalloenzymes. Therefore, they represent a great source of inspiration, and trying to mimic and even extend the scope of similar reactions in the laboratory is a goal worth of pursuit.

One of the best studied examples of a radical process involving a metalloenzyme is alcohol oxidation to aldehydes catalysed by the enzyme Galactose Oxidase (GoAse). Its active site contains a copper centre coordinated with histidine and tyrosine moieties that can be either reduced or oxidised by one electron. The mechanism (Scheme 2) shows us a first step in which this enzyme is activated via one-electron oxidation of the sulfur modified tyrosine-272 moiety to form an oxygen centred (tyrosyl) radical, 1. The CH₂OH-group on the galactose binds over the Cu–O-Tyr-495 bond to form the Cu(II) alkoxide complex 2 with release of Tyr-OH. Subsequent proton-coupled electron-transfer (PCET) shifts the radical to the galactose-alkoxide moiety which in turn reduces the Cu(II) centre of the enzyme to Cu(I) with formation of the oxidized product 4. The reduced enzyme then reacts with dioxygen via a PCET pathway to form complex 5, and upon release of hydrogen peroxide (H₂O₂) the catalytic cycle is completed.

Scheme 2. Alcohol oxidation to aldehydes catalyzed by Galactose Oxidase.

In this mechanism the metal and the ligand cooperate to facilitate the reaction. The initial enzyme activation produces a chemically active ligand-centred radical.
However, this ligand radical alone is incapable of performing the selective reaction. Binding of the substrate to the metal centre is also essential to bring the substrate and the ligand centred radical close together. This geometrical arrangement enables the actual bond activation process. Subsequent electron transfer from the activated substrate to the metal is also important, hence the need of the redox active Cu metal in the enzyme.

A synthetic example analogous to the GOase system was reported by Wieghardt and Chaudhary\textsuperscript{17} and presents a bioinspired Cu\textsuperscript{II}-thiophenol catalytic system (Scheme 3). The initial catalyst activation step occurs by cooperative activation of the catalyst and the ligand to form a diradical system. In contrast to the GOase enzyme, this system has biradical characteristics. Therefore it can carry out oxidation of two primary alcohols in a single catalytic turnover, enabling alcohole-derived radical C-C coupling reactions with formation of secondary diols.

Another example of metalloenzymes that control radical reactions are the family of cytochromes P450 (Figure 1).\textsuperscript{18} These are proteins that contain heme as cofactor and, therefore, are called hemoproteins. A large variety of substrates, ranging from small to big, are activated by cytochromes P450 during enzymatic catalysis. Generally, these proteins are used by nature as terminal oxidase enzymes in electron transfer chains. The term P450 comes from the UV-VIS absorption wavelength (450 nm) of the reduced state of the enzyme when complexed with carbon monoxide.

An important class of catalytic bio-synthetic transformations for which cytochrome P450 is responsible is the oxidation of alkyl chains of organic molecules, via C–H bond activation.\textsuperscript{19} A key step of the mechanism is presented in Figure 1, and involves radical species. A radical rebound step is presented, in which the active species is the high valent iron(IV) oxo heme complex. The C–H bond of the alkyl chain is activated by hydrogen atom abstraction, followed by a quick radical rebound step releasing the alcohol product with regeneration of the active iron species. The radical nature of
this reaction has been evidenced by using radical clocks and spin trapping techniques.\textsuperscript{20}

![Cytochrome P450 enzyme](image)

\textbf{Figure 1.} Cytochrome P450 enzyme (left) containing a iron heme complex active site (right) catalyzing conversion of molecules containing aliphatic chains to alcohols via the action of an iron(IV) oxide bound to a radical heme (bottom).\textsuperscript{21}

\section*{3. Substrate Radicals in Catalysis}

Being able to control radical reactivity is a difficult challenge in synthetic organic and organometallic chemistry, but in the coordination sphere of (transition) metals, radical-type reactions become easier to manipulate. This makes it possible to steer radical reactivity in specific directions. Forming ligand/substrate centered radicals and making use of their redox activity helps in that perspective. This concept was initially applied in stoichiometric reactions, but over the past few years it slowly transitioned into the area of homogeneous catalysis to enhance the reactivity and steer the selectivity of various catalysts.\textsuperscript{22, 23, 24}

Recently, several examples of catalytic reactions were disclosed in which formation and detection of discrete metal-bound substrate radicals was reported. These substrate-derived ligand radicals play a key role in a variety of synthetically useful C–C, C–N and C–O bond formation reactions. Furthermore, these reactions proceed without exception via one-electron substrate activation and subsequent controlled
radical steps. The carbene-radical (M–C•R₂) and nitrene-radical (M–N•R) examples discussed in this section provide some clear-cut examples of the usefulness of ligand/substrate ‘non-innocence’ involvement in catalysis. Similar one-electron steps and radical-type reactions have been disclosed in titanium(III)-catalysed epoxide ring-opening reactions, examples of which being included in this section.

![Figure 2](image)

**Figure 2.** Electron transfer from metal to substrate (transformation of a metalloradical into a substrate radical).

Carbene- and nitrene-radical species are usually formed upon reaction of open-shell metal complexes with high-energy carbene or nitrene precursors, such as diazo compounds (to generate carbenes) or iminoiodanes/azides (to generate nitrenes). By choosing a specific combination of a first-row transition metal and spectator ligands, one-electron transfer can occur from the metal to the metal-bound carbene or nitrene moiety, thus forming a carbon- or nitrogen-centered radical. The initial metalloradical is transformed into an organic radical, bound to the metal, and the resulting species are named ‘carbene radicals’ or ‘nitrene radicals’. This specific situation occurs only when the energy level of the pₓ orbital of the carbene or nitrene is lower than the d₂ₓ orbital of the metal (Figure 2).

### 3.1 Carbon-centered radicals

In recent years, ‘carbene radicals’ have emerged as particularly interesting examples of substrate-based ligand radicals that participate directly in catalytic reactions. These ligands can be regarded as one-electron reduced analogs of (Fischer-type)
carbenes. Catalytically relevant carbone radicals cannot be isolated, thus making many spectroscopic techniques such as X-ray diffraction impractical. Detection and characterization of these species with EPR provided important information. In these studies, carbone radicals revealed a small $g$-anisotropy, with $g$-values close to that of the free electron ($g_e = 2.0023$) and clear hyperfine couplings with the metal to which they bind. These are diagnostic features of carbon-centered radicals, and indeed confirm the redox-active nature of carbone ligands.

Combining EPR measurements with in situ IR spectroscopy has provided important details about the nature of such intermediates formed during a catalytic cycle, showing the intermediacy of radical carbenes as active species in several catalytic reactions. Quantum mechanical computations, mainly using DFT methods, often support the EPR spectra and help understanding the spectral properties and spin density distributions of these open-shell complexes.

Scheme 4. First example of a carbone radical complex.

The first examples of redox active carbone ligands were reported in the 1970s by the group of Casey and coworkers and were generated by one-electron reduction of Fischer-type carbenes of Group 6 transition metals using an external reducing agent.\textsuperscript{28,29} The radical was obtained by one-electron reduction of Fischer-type carbenes using external reducing agents (Scheme 4). Complexes of Fischer-type carbenes are known to be electrophilic, thus having their LUMO centered on the carbone carbon atom. Hence, reduction of the ligand instead of the metal can be expected.\textsuperscript{30} Reacting pentacarbonyl-(alkoxyaryl)-carbone complexes of group 6 transition metals (Cr, Mo, W) with sodium/potassium alloy leads to ‘persistent’ carbon-centered radical anions at $-50 \, ^\circ\mathrm{C}$ as shown by electron paramagnetic resonance (EPR) spectroscopic measurements.\textsuperscript{28} While interesting, these species were initially considered (in the 1970s) to be merely chemical curiosities rather than important intermediates in catalysis. Yet, these group 6 transition metal complexes stand out as the first, classical examples of carbone-radical complexes. C–C bonds could be formed in stoichiometric reactions by dimerization of tungsten aryl- or silylcarbone complexes or react with electron-poor olefins such as ethyl acrylate, as shown by Fuchibe and Iwasawa.\textsuperscript{31} More recently, the controlled radical-type reactivity of carbone radicals has been explored in catalytic reactions, using different metals than chromium.
The formation and reactivity of carbene radicals has been further explored and it was found that if carbenoids are formed at Group 9 transition metals in the oxidation state +II [CoII, RhII, IrII], the metal effectively reduces the carbene by one electron, thus forming a carbene radical in an intramolecular redox process without the need of an external reducing agent. Representative examples are cyclopropanation reactions mediated by metallo-radical cobalt(II) porphyrin complexes (Figure 3). Experimental evidence for formation of cobalt coordinated carbene radicals in these reactions has been demonstrated by the groups of De Bruin and Zhang by reacting ethyl diazoacetate (EDA) with the cobalt porphyrin complexes and monitoring the reaction mixtures with EPR spectroscopy (Figure 3).

An important consideration is that most cobalt porphyrins rapidly become EPR silent upon reaction with EDA in absence of other reagents (likely due to fast formation of diamagnetic, deactivated cobalt(III)-alkyl species), but for the bulky Co(3,5-DitBu-ChenPhyrin) (Figure 5) the EPR signals obtained when adding EDA are more persistent and reveal clear changes when compared to the starting complex. Spectral simulation of the reaction mixture revealed the presence of three species, which were assigned to a simple EDA adduct (I), a bridging carbene species (II) and a terminal carbene (III) as shown in Figure 4. While species I and II are both ‘cobalt-centered radicals’, species III is a carbon-centered radical having most of its spin density located at the carbene carbon p-orbital. This readily explains the observed
large differences in g- and A-anisotropy between the bridging carbene II and the terminal carbene III.

Figure 4. Top: Spectral simulations revealing the presence of species I, II and III. Bottom: Simplified representation of the structure of species I, II and III.32

Scheme 5. Dimerization of cobalt carbene radical complexes.35
Further evidence for the formation of cobalt(III)-carbene radicals has been obtained using ethyl-styryldiazoacetate and [Co(TPP)] in the absence of an alkene substrate.\textsuperscript{36} In this reaction a cobalt(III)-vinylcarbene radical is formed, which subsequently dimerizes to a diamagnetic, dinuclear cobalt(III) porphyrin complex via its γ-radical allylic resonance form (as evidenced by X-ray structural analysis; see Scheme 5). Furthermore, trapping the γ-radical allylic resonance form of the cobalt(III)-vinylcarbene radical with TEMPO proved possible, leading to formation of a mononuclear diamagnetic cobalt(III) complex via C–O bond formation.

EPR measurements, combined with supporting DFT calculations and \textit{in situ} IR spectroscopy have indeed shown that carbene radicals are detectable species, with the cobalt-porphyrin system allowing control over the reactivity of these radicals. As such, enantioselective carbene transfer reactions are possible, despite the fact that these reactions proceed via radical-type mechanisms. Hence, substrate redox non-innocence is not just a chemical curiosity, and the cyclopropanation reactions mediated by cobalt porphyrins provided prime examples of catalytic reactions proceeding via carbene radicals behaving as controlled radical species. Development of new chiral cobalt porphyrins\textsuperscript{37,38,39} (Figure 5) led to unprecedented reactivity and selectivity, which was explained by the increased nucleophilic character of the carbene radical compared to an unreduced Fischer-type carbene, allowing the pursuit of more challenging substrates. The cooperation between the carbene radical and the metal is of crucial importance for catalysis and is actually similar to the way metalloenzymes gain control over radicals in several enzymatic processes. The bulky
chiral porphyrins ensure a protective environment for the carbene radicals, similar to the protective nature of the protein of real enzymes and comparable to other approaches in the field of artificial metalloenzymes.

Figure 6. Metalloporphyrins Encapsulated in a Cubic $M_8L_6$ Cage.

An important aspect in eliminating side reactions and obtaining enantioselectivity is having confined space around the metal. Thus, inspired by the protective nature of the protein surrounding the active sites of metalloenzymes, De Bruin and coworkers have used artificial cages around the porphyrin in an attempt to better control radical carbenes (Figure 6). They described the synthesis and assembly of a new $M_8L_6$ cage which selectively encapsulates tetra-(4-pyridyl)-metalloporphyrins ($M^{II}$TPyP), $M = Zn, Co$) and its reactivity in radical-type transformations involving diazo compounds. The encapsulated cobalt porphyrin proved to have a significantly higher activity than the free $[Co^{II}(TPyP)]$ catalyst and shows that the cage does indeed have an important role in isolating the reaction site, similar to the protective protein capsule of a metalloenzyme.

A related example of carbene radical transformations is the cobalt-mediated catalytic one-pot synthesis of $2H$-chromenes (Scheme 6). This reaction involves activation of salicyl N-tosylhydrazones by cobalt(II) porphyrins forming cobalt(III)-carbene radicals that readily undergo radical addition to terminal alkynes such as phenylacetylene to form salicyl−vinyl radical intermediates. The latter ring closes to form the desired $2H$-chromene, after a prior intermediate hydrogen atom transfer step (Scheme 6). EPR measurements together with radical trapping experiments using TEMPO confirmed that the mechanism follows a radical pathway. Surprisingly, DFT calculations showed that after the hydrogen abstraction step by the vinyl radical an ortho-quinone-methide intermediate dissociates from the metal and undergoes an endocyclic, sigmatropic ring-closing step. A further interesting feature of this reaction is the fact that exactly the same reaction with copper, which
does not proceed via carbene radicals, led to the formation of benzofurans instead of $2H$-chromenes.

![Scheme 6. [Co$^{II}$(Por)]-catalyzed metalloradical coupling–cyclization using alkynes and salicyl tosylhydrazones to produce 2H-Chromenes.](image)

Other interesting examples that involve radical control via generation of carbene radicals include cyclopropanations,$^{45,46}$ C–H activations,$^{47}$ cyclopropenations,$^{48}$ as well as alkene,$^{49}$ and furane formation$^{50}$ (Scheme 7). They all have in common the use of a substituted cobalt(II) porphyrin as the catalyst and a diazo or tosyl hydrazone as a high energy substrate to generate the carbene radical intermediate. After formation of the intermediate radical species, trapping it with different substrates such as alkenes, alkynes or ketones yields an entire series of substituted organic molecules (Scheme 7). The reactivity difference between the carbene radical and that of a Fischer-type carbene is attributed to the more nucleophilic character of the carbene radical species. The carbene radicals can easily react with, for example, electron deficient alkenes during cyclopropanation making this method complementary to the more classical approaches towards cyclopropanation.$^{51,52,53}$
Examples of metalloradical [Co(por)]-catalysed reactions proceeding via carbene radical intermediates.

An alternative approach to generating carbon centered radicals in the vicinity of a metal center is the homolysis of C–O bonds. Epoxides represent an attractive class of precursors that can ring open and generate functionalized alkyl radicals, due to their ring strain and because they form strong metal-oxygen bonds to early transition metals such as titanium. When reacted with oxophilic titanium(III) metal catalysts such as “Cp₂TiCl“, they undergo ring-opening to generate alkyl radicals in the coordination sphere of titanium. “Cp₂TiCl” exhibits a low Lewis acidity while preserving a high selectivity for electron transfer to epoxides. Radicals derived from epoxide ring opening behave as typical nucleophilic alkyl radicals and can be used for addition reactions to Michael acceptors, reductions by HAT or 5-exo cyclizations.

An example of radical generation and subsequent radical reactivity is proposed by Gänssauer and co-workers, and is shown in Scheme 8. Here, the titanocene catalyst activates the epoxide and binds the oxygen end, generating a β-radical, species A. Radical A then adds to the benzene ring, temporarily destroying its aromaticity, forming species B, followed by an electron-transfer step to generate cationic species C. This species readily rearomatizes liberating the catalyst with formation of the cyclized organic product. The substrate radical intermediates remain coordinated to the metal during all steps of the catalytic cycle (until product release), allowing high reagent control of the selectivity.
The catalytic performance of the system can be tailored by tuning the ligand environment around the titanium center. Therefore, conceptual similarities between titanocene one-electron steps during catalysis and classical two-electron organometallic catalysis are becoming evident.\(^5\)\(^7\)

### 3.2 Nitrogen-centred radicals

Similar to the formation of carbene radicals, using azides or iminoiodanes as substrates instead of diazo compounds results in nitrene formation.\(^5\)\(^8\) In the presence of \([\text{Co}^{III}(\text{por})]\) complexes reduction by one electron of the nitrene is favoured, thus generating a nitrogen based organic radical. Depending on the source of the nitrene transfer reagent, either a mono-nitrene radical or bis-nitrene radicals can be formed, giving rise to interesting reactivity in catalysis (Scheme 9). Compared to their carbene counterparts, nitrene radicals are more persistent in solution, thus facilitating their detection (even at room temperature) using a variety of spectroscopic techniques.\(^5\)\(^9\)

Several examples of catalytic reactions in which nitrene radicals have been proposed and detected as intermediates are shown in Scheme 10. Addition to double bonds gives rise to aziridines,\(^6\)\(^0\) and activation of benzylic\(^6\)\(^1\) or aldehydic\(^6\)\(^2\) C–H bonds produces secondary amines or amides respectively. Based on reported examples published so far, nitrene radical intermediates seem to be more prone to C–H

**Scheme 8. Radical arylation catalysed by [Cp₂TiCl]**
activation than their carbene equivalents, for which more examples of addition reactions are reported. Cobalt complexes are not the only species that can give rise to metalloradical catalysis involving nitrene radicals. Betley et al. proposed an Fe$^{II}$ complex than can react with organic azides forming formally one-electron reduced nitrenes, which are key-intermediates in catalytic amination of benzylic C–H bonds to form secondary amines.\(^{63}\)

**Scheme 9.** Formation of bis-nitrene (left) and mono-nitrene (right) radicals.

**Scheme 10.** Examples of metallo-radical [Co(por)]-catalysed reactions with nitrene radicals as intermediates.

The controlled radical-type reactions described above constitute interesting ring-closure or ring-expansion reactivity, producing a variety of desirable ring-products taking advantage of formation of discrete substrate-based ligand radicals formed in the coordination sphere of the applied transition metals. Most of the known catalyst used in this type of reactions are cobalt porphyrins. While useful, such porphyrin-based catalysts also have some disadvantages. Porphyrin synthesis can be time consuming and low-yielding, often requiring several elaborate chromatographic purification steps. This makes porphyrins rather expensive as ligands, especially non D4h symmetric. As such, alternative ligands with similar properties which are easier to synthesize and purify, in fewer steps from cheap starting materials, are of interest to the field of metallo-radical catalysis. A particularly interesting class of ligands which closely resemble porphyrins has received quite some interest in the coordination chemistry community over the past fifty years or so are dibenzotetraaza[14]annulenes (Figure 7). Remarkably, however, these ligands have received surprisingly little attention in the field of catalysis thus far.

First reported by Hiller, Jäger and Goedken in the late 1960s, these ligands present many similarities with porphyrins, and namely the presence of four coplanar nitrogen donors, double deprotonation and formation of a dianionic species upon metal coordination, as well as the presence of conjugated double bonds in their framework. Tetraaza[14]annulenes present a 14-membered macrocycle. The ring size of these ligands is smaller than the 16-membered one in porphyrins, thus favoring shorter metal-nitrogen bonds. Furthermore, porphyrins are fully delocalized, aromatic (4n+2) systems, while dibenzotetraaza[14]annulenes are Hückel anti-aromatic (4n), with negligible delocalization between the 1,3-diminato and the two o-phenylene fragments. Upon deprotonation, the negative charge is delocalized only over the two 2,4-pentanediminato chelate fragments, in contrast to the complete delocalization found in porphyrins. This is due to the saddle shaped
geometry of the ligands, which favours the aromatic stability of each individual benzenoid ring, in contrast to the flat porphyrins which allow extended conjugation.

Figure 8. Saddle shaped structure of the dibenzotetraaza[14]annulene (H₂MeTAA) ligand.⁶⁸

Another important difference between porphyrins and dibenzotetraaza[14]annulenes represents the macrocycle coordination cavity. Due to the fourteen membered macrocycle, compared to the larger sixteen-atom ring for porphyrins, the distance between the centre of the macrocycle and any of the four nitrogens is 0.1 Å smaller for tetraaza[14]annulenes. This determines many coordinated metals to stick out of the plane to accommodate favorable coordination bond distances. The extent of the metal displacement from the N₄ plane is dependent on both metal radius and ligand field stabilization effects. For example, cobalt coordination in two oxidation states is illustrative. The cobalt(II) ion is small enough to fit in the cavity, therefore forming a low-spin [Co^{II}(MeTAA)] complex in which Co and N₄ are coplanar. In contrast, for [Co^{III}(MeTAA)Cl], the cobalt(III) ion lies 0.234 Å, above the N₄ plane.⁶⁴

The synthesis of dibenzotetraaza[14]annulenes is straightforward and facile.⁶⁶,⁶⁷ It typically involves a template condensation between o-phenylene diamine and a 1,3-dicarbonyl species in the presence of a small metal ion such as Ni²⁺ (Scheme 11). The metal can further be stripped away using gaseous hydrochloric acid to afford the free macrocycle.

\[ \text{R}^2,\text{R}^3 = \text{Me, Ph} \]

Scheme 11. Typical template synthesis for the synthesis of substituted dibenzotetraaza[14]annulenes
The template condensation works only for late transition metal ions, such as Co\textsuperscript{II}, Ni\textsuperscript{II} or Cu\textsuperscript{II}, due to the cavity size restriction. Bigger radius ions simply will not fit inside the macrocycle, and therefore the template condensation will not work. For the bigger ions, the free ligand is generally complexed with the desired metal ion. Cobalt(II) complexation affords a low-spin four-coordinate [Co\textsuperscript{II}(MeTAA)] complex, which is a very sensitive complex, especially towards oxygen. It readily coordinates a variety of axial ligands to satisfy its coordinatively unsaturated geometry, if not properly stored under inert conditions. It also gets easily oxidized using X\textsubscript{2} or CHX\textsubscript{3} (X = Br, I) to form [Co\textsuperscript{III}(MeTAA)X] species with a triplet (S= 1) ground state.\textsuperscript{69} All these features, together with both the similarities and differences with porphyrins, make [Co\textsuperscript{II}(MeTAA)] a good candidate for use in catalysis.

5. Research Goals and Thesis Outline

To address issues with material scarcity, sustainability and process costs, modern catalysis research is focused on replacing expensive and scarce noble metal (e.g. Pd, Pt, Rh, Ir) catalysts by much cheaper and more abundant base metal (e.g. Fe, Co, Ni) catalysts. Interestingly, this can also lead to fascinating new reactivity coupled to the intrinsically preferred one-electron reactivity of first-row transition metals. The research described in this Thesis aims at understanding and exploiting such metallo-radical reactivity. The goal of this research was to explore the scope of radical-type reactions mediated by square planar, low-spin cobalt(II) metallo-radical complexes, with a prime focus on uncovering novel reactivity of discrete cobalt(III)-bound carbene radicals generated upon reaction of the cobalt(II) catalysts with carbene precursors. Another important goal of the investigation described in this Thesis was to replace cobalt(II)-porphyrin catalysts by cheaper and easier to synthesize analogs. As such, the reactivity of planar, low-spin cobalt(II) complexes based on the dibenzotetraaza[14]annulene (MeTAA) ligand scaffold was explored. These complexes are not only much easier to synthesize, but are also more active than the corresponding cobalt(II)-porphyrins in a variety of ‘carbene transfer’ reactions.

Chapter 2 describes the use of [Co(MeTAA)]-type catalysts in cyclopropanation catalysis. The results not only show the superior cyclopropanation activity of these catalysts as compared to cobalt(II)-porphyrins, but also demonstrate the ability to use tosylhydrazones directly as carbene precursors in one-pot catalytic reactions, replacing diazo compounds. This not only makes the synthetic protocol safer, but also substantially expands the substrate scope of carbene transfer reactions in general. Chapter 3 describes a detailed kinetic and DFT mechanistic study of these cyclopropanation reactions, aiming at understanding both the superior activity and
higher sensitivity of [Co(MeTAA)]-type catalysts when compared to cobalt(II)-porphyrins. The intermediacy of cobalt(III)-carbene radicals was demonstrated using a combination of kinetic studies, experimental (EPR) spin-trapping experiments and supporting DFT studies.

Cobalt(II)-metalloradical catalysis, involving related carbene-radical reactivity was further applied in a series of novel carbene-carbonylation reactions. These reactions provide a novel one-pot catalytic synthetic protocol for the synthesis of beta-lactams, amides and esters. The reactions proceed via ketene-intermediates, formed upon reaction of the carbene radical intermediate with carbon monoxide. Trapping of the ketene intermediates with imines, amines or alcohols then leads to the desired beta-lactams, amides or ester products. The results of these investigations are described in Chapter 4 (using cobalt(II) porphyrins) and Chapter 5 (using [CoII(MeTAA)]-type catalysts).

In the final Chapter 6 we describe the use of cobalt(II)-metalloradical catalysts in ring-closure of o-cinnamyl-N-tosyl hydrazones to 1H-indenes. Also these reactions take advantage of the intrinsic reactivity of the unconventional cobalt(III)-carbene radical intermediates. The reaction uses readily available starting materials and is operationally simple, thus representing a practical method for the construction of functionalized 1H-indene derivatives. As was observed for the cyclopropanation reactions described in Chapter 2, the cheap and easy to prepare low-spin cobalt(II) complex [CoII(MeTAA)] (MeTAA = tetramethyltetraaza[14]annulene) proved to be the most active catalyst among those investigated. The metallo-radical catalysed indene synthesis in this paper represents a unique example of a net (formal) intramolecular carbene insertion reaction into a vinylic C(sp²)–H bond, made possible by a controlled radical ring-closure process of the carbene radical intermediate involved. The mechanism was investigated computationally and the results were confirmed by a series of supporting experimental reactions.
6. References

[18] Image released in the public domain by Klaus Hoffmeier.
Chapter 1


Controlled Radical-Type Catalytic Reactions


